Attentional Factors Underlying Binocular Vision Loss in Amblyopia

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

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Abstract

Amblyopia is a neurodevelopmental disorder of vision that results from abnormal visual experience during early development. In addition to significant vision loss in one eye, individuals with amblyopia experience binocular dysfunction, difficulty with visuomotor coordination and attentional deficits. A key component of the vision loss associated with amblyopia is strong, chronic suppression of the amblyopic eye. Clinically, suppression remains challenging to treat, and is a key obstacle to rehabilitating visual function in amblyopia. This thesis examines whether suppressed visual information from the amblyopic eye remains available for processing within the brain and whether higher-order attentional processing is affected in amblyopia. Emerging evidence suggests that attentional mechanisms may contribute to interocular suppression and vision loss in amblyopia. Across four experiments, the findings from this thesis provide several major insights about amblyopia. Visual information seen only by a suppressed amblyopic eye retains a presence within the brain that may subsequently be used for attentional processing. Attentional mechanisms in amblyopia were found to be intact to some extent and thus can be engaged. Orienting visual attention was effective for targets seen by a partially suppressed amblyopic eye and even for complex face cues. Selective attentional tracking by the amblyopic eye was intact in anisometropic amblyopia but was impaired for strabismic amblyopia. Additionally, the process of attentional disengagement and re-engagement may be impaired during amblyopic eye viewing. Overall, these results demonstrate that the amblyopic eye continues to influence visual perception despite being suppressed under normal viewing conditions. As a result, appropriate refractive correction of the amblyopic eye should be clinically prescribed to optimize image quality for binocular combination. Furthermore, amblyopia may affect how visual attention is allocated between the eyes, providing a therapeutic target to guide future rehabilitative efforts.

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List of Abbreviations

AE – amblyopic eye

BCEA - bivariate contour ellipse area

BOLD - blood-oxygen level dependent

CFS - continuous flash suppression

DE – dominant eye

Dmax – maximal displacement

EEG – electroencephalography

ERP – event-related potential

ETDRS – early treatment of diabetic retinopathy study

FE – fellow eye

FEF – frontal eye fields

FFA - fusiform face area

fMRI – functional magnetic resonance imaging

GABA - gamma-aminobutyric acid

IPS – intraparietal sulcus

LGN – lateral geniculate nucleus

logMAR – logarithm of the minimum angle of resolution

MOT – multiple-object tracking

MT/hMT+ – (human) middle temporal area

NDE – non-dominant eye

PPA - parahippocampal place area

PPC – posterior parietal cortex

PPRF – paramedian pontine reticular formation

RDK – random dot kinematogram

RT – reaction time

SD – standard deviation

SE(M) – standard error (of the mean)

tDCS - transcranial direct current stimulation

TMS - transcranial magnetic stimulation

V1/V2 – primary visual area 1/2

VA – visual acuity

List of Publications

This thesis contains several publications that have been accepted or submitted.

Included in the thesis:

1. Chapter 5: **Chow A**, Silva AE, Tsang K, Ng G, Ho C, Thompson B. (2021). Binocular integration of perceptually suppressed visual information in amblyopia. *Investigative Ophthalmology & Visual Science.* 62(12):11.
2. Chapter 6: **Chow A**, Raveendran RN, Erkelens I, Babu R, Thompson B. Examining the Role of Oculomotor and Attentional Factors Underlying Increased Saccadic Latencies in Amblyopia. *Submitted to Vision Research: Special Issue on Eye Movements in Visual Impairment.*
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Chapter 1
Introduction

Vision is one of our most important senses. Disruption of visual development during early childhood can cause a disorder known as amblyopia, resulting in profound visual impairment in one eye. Although children with amblyopia often present clinically with monocular vision loss, amblyopia is truly a binocular problem within the brain. Amblyopia has been a major focus of neuroscientific and clinical research because of the potential for novel treatment approaches that focus on binocular rehabilitation. One of the key obstacles to achieving binocular function in amblyopia is the presence of strong, chronic suppression of the amblyopic eye. Interocular suppression prevents what is seen by the amblyopic eye from reaching conscious awareness. Despite the latent binocular connections that remain within the amblyopic brain, suppression renders this structurally binocular system functionally monocular. As a result, it has been thought that visual information from the amblyopic eye does not contribute to visual processing in the brain under normal binocular viewing conditions. Emerging evidence suggests that attentional mechanisms may contribute to interocular suppression and vision loss in amblyopia.

The general aim of this thesis is to study whether suppressed visual information from the amblyopic eye remains available for processing within the brain and whether attentional mechanisms are affected by amblyopia. We begin with a literature review of amblyopia (Chapter 2), interocular suppression (Chapter 3) and attention (Chapter 4). Chapters 5-8 of this thesis present four individual experiments in the form of manuscripts either published (3) or submitted (1) at various vision science journals. In Experiment 1, we investigated whether suppressed visual information remains available in the amblyopic brain for subsequent processing (Chapter 5). In Experiment 2, we explored whether attentional cueing was effective for non-dominant eye when partially suppressed during binocular viewing conditions (Chapter 6). In Experiment 3, we studied whether the magnitude of exogenous attentional capture using complex cues (involving higher level processing) is affected in amblyopia (Chapter 7). In Experiment 4, we studied whether endogenous visual attention is preferentially directed towards the fellow eye in amblyopia (Chapter 8).

My hypotheses are:
Experiment 1: Suppressed visual information remains available for processing within the amblyopic brain (Chapter 5)

Experiment 2: Exogenous attentional cueing of the amblyopic eye can alleviate its saccadic latency deficit (Chapter 6)
Experiment 3: Exogenous attentional capture by complex cues (emotional faces) is affected by amblyopia (Chapter 7)
Experiment 4: Endogenous attention is preferentially allocated to the fellow eye in amblyopia (Chapter 8)

Our findings from Experiment 1 are detailed in Chapter 5. We studied whether visual information consciously suppressed under the conditions of binocular rivalry can influence visual perception in participants with and without amblyopia. Our experiment was motivated by findings that suppressed visual information can be integrated and alter perception in visually normal participants. We found that visual information seen only by a suppressed amblyopic eye remains available for visual processing and can affect visual perception despite being suppressed from conscious awareness.

Results from Experiment 2 can be found in Chapter 6. The amblyopic eye is partially suppressed by the fellow eye during normal binocular viewing. We studied whether exogenous attentional cueing of a partially suppressed eye was equally effective for both eyes in amblyopia. Using the response times of saccadic eye movements as an index of attentional cueing, we alternated a saccadic target between the eyes and found expedited saccadic response times regardless of which eye was fixating. These findings indicate that the magnitude of attentional capture is similar for both eyes in amblyopia, and that process of attentional disengagement and re-engagement may be affected under amblyopic eye viewing.

Studies demonstrating intact attentional cueing in amblyopia have employed simple spatial cueing tasks. Experiment 3 explores whether attentional deficits in amblyopia may become evident when the cue requires higher-order cognitive processing (Chapter 7). Using a dynamic gaze cueing task with emotional faces, we investigated whether attentional deficits would emerge if complex visual processing was required to process emotional face cues. We found that the magnitude of attention orienting effect using emotional face cues remained unaffected by amblyopia.

Experiment 4 studies whether interocular suppression involved a biased allocation of endogenous attention towards the fellow eye in amblyopia (Chapter 8). Using a dichoptic multiple-object tracking task, we measured tracking performance when tracked targets were seen only by the

amblyopic or fellow eye. Amongst our participants who had various etiologies of amblyopia, we found normal attentional allocation in anisometropic amblyopia but biased allocation favoring the fellow eye in strabismic amblyopia.

Altogether, the findings from this thesis highlight the importance of higher-level perceptual mechanisms that have largely remained unexamined in amblyopia. The new results challenge the idea that suppression of the amblyopic eye precludes its involvement in visual processing for perception and action. Visual information from the amblyopic eye retains a presence within the brain that can alter perception and expedite motor responses. These studies also reveal the cognitive mechanisms affected by amblyopia that can be targeted by novel treatment strategies.

Chapter 2
Amblyopia

Amblyopia is a visual disorder that is characterized by impaired vision in one or (rarely) both eyes. Since the majority of cases are unilateral, amblyopia is typically defined as an interocular difference in best-corrected visual acuity of 2 or more lines on a logMAR eye chart[1]. Clinically, it is diagnosed when vision in the amblyopic eye remains reduced despite the use of optical correction and no identifiable ocular pathology can account for the visual loss[1,2]. Amblyopia is a leading cause of visual impairment in children, affecting 1.3-3.6% of the general population[3,4]. This is because amblyopia typically arises between the ages of 6 months to 8 years[5], during a critical period of visual development. Amblyopia generally does not develop beyond 8 years of age, when the critical developmental period ends[6,7]. During this post-natal period of growth, both the eye and the brain rely on sufficient visual stimulation for visual development[8]. Thus, an abnormal visual experience can disrupt the development of critical visual functions. Many visual functions develop on different time courses, and have different periods where they are susceptible to disruption[9]. For instance, both contrast sensitivity and grating acuity develop quickly between the first 9 weeks to 6 months of life[10]. However, grating acuity reaches adult-like levels at 4-6 years[11,12], earlier than when the contrast sensitivity function resembles that of an adult around 7-9 years of age[13,14]. Contrast sensitivity at high spatial frequencies takes longer to develop than at low spatial frequencies[10]. As such, depending on when an amblyogenic factor impacts the visual system, a differential pattern of visual deficits can be experienced in amblyopia.

2.1 Causes of Amblyopia

The presence of one or more of the following amblyogenic factors (or etiologies) creates a decorrelated visual experience and an imbalance of visual input for the developing brain.

2.1.1 Anisometropia

Anisometropia is the most common cause of amblyopia, estimated to account for 50% of amblyopic patients[4,15]. The prevalence of anisometropia in the general population is around 1.01% and 4.7%[16,17]. The large asymmetry in refractive error between the eyes (anisometropia) is a significant risk factor for developing amblyopia, particularly if left uncorrected for more than 3 years[18]. Uncorrected refractive error produces retinal defocus as well as differences in retinal

image size (aniseikonia). Although children can accommodate to neutralize hyperopic refractive error, accommodation is a bilateral process. If there is unequal refractive error between the eyes, the more hyperopic eye will experience a chronically defocused image that interferes with subsequent binocular development[3].

Clinically, anisometropia is defined as >1.0 diopter difference in spherical equivalent between the eyes or >1.5 diopters of cylinder in one eye. Hyperopic anisometropia is more likely to cause amblyopia than myopic anisometropia due to the latter experiencing periods of clarity at near working distances[19]. Significantly hyperopic refractive error affecting both eyes can cause bilateral refractive amblyopia, although it is much less common. Large amounts of astigmatism can produce meridonal amblyopia, whereby vision along one axis is blurred. There is a strong genetic component to hyperopia[20–22] as well as astigmatism[21]. Anisometropia is most often associated with amblyopia for children older than 3 years of age[3,23]. The severity of amblyopia is known to be correlated with the depth of anisometropia[24].

2.1.2 Strabismus

Eye misalignment (strabismus) is the second most common cause of amblyopia, accounting for 15-20% of cases[4,25]. The prevalence of strabismus in the general population is 5.66%[26,27] and is known to be clustered in families[28]. Strabismus is most often associated with amblyopia for children younger than 3 years of age[3,23]. Strabismic children tend to fixate with their preferred eye, and the deviated eye is turned either inwards (esotropia) or outwards (exotropia)[29]. Esotropia is more amblyogenic than exotropia, and amblyopia is more likely to develop with constant strabismus as compared to intermittent or alternating strabismus[3,30]. Chronic misalignment of the eyes introduces two problems for the visual system: 1) double images (diplopia) as one object can appear at two non-corresponding retinal points and 2) visual confusion as two different objects can appear at the same retinal correspondence point[19].

2.1.3 Form Deprivation

Monocular deprivation is the rarest cause of amblyopia, estimated to account for 4% of cases[4]. Although most often associated with a congenital cataract, it may also be caused by any ocular disease that prevents light from reaching the retina, such as a corneal opacity or a drooping eyelid (ptosis). Of the amblyogenic factors, monocular deprivation usually has the earliest onset and can

cause more severe visual impairment. Despite early detection and treatment of a congenital cataract within 2 months of age, visual acuity can be restored to at least 20/40 in only 28% of cases[31,32]. Treatment initiated at 3 months of age or later has a worse prognosis, with a mean acuity of 20/150[33].

2.1.4 Mixed Mechanism

Amblyopia can also be caused by a combination of factors noted above, most commonly anisometropia and strabismus[4,34,35]. Mixed amblyopia accounts for around 15-30% of cases[4,36,37]. Patients with mixed mechanism amblyopia tend to have disproportionately more severe functional loss than from amblyopia with one factor alone[38]. This type of amblyopia is more difficult to treat, often involving longer treatment duration with worse visual prognosis[36].

2.2 Development of Amblyopia

Regardless of the cause of amblyopia, disruption of vision during the critical period alters the developmental course of the visual system. Amblyopia does not affect any of the structures within the eye, such as the retina. Instead, amblyopia affects areas and pathways in the brain associated with the amblyopic eye[39–44].

Much of our understanding about how amblyopia affects the structural development of the brain comes from animal studies. Studies in cats[40,45] and macaque monkeys[43,46–51] have revealed that the visual cortex is already highly organized at birth, resembling that of a normal adult. Neurons are arranged meticulously in orientation-specific columns and ocular dominance columns that are responsive to each eye[52]. There is a balanced representation of ocular dominance columns for each eye, and a majority of striate neurons receive inputs from receptive fields in corresponding retinal areas from both eyes[53]. Post-natal visual experience and correlated binocular stimulation are critical to preserving the existing architecture in V1[39,40,54–57].

An abnormal visual experience during the critical developmental period causes significant cortical reorganization. Monocular deprivation in cats and macaque monkeys produce a profound loss of vision that is accompanied by anatomical and physiological changes in striate area V1[40,41]. There is a significant loss of neurons in striate cortex V1 in the ocular dominance columns responsive to the deprived eye, reducing its cortical representation[58]. The remaining neurons in the residual

columns receive weakened signals from the amblyopic eye, as a result of poorer neural sensitivity[44,59,60]. The diffuse loss of binocular neurons further reduces the contributions of amblyopic eye[61]. In addition to this, neurons driven by the amblyopic eye have abnormal spiking dynamics, which contribute to increased noise within areas V1[62] and V2[63]. The end result is dominance of the non-deprived eye, both in terms of cortical representation[58,64–70] and function[44,60].

In contrast to animal models[71,72], the earliest part of the visual pathway known to be affected by amblyopia in humans is the lateral geniculate nucleus (LGN), both structurally[73–76] and functionally[75–77]. Specifically, the LGN has reduced activity and connectivity with V1[78]. As a result, there is overall less activation in V1 for stimuli seen by the amblyopic eye[79–84]. Structurally, V1 exhibits the same imbalances in ocular dominance columns in humans with amblyopia as seen in animal models[85,86]. These abnormalities in the early stages of visual processing have downstream effects on cortical areas that receive input from V1[82,87]. There is altered functional connectivity from V1 to other early cortical areas such as V2 and V3[88], as well as to extrastriate visual areas[78,88–90]. Many of these extrastriate areas also exhibit reduced levels of activity when compared to neurotypical controls[79,80,97,82,84,91–96], producing a broad constellation of functional deficits.

The vast array of sensory and motor deficits in amblyopia is beyond the scope of this thesis, and can be found in various comprehensive reviews[38,84,98–103]*. Below we consider some of the deficits pertinent to the thesis.*

2.3 Sensory Deficits in Amblyopia

Sensory deficits are a defining characteristic in amblyopia. Impairments of visual acuity and contrast sensitivity are common to all etiologies of amblyopia[38,104,105]. McKee and colleagues found that classifying visual deficits using these two factors could account for 80% of the variance amongst individuals with and without amblyopia[38]. Figure 2-1 represents a classification map across these two factors, and several clusters segregated by etiology emerge. Different etiologies fall along different sectors of this map, each with distinctive patterns of acuity and sensitivity deficits[38,104,106,107]. Individuals without amblyopia tend to have excellent visual acuity and contrast sensitivity (clustered to the eastern zone, in black). Individuals with anisometropic amblyopia and deprivation amblyopia have moderate visual acuity loss and subnormal contrast sensitivity

(clustered in the southern zone, in green). Those with strabismus (including strabismic amblyopia) tend to have moderate visual acuity loss but better contrast sensitivity than normal (clustered in the northern zone, in red). Mixed forms of amblyopia exhibit severe losses of visual acuity accompanied by normal or subnormal contrast sensitivity (in the western zone, in blue). The lines denote variability within each cluster, and the slope of the lines support the idea that acuity and contrast sensitivity decline together with increasing severity of amblyopia[38,108–110]. Although a useful classification, this map omits consideration of the numerous higher order visual deficits seen in amblyopia (see Chapter 2.3.3) as well as binocular impairments (see Chapter 3).

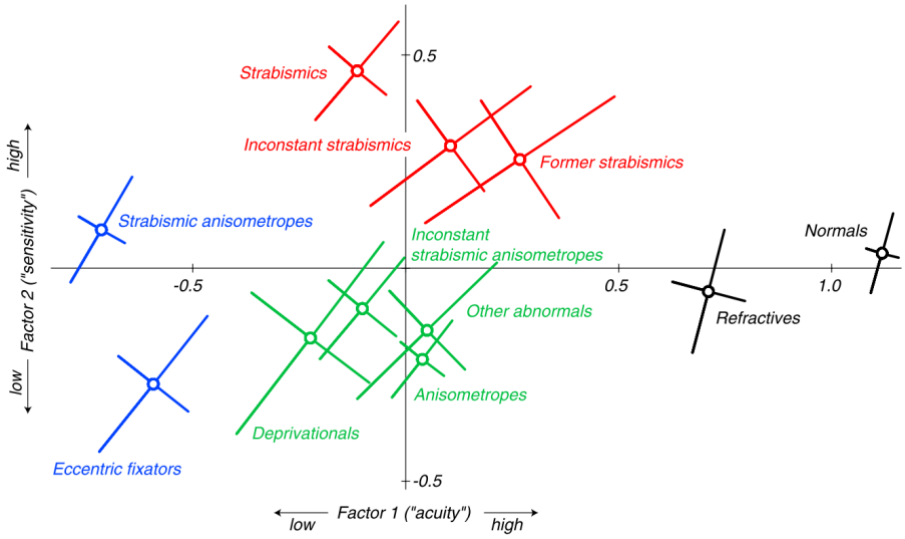

Figure 2-1. A "map" of sensory deficits as defined by factors of visual acuity (abscissa) and contrast sensitivity (ordinate) of the non-dominant eye in individuals with and without amblyopia. Figure reprinted from McKee et al, 2003 with permission.

2.3.1 Visual Acuity

Amblyopia translates from Greek as "blunt sight", in reference to a broad loss of visual acuity. Visual acuity losses can range from a mild 20/30 (the minimum to meet the definition of a 2-line difference on an eye chart) to severe losses in the realm of 20/400 (the largest E on a standard eye chart)[1,111–114]. Individuals with mixed or deprivation amblyopia tend to have a more severe visual acuity deficit as compared to anisometropic or strabismic amblyopia. The fellow eye is often unaffected, presenting with normal 20/20 acuity. While visual acuity is classically measured by discerning letters on an eye chart (optotypes), it seeks to measure one's upper limit of resolving spatial frequencies. High spatial frequencies typically correspond to details such as edges, in

close spatial proximity. In addition to optotype acuity losses, grating acuity and vernier acuity are also impaired for the amblyopic eye[38]. Grating acuity appears to be disproportionately affected in strabismic amblyopia as compared to optotype (letters) and vernier acuity[104,106,115–117]. On the other hand, both grating and vernier acuity appear normal for the fellow eye[99,104,118].

2.3.2 Contrast Sensitivity

Contrast sensitivity refers to the ability to distinguish the boundary between areas of differing luminance. It varies based on the spatial frequency of the pattern, as described by the contrast sensitivity function. Contrast sensitivity is conventionally measured with a Pelli-Robson chart, whereby letters of a fixed spatial frequency progressively have decreasing contrast. Early studies found that when viewing with the amblyopic eye, contrast sensitivity is reduced mildly across all spatial frequencies but particularly impacted at high spatial frequencies[119–128]. However, there seems to be subtle differences among the etiologies. The contrast sensitivity deficit in anisometropic amblyopia affects the visual field uniformly whereas in strabismic amblyopia, the deficit lies primarily within the central 30 degrees[107]. Using a larger sample of participants with amblyopia, McKee and colleagues found that those with strabismic amblyopia actually had supernormal contrast sensitivity in the amblyopic eye when compared to all other etiologies and those with normal vision[38]. Even those with mixed amblyopia had better contrast sensitivity than the pure anisometropic and deprivation amblyopia groups, despite more severe losses of visual acuity. It has been proposed that the loss of binocular cells enables the recruitment of those neurons to support the monocular processing to enhance performance at lower contrasts[38]. The contrast sensitivity function for the fellow eye appears normal in shape and amplitude[119,121,129], although subtle reductions have been noted[130,131].

2.3.3 Higher Order Processing

Local processing abnormalities in primary visual cortex have downstream effects as visual information is integrated across space and time in extrastriate areas. Due to the hierarchical nature of visual processing, higher order functions take longer to develop, and remain vulnerable during the developmental years[132]. Although there is extensive evidence of higher order processing deficits in the amblyopic visual system (for a review, see [101,133]), below we constrain discussion to relevant deficits for the thesis: form integration, motion integration and face processing.

2.3.3.1 Form Integration

Form integration refers to the ability to integrate visual information that is sampled from numerous small receptive fields into an overall form. Detection of collinear elements across larger retinal distances is mediated by short-range and long-range lateral connections between adjacent orientation-tuned cells in V1[134]. Crowding effects due to interference by nearby elements are particularly pronounced for the amblyopic eye[135,136]. Contour integration is deficient for stimuli seen by the amblyopic eye as well as the fellow eye to a lesser extent[137]. This suggests that the processing for contour integration may occur in binocular areas[138]. Due to positional uncertainty, it appears that contour integration is affected moreso in strabismic than anisometropic amblyopia[139,140]. Further details on spatial form integration may be found in Chapter 5.1.

Overall, perception of visual space as seen through the amblyopic eye is not always veridical, as compared to the view from the fellow eye[141]. Spatial distortions are common under monocular[141–143] and dichoptic viewing conditions[144,145]. Subjectively, it seems that visual space is warped with expansions and contractions of various parts of the visual field[143]. High spatial frequencies are particularly affected while low spatial frequencies are spared[143]. Individuals with strabismic amblyopia tend to perceive more spatial distortions than those with anisometropic amblyopia[119,142,144–146]. These spatial errors could not be predicted by monocular factors, such as visual acuity losses[145], contrast sensitivity[147,148], poor fixation, or eccentric fixation[142], but rather poor binocularity (such as stereopsis[144,145] and the magnitude of ocular deviation[144,145,149]). Both retinotopic representation in early visual cortex[119,150] as well as higher order processing are thought to be involved underlying these spatial deficits[151].

2.3.3.2 Face Processing

Although early studies in amblyopia found poor accuracy for identifying facial expressions during amblyopic eye viewing[92], poor performance was also found for inverted faces, suggesting that the deficit lies in featural component processing rather than face configural processing. A follow-up study by the same authors found that reduced activation of extra-striate areas was not face-specific and could be attributed to the reduced visibility of the facial features[79]. Individuals with amblyopia also showed no deficits on the Mooney face task, commonly used for assessing face detection and relying on holistic face processing[152]. These findings indicate that limitations on face perception in anisometropic and strabismic amblyopia are driven by resolution deficits rather than impaired face processing per se.

2.3.3.3 Motion Integration

Global motion perception refers to the ability to integrate various local motion signals over visual space into a perceived coherent direction. Deficits of global motion perception have been reported when viewing random dot kinematograms (RDK), where participants are asked to discern the overall direction of motion from a subset of signal dots moving in a consistent direction in a field of other randomly moving noise dots[153]. The local motion of each signal dot is picked up by direction-selective cells in V1, and is subsequently integrated by cells in the extrastriate middle temporal area (MT) covering a large segment of visual space[154,155,164,156–163]. Individuals with amblyopia require more signal dots to reliably discern the coherent motion direction as compared to neurotypical controls when viewing with the amblyopic eye[165–171], although see [172–174]. To a lesser extent, the fellow eye experiences a subtle deficit as well[166,169,170,173]. Global motion perception appears to be better in children with strabismic amblyopia than those with anisometropic amblyopia[173,175]. However, other studies have found a similar extent of deficits amongst the different subtypes[165–167,170,176].

These deficits of global motion perception reflect extrastriate deficits, not merely extensions of low-level deficits. These global motion deficits could not be attributed to low-level deficits such as visibility due to poor acuity or poor contrast sensitivity[165–167,169,170,177]. Passively viewing expanding and contracting rings produces less activation in the extrastriate area MT+ for participants with amblyopia[93]. Reduced activation of extrastriate areas V3A, MT+ and PPC was observed for individuals with amblyopia as they performed a global motion detection task[94]. These authors determined that the maximal displacement for a single tracked element (Dmax) appears reduced in amblyopia[94]. Dmax is supported by receptive fields of low-level motion detectors for small densely packed RDKs, but also by activation of extrastriate areas that perform high-level feature matching across larger spatial extents[178].

However, differential activation of extrastriate areas may not directly result in anomalous global motion perception. For instance, neuroimaging has revealed that plaid perception may be supported by different neural networks in individuals with amblyopia than individuals with normal vision. Specifically, perception of pattern motion in plaid stimuli was correlated with V5 activity in controls and pulvinar and V3 activity in the amblyopia group, suggesting the existence of compensatory mechanisms for motion processing[179]. As a result, plaid perception is normal in amblyopia[180,181].

Altogether, these findings of global motion deficits may indicate that integration of local motion signals into a global percept is largely intact[177], but rather the deficit for RDKs lies in the ability to segregate noise prior to integration[176,182]. The presence of visual noise impairs amblyopic performance significantly more than visually normal controls[182]. Added to internal noise inherent within the amblyopic system, this may result in increased global motion coherence thresholds observed for RDKs.

2.4 Motor Deficits in Amblyopia

Vision and movement are inextricably linked. Altered visual perception affects how we interact with the environment. Visuomotor deficits are prevalent in amblyopia, encompassing oculomotor abnormalities as well as manual reaching and grasping movements[103,183]. Below we highlight some oculomotor deficiencies in saccadic and fixational eye movements as well as how amblyopia affects manual responses.

2.4.1 Saccadic Eye Movements

Saccades are rapid eye movements that shift the fovea to different areas of interest within the visual environment. As one of the fastest movements that can be produced by the human body, saccades are used to optimally gather visual information. Saccades can be triggered involuntarily by a peripheral stimulus or initiated voluntarily to view a specific target.

Generating saccades involves a network of subcortical and cortical areas. One of the primary structures involved in facilitating saccades is the superior colliculus in the midbrain, which serves as the interface between the sensory and motor systems. The superior colliculus acts as internal retinotopic map of salient objects in the visual field. It receives signals directly from the retina as well as cortical and other subcortical areas that contribute to the programming of saccades[184–188]. Involuntary saccades can be elicited through the retina's direct connection to the superior colliculus or via the parietal eye fields that direct reflexive saccades to peripheral stimuli[189,190]. Parietal areas play an important role linking eye movements with shifts of attention, and will be discussed further in Chapter 3. Voluntary saccades are produced through areas such as the frontal eye fields (FEF) and supplemental eye fields (SEF), to coordinate movements of other parts of the body in conjunction with the eye movement, as well as successive saccades[185,189–

[191]. Other areas such as the dorsolateral prefrontal cortex play a role in saccade planning and higher-level processing involving spatial memory and response selection[185].

Initiation of a saccade begins with a series of neuronal pulses within the saccadic burst generator in the brainstem paramedian pontine reticular formation (PPRF)[187]. Excitatory burst neurons and inhibitory burst neurons act as the accelerator and brakes to generate the eye movement. At the end of the eye movement, omnipause neurons generate pulses to counteract the activity of the burst neurons to keep the eyes steady. These pulses from the PPRF are conveyed to the abducens nucleus (via cranial nerve VI), oculomotor nucleus (via cranial nerve III) and trochlear nucleus (cranial nerve IV) to execute coordinated actions of the six extraocular muscles surrounding the eye.

Saccades are relatively simple to measure and have been used to study the normal and abnormal functioning of the brain for decades. To describe saccade accuracy and kinematics, several important measurable properties include the latency, amplitude, peak velocity and gain. Saccadic latency refers to the time needed for detecting a target and initiating a response, conventionally defined as the duration between target onset and when the eye reaches 30-40 deg/s velocity threshold. Average saccadic latencies for a 5-10 degree saccade range from 120-280 ms. The magnitude of the eye movement, measured in degrees or minutes of arc, is referred to as the amplitude. Larger eye movements require more time to complete and reach higher peak velocities[192]. The main sequence describes the relationship between amplitude and peak velocity (see Figure 2-2)[192]. For saccades with an amplitude of <20 degrees, peak velocity scales linearly with amplitude, before it plateaus at a max of 300-500 deg/sec. Since saccades are completed so quickly, they are ballistic in nature, as visual feedback does not occur fast enough to modify the trajectory of the saccade once initiated. Often corrective saccades are necessary if the amplitude does not match the target displacement. The gain of the initial eye movement is the ratio of the saccade amplitude that was generated compared to the amplitude required.

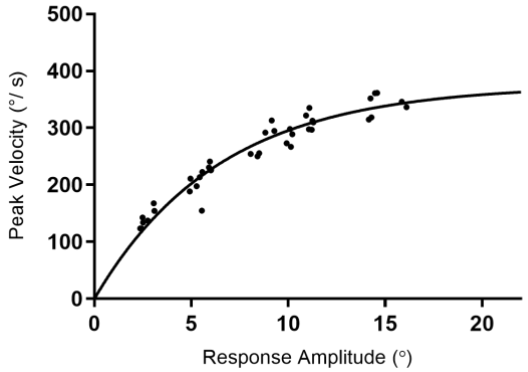

Figure 2-2. Sample main sequence from author AC, illustrating the relationship between peak velocity and amplitude. Data obtained from experiment detailed in Chapter 6.

In amblyopia, saccadic amplitude and peak velocity appear unaffected under amblyopic eye viewing[193,194]. However, increased saccadic latencies of the amblyopic eye have been well documented[193–198] and greater in adults with strabismic and mixed amblyopia[199,200]. This topic will be further explored in the introduction of Chapter 6.

2.4.2 Manual Responses

As was seen for saccadic responses, delays in response times are also evident for manual responses to targets presented to the amblyopic eye[199,201]. Manual response latency under amblyopic eye viewing is significantly delayed compared to fellow eye viewing[195,198,202]. Fellow eye performance appears unaffected, similar to monocular viewing for those with normal vision[202]. This delay for initiating a motor response is greater in strabismic amblyopia than anisometropic amblyopia[201,203], and is known to be correlated with the depth of amblyopia[199,202]. Equating visibility by matching contrast alleviated this interocular difference in latencies only for those with anisometropic amblyopia[201,204], but an irreducible delay remained for strabismic amblyopia observers[201]. For both saccadic and manual responses, it has been proposed that the deficit arises from poor fixational stability under amblyopic eye viewing[201], which will be covered in the subsequent section.

2.4.3 Fixational Eye Movements

To a normal observer, the eye appears still during prolonged fixation. Only by using high speed eye trackers can the miniscule fixational eye movements be discerned. These movements present during normal fixation consist of microsaccades (<1 deg), slow drifts (<2 deg/s) and high-frequency tremors[205]. Microsaccades serve to prevent sensory fading during fixation (Troxler effect)[206] and improve performance during tasks that require fine spatial judgment[207]. However, beyond a certain point, excessive fixational instability impairs acuity performance. Poor fixational stability is correlated with reduced visual acuity[208–210], and fixational eye movements can account for more than half of the variance seen in amblyopic eye's visual acuity[209].

Abnormal fixational eye movements were first identified in amblyopia through the observation that amblyopic eyes had relatively faster and larger amplitude slow drifts than the normal eye[211,212]. No deficit was evident for viewing with the fellow eye[209,213,214]. Later, studies using more advanced eye trackers found that microsaccades during amblyopic eye viewing were of larger amplitudes and had higher peak velocities[214]. Fixational stability then began to be quantified by the area of an ellipse fit over a scatterplot of fixation points (termed bivariate contour ellipse area, BCEA), whereby a larger ellipse represented poorer fixational stability. BCEA values are significantly higher for the amblyopic eye than the fellow eye in children[208] and adults with amblyopia[213]. Larger BCEA values were found for the amblyopic eye than for the eyes of non-amblyopic children with strabismus and/or anisometropia alone[208]. While multiple studies have not found any difference in fixation stability for children with varying etiologies of amblyopia[208,210,214], fixation stability is poorer in adults with strabismic amblyopia than those with anisometropic amblyopia[209,212]. A detailed analysis of fixational eye movements in amblyopia found that both anisometropic and strabismic forms of amblyopia exhibit larger amplitude of slow drifts and microsaccades that produce a larger displacement from the intended locus of fixation. In addition to this, individuals with strabismic amblyopia have faster, more frequent and larger amplitude microsaccades than their anisometropic counterparts[209]. These increased frequency of microsaccades in strabismic amblyopia had been previously noted earlier and described as "saccadic intrusions"[211]. These saccadic intrusions are more likely to leave the amblyopic eye in a motor refractory state[215], introducing delays in both sensory processing and subsequent motor action for both saccadic and manual responses[199,201,216–218].

2.5 Impact of Deficits on Quality of Life

Critically, failure to detect and treat amblyopia during childhood has lifelong consequences that significantly impact quality of life. Due to visual symptoms and concerns of cosmesis, amblyopia negatively affects personal self-esteem[219–222], social interactions[219,223,224], and reduces engagement in sports activities[219]. Children with amblyopia read more slowly than their children without amblyopia[225,226]. Individuals with amblyopia are less likely to attain higher degrees of educational qualifications than the general population[227] (although see also [228]) and experience limitations on career choices due to an inability to meet vision standards[219,229]. Individuals with amblyopia have a strong fear of losing their eyesight, negatively affecting their quality of life[230]. If the better-seeing eye becomes compromised, individuals with amblyopia are more likely to have bilateral blindness as compared to the general population[231]. The prospect of bilateral blindness amounts to an estimated $7.4 billion of lost earning power annually in the United States alone[232].

2.6 Treatment of Amblyopia

Conventionally, treatment of amblyopia begins with addressing the amblyogenic factor. Appropriate refractive correction for hyperopic anisometropia is provided to improve the quality of visual input for each eye. If caused by a cataract or strabismus, surgical intervention is performed to remove the cataract or realign the extraocular muscles. Subsequently, clinical treatment of amblyopia involves occlusion of the fellow eye to promote visual development for the amblyopic eye[1,233]. The fellow eye is either patched or blurred with a plus lens or atropine drops, with the duration of occlusion dependent on the severity of the amblyopic acuity deficit. This treatment continues on the order of months to years until acuity improvements for the amblyopic eye plateau. This intensive approach has been successful in around 60-75% of cases[234,235], whereby children recover to at least 20/40 VA in the amblyopic eye[236]. However, despite meeting the 20/40 criteria for treatment success, monocular acuity deficits still persist in 15-50% of children after treatment[3].

Treatment success also varies by the etiological cause of amblyopia. A meta-analysis found that patching therapy improved amblyopic eye visual acuity to better than 20/40 in 67%, 78% and 59% of patients with anisometropic amblyopia, strabismic amblyopia and mixed mechanisms amblyopia respectively[236]. Final visual acuity levels were better for anisometropic and strabismic amblyopia than for mixed mechanism amblyopia[236].

Despite improvements in visual acuity for the amblyopic eye with treatment, many functional visual deficits persist even after the interocular acuity difference is resolved. The amblyopic eye continues to have reduced contrast sensitivity[110,237,238] and spatial distortions[145]. Critically, many high-level motion deficits persist, such as impaired global form integration[138,239], global motion processing[165,168], motion- defined form perception[240,241] as well as difficulties with multiple object tracking[95,172,241]. Some of these deficits also extend to the fellow eye, previously assumed to be normal based on its visual acuity[95,99,173].

Treatment of amblyopia and its amblyogenic factor during the critical period is more likely to lead to a reversal of the disordered visual development. Clinicians are often reluctant to begin patching treatment beyond 7 years of age, thinking it to be the end of the developmental period. However, a large scale randomized clinical trial demonstrated that optical correction in combination with patching treatment was effective in children aged 7-17 who were never previously treated for amblyopia[242]. Thus, it seems that the critical period for developing amblyopia is not the same as that for its treatment[243–246]. Although the visual cortex may no longer have the capacity to change structurally and functionally beyond the critical period, efforts to restore neural plasticity in adults have been promising[247–250]. In the past decade, the focus has shifted from using monocular therapies that seem to be less effective in older populations to increasing use of binocular approaches that try to rehabilitate abnormal processing in amblyopia. A recent systematic review and meta-analysis found that these binocular approaches have similar efficacy in improving visual acuity as traditional monocular approaches[251]. These binocular approaches have been shown to be more efficacious in older populations than traditional monocular therapies. This may be since they attempt to address the underlying binocular impairment in amblyopia[105,252–255]. The next chapter explores one of the main obstacles to restoring binocular function, the presence of interocular suppression.

Chapter 3
Suppression

In the previous chapter, we explored some of the monocular deficits involving both the amblyopic and fellow eye. In this chapter, we will consider some of the binocular deficits experienced in amblyopia.

3.1 Interocular Suppression

Early clinical studies found that when individuals with amblyopia had both eyes open, there was a distinct blind spot in the central visual field pertaining to the amblyopic eye[6,30,256,257]. There appeared to be no conscious awareness of anything within the suppression scotoma, resembling the absolute blind spot from the optic nerve. Instead, that area of the visual field was dominated by what was seen by the fellow eye[6]. Newer quantitative techniques to document suppression scotomas have found that suppression of the amblyopic eye does not produce an absolute scotoma. Stimuli presented foveally to a suppressed amblyopic eye can be perceived, however luminance[258] and increment[29,259] thresholds are significantly elevated and contrast sensitivity is reduced to 10-30% of the stimulus strength[260,261]. Suppression is strongest within the foveal region[260] and declines towards the periphery, although a tonic level of suppression is present across the whole visual field[261]. Suppression of central vision has been observed in fMRI studies that have used dichoptic presentation of visual stimuli. In particular, interocular suppression is present when the fellow eye is open, regardless if it is stimulated or not[262]. There is a significant reduction in hemodynamic activity driven by the amblyopic eye when the fellow eye is open[262]. The foveal region of the amblyopic eye fails to activate the occipital pole in the brain as effectively as parafoveal regions of the amblyopic eye[263–266]. Thus, interocular suppression is thought to involve an active process in amblyopia to resolve decorrelated visual inputs from each eye.

Interocular suppression in amblyopia acts as a significant obstacle to simultaneous binocular perception and binocular combination. Originally, based on a small study of patients with either anisometropic or strabismic/mixed amblyopia, it was proposed that the strength of suppression is inversely related to the severity of amblyopia[267]. The reasoning was that weaker signals from the amblyopic eye are easier to suppress and therefore severe amblyopia required only weak suppression to avoid visual confusion and diplopia. Conversely, mild amblyopia required much stronger suppression to enable comfortable single vision. More recently, however, larger studies

have found that suppression is *positively* associated with the depth of amblyopia[59,105,268–272]. These results have driven an increasing shift towards seeing suppression as contributing to both the binocular and monocular deficits in amblyopia.

One of the most common deficits in amblyopia is a loss of stereoscopic depth perception[273]. It would be expected that suppression of the amblyopic eye would impair the binocular processing required for stereopsis. However, stereopsis appears to be relatively preserved in anisometropic amblyopia, while it is often absent in strabismic amblyopia[38,274,275]. A study using the Randot circles test found that 50% of participants with anisometropic amblyopia achieved some measure of stereopsis as compared to only 10% of individuals with strabismic amblyopia[38]. In anisometropic amblyopia, stereopsis is found only at low spatial frequencies[275] and stereoacuity is positively correlated with visual acuity[38]. Previously, it was thought that the loss of stereopsis in strabismic amblyopia was because stronger suppression was required in the presence of strabismus[65,276]. However, suppression appears similar in strength between the anisometropic and strabismic forms of amblyopia[105,260,261,270]. Nonetheless, despite the presence of interocular suppression, it appears that binocular processing is preserved to some extent in some forms of amblyopia.

3.2 Binocular Summation

Binocular dysfunction in amblyopia was originally attributed to a lack of binocular connections within the amblyopic brain (see Chapter 2.2). In contrast to the normal visual system where binocular summation augments monocular performance, a binocular advantage is not evident in amblyopia. For instance, binocular contrast detection thresholds are no different from monocular thresholds across a wide range of contrast levels tested[203,277,278]. The absence of interocular transfer for the motion aftereffect[279] and interocular contrast adaptation effects[277] suggested that binocular interactions were absent in amblyopia. However, binocular summation was found to be preserved in anisometropic amblyopia for low spatial frequency stimuli[122,275]. While binocular summation may be limited in the central visual field, normal binocular summation can be found in the periphery in anisometropic amblyopia[280]. These findings led to the hypothesis that binocular summation is masked by elevated contrast thresholds inherent for the amblyopic eye. Studies that adjusted for this interocular difference in contrast sensitivity by using each eye's contrast threshold revealed that binocular summation was possible in amblyopia[281–284]. Similarly, binocular combination of dichoptic global form and global motion stimuli are intact in amblyopia at each

individual's interocular contrast balance point[285]. Together, these results clearly demonstrate that residual binocular connections are preserved in the amblyopic brain, in both primary visual areas and extrastriate areas. Rather, interocular suppression renders the structurally binocular system functionally monocular under circumstances when the monocular inputs are not balanced. Restoring balanced visibility between the eyes can overcome suppression to reveal intact binocular summation. In fact, prolonged viewing of artificially balanced contrast inputs may strengthen binocular fusion as it produces improvements in both visual acuity and stereopsis[253,286,287]. There is also anecdotal evidence that vision in the amblyopic eye can spontaneously recover after significant vision loss in the fellow eye, due to the loss of the fellow eye's inhibitory influence[288,289]. Thus, suppression is increasingly seen to be a cause of amblyopia, as opposed to a response to amblyopia.

3.3 Models of Binocular Vision

Studies in both normal vision and in amblyopia have provided evidence that interocular suppression and binocular summation are not mutually exclusive. Prominent models of binocular vision feature at least two stages of processing: interocular suppression followed by binocular summation[290,291]. Generally, interocular suppression is defined as the reciprocal inhibitory influence of one eye over the other. Interocular suppression serves to modify contrast gain before the signals are summated[290]. As noted in Section 3.2, binocular summation appears intact in amblyopia, and is presumed to be normal in two prominent models of binocular vision in amblyopia[292–294]. Rather, where the models differ is in how suppression occurs. The Baker model finds that interocular suppression is a passive process in amblyopia, and proposes that binocular deficits are instead due to the summation of an attenuated amblyopic signal[281]. With this passive form of suppression, there is a significant inhibition within the primary or extrastriate cortex that attenuates the signals from the amblyopic eye[59,68,80]. However, signal attenuation alone does not explain the data obtained from human and animal studies. The model put forth by Huang and colleagues contends that in addition to an attenuated amblyopic signal from passive suppression, the fellow eye exerts stronger inhibition on the amblyopic eye signal directly than vice versa, as well as indirect inhibition of the amblyopic eye contrast gain control signal [292,293]. As compared to the normal visual system where the reciprocal inhibition is balanced, there is a significant asymmetry in amblyopia in active suppression that favours the fellow eye[42,68,292,293,295,296].

3.4 Mechanisms of Interocular Suppression

In animal models, suppression of the amblyopic eye involves GABAergic inhibitory circuits in the primary visual cortex[68,296]. Injections of the GABA antagonist bicuculline is able to restore binocularity in over 50% of the cortical neurons in strabismic cats[297,298]. However, the connection is less clear in human amblyopia due to the complexity of the brain and its interactions. Transcranial direct current stimulation (tDCS) is a non-invasive method to alter excitatory and inhibitory activity in the human brain. Anodal tDCS has been shown to increase cortical excitability by decreasing GABA concentrations[299–301]. Application of anodal tDCS in adults with amblyopia improves contrast sensitivity for the amblyopic eye, presumed to be through reducing interocular suppression[302].

Thus, the exact mechanism of interocular suppression remains unknown for human amblyopia. Identifying these suppressive mechanisms is critical for rehabilitation efforts and motivating new treatments of amblyopia. Suppression is a significant obstacle to restoring binocular vision, as stronger suppression is associated with poorer monocular and binocular outcomes[303]. It is unclear whether amblyopic suppression is an extreme form of the normal binocular interactions that take place, or a pathological process in addition to that. Interocular suppression has been approximated in various ways in psychophysical studies. Below we briefly outline some relevant techniques that allow the contribution of each eye to the binocular percept to be quantified and highlight different mechanisms of interocular suppression in normal vision.

3.4.1 Dichoptic Contrast Masking

Interocular suppression has been compared to dichoptic contrast masking, whereby a high-contrast mask presented in one eye strongly suppresses target detection in the other eye. This technique can be used to measure the strength of suppressive influence from one eye to the other. In amblyopia, it appears that the fellow eye exhibits a stronger masking effect than the amblyopic eye in return in both anisometropic and strabismic subtypes[126,304]. However, another study finds similar dichoptic masking effects between the eyes in strabismic amblyopia[294]. A recent study sought to measure the reciprocal directional effects of dichoptic masking after accounting for contrast sensitivity differences between the eyes[305]. They found that suppression from the fellow eye to the amblyopic eye was not abnormally strong, and comparable to normal controls[305]. Rather, it is the amblyopic eye that exerts reduced suppression on the fellow eye to produce an overall imbalance of interocular suppression[305]. Thus, interocular suppression in

amblyopia may be due to an imbalance in reciprocal suppressive signals, favouring the fellow eye.

3.4.2 Binocular Rivalry

Within the normal visual system, interocular suppression can be simulated by artificially presenting conflicting images to each eye, eliciting a phenomenon known as binocular rivalry[306]. During binocular rivalry, conscious visual perception is dominated by what is seen by one eye while the other eye is suppressed. Suppression and dominance alternate between the eyes periodically. Stimuli with high contrast and high spatial frequency information shown to one eye can dominate rivalry perception and altering these stimulus characteristics can change rivalry dynamics[307]. During periods of monocular dominance, the suppressed eye suffers from a substantial reduction in sensitivity[308–312], reminiscent of amblyopic eye suppression. Neuroimaging studies have revealed that blood-oxygen level dependent (BOLD) activity in V1 is tightly linked with dominance periods in rivalry, such that activity levels are reduced for suppressed stimuli[313–317]. It has been previously suggested that amblyopic suppression and binocular rivalry may rely on similar mechanisms[65]. However, amblyopic eye suppression may be stronger than the transient suppression of one eye during binocular rivalry. One of the features of binocular rivalry is the frequent alternating dominance of each eye, which seldom occurs in amblyopia. Nevertheless, binocular rivalry may be a useful tool to study interocular suppression in amblyopia.

For individuals with normal binocular vision, suppressed visual information remains available for cortical processing and can influence perception. For instance, form information from the orientation of a rivalry-suppressed grating can systematically bias the perceived orientation of a grating shown to the dominant eye[318]. Similarly, the perception of apparent motion[319] and the motion after-effect[320–322] persist despite being presented only to the rivalry-suppressed eye. Stereoscopic information can be combined for judgments of depth despite rivalry suppression[323]. It remains to be seen whether remnants of suppressed visual information can still be processed in amblyopia as well.

In particular, emotional content within facial expressions continues to be processed despite being suppressed in rivalry paradigms for individuals with normal vision. Neuroimaging studies have found that areas for face processing such as fusiform face area (FFA) and parahippocampal place

area (PPA) responded more strongly during periods of dominance than suppression. Activation of subcortical structures such as the amygdala persisted regardless of whether the emotional facial expression was dominant or suppressed[324]. These subcortical pathways may bypass the visual processing stages where suppression acts[325]. It remains unknown whether processing of emotional information inherent in suppressed visual stimuli may be preserved in amblyopia.

3.4.3 Continuous Flash Suppression

Strong suppression can be elicited by dynamic, high contrast, high spatial frequency stimuli. Continuous flash suppression (CFS) uses high contrast, Mondrian patterned blocks that flicker dynamically to suppress a lower-contrast stimulus presented to the other eye[326]. It is unclear whether CFS is simply a dynamic version of binocular rivalry where one eye remains strongly suppressed[327] or involves a different processing mechanism altogether[328]. Like binocular rivalry, V1 BOLD responses are muted when a stimulus is suppressed by CFS[329]. This suggests that CFS acts at an early stage of visual processing that modifies the gain response akin to other forms of visual masking[329]. However, some studies have attributed these changes in BOLD levels to attentional effects rather than suppression from conscious awareness[330].

Stimuli suppressed by CFS still appear to be processed within the brain for those with normal vision. In particular, there is some evidence that faces with direct gaze can break through the suppressive effects of CFS earlier than faces with averted gaze[331,332]. However, there was no difference in detection times among faces conveying fearful, neutral and happy expressions, suggesting that affective content is not privileged[332]. Suppression also has differential effects on dorsal and ventral areas of the brain[333]. Using CFS to suppress images of tools and faces, BOLD activity in ventral areas such as lateral occipital cortex and anterior fusiform gyrus was largely suppressed[333]. However, activity in dorsal regions V3A, V7 and intraparietal areas persisted despite being suppressed from conscious awareness[333]. While suppressed visual information is preserved for processing within the visually normal brain, it remains to be seen whether this is also the case for the amblyopic brain.

There is some evidence that CFS suppression in amblyopia may be different from interocular suppression in normal observers. In a CFS paradigm, participants with amblyopia demonstrated a form of CFS suppression that was not orientation-tuned, unlike the suppression seen in neurotypical controls[334]. For many of the amblyopic participants, increasing the contrast input to

the amblyopic eye increased its suppressive influence on the fellow eye, but the strength of these reciprocal interactions remained strongly biased for the fellow eye[334].

3.4.4 Involvement of Higher Order Areas

As mentioned above among the various paradigms of interocular suppression, suppressed visual information retains some representation within the brain of neurotypical individuals. For instance, activation of higher order areas FFA and PPA persisted in neurotypical individuals even when face and house stimuli were suppressed from conscious awareness by CFS as identified using functional magnetic resonance imaging[335] and magnetoencephalography[336]. Neuroimaging work in humans with amblyopia has found that even when stimuli were suppressed dichoptically, BOLD activity in early visual areas such as V1, V2 and V3 remained strong[337]. Thus, visual information from the suppressed amblyopic eye may still represented in the brain in both early cortical and subcortical areas and used for processing in higher order areas. In order to prevent suppressed visual information from reaching conscious awareness, an attentional mechanism may be involved to gate this visual information from consciousness. In the next chapter, we explore the hypothesis that amblyopia not only involves low-level visual processing impairments, but also alters higher-order cognitive processing, including attention.

Chapter 4
Attention

Visual attention refers to the prioritized processing of certain sensory inputs faster or deeper than other visual stimuli, and makes these stimuli available to short and long-term memory[338,339]. Orienting spatial attention to specific regions of the visual field confers processing advantages such as expedited detection or more accurate processing of attended stimuli[340–344]. In neurotypical observers, attending to stimuli enhances contrast sensitivity[345–353] as well as spatial resolution[354–360]. This priority processing even distorts our perception of time, as attended stimuli are perceived as appearing earlier than other simultaneously presented stimuli at unattended locations[361].

4.1 Forms of Attentional Processing

4.1.1 Exogenous and Endogenous Attentional Processing

Attentional processing can be engaged when driven by changes in the external environment (termed exogenous cueing) or deployed strategically based on one's goals (endogenous attention). If an object suddenly appears (onset), disappears (offset), flickers, moves, or is starkly different from nearby objects, it is deemed salient and stands out against other stimuli nearby[341,362]. These salient cues reflexively orient exogenous attention, as the processing of these cues is expedited regardless of whether the cue is relevant or of interest[363–367]. In contrast to the transient nature of exogenous attention, attentive processing can also be deployed in a sustained manner[343,352,368], as an intentional filter over the visual landscape. It can be constrained to a designated region in space (focal attention) or based on an object's features (feature and object-based attention)[341,362]. Endogenous cues may be in abstract form, such as an arrow or another's gaze that denote a specific area of interest. As such, the meaning of endogenous cues is shaped by an individuals' experience and long-term memory, and how it relates to their current goals and needs.

4.1.2 Covert and Overt Attentional Processing

Visual attention is often allocated to the locus of visual fixation and can be shifted to new points of fixation with eye movements (often referred to as overt attention)[369,370]. However, making eye movements to shift the fovea to a cue comes at a cost if the cue is invalid, impairing detection and processing of distractors. Thus, covert attentional processing can also be deployed from the

point of fixation, preferentially monitoring peripheral areas without changing fixation[371–374]. Both overt and covert attentional processing systems in vision involve similar brain areas[375–379]. This attentional network is comprised of visual areas such as V1 and V5, parietal areas IPS (intraparietal sulcus) and areas responsible for eye movements, such as the frontal eye fields (FEF)[380,381]. Neural activity in the frontal and parietal areas is also enhanced for the attended location moreso than in visual areas during covert attention tasks[391,392]. The premotor theory of attention proposes that activity in the FEF is involved in covert visual attention even when eye movements are not executed by the oculomotor system[370,377,378,382]. Functional imaging studies in humans have shown that the FEF is active during both overt and covert attention tasks[372,383]. Since the FEF generates saccadic commands during both overt and covert tasks[384–387], it seems that FEF does not drive saccadic activity directly[388,389]. Rather, strong inhibitory activity in frontal areas actively suppresses saccadic eye movements[390]. Thus, the FEF most likely serves as a salience map for potential targets for eye movements[393,394]. Indeed, inhibition of this area using transcranial magnetic stimulation (TMS) has been shown to modulate visual search performance[395] and increases the cost of invalid cues[396]. Nevertheless, even on a covert attention task, observers inadvertently make small microsaccades in the direction of the cued location[397,398]. These microsaccades may play an important role in covert attention as target discrimination is better when microsaccades are directed towards the target location[399]. This bias in microsaccade direction reflects sustained covert attention and is not due to saccade planning or triggered by the physical presence of a cue[400].

4.1.3 Attentional Mechanisms

Attentional processing enhances sensory processing by improving the signal-to-noise ratio, which subsequently is used to expedite a behavioural response[345]. In early visual areas, attentional processing functions as a noise-reduction system[401]. Subsequent attentional processing in higher visual areas amplifies a denoised signal[401]. An enhanced signal-to-noise ratio is reflected by enhanced signal gain[402] and results in increased synchronous activity for the attended stimulus. These preactivated patterns of neural activity then bias responses for specific stimuli[403]. Whereas both attended and unattended stimuli are well-represented at the level of primary visual areas, responses to unattended stimuli are muted in extrastriate areas[404]. This phenomenon resembles the effects of suppression in amblyopia. Thus, it remains an open question as to whether interocular suppression in amblyopia employs attentional mechanisms. Given the increased

internal and external noise present for the amblyopic eye's signal, it is unclear whether attentional mechanisms are intact or possibly biased against the amblyopic eye in amblyopia.

It remains unclear whether attentional processing can occur without conscious awareness of stimuli, as is seen for suppressed eyes in amblyopia. It appears that visual awareness is not necessary for attentional processing, as blindsight patient GY benefits from exogenous cueing even in his blind field[405–407]. However, this idea remains untested in amblyopia. Typically, visual processing begins with V1 and activation extends progressively to higher-order extrastriate areas that extract higher-level information for behavioural responses[408]. This feedforward pattern of activation can be altered by attentional selection using past experience and memory to change subsequent sensorimotor processing[403]. Nevertheless, it is thought that selective activation of feedforward mechanisms in extrastriate areas does not require conscious awareness, as phenomenal experience relies instead on recurrent feedback interactions[409,410]. Horizontal connections and feedback circuits may modulate the feedforward processing to produce the conscious visual experience[409,411,412]. Specifically, interrupting these feedback interactions using TMS can render stimuli invisible[413] or impair the perception of motion[414]. In Chapter 5, we will directly test the idea that visual information from the suppressed amblyopic eye may be used in attentional processing.

4.1.4 Eye of Origin

It has been proposed that pre-activated neuronal networks may even occur for a specific eye in biasing sensory processing[403]. In normal vision, attentional processing can be allocated independently to stimuli seen by one eye and modulate binocular combination of monocular information. Monocular cues presented under dichoptic viewing conditions can attract exogenous visual attention and expedite detection of a salient stimulus presented to only one eye under dichoptic viewing in participants with normal vision[415,416]. Similarly, monocular cues can affect perceptual dominance in binocular rivalry paradigms, even though they cannot be discriminated from binocular cues[417–420]. Eye-specific information is encoded within binocular cells to identify a visual signal's eye-of-origin[421,422]. It remains to be seen whether endogenous attention may be preferentially allocated to one eye depending on task goals. Eye-specific information may be lost with increasing binocular combination of information starting at V1 and beyond with higher order processing. It has been proposed that the dominance of the fellow eye in amblyopia may result from selective attention to the signals from the fellow eye over the amblyopic eye[423]. Over time,

this may reshape processing within the visual cortex, and lead to long-term suppression of the amblyopic eye.

4.2 Attentional Processing in Amblyopia

4.2.1 Electrophysiological Studies

Early electrophysiological studies were the first to identify an attentional deficit associated with inputs from the amblyopic eye. In particular, visual evoked potentials measured from V1 showed that attentive viewing with amblyopic eye was not significantly different from passive inattentive viewing[424]. In another study using electroencephalography, the modulatory effect of a simple central spatial cue was found to be reduced in areas V1, hV4 and hMT+ when viewed by the amblyopic eye for participants with strabismic amblyopia[268]. Even when viewing with the fellow eye, modulatory effects were reduced in areas hV4 and hMT+ compared to visually normal observers[268]. The extent to which this modulatory effect was reduced in V1 was correlated with the magnitude of interocular suppression as well as the depth of amblyopia[268]. Similarly, activation of an attentional network comprised of V1, V5, IPS and FEF was found to be generally reduced in participants with strabismic amblyopia[380]. These differences in cortical activation were found despite past treatment for nearly all of the participants[268,380]. Together, these studies provide evidence of attentional deficits in the amblyopic brain. However, since none of these studies examined anisometropic amblyopia, it is possible that these deficits pertain only to strabismic amblyopia.

4.2.2 Intact Attentional Function in Amblyopia

Despite these differences in attentional activation within the amblyopic brain, there is evidence that some attentional mechanisms remain intact in amblyopia. Several studies in both humans[425,426] and macaques[427] suggest that spatial cueing of attention is unaffected in amblyopia. In particular, valid cueing (congruency between cue and target) enhanced both contrast and response gain for the amblyopic eye to the extent that cueing effectively compensated for the amblyopic eye contrast sensitivity deficit[427]. Similarly, invalid cues (incongruency between cue and target) are equally effective distractors among adults with and without amblyopia[428]. In general, targets were detected faster and more accurately when preceded by either exogenous and endogenous cues in adults with amblyopia[425]. The magnitude of the cueing effect was similar regardless of the eye[425]. Although the presence of exogenous cues improved accuracy more than

endogenous cues, endogenous cues sped up reaction times moreso than exogenous cues[425]. These attentional benefits also seem to extend to children with amblyopia, as endogenous cues improved accuracy and reduced reaction times regardless of eye[426]. However, this study consistently tested the fellow eye prior to the amblyopic eye, and thus practice effects may have masked any effects of eye[426]. Common to all studies finding intact attentional function in amblyopia is the use of simple low-level spatial cues, such as a salient spot of light or an arrow. While attentional mechanisms are intact to some extent in amblyopia, increased complexity of attentional processing may reveal attentional deficits.

4.2.3 Attentional Deficits in Amblyopia

Attentional deficits tend to be found in complex tasks involving higher order processing, suggesting a possible attentional bottleneck in amblyopia. Below is a general summary of several key paradigms where attentional deficits have been revealed. To avoid repetition, a detailed literature review can be found in the introduction section of Chapters 6-8.

Enumeration

An early study noted that individuals with strabismic amblyopia significantly underestimated the number of visible targets when briefly presented to the amblyopic eye[428]. This undercounting of Gabor patches could not be attributed to poor visibility, undersampling or crowding effects[428]. In particular, the effect became pronounced when more than 5 patches were presented. Counting targets when fewer than 5 is considered a pre-attentive task, one that relies on low-level processing in the visual system. When the number of targets exceeds 5, higher level attentional processing becomes involved[429–431]. This process is slower and more error-prone[432–434]. Although the original study only examined individuals with strabismic amblyopia[428], a more recent study extended these findings to also include individuals with anisometropic amblyopia[435]. Examining the contributions of each eye separately, the amblyopic eye was less effective in enumerating targets when compared to the fellow eye[435]. There was a larger interocular imbalance in strabismic amblyopia than anisometropic amblyopia[435,436]. Notably, undercounting with the fellow eye was only evident in those with strabismic amblyopia, as those with anisometropic amblyopia performed similarly with their fellow eye to visually normal observers[436]. This enumeration deficit is further impaired when the task is alternated between the eyes, indicating that the ability to quickly redirect attention to one eye may be impaired in amblyopia[436]. The poorer enumeration performance could not be attributed to poor visibility (as the Gabor targets were contrast-matched

between the eyes) or visual acuity (since the fellow eye also undercounted in strabismic amblyopia)[435,436].

Multiple-Object Tracking

Multiple-object tracking involves using endogenous attention to selectively track the movement of several cued targets amongst other moving distractors[437]. Individuals with normal vision are able to track up to 5 targets before accuracy begins to suffer, but individuals with amblyopia begin to experience difficulty when asked to track 3 targets[95,172]. This tracking deficit is present in both the amblyopic and fellow eye, thus reflecting an attentional deficit as opposed to deficient motion processing[95,172]. Although another study failed to replicate the tracking deficit for the fellow eye in a similar paradigm, the effective number of tracked trajectories was found to be 15% lower for the amblyopic eye relative to the fellow eye[438]. Neuroimaging during multiple-object tracking shows reduced activation of areas MT+, FEF and IPS during high attentional load compared to neurotypical observers[95]. These tracking deficits were found even in children who were previously treated and had some form of binocularity (stereopsis)[95,172].

Visual Search

A simple visual search task involves finding a target with a distinctive feature among a field of distractors. Due to its uniqueness, the search task can occur in parallel by filtering for a specific low-level feature[439,440]. For example, the location of a red circle amongst other blue circles can be identified quickly and easily. On the other hand, searching for a target with a certain set of features (termed conjunctive visual search) requires more nuanced processing and must occur with a serial search strategy. This would be akin to searching for a red square amongst other blue squares and red circles. Participants with amblyopia do not experience any difficulty performing a simple visual search task[423]. However, for conjunctive visual search task, participants with amblyopia processed items at a slower rate (with either eye) than visually normal participants, suggesting a bottleneck of attentional processing[423].

Stimulus-Response Conflict Resolution

Visual processing of stimuli in the environment may occur automatically, but this is not always informative or conducive to one's goals. The standard Eriksen flanker task can be used to assess one's ability to suppress responses to stimuli flanking a central target. While participants are asked to discern only the direction of a central target arrow, automatic responses to flanking stimuli (arrows in opposite directions) can interfere with the intended response in an incongruent

trial. Participants with normal vision exhibit the Gratton effect, whereby an incongruent trial expedites subsequent incongruent trials due to an increased recruitment of top-down attentional and cognitive control resources for conflict monitoring. The absence of the Gratton effect in individuals with amblyopia suggests this recruitment of additional attentional resources may be affected by amblyopia[441]. Stimulus-response conflicts have also been tested with the Stroop task, where participants must suppress the automatic reading of a word when written in a different colour. While reading a word occurs automatically, naming the colour involves executive processing[442,443]. Children with amblyopia require longer response times to perform to the same level of accuracy as children without amblyopia[444]. The concurrent use of EEG in this study found that the amplitudes and timing of P1, N1 and N270 characteristics of the event-related potential response differed between children with and without amblyopia[444]. Akin to plaid perception that remains intact in amblyopia, it appears that abnormal cortical processing mediates perception and behavioural performance[179].

Altogether, it appears that low-level attentional mechanisms may be intact in amblyopia while attentional deficits are often seen only with higher-level attentional demands. It has been proposed that interocular suppression may involve an inability to direct visual attention to the amblyopic eye[423]. In this thesis, we will explore whether visual attention plays a role in mediating interocular suppression, and whether higher-level attentional processing is affected in amblyopia.

Chapter 5
Binocular Integration of Perceptually Suppressed Visual Information in Amblyopia

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5.1 Introduction

Abnormal visual experience in early childhood, typically caused by the misalignment of one eye (strabismus) or a large difference in focusing power between the eyes (anisometropia), can alter the course of normal visual development resulting in a disorder called amblyopia. Amblyopia causes reduced visual acuity when viewing with the affected eye, monocular losses such as poor contrast sensitivity and positional acuity as well as binocular losses including impaired stereoacuity[3,98,99,101,102,445]. A key component of amblyopia is the presence of strong, chronic suppression of the amblyopic eye. Early clinical studies identified a distinct blind spot (termed a scotoma) within the amblyopic visual field when both eyes were open[30,256,257]. There was no conscious awareness of stimuli presented within the suppression scotoma, suggesting that the scotoma was absolute (similar to the blind spot created by the optic nerve). Instead, overall visual perception was dominated by what was seen by the non-amblyopic fellow eye. Since then, quantitative techniques have been developed to measure the extent and severity of suppression scotomas[260,261,446,447]. Although there is marked suppression across the entire amblyopic eye visual field[261], suppression is strongest within the foveal region[260]. Within the central region of a suppression scotoma, luminance[258] and increment[29,259] thresholds are significantly elevated and contrast sensitivity is reduced to 10-30%[260,261] of the stimulus strength, resulting in a significant weakening of the amblyopic eye signal. Suppression appears similar in strength between the anisometropic and strabismic forms of amblyopia[105,260,261,270], and suppression strength is positively correlated with the severity of amblyopia[105,268–270]. Although interocular suppression resolves conflicting visual input from each eye to avoid diplopia and visual confusion, it acts as a significant barrier to the recovery of binocular vision in the treatment of amblyopia.

Due to the weakened amblyopic eye signal, the suppressed amblyopic eye contributes little if anything to the binocular experience, since the fellow eye signal dominates conscious visual perception[285,293,448,449]. Suppression of the amblyopic eye has been thought to preclude its contribution to binocular processing and conscious visual perception[122,277,278,280]. For instance, the lack of stereopsis in amblyopia is largely due to suppression and subsequent abnormal binocular processing rather than the monocular loss of resolution and sensitivity[296,450]. This is in part due to the asymmetrical suppressive influence between the eyes in favour of the fellow eye[282,285,292,451,452]. These suppressive interactions are contrast- and spatial frequency-dependent, with stronger suppression being generated by high contrast and high spatial frequencies[292,304,449,452]. Suppression can be alleviated by presenting higher contrast stimuli to the amblyopic eye than the fellow eye[281,285,292–294,448]. At a particular, personal, interocular contrast ratio (known as the balance point), the asymmetrical suppressive interactions favouring the fellow eye can be neutralized, enabling simultaneous visual perception[285,446] as well as binocular combination[281,285,292–294,448]. Although these findings demonstrate that the binocular architecture within the amblyopic brain is structurally intact, the amblyopic visual system is still considered to be functionally monocular due to interocular suppression during normal binocular viewing.

Within the normal visual system, interocular suppression can be simulated by artificially presenting conflicting images to each eye, eliciting a phenomenon known as binocular rivalry[306]. During binocular rivalry, conscious visual perception is dominated by one eye while the other eye is suppressed. Suppression and dominance alternate between the eyes periodically. During periods of monocular dominance, the suppressed eye suffers from a substantial reduction in sensitivity[308–312], reminiscent of amblyopic eye suppression. In individuals with normal binocular vision, suppressed visual information remains available for cortical processing and can influence perception. For instance, form information from the orientation of a rivalry-suppressed grating can systematically bias the perceived orientation of a grating shown to the dominant eye[318]. Similarly, the perception of apparent motion[319] and the motion after-effect[320–322] persist despite being presented only to the rivalry-suppressed eye. Stereoscopic information can be combined for judgments of depth despite rivalry suppression[323]. Furthermore, neuroimaging studies have shown that information from a suppressed eye retains a presence within the brain[333,335,336]. These results indicate that suppressed visual information remains available for cortical processing.

Experiments using plaid stimuli have generated critical insights into motion integration within striate and extrastriate visual cortex. Comprised of two gratings with different orientations and

motion directions drifting within a circular aperture, plaid stimuli can be perceived as two individual gratings moving in their respective directions (referred to as component motion) or a plaid pattern moving coherently in a single direction that is distinct from the two component directions (referred to as pattern motion)[156]. These two percepts alternate for dominance when plaid stimuli are viewed for an extended period of time[180,453,454]. Plaid stimuli have been used to investigate how the brain solves the aperture problem; the fact that motion direction signals are ambiguous when seen through an aperture such as an individual receptive field in V1. In particular, the motion direction of an edge appears to be perpendicular to its orientation when viewed through an aperture, regardless of its actual motion direction[154]. Therefore, to identify the veridical motion direction of an edge or moving object, the visual system must integrate motion information across multiple adjacent receptive fields[154]. Hierarchical two-stage models have proposed that local, component motion signals (susceptible to the aperture problem) are extracted within the primary visual cortex (V1). Component motion signals are then integrated in the extrastriate middle temporal (MT) cortex to compute the veridical motion direction[154,155,164,156–163]. Indeed, neurophysiological studies using plaid stimuli found that nearly all V1 cells responded to the direction of the individual grating components with none responding to the pattern direction[158,160,455,456]. On the other hand, a subset of MT neurons displayed responses that matched the pattern motion direction indicating integration of the local component motion directions[158,163,457]. While a small number of pattern-selective cells do exist in V1[458,459], it appears that pattern cells in MT use the outputs of V1 cells to compute motion over a larger spatial extent than V1[460] (though see [461]). Computation of the overall pattern direction is determined by a geometric solution using the intersection of constraints or vector averaging[462–464] and has been the subject of extensive modelling[164,463,465]. Consistent with this hierarchical model, application of repetitive transcranial magnetic stimulation (rTMS) to reduce cortical excitability over striate cortex in humans increased pattern motion percepts, whereas rTMS over extrastriate V5 (the human analogue of MT) cortex reduced pattern motion percepts[466]. This result reveals the critical role of V5, such that disruption of function reduces pattern motion computation and biases perception in favour of component motion percepts[466].

Plaid perception is normal in amblyopia[180,181]. However, neuroimaging has revealed that plaid perception may be supported by different neural networks in individuals with amblyopia than individuals with normal vision. Specifically, perception of pattern motion in plaid stimuli was correlated with V5 activity in controls and pulvinar and V3 activity in the amblyopia group, suggesting the existence of compensatory mechanisms for motion processing [179]. The perception

of pattern motion depends on the spatial and temporal properties of the two component gratings. Pattern motion is more likely to be perceived for component gratings with similar contrast[467–471], spatial frequency[180,467,468,472] and speed[156,467,468]. If the gratings are unbalanced, perception is biased towards the component grating with higher contrast[470], higher spatial frequency[180,467,468,472] or faster speed[156,467,468]. When plaid stimuli are presented dichoptically (one component grating to each eye), form rivalry can occur whereby the spatial properties of only one component grating are perceived. However, form rivalry does not prevent the binocular combination of motion information when viewing dichoptic plaids[467,473–476]. Specifically, observers may perceive a single component grating (form suppression) moving in the pattern motion direction, suggesting binocular integration of motion. If motion information from a suppressed eye can be integrated binocularly in the normal visual system, it remains an open question whether this phenomenon can occur in amblyopia. How inputs from the suppressed amblyopic eye are handled by the brain remains unknown.

In this study, we explored whether visual information from a suppressed amblyopic eye can influence the conscious perception of stimuli presented to the fellow eye. Using 100% contrast dichoptic gratings to maximally engage suppression of the amblyopic eye, we explored whether binocular integration of motion can occur during periods of amblyopic eye form suppression in binocular rivalry. Based on previous work in individuals with normal vision[467,473–476], we reasoned that if binocular combination can occur despite suppression of the amblyopic eye, motion presented to the suppressed amblyopic eye would influence the motion direction perceived by the fellow eye. Such a result would demonstrate that despite strong amblyopic eye suppression, amblyopic eye information can still contribute to binocular vision.

5.2 Materials and Methods

Observers. Participants with normal vision (n=20, mean ± SE 23.9±0.7 years, 16 females) and amblyopia (n=20, 39.5±3.1 years, 9 females) took part in this study. All participants were naïve to the experimental hypothesis and were reimbursed for their time. Participants provided written informed consent to take part in the study, and the study protocol was approved by the institutional ethics committee at the University of Waterloo, in accordance with the Declaration of Helsinki. Participants were screened at the School of Optometry and Vision Science at the University of Waterloo, Waterloo, ON or at the Mount Pleasant Optometry Centre, Vancouver, BC. Clinical assessment included visual acuity (electronic ETDRS chart), eye alignment (distance and near

cover test) and stereoacuity (Randot Preschool Stereotest; Stereo Optical Co. Inc., Chicago, IL, USA). Amblyopia was defined as a minimum of a 2 logMAR line difference in visual acuity between the eyes associated with either anisometropia (>1 dioptre difference in spherical equivalent between the eyes or >1.5 dioptres of cylinder in one eye) and/or strabismus (including history of strabismus surgery), with otherwise normal ocular and general health. All participants had a 0.2 logMAR interocular visual acuity difference except for participant A07, who had undergone successful treatment of amblyopia with previous patching. All participants wore their habitual correction as needed. In participants with normal vision, the preferred eye was determined as the eye more sensitive to blur when a +2.00 DS lens was held over one eye while binocularly observing letters 0.2 logMAR above their best-corrected visual acuity (a measure of sensory dominance). The preferred eye in participants with amblyopia was defined as the eye with better best-corrected visual acuity. Henceforth the term non-preferred eye will be used to refer to amblyopic eyes in the amblyopia group and non-dominant eyes in the normal vision group. Clinical details for individuals with amblyopia (11 anisometropic, 9 strabismic/mixed) are summarized in Table 5-1. Data and analysis code are available online from the University of Waterloo's repository.

Table 5-1. Clinical details for participants with amblyopia. Some identifier codes are omitted as some participants could not fuse in the stereoscope. Participants with ID A## were tested in Waterloo and ID A### were in Vancouver. M = male, F = female, VA = visual acuity, A = anisometropia, S = strabismus, M = mixed (anisometropia and strabismus), NS = non-strabismic, XP = exophoria, RET = right esotropia, Δ = prism dioptres, Dx = diagnosed, FT = full-time, PT = part-time, VT = vision therapy (orthoptics and/or dichoptic binocular amblyopia treatment).

ID	Age/ Gender	Type	VA (FE)	VA (AE)	Stereoacuity	Ocular Deviation (Near)	Clinical History
A01	25/F	A	20/20	20/100	>800"	NS, 12Δ XP	Unknown history
A02	24/F	A	20/20	20/40	>400"	NS, ortho	Dx at 3-4 y, patched 2-3h/day until 8 y
A03	29/M	A	20/20	20/50	>800"	NS, ortho	Dx since childhood, no patching or surgery

A04	66/F	A	20/25	20/200	>800”	NS, ortho	Dx at 10 y, patched all day
A05	44/M	M	20/20	20/60	>800”	4Δ RET	Dx and surgery for ET at 4 y, patched 8h/day at 5 y, had VT
A06	42/M	M	20/15	20/80	>800”	4Δ LXT	Dx 4-5 y, FT glasses at 13 y, eye surgery at 31 y for XT, patched 1h/day
A07	21/F	A	20/20	20/25	60”	NS, ortho	Patched at 2-3 y
A08	28/M	A	20/15	20/200	>800”	NS, 2Δ XP	Dx 5-6 y, patched all day
A09	28/M	S	20/15	20/25	>800”	17Δ LXT	Dx 3-4 y, glasses, surgery for XT at 7-8 y, had VT
A10	45/M	A	20/15	20/50	>800”	NS, ortho	Dx at 4-5 y, patched until 6 y, had VT
A11	40/F	S	20/15	20/30	>800”	8Δ RET	Unknown history
A12	24/M	A	20/15	20/30	60”	NS, ortho	Dx at 16 y, glasses, had VT
A001	46/F	M	20/20	20/40	>800”	12Δ RXT	Glasses and patching during childhood, had VT
A002	57/F	M	20/20	20/70	>800”	16Δ RXT	ET in childhood, had surgery for ET, was non-compliant with patching, had VT
A004	36/M	M	20/20	20/40	>800”	10Δ LET	Dx at 1-2 y, had surgery, patched until 9 y, had VT
A005	39/M	S	20/20	20/60	>800”	8-10Δ RET	PT glasses
A006	61/M	A	20/20	20/70	>800”	NS, ortho	Dx at 5 y, was non-compliant with patching
A007	60/M	A	20/20	20/30	>800”	NS, 6Δ XP	Dx in adulthood
A009	28/F	A	20/20	20/30	100”	NS, 8-10Δ XP	Patching from 2-7 y

A010	46/F	M	20/25	20/60	>800”	Constant alternating 10Δ ET	Patching from 5-8 y

Experimental Design. Participants viewed drifting dichoptic orthogonal gratings (1 cpd, 4 deg diameter, 100% contrast, moving at 0.25 cycles/s) through a mirror stereoscope (Figure 5-1). The optical path length from the stereoscope to the display was 67 cm. Stimuli were presented on an Acer 27” LED monitor (HA270) at a resolution of 1920 x 1080 and 75 Hz. Mean luminance of the grating and uniform grey background was 15.6 cd/m^2 and 14.5 cd/m^2 respectively. Each trial lasted 60 seconds and participants performed 42 trials in total. Initial alignment was performed using a Nonius cross (2.5^o in width and height) and participants maintained fixation on a smaller Nonius cross (0.63^o in width and height) during rivalry periods. A binocular fusion square subtending 8.95^o (width and height) was present at all times. Through the stereoscope, the preferred eye always viewed a grating oriented 45^o moving up and to the left (motion direction 135^o), and the non-preferred eye always viewed a grating oriented 135^o moving up and to the right (motion direction 45^o). As the gratings underwent binocular rivalry, participants continuously reported their form percept using 3 keys (single grating oriented 45^o, single grating oriented 135^o, or any piecemeal combination). Participants were instructed that any mixture or superimposition of the two gratings, even partially, should be considered as piecemeal. Motion direction percepts were reported by using a mouse to control an on-screen arrow. Due to inherent response variability, mouse responses were binned to the nearest 45^o, 90^o or 135^o motion direction (ie. any mouse responses with a polar angle between 113-158^o were counted as a motion direction of 135^o). This small range of angles around each expected direction of motion took into consideration the need for participants to provide form and motion direction responses concurrently. Transparent motion (i.e. the percept of two separate motion directions, one for each grating) was reported by pressing the piecemeal key without a concurrent mouse button press. Participants were given an unlimited practice period to master the controls prior to starting the test trials. To ensure participants were responding accurately, 6 catch trials with monocularly presented stimuli were randomly interleaved within trial blocks.

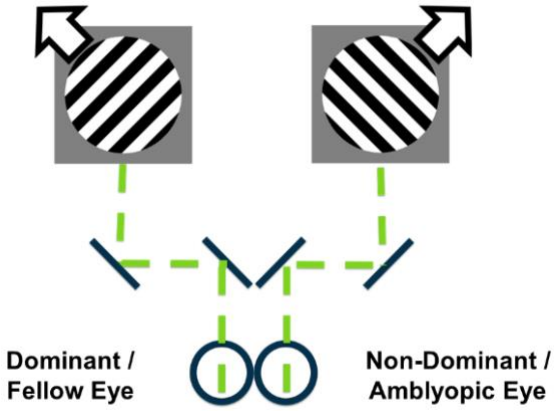

Figure 5-1. Plaid stimuli comprised of two high-contrast orthogonal drifting gratings were presented dichoptically using a mirror stereoscope. The dominant eye always viewed a grating oriented 45^{o} moving up and to the left, and the non-preferred eye always viewed a grating oriented 135^{o} moving up and to the right. Arrows indicate the direction of motion.

Responses were binned into one of the following response categories (see Figure 5-2 for schematics of the associated percepts):

1. Full binocular integration of form and motion information
2. Transparent motion
3. Preferred eye form suppression with concurrent binocular integration of motion
4. Preferred eye motion suppression with simultaneous binocular form perception
5. Non-preferred eye form suppression with concurrent binocular integration of motion
6. Non-preferred eye motion suppression with simultaneous binocular form perception
7. Full suppression of non-preferred eye
8. Full suppression of preferred eye

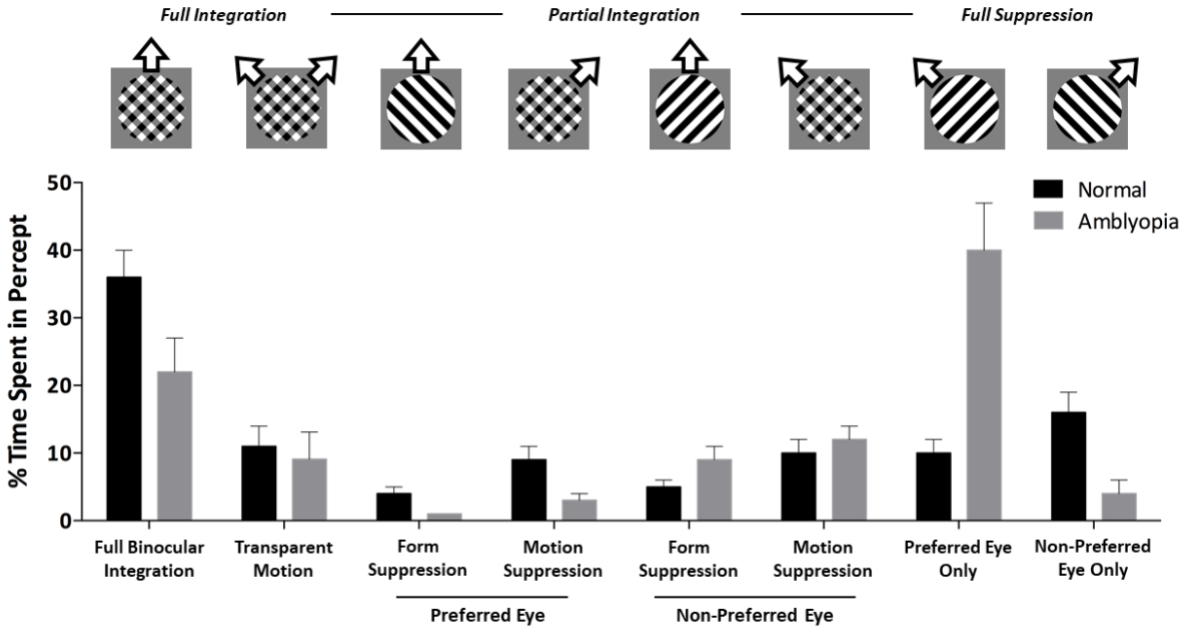

Figure 5-2. Proportion of time spent in each defined category of percept. Error bars denote standard error.

To examine the extent of motion integration while the non-preferred eye was suppressed (Figure 5-3), data were considered from participants who reported non-preferred eye suppression for at least 2 minutes (5% of total viewing time). During periods of non-preferred eye form suppression, corresponding motion information from the non-preferred eye was determined to be either integrated (category 5) or suppressed (category 7; see Figure 5-3 for a schematic). Figure 5-3 shows the extent of motion integration respectively between the two groups, computed as the ratio (category 5/category 5+7) for motion integration[473].

Statistical Analysis. Comparisons between the normal vision and amblyopia groups were made using an independent samples t-test, and comparisons within each group were made using paired samples t-tests. Periods of partial integration (categories 3-6) were analyzed with a 2 (eye: preferred eye, non-preferred eye) x 2 (suppression: form, motion) x 2 (group: normal, amblyopia) repeated measures ANOVA. Post-hoc analyses were conducted on significant interactions using Tukey's correction for multiple comparisons. A one-sample t-test was used to determine whether the mean percentage of motion integration during non-preferred eye suppression in the amblyopia group differed from zero. Pearson's r correlation coefficients were used to investigate the

association between interocular acuity difference and non-preferred eye suppression during rivalry in the amblyopia group, as well as the extent of motion integration during form suppression of the non-preferred eye. To assess whether adaptation to the stimuli over the course of the experiment influenced integration responses, we analyzed the proportion of pattern motion responses (categories 1, 3, 5) in the first 3 and last 3 trials of the experiment using a 2 (group: normal, amblyopia) x 2 (order: first, last) x 3 (trials: 1, 2, 3) repeated measures ANOVA.

5.3 Results

Responses for motion direction revealed three peaks around each of the expected motion directions. In participants with normal vision, peak medians ± SD were located at 46º±10.8º, 90º±6.0º, 130º±9.9º. For participants with amblyopia, peak medians ± SD were located at 51º±9.6º, 91º±7.6º, 132º±7.9º.

Figure 5-2 illustrates the proportion of time spent in each percept category for participants with normal vision or amblyopia. As expected, individuals with amblyopia experienced longer periods of non-preferred eye suppression (category 7; mean±SEM 40±7% of the time) than preferred eye suppression (category 8; 4±2%; t_{19}=5.1, p<.001). In contrast, individuals with normal vision had similar periods of preferred eye suppression (category 8; 16±3%) and non-preferred eye suppression (category 7; 10±2%; t_{38}=1.2, p>.05). The duration of non-preferred eye suppression during rivalry was positively correlated with the interocular acuity difference in the amblyopia group (r=0.59, p=.008; Figure 5-4A), whereby the non-preferred eye was more often suppressed at larger interocular acuity differences. Full binocular integration of form and motion information (category 1) occurred more frequently in the normal vision group (36±4%) than in the amblyopia group (22±5%, t_{38}=2.14, p=.039). Occurrence of simultaneous perception/transparent motion (category 2) was similar amongst the two groups (normal vision: 11±3%; amblyopia: 9.1±4%; t_{38}=0.4, p>.05). For periods of partial integration (categories 3 to 6; Figure 5-2, middle), a 2 (eye) x 2 (suppression) x 2 (group) repeated measures ANOVA found a significant interaction of eye x group ($F_{1,38}$=23.39, p<.001), as well as a main effect of suppression ($F_{1,38}$=14.79, p<.001). No interaction of eye x suppression x group was evident ($F_{1,38}$=0.24, p>.05). Motion information was more often suppressed than form information in individuals with normal vision (t_{38}=4.46, p<.001), regardless of whether the preferred eye (motion 9±2%; form 4±1%) or non-preferred eye (motion 10±2; form 5±1%) was suppressed (form vs motion: t_{38}=0.72, p>.05). However, in individuals with amblyopia, form and motion were similarly suppressed (t_{38}=1.45, p>.05), moreso for the non-

preferred eye (motion 12±2%; form 9±2%) than the preferred eye (motion 3±1%; form 1±0.3%; form vs motion: t_{38}=5.95, p<.001).

Periods where participants reported more than 2 minutes (5% of total viewing time) of non-preferred eye form suppression (category 5; 16 normal vision, 19 amblyopia; Figure 5-3) were analyzed further. Binocular integration of motion information from the suppressed non-preferred eye occurred 48.1±6.2% of the time in participants with normal vision and 31.2±5.8% of the time in participants with amblyopia (t_{33}=-2.0, p=0.054; Figure 5-3). A post-hoc power calculation (using G*Power v.3.1.9.7) with d=0.68 found that observed power was 0.49. Notably, the proportion of time that participants with amblyopia experienced binocular motion integration during suppression of the non-preferred eye was significantly non-zero (t_{18}=5.4, p=.000004). The extent of motion integration during non-preferred eye suppression was not correlated with interocular acuity difference (r=-0.43, p=.07; Figure 5-4B).

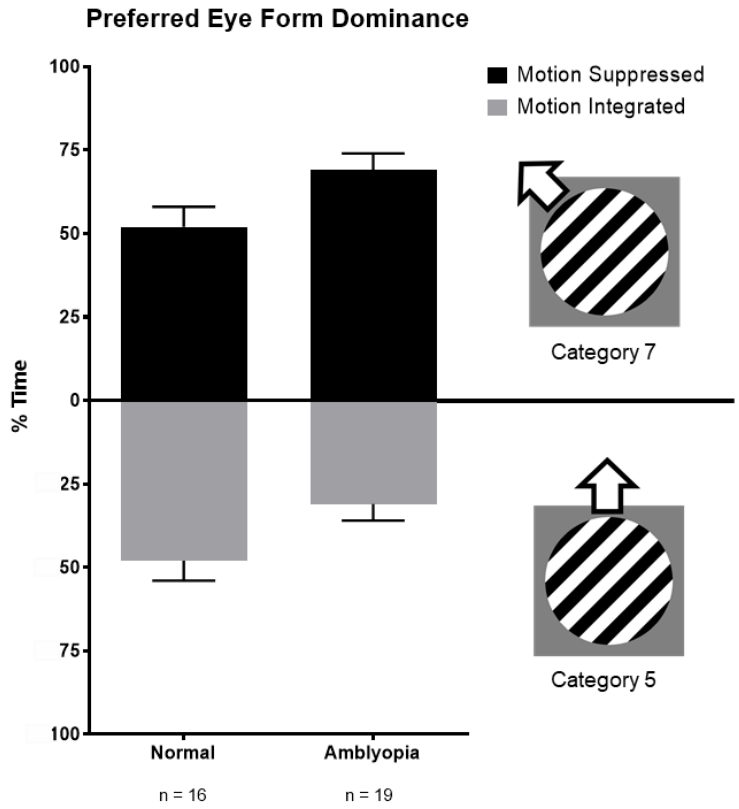

Figure 5-3. Extent to which binocular integration of motion information occurs during periods of non-preferred eye suppression. Error bars denote standard error. Figure designed in style as per Andrews & Blakemore[473].

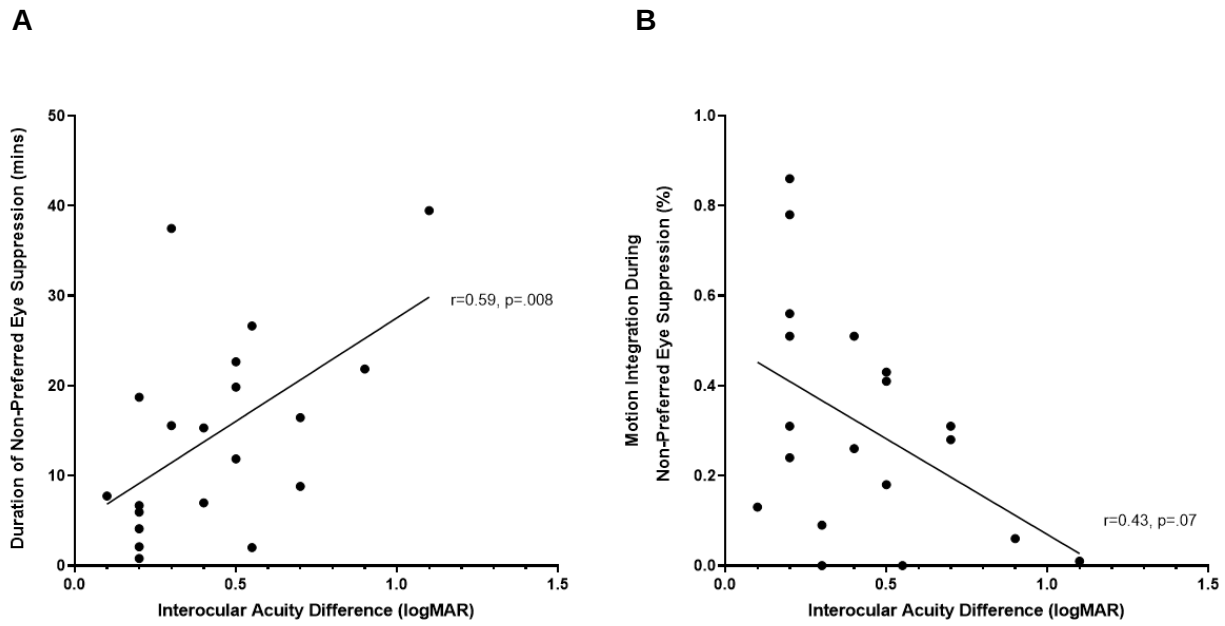

Figure 5-4. (A) Scatterplot demonstrating the relationship between interocular acuity difference (logMAR) and the duration (mins) of non-preferred eye suppression in the amblyopia group (n=20). (B) Scatterplot showing the relationship between interocular acuity difference (logMAR) and the extent of motion integration during non-preferred eye suppression (% of time in category 5 vs category 7) in the amblyopia group (n=19). In all panels, different dots represent individual participants and the solid line represents the best linear fit.

We chose to exclude participants with less than 2 minutes of non-preferred eye suppression because such a small sampling of time would skew the subsequent percentage calculation. Nevertheless, inclusion of these participants does not change our results. With all participant data included, motion integration occurred 56.5%±6.4% (mean±SE) of the time in the control group and 29.7±5.7% of the time in the amblyopia group. 3 out of the 4 excluded control participants had a motion integration rate of >95% despite averaging 70 seconds of non-preferred eye suppression. The remaining participant reported non-preferred eye suppression of only 1 second. The only participant excluded from the amblyopia group reported a 1% motion integration rate from 58 seconds and 41% form integration rate from 82 seconds of non-preferred eye suppression.

Adaptation is to be expected for any long-term stimulus presentation, and we used a repeated measures ANOVA to determine whether adaptation influenced motion responses. We found no

effect of order ($F_{1,37}$=0.26, p>.05) or trials ($F_{2,74}$=2.5, p>.05) for the motion responses. There was a significant effect of group ($F_{1,37}$=6.2, p=.017), such that control participants reported 20.9±8% more pattern motion than participants with amblyopia, consistent with our overall results. No interactions were significant (p>.05).

5.4 Discussion

Overall, our findings show that a lack of conscious awareness of visual information does not preclude its contribution to binocular processing in both normal vision and in amblyopia. Previously, binocular integration in amblyopia has only been demonstrated after alleviating interocular suppression by rebalancing the signal strength from each eye[282,285,292,293,451,452]. Suppression of amblyopic eye information from conscious awareness was thought to preclude its contribution during binocular viewing. Our results show that despite strong suppression using high-contrast stimuli[282,448,449,477,478], visual information seen only by the suppressed amblyopic eye can be binocularly integrated and influence the overall visual percept. We further corroborate previous findings for the normal visual system that suppressed stimuli can be binocularly integrated[319,322,467,473,474]. We also observed that periods of rivalry and simultaneous perception do occur for high-contrast dichoptic stimuli in observers with amblyopia.

Using perceptual states to infer underlying processing, our findings suggest that consciously suppressed visual information remains available for binocular processing even in amblyopia. This observation is consistent with recent neuroimaging data indicating that the neural signature of amblyopic eye suppression is not evident in early visual areas V1, V2 and V3[337], thereby raising the possibility that suppressed information is available for downstream processing. Monocular viewing of plaids with the amblyopic eye is correlated with activity in the pulvinar and area V3 rather than V5 as is the case for non-amblyopic eye viewing and control eyes[179]. This thalamo-cortical network may also support binocular integration of motion in the presence of interocular suppression. For example, although MT/V5 is thought to be critical for motion perception, lesions to this area only elevate motion thresholds and do not eliminate motion integration entirely[479–481]. Further neuroimaging studies are required to explore these possibilities.

Although using a binocular rivalry paradigm enabled us to measure the extent of motion integration, we were not able to draw any conclusions regarding the extent of form integration. It is difficult to distinguish between form integration and superimposition of piecemeal percepts,

which inevitably occurs during rivalry. We were not able to add additional response categories to differentiate mixed from piecemeal percepts due to the already complex nature of the psychophysical task and this is a limitation of our study. The strength of suppression also varies among individuals with amblyopia. We used stimuli with 100% contrast to encourage maximal suppression of the amblyopic eye, but individual variability in suppression exists[105]. Other than the relative viewing dominance of each eye during binocular rivalry, we did not have an independent measure of suppression to determine each participant's suppression strength. In addition, we chose to fix the grating orientations presented to the preferred and non-preferred eyes to simplify participant responses. The direction of motion was always balanced between the eyes as both eyes were presented with nasal to temporal motion. Using a range of different motion directions would have made it difficult to control for differences in plaid coherence that can occur between horizontal and vertical motion directions[454]. However, our experimental design inevitably led to adaptation over the course of the experiment. Although we cannot rule out an effect of adaptation on our results, an analysis comparing pattern motion responses at the start and the end of the experiment did not reveal any adaptation effects.

In summary, our results demonstrate that visual information from a suppressed amblyopic eye remains available for visual processing. Our results have direct implications for the management of amblyopia in clinical practice. Adults with amblyopia are often not given proper refractive correction for their amblyopic eye because it is considered to be of no added benefit[482]. There may be value in providing appropriate optical correction for the amblyopic eye in adults with amblyopia, not only for improving visual acuity[482], but also for enhancing the quality of visual information available for binocular integration. Our findings also support the theory underlying binocular approaches to amblyopia treatment[253,483], as suppressed information may remain available to intact binocular mechanisms in amblyopia[281,282,487,488,285,292,293,447,483–486]. Since suppression renders a structurally binocular system functionally monocular, it remains a significant obstacle in the treatment of amblyopia[281,282,292,293,484]. While amblyopia is most successfully treated during childhood when cortical plasticity remains high, the visual system retains considerable plasticity even in adulthood[249,250,489]. Efforts to identify and remove the factors that limit plasticity in adults have been promising, employing methods such as perceptual learning[490], video games[491], dichoptic treatments[251] and non-invasive brain stimulation[302,492,493]. Ongoing research into the nature of interocular suppression in amblyopia will enable refinement of these potential treatment approaches.

Chapter 6

Examining the Role of Oculomotor and Attentional Factors Underlying Increased Saccadic Latencies in Amblyopia

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6.1 Introduction

Amblyopia is a neuro-developmental disorder of vision that typically arises from abnormal binocular visual experience during early childhood. Visual development can be disrupted by a large difference in refractive error between the eyes (anisometropia) or a deviated eye (strabismus), resulting in abnormal visual cortex development and a unilateral reduction of visual acuity in the affected amblyopic eye[5]. Individuals with amblyopia experience a broad range of sensory deficits when viewing with their amblyopic eye, such as reduced contrast sensitivity[120,121,294,485,494] and poor positional and grating acuity[3,98,99,101,102,445]. Higher-level form and motion perception is also affected[101,167,170,173,174,182,240,495–497]. Many of these deficits are also experienced when viewing with the dominant fellow eye, despite exhibiting normal visual acuity[99,498]. Furthermore, amblyopia causes stereopsis deficits[3,101] and impaired visuomotor control[103,183,200,499–501].

Visuomotor behaviour is finely tuned over the course of neurodevelopment. It encompasses goal-directed reaching and grasping movements[103,183,200,499–501], as well as eye movements to identify salient objects. Oculomotor dysfunction has been extensively reported in amblyopia. The amblyopic eye exhibits poor fixation stability with frequent small eye movements known as microsaccades and ocular drifts[208–211,213,502–504]. Eye movements that bring peripheral targets into the zone of central fixation (saccades) and hold a moving target within that central zone (smooth pursuit)[505] are also impaired. Although saccades initiated by the amblyopic eye are no less accurate or precise than those of the fellow eye, reaction time (saccadic latency) is longer[193–198]. Increased amblyopic eye saccadic latency is evident for both reflexive[193,194,197,199,201] and delayed[506–508] saccade tasks. On the other hand, saccadic latency under fellow eye viewing

appears unaffected, comparable to monocular saccadic latencies in individuals with normal vision. A larger difference in saccadic latency between amblyopic and fellow eye viewing conditions (interocular saccadic latency) is associated with more severe amblyopia[199,200] and the absence of stereopsis[194,199]. Strabismic amblyopia also tends to be associated with a larger interocular latency difference than anisometropic amblyopia (40-80 ms vs 25 ms), although severity serves as a confounding factor[193,194,199,200,506,507]. In addition, individuals with amblyopia do not demonstrate the normal binocular advantage in saccadic latency. In amblyopia, binocular latencies are the same as monocular fellow eye latencies[193,194,197,507].

Execution of saccadic eye movements depends on sensory detection of a peripheral target, sensorimotor integration and finally motor execution. Consequently, initiation of a saccade could be delayed due to either: 1) a sensory deficit in target detection and localization; 2) a deficit in the descending neuronal pathway to the oculomotor plant; or 3) delayed integrative processing linking the sensory and motor systems. A number of studies have ruled out the oculomotor system (specifically the motor controller and plant elements) to be the cause of increased latencies, since the motor dynamics of saccades initiated by the amblyopic eye appear normal[193,194,196,197]. Specifically, saccades initiated by the amblyopic eye have normal amplitudes and peak velocities[193,194], similar to fellow eye saccades and saccades in individuals with normal vision. Corrective saccades (secondary saccades that are executed when the primary saccade did not hit the target as intended) under amblyopic eye viewing also have normal latencies[193,194,197], suggesting that the programming of saccades using prior sensory information is intact. These corrective saccades also have normal amplitude and peak velocity[193,194]. Furthermore, the amblyopic eye has normal saccadic latencies when driven by the fellow eye under binocular viewing conditions[193,194,196,197].

These findings indicating normal oculomotor dynamics in amblyopia suggest that the delay may instead originate from impaired detection of the saccade target or processing delays in sensorimotor pathways[193,194,196,197,506]. Indeed, delays in cortical visual evoked potentials following amblyopic eye stimulation have been described in various electrophysiological studies[509–513]. Although sensory deficits such as contrast sensitivity and resolution acuity have been well-documented in amblyopia, they are unable to account for between-subject variations seen in amblyopic eye saccadic latencies[199,201]. Individuals with strabismic amblyopia have significantly longer saccadic latencies than those with anisometropic amblyopia, despite both groups having similar visual acuity and contrast sensitivity losses[199]. Another recent study found that increasing

the contrast of a saccade target improved saccadic latencies under amblyopic eye viewing only for participants with anisometropic amblyopia, but not strabismic amblyopia[201]. For participants with strabismic amblyopia, there remained an irreducible delay (when compared to the fellow eye) that sensory differences could not account for[201]. This irreducible delay in strabismic amblyopia was thought to be due to poorer fixation stability (ie. frequent microsaccades) that introduced unintentional shifts of attention[199,216]. Indeed, previous neuroimaging studies have found deficient activation of areas forming the attentional network (comprised of areas V1, V5, IPS and FEF) as participants with amblyopia performed voluntary saccades with the amblyopic eye as compared to the fellow eye[380]. To test whether increased amblyopic eye saccadic latency had an attentional component, Gambacorta and colleagues manipulated the ease of attentional disengagement from the fixation point by introducing a delay or "gap" between the offset of the fixation point and the onset of the saccade target[201]. However, removing the fixation point prior to peripheral target onset expedited reaction times similarly among participants with and without amblyopia[201,508]. This advantage, termed the gap effect, was similar in magnitude for amblyopic and fellow eyes, and did not differ between participants with anisometropic or strabismic amblyopia[201].

Building on this prior work, two experiments were conducted to further investigate oculomotor and attentional factors that may play a role in the abnormal saccadic latencies found in amblyopia. In Experiment 6-1, we sought to replicate the amblyopic eye saccadic latency deficit using a dichoptic presentation system and measure specific saccade kinematics for both eyes. Although the findings of previous studies indicate that oculomotor control remains unaffected by amblyopia[193,194,196,197], these studies did not record the movements of the non-viewing eye under monocular fixation conditions. It has been assumed that the non-viewing eye is conjugate with the viewing eye due to Hering's law of equal innervation and Descartes' law of reciprocal innervation. However, disconjugate saccades have been noted in patients with strabismus[514–517]. Thus, we recorded the movements of both eyes during horizontal saccades to binocularly or monocularly presented stimuli and measured saccadic response gain and peak velocities. We hypothesized that similar or worse saccadic latencies would be found when targets are presented to the amblyopic eye alone under dichoptic conditions as previously seen under purely monocular conditions.

In Experiment 6-2, we explored whether attentional deficits play a role in amblyopic eye saccadic latencies under dichoptic circumstances, since intraocular shifts of overt attention may be impaired in amblyopia[436]. Shifting visual attention involves disengaging from a point of fixation,

orienting attention to a new target and re-engaging[518]. Here, we shifted saccadic targets between the eyes by presenting the fixation point and peripheral saccadic target (termed saccadic error signal) alternately under dichoptic viewing conditions. By presenting the fixation signal and saccadic error signal to different eyes and inducing an 'interocular gap effect', we hypothesized that saccadic latencies would be expedited compared to maintaining attention monocularly with the amblyopic eye. We also expected similar saccadic latencies regardless of whether the saccadic error signal was presented to the fellow or amblyopic eye. Conversely, if poor fixation stability of the amblyopic eye is responsible for increased saccadic latencies, we would expect latencies to be longer when the fixation target is seen by the amblyopic eye (error signal fellow eye condition) than vice versa. This is because amblyopic eye fixation stability improves when the fellow eye has a fixation target[504].

6.2 Materials and Methods

Participants. 10 participants with amblyopia (age mean±SD 29.4±14.6 years) and 10 age-matched control participants (28.2±5.5 years) took part in this study at the University of Waterloo, Canada. Participants with normal vision were required to have corrected visual acuities of no worse than 0.1 logMAR in each eye with normal stereoacuity (<60" at near with Randot Stereoacuity test, Stereo Optical Co. Inc., Chicago, IL) and no history of strabismus, amblyopia or any ocular surgery. Participants with amblyopia had a minimum of a 2 logMAR line difference in visual acuity between the eyes and best-corrected visual acuity in the amblyopic eye no better than 0.3 logMAR. Participants with amblyopia included purely anisometropic (n=4) and strabismic/mixed (n=2 strabismic, 4 mixed) cases. Clinical details for participants with amblyopia can be found in Table 6-1. Eye dominance was determined using the Porta sighting test [519]. Stereopsis was scored as present or absent depending on any sensitivity (≤ 800 arc sec) as measured on the Randot Stereoacuity Test (Stereo Optical Co. Inc., Chicago, IL). The study was approved by the institutional review board and adhered to the principles of the Declaration of Helsinki. Informed consent was given by all adult participants and all parents/guardians of younger participants alongside assent given by younger participants.

Table 6-1. Clinical details for participants with amblyopia. M = male, F = female, RE = right eye, LE = left eye, DS = dioptre sphere; DC = dioptre cylinder; NS = non-strabismic, PD = prism dioptres; W4D = Worth 4 Dot test; mixed = both anisometropia and strabismus, BO = base out.

Observer	Age/Sex	Type	Refraction	Visual Acuity	Stereo & suppression	History
AMB1	16/M	Mixed Constant right 12 PD esotropia	RE: +3.50 DS LE: plano	RE: LogMAR 0.86; 20/160 (6/48) LE: LogMAR -0.22; 20/12 (6/3.8)	Stereo: none W4D: suppression at distance, diplopia at near	Detected at 6 years of age Patching for 6 years, for 2 hours/day Has been wearing glasses since age 6
AMB2	15/M	Anisometropia Microtropia as detected with 4 PD BO test	RE: plano LE: +0.25/-1.00x160 LE (cyclo): +1.50/-0.75x160	RE: LogMAR -0.1; 20/16 (6/4.8) LE: LogMAR 0.54; 20/80 (6/24)	Stereo: None W4D: fusion (distance and near)	Detected at 8 years of age Patching for 1 year, for 1 hour/day Denies wearing glasses
AMB3	20/M	Anisometropia	RE: +5.00/-1.50x180 LE: +0.50 DS	RE: LogMAR 0.58; 20/80 (6/24) LE: LogMAR -0.06; 20/20 (6/6)	Stereo: None W4D: fusion (distance and near)	Detected at 6 years of age Patching for 3 years, for 10 hours/day Has been wearing glasses

						since age 6
AMB4	50/M	Strabismus Constant left esotropia (6 PD at distance, 4 PD at near)	RE: -1.00/-2.00x 070 LE: -0.75/-1.50x060	RE: LogMAR -0.1; 20/16 (6/4.8) LE: LogMAR 0.52; 20/63 (6/19)	Stereo: None W4D: fusion at distance, suppression at near	Detected at 6 months of age Denies patching Has been wearing glasses since age 38
AMB5	27/M	Mixed Constant right esotropia (8PD at distance, 12PD at near)	RE: +2.50/-1.25x020 LE: plano	RE: LogMAR 0.5; 20/63 (6/19) LE: LogMAR -0.10; $20/16^{-2}$ ($6/4.8^{-2}$)	Stereo: 200” W4D: fusion (distance and near)	Detected at 11 years of age Not compliant for patching, tried for 2 months at age 20 Does not wear glasses
AMB6	11/M	Mixed Constant left 4 PD esotropia	RE: +7.00/-4.00x005 LE: +8.00/-4.50x180	RE: LogMAR -0.06; 20/20(6/6) LE: LogMAR 0.3; 20/40 (6/12)	Stereo: None W4D: fusion (distance and near)	Detected at 5 years of age Patching for 5 years, 3 hour/day Has been wearing

						glasses since age 5
AMB7	39/F	Anisometropia NS at distance, right 1 PD accommodative esotropia	RE : +5.00 DS LE : +2.50/-0.75 x 095	RE: LogMAR 0.42; 20/50 (6/15) LE: LogMAR: -0.06; 20/20 (6/6)	Stereo : 100” W4D: suppression in distance, fusion at near	Detected at 33 years of age Denies patching Has been wearing glasses since age 11
AMB8	20/F	Mixed Constant right 3 PD hypertropia at distance, NS at near	RE : +6.25/-1.25x150 LE: plano	RE: LogMAR 0.72; 20/100 (6/30) LE: LogMAR; -0.02; 20/20 (6/6)	Stereo: 400” W4D: diplopia (distance and near)	Detected at 5 years of age Patching for 1 year Has been wearing glasses since age 5
AMB9	47/F	Anisometropia Microtropia as detected on 4 PD BO test	RE: +4.00 DS LE: plano	RE: LogMAR 0.44; 20/63 (6/19) LE: LogMAR -0.14; 20/16 (6/4.8)	Stereo: 400” W4D: fusion (distance and near)	Detected at 5 years of age Wore glasses from age of 5 until 16.
AMB10	43/M	Mixed Constant right esotropia (4 PD at distance, 8 PD at near)	RE: +7.00/-2.75x030 LE: +5.00/-1.75x170	RE: LogMAR 0.38; 20/40 (6/12)	Stereo: None W4D: Fusion (distance and near)	Detected at 4 years of age Patching for 1 year,

				LE: LogMAR 0.02; 20/20 (6/6)		for 8 hours/day Has been wearing glasses since age 4 Surgery for R esotropia at 4 years of age

Apparatus. Eye movements were recorded at 250 Hz for each eye using an Eyelink II head-mounted infrared eye tracker (SR Research, Ottawa, ON). Visual stimuli were presented dichoptically on two 7-inch LCD monitors (Lilliput® 619GL-70NP/C, 800x480 resolution, 66 Hz refresh rate) separated by two haploscopic mirrors to allow for binocular recording in all viewing conditions. The optical path length from each eye to the visual target on the screen was 40 centimeters. Head stabilization was achieved using a custom chinrest. Full refractive correction was worn or provided with a trial frame.

Experimental Design. A custom 9-point calibration and validation was performed for each eye separately at the beginning of each block. The procedure was repeated if accuracy differed by >0.5º for any point between the calibration and validation phases. Stimuli were designed and presented using Experiment Builder software (SR Research, Ottawa, ON). Participants started each block looking at a central fixation target (white fixation square subtending 0.5º underlying a central black square of 0.2º) on a black screen. After 5 seconds, the fixation target moved to one of six eccentricities (3°, 6°, 9°, 12°, 15° and 18°) to the left or right. Participants were instructed to fixate the target as quickly and accurately as possible without moving their head. Subsequent targets were presented randomly across the 6 amplitudes appearing with equal probability to the left or right relative to the previous stimulus location, with a pseudorandom delay of 1000-2000 ms between trials. To ensure that eye movements would remain in the range of the Eyelink II system, the target was never presented beyond 30 degree of central fixation and was located on the same vertical plane throughout the experiment, based on initial alignment at fixation.

Eye movements were recorded from both eyes during all viewing conditions. In Experiment 6-1, the target was presented monocularly to the dominant/fellow eye, the non-dominant/amblyopic eye, or binocularly to both eyes (see Figure 6-1A). Participants performed 48 trials for each viewing condition in a block-randomized order. In Experiment 6-2, the fixation target and saccadic error signal were presented to different eyes. For example, the dominant/fellow eye fixated on the target prior to its offset, and the target reappeared for only the non-dominant/amblyopic eye away from its original position (error signal-non-dominant condition, see Figure 6-1B). In the next trial, the non-dominant/amblyopic eye served as the fixating eye and the saccadic error signal was presented to only the dominant/fellow eye (error signal-dominant condition). The error signal alternated between the eyes for the remainder of the 48 trials. Following data collection, participants were asked if they were aware of which eye the targets were presented to, and whether they noticed any diplopia throughout the experiment.

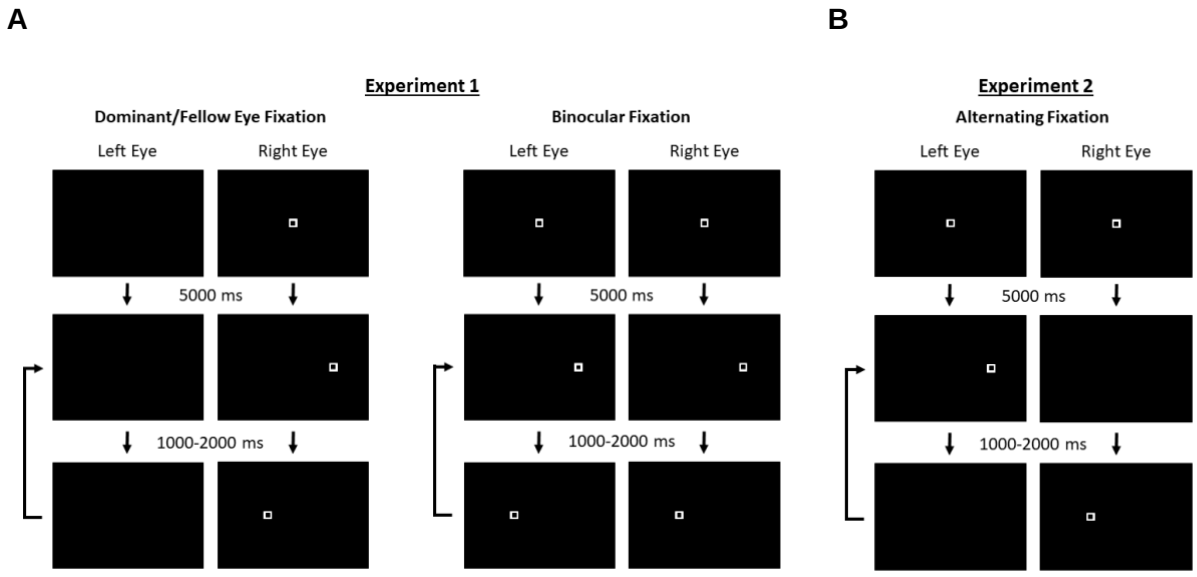

Figure 6-1. Example trial sequence for Experiments 6-1 (A) and 6-2 (B). (A) Participants performed saccades as targets moved 3°, 6°, 9°, 12°, 15° or 18° to the left or right of any previous target location. Eye movements were measured binocularly across 3 viewing conditions: dominant/fellow eye fixation, non-dominant/amblyopic eye fixation and binocular fixation. (B) Participants performed saccades as the target alternated between the eyes. The saccadic error signal could be presented to either the dominant/fellow eye or non-dominant/amblyopic eye.

Eye Movement Data Analysis. Eye position data were analyzed offline using a custom script in MATLAB 2016a (MathWorks, Natick, MA). After removal of blinks and other artifacts, only primary saccades in the correct direction were considered for analysis. Saccade initiation was determined using a 40°/s velocity threshold. Saccadic latency was computed as the difference between the start of the eye movement and target onset. Anticipatory saccades (latency <80 ms) and inattentive trials (latency >350 ms) were excluded from analysis. Saccadic gain was computed as the ratio between target amplitude and saccadic response amplitude. Main sequence plots were generated for each viewing condition by plotting saccadic response peak velocity versus response amplitude. GraphPad Prism (version 8.4.3; San Diego, CA) was used to fit a first-order exponential function to each plot (Equation #1), with the plateau of the function (Y_0) defining the motor response amplitude saturation limit, the growth rate constant (K) defining the recruitment rate and intersecting with [0,0][520].

$$\text{Equation \#1: } Y = (Y_0 - \text{Plateau})^{(-K*X)} + \text{Plateau}$$

Statistical Analysis. Statistical analyses were performed with JASP (version 0.12.1; Amsterdam, Netherlands) and GraphPad Prism. Normality of data was evaluated using the Kolmogorov–Smirnov test. The homogeneity of variance was tested by Levene's test, and sphericity was evaluated using Mauchly's test. In cases where Mauchly's test indicated that the assumption of sphericity was violated, the Greenhouse-Geisser correction was used when ε was <0.75 otherwise the Huynh-Feldt correction was used. In Experiment 6-1, mean saccadic latency and main sequence parameters (plateau and rate constant) were analyzed with a 2 (group: control, amblyopia) x 3 (viewing condition: dominant/fellow eye fixation, non-dominant/amblyopic eye fixation, binocular fixation) x 2 (eye: dominant/fellow eye, non-dominant/amblyopic eye) repeated measures ANOVA. Mean saccadic latencies were also analyzed with a 6 (amplitude: 3°, 6°, 9°, 12°, 15°, 18°) x 2 (group: control, amblyopia) x 3 (viewing condition: dominant/fellow eye fixation, non-dominant/amblyopic eye fixation, binocular fixation) repeated measures ANOVA. Since no main effect of eye emerged, subsequent repeated measures ANOVAs on saccadic latency variability and gain only included factors of group and viewing condition. In Experiment 6-2, saccadic latency was analyzed using a 2 (group: control, amblyopia) x 2 (saccadic error signal: dominant/fellow eye, non-dominant/amblyopic eye) repeated measures ANOVA. Post-hoc analyses were conducted on significant interactions using Tukey's correction for multiple comparisons.

6.3 Results

Across both experiments, none of the participants reported diplopia within our dichoptic setup and were unaware that some stimuli were presented to only one eye. In Experiment 6-1, the percentage of eye movements used in the analysis were as follows (mean±SD): under dominant/fellow eye fixation, 78.5±7.6% (control) and 80.5±7.7% (amblyopia); under non-dominant/amblyopic eye fixation, 82.6±8.9% (control) and 71.2±12.4% (amblyopia); under binocular fixation, 82.7±9.4% (control) and 79.8±7.5% (amblyopia).

Increased saccadic latencies for monocular amblyopic eye viewing

The repeated measures ANOVA on mean saccadic latency found significant main effects of group ($F_{1,18}$ = 5.2, p=.035) and viewing condition ($F_{2,36}$ = 43.94, p<.001) as well as a significant group x viewing condition interaction ($F_{2,36}$ = 20.5, p<.001; see Figure 6-2). No effect of eye ($F_{1,18}$ = 0.12, p>.05) was found, indicating that saccades were conjugate across all conditions. Post-hoc testing revealed that saccadic latencies were significantly longer under amblyopic eye fixation (mean ± SE 202.99±8.2 ms), as compared to fellow eye fixation (174.5±7.1 ms, t_{19}=7.58, p<.001) and binocular fixation (163.4±18.8 ms), t_{19}=10.5, p<.001) in the amblyopia group, and all viewing conditions in the control group (vs dominant eye fixation: 165.2±4.5 ms, t_{19}=4.2, p=.004; vs non-dominant eye fixation: 164.3±4.0 ms, t_{19}=4.4, p=.003; vs binocular fixation: 154.2±6.9 ms, t_{19}=5.5, p<.001). No binocular advantage (significant difference vs dominant eye fixation) was evident in either group (control: mean difference ± SE 10.5±4.0 ms, t_{19}=2.6, p>.05; amblyopia: 10.4±4.0 ms, t_{19}=2.6, p>.05). No correlation was found between interocular acuity difference and saccadic latencies under amblyopic eye fixation (r=.027; p>.05) or interocular latency difference (r=-0.29, p>.05) in the amblyopia group. There was also no association between interocular latency differences and the presence of stereoacuity (τ_B=0.43, p>.05).

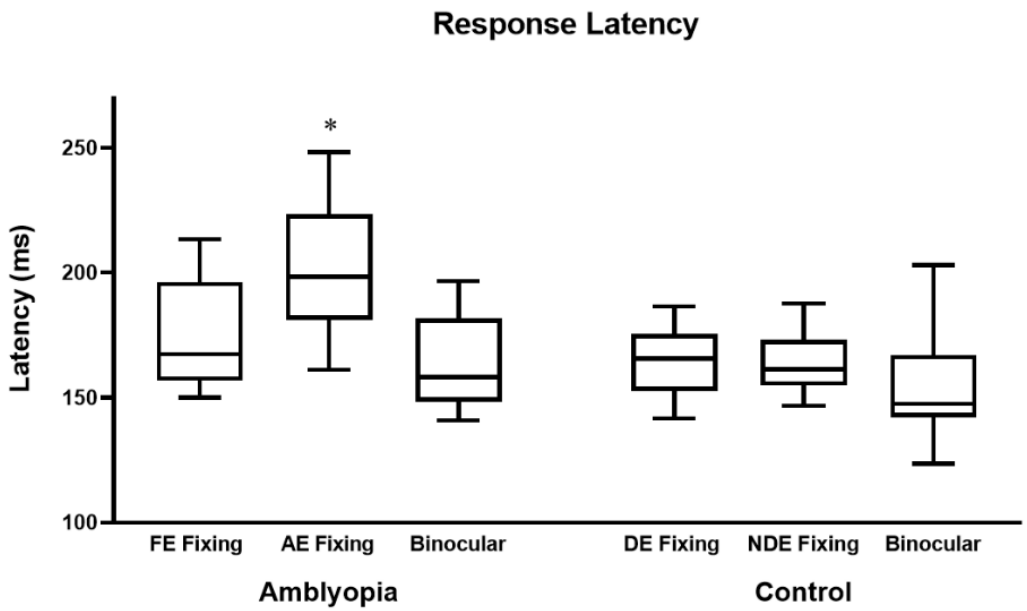

Figure 6-2. Box plot diagram showing mean saccadic latency for participants with normal vision (n=10) and amblyopia (n=10) in Experiment 6-1, collapsed across eyes. Box boundaries denote 25th and 75th percentiles with the line inside box representing the median. Whiskers represent the full range of data points. Saccadic latencies were significantly longer under amblyopic eye fixation as compared to fellow eye and binocular fixation conditions in the amblyopia group, and all viewing conditions in the control group. Statistical significance * denotes p<.001. Abbreviations: DE, NDE – dominant and non-dominant eye of control observers; FE, AE – amblyopic and fellow eye of observers with amblyopia.

Mean saccadic latencies plotted across target amplitude can be seen in Figure 6-3. There were significant main effects of group ($F_{1,18}$=4.7, p=.045), amplitude ($F_{4.5,80.6}$=2.9, p=.021) and viewing condition ($F_{2,36}$=34.3, p<.001). The group x viewing condition x amplitude interaction was significant ($F_{10,180}$=1.9, p=.043). Post hoc tests revealed a significant group x amplitude interaction only under amblyopic eye fixation ($F_{5,90}$ = 2.92, p=.017; fellow eye fixation: $F_{5,90}$ = 0.77, p>.05; binocular fixation: $F_{5,90}$=0.45, p>.05). Saccadic latencies were significantly longer for 3^{o} targets in the amblyopia group (mean difference ± SE 57.9±11.3 ms, t_{19}=5.1, p<.001). No other pairwise amplitude comparisons were statistically significant.

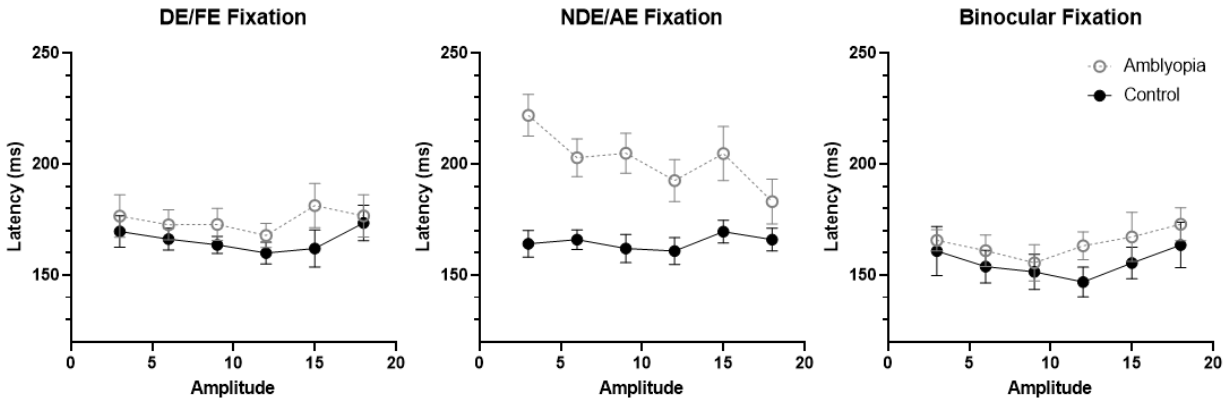

Figure 6-3. Mean saccadic latencies as a function of target amplitude for each viewing condition for Experiment 6-1. Error bars represent SEM. Abbreviations: DE, NDE – dominant and non-dominant eye of control observers; FE, AE – amblyopic and fellow eye of observers with amblyopia.

Increased saccadic latency variability in amblyopia

Saccadic latency variability within a condition was determined as the standard deviation of the mean individual participant saccadic latencies. A repeated measures ANOVA revealed a significant main effect of viewing condition ($F_{2,36}$=12.8, p<.001) and a group x viewing condition interaction ($F_{2,36}$=8.2, p=.001). Post-hoc testing revealed that variability was significantly higher for the amblyopic eye than for the fellow eye fixation (mean difference ± SE 15.2±2.8 ms, t_{19}=5.4, p<.001) and binocular fixation (15.7±2.8 ms, t_{19}=5.5, p<.001). This increased variability under amblyopic eye fixation was significantly higher than the control group under all viewing conditions (vs dominant eye fixation 15.1±4.9 ms, t_{19}=3.1, p=.04; vs non-dominant eye fixation 15.3±4.9 ms, t_{19}=3.2, p=.04; vs binocular fixation 18.9±4.9 ms, t_{19}=3.9, p=.006).

Subtle differences in gain and peak velocity

Gains were computed as saccadic response amplitude as a fraction of target displacement. There was a significant main effect of stimulus amplitude ($F_{3.0,53.8}$=8.2, p<.001) and group ($F_{1,18}$=9.0, p=.008) but no main effect of viewing condition ($F_{1.4,25.1}$=0.23, p>.05; see Figure 6-4). Except for a significant interaction between viewing condition x amplitude ($F_{3.9,69.8}$=2.6, p=.047), no other interaction was significant, of particular note the group x viewing condition x amplitude ($F_{3.9,69.8}$=1.2, p>.05) and group x amplitude ($F_{3.0,53.8}$=0.7, p>.05).

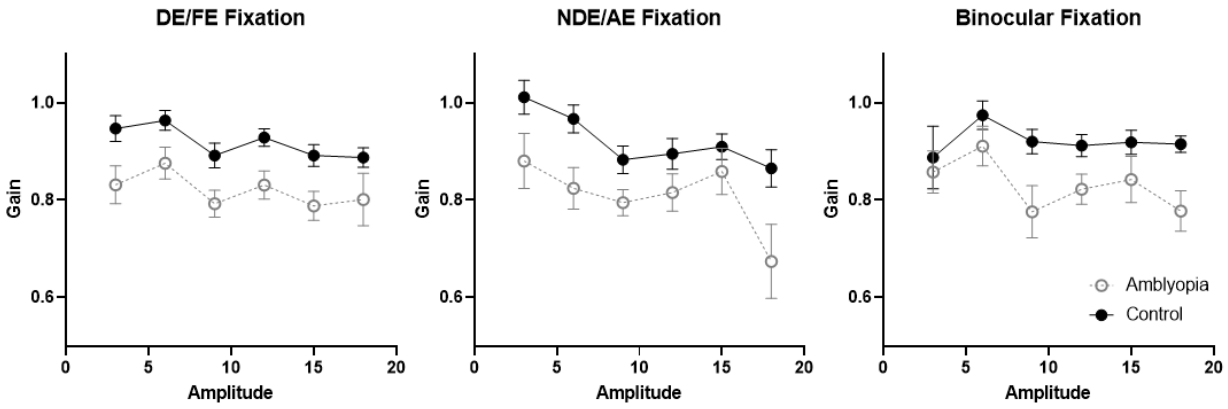

Figure 6-4. Saccadic response gain plotted across target amplitude for each viewing condition. Error bars represent SEM. Abbreviations: DE, NDE – dominant and non-dominant eye of control observers; FE, AE – amblyopic and fellow eye of observers with amblyopia.

Main sequence data (plots of peak velocity vs response amplitude) can be seen in Figure 6-5. An analysis of the plateau parameter for dominant eye/fellow eye movements revealed main effects of viewing condition ($F_{2,2022}$=7.5, p=.0006) and group ($F_{2,2022}$=13.37, p=.0003), but no significant interaction ($F_{2,2022}$=1.4, p>.05). Between-group pairwise comparisons were only significant under binocular fixation (t_{2022}=3.4, p=.002; see Figure 6-5), not for fellow eye fixation (t_{2022}=2.0, p>.05) or amblyopic eye fixation (t_{2022}=0.9, p>.05). There were no significant differences across viewing conditions for the control group for the movements of either eye (p>.05). In the amblyopia group, the plateau reached by the fellow eye during binocular fixation was higher than that during amblyopic eye fixation (542.8±15.8°/s vs 468.1±14.4°/s, t_{2022}=3.8, p=.0005). Similarly, the plateau reached by the amblyopic eye during binocular fixation was higher than fellow eye fixation (553.5±16.8°/s vs 485.7±12.2°/s, t_{1997}=3.7, p=.0008) and amblyopic eye fixation (485.5±16.8°/s, t_{1997}=3.5, p=.0013).

Analysis of the rate constant parameter revealed that for movements of the dominant eye, there was a main effect of viewing condition ($F_{2,2022}$=3.6, p=.03) as well as group ($F_{1,2022}$=4.3, p=.04) but the interaction was not significant ($F_{2,2002}$=0.3, p>.05). No significant pairwise comparisons emerged after Tukey correction. For the non-dominant eye, only the factor of group was significant ($F_{2,1997}$=6.1, p=.01). Between-group pairwise comparisons were not significant after Tukey correction (t_4=1.9, p>.05).

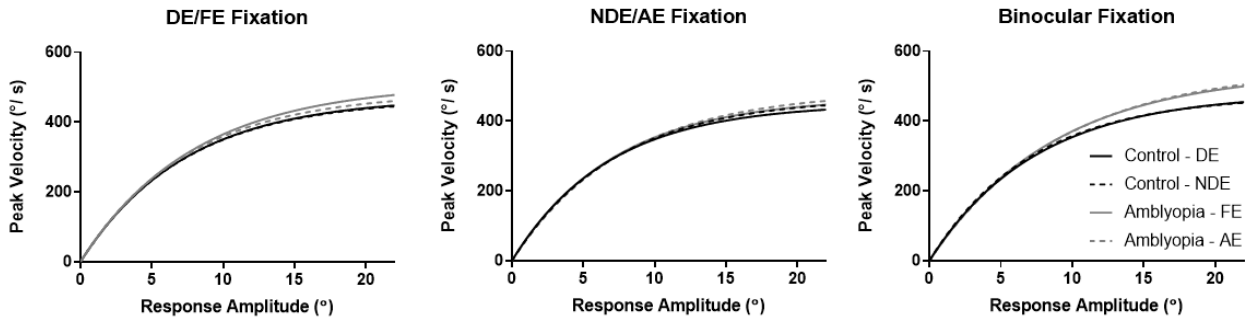

Figure 6-5. Main sequence plots for each viewing condition. Error bars represent SEM. Abbreviations: DE, NDE – dominant and non-dominant eye of control observers; FE, AE – amblyopic and fellow eye of observers with amblyopia. Lines in black represent the control group and lines in grey represent the amblyopia group.

Alternating saccade targets between the eyes expedited saccadic latencies

In Experiment 6-2, the percentages of eye movements used in the analyses were as follows (mean±SD): error signal to dominant eye, 82.8±8.4% (control) and 76.8±11.0% (amblyopia); error signal to non-dominant eye, 77.8±8.9% (control) and 70.7±12.5% (amblyopia).

Mean saccadic latencies were similar regardless of which eye received the saccadic error signal for both groups (Figure 6-6) and across amplitudes (Figure 6-7). In the control group, mean saccadic latency was 169.5±5.4 ms (mean±SE) in the dominant eye error signal condition and 164.9±1.9 ms in the non-dominant eye error signal condition. In the amblyopia group, mean saccadic latency was 179.3±7.5 ms in the fellow eye error signal condition and 185.1±10.6 ms in the amblyopic eye error signal condition. There was no main effect of group ($F_{1,18}$=2.32, p>.05) nor error signal ($F_{1,18}$=0.20, p>.05) nor amplitude ($F_{3.2,57.8}$=2.1, p>.05) on mean saccadic latencies. No interactions were significant (p>.05). Furthermore, there was no main effect of group ($F_{1,18}$=3.0, p>.05) nor error signal ($F_{1,18}$=0.01, p>.05) nor a significant interaction ($F_{1,18}$=.86, p>.05) for the variability (SD) of saccadic latencies.

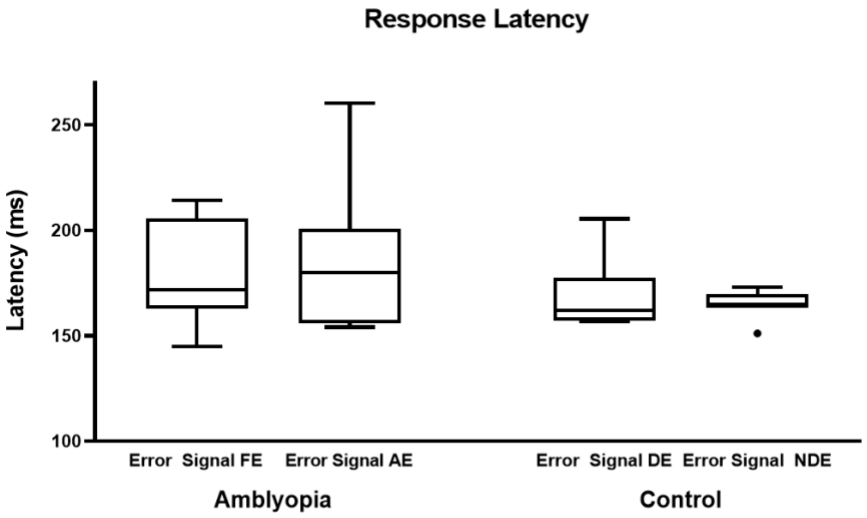

Figure 6-6. Box plot diagram showing mean saccadic latency for participants with normal vision (n=10) and amblyopia (n=10) in Experiment 6-2. Box boundaries denote 25th and 75th percentiles with the line inside box representing the median. Whiskers represent the full range of data points and a dot represents an outlier. Abbreviations: DE, NDE – dominant and non-dominant eye of control observers; FE, AE – amblyopic and fellow eye of observers with amblyopia.

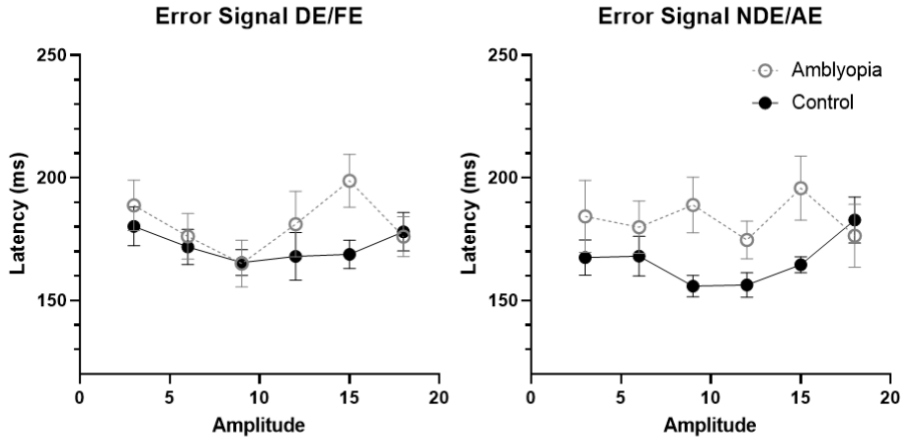

Figure 6-7. Mean saccadic latencies plotted across target amplitude for each viewing condition for Experiment 6-2. Error bars represent SEM. Abbreviations: DE, NDE – dominant and non-dominant eye of control observers; FE, AE – amblyopic and fellow eye of observers with amblyopia.

Alternating Attention vs Maintaining Attention Monocularly

A post-hoc paired samples t-test found that saccadic latencies when targets were presented to only the amblyopic eye in Exp 1 were significantly longer than the error signal fellow eye condition (mean±SE 203.0±8.2 ms vs 179.3±7.5 ms respectively; t_9=4.2, p=.002) and the error signal amblyopic eye condition (185.1±10.6 ms; t_9=2.3, p=.045) in Exp 2.

6.4 Discussion

In this study, we replicated the previously documented increases in saccadic latency for amblyopic eyes[193–199,201] under dichoptic viewing conditions. The results from Experiment 6-1 suggest that oculomotor kinematics are unlikely to be responsible for this delay since amblyopic eye saccade dynamics were similar for all viewing conditions. The subtle reduction of gain and normal peak velocity for the amblyopic eye fixation are in line with previous studies[193,194]. We also found subtle differences in the plateau parameter of the main sequence and similar rate constants between the groups. However, these differences do not explain the latency deficit since across all conditions, the amblyopic eye showed similar or higher peak velocity plateaus as compared to control eyes. Furthermore, we found that the amblyopic eye had a normal saccadic latency under fellow eye viewing conditions. This had never previously been observed and only assumed based on Hering's and Descartes' laws.

In Experiment 6-2, we tested the hypothesis that impairments specific to intraocular shifts of attention may be responsible for the saccadic latency delays in amblyopia. Compared to when attention was maintained monocularly, alternating saccadic targets between the eyes to introduce an interocular gap effect expedited latencies regardless of whether the saccadic error signal was presented to the fellow or amblyopic eye. We found that we could eliminate previously reported irreducible differences between the fellow and amblyopic eyes[199,201] by shifting the saccadic error target between the eyes. Thus, we propose deficiencies in the shifting of overt attention between targets seen by the same eye may contribute to increased amblyopic eye saccadic latencies. By separating the process of fixational disengagement from attentional re-engagement of a new target, any target presented to the non-fixing eye may benefit fully from the effects of exogenous attentional capture. Peripheral spatial cues have been shown to readily orient covert attention in amblyopia[425–427]. In contrast, alternating saccadic error targets between the eyes in our control group did not expedite saccades further, suggesting a possible floor effect.

Previous studies have proposed that the amblyopic latency deficit is due to poor fixational stability of the amblyopic eye[199,216]. The presence of microsaccades creates a motor refractory period (ranging from 150-200 ms) that can delay the initiation of subsequent saccades[209,212,521]. In studies with participants with normal vision, saccadic latencies were shorter on trials without microsaccades[522,523] and the occurrence of a microsaccade shortly before the presentation of a saccadic target delayed the latency of subsequent saccades by approximately 40 ms[215]. Given the increased frequency and amplitude of microsaccades in amblyopia[209], a peripheral target is more likely to appear during motor refractory periods for individuals with amblyopia[199,216]. Indeed, the presence of fixational eye movements may account for our observation of increased saccadic latency variability for amblyopic eye fixation as compared to the fellow eye fixation and binocular fixation, corroborating previous studies[193–195,201,507]. Although we did not directly measure fixational eye movements, our data suggests that fixational eye movements may not be primarily responsible for increased saccadic latencies based on two observations. Under similar dichoptic viewing conditions, Raveendran and colleagues found that fixation stability is determined by the eye seeing the fixation target, with both eyes exhibiting similar levels of stability[504]. If poor fixational stability interfered with subsequent saccade generation, 1) longer latencies would be expected under amblyopic eye fixation (error signal fellow eye condition in Exp 2) than fellow eye fixation (error signal amblyopic eye condition). Instead, we found that saccadic latencies under the two viewing conditions were similar. 2) Similar or longer latencies would be expected under amblyopic eye fixation (error signal fellow eye condition in Exp 2) than amblyopic viewing monocularly (Exp 1). Instead, we found faster saccadic latencies when the error signal was presented to the fellow eye. Nonetheless, we cannot rule out the involvement of fixational eye movements because they could not be measured within our experimental design. Future experiments measuring fixational eye movements directly would be informative in clarifying their association with saccadic latency in amblyopia.

Our data corroborate previous work showing the effects of interocular suppression on saccadic latencies. Individuals with strabismic amblyopia had longer saccadic latencies for targets located at 5^{o} as compared to 10^{o} from fixation[524], consistent with stronger sensory suppression in perifoveal regions under amblyopic eye viewing[260]. We also found longer saccadic latencies for perifoveal targets in our study involving both anisometropic and strabismic/mixed amblyopia. It is difficult to account for the influence of suppression for peripheral targets since our measures of suppression using the Worth 4-Dot and Randot stereoacuity are primarily tests of central fusion. Furthermore, there are some inconsistencies in suppression as measured by the Worth 4-Dot

and Randot Preschool Stereotest, possibly due to differences in target size and lighting conditions[525]. Differences in binocular motor fusion status at distance and near may also contribute to these discrepancies. In amblyopia, larger interocular differences in saccadic latency have been associated with impaired binocularity[199] and more severe amblyopia[194,199,201]. However, in one previous study, only 28% of the saccadic latency variance could be explained by visual acuity[200], pointing to other factors that could be involved in the latency delay. While we did not observe a correlation between interocular latency differences and interocular acuity differences, our correlation analysis may be complicated by our small heterogenous sample. In addition to this, saccadic latencies under dichoptic viewing were measured without correcting for each participant's angle of strabismus, and our measurements instead reflect each participant's preferred fixation stance. Nevertheless, our sample had relatively small angles of strabismus, ranging from 4-12 PD.

6.5 Conclusions

The present study explored oculomotor and attentional factors that may contribute to increased saccadic latencies in amblyopia. Our results indicate that oculomotor factors related to saccade generation are unlikely to be responsible for saccadic latency delays under amblyopic eye fixation. We propose that the inability to shift overt attention from fixation target to a peripheral target when both targets are seen by the amblyopic eye could contribute to increased saccadic latency.

Chapter 7

Orienting of Covert Attention by Neutral and Emotional Gaze Cues Appears to be Unaffected by Mild to Moderate Amblyopia

This paper is currently in press with the Journal of Vision. Individual author contributions can be found in the Summary of Contributions section. This work was made possible by funding from a NSERC PGS-D Grant (AC) and NSERC Grants RPIN-05394 and RGPAS-477166 (BT). None of the authors have any conflicts of interest to declare.

7.1 Introduction

Amblyopia is a neurodevelopmental disorder of vision caused by an impediment to binocular vision such as anisometropia, strabismus or visual deprivation that is present during early childhood development. Clinically, amblyopia presents as a unilateral loss of visual acuity and impaired stereopsis associated with chronic interocular suppression of the amblyopic eye[1,3,99,101,102]. More generally, amblyopia affects a broad range of sensory functions in both the amblyopic[98,120,121,294,445,485,494,526,527] and non-amblyopic fellow eye[99,498]. These sensory deficits impact visuomotor behaviours such as saccadic eye movements[193–198,201,506–508] and hand-eye coordination[103,183,200,499–501]. In particular, saccadic and manual response times are significantly delayed for stimuli viewed through the amblyopic eye[201–203]. Even after visibility is accounted for, an irreducible response latency delay remains in strabismic amblyopia[201,203,204].

Amblyopia is associated with reduced fixation stability and it has been proposed that frequent fixational eye movements cause unintended shifts of spatial attention that may contribute to attention deficits in amblyopia[199,216]. In amblyopia, fixation stability is poorer for the amblyopic eye due to increased microsaccades and ocular drifts[208–211,213,502–504,528]. Fixation is less stable in strabismic amblyopia than anisometropic amblyopia[209,212], with more frequent microsaccades and overall displacement from the locus of fixation[209]. The presence of microsaccades creates a motor refractory period ranging from 150-200 ms that can delay the initiation of subsequent saccades[209,212,521] and delay target detection[199,216]. Eye movements and visual attention are intricately linked, as attention is often allocated to the locus of visual fixation and overtly shifted in conjunction with eye movements[369,370]. Spatial attention can also be deployed covertly, whereby the locus of attention is shifted without a change in fixation[371–374]. Nevertheless, even on a covert attention task, observers inadvertently make small microsaccades in the direction of the cued

location[397,398] (although see [529–531] with gaze cueing). Target discrimination appears to be better when microsaccades are directed towards the target location[399]. As a result, microsaccades may interfere with the orienting of covert attention in amblyopia.

There remains considerable debate as to what extent attentional processing is impaired in amblyopia. Several studies in both humans[425,426] and macaques[427] found normal spatial cuing of attention in amblyopia, even demonstrating that valid cueing (congruency between cue and target) alleviated the amblyopic eye contrast sensitivity deficit[427]. In addition, participants with amblyopia performed normally on a simple visual search task involving a distinctive target feature that readily captured attention[423]. Conversely, in a conjunctive visual search task requiring a serial search strategy, participants with amblyopia processed items at a slower rate (with either eye) than controls, suggesting a bottleneck of attentional processing[423]. Several other psychophysical studies have reported attentional deficits affecting both eyes in amblyopia. For example, when performing a line bisection task with either eye, individuals with amblyopia demonstrated a rightward bias similar to patients with a lesion to the right posterior parietal cortex, an area involved in the orienting of spatial attention[532]. This effect was more pronounced in participants with strabismic amblyopia than anisometropic amblyopia. In addition, attentional tracking of multiple moving objects performed monocularly revealed an amblyopic eye deficit that extended to the fellow eye under high attentional loads[95,172]. This tracking deficit could not be attributed to impaired motion perception alone and therefore reflected a visual attention deficit[95,172]. A subsequent study employed a dichoptic multiple-object tracking task to assess whether attention was allocated unevenly between the two eyes when both eyes were open. A bias in the allocation of attention toward the fellow eye was observed in strabismic but not anisometropic amblyopia[533]. A similar effect has recently been reported for a dichoptic enumeration task whereby amblyopic eyes contributed less to task performance than fellow eyes, and strabismic amblyopia was associated with a larger interocular imbalance than anisometropic amblyopia[435]. The recruitment of additional attentional resources under high attentional load also appears to be impaired in amblyopia[441]. Overall, psychophysical studies indicate that although spatial cueing appears to be intact, higher-order attentional processes may be impaired in amblyopia.

Many of the attentional deficits documented in amblyopia persist despite prior treatment. Although treatment is generally successful in recovering visual acuity in the amblyopic eye, visual processing in amblyopia remains abnormal[99,101,498,513,534]. In particular, individuals with previous treatment of amblyopia still display attentional deficits that affect both the amblyopic and fellow

eyes[95,172,268,380,435,532,533]. An electrophysiological study found that despite past treatment, the modulatory effect of a simple central spatial cue is reduced in primary visual area V1 as well as in higher-order visual areas V4 and MT+ for both the amblyopic and fellow eye in strabismic amblyopia[268]. Similarly, a generalized reduction of activation across the brain areas comprising the attentional network has been observed in strabismic amblyopia even after surgical treatment to alleviate the amblyogenic factor[380]. On the other hand, some psychophysical studies in mild and treated populations found no attentional deficit[425,426]. Additionally, a correlation between the depth of attentional deficit and the severity of amblyopia (defined as interocular VA difference) is seldom observed[425,426,435,441,533] (although see [268,423,535]). This discrepancy merits further investigation.

In this study, we explored cueing of covert spatial attention with cues that involve higher-order processing. We were interested in the possibility that amblyopic eye attentional deficits would emerge within a cueing task if complex visual processing was required to process the cue. Attention can be engaged by social cognition[536–538], so we employed a dynamic gaze cueing task[539–541] that oriented visual attention using gaze directions embedded within emotional faces[542,543]. Compared to spatial cueing using arrow cues, the gaze direction of a face is more ecologically valid and reflects social interactions in real-world situations. Following another's gaze is critical for joint attention and inferring the mental states of others[544,545]. This form of social attention, which relies on intact face processing[546], integrates local processing of gaze cues with global processing of a face and its emotional expression and involves a distributed network of thalamic and cortical brain regions[537,547]. By using a dynamic sequence in which a face morphs from a neutral expression to an affective state, a stronger gaze cueing effect is elicited (for gaze cueing reviews, see [541,548]). Although early studies in amblyopia found poor accuracy for identifying facial expressions during amblyopic eye viewing[92], poor performance was also found for inverted faces, suggesting that the deficit lies in featural component processing rather than face configural processing. A follow-up study by the same authors found that reduced activation of extra-striate areas was not face-specific and could be attributed to the reduced visibility of the facial features[79]. Individuals with amblyopia also showed no deficits on the Mooney face task, commonly used for assessing face detection and relying on holistic face processing[152]. These findings indicate that limitations on face perception in anisometropic and strabismic amblyopia may be driven by resolution deficits rather than impaired face processing per se.

In normal vision, processing of gaze cues occurs spontaneously, improving detection of peripheral targets in the direction of gaze (congruent) as compared to targets that appear on the opposite side (incongruent)[539–541,549]. While spatial cueing using salient flashes or arrows may be intact in amblyopia[425–427], it is unclear whether social cueing based on gaze and emotional cues is affected. Emotional facial expressions modulate the gaze cueing effect in neurotypical observers, especially when the face reacts with an emotional expression after gaze aversion, akin to someone reacting to what they were seeing[550]. Fearful expressions (which signal nearby danger) orient spatial attention more strongly than neutral expressions[542,543,558,550–557]. Happy expressions (which suggest a possible reward) orient attention to a similar degree as neutral faces[550–552,554–556,558–560]. Recent studies have reported a slightly larger orienting response for happy compared to neutral faces as well, but still of smaller magnitude than the orienting response to fearful faces[542,543].

In this study, we explored whether amblyopia reduces the extent to which emotional face cues orient covert attention. We recruited participants with mild, moderate or previously treated amblyopia to ensure that the face images were clearly visible to the amblyopic eye and that the local processing of gaze position required for the gaze cueing effect could occur. If the development of social attention to visual cues is affected by amblyopia, we would expect that the gaze cueing effect of a fearful emotional face would be weaker when viewing with an amblyopic eye compared to the fellow eye and to normal control eyes. We also explored whether the magnitude of the gaze cueing effect differed by amblyopia etiology, since attentional deficits may be more pronounced in strabismic amblyopia.

7.2 Methods

Participants. 30 participants with normal vision (mean age ± SD: 20.8±2.4 yrs; 22 female) and 12 participants with amblyopia (mean age ± SD: 27±11.1 yrs; 5 female) were recruited at the University of Waterloo. We aimed to recruit 30 participants in both groups, but we were not able to reach this number for the amblyopia group during the recruitment period. All participants provided written informed consent and the study protocol was approved by the institutional ethics committee, in accordance with the Declaration of Helsinki. Participants either received course credit or were remunerated for their time. Individuals were ineligible for the study if they self-reported a history of psychiatric or neurological disorder (including seizures or epilepsy) or a past loss of consciousness longer than 5 minutes associated with head trauma. Participants also

reported no recent use of antidepressant or antipsychotic drugs, or medications containing cortisone and no regular or recent use of drugs or alcohol.

Clinical assessment included visual acuity (using an electronic ETDRS chart), eye alignment (distance and near cover test) and stereoacuity (Randot Preschool Stereotest; Stereo Optical Co. Inc., Chicago, IL, USA). All participants wore their habitual correction as needed. Participants with normal vision had best-corrected visual acuity better than 20/25, with no greater than a 1 logMAR line difference in visual acuity between the eyes, and no history of binocular vision disorders. Amblyopia was defined as a minimum of a 2 logMAR line interocular difference in visual acuity or a 1 logMAR line difference with a history of amblyopia treatment, caused by anisometropia (>1 dioptre interocular difference or >1.5 dioptres of cylinder in one eye) and/or strabismus (including history of strabismus surgery), with normal ocular and general health. Clinical details for individuals with amblyopia are summarized in Table 7-1.

Table 7-1. Clinical details for participants with amblyopia. M = male, F = female, VA = visual acuity, A = anisometropia, S = strabismus, M = mixed (anisometropia and strabismus), NS = non-strabismic, XP = exophoria, X(T) = intermittent exotropia, RET = right esotropia, Δ = prism dioptres, Dx = diagnosed, y = years, yo = years old, VT = vision therapy (orthoptics and/or dichoptic binocular amblyopia treatment).

ID	Age/ Gender	Type	Fellow Eye VA (logMAR)	Amblyopic Eye VA (logMAR)	Stereoacuity	Ocular Deviation (Near)	Clinical History
A01	28/M	A	0.00	0.40	>800”	NS, ortho	Dx at 22 yo, no patching or surgery
A02	25/F	A	0.00	0.70	>800”	NS, 12Δ XP	Unknown history
A03	18/F	A	-0.10	0.20	>200”	NS, 4Δ XP	Patched 1h/day, no surgery or VT
A04	19/M	S	0.00	0.20	>800”	4Δ LXT	Dx at 4 yo, wore glasses and patched for 4 y, no surgery
A05	19/M	M	0.00	0.10	800”	4Δ RX(T)	Patched x 3 y, VT 30 mins/day, 5x/week

A06	46/M	S	0.00	0.40	>800”	8Δ RET	Dx at 4 y, surgery for ET, patched 8h/day
A07	46/M	S	0.00	0.20	>800”	35-40Δ LET	Dx at 1 y, had 4 surgeries at 1, 2, 3, 10 yo, patched, no diplopia
A08	24/M	A	-0.10	0.20	60”	NS, ortho	Dx at 16 yo, wore glasses, no patching, VT x 2 months
A09	20/F	A	0.00	0.10	100”	NS, 4Δ XP	Dx at 4-5 yo, patched, no surgery, OS suppression
A10	42/M	A	-0.10	0.20	100”	NS, 4Δ XP	No patching or surgery
A11	18/F	S	0.00	0.10	400”	4Δ LXT	Dx at 5 yo, wore glasses since 5-6 yo, patched x 2 y, no VT, OS suppression
A12	19/F	A	-0.10	0.10	200”	NS, ortho	Dx at age 7, patched 4-6 hrs/day, no VT or surgery

Apparatus. Participants performed the experiment in a chinrest with head stabilization while wearing an Eyelink II head-mounted eye tracker (250 Hz; SR Research; Mississauga, Canada). Eye tracking data were used only to ensure central fixation. Stimuli were presented using Experiment Builder (SR Research; Mississauga, Canada) on a 27” ASUS PG278QR LCD monitor (2560 x 1440 resolution, 120-Hz refresh rate; Taipei, Taiwan) from a viewing distance of 50 cm.

Stimuli. Face stimuli previously used in McCrackin & Itier (2018) were employed in this experiment. These faces (4 male and 4 female; identities 02, 03, 06, 09, 20, 22, 24, 27) were selected from the widely available NimStim database[1] [561] and cropped to remove the hair, ears, and clothing. Each face expressed one of three emotions (fear, neutral and happy) and had averted left or right gaze. Each face was vertically flipped to counterbalance any facial

[1] Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at tott0006@tc.umn.edu for more information concerning the stimulus set.

asymmetries. To account for apparent motion of the mouth in happy and fearful expressions, neutral expressions with averted gaze featured tongue protrusion[542]. Each face (15.9° wide x 23.1° tall) was presented centrally on a white background with a fixation cross between the nasion and the nose.

Procedure. For participants with normal vision, the dominant eye was defined as the eye more sensitive to blur in the presence of a +2.00 DS lens placed monocularly over each eye while binocularly observing letters 2 logMAR lines above their best-corrected visual acuity threshold[562]. The dominant eye in participants with amblyopia was defined as the eye with better best-corrected visual acuity.

First, to control for any effect of amblyopia on the perception of emotional faces, all participants rated valence and intensity for 48 faces (across all emotional expressions and gaze directions). Each face was presented to only the non-dominant/amblyopic eye for 400 ms. Participants rated the valence (1 = very negative to 9 = very positive) and intensity (1 = not intense to 9 = very intense) for each face on a visible Likert scale using keyboard presses.

Second, to measure attentional cueing with emotional face cues, we used an established spatial cueing task[542]. After a brief period of fixation (pseudo-random period of 500-800 ms), a neutral face with direct gaze appeared for 300 ms. Gaze was averted to the left or the right for 100 ms and the expression then changed to fearful, neutral (with tongue protrusion) or happy for 400 ms (Figure 7-1). After face offset, a target asterisk (1.3° x 1.3°) was presented 20° to the left or right of fixation and participants had up to 500 ms to respond to the location of the target using arrow keys while maintaining central fixation. Reaction time and accuracy were measured.

All participants were informed that gaze direction was not predictive of target location, but to still attend to the emotional expressions as participants would occasionally be asked to verbally report the most recent emotional expression. Gaze cues were congruent or incongruent with target location and had 50% validity. Each block consisted of 384 trials (64 trials per condition) presented in a randomized order and took 30 mins to complete.

All participants completed 3 blocks (viewing conditions: dominant eye, non-dominant eye, both eyes) within one session (1.5-2 hours) in a randomized order. Participants were encouraged to take breaks between blocks to avoid fatigue. The task was self-paced as participants completed

16 trials at a time before being presented with a break screen. Upon resumption, eye tracking drift correction was performed prior to starting the next set of trials. Prior to formal data collection, 24 practice trials were provided to familiarize participants with the detection task.

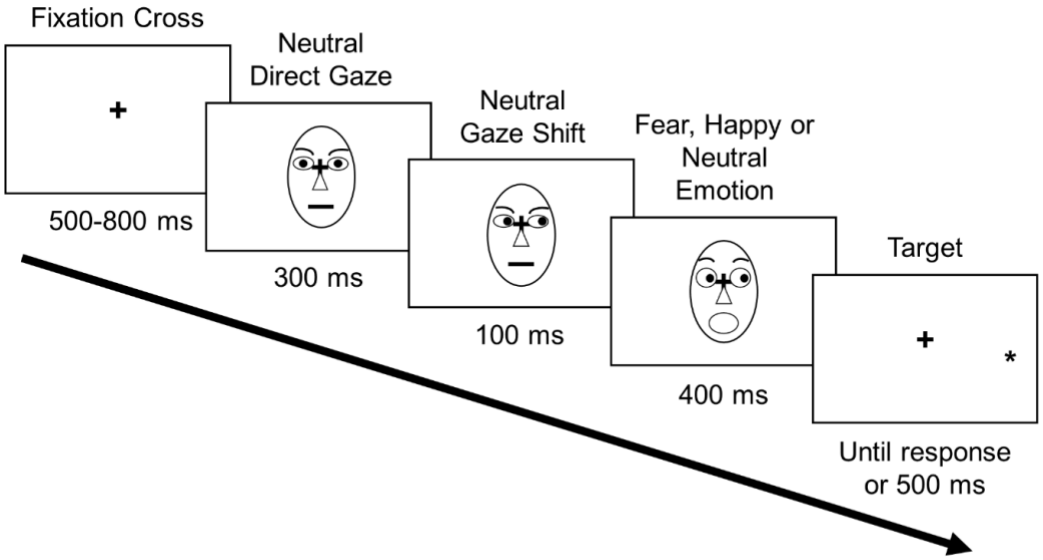

Figure 7-1. Sample trial sequence. Fearful, happy and neutral faces from the NimStim database [561] were used in the experiment, represented here with schematics.

Statistical Analyses. Only correct responses within 2.5 standard deviations of the mean reaction time were used to compute average reaction times for each condition[563]. Incorrect trials were excluded because reaction times in the presence of a task error do not reflect an appropriate orientation of attention. The gaze cueing effect was computed as the difference in reaction times between incongruent and congruent trials.

Statistical analyses were performed with JASP version 0.12.1 (Amsterdam, Netherlands). Accuracy was analyzed with a 3 (eye: dominant eye, non-dominant eye, both eyes) x 2 (group: control, amblyopia) repeated measures ANOVA. Perception of emotional faces was evaluated using a 3 (emotion: fear, neutral, happy) x 2 (group: control, amblyopia) repeated measures ANOVA on valence and intensity ratings. Reaction times were analyzed with an omnibus 3 (eye: dominant eye, non-dominant eye, both eyes) x 2 (congruency: congruent, incongruent) x 3 (emotion: fear, neutral, happy) x 2 (group: control, amblyopia) repeated

measures ANOVA. In cases where Mauchly's test of sphericity was significant, the Huynh-Feldt correction was applied. Post-hoc analyses were conducted on significant interactions using Tukey's correction for multiple comparisons.

7.3 Results

A significant main effect of emotion ($F_{2,80}$ = 310.4, p<0.001, ω^2 = 0.82) was found for valence ratings. There was no main effect of group ($F_{1,40}$ = 1.8, p>.05) nor an emotion x group interaction ($F_{2,80}$ = 1.6, p>.05). Post-hoc t-tests showed that fearful expressions had a significantly lower (negative) valence rating than both neutral (Table 7-2; mean difference ± SE -1.48±0.18, p<.001) and happy (-4.4±0.18, p<.001) expressions. Neutral expressions had a significantly lower valence rating than happy expressions (-2.9±0.18, p<.001).

For intensity ratings, significant main effects of emotion ($F_{1.6,65.2}$ = 81.3, p<.001, ω^2 = 0.47) and group ($F_{1,40}$ = 4.1, p=.049, ω^2 = 0.04) but no emotion x group interaction ($F_{1.6,65.2}$ = 0.4, p>.05) were found. Participants with amblyopia rated faces to be marginally more intense than participants with normal vision (Table 7-2; 0.52±0.26, Bonferroni corrected p=0.049). Fearful and happy faces were perceived as more intense than neutral ones (fearful vs neutral: 2.2±0.2, p<.001; happy vs neutral: -2.2±0.2, p<.001), and there was no difference between fearful and happy expressions (0.003±0.2, p>.05).

Table 7-2. Participants' mean ratings of valence and intensity for each emotional face. Reported as mean rating (standard error of the mean).

Measure	Fear	Happy	Neutral
Valence			
Control	3.06 (0.16)	7.22 (0.14)	4.62 (0.12)
Amblyopia	2.74 (0.15)	7.36 (0.18)	4.14 (0.31)
Intensity			
Control	6.37 (0.20)	6.54 (0.14)	4.17 (0.17)
Amblyopia	7.03 (0.15)	6.86 (0.32)	4.76 (0.48)

Overall target detection accuracy was high in both control (mean ± SE; 96.9±0.7%) and amblyopia (97.6±0.3%) groups. No main effects of eye ($F_{2,80}$ = 0.3, p>.05) nor group ($F_{1,40}$ = 0.6, p>.05) nor an eye x group interaction ($F_{2,80}$ = 1.6, p>.05) were present. Error rates were slightly higher in the

control group (2.1±0.5%) than the amblyopia group (1.5±0.2%) and the percentage of trials with delayed responses were comparable between the two groups (control: 1.0±0.4%; amblyopia: 0.9±0.2%). After trimming reaction times exceeding 2.5 SD of each individual's reaction time to mitigate the influence of outliers, an average of 95.5±0.2% (controls) and 96.7±0.1% (amblyopia) of the data remained for further reaction time analysis.

A 3 (eye) x 2 (congruency) x 3 (emotion) x 2 (group) analysis on mean reaction time revealed significant main effects of emotion ($F_{1.6,65.5}$ = 6.1, p=.006, ω^2 = 0.0007; see Figure 7-2A) and eye ($F_{2,80}$ = 5.2, p = .008, ω^2 = 0.01; see Figure 7-2B) but no effect of group ($F_{1,40}$ = 1.4, p>.05). Other significant interactions included eye x group ($F_{2,80}$ = 4.8, p=.011, ω^2 = 0.01), emotion x group ($F_{1.6,65.5}$ = 5.6, p=.009, ω^2 = 0.0006), and eye x emotion x group ($F_{4.1,\ 164.6}$ = 3.2, p=.013, ω^2 = 0.0004). However, no significant pairwise comparisons emerged after Tukey correction. A significant interaction of congruency x emotion was present ($F_{2,40}$ = 20.6, p<.001, ω^2 = 0.002) replicating the established emotional gaze cueing effect[542,543,558,550–557]. Post-hoc analyses revealed that the gaze cueing effect (i.e. the RT difference between incongruent and congruent trials) was stronger for fearful than neutral faces (main difference ± SE 12.2±2.0 ms, Bonferroni corrected p<.001) and for fearful than happy faces (8.6±2.0 ms, Bonferroni corrected p<.001); neutral and happy faces did not differ (-3.7±2.0 ms, Bonferroni corrected p>.05; see Figure 7-3). Importantly, the interaction of eye x congruency x emotion x group was not significant ($F_{3.9,157.8}$ = 1.1, p>.05), nor was the congruency x emotion x group interaction ($F_{2.1,82.4}$ = 0.79, p>.05)[2], suggesting that the emotional cueing effect was similar across groups and eye conditions[3].

[2] A power analysis computed using G*Power (v3.1.9.6) post-hoc revealed that in order to find a significant group difference in the gaze cueing effect for the non-dominant eye with 95% power, we would require a total sample size of 364 participants, indicating the likely absence of an effect even with larger groups.

[3] Please note that using a gaze-cueing index as a percentage of overall speed (($RT_{incongruent} - RT_{congruent}$)/[($RT_{incongruent} + RT_{congruent}$)/2] x 100) to account for longer reaction times in the amblyopia group did not change any of the results (approach used in Chen et al., 2021; Pecchinenda & Petrucci, 2016; Ramon et al., 2010).

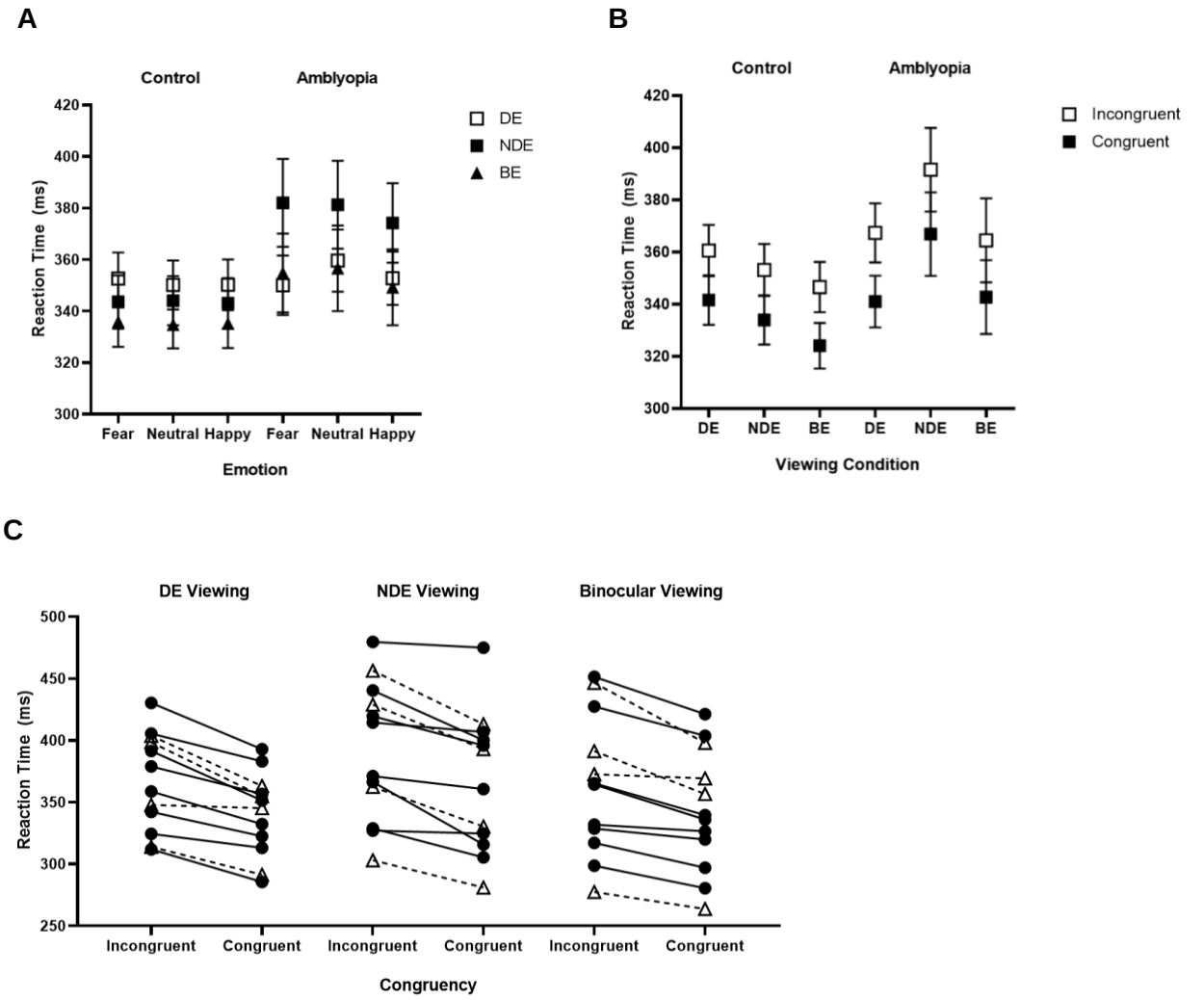

Figure 7-2. Mean reaction times across emotion (A) and viewing condition (B). (C) Individual reaction time data from the amblyopia group, segregated by amblyopia subtype. Circles (with solid lines) = anisometropic amblyopia; triangles (with dotted lines) = strabismic/mixed amblyopia. DE = dominant/fellow eye, NDE = non-dominant/amblyopic eye, BE = both eyes. Error bars denote standard error.

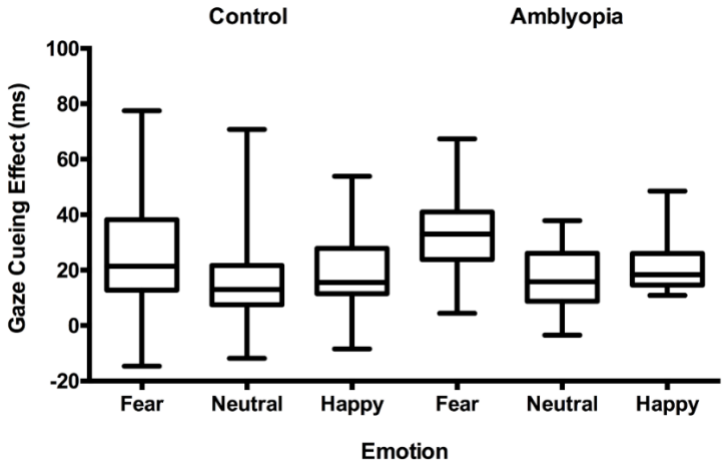

Figure 7-3. Box plot diagram showing emotional gaze cueing effects for fear, neutral and happy expressions for participants with normal vision (n=30) and amblyopia (n=12). Box boundaries denote 25th and 75th percentiles with the line inside box representing the median. Whiskers represent the full range of data points.

As an exploratory analysis to discern whether there were any differences amongst subtypes of amblyopia, we separated the amblyopia group into anisometropic (n=8) and strabismic/mixed (n=4) subtypes. A 3 (eye) x 2 (congruency) x 3 (emotion) x 2 (subtype) repeated measures ANOVA showed no main effect of subtype ($F_{1,10}$=0.11, p>.05) nor any interaction of subtype with other factors including congruency ($F_{1,10}$=2.3, p>.05). While the congruency x emotion interaction remained significant ($F_{2,20}$=7.8, p=.003), it did not interact with amblyopia subtype ($F_{2,20}$=1.47, p>.05). As seen in Figure 7-2C, the strabismic/mixed subtype group did not have slower reaction times (mean±SE: anisometropia 366.86±19.45 vs strabismic/mixed 357.79±19.45) and trended towards larger gaze cueing effects (anisometropia 19.80±4.1 vs strabismic/mixed 28.73±4.1) although the difference was not statistically significant.

Some participants in the amblyopia group reported previous successful treatment of amblyopia and had an interocular acuity difference less than 0.2 logMAR despite residual functional deficits in stereoacuity. We conducted an independent samples t-test to determine whether the magnitude of the gaze cueing effect was driven by this successfully treated group. We found no significant difference in gaze cueing effects between the successfully treated group (n = 3; mean±SE 33.6±6.5 ms) and the rest of our sample (n = 9; 21.2±2.9 ms; t_{10} = -1.98, p = 0.08). Omission of these participants from the analysis did not change our main findings. Neither the eye x congruency x emotion x group interaction ($F_{4,148}$ = 0.98, p>.05) or the congruency x emotion x

group interaction ($F_{2,74}$ = 0.2, p>.05) were significant. The magnitude of the gaze cueing effect appears to be independent of interocular acuity differences (ρ=-0.11, p>.05; see Figure 7-4).

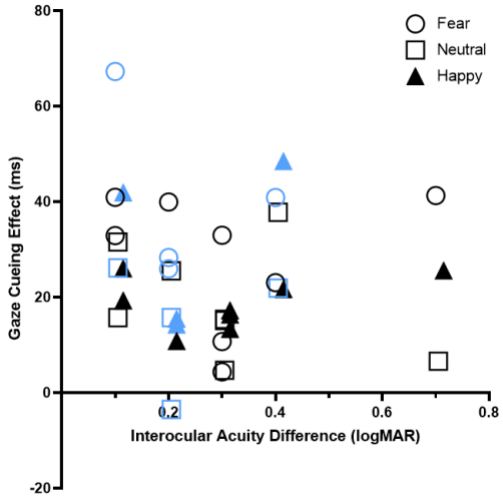

Figure 7-4. Gaze cueing effect as a function of interocular acuity difference in the amblyopia group across different emotions. Each participant is represented by a shape for each emotional cue condition (open circle = fear, open square = neutral, filled triangle = happy). Black = anisometropic, blue = strabismic/mixed. Shapes are slightly offset to avoid overlapping each other.

Previous studies have reported larger gaze cueing effects in females than males for neutral expressions[543,564–568]. However, there is no evidence that this difference in gaze cueing effect between sexes varies across emotional expressions[543]. Within our sample of 27 females and 15 males, no effect of gender was evident for the gaze cueing effect based on an independent samples t-test (fear: t_{40} = 0.75, p>.05; neutral: t_{40} = .034, p>.05; happy: t_{40} = 0.21, p>.05).

7.4 Discussion

The present study explored whether amblyopia affects the attention orienting effect generated by the gaze direction of emotional face cues. We first verified the emotional valence of the stimuli to ensure that any attentional capture effects were not limited by low level visual deficits. Despite using a complex attentional task requiring integration of gaze and emotional cues from face processing, our results suggest that orienting covert attention using emotional face cues is not affected by amblyopia across all viewing conditions. Specifically, no deficit in spatial cueing was seen under amblyopic eye viewing and we did not find an attentional imbalance favouring the

fellow eye in amblyopia under monocular viewing conditions. While we constrain our findings to those with treated, mild and moderate amblyopia, we find a comparable (even nominally larger) gaze cueing effect in our amblyopia group compared to the control group[542,550,551,553,558] and determined that this result was not driven by the subset of participants with treated amblyopia. In particular, fearful facial expressions oriented covert attention more strongly than happy and neutral expressions[542,543,550–552,556,558,560,569]. Additionally, we did not find a correlation between the strength of the gaze cuing effect and severity of amblyopia, similar to other previous studies with their attentional measures[425,426,435,441,533].

Regardless of emotion, we found that spatial cueing using gaze cues within face stimuli can orient covert attention in amblyopia. These findings corroborate previous work showing that simple attentional cueing is effective in amblyopia regardless of viewing eye[425–427]. Since emotional processing augmented the basic cueing effect, perception of emotional faces may be similar amongst our control and amblyopia groups. Indeed, subjective ratings of emotional valence and intensity did not differ substantially between our groups of participants. We were limited in this study to less severe cases of amblyopia so that participants would be able to resolve individual facial features. Nevertheless, our results are consistent with previous work demonstrating intact global facial processing as long as stimuli can be fully resolved by the amblyopic eye[79,152]. Our findings of emotion-specific effects suggest holistic face processing may be unaffected by amblyopia in our sample.

While we postulate that cortical integration of gaze and emotional cues for the purpose of attention orienting remains intact in mild, moderate and treated amblyopia, it is also possible that the intact cueing effect is mediated by a different route. A subcortical pathway may expedite face detection and gaze processing, even before detection by cortical routes[570–572]. This pathway involves the superior colliculus, pulvinar and amygdala[573]. In neurotypical individuals, a stronger functional connection between the pulvinar and amygdala is associated with better recognition of fearful facial expressions[574]. Neuroimaging of the amygdala in neurotypical individuals reveals residual amygdala activity even when fear-conditioned stimuli are masked[575]. Through this subcortical route, stimuli continue to be processed despite being perceptually suppressed and this processing occurs in parallel with cortical routes[575]. A previous report has suggested that motion integration in amblyopia involves intact pulvinar processing and engages a different neural network than individuals without amblyopia[179]. These subcortical pathways may mediate the seemingly intact emotional face gaze cueing effect in amblyopia.

Evidence remains mixed as to whether the severity of any attentional deficit differs by amblyopia etiology. Many of the attentional deficits reported in the literature involve individuals with strabismic amblyopia who often have more severe amblyopia[268,380,532,533]. Under monocular viewing conditions, spatial bias on a line bisection task was more pronounced in strabismic amblyopia than anisometropic amblyopia[532]. On the other hand, multiple-object tracking under monocular viewing revealed no difference in performance between anisometropic and strabismic amblyopia[172]. However, when multiple-object tracking was performed under dichoptic conditions, a tracking deficit was found only for participants with strabismic amblyopia[533]. Participants with anisometropic amblyopia were equivalent to neurotypical controls[533]. In another dichoptic attention study, the fellow eye contributed substantially more than the amblyopic eye, with the imbalance greater for strabismic amblyopia than anisometropic amblyopia[435]. Unfortunately, our limited sample size in this study did not permit us to conduct a subgroup analysis to address this question. In the future, a better understanding of the association between attentional deficits and amblyopia etiology will better inform efforts to recover visual acuity and stereopsis using attention-based amblyopia treatments[576–578].

Previous studies have reported that the size of the gaze cueing effect differs between the sexes for neutral expressions. In particular, females demonstrate a larger gaze cueing effects than males[371,543,565–568]. There is no evidence that this difference in gaze cueing effect between sexes varies across emotions[543]. Exploratory analysis using an independent samples t-test did not find a statistically significant difference in gaze cueing effect between males and females in our data, although we cannot draw a strong conclusion based on our limited sample size. Even if there was a difference that we did not capture with our small sample size, the distribution of females was higher in the control group than the amblyopia group, whereby the absence of an attentional deficit in the amblyopia group would not be driven by gender.

The NDE in both groups was exposed to the emotional face stimuli for 12.5% more trials than the DE as part of the subjective rating procedure at the beginning of the experiment. Although we cannot rule out the presence of a practice effect for the NDE driven by this increased exposure, this is unlikely to be responsible for our results for a number of reasons. 1) The rating procedure did not involve target detection practice to expedite reaction times for the detection of a peripheral stimulus. 2) Cue validity was 50% within the main experiment. Therefore, the effect of prior stimulus exposure would apply equally to both incongruent and congruent trials. 3) Any practice

effect would apply to the NDE viewing condition for both groups and thus our between-group comparison remains valid. Even if it reduced the interocular effect, no monocular difference was evident for the NDE between the groups. 4) We have no reason to believe that any practice effect would remain monocular as face processing involves cortical areas that are binocular.

Although our main analysis considers the magnitude of attentional orienting effect, we did note the overall increased reaction times for the amblyopia group (despite not being statistically significant). This is likely due to the mild nature of amblyopia amongst our participants as 9 out of 12 participants with amblyopia had an amblyopic eye acuity of 0.2 logMAR or better, and reaction time deficits may be correlated with visual acuity[201,202]. Previous studies that have found prolonged manual responses when stimuli were viewed with the amblyopic eye as compared to fellow eye or binocular viewing[195,198,201,203,204]. Increasing stimulus strength to the amblyopic eye can reduce this reaction time difference between the eyes only in anisometropic amblyopia[201,204], but an irreducible delay remains for strabismic amblyopia[201]. Within our small sample of anisometropic and strabismic participants, we did not find any differences amongst subtypes, as reaction time data from our strabismic amblyopia group fell within the range of the anisometropic amblyopia group (see Figure 7-2C). Nevertheless, the comparable magnitude of gaze cueing effects for both subtypes suggests that both groups benefit similarly from attentional cueing, although we cannot extrapolate these findings to severe amblyopia. By taking the difference between incongruent and congruent reaction times or a gaze-cueing index as a percentage of overall speed, we are able to exclude any overall reaction time delay inherent to the amblyopia group.

7.5 Conclusions

We explored whether amblyopia impairs the development of social attention by examining the orienting of covert attention by emotional face cues. Our results indicate that spatial cueing with emotional cues is unaffected by mild, moderate and treated amblyopia under monocular and binocular viewing conditions, and that the magnitude of social cueing is similar to neurotypical controls. Future studies should explore attentional cueing in more severe cases of amblyopia. These results place constraints on the range of attentional mechanisms affected by amblyopia and indicate normal processing of emotional face stimuli in mild and treated amblyopia. A better understanding of the attentional mechanisms in amblyopia may help to accelerate the development of new treatments.

Chapter 8

Dichoptic Attentive Motion Tracking is Biased Towards the Non-Amblyopic Eye in Strabismic Amblyopia

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8.1 Introduction

Abnormal binocular visual experience during early childhood, typically due to a large difference in refractive error between the eyes (anisometropia) or a deviated eye (strabismus), can disrupt visual development and cause amblyopia. Amblyopia is characterised clinically by decreased visual acuity in the affected eye that cannot be entirely accounted for by refractive error or pathology[1,5]. Beyond the reduction in visual acuity, amblyopia also causes a broad range of visual deficits ranging from impairments in contrast sensitivity[120,121,294,485,494] to the global processing of motion and form[101,167,170,173,174,182,240,495–497]. A number of these deficits also extend to the non-amblyopic fellow eye[99,101,165,166,173,495,579].

Beyond the loss of monocular visual function, amblyopia also impairs binocular vision, in part because visual information from the amblyopic eye is suppressed from conscious awareness when both eyes are viewing[29,105,258,262,285,580]. Suppression can affect large areas of the amblyopic eye visual field[260,261] and may play an important role in the visual deficits experienced by patients with amblyopia[105,258,581]. Stronger suppression is associated with poorer visual acuity in the amblyopic eye[105,271,272] and treatments that aim to reduce suppression improve amblyopic eye visual acuity to some extent[252,253,255,493,582–585], although randomized clinical trial evidence for this approach is mixed[586–588].

The abnormal patterns of interocular excitation and inhibition that may contribute to suppression are evident within early visual areas of amblyopic primates[59,68,295,296,451,589]. However, it has recently been suggested that abnormal allocation of visual attention between the two eyes may also play a role in suppression[268]. Using electroencephalography (EEG), Hou and colleagues[268]

observed a reduced effect of attentional modulation in areas V1, V4 and V5 when participants with strabismic amblyopia viewed monocularly with their amblyopic eye. Importantly, they also found a strong positive correlation between the extent of the attentional modulation deficit in V1 and the strength of amblyopic eye suppression. Reduced attentional modulation was also observed for fellow eye viewing in V4 and V5, but not V1. Similarly, another study identified differences in event-related potential (ERP) waveforms during processing of the Stroop task for children with amblyopia relative to controls[444]. Other studies have used psychophysics to investigate attentive processing in amblyopia under monocular viewing conditions, with mixed results. Impairments have been reported in multiple-object tracking[172,438], conjunction visual search[423] and attentional blink tasks[535], suggesting an attention deficit associated with not just the amblyopic but also the fellow eye, that affects both spatial and temporal components of visual attention. On the other hand, studies using attentive cueing paradigms in humans[425,428] and primates[427] have reported that attentional modulation is comparable to a normal visual system. Thus, the extent of any attentional deficit in amblyopia remains unclear. This may be due to previous studies employing monocular presentation of visual stimuli. Presumably, if attentional allocation is abnormal between the eyes, it would be most evident under dichoptic viewing conditions.

In normal vision, attention can be allocated independently to each eye and modulate binocular combination of monocular information. Monocular cues presented under dichoptic viewing conditions can attract visual attention[415,416] and can affect perceptual dominance in binocular rivalry paradigms, even though they cannot be discriminated from binocular cues[417–420]. Therefore, it is conceivable that a biased allocation of attention between the eyes may contribute to interocular suppression and the loss of binocular vision in amblyopia.

We used a dichoptic multiple-object tracking task to directly address the question of whether interocular suppression in amblyopia involves an attentional bias in favour of the fellow eye[268]. By presenting target elements to only one eye and distractors to the other eye, we determined whether attention was biased towards one eye or allocated equally across both eyes. In Experiment 8-1, we tested whether dichoptic viewing affected multiple-object tracking in binocularly normal controls. In Experiment 8-2, we measured dichoptic multiple-object tracking performance in controls and participants with anisometropic and/or strabismic amblyopia. We considered the two amblyopia groups separately because a previous study of attentional modulation within the visual cortex only involved strabismic amblyopia[268]. Interocular contrast

balancing[272,281,303,446,449,452,590] and an enumeration control task were used to ensure that the stimulus elements presented to each eye were continuously visible in the amblyopia group. If a bias in the interocular balance of attention does play a role in suppression of the amblyopic eye, we would expect participants with amblyopia to have worse multiple-object tracking task performance when the target dots are presented to the less attended (amblyopic) eye vs. the more attended (fellow) eye. We hypothesized that if such an attentional imbalance was a fundamental component of amblyopia, it would still be present after interocular contrast balancing was used to ensure that dots were equally visible to each eye.

8.2 Methods

Participants: Experiment 8-1 involved 12 participants with normal vision (8 female; mean age 25 ± 2.8 yrs), and Experiment 8-2 involved 17 participants with amblyopia (9 anisometropic amblyopia, 8 strabismic/mixed amblyopia, mean age 37 ± 13.5 yrs) as well as 15 controls with normal vision (14 female; mean age 23 ± 1.5 yrs; only 1 of whom also participated in Experiment 8-1). Participants with normal vision had best-corrected visual acuity better than 0.1 logMAR (20/25), with no greater than 1 logMAR line difference between the eyes, and no history of binocular vision disorders. Inclusion in the amblyopia group required: (a) at least a 2 logMAR line difference in best-corrected visual acuity between the eyes (all participants had AE acuity worse than 0.2 logMAR with exception of A12, who had received successful treatment), (b) either anisometropia (>1 dioptre difference in spherical equivalent between the eyes or >1.5 dioptres of cylinder in one eye) and/or strabismus (including history of strabismus surgery), (c) normal ocular and general health. All participants, except for author AC, were naïve to the experimental hypothesis and were reimbursed with $15 for their time. Participants provided written informed consent to take part in the study, and the study protocol was approved by the institutional ethics committee, in accordance with the Declaration of Helsinki.

Apparatus: Stimuli were presented on an ASUS 27” VG278 3D monitor (1280 x 720 resolution, 120Hz refresh rate), which was synchronized to the alternation rate of a pair of NVIDIA 3D VISION LCD shutter glasses. Participants viewed the screen (subtending 48° x 27°) through the shutter glasses at a distance of 67 cm. Stimuli were presented using MATLAB (The MathWorks, Natick, MA, US) and Psychtoolbox[591,592].

Procedure: All participants were screened at the School of Optometry and Vision Science, University of Waterloo by author AC, who assessed visual acuity (electronic ETDRS chart), binocular status (distance and near cover test) and stereoacuity (Randot Stereotest, Stereo Optical Co. Inc.). Refraction was conducted if an eye exam had not been completed within the last 2 years. Participants wore their optimal refractive correction either through their habitual corrective lenses or a trial frame. Clinical details for individuals with amblyopia are summarized in Table 8-1. Sensory eye dominance was determined for all participants using an established dichoptic motion coherence paradigm, assigning the eye with a lower dichoptic motion coherence threshold as the dominant eye[303,590]. This dichoptic global motion task was then used to identify the balance point contrast required for normal binocular combination. Each participant viewed the experimental stimuli at 100% contrast with their non-dominant or amblyopic eye, and at their balance point contrast for the dominant or fellow eye. Any ocular misalignments were accounted for subjectively with the alignment of a central Nonius cross prior to the start of each task.

Table 8-1. Clinical Details for Amblyopic Participants. VA = visual acuity; FE = fellow eye; AE = amblyopic eye; Dx = diagnosed; A = anisometropia; S = strabismus; M = mixed; NS = non-strabismic, E(T) = esophoria; X(T) = exophoria; RET = right esotropia; LXT = left exotropia; OD = right eye; OS = left eye; Δ = prism dioptre, yo = years old.

ID	Age/ Gender	Type	VA (FE)	VA (AE)	Stereo	Ocular Deviation (near)	Refraction	Clinical History
A01	24/F	A	20/20	20/100	> 500”	NS, 12Δ X(T)	OD: +6.50 DS OS +0.50 DS	Unknown history
A02	43/M	M	20/20	20/40	> 500”	8Δ constant RET	OD: +7.00/-2.75x030 OS: +5.00/-1.75x170	Dx at 4 yo, sx for RET at 4 yo, patched, vision therapy
A03	43/M	M	20/15	20/60	> 500”	NS, ortho	OD: +2.75/-2.50x175 OS: +1.75/-0.50x060	Dx at 4 yo, for ET, patched

A04	54/F	S	20/20	20/60	> 500”	12Δ constant LET	OD: +4.00 DS OS: +4.25/-0.50x140 ADD +2.25 D	Patched
A05	28/M	A	20/20	20/70	500”	4Δ X(T)	OD: +5.00 DS OS: +3.75 DS	Poor compliance with patching
A06	28/M	A	20/20	20/50	> 500”	NS, ortho	OD: +3.00/-0.25x140 OS: plano	No patching or surgery
A07	23/F	M	20/15	20/30	250”	6Δ constant LXT	OD: pl/-0.25x179 OS: +4.50/-1.50x064	Dx at 3-4 yo, patched
A08	25/F	A	20/20	20/150	> 500”	NS, ortho	OD: pl/-0.25x005 OS: +4.50/-3.00x058	Dx at 10 yo, no patching, training or surgery
A09	51/F	A	20/20	20/50	> 500”	NS, 6Δ X(T)	OD: +0.75 DS OS: -2.25/-0.75x161 ADD +1.75 D	Dx at 8 yo, Rx given but did not wear until 25 yo
A10	25/M	M	20/15	20/40	> 500”	6Δ constant RET	OD: +1.25/-0.75 x 170 OS: -1.75/-0.75 x 002	Dx at 1 yo, minimal patching and training
A11	38/F	A	20/15	20/30	250”	NS, ortho	OD: +1.00 DS OS: +4.50/-1.00x025	Dx 4 yo, patched, FT Rx wear
A12	21/M	A	20/15	20/25	250”	NS, ortho	OD: +0.25/-0.25 x 153	Dx 14 yo, inconsistent

							OS: +3.75/-2.00 x 180	patching, no sx or training, FT Rx wear
A13	41/M	M	20/20	20/60	> 500”	18Δ constant RET	OD: +4.00/-1.25 x 090 OS: +0.75/-0.50 x 090	Dx 11-12 yo, wore Rx for 2 y, but discontinued
A14	47/F	M	20/15	20/40	> 500”	14Δ constant RET	OD: +4.50/-0.50 x 171 OS: +2.75/-0.25 x 155 ADD +1.75 D	FT Rx wear, patched, no sx
A15	46/F	A	20/15	20/40	> 500”	NS, 10Δ E(T)	OD: -0.50 DS OS: +1.25/-0.75x105	No patching or sx
A16	68/M	M	20/20	20/100	> 500”	12Δ constant LET	OD: +2.25/-0.25x140 OS: +5.75 DS ADD +2.50 D	Wore Rx since 25 yo, no patching/training/sx
A17	26/F	A	20/20	20/50	> 500”	NS, 4Δ E(T)	OD: -1.00/-0.50x150 OS: +0.75/-1.25x165	Wore Rx since 12 yo, minimal patching, no training/sx

Participants performed a multiple-object tracking task (similar to that employed by Giaschi et al.[241] and illustrated in Figure 8-1A and 8-1B) that involved tracking 4 target dots among 6 identical distractor dots (Experiment 8-1) or tracking 3 target dots among 7 distractor dots (Experiment 8-2). This change was made because participants with amblyopia had difficulty tracking 4 dots, so we opted for a task that allowed for near normal overall performance. Previous work has noted this tracking deficit, whereby participants with amblyopia demonstrated 75% accuracy tracking a mean of 4 dots with the fellow eye and 3.7 dots with the amblyopic eye, as compared to 5.16 dots

in control participants[172]. At the start of each trial, 10 stationary dots (1° in diameter, presented within a Gaussian envelope) were presented and the target dots were highlighted in green for 2 seconds. The dots then moved at 10°/s within a 14° x 14° field along random but non-overlapping trajectories. Participants tracked the dots for 5 seconds while fixating a central cross. Using a partial report procedure, participants indicated whether a highlighted dot was a target dot at the end of each trial. Audio feedback was given after each trial.

In Experiment 8-1, a monocular awareness task (illustrated in Figure 8-1C) was used to assess whether participants were aware of which eye a stimulus of interest was being presented to. In a 14° x 14° field, a single dot moving at 10°/s was presented to only one eye amongst 4 static dots displayed to the other eye. Participants were asked to identify which eye was viewing the moving dot using a key press. No feedback was provided, and participants were monitored to ensure they were viewing the display with both eyes open. The moving dot was presented to either eye with equal probability, and each participant completed 48 trials.

In Experiment 8-2, an enumeration task was also performed at each participants' contrast balance point to ensure that participants with amblyopia were not suppressing the dots presented to the amblyopic eye. Dot parameters were the same as the multiple-object tracking task (dots moving at 10°/s in a 14° x 14° field), except the target dots were presented in red and remained red throughout the entire 5 second viewing period. Participants were asked to report the number of red dots (either 3 or 5) that were present with a key press on a number pad. Target dots were split between the dominant and non-dominant eyes in either a 2/1 or 3/2 ratio, or all targets and distractors were presented to both eyes as catch trials. Splitting the target dots between the eyes allowed us to determine by numeric report whether amblyopic eye dots were being suppressed. Participants also provided a subjective yes/no report of whether any of the dots disappeared during the trial. This provided an indirect measure of transient suppression. Participants performed 60 trials in this self-paced task.

The multiple-object tracking and enumeration tasks were performed across three conditions in a randomized order: 1) binocular viewing, 2) dichoptic viewing with target dots presented to the dominant eye (DE condition) and distractor dots to the other eye, and 3) dichoptic viewing with target dots presented to the non-dominant eye (NDE condition) and distractor dots to the other eye. In both experiments, participants were given 12 practice trials prior to completing 120 test trials, with an opportunity to take a break every 60 trials.

Statistical Methods: The one-sample Kolmogorov-Smirnov test was used to test for normality. Data that were not normally distributed were analysed with non-parametric statistics. For the multiple-object tracking task in Experiment 8-1, one-way analysis of variance (ANOVA) was used to assess the effect of viewing condition. Pairwise t-tests were used for post-hoc analysis. Multiple comparison corrections were not applied due to the limited sample size. For the monocular awareness task in Experiment 8-1, a one-sample t-test was used to test whether task performance differed from chance.

For Experiment 8-2, three analyses were conducted on the multiple-object tracking accuracy data. First, the three different viewing conditions were compared within each group using Wilcoxon signed ranks tests. Second, the binocular condition results were compared between the three groups to assess whether any group exhibited a general multiple-object tracking deficit. Since the binocular condition accuracy data were normally distributed, a univariate ANOVA with a factor of group (control vs. anisometropia vs. strabismic) was conducted. Third, an interocular asymmetry score was computed for each group by subtracting NDE from DE accuracy to enable between-group comparisons in the allocation of attention between the two eyes. Asymmetry scores were analyzed using the independent samples Kruskal-Wallis test and post-hoc testing was conducted using Mann-Whitney U tests. Asymmetry scores were also calculated for the enumeration task and analysed in the same way. Spearman's rho correlation coefficients were used to investigate the association between NDE enumeration task accuracy and multiple-object tracking asymmetry scores.

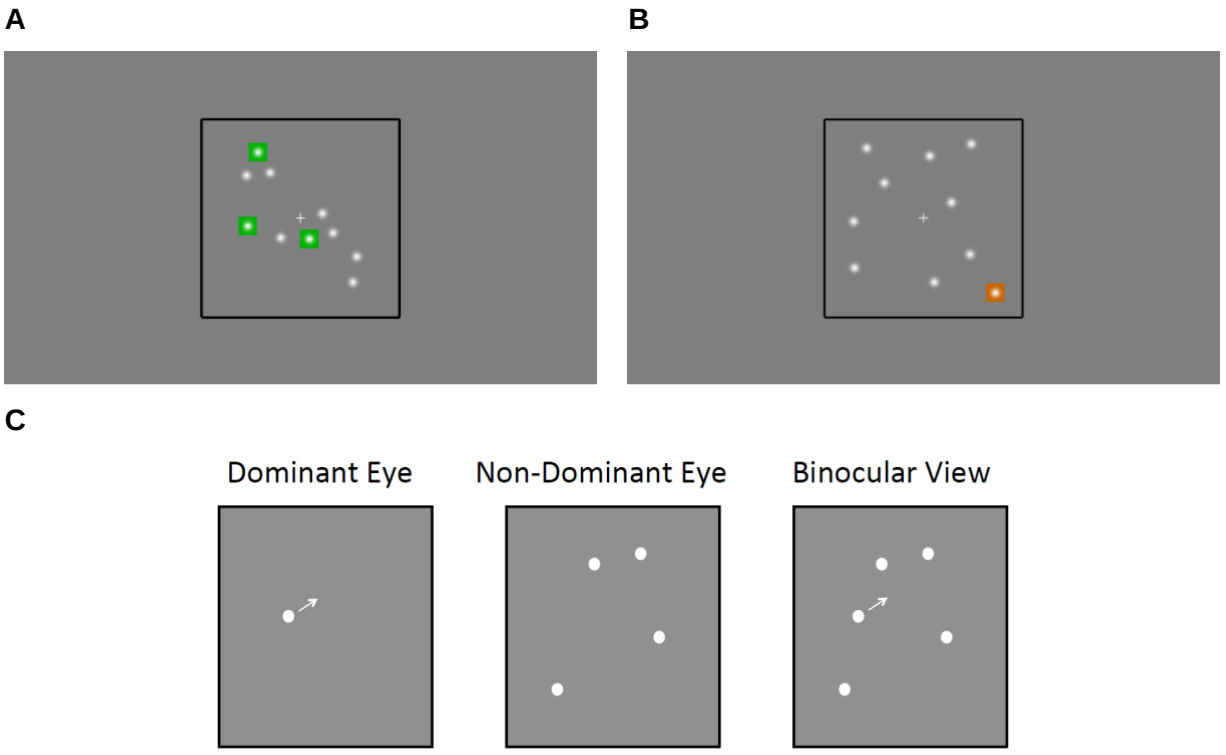

Figure 8-1. (A) The multiple-object tracking task, consisting of 4 (Experiment 8-1) or 3 (Experiment 8-2) target dots to be tracked (highlighted in green) amongst distractor dots. (B) The two-alterative force choice (2-AFC) partial report screen. Participants reported whether the highlighted dot was a target dot. (C) The monocular awareness task. Participants reported the eye that was presented with the moving dot. All dots were presented within a Gaussian envelope.

8.3 Results

8.3.1 Experiment 8-1

Multiple-object tracking performance (percent accuracy, mean ± SE) was 86±3% for binocular viewing, 79±2% for the DE condition and 81±3% for the NDE condition (see Figure 8-2). There was a significant main effect of viewing condition ($F(2,11)=4.2$, $p=.048$). Pairwise t-tests revealed a significant difference between performance under binocular viewing compared to the DE condition ($t(11)=-2.96$, $p=.013$) and no significant difference between binocular viewing compared to the NDE condition ($t(11)=-2.00$, $p=.07$). Performance between the DE and NDE conditions did not differ significantly ($t(11)=-0.776$, $p=.45$). In the conscious monocular awareness task,

participants were unable to consciously report which eye the signal was being presented to and did not perform significantly better than chance ($t(11)=1.03$, $p=.33$).

These results demonstrate that in participants with normal vision, dichoptic viewing with target dots presented to one eye and distractor dots presented to the other eye did not benefit multiple-object tracking. In fact, dichoptic presentation slightly impaired task performance relative to binocular presentation. Furthermore, participants were not consciously aware of which eye was receiving target information and were unable to use this information to their advantage. As a whole, the results indicate that attention was allocated equally between the two eyes in participants with normal vision, even when task performance would have benefited from preferential allocation of attention to the eye that saw the target dots.

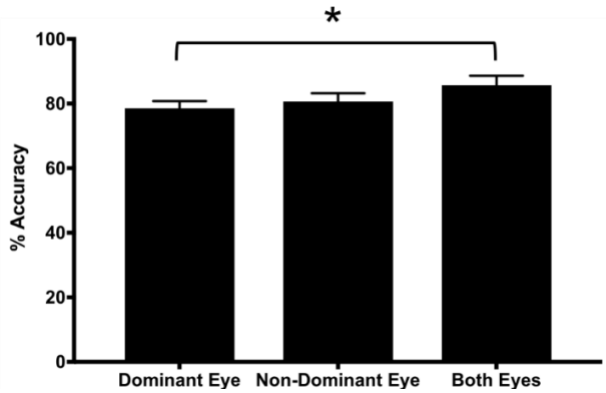

Figure 8-2. Mean percent accuracy on the multiple-object tracking task in Experiment 8-1. Participants with normal vision showed slightly improved tracking performance under binocular viewing conditions than dichoptic viewing conditions. Error bars denote ±1 SEM.

8.3.2 Experiment 8-2

Multiple-object tracking performance (Figure 8-3A) was quantified as percent accuracy (mean ± SE) for the normal group (DE 83±3%; NDE 80±4%; binocular 92±2%), anisometropia group (DE 81±6%; NDE 86±3%; binocular 78±6%) and strabismic/mixed group (DE 88±1%; NDE 65±5%; binocular 84±5%). Within each group, the multiple-object tracking accuracy scores for each viewing condition were compared to determine whether there was an effect of viewing condition. For the normal vision group, no significant difference was found between the DE and NDE conditions ($W=24.5$; $p=.3$), but both differed significantly from the binocular condition (DE vs.

binocular: W=117.5, p=.001; NDE vs. binocular: W=117.5, p=.001). In the anisometropic amblyopia group, none of the pairwise comparisons were significant (DE vs. NDE: W=25, p>.05; DE vs. binocular: W=8.5, p>.05; NDE vs. binocular: W=17, p>.05). In the strabismic/mixed amblyopia group, there was no significant difference between the DE and binocular conditions (W=7.5, p>.05). However, the NDE condition was worse than both the DE (W=3, p=.04) and binocular (W=26, p=.04) conditions. Each participant's multiple-object tracking task accuracy under the two dichoptic conditions can be seen in Figure 8-4.

Binocular multiple-object tracking accuracy was compared between groups in a separate analysis to evaluate whether the strabismic/mixed group had a general multiple-object tracking deficit compared to the other groups. There was a significant main effect of group (F(2,29)=3.89, p=.03). Pairwise t-tests showed that performance in the anisometropic amblyopia group was significantly worse than controls (t(9.49)=-2.34, p=.043). There was no significant difference between the strabismic/mixed amblyopia and control groups (t(8.86)=-1.59, p=.15), nor between the anisometropic and strabismic/mixed amblyopia groups (t(15)=-.77, p=.45).

Asymmetry scores (normal 3±2%; anisometropia -5±4%; strabismic/mixed 24±6%) varied significantly across groups as seen in Figure 8-3B (H(2)=8.4, p=.02). Pairwise comparisons revealed a significant difference between the normal and strabismic/mixed groups (U=24, p=.02) and between the anisometropia and strabismic/mixed groups (U=60.5, p=.02). Asymmetry scores between the normal and anisometropia groups did not significantly differ (U=92, p>.05).

To explore whether the differences in multiple-object tracking accuracy could be explained by suppression, we analyzed the contrast balance points for our participants with amblyopia. There was no significant difference in contrast balance points between the anisometropic amblyopia and strabismic/mixed amblyopia groups (t(12.9)=-.11, p=.91). Similarly, when the enumeration task was performed at each participants' contrast balance point, participants exhibited high accuracy (mean ± SE) across all three groups: anisometropia DE 97±2%, NDE 96±2%, BE 99±1%; strabismic/mixed DE 89±3%, NDE 86±3%, BE 87±12%; normal DE 99±0%; NDE 99±1%, BE 99±1%. Enumeration performance differed across the groups for both DE and NDE conditions (H(2)=10.5, p=.005 and H(2)=13, p=.001 respectively), but not for the binocular condition (H(2)=0.3, p=.86). Pairwise comparisons showed a significant difference between the normal and strabismic/mixed groups (DE: U=19, p=.007; NDE: U=11.5, p=.001) and between the anisometropia and strabismic/mixed groups (DE: U=17, p=.05; NDE U=14, p=.03). No significant

difference between the anisometropia and normal groups were found in the dichoptic conditions (DE: U=53, p>.05; NDE: U=42, p>.05). Analysis of the enumeration task interocular asymmetry scores revealed that the groups did not differ in interocular difference in enumeration task performance (H(2)=0.7, p=0.72).

Additionally, the multiple-object tracking task asymmetry scores did not correlate significantly with enumeration performance in the NDE condition (ρ(16)= -.395, p=.12), contrast balance point (ρ(16)=-.08, p=.77), or visual acuity difference between the eyes (ρ(16)=.131, p=.62).

Participant A16 subjectively reported intermittent diplopia during the tracking task. When this participant was removed from the analysis, the asymmetry scores still varied significantly across groups (H(2)=7.06, p=.02) and a significant difference between the normal and strabismic/mixed groups persisted (although the p value was very close to 0.05: U=26.5, p=.047) as well as between the anisometropia and strabismic/mixed groups (U=51.5, p=.03).

The results show that participants with anisometropic amblyopia had an equal distribution of attention between the two eyes, similar to those with normal vision. However, those with strabismic amblyopia displayed a significant deficit when targets were presented to their amblyopic eye and distractors their fellow eye, despite the dots being adequately visible to both eyes. This asymmetry cannot be attributed to suppression of dots presented to the amblyopic eye, as seen by the poor correlation between enumeration performance in the NDE condition and the asymmetry scores seen on the multiple-object tracking task. Similarly, a general motion tracking deficit cannot explain this effect, as task performance in the strabismic/mixed group under binocular viewing conditions did not differ from controls. Instead, these results suggest an imbalance in the allocation of attention to each eye for the multiple-object tracking task.

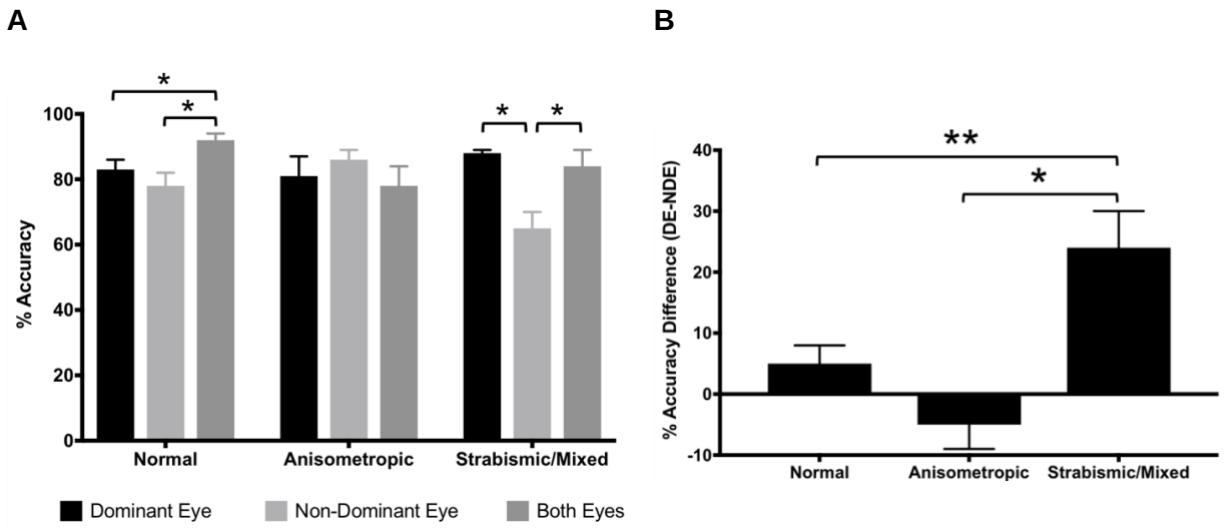

Figure 8-3. (A) Mean percent accuracy on the multiple-object tracking task for each group in Experiment 8-2. (B) Multiple-object tracking asymmetry scores calculated from the difference between FE and AE accuracy in the amblyopia groups and DE and NDE accuracy in controls). Interocular asymmetry scores were significantly higher in the strabismic/mixed amblyopia as compared to the anisometropic amblyopia or control groups. Error bars denote ±1 SEM.

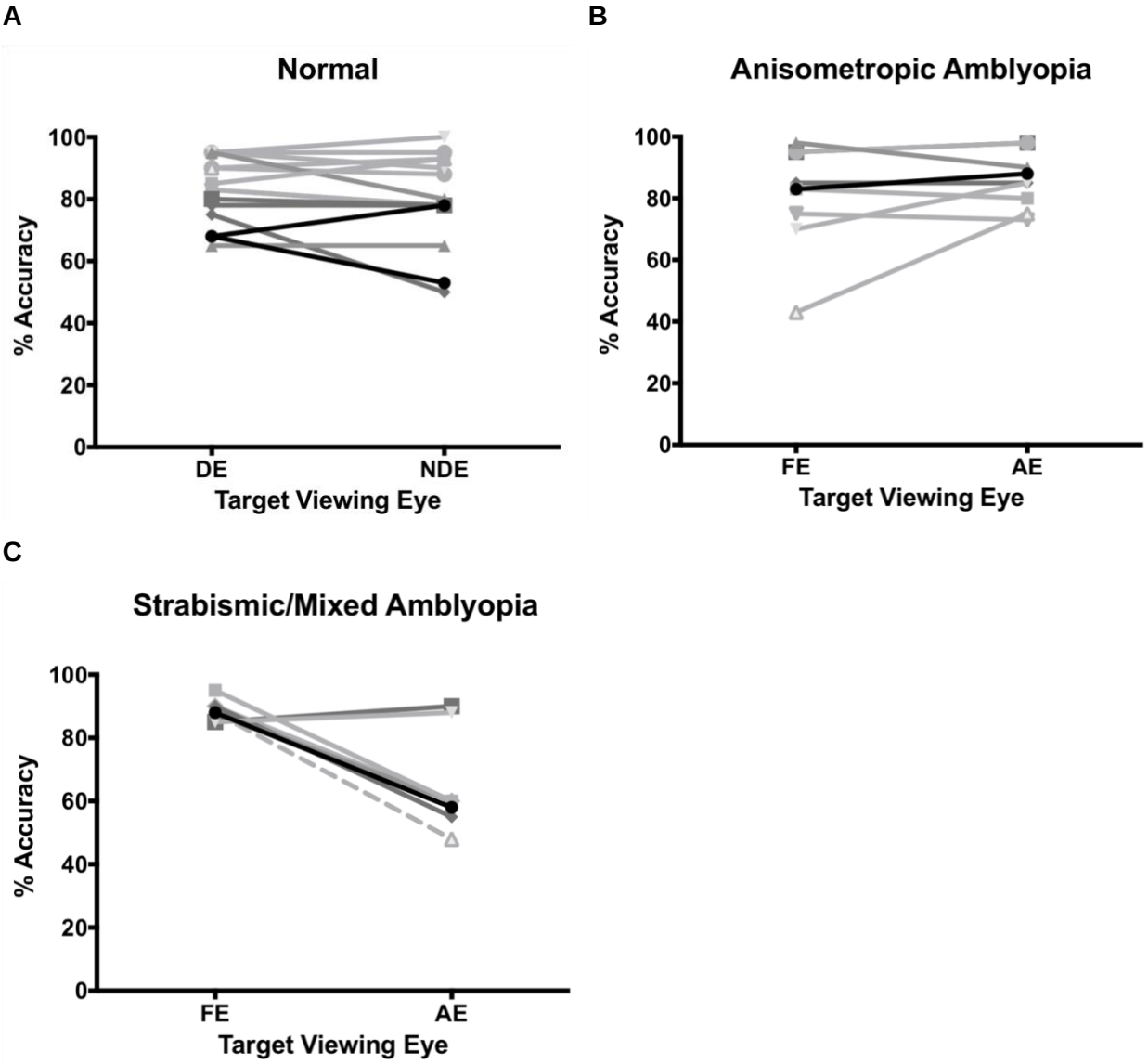

Figure 8-4. Individual participant multiple-object tracking task performance accuracy under each dichoptic condition for each group (A – controls with normal vision; B – anisometropic amblyopia; C – strabismic/mixed amblyopia). Participants with anisometropic amblyopia and normal controls had similar patterns of attentional allocation. Participants with strabismic/mixed amblyopia showed a significant deficit when target dots were presented to the amblyopic eye. Data points from the same participant across the two separate viewing conditions are connected with a line for ease of interpretation. The dashed line in Panel C denotes participant A16, who reported intermittent diplopia sporadically during the multiple-object tracking task. DE = dominant eye; NDE = non-dominant eye; FE = fellow eye; AE = amblyopic eye.

8.4 Discussion

The aims of this study were to determine whether interocular attention is biased in visually normal participants (Experiment 8-1), and whether interocular attention is biased in favour of the fellow eye in anisometropic and strabismic/mixed amblyopia (Experiment 8-2) when both eyes are viewing. Experiment 8-1 revealed that the normal visual system has an equal distribution of attention between the two eyes when performing the multiple-object tracking task, and that dichoptic presentation of target dots to only one eye did not benefit task performance. In fact, splitting targets and distractors between the two eyes impaired performance, as we found an advantage of binocular over dichoptic stimulus presentation for multiple-object tracking accuracy. This is the opposite of what we would expect if attention could be biased in favor of the eye viewing only target elements during dichoptic viewing. Therefore, despite previous evidence that attentive processing of monocular information can be used in an advantageous manner to expedite stimulus detection in dichoptic tasks[415,416], we found that it does not benefit performance within a motion tracking paradigm.

Experiment 8-2 revealed an equal allocation of attention between the two eyes in anisometropic amblyopia and an attentional bias in favour of the fellow eye in strabismic amblyopia. These findings are consistent with the relatively reduced attentional modulation effect of the amblyopic eye in strabismic amblyopia[268]. Our results are also broadly consistent with previous neuroimaging studies that have reported abnormalities within the motion processing and attentional networks that contribute to multiple-object tracking task performance in amblyopia[93–95,179,380,593–596]. However, other studies have observed normal performance on attentional tasks in amblyopia. For example, Roberts and colleagues[425] found normal accuracy and reaction times for a group of participants with amblyopia who performed involuntary and voluntary attentive cueing tasks under monocular viewing conditions. Furthermore, they found that the extent of attentional modulation did not correlate with amblyopia severity. However, when only considering the participants in their study who had at least a 2 logMAR line difference in acuity, those who remain (7 out of 19 participants) predominantly had anisometropic amblyopia. The results of the current study are consistent with this previous study in finding no attentional deficit in anisometropic amblyopia.

An inspection of Figure 8-4 reveals variability in the control and strabismic/mixed groups with some participants exhibiting a bias towards the fellow/dominant eye and others showing no bias. This indicates that an attentional bias was not present in all participants with strabismic amblyopia and that a bias can also exist in controls. A study with a larger sample size is required understand this variability and to enable stronger conclusions to be drawn regarding the allocation of interocular attention in strabismic/mixed amblyopia.

Unlike controls, participants with amblyopia did not exhibit an advantage of binocular over dichoptic presentation. This effect may be related to previous work demonstrating that binocular summation may be impaired in amblyopia[176,293,294,483]. However, the reason for a multiple-object tracking task advantage for binocular vs. dichoptic presentation of the multiple-object tracking task remains to be explained. Similarly, the reason for an interocular attention asymmetry for the strabismic/mixed group and not the anisometropic group is unclear. Stronger dichoptic masking in strabismic relative to anisometropic amblyopia has been reported[126]. However, other studies have not observed differences in interocular suppression strength between strabismic/mixed and anisometropic amblyopia[105,260]. In agreement with these latter studies, we did not find a difference in interocular suppression strength between the two amblyopia groups in terms of balance point contrast. In addition, once interocular suppression was neutralized with an appropriate interocular contrast balance, interocular asymmetries in enumeration task performance did not differ between groups - although the strabismic/mixed group did exhibit worse overall performance on this task than the other groups. If we assume that an interocular bias in attention contributes to interocular suppression in amblyopia[268], then our measurements reveal a residual attentional bias in strabismic/mixed amblyopia that is maintained when suppression is minimized.

To rule out the potential confound of a general motion tracking deficit in amblyopia, we examined multiple-object tracking performance under binocular viewing conditions to provide an index of multiple-object tracking accuracy without any interocular manipulations. Both amblyopia groups exhibited numerically poorer multiple-object tracking accuracy than controls in agreement with previous studies of monocular multiple-object tracking in amblyopia[95,172,438], however the difference from controls only reached significance for the anisometropia group, perhaps due to limited sample size. Critically, the two amblyopia groups did not differ significantly from one another, confirming that the interocular attentional bias in the strabismic/mixed group could not be explained by a general tracking deficit. Both amblyopia groups had greater mean ages than the control group, however the mean age of the two amblyopia groups did not differ. As all

participants were adults with mature visual systems and healthy eyes, we do not anticipate age to have affected our results.

It has been proposed that the spatial attention deficits may be involved in the multiple-object tracking impairments in amblyopia[95], whereby the spatial resolution of attention is coarser in the amblyopic eye[428]. This may cause crowding of dots presented to an amblyopic eye[597–599]. Although we cannot eliminate crowding as a confounding factor in our study, contour interactions were minimized by the use of Gaussian blur on dot edges. It is also important to note that our target dots were generally perceived to be separate dots in the enumeration task. Although the strabismic/mixed group displayed poorer overall enumeration accuracy in both dichoptic conditions, no interocular differences were present and binocular performance was similar to the anisometropic and visually normal groups.

Overall, our results provide new evidence that an interocular imbalance in attention occurs in strabismic/mixed amblyopia. Interocular attention may be important to consider within the rapidly developing field of binocular amblyopia treatments.

Chapter 9
Discussion

9.1 Summary of Findings

The purpose of this dissertation was to determine whether suppressed visual information from the amblyopic eye remains available for processing within the brain and whether attentional mechanisms are affected by amblyopia. Across 4 experiments, there are several major insights about amblyopia to be gained from this thesis. Visual information seen only by a suppressed amblyopic eye remains available for visual processing and can affect visual perception (Chapter 5). In particular, this result indicates that visual information from the amblyopic eye retains a presence within the brain that may subsequently be used for attentional processing. Attentional mechanisms in amblyopia were found to be intact to some extent and thus can be engaged. Attentional capture was effective for targets seen by a partially suppressed amblyopic eye, expediting saccadic latencies to alleviate the amblyopic deficit (Chapter 6). Even when using complex face cues, simple spatial cueing remains unaffected by amblyopia (Chapter 7). Selective attentional tracking by the amblyopic eye was intact in anisometropic amblyopia but impaired for strabismic amblyopia (Chapter 8). Additionally, we found that the process of attentional disengagement and re-engagement may be impaired under amblyopic eye viewing (Chapter 6). These findings support the notion that amblyopia affects the allocation of visual attention for each eye[423]. This unequal allocation of attention for the amblyopic eye may be part of the developmental process of strabismic amblyopia.

We propose that it may be the level of attentional demand that determines whether an attentional deficit is manifest in amblyopia. The presence of a single salient cue is processed effectively with robust cueing effects[425–427] (see Table 9-1), as we also found in Chapters 6 and 7. However, deficits begin to emerge under higher attentional loads. In a conjunctive visual search task, individuals with amblyopia processed items at a slower rate (with either eye) than those without amblyopia, suggesting a bottleneck of attentional processing[423]. On an enumeration task necessitating higher level attentional processing, counting deficits begin to emerge when more than 5 targets are present, a threshold lower than for individuals without amblyopia[435]. The amblyopic eye was less effective in counting targets when compared to the fellow eye[435]. This enumeration deficit is more evident under conditions where quick attentional shifts between the eyes was required under high attentional load[436]. Similarly, both the amblyopic and fellow eyes have lower tracking thresholds in multiple-object tracking paradigms than individuals without

amblyopia[95,172]. Accordingly, we had to lower the level of difficulty from tracking 4 dots to 3 in our experimental design to accommodate these elevated thresholds for participants with amblyopia (Chapter 8). The presence of fellow eye deficits demonstrates that this is a higher-level cortical deficit of attentional processing, instead of general tracking or motion perception deficits (Chapter 8). Altogether, this leads us to speculate that attentional capacity may be reduced in amblyopia, resulting in noticeable deficits on high-demand attentional tasks in individuals with amblyopia compared to those without amblyopia.

It appears that this attentional bottleneck is present irrespective of the severity of amblyopia (see Table 9-1 for overview of relevant studies), as we did not find a correlation between any of our attentional measures in Chapters 6-8 and amblyopia severity (based on interocular acuity differences) or depth of suppression (contrast imbalance between the eyes). This is in line with other studies that did not find a correlation between behavioural deficits and severity of amblyopia[423,435] or depth of suppression[436]. The extent to which attentional processing is affected in amblyopia may however differ by etiology. We found that selective attentional tracking using the amblyopic eye was affected particularly in strabismic amblyopia (Chapter 8). In contrast, attentional allocation to each eye appears balanced in anisometropic amblyopia. These findings support a general trend that attentional deficits are more evident in strabismic than anisometropic amblyopia. Individuals with strabismic amblyopia tended to undercount with either their amblyopic or fellow eye, whereas in anisometropic amblyopia this deficit was only present when counting with the amblyopic eye[435,436]. The amblyopic eye contributes less to overall counting than the fellow eye moreso in strabismic than anisometropic amblyopia[435]. Spatial distortions elicited by cues are also stronger in strabismic/mixed amblyopia[532]. On the other hand, few studies using multiple object tracking[172] and attentional blink[535] have found no significant differences between these two etiologies. These behavioural deficits in strabismic amblyopia are supported by electrophysiological and neuroimaging evidence of reduced modulatory activity in attentional networks in strabismic amblyopia[268,380]. It remains to be seen whether this is also the case in anisometropic amblyopia, which has yet to be been studied.

Table 9-1. Behavioural data extracted from published studies involving attentional function in amblyopia. While this table focuses on the principal findings in the literature, the list of included papers is not exhaustive.

Study	Task	N	Attentional Load	Finding	Deficit (Anisometropia)	Deficit (Strabismic/Mixed)	Subtype Differences	Correlated with Severity	Treated
Roberts et al, 2016	Spatial Cueing	19 adults (6 aniso, 13 strab/mixed)	Low	Similar cueing effects (RT, accuracy) regardless of eye or group	No (FE, AE)	No (FE, AE)		No	Most
Ramesh et al, 2020	Spatial Cueing	13 children (8 aniso, 5 strab/mixed)	Low	Similar cueing effects (RT, accuracy) regardless of eye or group	No (FE, AE)	No (FE, AE)	-	No	Most
Chow et al, 2021	Spatial Cueing	12 adults (7 aniso, 5 strab/mixed)	Low	Similar cueing effect (RT) regardless of eye or group	No (FE, AE)	No (FE, AE)	No	No	Some
Hou et al, 2016	Spatial Cueing	13 adults (strab)	Low	Reduced attentional modulation in areas V1, hV4 and hMT+	-	Yes (FE, AE)	-	Yes	Most

Wang et al, 2017	Motion Salience; Saccade	8 adults (strab)	Low	Reduced activation of IPS, FEF, V5 for both tasks for AE < FE = controls	-	Yes (AE)	-	-	Yes
Thiel & Sireteanu, 2009	Line bisection	15 adults (5 aniso, 10 strab/mixed)	Low	Stronger rightward bias in strabismic/mixed (FE, AE) > anisos (AE) > anisos (FE) > controls	Yes (AE only)	Yes (FE, AE)	Strab > Aniso	-	Yes
Sharma et al, 2000	Enumeration	7 adults (strab)	High	75% accuracy enumeration threshold FE 5.6; AE 2.2 (vs 7.3 for controls)	-	Yes (FE, AE)	-	-	-
Wong-Kee-You et al, 2020	Enumeration	17 adults (8 aniso, 9 strab/mixed)	High	Larger undercounting error in amblyopia (AE>FE>controls)	Yes (FE, AE)	Yes (FE, AE)	Strab > Aniso	No	Most
Hou & Acevedo Munares, 2021	Enumeration	13 adults (6 aniso, 7 strab/mixed)	High	Larger undercounting error in amblyopia (AE>FE>controls)	Yes (FE, AE)	Yes (FE, AE)	Strab > Aniso	No	-

Ho et al, 2006	Multiple Object Tracking	18 children (10 aniso, 8 strab/mixed)	High	75% accuracy tracking threshold FE 4.0; AE 3.7 (vs 5.16 for controls)	Yes (FE, AE)	Yes (FE, AE)	No	-	Yes
Secen et al, 2011	Multiple Object Tracking	2 children, 5 adults (3 aniso, 4 strab/mixed)	High	75% accuracy tracking threshold control > FE = AE	Yes (FE, AE)	Yes (FE, AE)	-	-	Yes
Chow et al, 2018	Multiple Object Tracking	17 adults (9 aniso, 8 strab/mixed)	High	No tracking deficit in anisometropia, AE tracking deficit for strabismic amblyopia	No (FE, AE)	Yes (AE)	Strab > Aniso	No	Most
Farzin & Norcia, 2011	Eriksen flankers	10 adults (2 aniso, 8 strab/mixed)	High	Post-conflict sequence effect absent for amblyopia	Yes (FE, AE)	Yes (FE, AE)	-	No	-
Zhou et al, 2015	Stroop Task	12 children (unspecified etiology)	High	Longer RTs for amblyopia group	-	-	-	-	Yes
Tsirlin et al, 2018	Conjunctive Visual Search	10 adults (6 aniso, 4 strab/mixed)	High	Higher RT for AE = FE > controls	Yes (FE, AE)	Yes (FE, AE)	-	No	-

Aniso = anisometropia; strab = strabismus; RT = reaction time; FE = fellow eye; AE = amblyopic eye. Strab > Aniso refers to larger deficits in the strabismic than anisometropic group. “-“ indicates unspecified.

9.2 Impact of Work

Visual impairment from amblyopia has lifelong consequences that significantly impact quality of life. Vision loss in the amblyopic eye limits career choices and recreational options, and has psychosocial consequences for an affected child. For clinicians, amblyopia remains a disorder that is extremely challenging to treat once conventional occlusion therapy has reached its limits. Beyond visual acuity, a myriad of perceptual and functional deficits persist despite treatment. Suppression has proven to be a major obstacle to restoring monocular and binocular visual functioning in amblyopia. A better understanding of the underlying basis of suppression in the amblyopic brain can determine alternative avenues for broader visual rehabilitation. Our finding that the amblyopic eye continues to contribute to binocular processing even when suppressed highlights its potential to augment both perceptual experience and guidance for motor action.

In visually normal adults, visual attention plays a critical role in altering ocular dominance plasticity[600]. In this thesis, we have identified the range of attentional mechanisms affected by amblyopia. Prospective treatments can leverage the intact attentional mechanisms in anisometropic amblyopia for visual rehabilitation of monocular and binocular functions. For example, a perceptual learning protocol that altered the interocular balance of visual attention in a small group of individuals with anisometropic amblyopia produced modest improvements in visual acuity and stereopsis[576]. This mode of binocular treatment has also been used in amblyopia to improve attentional function[577,578]. Binocular treatments are a promising avenue of treatment, as a recent meta-analysis found that binocular treatments had similar efficacy to conventional monocular treatments of amblyopia[251]. The authors identified adherence rates and treatment engagement to be significant factors limiting treatment gains. A better understanding of the attentional mechanisms in amblyopia can help craft more engaging and effective binocular treatments.

9.3 Limitations and Future Work

Limitations have been detailed within each respective discussion section of Chapters 5-8. In general, we were limited by small sample sizes for each of our studies, precluding us from further analysis on factors of etiology and severity of amblyopia. Sample size is an endemic issue in the amblyopia literature, with few large-scale studies that allow for examining the subtleties of visual

deficits. Additionally, human research became a challenge with the emergence and persistence of COVID-19. Nevertheless, our findings provide a basis to further explore the prospect of an attentional bottleneck in amblyopia. Within our studies, we also included participants with mild or treated amblyopia, which could have made it more difficult to detect a deficit. Nonetheless, previous work in participants with treated amblyopia has shown that despite recovery of visual acuity in the amblyopic eye, other perceptual and functional deficits persist.

Further neuroimaging work has been planned to investigate the neural signature of suppressed visual information in the amblyopic brain. Evidence from Chapter 5 suggested that while suppressed visual information is not available to conscious visual processing, it is possible that it continues to be processed along the dorsal stream for the guidance of motor actions. This is indeed the case for individuals with normal vision, whereby images of tools suppressed from conscious awareness continued to elicit activation of areas along the dorsal stream[333]. In a collaborative effort with Dr. Robert Hess and Dr. Melvyn Goodale, we plan to use fMRI to determine whether images of tools shown to a suppressed amblyopic eye will activate the dorsal and not ventral processing stream. This project would illuminate the neural mechanisms underlying amblyopic eye suppression and guide efforts to rehabilitate visuomotor functioning in amblyopia.

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> My name is Amy Chow and I am currently finishing up my PhD thesis in the area of visual attention and amblyopia. I am looking for your permission to reprint your acuity-sensitivity plot (Figure 9 of McKee, Levi & Movshon, 2003, JOV) as part of my thesis. Please let me know if this is possible.
>
> Many thanks,
> Amy Chow
>
> ---
>
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