The adaptive elements of disparity vergence: Dynamics and directional asymmetries

by

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Authors' 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.

Statement of Contributions

I would like to acknowledge the names of my co-authors who contributed to this thesis:

- Dr. William R Bobier (Chapters 6 – 10)
- Dr. Benjamin Thompson (Chapter 6)

Abstract

Vergence eye movements alter the angle between the two visual axes, creating changes in binocular fixation distance. They are primarily stimulated by retinal image disparities, but can also be driven by inputs from ocular accommodation (accommodative-vergence) and perceived proximity (size) changes. Because of these diverse and complex sensory inputs, the neuro-motor substrates that sub-serve vergence control possess robust adaptive capabilities to manage the interactions with other oculomotor systems (accommodation). This adaptive plasticity in vergence allows for a high degree of precision in binocular alignment to be maintained throughout life in the face of constantly changing environmental demands.

The precise alignment of each eyes' fovea is a fundamental requirement for stereopsis and the perception of depth in 3 dimensions. In a significant portion of the ophthalmic clinical population, the adaptive capacities of vergence are reduced or dysfunctional, leading to difficulties focusing clearly and comfortably at near distances such as books, computer screens and other hand-held devices. Furthermore, new wearable technologies such as virtual and augmented reality increase the demand on the adaptive capacities of vergence by drastically altering the congruency of the sensory inputs to vergence. Currently, our understanding of the mechanisms that underlie this adaptive control and their behavioral limits are limited. This knowledge gap has led to conjecture in the literature regarding proper rehabilitative therapies for clinical dysfunctions of vergence control and in the optimal environmental design parameters that should provide comfortable and compelling user experiences in wearable technologies like VR and AR.

The inward (convergence) and the outward (divergence) turning of the eyes in response to retinal disparities are controlled by two separate systems and demonstrate significant directional asymmetries in their reflexive response properties. In general, reflexive divergence responses tend to be slower and longer than their convergence counter-parts. It is unclear whether the adaptive mechanisms are influence by these reflexive asymmetries. It is also unknown whether similar directional differences exist in the different adaptive capacities possessed by vergence. The purpose of the following dissertation was to characterize the effects of stimulus direction on the adaptive behavior of disparity-driven vergence eye movements with an end goal aimed at improving rehabilitation therapies for clinical populations with vergence dysfunction and providing valuable insight for the design and future development of wearable technologies like virtual and augmented reality environments.

A series of 4 experiments were conducted in order to characterize the effect of stimulus direction and the physiological limits of the adaptive behavior within the two-main disparity vergence motor controllers, fast-phasic and slow-tonic. In each study, binocular viewing conditions were dichoptic, which allowed retinal disparity to be altered while the accommodative and proximity cues were clamped. Such designs create incongruencies between the sensory stimuli to vergence and thus elicits a much stronger adaptive response for observation than would normally occur when viewing real-world objects. Eye movements were monitored binocularly with a video-based infrared eye-tracking system at 250Hz using the head-mounted EyeLink2 system. A total of 14 adult binocularly normal controls and 10 adult participants with dysfunctional convergence control (convergence insufficiency) were recruited for the main studies. 4 controls completed the first two studies, 10 additional controls completed the third and fourth studies while the 10 participants with convergence insufficiency completed the fourth study.

The results of this dissertation make four significant contributions to the current scientific literature pertaining to vergence oculomotor control and plasticity. 1) Both fast-phasic and slow-tonic vergence controllers display directional asymmetries in their general behavior and adaptive responses. 2) Reflexive fast-phasic divergence responses in controls tend to saturate at lower disparity-stimulus amplitudes than convergence under specific viewing conditions. This saturation limit is defined when the primary vergence response amplitude and peak velocity are unable to increase when the stimulus amplitude increases, suggesting saturation in neural recruitment and firing rates. Saturated reflexive vergence responses instead recruit an increased response duration (neural firing time) in order to produce larger amplitude responses. 3) Saturation in the fast-phasic divergence mechanism leads to saturation in the speed slow-tonic vergence adaptation. The function of the underlying reflexive fast-phasic response was found to be associated with the adaptive behavior of the slow-tonic mechanism, suggesting one drives the other, which is consistent with model predictions. 4) Convergence responses from individuals with convergence insufficiency are generally indistinguishable from that of the slower divergence responses of controls. These impaired convergence responses lead to impairment of the adaptive mechanisms underlying each fast-phasic and slow-tonic controller. Clinically, these results suggest that rehabilitative therapies for vergence control dysfunctions should primarily target the performance of the fast-phasic reflexive vergence mechanism. This work also suggests that improvements in adaptive capacities of vergence, known to be the mechanism under-pinning symptom reduction in these patient populations, should follow when reflexive fast-phasic responses are normalized. In terms of wearable technology, the generally limited adaptive plasticity

demonstrated within divergence responses when compared to convergence in controls, provides a behavioral explanation for the increase in symptoms of discomfort when viewing distant objects in virtual reality environments.

Future investigations should seek to determine the effects of other disparity stimulus parameters, such as contrast and spatial frequency on the adaptive behaviors of both fast-phasic and slow-tonic mechanism. Finally, the cerebellum is known to be central to the adaptation of almost every motor system and yet its role in the different adaptive capacities of disparity-vergence control remain unclear. Future studies should aim to characterize these neural structures role in the different vergence oculomotor adaptive mechanisms described here.

Acknowledgements

A wise person once wrote in their PhD dissertation acknowledgements;

"One does not accomplish a PhD in isolation, but only with the support of colleagues, friends and family." – Dr. Hendrik Walther.

I fully agree with you Dr. Walther. This work would not have been possible without the support of an extremely large group of people.

First, I would like to thank my supervisor Dr. William R Bobier. Your patience, guidance and expertise were paramount in keeping my research advancing and my mentality positive during the most difficult times.

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Some would say I have a tendency to choose the more difficult path and seek the most difficult challenges in life. For this trait, I thank my mother Janice. You taught me to always push myself and to never be satisfied with average. While the expectations I set for myself may be unrealistic at the best of times, this has always been the driving force behind my success. I was very lucky to have someone who pushed themselves this much as a role model when I was growing up. Your constant loving encouragement and true belief in my abilities were always there to pick me up when I would not meet my own (sometimes unattainable) expectations. Thank-you Mom, for teaching me that failure doesn't have to define us, it can motivate us.

My relentless curiosity I owe to my father John, who spent hundreds of hours stuck in a vehicle with me and my endless questions over the years. I cannot recall a time when I would ask a question and you would not attempt to provide an answer. Even when I wanted to know how a nuclear fusion reactor worked when I was 6 years old and it was 1am during a drive back from a baseball or hockey tournament. You taught me to expect more from myself than anyone else and to lead by example, qualities that consistently help me succeed and played no small part in the

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Dedication

This work is dedicated to all the people in my life who chose to encourage my unrelenting curiosity and passion for learning, no matter how exhausting it may have been.

For my beautiful daughter Reese, the newest and brightest light in my life. Never give up on your dreams, no matter how old you get. Let this document be proof to you that if you are willing to work your hardest and make sacrifices, any dream is possible.

"Success is nothing more than the progressive realization of a worthy goal or ideal."

- Earl Nightingale -

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List of Abbreviations

ACT – alternating cover test

ANOVA – analysis of variance

AR – augmented reality

AV – accommodative vergence

AV – vergence accommodation

BI – base-in prism

BO – base-out prism

CB – ciliary body

CI – convergence insufficiency

CISS – convergence insufficiency symptom survey

CGD – convergence gain decreasing

CGI – convergence gain increasing

DGD – divergence gain decreasing

DGI – divergence gain increasing

DoG – Difference of Gaussian's

EOM – extraocular muscle(s)

FD – fixation disparity

ICA – independent component analysis

IPD – interpupillary distance

MTT – Modified Thorington Technique

mTBI – mild traumatic brain injury

MS – main sequence

NFV – negative fusional vergence

NTAI – normalized temporal asymmetry index

NPC – near point of convergence

PA – phasic accommodation

PCA – principal component analysis

PFV – positive fusional vergence

PV – phasic vergence or fast-phasic vergence

SA – slow-tonic accommodation

SD – standard deviation

SE – standard error

SV – slow vergence

TBI – traumatic brain injury

TV – tonic vergence

VOR – vestibulo-ocular reflex

VR – virtual reality

Chapter 1
Introduction

Preface

The following dissertation was written in the form of 5 separate manuscripts that are published, in review or awaiting submission at peer-reviewed, vision science journals.

Chapter 1 provides a general introduction to the subject matter and the relevance of the dissertation aims to clinical and technology fields, while Chapters 2 and 3 provide a literature review of the main subjects and a framework for the main dissertation questions. Chapter 2 addresses the current background literature regarding the different types of horizontal disparity vergence adaptation. Chapter 3 reviews the existing literature pertaining to differences between divergence and convergence responses. Importantly, this chapter addresses the wide range of experimental conditions that have been used to define convergence and divergence and differences between them. Because the literature varies dramatically how these movements are defined, this chapter also serves to develop the experimental design and methods to be used within this dissertation.

A discussion of the pertinent literature to each thesis aim is provided in the introduction section of each manuscript chapter, while full discussions of the models of vergence control and the evolution our basic understandings of disparity-driven vergence are fully described in Appendix A. Footnotes are provided to sections in the appendix where additional explanation and detail may be required by the reader. The general methods section (chapter 5) provides a description of the apparatus and equipment used, as well calibration data from pilot studies. A description of each experiment's procedures, protocols, participants, selection/exclusion criteria and data analyses are discussed in detail in the corresponding manuscript chapters.

1.1 Vergence Eye Movements

Horizontal vergence eye movements are disjunctive in nature, meaning the eyes move in opposite directions. Their purpose is to align each eye's visual axis[*] to a specific depth and allow the object of regard to fall on the fovea of each eye (Figure 1-1). This bi-ocular alignment is precise, having horizontal

[*] While the visual axis and line of sight are different if the pupil is not centered on the optical axis we will assume that the two are equal for simplicities sake

errors of generally less than 0.15 (10 minutes of arc)[1,2]. It is these eye movements and their high degree of precision that are a fundamental building block for the sensory perception of stereopsis[3]. Simply put, vergence provides the motor substrate with which to align our eyes at the object of regard, within the range of quantitative stereopsis[4].

1.2 Unique Aspects of Vergence

Vergence is a very unique oculomotor system as it synkinetically linked to other oculomotor systems, namely accommodation. The main sensory input to vergence is retinal disparity, where the image of an object falls on two non-corresponding retinal points (Figure 1-1). Vergence alters the fixation distance in response to this disparity in order to obtain binocular motor fusion.

Vergence is also stimulated by optical blur through a synkinetic connection with the accommodative (ocular focusing) system via the output of the accommodative-vergence crosslink[5,6] (AV crosslink; Figure 1-1, Figure 0-2 and Figure 0-4). Through a reciprocal innervation, retinal disparity can also drive changes in ocular accommodation via the vergence-accommodation cross-link[7] (VA crosslink.) Combined with changes in pupil size, these 3 systems form what is classically known as the near-triad[4†]. The triad allows a coordination of accommodation and vergence for an object changing in depth. The primary function of these mechanisms' synkinetic relationship is to maintain single, clear binocular vision.

1.3 Vergence Plasticity

In order to manage these complex oculomotor interactions with accommodation and to maintain precise binocular alignment throughout life, the neural-motor control mechanisms of vergence possess robust adaptive capacities[8]. Such neural plasticity allows for rapid adaptation to changes in the sensory inputs to vergence, especially when the changes affect one input (blur or disparity) more than the other. The changes can occur slowly, like the increases in the distance between the two eyes (IPD = interpupillary distance[‡]) through the first years of life[9]; or more acutely, as one would experience when first putting on new spectacle lenses[10] or when first donning a head-mounted display like a virtual reality (VR) system[11].

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† See Appendix A p285 for background
‡ See Appendix A p281 for discussion of IPD

Unfortunately, functional deficits in vergence control and plasticity are relatively common in the general school-aged population (5-12%)[12] in the form of a clinical condition known as convergence insufficiency (CI). Individuals with CI display a poor ability to maintain proper binocular alignment to a near target (convergence), such as a book, computer screen or handle held device. The condition is hypothesized to negatively impact academic achievements and attention in children[12]. Patients with CI often complain of eye strain, blurred vision, double vision, headaches and even potentially nausea during sustained near work. CI is also one of the most frequent sequela of mild traumatic brain injuries (especially in veterans suffering blast related injuries)[13] and is also commonly seen in Parkinsonian patients[14–17§].

The adaptive mechanisms of horizontal vergence motor control are the central focus of the following dissertation. This topic has seen a resurgence in scientific interest due to poor user experience and comfort encountered in new wearable technologies like virtual and augmented reality (AR) environments and the prevalence of vergence dysfunctions resulting from traumatic brain injuries (TBI). Yet the general control strategies, physical behaviors and functional limits of these adaptive processes remain unexplored in healthy binocularly normal populations and clinical populations with vergence dysfunctions such as CI. These knowledge gaps contribute to the diversity of rehabilitation strategies used by clinicians for patients with vergence dysfunctions[18,19], while also contributing to the limitations in user comfort and experience in VR and AR environments[11].

Providing a greater characterization of the adaptive capacities of vergence will improve clinical definitions of vergence dysfunction, providing more accurate biomarkers for diagnosis and treatment of such disorders. This data will also provide some of the general framework with which the technical parameters of future VR and AR technologies should be designed.

1.4 Vergence Control

It is important to understand the general sensory inputs and motor control structure of vergence in order to comprehend the different types of adaptive plasticity that exist within it.

The models of vergence control outline 4 basic inputs that were originally introduced by Maddox in 1893[20]. The primary sensory input to vergence is retinal disparity. The second input is optical blur, which drives a vergence response through the AV cross-link. A third input arises from the perception of object proximity, or ‘awareness of nearness’. Finally, a fourth input, known as tonic vergence (TV),

§ See Appendix A p306 for a detailed review of CI

provides a physiological resting position of the eyes when all other vergence stimuli have been removed[**].

A fundamental component of all vergence models is feedback (Figure 1-1). These feedback loops are the mechanisms that allows us to maintain accurate binocular alignment[21††]. Errors in dynamic vergence movements are fed back into the system and elicit additional vergence responses until the binocular alignment is within Panums' Fusion Area[22,23]. The steady-state vergence response is precise but not perfect, therefore small steady-state retinal disparities exist (less than 10 of arc)[23]. It is these steady state errors that feedback into the motor control mechanisms that allows for the continued maintenance of a convergence posture[24‡‡].

In response to retinal disparity, the vergence system generates a reflexive response via the fast-phasic, or simply 'phasic vergence' (PV) vergence mechanism. Such responses can be elicited even if the stimuli presented to each eye are dissimilar. Because of this, the phasic vergence mechanism is often referred to as 'reflexive', in that it cannot be suppressed when coarse disparities are presented in a gap-step paradigm[25–27]. It is important to bare in mind that such responses do require the individual to attend to the target and therefore are not truly reflexive in the context of other oculomotor responses that occur even under anesthesia, like the vestibulo-ocular reflex (VOR). For ease of convention with the current literature we will use the term 'reflexive' to describe fast-phasic responses.

Phasic vergence responses are characterized by a 'phasic-tonic' or 'pulse-step' drive of neural innervation both behavirourally[28] and at the level of the oculomotor motor neurons in the medial and lateral recti[29]. The pulse response is open-loop and not under feedback control, while the step mechanism receives feedback and guides the latter portions of the reflexive vergence response to its end point[30–32].

Behavioral data has shown the open-loop pulse response of the phasic system follows a similar main sequence relationship[33,34] previously defined in saccades[35]. The main sequence is a direct (linear) relationship between the response amplitude and response peak velocity over a specified range of stimuli, whereby larger response amplitudes are accompanied by greater response velocities. There is also neurophysiological data from the midbrain premotor areas in non-human primates that support the pulse-step model of phasic vergence control[36–38] as well a main sequence relationship between vergence

[**] See Appendix A p281 for sensory inputs to vergence
[††] See Appendix A p292 for current and past theoretical control models of vergence
[‡‡] See Appendix A p286 and p292 for background

velocity and neural firing rates[§§]. The output of the reflexive 'fast-phasic' response to disparity also drives a cross-coupled change in ocular accommodation via the VA crosslink (Figure 1-1)[39,40]. Interestingly, many of the premotor vergence neurons in the macaque monkey appear to discharge for both vergence and accommodation[41].

During prolonged fixation, the initial fast-phasic vergence innervation is slowly replaced by the slow-tonic vergence mechanism (SV)[28,42,43***]. This mechanism alters the degree of tonic vergence innervation in the direction of the new fixation distance. Clinically, the slow-tonic mechanism is assessed by measuring the heterophoria, which is the vergence angle when disparity information is removed[44,45]. It represents the sum of the accommodative-vergence, proximal vergence and tonic vergence drive[†††]. Changes in the heterophoria over time therefore represent changes in the output of the SV mechanism which acts to shift tonic levels. It is not clear where, neurophysiologically, this mechanism resides; however, there is evidence that at least part of the heterophoria signal is housed in the midbrain of non-human primates[46]. Neurons identified in the macaque midbrain that alter their firing rates proportionally to the change in vergence position, so-called "tonic-cells"[37,47], may provide the physical basis for this signal[‡‡‡].

As the output of the slow-tonic vergence mechanism increases, a proportional decrease is observed in the fast-phasic output and the associated accommodative response driven by the VA crosslink[48,49]. Thus, SV provides a mechanism with which to manage the synkinetic VA crosslink with accommodation. These responses are vital for binocular coordination when the accommodative, proximal and disparity vergence stimuli are not congruent, as is the case when viewing through base-in and base-out horizontal optical prism or when retinal disparity is varied on a fixed image plane (such as in VR and AR environments, as well as in 3D movies and 3D televisions). Intrinsically then, the SV mechanism is an adaptive process. It adapts the level of TV innervation to better match the required fixation distance or disparity stimulus and allows disparity vergence to act independently from accommodation.

The PV mechanism also displays adaptive plasticity that is different from that of SV. This type of plasticity is engaged when new spectacle lenses are worn and changes in each eyes image size occur. Here, magnification of the visual environment results in PV responses that undershoot the desired target. Overtime, the PV responses are recalibrated via the internal model of the system in order to eliminate

[§§] See Appendix A p289 for main sequence and p298 for neurophysiology of fast-phasic vergence
[***] See Appendix A p302 for review of slow-tonic vergence (SV)
[†††] See Appendix A p286 for heterophoria
[‡‡‡] See Appendix A p303 for further neurophysiology of slow-tonic vergence

these end-point errors[50–54]. This is affect also holds true in VR environments when high plus-powered lenses are used in order to reduce the focusing demand on the user, since each eye's display screen is mere centimeters from the corneal surface.

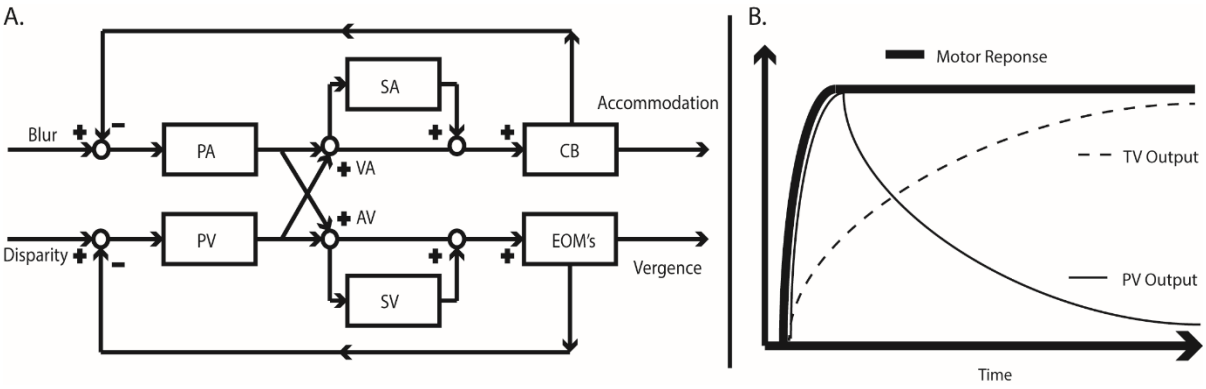

Figure 1-1: A) Simplified vergence and accommodation control model; adapted from Schor, 1992[43]. (PV = phasic vergence, PA = phasic accommodation, SV = slow-tonic vergence, SA = slow-tonic accommodation, VA = Vergence-accommodation, AV = Accommodative-vergence, EOM's= extraocular muscles, CB = ciliary body) **B):** Graphical illustration of the replacement of PV by SV as fixation time increased; adapted from Schor, 1979[55].

1.4.1 Vergence Direction

Convergence constitutes the inward turning of the eyes to shift our fixation distance nearer, while divergence involves the outward turning of the eyes to shift our fixation distance further away (Figure 1-2)[§§§]. It is well established that, behaviorally, vergence responses to retinal disparity differ based on the direction of the disparity (crossed versus uncrossed)[56–58]. Clinically, the ability to binocularly fuse horizontal prism has long been known to be directionally asymmetric, with convergence fusional ranges being much larger than divergence ranges in young health adults[59]. Furthermore, the capacity for divergence to be improved through orthoptic exercises is significantly less than what is observed in the convergence system[59]. Experimentally, PV responses to step changes in disparity have been shown to differ significantly in a variety of parameters by multiple different groups; although the differences

[§§§] See Appendix A p279 and p279 for eye moment and vergence taxonomy

reported are often not the same. Combined with the fact that disparity tuning in the visual cortices is specific to uncrossed or crossed disparity directions[60], the most current models of vergence control represent the sensory and motor aspects of divergence and convergence as completely separate neural substrates[57,58]. There is also ample evidence in the neurophysiological literature demonstrating a selectivity for convergence or divergence in the premotor neurons in the macaque midbrain[37,47,61,62] and superior colliculus[63,64], further reinforcing the neural separation of the convergence and divergence.

Vergence eye movements are typically not encountered in isolation in the natural world. A purely symmetric vergence response along the mid-sagittal plane is almost never required. Most often, a change in the depth of fixation is also accompanied by a lateral shift in gaze (Figure 1-2) and thus the motor response measured is a summation of both saccadic and vergence motor commands. Experimentally and clinically, disparity is used in isolation to provide a pure vergence stimulus and response. This allows for the observation of the disparity-driven vergence motor command alone.

In the study of phasic vergence control, responses to symmetric disparity stimuli that contained significant conjugate components were typically discarded from analysis. This was based on the earlier evidence showing a facilitation of vergence response dynamics with the addition of the saccade/conjugate response[65]. It was previously hypothesized that this saccadic facilitation of phasic vergence peak velocities was a result of a gating effect the omni-pause neurons also had on the premotor vergence burst generating cells in addition to their well-known effects on the saccadic burst neurons[37,66,67]. More recent evidence suggests that pure vergence and saccadic-vergence responses are actually the result of two separate neural processes and not the result of an additive gating-release effect form omni-pause neurons. Cell-recording data from the macaque superior colliculus has demonstrated that the vergence component of a saccadic-vergence response is actually encoded almost entirely as the difference between the two monocular signals from saccadic burst neurons[64,68].

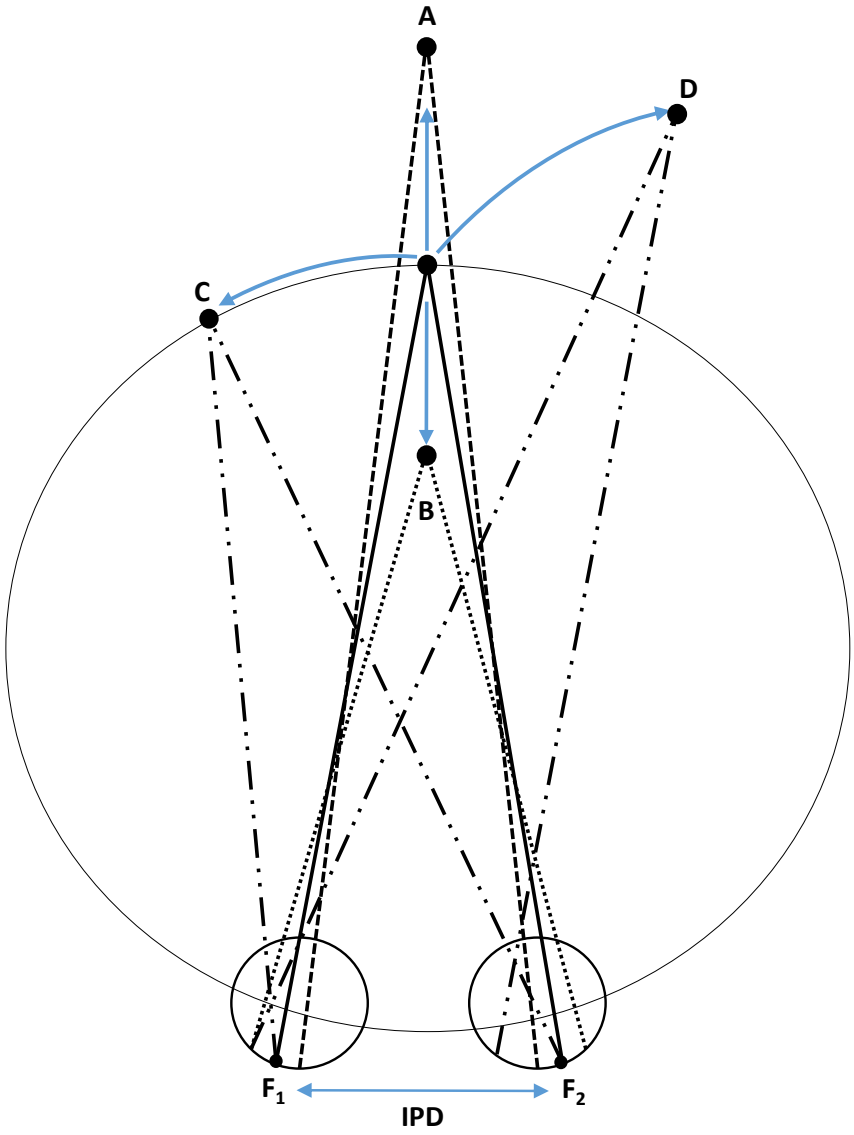

Figure 1-2: Schematic of the isovergent plane (large circle). Solid lines represent initial fixation plane/distance. An eye movement that shifts the gaze along the isovergent plane (as in C) is completely conjunctive and does not change the vergence angle. The movement depicted by 'A' is a purely divergence movement while 'B' is purely convergence. The movement depicted by 'D' is a combination of both saccadic and (di)vergence commands. IPD represents the distance between each eyes' optical center. As can be extrapolated from the illustration, as IPD increases the degree of convergence required to maintain fixation on the same isovergent plane is increased.

1.5 Directional Asymmetries of Vergence Adaptation

The behavioral and neurophysiological data clearly indicate that convergence and divergence are different systems with different behavior. It is logical then to suspect the adaptive capacities are vergence control are also influenced by disparity direction. It is curious that there is little empirical evidence describing the effects of disparity direction on the different adaptive mechanisms of vergence control.

Clinical dysfunctions of vergence control are much more common in the convergence system than divergence[59]. In VR and AR environments, uncrossed disparities induce greater user discomfort and reduced overall immersive experience, especially at larger viewing distances. These two facts suggest the adaptive control mechanisms have directional asymmetries that are very relevant to understanding clinical conditions and improving wearable technology.

1.6 Summary

The adaptive capacities of convergence and divergence are hypothesized to be functionally different. These adaptive mechanisms and their differences are important and relevant across numerous scientific fields. Currently, we know very little regarding the behavior and control mechanisms underlying these adaptive capacities. The central aim of this dissertation was to characterize the directional differences in the two main mechanisms of vergence adaptation in order to provide insight into the underlying control mechanisms and how they may become dysfunctional.

The following two chapters will review, in detail, the current literature surrounding horizontal disparity driven vergence adaptation, the known effects of disparity direction on vergence response and adaptive parameters and the effects of experimental apparatus on these measures.

Chapter 2
Vergence Adaptation

The shifting of gaze from near to far or far to near constitutes a change in the visual environment. As such, the near-triad oculomotor systems have developed multiple adaptive processes in order to optimize binocular coordination over a wide range of viewing environments. This chapter will focus on two of the primary adaptive processes known to exist in the disparity driven vergence system.

The slow-tonic vergence controller is considered an adaptive process whose effects can be measured by changes in heterophoria magnitude over time, with heterophoria providing an indirect measure of tonic innervation. The advantages of this mechanism have been discussed in the context of managing the crosslinked interactions between vergence and accommodation[****]; however, the effects are much broader reaching and complex than this and will be discussed in further detail.

Adaptive mechanisms have recently been identified in the fast-phasic response dynamics[50,69]. Adaptation in the fast-phasic mechanism constitutes a completely different type of motor/oculomotor adaptation and will be addressed separately. Of note, this form of oculomotor adaptation has been documented extensively in both upper limb reaching and saccadic eye movements; however, there is a paucity of literature exploring this adaptive mechanism in disparity driven vergence.

Here we will review what is known about both these adaptive mechanisms in the context of fast-phasic and slow-tonic vergence control models (Figure 0-4). Directional asymmetries in these mechanisms will be reviewed in the following chapter.

2.1 Slow-Tonic Vergence & Heterophoria Adaptation

The slow-tonic vergence controller represents an adaptive process that grew out of a need to manage the complex interactions of the near-triad by altering the tonic innervation bias to the disparity vergence system.

In the late 1940's and early 1950's the adaptive behavior of tonic vergence was described using optical prisms. It was shown that the vertical heterophoria would initially be altered upon the placement of vertical prism in front of one eye. With prolong wear-time, the induced vertical heterophoria would eventually return back to its baseline, pre-prism magnitude[70,71]. This change in the vertical heterophoria was interpreted as changes in the tonic levels of vergence innervation. This effect became known then as

[****] See Appendix A p284 and p285

either ‘prism-adaptation’ or ‘heterophoria adaptation’[45,72]. Heterophoria adaptation has since been truncated to ‘phoria adaptation’ by some.

Carter demonstrated that both the fixation disparity and heterophoria were altered initially after horizontal optical prism was introduced in front of one eye, but that both measures slowly returned to their baseline states with longer periods of vision through the prism[73]. Similar effects in the fixation disparity had been reported in the vertical direction in the 15 years before[2,24,70]. In these instances, the amplitude of the fixation disparity would initially be enlarged by the introduction of optical prism but would slowly return to baseline pre-prismatic levels in minutes to hours.

Others have demonstrated that changes in horizontal heterophoria, and thus tonic vergence, can occur simply through prolonged near fixation, in the absence of additional prismatic demands[74–76]. Such results imply that simply sustaining a convergence posture that is nearer than the dark vergence position is enough to induce changes in tonic innervation. In these studies, it was also observed that if monocular occlusion was maintained for a longer period of time, the induced changes in heterophoria would eventually decay, suggesting that the tonic innervation was unchanged and what was being observed was the output of a second vergence controller with a longer time constant than the fast-phasic mechanism. This was in line with what Marlow had originally reported and argued was the basis for the prolonged occlusion test to assess tonic vergence innervation[77].

Schor was the first to conceptualize the ‘slow-tonic’ mechanism as a replacement for phasic innervation and factor this mechanism into his control model of disparity vegernece[78]. This was based on his own observation that the rate of vergence angle decay after occlusion was different after a short (5-second) versus long (60-second) period of sustained fusion through horizontal. In this model (Figure 1-1 & Figure 0-4 Bottom), the fast-phasic mechanism had a short time constant (1-second) and was responsible for obtaining fusion when presented with disparity. The second, slow-tonic mechanism had a longer time constant (seconds to minutes) and was responsible for maintaining the new vergence posture[42,79]. When retinal disparity was present, the resulting motor response would be a summation of the two control mechanisms inputs[43]. Initially, the vergence response would be dominated by the fast-phasic mechanism. Over time, the slow-tonic mechanism would build up innervation and reduce the required output of the fast-phasic mechanism (Figure 2-1).

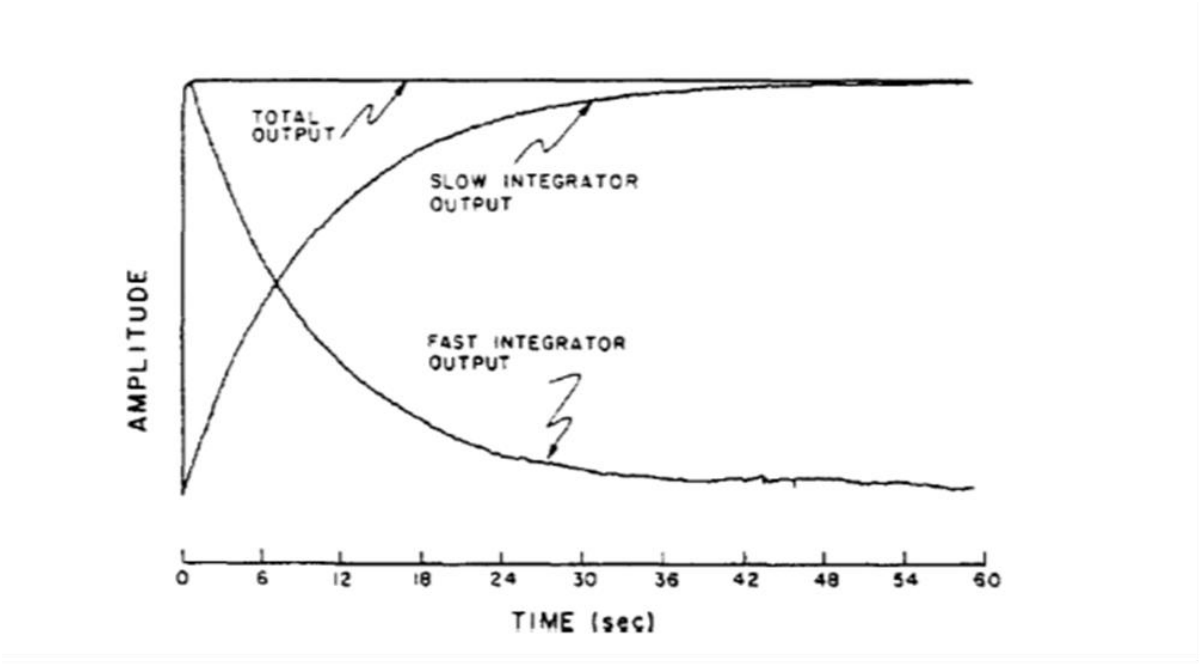

Figure 2-1: Schor's original model of the fast and slow vergence control. The total output represented the summed innervation of the fast and slow control mechanisms that contributes to the change in vergence angle. As this model was developed, the 'fast' integrator became synonymous with the transient-sustained mechanism and/or the 'pulse-step' mechanism (see Figure 0-4) and the 'slow' integrator became as the 'slow-tonic' mechanism. It is important to delineate the function of the slow-tracking vergence mechanism (not depicted here) from the slow-tonic mechanism that Schor was describing. Reprinted from Schor et al 1979[79], with permission from Pergamon Press (see Letter of Copyright Permission).

The systematic error signal that drives slow-tonic adaptation has been suggested to be both the response output of the fast-phasic system and the resulting fixation disparity that it creates. The fixation disparity serves the purpose of providing a steady-state error signal used in the negative feedback loop to prevent the vergence angle from decaying back to the tonic position. This was born out of both nature and necessity, since the neural integrator of the step component of the fast-phasic response has been observed and modelled to be 'leaky' and thus a steady state error would be required to maintain the vergence posture[28,42,43]. Therefore, slow-tonic vergence can be thought of as a kind of gaze-holding mechanism[8].

Thus far, we have defined slow-tonic adaptation pertaining in regards to heterophoria changes when viewing along the midline to either equal (congruent) or unequal (non-congruent) stimuli to the near-triad. Congruent stimuli reflect real world targets shifting in distance, requiring symmetrical changes

in focus and alignment, whereas non-congruent visual stimuli are created when viewing through horizontal optical prisms that alter vergence demand to a greater degree than accommodation and proximity. The latter visual environment is known to drive a much larger and faster change in tonic vergence in order to reduce an unnecessary drive to the accommodation, allowing for an equilibrium to be reached between vergence and accommodative innervation under the new incongruent near-triad viewing conditions[80,81]. The visual environments created in VR and AR devices currently provide little change in the blur stimulus and thus the disparities used created to produce the perception of depth are incongruent and in conflict with the accommodative demands. This effect and is known as the accommodative-vergence 'cue-conflict' by the engineers designing VR and AR systems. Such environments create functionally similar demands to that of optical prism and thus require a much stronger more robust response from the slow-tonic adaptive system in order to maintain clear, comfortable and compelling visuals experiences. Finally, the symptoms of CI seem to be related to the inability to adapt tonic vergence to nearer spaces and reduce the output of the VA cross-link via the PV response[49].

2.1.1 Reciprocal Actions of Slow-Tonic Vergence on Fast-Phasic Vergence

In addition to replacing PV innervation and reducing the crosslinked AV response, increases in SV innervation also have a reciprocal effect on future PV response characteristics.

Carter originally suggested that the fast-phasic mechanism is susceptible to rapid fatigue, ergo the purpose of the slow-tonic controller would be to replace this process with a mechanism less susceptible to fatigue[73]. He suggested vergence control as a whole is one of the first oculomotor systems to become perturbated during fatigue or injury. Empirical evidence was provided for the rapid fatigue hypothesis in 2000 when Semmlow et al. demonstrated a 20% decrease in vergence response dynamics to step changes in disparity after only 100 trials[69]. This was in contrast to saccades, where the same level of fatigue was only observed after more than 1000 trials were completed[69]. Extending this, it is logical for one to then assume that changes in slow-tonic vergence innervation would have a positive effect on the response parameters of subsequent fast-phasic responses in the same direction. The opposite would be expected for fast-phasic responses in the opposite direction of the TV change. Indeed, there is ample and consistent empirical evidence to support this [82].

Three separate groups have directly or indirectly investigated the effects of slow-tonic changes on the behavioral characteristics of the fast-phasic system. The results consistently indicate that slow-tonic vergence innervation serves not only to manage the cross-linked interactions with accommodation, but also to improve the response dynamics of future PV responses in the direction of the tonic change.

In 1999, Patel et al. observed that fast-phasic divergence responses to 2° step changes in retinal disparity (fixed accommodative demand) were slower when a prolonged convergent disparity was viewed immediately before[83]. The reflexive divergence peak velocity was reduced by 25% after 90s of convergence viewing (see Figure 2-2). Unfortunately, they did not assess heterophoria before or after, so it was unclear if the change in divergence dynamics were due to adaptation of tonic innervation via the SV mechanism, or some other neurophysiological effect. Curiously, they did not observe a significant increase (or decrease) in any of the convergence properties after prolonged disparity viewing. This is in direct contradiction to what would be expected given the previous interpretation of Carter[73] and Schor's[42,78] work. Specifically, if SV innervation adapted the tonic vergence posture in the convergent direction, one would expect that future fast-phasic convergence responses would be faster than pre-adaptation states. One explanation would be that the time course of prolonged disparity viewing was much shorter than what is typically used to engage significant changes in SV innervation (90s versus 4 minutes), so it is possible that convergence dynamics would have increased, given more time. Experimental conditions may have also played a role in these results. The measures of convergence and divergence response dynamics were made from an initial position that was significantly greater (nearer) in disparity demand than what the accommodative and proximal demands were. It will be argued in Chapter 3 that this incongruency in starting position leads to asymmetries between divergent and convergent responses due to accommodative and proximal factors. Such factors would explain why their divergence response dynamics were always faster than convergence at the baseline measure, an observation that is directly opposite to what other groups at the time were reporting[84–87]. The authors concede that the initially incongruent demand of 0 diopters of accommodation and 6° convergence could account for the divergence dynamics measuring faster than convergence. This is significant in that it demonstrates how the experimental conditions can affect the dynamics of vergence responses.

Satgunam devoted her thesis to investigating the effects of heterophoria adaptation on fast-phasic vergence responses[82]. PV convergence and divergence dynamics were measured to 4° disparity steps before and after 5-minutes of viewing of 8° of additional crossed retinal disparity. The purpose was to characterize divergence and convergence response dynamics before and after TV was convergently adapted. They observed an esophoric shift in heterophoria, indicating an increase in tonic vergence was adapted as expected. This was accompanied by in increased in convergence response dynamics. The opposite effect was observed in divergence responses. Satgunam et al. concluded that indeed changes in heterophoria and thus slow-tonic vergence had direct effects on both fast-phasic convergence and divergence responses. This is in line with what we would predict. Interestingly, the authors did not seem

to attribute this adaptive change to the neural innervation provided by the slow-tonic mechanism and instead suggested that prolonged fixation under these incongruent accommodative-vergence conditions results in a shift in disparity detection sensitivity, rectifying their results with the model presented by Patel et al.[58] that was originally introduced by Erkelens et al. in 1989[88,89]. Whether tonic changes act to alter sensory components as well as motor remains uncertain.

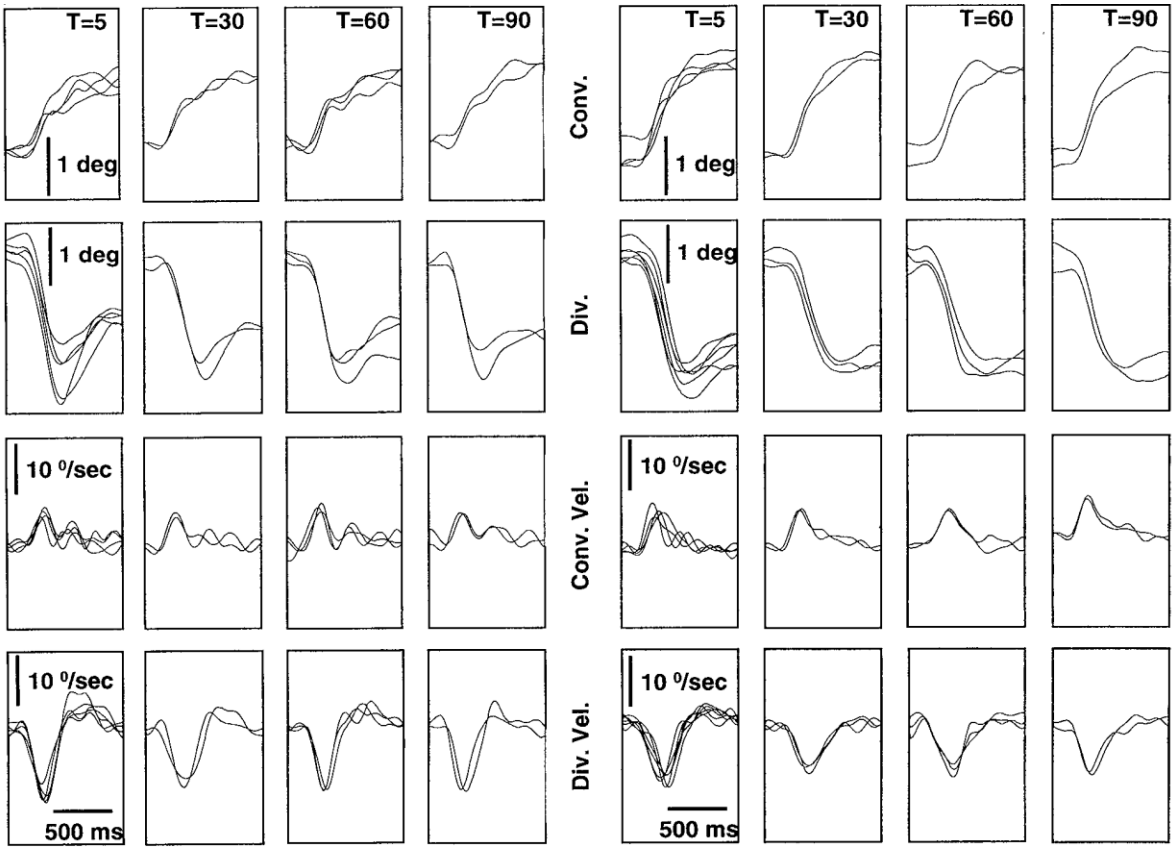

Figure 2-2: Convergence and Divergence response amplitudes (top) and velocity (bottom) from two subjects (left and right) after varying times of sustained convergence viewing (from 5-seconds to 90-seconds). Note that as the duration of convergence viewing increases (from left to right panels) divergence response velocities decrease, while convergence appears unaffected. Reprinted from Patel et al. 1999[83], with permission from Wolters Kluwer Health Inc. (see Letter of **Copyright Permission**).

Over a series of studies, the Kim and Alvarez group attempted to address the issue of starting position bias[90–93], as well as the effects of heterophoria change of fast-phasic convergence and divergence dynamics[94–96]. In this work, vergence was stimulated by step changes of disparity produced dichoptically in a haploscope at a 40-50cm viewing distance. The accommodative loop was closed (blur information available for feedback) and the blur demand was fixed at the working distance (2-2.5D or 50-40cm). In the first investigation, Kim et al. characterized the changes in fast-phasic divergence responses after tonic vergence was adapted using prolonged viewing of crossed (16°) or uncrossed (0.5°) disparity. A congruent vergence-accommodation demand would be 8.44° based on a 60mm IPD at the viewing distance of 40cm (see Appendix B). After sustained fixation at 16° of convergence, tonic adaptation was confirmed by an increase in esophoria. Following this, fast-phasic divergence peak velocities were decreased from the 16° ('near') starting position. This confirms what Satgunam reported previously[82]. The effect was not significant for divergence stimulated from the 4.5° ('far') starting position. Convergence responses were not assessed in this study; but subsequently under the same conditions, convergence peak velocities were found to be significantly increased at both the 12° and more distant 1° starting demands (see Figure 2-3)[94]. The effects appeared to be larger for the 1° initial starting demand indicating that tonic vergence changes could transfer to distances other than that where the adaptation took place. There was also a small but significant correlation between the degree of adaptation (heterophoria change) and the degree of change in the fast-phasic convergence response dynamics, indicating a commonality between the different adaptive processes. It is interesting that divergence was more affected starting from a near distance after sustained near fixation and convergence was more affected at the far starting demand under the same adapting circumstances. This was taken to suggest that the tonic innervation acts as an anchor to each of the respective fast-phasic systems[97]. Based on this evidence a second purpose of the slow-tonic mechanism is hypothesized, where the TV ("anchor") position is altered in order to optimize future responses around this new binocular fixation posture[95,96].

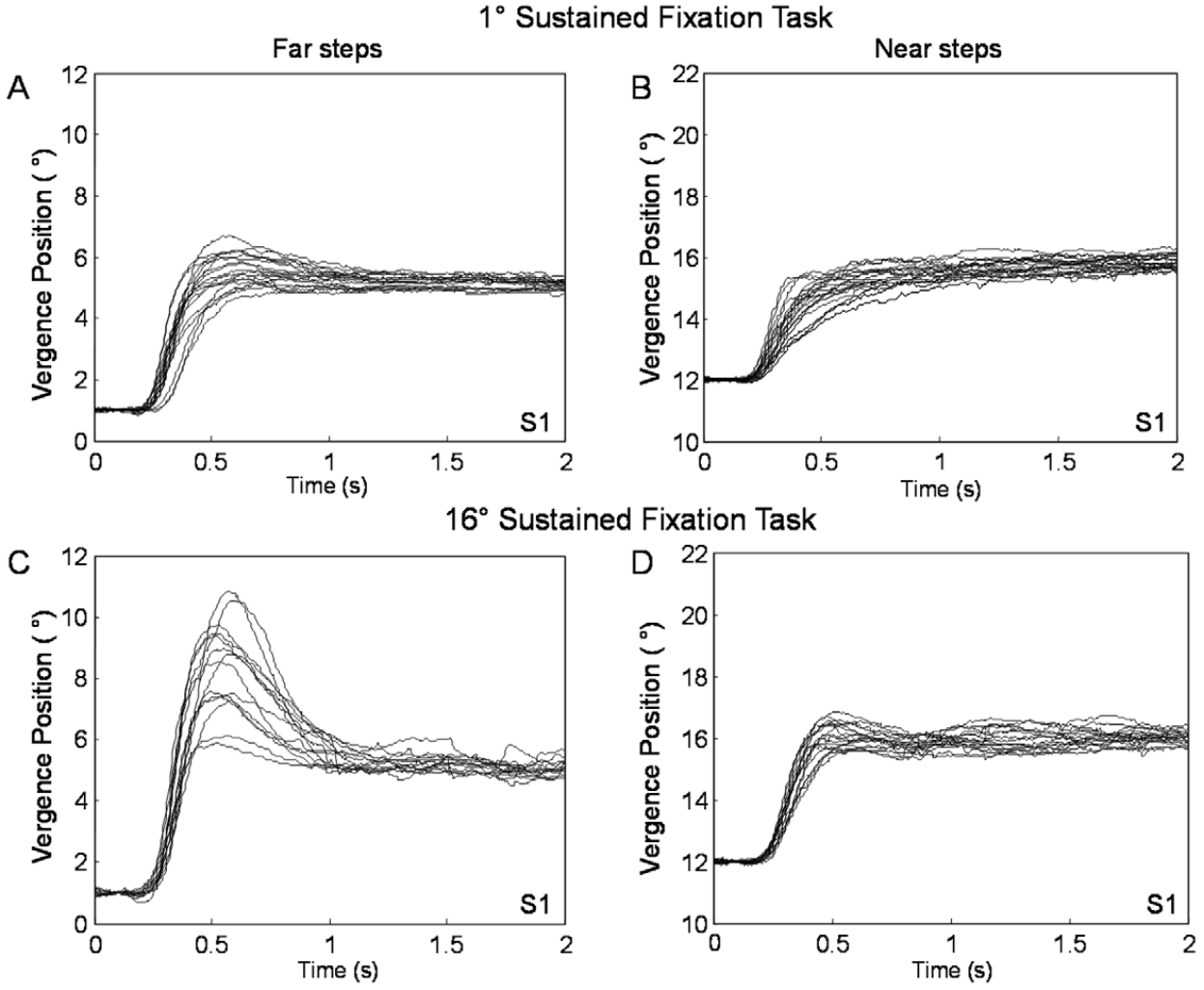

Figure 2-3: Convergence responses from a distant (left) and near (right) starting position after either prolonged far-viewing (top row) or near-viewing (bottom row). It is clear from this data that after sustained near-viewing the dynamics of convergence responses from both starting positions are significantly enhanced. Reprinted from Kim et al. 2011[94], in accordance with open access permission granted from PLOS (see Letter of **Copyright Permission**).

Evidence for the anchor effect of slow-tonic vergence can be found indirectly in other literature. Ying and Zee looked at the decay of the convergence response immediately after fixation at a vergence demand of 30° (40cm viewing and accommodative demand, dichoptically). They reported that the divergence movements (referred to as convergence relaxation) observed after occlusion were significantly

different based on the length of time fixation was held on the 30° stimulus[98]. After prolonged fixation, the velocity of the divergence was slower and tonic vergence was adapted more convergently. The reduced divergence velocities support the anchoring effect of greater SV convergence innervation. In earlier work Stephens and Jones observed that if prism fusional reserves were measured through additional prism, the reserves would be shifted in the opposite direction of the additional prism induced disparities. After prolonged viewing through the first prism however, the heterophoria fully adapted back to pre-adaptation amplitudes the fusional reserves measured clinically were unchanged from pre-adaptation levels[99,100].

2.1.2 Slow-Tonic Response Dynamics

One would expect that the response properties of the fast-phasic and slow-tonic mechanisms should share similarities if the output-input relationship between these two neural integrators as suggested by Schor[43,78,79] is correct. Specifically, it could be expected that SV would display a main sequence effect, whereby larger changes in tonic innervation in response to larger amplitudes of prolonged disparity viewing should occur at a faster rate (greater velocity of tonic innervation change). This is predicated on the fact that both PV convergence and divergence responses have been shown to exhibit this type of behavioral and neurophysiological linkage between velocity and response amplitude[101]. Schor provided evidence that the amplitude of the heterophoria change is likely proportional to the amplitude of the prolonged retinal disparity viewed, but failed to obtain an actual rate of heterophoria change that could be used in a main sequence analysis[42,78].

Sethi and North's observations of heterophoria change to various amplitudes of prism-induced disparities suggest the time constant of SV activation were different when compared between prism direction orientation (in, out, up, down). Horizontal prisms induced a faster change in tonic innervation than vertical (as evidenced by different rates of heterophoria change). They also suggested that the rate of heterophoria adaptation will be the greatest when the disparity is quickly fused and 'does not put excessive demand on the reflexive fusional vergence system'[102]. This last statement is somewhat ambiguous to interpretation, given that vertical prisms engaged a much different system with a much more limited range when compared to horizontal heterophoria capacities. On one hand, the main sequence properties of the fast-phasic system dictate that larger responses to larger disparities are innately faster. On the other hand, such responses would be predictably longer in duration and inherently more strenuous on fast-phasic system. So, this last statement was inherently contradictory.

Unfortunately, no main sequence analysis of the slow-tonic mechanism has been published as of yet. Such data would clearly be of use in the development of future models. In fact, the overall dynamic

behaviors of the slow-tonic mechanism remain largely unexplored. These knowledge gaps were the initial motivation for this dissertation.

2.1.3 Summary of Slow-Tonic Vergence Purpose

The slow-tonic vergence control mechanism appears to serve 2 purposes. The first is to replace the output from fast-phasic vergence. This mechanism allows the crosslinking between vergence and accommodation found in the fast-phasic response to be suspended and prevents fatigue from developing in the PV mechanism. This is especially important when the accommodative demands are incongruent to the disparity vergence demands, in VR and AR environments. Here, the SV mechanism provides the appropriate neural control substrate for this uncoupling of the accommodative and vergence positions.

The second purpose serves to improve future fast-phasic and slow-tonic response dynamics. Therefore, optimizing binocular coordination within a new viewing environment/distance and improving the dynamics of future shifts in this viewing distance. The results of the studies discussed above do not directly address the influence of the initial stimulus demand on vergence dynamics, even though others have suggested that there is an additional anchor effect of accommodation from over-converged (incongruent) positions[103,104]. Future work will need to take into account such effects, as they seem to have significant impacts on the dynamics of fast-phasic vergence responses, as will be outlined in the following chapter.

In keeping with the optimal control strategies required to provide both a fast and accurate neural response, the slow-tonic vergence mechanism adds an additional layer of neural control to allow for precise ocular alignment. It is not surprising then, that conditions such as CI that demonstrate significantly reduced adaptive capacities of the slow-tonic mechanism[105–108], resulting in a diverse set of ocular discomfort symptoms when attempting to fixate at nearer distances for prolonged periods of time[109–111]. It is unclear at this point whether this reduced capacity to adapt tonic vergence is an isolated oculomotor dysfunction or if this is merely a symptom of a greater disparity vergence deficiency.

The first aim of this dissertation will be to characterize the behavior of the slow-tonic mechanism over a range of disparity stimuli and construct a velocity-based main sequence for both convergence and divergence. We expect to find directional differences in the SV behavior, given that the PV systems output is modeled to be the input to the slow-tonic system and there are varying reports of directional asymmetries this mechanism as well. From this, the function and behavior of the slow-tonic mechanism will be compared with the fast-phasic systems response dynamics over the same range of disparities. This will directly explore the relationship between these two vergence control systems, which is the second

aim of this dissertation. The results of such studies will provide evidence of the appropriate biomarkers for monitoring rehabilitation of vergence dysfunctions in patient populations and will also help better define the range of cue-conflict disparities that can be presented and still adequately managed by the SV mechanism.

2.2 Fast-Phasic Vergence Adaptation

The concept of resting or tonic levels and their adaptations during prolonged viewing are unique to vergence (and accommodation). Adaptation has long been identified in reflexive saccades[112–115], but in the context of changing saccadic response gains and velocities when faced with repeated systematic errors occur in movement execution[112]. This form of adaptation is known as 'error-based' adaptation or 'sensorimotor adaptation' are a separate and distinct process from what has been discussed already in terms of changes in tonic innervation. Recent evidence has informed us that reflexive adaptations, as seen in saccades, is present in PV vergence as well[10,50–52,95,116–119].

This dissertation will focus on the error-based adaptive capacities of PV as they are known to be central to the ability of clinical populations to adapt to new spectacle lenses, specifically multifocal lenses prescribed for the condition of presbyopia[**10**], where the ageing eye loses its ability to alter its focal power. In keeping with the investigations to be conducted on slow-tonic vergence function, we aim to understand both the directional effects of disparity on the adaptation of fast-phasic vergence. The following will review the current understanding of error-based reflexive vergence adaptation and will include a brief discussion on the effects of fatigue and habituation (also known as prediction).

2.2.1 Sensorimotor Adaptation in Oculomotor Systems

Adaptation of reflexive limb and saccadic movements to external 'force-field' perturbations have formed the basis of our current models of sensorimotor adaptation in humans. In these experiments, the results of a movement are manipulated in order to induce the perception of an execution error. If these errors are repeated in a systematic way, the motor system eventually 'learns' to compensate. This motor learning recalibrates future movements over time in order to eliminate the systematic error. As described earlier, these 'error-based' adaptations in limb and saccadic eye movements are referred to as short-term 'sensorimotor' adaptations, as they are acquired and decay rapidly[120]. In saccadic research, the most common way to induce such errors is through the double-step paradigm[112]. In this design, the target of the initial reflexive saccade is shifted after the movement initiation, resulting in visual error. If repeated in the same direction and amplitude, the subsequent reflexive saccades change overtime to reduce and

eventually eliminate this systematic error. The more random the error signal, the less adaptation that occurs[121]. The theory here is that random errors are simply noise in the system and thus altering future movements based on random occurrences is a waste of neural resources. For a more detailed review of the saccadic literature in the context of what will be discussed in vergence, refer to the introduction section of Chapter 9.2.

2.2.2 Sensorimotor Adaptation in Fast-Phasic Vergence

The reflexive fast-phasic disparity vergence control system possesses adaptive capacities similar to saccades and limb movements. In contrast to the adaptive effects of slow-tonic vergence to prolonged viewing of retinal disparity, fast-phasic vergence adapts to systematic, repetitive errors in dynamic vergence responses. Here the internal model of the system guiding future responses is altered in order to eliminate the systematic bias induced experimentally Figure 0-4[††††]. Such error signals can be encountered clinically when a new spectacle lens prescription is worn for the first time. In this case, changes in magnification of the visual field occur, which can alter the disparity amplitude signal. In anisometropic prescriptions this effect is exaggerated and the adaptive changes in PV may be non-linear across the visual field. In multifocal lens technology, where the optical power of the lens is varied in different directions of gaze, these non-linear effects tend to be the greatest. As detailed in the slow-tonic adaptation section, such spectacle prescriptions induce changes in the prismatic effects in peripheral gaze, resulting in a heterophoria that is initially incomitant. While slow-tonic adaptation addresses the incomitant demand of the static vergence position, the fast-phasic system must also recalibrate its dynamic responses to quickly and accurately move the eyes to these new positions. The feedback mechanism responsible for fast-phasic vergence adaptation is likely the same efference copy-cerebellar circuit model as saccades and limbs movements[122].

2.2.2.1 Fast-phasic Adaptation Stimuli

Experimentally, fast-phasic vergence adaptation can be observed by using the same double-step stimulus principals to that used in saccadic research[112,123]. A full description of these experimental conditions can be found in the methods section of Chapter 9.3. The typical viewing conditions of the studies to be reviewed are dichoptic via a haploscope, unless otherwise noted.

Two variations of the disparity vergence double-step stimuli have been used. The first is the disparity based version of the classic double-step stimulus originally described by McLaughlin[112,124]. In

[††††] See Appendix A p300 for vergence efference copy, internal model and cerebellum review

the disparity double-step paradigm the initial step change in disparity is followed by a second shift in disparity during movement execution (between 100-200ms delay). The repetition of this stimulus results in changes in subsequent reflexive fast-phasic responses. If the second step is in the same direction as the initial disparity step, it is referred to as 'gain increasing' as it aims to generate the recruitment of a larger response from the adaptive mechanism (see Figure), whereas if it is in the opposite direction it is deemed 'gain decreasing' and aims to generate a reductive recalibration in future fast-phasic responses (see Figure 9-1B). To date, both gain increasing and gain decreasing stimuli have been used to initially crossed steps in disparity (convergence)[51], with the majority of the work focusing on gain increasing adaptation in convergence[10,51,53,95,117,118,125,126]. The adaptive capacities of fast-phasic divergence adaptation have not yet been explored using double-step stimuli.

The second paradigm uses a step-ramp stimulus, where the initial vergence step is followed immediately after by a ramp stimulus of fixed velocity for a fixed amplitude. This adaptive paradigm was only used briefly in attempt to study the adaptive elongation (gain increasing) of convergence and divergence responses[50]. The paradigm employed an initial step of 4° crossed or uncrossed disparity followed by a 16°/s ramp in the same direction. In later work, Alvarez et al. would provide evidence that suggests these adaptive effects were likely due to prediction and habituation rather than sensorimotor adaptation[127].

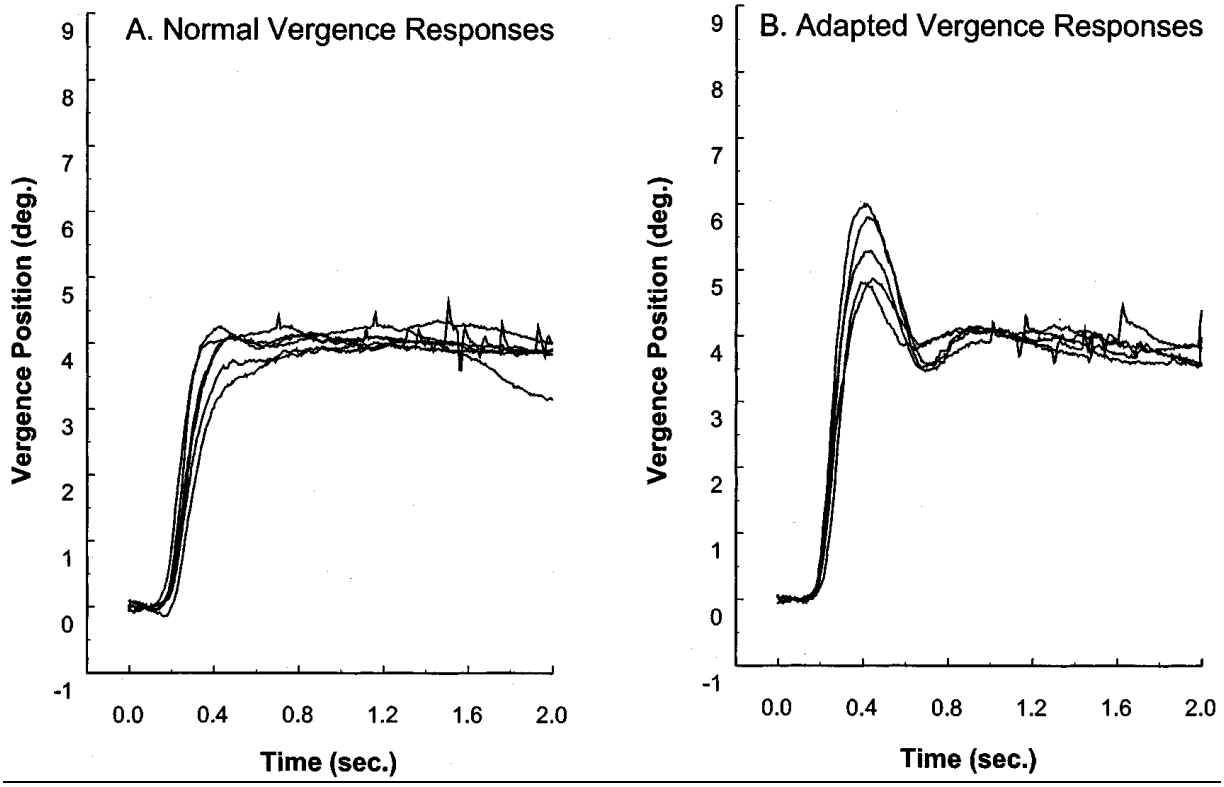

Figure 2-4: Convergence response traces to a 4° (single) disparity step stimulus from an individual before (left) and after (right) double-step adaptive lengthening using a 4° + 4° double-step stimulus. The vergence responses on the right clearly overshoot the desired response amplitude initially. The response peak velocities are also greatly increased after adaptation. Reprinted from Yuan et al 2001, with in accordance with open access permission granted from IEEE (see Letter of **Copyright Permission)**

2.2.2.2 Characteristics of Fast-Phasic Adaptation

In the first observations of fast-phasic adaptation to a step-ramp conditioning stimulus, Munoz et al. observed that convergence responses to single step stimuli had significantly larger peak velocities and pulse response amplitudes than the pre-adaptation responses after gain increasing step-ramp stimuli were viewed[50]. The adapted phasic vergence responses fell within the regression predicted by the main sequence of the baseline responses. Significant changes were observed after less than 10 double-step stimuli we viewed, leading the team to believe they had measured an adaptive process that was more cognitive in nature (conscious awareness of the stimuli) than truly a recalibration of the reflexive

responses. This was based on the time course of saccadic adaptation to double step stimuli, where 50 trials were are needed in order to reach a significant change and plateau. This was later attributed to the fact that the step-ramp adapting stimuli (instead of s double-step stimulus) provided predictive information that resulted in the convergence response changes observed post-adaptation. In general, the major conclusions from this study were that the majority of the adaptive changes occurred in the open-loop pulse response mechanism and that the adaptive capacity was active and engaged for both convergence and divergence directions. Unfortunately, comparisons were not made between the convergence and divergence directions, even though the baseline response dynamics differed from what was previously published[32,33].

Just after the study by Munoz et al. was published, a second group investigated the adaptive capacities of fast-phasic convergence to gain decreasing and increasing double-step stimuli within a head mounted display (HMD) environment[51]. Such a visual environment is similar to a haploscope, in that accommodative stimuli are fixed in the presence of a variable vergence demand; however, the HMD itself would induce significant alterations in the proximal inputs to vergence. Regardless, the authors reported that each stimulus paradigm induced the appropriate increases and decreases in response gain and peak velocity according to the adapting stimulus viewed. Extending this, they compared the adaptive behavior between the two conditions and reported differences in the strategy employed. In the gain increasing conditions, the peak velocity increase was a result of prolonged acceleration, while in the gain decreasing condition, a reduced time of acceleration duration formed the basis of the adaptive response. The authors also reported idiosyncratic changes in these main sequence relationships after adaptation; however, their phase-plane analysis was restricted to the first 150ms of the convergence response. This would have influenced the maximum amplitude of the pulse component that could be observed in participants with larger and longer firing open-loop pulse responses. Furthermore, the study was comprised of only 4 individuals and so a single outlier (as was the case in the gain decreasing condition) limited the interpretations.

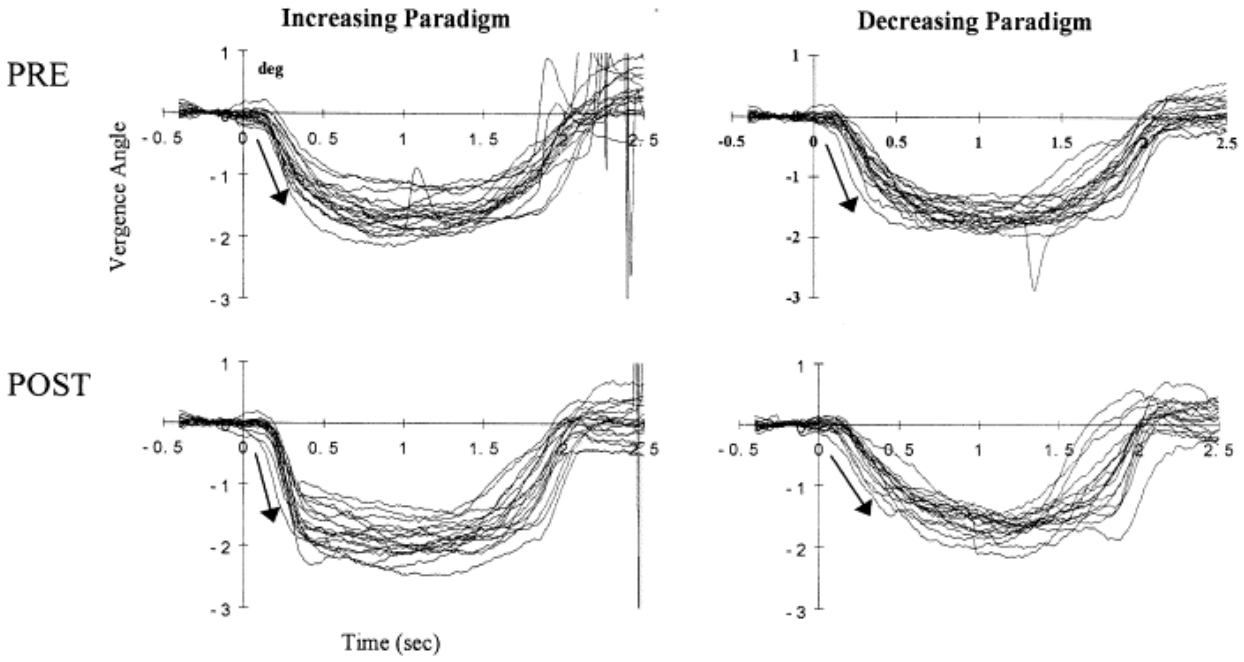

Figure 2-5: Convergence response traces to a 2° single step disparity stimulus before (pre) and after (post) double-step adaptation. In the increasing paradigm, an increase in response amplitude, peak velocity and acceleration occur, while the opposite affect is observed in the decreasing paradigm. Reprinted from Takagi et al. 2001[128], with permission from Elsevier (see Letter of **Copyright Permission**).

In a series of modelling experiments Semmlow et al. attempted to rectify their behavioral recordings with what the disparity vergence control models would predict[52,69,85,86,116,129–132]. In the first study, Semmlow et al. reasoned that convergence responses adapted a step-ramp stimulus, could only be accurately simulated if a variable time delay switch component was added between the pulse and step mechanism[52]. Later, Semmlow et al. used the same stimulus and applied an independent component analysis (ICA)‡‡‡‡ on the data to attempt to parse out the changes that occurred in either the pulse or step mechanisms of the fast-phasic vergence response[116]. In contrast to their first study, they found that better isolation of the pulse response in both baseline and adaptation trials removed the need of a variable time delay between pulse and step mechanism engagement in order for simulations to match the behavioral

‡‡‡‡ See Appendix A p297 for mathematical techniques used to separate the pulse and step response contributions

data. They further hypothesized that the changes in the step component were a result of a saturation in the recruitment of a greater pulse response. Of significance, both studies showed similar overall adaptive behavior of fast-phasic convergence responses to gain increasing stimuli; that is, an increase in the pulse response recruitment (peak velocity and amplitude). It was suggested that participants with the fastest initial peak velocities tended to show the greatest amount of adaptive increases in the PV responses, although this observation was limited by the small sample size (n=4).

It wasn't until 2007 that an investigation into the adaptive capacities of fast-phasic vergence was published. Alvarez et al. used both double-step and step ramp stimuli to adaptively modify convergence responses and found that there was strong relationship (r=0.88) between the baseline convergence pulse amplitude and the absolute amount of peak velocity change after adaptation[117].

Alvarez et al. continued to use double-step disparity experiments to investigate the adaptive capacities of fast-phasic vergence, but more in the context of its relationship to other oculomotor adaptive functions[95,118] and qualitative adaptive experiences reported by patient populations[10,126]. The results of these studies will be discussed in later sections in this chapter.

2.2.2.3 Inter-Step Stimulus Delay

In saccadic double-steps, the second error-inducing step occurs while the saccade is inflight and thus leverages the mechanism of saccadic suppression to mitigate visual feedback of the second step[133]. This is important because it is possible for participants to engage high-level cognitive processes to help in this adaptation if this feedback is available. These mechanisms represent a total different form of motor learning and confound the measurement of what is purely unconscious (reflexive) that, arguably, are the most vital for general function.

Vergence lacks the visual suppression capacity found most notably in saccades. This is likely due to the much smaller amplitude, slower velocities and longer time constants of fast-phasic vergence responses[134]. Therefore, it is crucial to keep the size of the steps being studied experimentally small in both the initial and second step. The time delay between the first and second step that has proven most successful in limiting visual feedback has been reported to be between 100-200ms. This is not surprising, given that the latency of reflexive step vergence responses is between 130-160ms. It is assumed that visual feedback is minimally available when the eyes are accelerating, just after response onset. In her initial studies of fast-phasic adaptation, Alvarez et al. used an inter-step delay of 100ms[50,95]. In later studies, after their work on prediction and habituation, the inter-step delay was extended to 200ms[10,118]. Personal communications with these authors revealed the latter delay was most optimal in limiting the

participant's conscious awareness of the second step, or at least its amplitude and direction. In our own pilot studies, we found that an inter-step delay of 175ms was the least noticeable to well-trained observes. The 175ms inter-step stimulus delay was also most effective It in masking also subjectively provided the least feedback on the second step amplitude and or direction of the second step, if the subject was aware of a second step at all. These results are consistent with what Hung et al. reported when they investigated the sensitivity of disparity detection before, during and after step convergence movements. The time period of least sensitivity was centered around the onset of convergence[134]. Therefore, setting the inter-step delay to match targeting the average vergence latency would be the best solution ideal in double-step experiments where the peak velocities are so low they do not offer a viable marker for double-step onset.

2.2.2.4 Applications and Advantages of Fast-Phasic Vergence Adaptation

It is not hard to see why plasticity in reflexive disparity-driven vergence movements is vital to the continued speed and precision of binocular alignment throughout our lives. It is easy to identify situations where changes in the sensorimotor environment would engage these processes, especially given the recent development of wearable technologies. The importance of fast-phasic vergence plasticity has already been discussed in the context of ophthalmic dispensing and spectacle lens wear, as well as the effects of fatigue and prolonged near fixation. Multifocal spectacle lens wear and anisometropia represent much more acute changes in the visual environment when compared to the effects of fatigue and near fixation. Likewise, such changes occur much more infrequently in our daily lives. One could argue then, that the paucity of data regarding the behavior and limits of this fast-phasic adaptive capacities is a reflection of this. The majority of research time has been spent understanding the unique adaptive capacities of the slow-tonic system, as it was assumed that this mechanism was the most vital given the complex near-triad cross-linked interactions. However, the lack of literature on double-step adaptation in phasic vergence limits our understanding of its global role and effect on visual perception and stereopsis.

The recent drive to commercialize new technologies like VR and AR HMD's changes this completely. In these environments significant amounts of plasticity in the sensorimotor systems are required for the user to experience comfortable immersion. Changes in the congruency of sensory inputs to the vestibular, proprioceptive and visual systems (oculomotor included) require rapid neural recalibrations, the limits of which are far from understood. The need for adaptation extends clearly into the oculomotor systems and vergence control, given the obvious changes in how retinal disparity is altered in order to simulate stereopsis[11,135–138].

It is surprising then that there is still little behavioral or neurophysiological data characterizing these processes any further than what has been discussed. Especially given the immense number of studies addressing a wide variety of motor neuroscience and sensorimotor plasticity questions using saccadic adaptation to double-step stimuli. It can be argued that full, comfortable immersion of users in such environments demands a greater amount of plasticity within the near-triad control and specifically disparity driven vergence control than it would from saccadic, pursuit or other non-vestibular related eye movements. Given this, the lack of information on fast-phasic vergence plasticity it is even more surprising. Add in the fact these technologies will have huge applications in the global video game, television, movie, education and business communication markets (and virtually anything else we do) the monetary value of this technology is immeasurable and yet astounding.

The central aim of Chapter 9 and Chapter 10 will attempt to provide better insight into the behavior and limits of fast-phasic reflexive convergence and divergence plasticity in both healthy control groups and patients with oculomotor binocular vision dysfunctions (CI). Contrasting the different behavior of fast-phasic divergence and convergence adaptation and their respective baseline directional asymmetries should provide insight into their basic control mechanisms as well.

2.2.2.5 Relationships Between Slow-Tonic and Fast-Phasic Vergence Adaptation

As alluded to in earlier sections, the majority of the research post-2002 focused on how this fast-phasic vergence plasticity is related to other oculomotor functions and not on its general behaviors and limits. It seems the relationship modelled between vergence peak velocity and change in response amplitudes to double-step stimuli by Semmlow et al. in their 2002 paper[54] sparked an interest in understanding how all these adaptive mechanisms relate and how they may be predicted.

It should be noted that between the publication of this paper in 2002 and the reemergence of this work in 2007 by Alvarez, Yuan and Semmlow et al. published multiple works addressing the effects of habituation and predictability on reflexive, fast-phasic vergence responses. Therefore, the results of the earlier double-step studies may have been influenced by these factors, something that was addressed by manipulating the temporal spacing of step stimuli and the inter-step delay time, as discussed previously.

In follow-up studies to the 2002 work by Semmlow et al., the Alvarez group first demonstrated that the change in peak velocity after convergence double-step gain increasing adaptation was directly (and very well, $r = 0.8$) correlated to the amplitude of the open-loop pulse response[117]. In 2009 they provided evidence that there was a relationship between the adaptive lengthening capacities of fast-phasic convergence and the ability for presbyopic patients to successfully adapt to progressive lenses[126]. This

work was formally published in 2017, where the authors enlarged the sample size. They also reported the ability to adapt heterophoria and the clinical measure of vergence facility were greater in multifocal lens adapters versus non-adapters[10]. This brings up an interesting question regarding the relationship between these laboratory and clinical parameters.

In parallel work, Kim and Alvarez et al. explored the relationship between heterophoria change (SV) and fast-phasic vergence plasticity. They found that both the maximum rate and amplitude of heterophoria change was well correlated to the change in peak velocity of convergence responses after double-step gain increasing conditioning[95]. These findings build on the relationship that was first suggested by Alvarez et al. in 2007, where the 'vergence transient component' could be an index to oculomotor learning, with potential generalizability to other types of motor learning[117]. There is yet to be any evidence of the latter extension.

2.2.2.6 Dysfunction & Rehabilitation of Fast-Phasic Adaptation

Understanding the function of the fast-phasic convergence adaptive mechanism may provide insight to the neurophysiological cause(s) of CI. Currently, the function of this adaptive mechanism has yet to be explored in individuals diagnosed with anomalies of vergence motor control. Assuming the vergence pulse response amplitude and peak velocity can predict the degree of adaptive plasticity in this mechanism as Semmlow[116] and Alvarez et al.[117] suggested, it is logical to then hypothesize that this adaptive capacity would be reduced in CI, given the well documented reduction in the convergence response peak velocities in this population[139–142].

Interestingly, double-step stimuli have been used (and patented, according to the authors) as a training tool in the rehabilitation of patients with CI[119]. Kapoula et al. used real world targets shifting in depth to quantify the behavior of convergence and divergence responses in participants with CI before and after 5 weeks of repetitive training with double-step gain increasing stimuli for both convergence and divergence (one 35-minute session was completed per week). They reported that initial convergence responses were more variable in the CI participants than found for controls, with greater response latencies. They did not find a difference in the mean gain or peak velocities between the two groups, which was surprising given the opposite (and repeated) findings from the Alvarez group. Subsequent to double-step intervention therapy, the CI group convergence variability reduced to match controls, while the latencies improved to levels even shorter than controls. Unfortunately, the study used the same apparatus in the weekly training sessions as it did for pre- and post-test measures. The control group also did not participate in the therapy, so it is impossible to parse out how much of the therapy effects were

due to habituation to the apparatus and stimuli itself. The shorter latencies of the CI participant's post-therapy compare to controls would suggest the effects of therapy were due to habituation and prediction and not neural rehabilitation of the fast-phasic reflexive vergence response. Furthermore, the response velocities reported in both groups are much greater than what has been reported[34,139,141,143]. Although Kapoula et al. used larger step changes in target distance than what is typically used in disparity only vergence experiments conducted in a haploscope (4° or less), the peak velocities reported were much greater than the main sequence slope generated by other groups would predict (between 30-60°/s for an 8-10° step change)[34,143]. Based on the data provided, it is likely that the convergence responses measured by Kapoula et al. in both groups contained large saccadic components. This is one of the only feasible explanations for the peak velocities reported (range 42-181°/s, mean: 73 ± 41°/s vs controls mean: 89 ± 27°/s), as the facilitatory effects of saccades on vergence peak velocity have been well documented, as well as their increased frequency with larger changes in target distance or disparity amplitude[32,66,84,88,89,144]. The latter fact is why much of the vergence research in CI is limited to below 4° step changes in disparity (the most recent literature uses 2° step changes[97,140]).

While the usefulness of double-step stimuli may very well provide a viable tool for CI rehabilitation, a greater understanding of the deficits in the adaptive control of fast-phasic vergence in these populations is needed before clinical practices should integrate such therapies into their standard training regimes. Chapter 10 attempts to address this set of open questions directly.

2.2.3 Fatigue and Habituation

PV responses can fatigue with repeated testing or habituate to constantly repeated stimuli. The resulting changes observed in the PV response characteristics can confound the adaptive sensorimotor adaptive changes that are being observed. The following section will briefly review what is known about fatigue and habituation in PV in order to provide the framework for an experimental design that will significantly limit if not eliminate their influence.

2.2.3.1 Fatigue and Habituation in Motor Systems

Changes in movement kinematics due to repetition are a common trait of nearly all motor systems[145]. Such changes can occur because of physical fatiguing of the motor end-units and neural control substrates, or through habituation. In the latter, changes in movement dynamics occur due to the perceived importance of a stimulus that is presented and the characteristics of the preceding stimuli[146,147]. The response characteristics to a novel target or stimuli are very different from those observed after the

same stimulus is sequentially presented in both limb and saccadic movements. In essence, the system begins to predict the next stimuli and tailor its responses accordingly. Repeated stimuli are suggested to lose 'importance' to the sensory system detectors and thus resulting movement kinematics become slower and longer. In a similar way, if a novel stimulus is presented after this the batch of repeated stimuli and the novel stimulus is larger, the movement response dynamics can be slower than if the novel stimulus was not preceded by smaller repeated stimuli. In this instance, the preceding stimuli 'conditioned' the response to the novel stimulus. The converse is also true if the conditioning stimuli are much larger than the novel stimulus.

2.2.3.2 Fatigue and Habituation of Fast-Phasic Vergence

Yuan and Semmlow first reported the fatiguing effects of repeated step stimuli on fast-phasic convergence responses[69]. In contrast to these findings, the same effect was not observed in sinusoidal tracking of disparity vergence targets, suggesting the slow-tracking system may not fatigue, at least not after 100 repetitions. Unfortunately, this study did not differentiate between habituation and fatigue, so the reduction in peak velocity may not have been due to fatigue at all, but a lack of other novel stimuli to keep the observer engaged.

Building on this work, Alvarez et al. investigated the conditioning effects of preceding disparity stimuli on subsequent reflexive PV convergence responses. In two studies they first observed that if a 4° crossed disparity step was presented after a series of repeated 1° crossed steps, the response dynamics were slow and movement durations longer than if the 4° step was presented in isolation or in a random order with various other step stimuli amplitudes. The opposite effect was seen in the second study if the 1° step stimulus was preceded by a series of repeated 4° step stimuli[53,127].

Prediction and habituation have also been shown to affect the latencies of convergence responses. In a second series of studies, Yuan and Alvarez observed that step changes in retinal disparity presented with predictable delays, resulted in subsequent fast-phasic convergence responses that had shorter latencies and greater initial acceleration values[129,132]. These effects were significantly diminished if the delay between trail onset and disparity step changes were randomized between 2-5 seconds[132].

Clearly, an experiment must take into account these factors in its design in order to avoid confounding. As a general guideline, less than 100 step stimuli should be presented in a single trial without a break. Each step stimulus should be as random as possible within the confines of the experimental goals in both temporal occurrence and amplitude/direction.

2.3 Summary & Open Questions

To summarize, it has been suggested that the fast-phasic vergence response characteristics are related to the capacity to adaptively lengthen responses. Specifically, the peak velocity and pulse response amplitude. It has been suggested that the adaptive capacities of fast-phasic vergence are related to the ability of slow-tonic vergence to adapt the heterophoria, at least in the convergent direction. It is interesting then, that no one has provided evidence of a relationship between slow-tonic adaptation and fast-phasic response or adaptive characteristics, although logic would dictate that such a relationship should exist given the above information. On an even more basic level, the general response behavior of slow-tonic vergence to different disparity stimuli amplitudes and directions remains largely unexplored. We aim to provide this data in the slow tonic response and then relate this to the function of the fast - phasic response.

A goal of the current dissertation is to provide a greater understanding of the relationship between these control mechanisms in binocularly normal controls. It is expected, as most models suggest, that there is a relationship between the major control mechanisms of disparity driven vergence. In order to provide a more complete foundation with which to investigate the root cause(s) of CI, a greater understanding of the relationships between these neuro-motor control functions is required.

Finally, the adaptive capacities of fast-phasic vergence remain largely unexplored, particularly in the divergence direction. The effects of binocular control dysfunctions such as CI on these adaptive capacities is also unknown. We aim to provide a better understanding of the behavior and limitations of fast-phasic vergence adaptation and the effects that CI has on these capabilities.

Chapter 3
Directional Asymmetries in Disparity Vergence

A theme in the literature reviewed thus far has been the paucity of data exploring the effects of the disparity direction (uncrossed vs crossed) on the behavior of the adaptive mechanisms. This is surprising given that the motor control units of convergence and divergence have very different response characteristics and have long been held to be controlled by separate premotor[29,36–38,62] and cortical[36,37,148–154] neural substrates. This dissertation leverages the directional asymmetries in PV responses to help elucidate the mechanisms underlying slow-tonic vergence adaptation (SV) and sensorimotor adaptation in PV.

The following chapter will first tackle the impact of the physical experimental design on the measures of disparity vergence responses. Such a review is vital as the current body of literature is not cohesive in the differences reported between convergence and divergence responses. This is because the apparatus used in each study varies dramatically and this directly affects the implied definitions of convergence and divergence. Specifically, the influence of congruency between blur, proximity and disparity demands on vergence responses observed will be addressed (see Figure 3-1). The remaining sections of this chapter will then provide a general outline of known directional asymmetries (or lack thereof) in both PV and SV responses in this context in order to refine the specific aims of the dissertation.

3.1 Phasic Convergence & Divergence

There has been a wide variety of reports over the past 6 decades in both the clinical and experimental literature describing differences between convergence and divergence responses. The range of experimental conditions used to assess phasic vergence responses has varied almost as much as the data themselves. The issue of exactly how to define what type of vergence response is being measured is rarely addressed in any detail. Chen outlines a few of the conflicting study results in their review of disparity driven vergence control[57]. The experimental conditions are vital to the interpretation fast-phasic vergence observations. This will be discussed in detail to provide the context for the experimental apparatus used in the investigations that were conducted for this dissertation.

3.1.1 Stimulus Conditions & Phasic Vergence

In their initial investigations of disjunctive eye movements Westheimer and Mitchell acknowledged that while step changes in crossed or uncrossed disparities could elicit reflexive convergence and divergence responses, such conditions were always from an initial starting position that was converged from parallel visual axes[103]. They suggested that true divergence occurred only when the eyes continued past parallel, which is almost never observed in natural settings in humans. Thus, they referred to their measurements of divergence as 'convergence relaxation'[56,103]. Toates reinforced this belief in 1974, when he argued that divergence responses were a result of the extraocular muscle and orbital tissue mechanics because the anatomical position of rest was divergent[104]. This is analogous to the convergence relaxation theory. Perhaps then, this is why the vast majority of the subsequent work focused almost entirely on convergence responses; as this subtype of disjunctive eye movements was considered to be a much more active neural process. This is also based on the anatomical and physiological positions of rest and their suggested anchoring effects on the vergence angle[155]. Convergence would be required to overcome these basil neurophysiological functions while divergence, at least toward the dark vergence/tonic vergence position[§§§§], could be achieved by a simple relaxation or disengagement of the convergence response. This also may explain why PV divergence latencies were shorter with the use of a gap stimuli when compared to no-gap stimuli, while convergence latencies were unaffected. In convergence, an active response is required in both circumstances[156]. For divergence, if the tonic innervation is pulling the eyes to a more divergent posture already, a gap-stimulus where the initial fixation target is first extinguished before the second target is presented, would not require an active neural process, at least not to initiate a divergent movement. In a no-gap stimulus, where the initial fixation target is not extinguished before the second target appears, a cognitive disengagement and generation of a voluntary motor response is required from the initial target. This disengagement could then theoretically be responsible for increasing the response latency. In this model, a motor command must always be issued in order to rotate the visual axes inward for convergence, so the latency is always consistent. Perhaps if one were to be able to diverge naturally past their anatomical or physiological positions of rest this effect could be observed in convergence. As others have pointed out though, participants are rarely ever able to divergence past 1° in a laboratory setting[33].

While the literature on fast-phasic vergence has been, at times, careful to address this idea of tonic vergence anchoring the binocular alignment, the effects of accommodative and proximal cues are

[§§§§] See Appendix A p282 for review of review of tonic vergence

generally not considered in the same context. This is surprising given that much of the vergence literature relies on dichoptic presentations of stimuli to manipulate vergence, while accommodative and proximal stimuli remain fixed. There is a large variance in the stimulus conditions used to generate disparity vergence responses in the general literature.

The concept of convergence relaxation provided by Westheimer can also be applied in the context of the various sensory inputs to vergence, whereby the proximal and accommodative demands may also act as anchors for the vergence systems. Most of the literature uses one of 3 different environments to generate and record vergence responses. The first, and most straight forward, is natural gaze shifts in depth between real world targets, such as LED lights. Here, the accommodative, proximal and disparity stimuli to vergence are all congruent (matching). This makes it difficult to separate the contributions of each to the fast-phasic responses measured. In the second and third most common conditions the disparity stimuli are varied in isolation with dichoptic image presentation, generally via a haploscope or binocular HMD. In these apparatus, authors have either left the accommodative loop closed and provided blur feedback to the system, or have attempted to mitigate blur feedback via the use of optical pinholes[34,157,158] or by using low spatial frequency difference of Gaussian (DoG) targets that have limited blur cues[43,159]. Optically imaging pinhole pupils is much more technically difficult and therefore most of the recent studies use a low spatial frequency target to impair blur feedback and assume that accommodative responses are negated. It is interesting then, that this is almost never verified within the design. The authors simply cite the original data reported by Kotulak and Schor[159] (which was on a sample of 4 well-trained observers) as the justification of these assumptions. In addition, the actual spatial frequency of these DoG targets used has varied from what was originally reported. Schor and Kotulak demonstrated negligible responses to 0.2 cycles per degree (cpd) DoG targets[159] and yet Alvarez et al. report using a 2cpd DoG target to minimize blur cues[160]. Clearly these two frequencies are very different and the work by Kotulak and Schor demonstrated obvious blur-driven vergence responses (via the AV crosslink) to targets of this spatial frequency[159]. It is possible that the latter study simply reported an inaccurate frequency in their methods which was overlooked in the review process.

Authors who allow for blur feedback to remain argue that the responses of reflexive, PV are minimally affected by accommodation in the initial 500-1000ms[27,30,86,161]. This is predicated on the fact that the response latency for vergence is roughly 150ms[57], while accommodative latencies are roughly 300-250ms[162–164]. Accommodative-vergence latencies are even longer, around 400ms[28,161,165]. The reasoning follows this example; A step change in disparity would trigger both a vergence and accommodative response. The accommodative response would lag the vergence response by at least

100ms. Now, if the accommodative response driven by the VA crosslink was enough that the blur was outside the depth of focus, an opposite accommodative response would then be generated. This would require an additional ~350ms from the first perception of the blur. The resulting accommodative and vergence response generated via the AV crosslink that would act in opposition to the initial vergence response would occur at least 500ms after the first vergence response had started. Thus, the majority of small and medium amplitude (duration) fast-phasic vergence responses are assumed to be free from opposing accommodative influences. Hung at el. provided evidence for this in 1983 when he studied the temporal characteristics of vergence responses to different combinations of blur and disparity changes[161].

The effects of different combinations of disparity, proximity and blur on fast-phasic vergence responses have been sporadically investigated in the literature. It has been shown that vergence responses to real world targets, which are congruent across all stimuli, fall within the predicted main sequence regression[166] and have similar response dynamics[34,160,166] as vergence responses to disparity only. The former is an expected finding, as the 3 different signals to vergence (proximity, blur and accommodation) all pass through the same neuro-motor controller and end-organs (extraocular muscles). It has further been demonstrated that the dynamic vergence responses of accommodative-convergence are slower and smaller when compared to similar disparity driven responses[28,157].

In contrast to this, it has been suggested that when disparity is changed in conjunction with accommodation, the vergence responses are larger and faster than when disparity is changed alone and blur cues are fixed[167] (such as when viewing through an optical prism). The authors of this study also demonstrated a difference in the main sequence slope between congruent (equal) and non-congruent (unequal) disparity and accommodative stimuli. Unfortunately, the authors failed to recognize that their experimental design also provided changes in the proximal stimuli in the congruent conditions, in addition to changes in blur cues. It is not clear if the differences recorded between the two conditions were due to one stimulus, or some combination of both (more likely). Furthermore, the starting position demand of the disparity, blur and proximity cues always started from a congruent position, so it is also not clear what these effects would be if this was not the case. This point will be elaborated upon and discussed in the next section. What is important to note is that disparity and proximity driven vergence responses are the largest and fastest, while there is also likely to be an effect of the initial congruency of the 3 major vergence stimuli (disparity, proximity and blur) on the response dynamics.

3.1.1.1 Impact of Stimulus Congruency on Vergence Measures

As pointed out, the current literature fails to address the effects of the initial vergence starting stimulus congruency and its potential biasing effects on the proceeding disparity-driven vergence responses measured. If the initial vergence demand is non-congruent with the accommodative and/or proximity stimulus, the steady state vergence position being held before the disparity step stimulus is presented includes the additional disparity vergence innervation needed to overcome the accommodative-vergence and proximity drive. This additional vergence innervation from the blur driven accommodative-vergence response would be "pulling" the vergence position back towards the accommodative plane. This is also contingent upon where the heterophoria is located in relation to the blur and disparity vergence demands.

In general, the haploscopic designs used in most studies of PV place the physical display screen at a distance of 40-50cm. From this clamped accommodative and proximity demand, disparity steps are presented from various positions, typically ranging from 1° to 16° of convergence[57]. For reference, the congruent disparity demand to a 40cm accommodative working distance is 8.44° (for a 6cm IPD, see Figure 3-1). The historical starting disparity demand in assessments of PV have then varied both distally and proximally from the fixed accommodative and proximity planes throughout an experiment. In the former case, active accommodative-convergence would add to disparity driven convergence but subtract from disparity driven divergence. In the latter case, the influence of accommodative-convergence would be reversed, adding to disparity driven divergence and attenuating disparity driven convergence. This factor would impact the measured properties of fast phasic vergence and resulting tonic changes.

As an example (see Figure 3-1) a divergence response to a 4° step in uncrossed disparity from a 12.44° starting demand likely involves a combination of mechanisms that is different than if the initial starting disparity demand was placed at 4.44° distance. In the former condition a convergence response is required to fuse the additional 4° of over-converged disparity to begin with (in reference to accommodation and proximity demands at 40cm). The divergence responses observed from this position could then include an additional relaxation of the convergence response required to fuse this additional 4° of over-converged disparity (in reference to the accommodative and proximity demands). Whereas in the latter condition the divergence responses observed would be in addition to the initial 4° of divergence that would be required to fuse the starting stimulus demand at 4.44° (under-converged in reference to the accommodative and proximity planes). In one case, the divergence response can be facilitated by the over-converged starting position (relaxation of convergence) and hindered in the opposite situation. For convergence, a similar effect could be expected under the same logic.

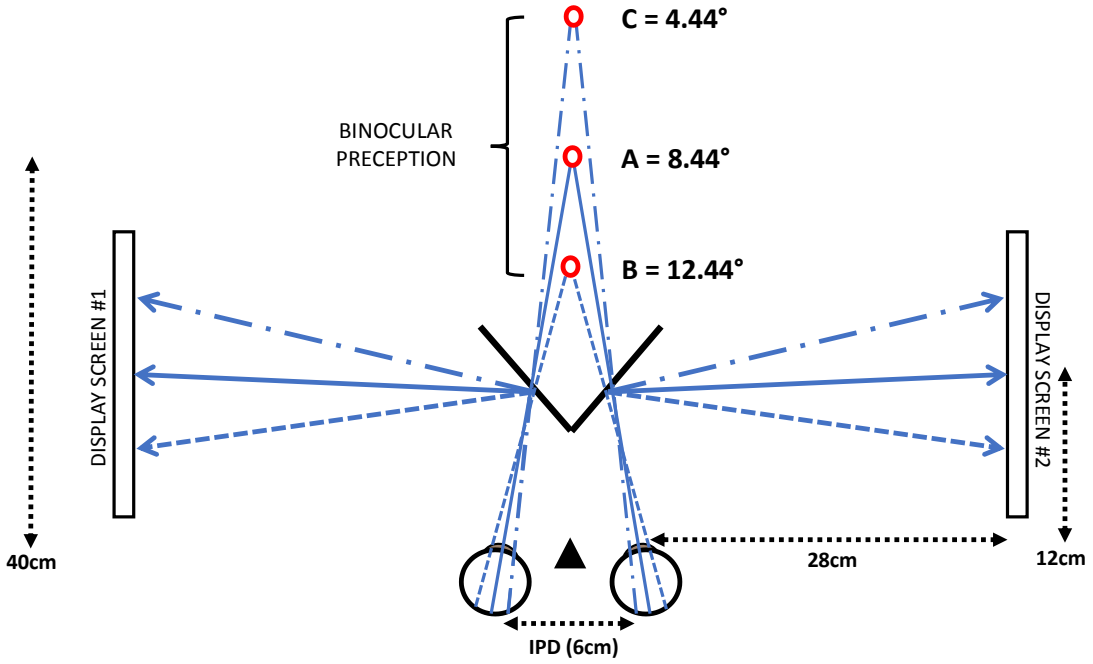

Figure 3-1: Schematic representation of the haploscopic design used in most of the disparity vergence research and the current dissertation. The thick solid black lines in the center represent 2 partially reflecting mirrors placed at 45° to each other, with a display screen set orthogonal to each eye's visual axis and placed 28cm away from the mirrors center of rotation. The corneal apex is 12cm from the mirrors' center of rotation for a total viewing distance of 40cm. This demand represents the fixed blur and proximity stimulus, which is congruent to the 8.44° disparity demand (A) based upon a 6cm IPD (the filled triangle represents the participants' nose). The projections behind the mirrors represent the participants' perceived disparity viewing distance based on the lateral placement of the image on the display screens. The even dashed lines depict a 12.44° disparity demand (B), while the uneven dashed lines represent a 4.44° disparity demand (C). These two points represent demands that are incongruent to the accommodative and proximal demands with a total optical viewing distance of 40cm. The 16.44° vergence demand used by some groups is not depicted for simplicity but would be even further converged from (B).

Examination of past investigations comparing divergence and convergence responses using a haploscopic design suggests that this variable may be operating. Alvarez et al. reported that fast-phasic

divergence responses to step changes in disparity were affected by the initial starting position but convergence responses were not. In two separate publications, Alvarez et al. observed that ramp[90,93] and step divergence responses from nearer working distances were larger and faster than what was observed at more distant starting positions. Convergence response characteristics were similar at all starting positions. The authors concluded that the divergence response variations seen with changes in initial disparity demand were due to the physical properties of the extraocular muscles. While this may be true, it likely does not fully explain the variations observed. The authors failed to address the initial congruency of the starting stimulus. Because the experimental conditions left the accommodative and proximal demands fixed at 40cm, the starting position bias observed in divergence may not represent just the non-linear physiological resistance of the extraocular muscles. Instead, this starting position bias may have been demonstrative of the congruent versus non-congruent starting demands, at least for divergence responses (see Figure 3-1).

The theoretical roots for this hypothesis of accommodative and proximal systems/stimuli 'anchoring' the vergence angle was acknowledged by one of the only groups to produce a model with separate control systems for convergence and divergence. In their study of fast-phasic vergence plasticity and heterophoria adaptation, divergence response peak velocities were much greater than what had been previously reported (see Figure 2-2)[83]. The authors argued that this result was a product of the initial incongruency between the disparity vergence demands, which varied between 4° and 6°, and the accommodative and proximal demands that were held constant at optical infinity (0 diopters). They recognize that this design may have engaged some degree of accommodative divergence, which would have facilitated greater fast-phasic divergence peak velocities when compared to what was reported by Hung et al. who used an open-loop accommodative stimuli placed at 40cm[33,34,166].

In the following discussion of fast-phasic vergence asymmetries, the congruency of the disparity, blur and proximal stimuli will be noted. This will give context to the directional differences that are reported and whether or not they may be artefactual based on the starting demand congruency. We will assume that divergence responses from an over-converged starting position would be facilitated by disparity convergence relaxation, while the under-converged condition would impair divergence response dynamics. The term "over-converged" will refer to the case where convergence is set proximal to accommodation (and proximity) and under-converged to represent the opposite, where convergence is set to a plane distal to the accommodative and proximal stimulus.

3.1.1.2 Correcting Heterophoria Dichoptically

A common modification in dichoptic apparatus aims to control for different levels of slow-tonic vergence innervation by correcting the heterophoria measured at the monitor(s) viewing distance at the beginning of the experiment[30,97,140]. It is argued that from this heterophoria corrected demand there is no initial engagement of disparity vergence system required to achieve motor fusion. In this case however, when the heterophoria is first corrected in a dichoptic apparatus, the initial disparity demand is now non-congruent to both the blur and proximity cues (depending on heterophoria magnitude). Such formats do not simulate natural binocular viewing conditions for an object being viewed at a given distance.

Alvarez et al. have reported the amplitude of heterophoria is directly related to the difference between convergence and divergence dynamics[91,96]. They claim, based on additional evidence from a more recent study[97], that the heterophoria acts like and anchor for the vergence angle in much the same way as accommodative and proximity provide an anchoring effect. Therefore, they argue that one should then be corrected before measuring fast-phasic vergence. Unfortunately, the initial study that defined this peak velocity relationship did not address the potential anchoring effects of the accommodative and proximal demands, which were clamped (with feedback available) at 40cm in a haploscope[91]. In the follow-up study data, group mean heterophoria was close to zero and so the effects of correcting these very small angle heterophoria's, if any, would have been minimal. Interestingly, in a separate study they found that fast-phasic vergence responses away from the corrected heterophoria position are slower in both convergence and divergence than when the stimulus steps towards the heterophoria position[97]. Thus, by setting the initial disparity demand to match the heterophoria position an asymmetry in velocities between convergence and divergence is created which will vary with the direction and magnitude of the subject's heterophoria. They interpreted this finding as evidence that the phoria itself will influence or "anchor" for dynamics of disparity convergence and divergence.

Consideration of incongruency provides a more parsimonious explanation, if one considers that heterophoria is a product of the accommodative, proximal and tonic inputs to vergence. Because the majority of subjects' heterophoria were near zero, the starting stimulus demand from which PV responses were measured would have been almost congruent between blur, disparity and proximity. Therefore, the facilitation of the fast-phasic response velocities observed when moving towards the heterophoria could have been due to the addition of accommodative convergence. Divergence would then be slowed by oppositely directed accommodative vergence. It is not clear if correcting the heterophoria actually provides any distinct changes in vergence dynamics at this time, especially when the amplitude is small in binocularly normal control participants.

It should also be noted that correcting heterophoria, as Alvarez et al have suggested[91,97], would also engage a change in slow-tonic vergence to this non-congruent vergence-accommodative demand. There is ample evidence in the clinical literature of this, where the heterophoria returns after wearing the appropriate correcting/relieving prisms[70,71,168]. This change in SV would influence then future measurements of fast-phasic vergence made over the duration of the experiment, as others have shown (and section 2.1.1 reviews thoroughly)[82,94]. Such effects add a significant confounding variable to the measurement of fast-phasic vergence, especially if the temporal effects of double-step adaptive stimuli are the specific outcome measure of the experiment. It is still an open question as to whether correcting the heterophoria actual affects the fast-phasic vergence responses, or if the initial congruency of the 3 stimuli are the more important confounder to control.

The set of experiments within this dissertation chose to not correct heterophoria, but rather to give prominence to an initial starting position that would be congruent in all vergence inputs. Therefore, we have chosen to define and measure all PV responses from a congruent disparity, blur and proximal starting position based on the individuals IPD. This approach was temporally stable (IPD doesn't change in adulthood, heterophoria can vary from day to day) and was easily defined for each subject. It also represents a design found in both clinical and experimental studies, where an object is binocularly fixated and vergence changes are induced by a prism.

3.1.2 Directional Asymmetries in Fast-Phasic Vergence Dynamics

There have only been a few studies that have directly compared fast-phasic convergence and divergence responses within the same experimental conditions. The majority of which have concluded that convergence response peak velocities are typically greater than divergence. This also appears to hold true for the amplitude of the open-loop pulse response. Differences in fast-phasic response latencies are generally reported as similar. As the preceding discussion has demonstrated, the initial congruency of the target demands can confound the asymmetries reported and thus are vital to consider in the context of each individual experiment that will be discussed in the following section.

Zee et al. recorded pure vergence responses along the midline and found that convergence responses were faster and generally larger than divergence responses for all of the subjects they studied[65]. In this work the stimuli were real world targets shifting in depth and thus, conclusions about the disparity driven vergence system were limited, although these were not an aim of the study. Interestingly, they did report that the divergence responses of their subjects to pure vergence stimuli had more saccadic-vergence responses compared to convergence.

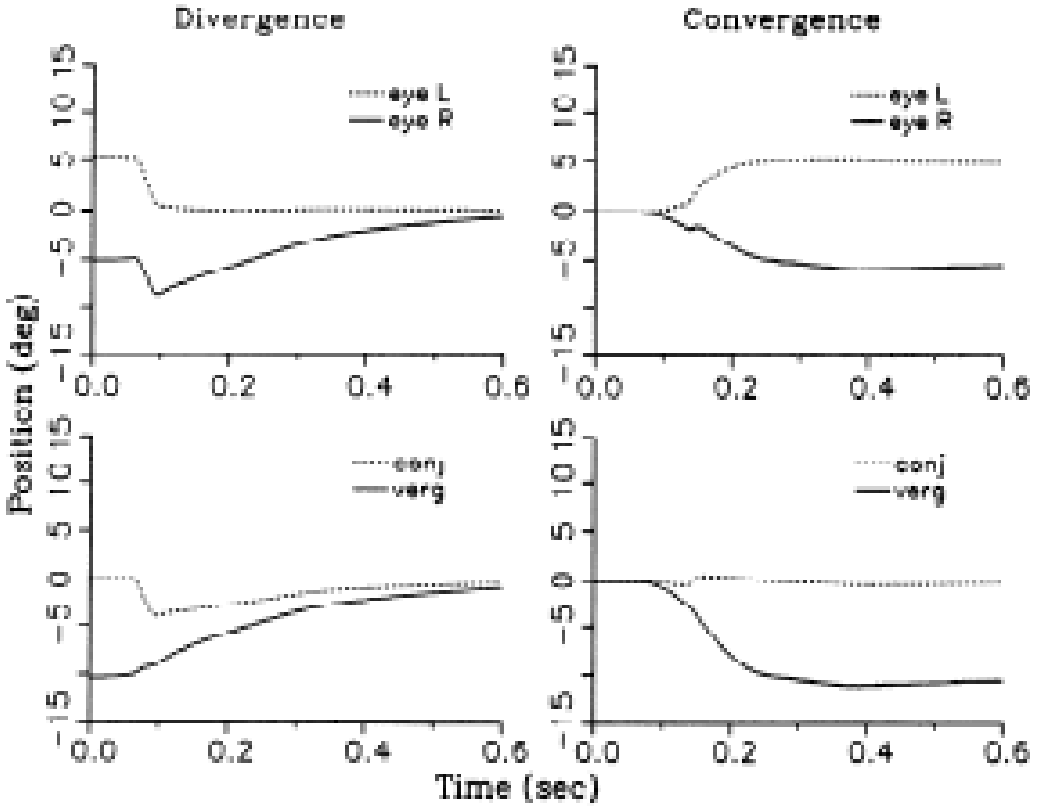

Figure 3-2: Monocular eye movement traces (top) and binocular conjugate and vergence response amplitudes to real-world targets shifting in depth by 10°. Notice that the convergence response (right) is faster and contains no significant conjugate component when compared to the divergence trace on the left, which is much slower and contains an obvious conjugate (saccadic) component during the initial stages of the response. Reprinted from Zee et al. 1992[65], with permission from Elsevier (see Letter of **Copyright Permission**).

Collewijn and Erkelens confirmed this finding in 1995 over an increased range of step stimuli (still real-world targets)[169]. Here they reported that pure divergence responses were almost never observed without some significant conjugate component. The large degree of saccadic-vergence responses to pure vergence stimuli was likely a product of the large disparity stimuli amplitudes used. They also reported that convergence and divergence responses had similar peak velocities. It is difficult to interpret this claim however, because none of their divergence responses were free from saccades. Thus, the true peak

velocity of pure divergence was not known. It is also worth noting that both studies used constantly visible targets and gaze shifts were self-initiated by the participant. Such conditions also involve other cognitive factors in motor planning and execution that may have played a role in the response dynamics measured. In an earlier study Collewijn et al. had identified directional differences in vergence response peak velocities, but concluded that these differences were idiosyncratic, as there was no observable trend in the data collected between participants[88,89].

After recording but not analyzing reflexive fast-phasic divergence responses to step changes in disparity created dichoptically with no blur information (optically imaged pinholes) for many years[31,34,143], Hung et al. eventually compared them with convergence in 1997[33]. They reported that convergence responses were faster and larger in amplitude than divergence (see Figure 0-1)[32,33]. This confirmed some of the original observations made by Hung et al. in the development of their dual-mode model of vergence control, where slow-ramp divergence responses appear to saturate at much lower disparity velocities than convergence[158].

At roughly the same time, Patel et al. reported divergence response velocities that were significantly greater than what Hung et al. had reported. As discussed over a number of preceding sections, the authors concluded that this was due to facility effects of a distant accommodative demand that was clamped. Hung et al. reported that in addition to the differences in response dynamics, the slopes of the main sequence plots were much steeper for convergence than divergence[33]. This suggests a reduced capacity for recruitment within the fast-phasic divergence response when compared to convergence. In this experimental design, feedback to the accommodative system was nullified by optically imaged pinholes. The overall proximal cues in this apparatus were not clear. The conclusions of this work were confirmed in the later work by Horng et al and the Hung group. They observed that the amplitude of the open-loop pulse response of the divergence mechanism was significantly smaller than convergence using a phase-plane analysis[32,170]. The authors suggested from this that divergence may lack a significant pulse component in the fast-phasic system.

In later work, Alvarez et al. directly addressed this question and reported high velocity, open-loop divergence responses could be elicited by step changes in retinal disparity over a series of studies[92,93,171]. In this work, the dichoptic apparatus provided both accommodative and proximal information that was clamped at ta 40cm distance. In the divergence data reported, the initial starting stimulus began at a very over-converged, non-congruent accommodative-proximity-disparity position of between 12° and 16° (a congruent disparity demand would have been approximately 8°). It is unclear if these high velocity fast-

phasic divergence responses observed were influenced by the anchoring effects of both the heterophoria and the accommodative demand.

If the data presented in the distance dependency study from Alvarez et al. is carefully assessed, it can be seen that indeed, fast-phasic vergence responses are faster than divergence when the initial starting demands are congruent[90]. To observe this, one must compare the convergence responses to 4° steps from the 8.44° - 12.44° condition to the divergence responses to the same stimulus amplitude in the 8.44° - 4.44° condition. The mean of the divergence peak velocities here are roughly 10°/s, while convergence peak velocities are consistent at all starting demands (whether congruent or non-congruent) at roughly 20°/s. It is also interesting to observe the reduced variance in the data when a congruent starting demand is used for both convergence and divergence. Finally, one more important piece of information can be harvested from this study; convergence latencies were unaffected by stimulus direction, while divergence response latencies were fastest for the over-converged starting demand that was the closest (and most non-congruent with the accommodative and proximity demands). This reduction in latency can be related to what has been discussed previously in divergence latencies and the general spring/anchoring effects of tonic vergence and the anatomical position of rest[156].

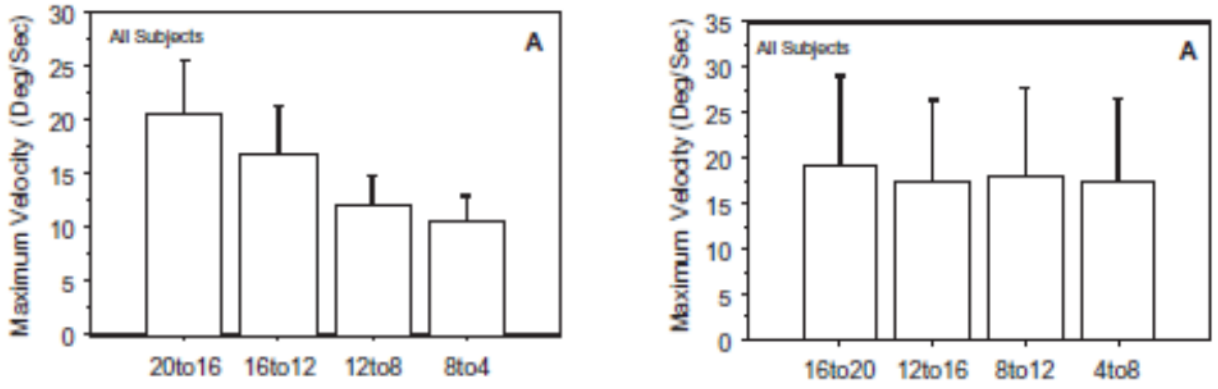

Figure 3-3: Group mean (SD) peak velocities for divergence (left) and convergence (right) responses to a4° step change in retinal disparity from different starting positions (x-axis). Clearly the divergence data shows a trend towards slower responses at further starting positions. Comparing the response velocities from a congruent starting position between directions (8-4 for divergence and 8-12 for convergence) the convergence responses are clearly faster. Note the y-axis scale difference between the two bar graphs.

Reprinted from Alvarez et al. 2005[90], with permission from Elsevier (see Letter of **Copyright Permission**).

In general, there is no consensus as to the existence of any difference in response latencies between fast-phasic convergence and divergence. Rashbass and Westheimer reported similar latencies in their original work[56,172], while Stark et al reported shorter latencies for divergence as compared to convergence[173], where as in the Hung et al work, the convergence latencies were shorter[32,33,170]. The variations in these reports is likely due to the stimulus conditions and design, namely the congruency of the initial stimulus demands.

In a larger sample size (n= 68), Tyler et al. reported similar idiosyncratic asymmetries between divergence and convergence[174]. Here, the authors used a large field random-dot stereogram with a central 1° fixation target that made 2° step changes in disparity while the peripheral disparity demand remained fixed. The dichoptic design was achieved by using commercially available crossed polarizers and a passive 3-D monitor, which provides a congruent accommodative-vergence demand at the zero-disparity setting. They found that the majority of participants had convergence responses that were either equal to or faster than their divergence responses. They also reported that divergence latencies were significantly greater than convergence, although this finding may be related to the stimulus conditions used (previous work has used central stimuli only, while the Tyler study used random dot stereograms which have additional peripheral fusion locks). Of note, the authors observed subgroups within the population that had anomalous divergence (n = 18) or convergence responses (n = 6). Here vergence responses to step changes in disparity were not observable. It is possible that these subpopulations were representative of individuals with vergence dysfunctions, given that the screening criteria used only visual acuity and random-dot stereopsis as exclusion criteria. If this were the case, it would be expected that the number of convergence anomalous participants would be the largest, since CI is the most common non-strabismic binocular vision oculomotor dysfunction[12]. Instead, the larger amount of divergence anomalous participants may be demonstrative of a subgroup with a very reduced or non-existent open-loop pulse response, as Horng et al had previously hypothesized[32].

What is consistent across the literature is a systematic bias, albeit variable in magnitude, of PV response dynamics that are greater/faster in the convergence direction. This is consistent with what was originally hypothesized based on the orbital mechanics and tonic innervations, where divergence is simply facilitated by the dark vergence innervation and the elastic properties of the EOM's[56,103,104,175].

3.1.2.1 The Peak Velocity Ratio

Kim et al and the Alvarez group investigated the relationship between fast-phasic vergence response asymmetries and the level of heterophoria measured[91,96]. The purpose of their work was to understand what role the heterophoria played in the directional asymmetries of reflexive fast-phasic vergence. Their work was spearheaded by the modelling studies of Patel et al[58,83] and the experimental data later provided by Jaschinski et al[176]. In this earlier work it was demonstrated that the fixation disparity was directly related to the difference between convergence and divergence response velocities[176], as predicted by the model put forth by Patel[58]. Because the participants in Jaschinski's study with exophoria and under-converged fixation disparities all demonstrated reduced convergence dynamics, Kim et al hypothesized that the heterophoria must play a role as well in governing the dynamics of fast-phasic vergence[91]. It is crucial to point out that in the 16 subjects examined in Jaschinski's study half (n = 8) showed little to no convergence responses to 1° step changes in retinal disparity from an initially congruent disparity, blur and proximity demand at 60cm. This is highly atypical from what was described earlier in binocularly normal controls[33,174], where divergence was generally the more difficult type of pure, symmetrical reflexive vergence response to elicit. A significant confounder in this study was the method of participant selection. The authors purposefully sought out subjects with larger fixation disparities (particularly in the under-convergence, exophoric direction) without assessing their binocular function. As it is known that larger fixation disparities are a very common finding in dysfunctions of binocular vision[177], the results of this study are likely to be convoluted by the inclusion of participants with vergence dysfunction in their assumed to be control data. It is not surprising then that Jaschinski et al. reported all of the subjects that demonstrated a large exophoria and fixation disparity had almost no measurable convergence responses.

Kim et al. attempted to quantify the effects of heterophoria on these directional asymmetries in fast-phasic vergence responses by comparing the ratio between convergence and divergence peak velocities at various starting distances. Their assumption was that the heterophoria would play a significant anchoring role and should result in directional asymmetries in fast-phasic vergence responses based on where they were measured in reference to the heterophoria. As expected, they reported a strong correlation between the ratio of convergence to divergence fast-phasic response peak velocity and the baseline amplitude of heterophoria at the 40cm testing distance[91]. This led them to conclude heterophoria did play a significant role in these response dynamics. When the methods of this study are further dissected, one major issue can be identified in the comparison of directional fast-phasic response characteristics. The authors defined 3 different types of step changes in retinal disparity within the

haploscopic design (Figure 3-1), where the accommodative and proximal demands were held constant at 40cm. The 'far steps' condition involved 4° step changes in disparity between 4.44° and 8.44°. Here the initial starting stimulus to initiate divergence is congruent, and the convergence step stimulus starts at an non-congruent, under-converged stimulus where convergence will be enhanced by accommodative and proximal parameters. Interestingly, the ratio of convergence to divergence peak velocity was always greater than 1 (mean = 1.25) for this condition, meaning fast-phasic convergence was always faster than divergence. In the 'middle steps' condition, the 4° disparity step stimuli were altered between 12.44° and 8.44°. Here, the initial convergence starting demands are congruent, while divergence is initiated from an over-converged position and would thus be enhanced by accommodative and proximal factors. Interestingly, the peak velocity ratios remained close to 1 (mean = 0.93). This is surprising because the excepted facilitation of divergence by accommodation (and likely heterophoria due to the majority of the participants being exophoric) did not result in significantly faster divergence responses. The final 'near steps' condition presented the 4° disparity steps between 16.44° and 12.44°. In this over converged position convergence-accommodative and proximal factors would enhance divergence but attenuate convergence. Here they showed the lowest average peak velocity ratio (mean = 0.88) consistent with what would be expected from the non-congruent design. What is confusing and confounding about these conditions is that convergence and divergence response velocities from congruent starting demands are not compared. If one attempts to assess this qualitatively from the data published, it is clear that when the 8.44° to 4.44° divergence step responses ('far steps') are compared with the 8.44° to 12.44° convergence steps ('middle steps') clear directional asymmetries exist that is greatly skewed towards faster PV convergence response peak velocities. This is not to say that the heterophoria does not play a role in governing the response dynamics of fast-phasic vergence responses as the authors concluded, but that the results are also likely indicative of the accommodative and proximal stimulus conditions and their anchoring effects as well. What is more interesting is that the authors assumed a 6cm IPD for all subjects. Without properly addressing differences in IPD in the haploscopic apparatus, the results are even further confounded. Participants without a 6cm IPD would be exposed to periscopic effects driving adaptation, similar to that described by Judge et al[9,178] and later by Bobier et al[179].

3.1.3 Fast-Phasic Adaptive Directional Asymmetries

As outlined in the review of fast-phasic vergence plasticity, Alvarez and Semmlow et al. put forth the hypothesis that the 'vergence transient' component could be an index to oculomotor learning[117]. This was driven by their observations that individuals with larger, faster open-loop pulse responses appeared to

be able to adapt their fast-phasic response the most[116]. In addition, the participants with the greatest amount of adaptive changes in fast-phasic reflexive vergence responses to convergence gain increasing double-step stimuli also exhibited the fastest changes in heterophoria[95].

It is interesting then that there is very little research describing the adaptive capacities of the fast-phasic divergence system. One would assume that the directional asymmetries in the fast-phasic vergence responses would provide insight into this relationship between baseline fast-phasic vergence response characteristics and their adaptive capacities. Unfortunately, Munoz et al did not compare directional differences in their small sample of participants that adaptively lengthened both fast-phasic convergence and divergence on separate days[50].

As such, one of the primary aims of this dissertation was to investigate the relationship between fast-phasic vergence plasticity and the baseline, non-adapted response characteristics. The specific hypothesis based on the studies discussed here and the cell-recording data of Mays from previous sections is synthesized in the introduction section of Chapter 9.

3.1.4 Additional Comments on Fast-Phasic Reponses Asymmetries

Extending the logic from what has been surmised thus far, studying the adaptive plasticity of fast-phasic vergence in patient populations with dysfunctional binocular oculomotor control such as CI would provide a unique opportunity to assess other functional deficits created by such disorders. Such investigations may provide additional insight into the specific control deficiencies and root causes of these dysfunctions.

Specifically, the fast-phasic convergence responses in patients with CI are known to be smaller and more sluggish than controls. It is unclear if there is any difference between the fast-phasic divergence response properties in this population. If the vergence transient component (pulse response) is a biomarker for the adaptive capacities of the system as Alvarez and Semmlow have suggested, one would expect fast-phasic vergence plasticity to be impaired in patients with CI. In addition to exploring this specific hypothesis, Chapter 10 will also compare the baseline reflexive responses of fast-phasic divergence and their adaptive capacities to that of controls.

3.2 Slow-Tonic Vergence Asymmetries

Differences in the function of slow-tonic vergence control to prolonged uncrossed and crossed disparities have a well detailed history in the clinical literature[59,81,180]. It has long been noted that the magnitude of positive fusional vergence ranges are larger than the corresponding negative fusional

ranges[*****]. Given that fusional reserves provide a clinical assessment of SV function, the directional effects of prolonged disparities appear clear.

It is curious then, that there is little laboratory evidence that confirms these findings using more repeatable, rigorous testing methods, such as infrared oculography. As described in Appendix A 0, slow-tonic vergence has been assessed using clinical metrics a great deal more than fast-phasic vergence (there is no real clinical test that assess fast-phasic responses, aside from perhaps vergence facility[†††††]). There is a paucity of literature comparing the actual response kinematics of the slow-tonic system when heterophoria is being adapted using prolonged prism or non-congruent disparity viewing. There have only been reports of such measures presented by 2 different groups, one in the 1980's (Henson, North and Sethi) and a second in the 2000's (Alvarez et al). The results of these findings are discussed at length in the preceding chapter (see section 2.1 and Appendix A section 0). From Henson et al. it was hypothesized that plasticity of heterophoria was directly related to the effort being exerted by the fast-phasic vergence system[102]. They concluded that larger and longer PV responses resulted in slower changes in heterophoria (reduced rate of SV change; see Figure 3-4). This would imply a negative slope in the main sequence regression, which is opposite from what has been observed in fast-phasic convergence[34,143]. Oddly, the data they presented appears to contradict this conclusion, at least for much of the slow-tonic convergence data. The data clearly shows that the rate of heterophoria change actually increases as the magnitude of prism that is adapted to increases. In contrast to this, the heterophoria changes to prolonged uncrossed disparities (slow-tonic divergence) was the opposite, as many of the participants were unable to fuse the larger magnitudes of base-in prism. This resulted in virtually no adaptation and a very long time constant of slow-tonic divergence to larger uncrossed disparities. A similar result was also obtained with vertical prisms. It is likely the two latter findings led to the conclusion of an inverse relationship between PV 'effort' and SV change.

[*****] See Appendix A p286 for review of clinical vergence tests
[†††††] See Appendix A p288 for further details on vergence facility

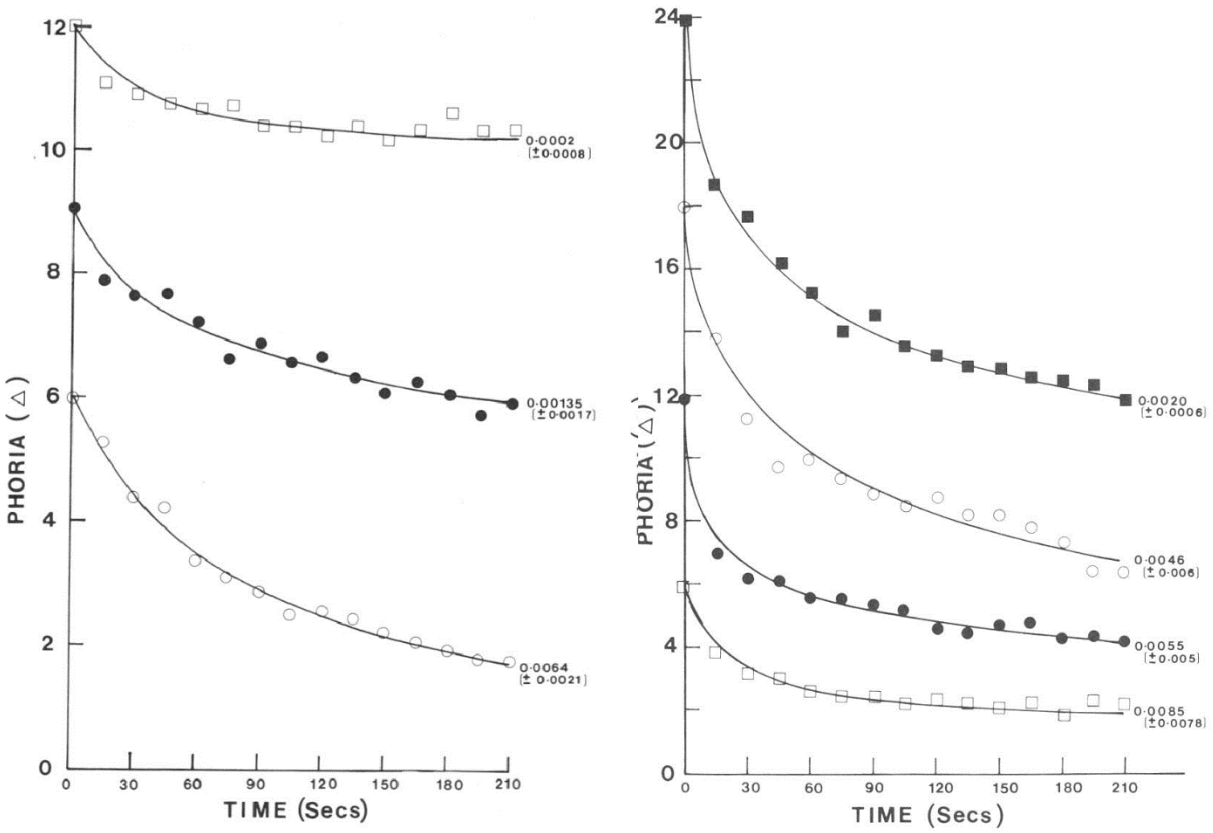

Figure 3-4: Change in heterophoria over time during prolonged binocular fusion through 3 different amplitudes of base-in (left) and 3 different amplitudes of base-out (right) optical prism. The initial heterophoria (phoria) amplitude was normalized to zero for each subject, therefore the y-intercept represents the amplitude of the optical prism being viewed through in each trial. The change in heterophoria represents adaptation of tonic vergence via the slow-tonic mechanism. In the right plot it can be seen that as the amplitude of prism increases the amplitude and apparent rate of adaptive change in heterophoria also increases. On the left graph this relationship does not appear to exist. When larger amplitudes of prism are fused it appears less adaptation has occurred and at a slower rate on the left; however the authors do report that at these optical prism demands individuals often lost the ability to maintain binocular fusion. Reprinted from Sethi et al. 1987[102], with permission from Wolters Kluwer Health Inc. (see Letter of **Copyright Permission**).

It is no surprise that Rosenfield[155] misinterpreted the conclusions of Henson, North and Sethi[81,102], when he stated their studies provided evidence of a directly proportional relationship between PV and SV response dynamics[155]. Given the clear suggestion of this hypothesis by Schor[78,79] and the current models of disparity-driven vergence[28,43,162,181], such a conclusion is quite logical; however, no empirical evidence has ever been provided.

The work by Alvarez et al in the past 10 years has demonstrated an overall relationship between the different adaptive capacities of vergence, while suggesting that said adaptive capacities (at least in the fast-phasic mechanism) could be predicted from the peak velocity and response amplitude of the open-loop pulse response of the fast-phasic system[117,118]. In addition, the degree of plasticity in each system (fast-phasic and slow-tonic) appears to also be directly related[10,91,96,118]. Yet, no one has directly compared the two systems' baseline responses (fast-phasic peak velocity and rate of slow-tonic innervation change). Again, it cannot be overstated that this is likely the most fundamental relationship that binds and forms the neurophysiological basis of the two relationships developed by this group.

3.3 Summary

At a very basic level one would expect there to be directional asymmetries in slow-tonic vergence that parallel what has been reported in the response dynamics of the fast-phasic vergence mechanisms[31,33,174]. This hypothesis is predicated on the fact that the initial stimulus demands from which PV and SV vergence responses are measured are congruent. Should the experimental design differ in this regard, it is difficult to predict what, if any, relationship would be observed between the two systems response dynamics.

If the output of the PV vergence mechanism serves as the input to the SV controller, as Schor et al have suggested[28,43], then a direct relationship should exist between the two responses. The primary aim of Chapter 6 and Chapter 7 was to first define the directional response characteristics of slow-tonic convergence and divergence to a range of prolonged disparity amplitudes in order to assess the differences (or similarities) between the main sequence relationships of each. As discussed above, care will be taken to avoid directional biases created by non-congruent starting positions. Building upon this work, Chapter 8 will compared the directional effects on both fast-phasic and slow-tonic main sequence relationships and directly compare the speed at which step changes in disparity can be fused (fast-phasic vergence peak velocity) and the rate at which heterophoria is able to adapt (via changes in the slow-tonic vergence innervation.).

Chapter 4
Objectives of Thesis

4.1 Rationale

The aims of each individual study chapter are outlined below. Combined, they aim to provide a more thorough understanding of the adaptive capacities of disparity-driven horizontal vergence eye movements and the effects of disparity direction on these capabilities. Currently, there is limited empirical data that defines the behavior of these adaptive processes. Leveraging the known asymmetries between convergence and divergence this work will aim to improve our understanding of the underlying neural dysfunctions responsible for vergence control dysfunctions, provide a general framework of the limits of these adaptive responses for the future development of VR and R environments and also provide insight into the general strategies and neural mechanisms that underpin our brains ability to adapt and control these movements.

4.2 Study #1 Objectives

A main sequence relationship has been well characterized in reflexive (fast-phasic) convergence. There is no quantitative data defining such an amplitude vs response velocity relationship in slow-tonic convergence adaptation. Study Chapter 6 will define the main sequence of slow-tonic convergence over a range of crossed disparity amplitudes typically used in clinical settings. The primary goal is to investigate whether a similar recruitment pattern seen in fast-phasic vergence exists in the slow-tonic convergence mechanism. From this the work in Chapter 7 will contrast the main sequence plots of slow-tonic convergence and divergence with an aim to better characterize their response asymmetries.

4.3 Study #2 Objectives

The pulse-step output of the fast-phasic vergence response is modeled to be the input stimulus for the slow-tonic vergence adaptation mechanism. This implies a relationship between the two systems should exist. No empirical data exists demonstrating this relationship to date. The response dynamics and main sequence relationships of slow-tonic vergence developed in Chapter 6 and Chapter 7 will then be compared to the same characteristics of the fast-phasic response properties to the same disparity stimuli in the same binocularly normal control participants in Chapter 8. The primary aim of this study chapter will be to quantitatively define the relationship between these two disparity vergence control mechanisms and assess the overall effects of disparity direction on these functions.

4.4 Study #3 Objectives

Plasticity also exists in fast-phasic vergence responses to repetitive end-point errors (double-step stimuli). The results of the preceding studies and earlier work suggest the reflexive fast-phasic divergence motor substrate is limited in both response dynamics[32,34] and neural cell populations in the premotor[36–38,47] and cerebellar[182–185] vergence regions. This hypothesis is further tested in Chapter 9 by attempting to adaptively alter both reflexive convergence and divergence using a modified-double step paradigm. This adaptive plasticity is expected to be a function of the underlying fast-phasic response.

4.5 Study #4 Objectives

The function of the fast-phasic and slow tonic convergence mechanisms have been shown to be impaired in patients with convergence insufficiency. It is unclear what effect these impairments have on the adaptive capacities of fast-phasic vergence responses. The published literature and the preceding thesis chapter results suggested that the plasticity in the disparity vergence system is directly related to the overall strength and quality (peak velocity and pulse response amplitude) of the fast-phasic reflexive vergence response. The primary aim of Chapter 10 will be to characterize and compare the adaptive capacities of fast-phasic convergence and divergence in patients with convergence insufficiency and the binocularly normal controls from Chapter 9.

Chapter 5
Methods

5.1 Study Protocol

To test these 4 main hypotheses vergence response dynamics and adaptive response properties were measured to 3 separate stimulus conditions in 2 separate control groups and one patient group with convergence insufficiency. A full description of the participants can be found in the following section 5.2. A brief summary of the 3 main stimulus conditions used follows;

- *Condition #1* –Fast-Phasic Vergence Response Dynamics

  Step changes in disparity from a congruent accommodative-vergence demand at 40cm. The disparity step amplitudes used were; 2°,4°,8°,12° crossed (fast-phasic convergence) and 2°,4°,6° uncrossed (fast-phasic divergence).

- *Condition #2* –Slow-Tonic Vergence Adaptation:

  4 minutes of prolonged viewing of the same non-congruent vergence and accommodative stimuli above (4°,8°,12° crossed and 2°,4°,6° uncrossed). The change in heterophoria was measured every 15 seconds and defined adaptation of tonic vergence via the slow-tonic mechanism. Main sequence plots were defined for convergence (additional crossed disparity) and divergence (additional uncrossed disparity) and compared.

- *Condition #3* – Fast-Phasic Vergence Adaptation

  Double-step changes in retinal disparity (2° ± 1.5°) in both crossed and uncrossed directions from a congruent accommodative-vergence starting demand. The change in fast-phasic vergence response dynamics compared to the pre-adaptation responses defined the adaptive response of fast-phasic vergence.

A complete description of the conditions and protocols used in each experiment can be found in the methods section of each manuscript chapter, as well as the participant sub-groups that completed each.

5.2 Study Participants

Study participants were recruited from the University of Waterloo undergraduate and graduate student population. Informed consent was received from each participant at the beginning of each study after both verbal and written explanations of the study aims and procedures were provided. The study

protocols adhered to the tenets of the Declaration of Helsinki and received approval from the University Of Waterloo Office Of Research Ethics (ORE #20258, #20873 & #21512).

A total of 24 participants were involved in this dissertation. 3 separate cohorts of participants were recruited for the main studies. In the first 2 studies, 4 binocularly normal control subjects were recruited. These participants were screened with clinical optometric tests to ensure normal binocular oculo0motor function (summary of screening results in Table 5-1 and also were able to the maximum disparity stimuli in both directions. In the third study, where the disparity step amplitudes were significantly smaller, 10 binocularly normal controls were recruited and screened. In the final study, 10 participants with convergence insufficiency were recruited. The latter two groups screening results can be found in Chapter 10, along with the criteria used to define CI.

Subject	MSRE	Age	Stereopsis ('arc)	Facility (cpm)	Phoria (6 m)	Phoria (40 cm)	NPC (cm)	PFV	NFV	CISS Score
s1	-6.00	25	60	18	-1	-2	2	40	-25	2
s2	-1.50	29	30	0	0	1	0	40	-20	5
s3	-0.25	26	60	16	1	0	2	30	-18	7
s4	-4.00	32	30	21	1	-1	0	35	-20	0

Table 5-1: Summary of 4 control participants that completed the studies in Chapter 6 and Chapter 7. MSRE = mean sphere refractive error, NPC = near point of convergence.

5.3 Dichoptic Apparatus

In order to isolate the response properties of the various disparity driven vergence mechanisms, each experiment was conducted using an identical haploscopic design. In this apparatus, the accommodative and proximity stimuli remain fixed/constant, while the disparity demand can be varied. The accommodative stimulus remained constant and feedback was available to the blur-driven accommodative system. The accommodative-loop was intentionally left closed in order to generate the strongest adaptive response possible in the slow-tonic vergence mechanism. The specific design and stimulus parameters have been developed in detail in section 3.1.1.

5.3.1 Haploscopic Design

A schematic representation of the haploscope is given in Figures 3-1, 6-2 and 8-2 and the actual apparatus is depicted in Figure 5-1. Two 7-inch LCD monitors (Lilliput®) were placed at each end of the haploscope arms. The total viewing distance of the monitor was 40cm. This represents the proximal and accommodative demands. Two infrared-passing mirrors were placed orthogonally to each other, 12cm from the participant. Each LCD monitor was then paced 28cm from these mirrors, for a total optical path distance of 40cm. Infrared-passing mirrors were required for the head-tracking software of the eye-tracker to operate (Figure 5-1). The participants head was immobilized using a custom chinrest. The entire haploscope was placed inside an enclosure in order to eliminate other peripheral vergence cues or distractions. The total distance from the chinrest to the back surface of the enclosure was 40cm so that the infrared head tracking sensors could be placed at the same distance as the monitors and so that the proximal distance cues of the back of the enclosure matched the total optical viewing distance of each monitor.

IPD was corrected for at the beginning of each experimental trial by adjusting the center of rotation of each mirror to fall along the visual axis, given a 40cm viewing distance. Because the mirrors were placed 12cm from the corneal plane, the IPD between mirror centers was less than the IPD of the eyes center of rotation. A conversion was made for each participant's near IPD, measure manually with a ruler, to the appropriate IPD required for the mirrors. See Appendix B for calculations of the mirror IPD conversions. While it is true that changing the distance between the mirrors effectively alters the distance from the mirrors to the LCD monitors, the size of the change was so small (less than 1cm between all subjects) that this change in optical viewing distance would have minimal effect of the proximal and accommodative demands presented between participants.

In order to provide a congruent disparity, accommodative and blur stimulus to the participant, each arm of the haploscope was rotated in order to produce the required vergence demand, based on the individuals IPD. A scale indicated the angular rotation of each arm in degrees. As larger IPD's require a greater degree of convergence to achieve binocular alignment at 40cm than would smaller IPD's, the initial congruent vergence starting demand was calculated for each individuals IPD (see Table 5-2 for a summary and Appendix B for calculations of conversions). Because the mirrors' centers of rotation were not coincident with the eyes' center of rotations another conversion was required in order to determine the appropriate initial haploscopic arm vergence demand required to produce a congruent accommodative, proximity and vergence demand at 40cm for a given IPD. Previous work in our lab has shown that this conversion factor is ~1.2x, meaning that for every 1° of vergence required in real-space, 1.2° of

haploscopic arm rotation is required to produce the same vergence effect[186]. This conversion is summarized as the 'Initial Haploscope Vergence Demand' in Table 5-2.

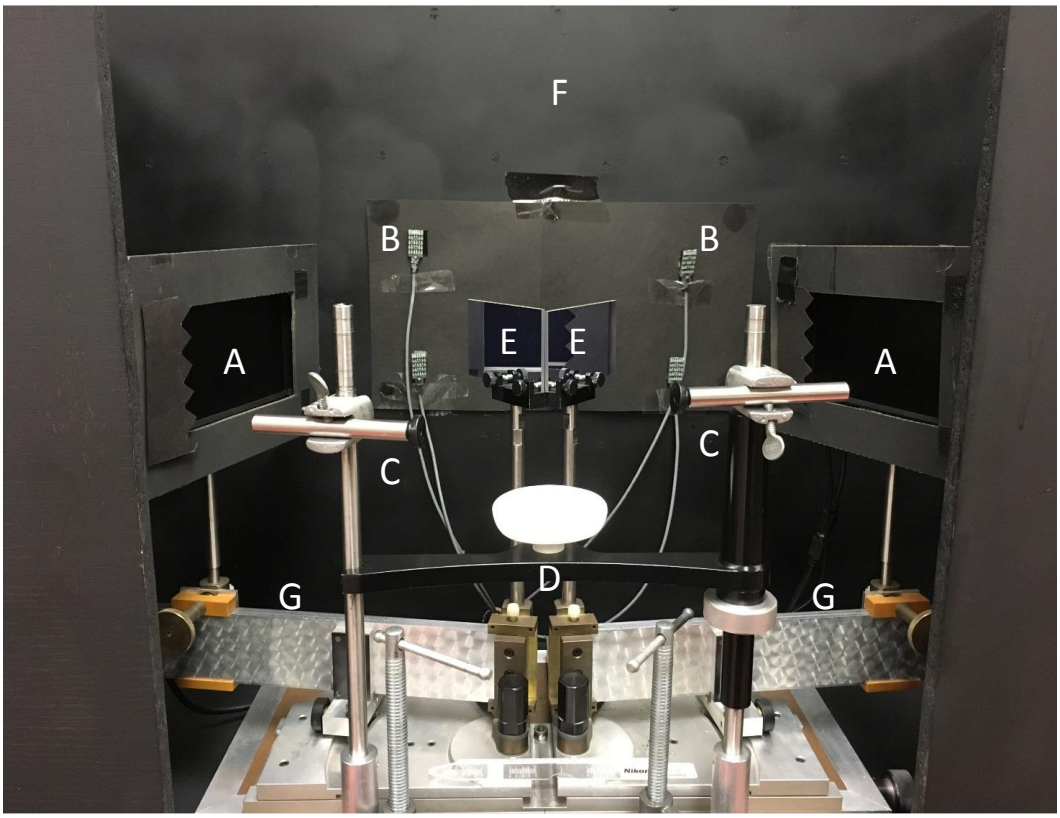

Figure 5-1: Image of the haploscope and surrounding apparatus used. A) 7-inch LCD monitors. Note that the opposite side of each monitor's edge has been corrugated to prevent the screen edges from providing a constant peripheral fusion lock while central disparities are changed. B) Head-tracking infrared sources. C) Head restraints. D) Chin Rest. E) Infrared passing mirrors (visible light reflected). The distance between the two mirror centers represents the calculated IPD. F) Enclosure box for the apparatus. G) Haploscope arms.

Binocular IPD (cm)	Binocular Mirror IPD (cm)	Initially Congruent Vergence Demand (°)	Initial Haploscope Vergence Demand (°)
6	4.2	8.44	10.13
6.5	4.6	9.2	11.1
6.4	4.5	9.1	10.9
6.3	4.4	9.0	10.7
6.2	4.3	8.8	10.6
6.1	4.3	8.6	10.4
6	4.2	8.5	10.2
5.9	4.1	8.4	10.1
5.8	4.1	8.3	9.9
5.7	4.0	8.1	9.7
5.6	3.9	8.0	9.6
5.5	3.9	7.8	9.4
5.4	3.8	7.7	9.2
5.3	3.7	7.5	9.1
5.2	3.6	7.4	8.9
5.1	3.6	7.3	8.7
5	3.5	7.1	8.6

Table 5-2: Haploscope settings based on the IPD of a given participant. The Mirror IPD and initial haploscope vergence demand were set at the beginning of each experimental trial based on this table and the conversions detailed in Appendix B. The first row highlighted in grey denotes the values derived from the previous calculations and figures, based on a 6cm IPD.

5.3.2 Haploscopic Design Validation

To assess the accuracy of the haploscopic design described above and the necessary correction factors detailed in Appendix B we measured 10 participants' heterophoria dichoptically and then again non-dichoptically using the Modified Thorington Technique (MTT). If any of the conversion factors or calculations given in Appendix A and from the previous section were incorrect, we would expect that the

overall heterophoria measured in the haploscope would be different from the heterophoria measured non-dichoptically with the same technique.

5.3.2.1 Methods

10 binocularly normal control participants completed the procedures in one visit. Heterophoria was measured using the Modified Thorington technique (MTT) 5 times dichoptically and 5 times non-dichoptically. The starting test condition was randomized and then alternated between each condition until completion.

In the free-space condition (non-dichoptic) a Saladin Card was placed at 40cm from the participant and their heterophoria was measured using the Modified Thorington Technique (MTT) via a flashed horizontal Maddox rod placed in front of the right eye behind an occluder. In the dichoptic (haploscope) condition, the same MTT scale as was reproduced on the left eye's monitor and a red line was flashed for 250ms at the center of the right eye's monitor to simulate the same vertical red line that would be seen in the non-dichoptic condition due to the horizontal Maddox rod.

At the start of a single trial the participant binocularly viewed a 6/9 line of Snellen acuity sized font for 15 seconds before occlusion of the right eye. In the non-dichoptic condition, the text was located just above the MTT scale on the Saladin Card and the right eye was occluded manually while the Maddox rod was placed behind the occluder. In the dichoptic condition the right eye was occluded by rendering the screen blank while the left eye's stimulus changed from the 6/9 font to the MTT scale. After 12 seconds of occlusion the right eye was flashed through the Maddox rod (non-dichoptic) or with a red line at the monitors' center (dichoptic) and the participant was asked to report where the red line fell on the MTT scale. The right eye was flashed 3 times in 3 seconds and the average of these 3 measures defined one measurement of heterophoria. The participant was then given a 2-minute break before switching conditions and repeating the procedures. A total of 5 heterophoria measures were obtained for each condition.

Because the MTT relies on subjective feedback from the participant we also wanted to compare the objective heterophoria assessment produced by the eye-tracker during these procedures. Therefore, during the dichoptic heterophoria assessments the participant wore the eye-tracking apparatus described in the next sections. At the beginning of each dichoptic trial the eye-tracker was calibrated monocularly using a custom 9-point calibration procedure (also detailed in the eye-tracker section). An objective heterophoria was calculated for each dichoptic trial by taking the difference between mean of the vergence angle of the last 3 seconds of binocular fixation and the mean of the vergence angle during the 3

seconds that the red line was flashed to the right eye. This defined the objective dichoptic heterophoria. This data will be discussed in later sections of the calibration procedures.

5.3.2.2 Results

The mean and standard deviation of each participant's heterophoria measured (in prism diopters) with the 2 different conditions and with the eye-tracker is summarized in Table 5-3. A Pearson correlation analysis was conducted on the non-dichoptic and dichoptic data to compare the relationship between each method. The results of this analysis demonstrated a strong correlation between the two measures ($r = 0.92$, $p < 0.0001$, $R^2 = 0.84$). To further this comparison between the dichoptic and non-dichoptic heterophoria, a paired, two tailed t-test was conducted with the null hypothesis of no difference between measures. The results indicate that there was no significant difference between the measures obtain in the subjective measures of heterophoria in the 2 different conditions ($t(9) = 1.6$, $p = 0.13$). Finally, a Bland-Altman analysis was competed on the two subjective heterophoria datasets to compare the agreeance between them. The results of this analysis are depicted in Figure 5-2. The results demonstrate a 0.30 PD (SD = 0.68 PD) exophoric bias in the dichoptic MTT heterophoria condition. The 95% limits of agreement largely overlap zero (1.05 PD esophoric – 1.63 PD exophoric) and thus the two measures are in good agreeance with each other. Furthermore, the overall variance between the two measures (2.6 PD) is within the repeatability limits of heterophoria measured with the alternating cover test and MTT in other studies[187,188]. Given the level of agreeance and similarity between the two measures it can safely be assumed that the dichoptic conditions created by the haploscope mimic the real-world, non-dichoptic environments when the appropriate corrections are made for initial vergence demand and IPD.

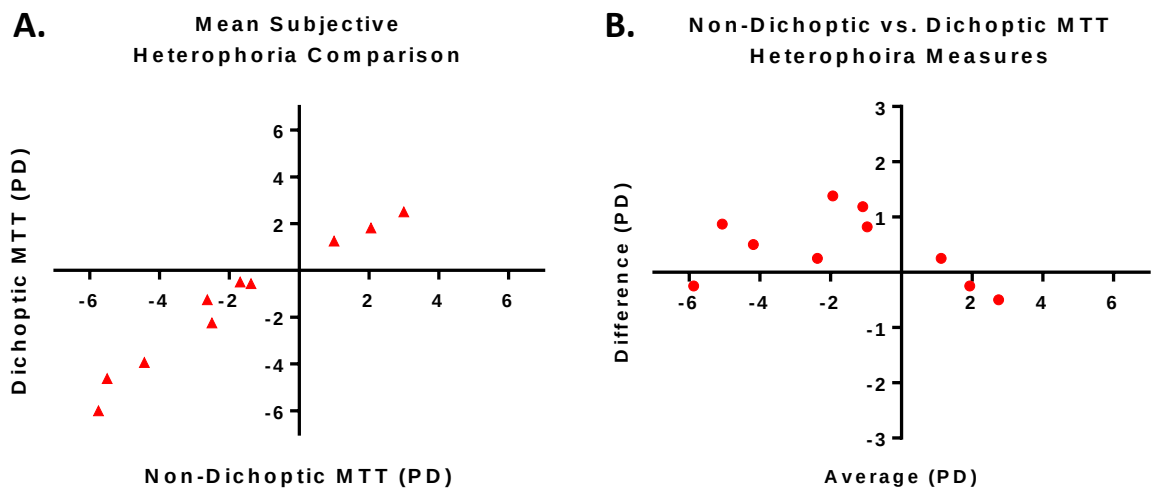

Figure 5-2: A) Plot of each participants mean heterophoria measured subjectively via the Modified Thorington Technique (MTT) for the dichoptic and non-dichoptic conditions. Note the strong correlation between the two measures (r = 0.96). B) Bland-Altman plot of the difference between the mean heterophoria measures obtain in each condition. The greatest difference is 1.5PD and there does not appear to be any systematic bias.

Subject	Non-Dichoptic MTT Heterophoria	Dichoptic MTT Heterophoria	Objective Dichoptic Heterophoria
S1	1.00 (0.52)	1.25 (0.86)	0.94 (0.93)
S2	3.00 (0.51)	2.00 (0.52)	2.01 (0.87)
S3	2.06 (0.44)	1.81 (0.54)	1.12 (0.85)
S4	-5.75 (0.68)	-6.00 (1.26)	-6.34 (1.38)
S5	-2.50 (1.10)	-2.25 (0.77)	-2.52 (0.71)
S6	-1.38 (1.41)	-0.56 (0.73)	-0.71 (0.72)
S7	-2.63 (0.89)	-1.75 (0.93)	-1.17 (1.03)
S8	-4.44 (0.51)	-3.94 (0.57)	-4.18 (1.03)
S9	-5.50 (0.52)	-4.63 (0.96)	-5.15 (1.35)
S10	-0.69 (0.70)	-0.50 (0.89)	-0.17 (1.05)

Table 5-3: Mean and standard deviations of the heterophoria measures obtained in the validation procedures of the haploscopic set-up.

5.4 Measurement of Vergence Responses

A central theme to this dissertation is to objectively quantify the adaptive capacities and any associated directional asymmetries of vergence. To achieve this, it was imperative that eye-tracking be used in place of clinical measures of vergence plasticity, such as fusional reserves, since these subjective tests have large degrees of variability and are vulnerable to participant bias, should they be aware of the study goals.

5.4.1 Eye-tracker

Eye movements were measured using a video-based infrared eye-tracker depicted in Figure 5-3 (EyeLink2, SR Research, Ottawa, Canada). The video sampling rate of this infrared oculographer was set to 250Hz, which is well above the theoretical Nyquist limit required to accurate characterize the first and second order dynamic characteristics of vergence[34,170]. Important to note however, that this specific point

is assumed based on the Nyquist sampling limit of saccades, which are inherently faster (and require a higher sampling frequency than vergence). The eye-tracker has a spatial resolution of 0.03° in the 250 Hz-pupil-tracking-only mode and an average accuracy of less than 0.5°.

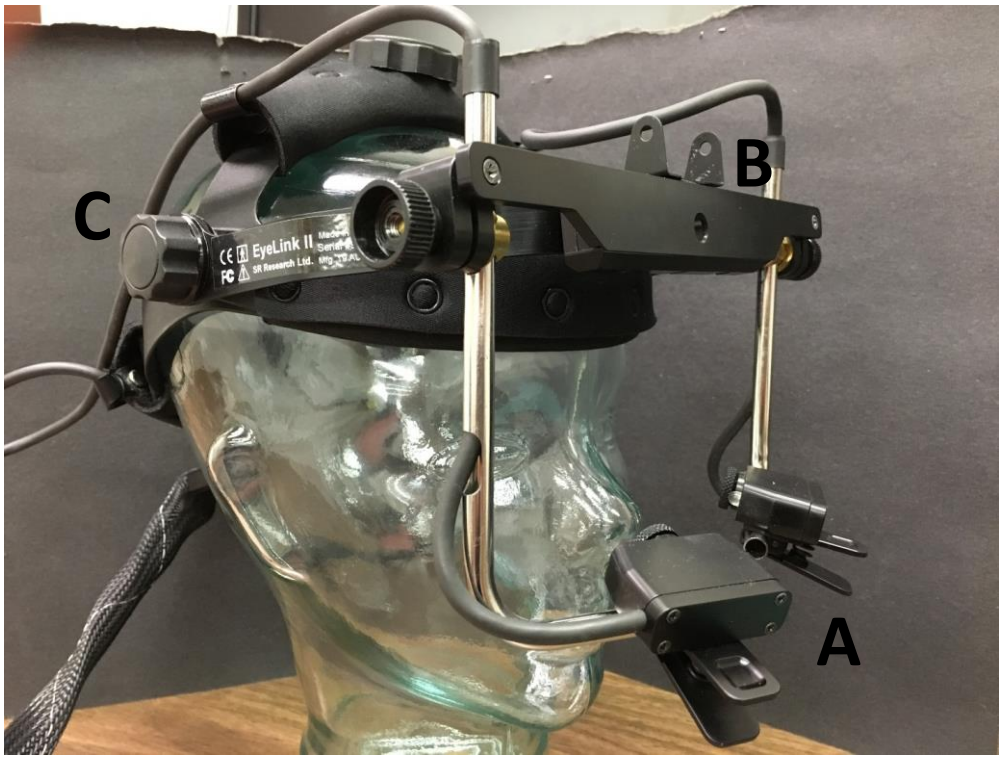

Figure 5-3: Eyelink2 video based infrared eye tracking system. A) Infrared emitting diodes and video cameras to monitor pupil center. B) Infrared sensor for head-tracking sensors (see Figure 5-1). C) Adjustable head-mount.

This eye-tracker simultaneously monitors participant head movement through the use of 4 infrared markers placed on the edge of each screen (Figure 5-1). Because the dichoptic apparatus would not allow of these markers to properly register with the sensor mounted to the forehead region of the tracker, they were placed behind the infrared passing mirrors where the screen edges would be perceived to exist to the observer. The proper acquisition of these signals is vital to accurate eye movement data as the on-board software compensates for such movement in the data produced. As an additional control

mechanism, each participant's head was restrained using a custom chinrest to limit the degree of head movement possible.

5.4.1.1 Calibration

Before commencing any eye movement data acquisition, the eye-tracker was calibrated using a custom 9-point calibration procedure. In this procedure, each eye was calibrated and then validated monocularly. If the mean difference between the initial calibration and validation results were ≤0.5° at each of the 9 points, the calibration was deemed successful. If even one of the points exceeded this limit the procedures were repeated until successful calibration was achieved. Overall the calibration procedure was successful on the first attempt for each eye 80% of the time.

5.4.2 Slow-Tonic Vergence & Heterophoria

Previous work has shown that heterophoria can be assessed objectively[188] within similar haploscopic conditions that were previously described and validated in this section. We used these same procedures to objectively quantify heterophoria. See Chapter 6 for a full description of the procedures and analysis used.

5.4.2.1 Objective Heterophoria Measure Validation

To confirm that our apparatus and eye-tracking set-up was providing an accurate assessment of heterophoria the objective data collected in the previous haploscope validation study was compared with the subjective findings in the dichoptic and non-dichoptic MTT heterophoria measures.

To test the hypothesis that there was no difference between the 3 measurement conditions, a one-way repeated measures ANOVA was conducted on the data detailed in Table 5-3. There was no main effect of measurement condition, $F(1.2, 11.1) = 0.94$, $p = 0.37$.

A Bland-Altman analysis was conducted on the objective heterophoria data compared to both subjective conditions to assess the degree of agreement and any systematic bias present between measures. When compared to the dichoptic MTT heterophoria measures, the bias was 0.24 (SD = 0.29) more esophoric in the objective eye-tracking measures. The 95% limits of agreement were from 0.61 exophoric to 0.87 esophoric. When compared to the non-dichoptic heterophoria measures, the dichoptic eye-tracking heterophoria measures were 0.20 PD (SD = 0.88) more exophoric; however, the 95% limits of agreement were largest between these two conditions (-1.9 PD exophoric to 1.6 PD esophoric). In all cases the bias was insignificant and the limits of agreement were within typical clinical variability.

5.4.2.2 Heterophoria Adaptation Validation

Heterophoria adaptation is generally assessed using optical prisms, presented monocularly for prolonged periods while the heterophoria is intermittently measured. The advantage of dichoptic apparatus is that it allows for symmetrical disparity to be presented, meaning the disparity is created by shifting each eyes image. This is quite different from clinical measures for tonic vergence plasticity, where the additional disparity stimulus is rendered by shifting the image of only one eye. While theoretically the two situations are similar, the resulting eye movements created to fuse these disparities can be very different‡‡‡‡‡. In the latter condition, one eyes image remains centered on the fovea while in the former dichoptic condition the image shifts on both fovea. It could be argued that the single non-foveal point in the optical prism condition would generate more frequent and consistent saccadic responses. There is little information addressing this specific issue in the existing literature. Therefore, a small pilot study was completed in order to assess the effect of these two condition on the change in heterophoria overtime. In addition, this dissertation requires that both fast-phasic vergence and slow-tonic vergence be stimulated in similar ways in order to allow for a valid comparison. In reality, this may not reflect the previous data describing slow-tonic vergence response characteristics that were obtained using monocular optical prism. To compare the effects of dichoptic symmetric disparity and non-dichoptic asymmetric disparity created with optical prism 4 binocularly normal participants were recruited to complete both tasks.

5.4.2.2.1 Methods

In this validation study the participants viewed the same fixation stimulus described in Chapter 6 either dichoptically in the haploscope while wearing the eye-tracker, or non-dichoptically where heterophoria was assessed subjectively via the MTT. A 20PD crossed disparity amplitude was chosen as the test stimulus as this was the largest amount of disparity to be used in the experimental chapters and thus any differences between the conditions adaptive effects on heterophoria would be expected to be the greatest.

In the non-dichoptic MTT condition, the 20 PD of disparity was induced using a single horizontal base-out prism, while in the dichoptic condition this disparity amplitude was achieved by moving each monitors image and equal amount in opposite (convergent) direction. The participant viewed the disparity for a total of 4 minutes while heterophoria was assessed every 15 seconds. Each participant

‡‡‡‡‡ See 0 for a discussion on saccadic and asymmetric vergence

completed three trials for each condition, all on separate days (6 study visits total). The condition of the first trial was randomized for each participant and only one trial was completed per day.

An exponential decay function was fit to the change in heterophoria for each condition using the robust fitting function in GraphPad Prism® (GraphPad Software Inc, La Jolla, CA, USA). The span (amount of heterophoria change) and time constants of these functions were compared. In addition, the rate of heterophoria change was calculated by dividing the span of the exponential function by its (63%) time constant. This calculation gives an estimate of the maximum velocity (rate) of heterophoria change Table 5-4.

5.4.2.2.2 Results

A paired two-tailed t-test was used to compare the results of the two conditions. There was no significant difference found in any of the three measures compared (span: $t(3) = 1.70$, $p = 0.19$; time constant: $t(3) = 0.25$, $p = 0.81$; maximum rate of heterophoria change: $t(3) = 0.14$, $p = 0.89$). We therefore conclude, as others have before, that this apparatus and stimulus aimed at isolating the adaptive element of slow-tonic vergence provides a comparable metric to the data obtained clinically using monocular horizontal prism.

	Heterophoria Change (PD)		Time Constant (s)		Rate of Change (PD/s)	
Subject	**ND-MTT**	**D-ET**	**ND-MTT**	**D-ET**	**ND-MTT**	**D-ET**
S1	7.91 (1.19)	8.00 (1.33)	18.61 (10.42)	17.00 (9.42)	0.52 (0.39)	0.63 (0.35)
S2	11.02 (2.19)	12.41 (2.07)	10.49 (7.29)	11.14 (7.44)	1.63 (1.35)	1.38 (0.69)
S3	13.24 (1.07)	11.22 (2.25)	26.46 (11.12)	21.55 (8.63)	0.56 (0.33)	0.59 (0.30)
S4	4.90 (1.34)	5.73 (2.97)	52.85 (27.24)	42.08 (28.44)	0.10 (0.09)	0.14 (0.12)

Table 5-4: Summary of the exponential decay curve properties fit to each participant's dataset. The mean and standard deviation (in brackets) are given. ND-MTT = non-dichoptic Modified Thorington Technique condition, D-ET = dichoptic eye-tracker condition.

Of note from this data is the similarity between subjects 1-3 and the very different data obtained from subject 4. The 4th subject's data shows a significant reduction in the amplitude of heterophoria change and an increase in the overall time constant and maximum rate of this adaptation. During testing

this participant reported that the stimuli in either condition would not fuse 'automatically' but that they could achieve fusion if they voluntarily crossed their eyes. While this clearly appears to have affected the behavior of the heterophoria change in this participant, the effect is consistent between conditions. This behavior parallels what North et al. reported in their data characterizing heterophoria change to different amplitudes of optical prism. In this work, when the prismatic demand reached the limit of what was fusible, the amount of adaptive change in heterophoria reduced. It is possible then that the change in heterophoria in this condition may actually be the result of a different neural process, outside of what has already been discussed. Given this consistent finding between our pilot data and the previous work described, participants were excluded if they reported having to voluntarily alter their vergence in order to obtain binocular fixation and motor fusion.

5.4.3 Fast-Phasic Vergence

Fast-phasic vergence responses were identified and quantified using customized analysis software in MatLab® (MathWorks, Waltham, MA, USA). The details of this analysis can be found in each methods section of Chapters 6-11. In this analysis the first derivative of the position data was used to define the stop and start criterion for a step vergence response (velocity thresholds). This analysis also identified the open-loop, pulse response using methods described in previous work[34,85]. The methods section of each manuscript chapter provides a summary of the specific velocity thresholds and other variables used to quantify the fast-phasic vergence response.

5.4.3.1 Fast-Phasic Vergence Assessment Validation

A final pilot study was conducted to assess the accuracy of the analysis software and to confirm the calculations used to determine the screen pixel displacement that is equivalent to the desired optical prism power.

5.4.3.1.1 Methods

7 binocularly normal control participants completed this final pilot study. Each participant completed 2 sessions on the same day. Stimuli were presented dichoptic in the haploscope while eye movements were tracked using the EyeLink 2 system. In one trial, 4° step changes in retinal disparity were created by changing the image position on the haploscope monitors. In the second condition, the stimuli remained fixed on the screen and a 7PD base-out optical prism was placed in front of one eye. The 7PD prism is roughly equivalent to a 4° step change in disparity. Participants completed 10 trails for each

condition and were given a 10-minute break between sessions. The starting condition was randomized and the eye-tracker was calibrated at the beginning of each session.

5.4.3.1.2 Results

The total response amplitude, open-loop pule response amplitude, peak velocity and response latency were calculated for each response and then averaged for each participant. Responses containing saccades were omitted from this analysis. Results are detailed in Table 5-5. A two-tailed paired t-test was conducted comparing individual's mean response properties between stimulus conditions. There were no significant differences found between conditions (total response amplitude: $t(6)=0.85$, $p = 0.43$; pulse response amplitude: $t(6)=0.61$, $p = 0.56$, peak velocity: $t(6)= 0.22$, $p = 0.84$; latency: $t(6)=1.41$, $p = 0.21$). In addition, the open-loop pulse response amplitudes and peak velocities observed in the pilot data are consistent with previously published data from various different groups using similar apparatus and stimuli amplitudes. These findings validate the disparity stimuli and analysis code that will be used in the following dissertation.

Subject	Screen Disparity				Prism Disparity			
	Response Amplitude (°)	Pulse Response Amplitude (°)	Peak Velocity (°/s)	Latency (ms)	Response Amplitude (°)	Pulse Response Amplitude (°)	Peak Velocity (°/s)	Latency (ms)
S1	4.31 (0.3)	2.48 (0.5)	14.04 (1.9)	120 (9)	4.37 (0.3)	2.52 (0.6)	16.24 (2.5)	118 (6)
S2	4.11 (0.2)	2.40 (0.5)	13.86 (2.1)	151 (14)	4.34 (0.3)	2.63 (0.7)	11.30 (2.4)	163 (16)
S3	4.27 (0.2)	2.97 (0.3)	20.39 (2.6)	139 (10)	4.41 (0.2)	2.96 (0.4)	20.88 (2.3)	131 (9)
S4	3.53 (0.3)	2.70 (0.3)	19.72 (2.0)	122 (15)	3.91 (0.2)	2.67 (0.7)	20.10 (1.7)	134 (8)
S5	4.25 (0.3)	2.73 (0.5)	17.43 (2.4)	122 (17)	4.63 (0.2)	2.91 (0.3)	19.49 (2.2)	131 (18)
S6	3.94 (0.2)	1.83 (0.4)	14.59 (2.5)	118 (11)	3.46 (0.4)	1.59 (0.6)	11.94 (3.1)	130 (10)
S7	4.08 (0.3)	2.82 (0.4)	17.18 (2.4)	141 (9)	4.04 (0.3)	2.90 (0.3)	18.42 (1.6)	138 (7)
Mean	4.07 (0.3)	2.56 (0.4)	16.75 (2.7)	130 (13)	4.17 (0.4)	2.60 (0.5)	16.91 (3.9)	134 (13)

Table 5-5: The mean and (standard deviation) of the fast-phasic response properties for step changes in disparity created using image displacement on the haploscope screens, or with the equivalent optical prism power.

5.5 Sample Size Calculations

Based on previous work from Hung et al. and North et al.[102] the sample size (based on the estimated effect size; Cohen's d) required to identify directional differences in the response properties of both the fast-phasic and slow-tonic vergence mechanisms was determined.

From the work of Hung et al.[33] on the directional differences in fast-phasic vergence, the size of the effect between open-loop vergence response amplitudes to a 2° and 4° disparity step stimulus was 2.6 and 3.1 respectively. For differences in movement duration between directions the effect size was 2.5 and 3.9 for the same stimulus amplitudes. From these effect sizes, a one-tailed pair t-test would require a sample size of 3 to reach significance (as the size of the effect is very large). A two-tailed t-test would require a sample size of 4-5, depending on which calculated effect size is used.

The work published by North et al. has provided data the compares the differences between the slow-tonic vergence responses (heterophoria change) to various prolonged prism demands. Using their data, the size of the effect ranges from 1.5 to 10.7, depending on the amplitude of prism demand used (1.5 = 6BI vs 6BO; 10.7 = 12BI vs. 12BO). These effect sizes then suggest a sample size of between 2 and 7 participants be used to find a significant difference in a one-tailed t-test. A two-tailed test would increase the required sample size by one.

Given the large effect sizes evident in the data reported by previous groups we set our initial sample size goal at 4 participants health control participants. We further assume that a one-tailed t-test would be sufficient, as the differences between convergence and divergence are expected to be greater in the convergence direction. There is little evidence to suggest that divergence would be expected to be faster under any of the conditions we have described.

Chapter 6

Unmasking the linear behavior of slow motor adaptation to prolonged convergence.

This chapter is published as follows:

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6.1 Overview

Adaptation to changing environmental demands is central to maintaining optimal motor system function. Current theories suggest that adaptation in both the skeletal-motor and oculomotor systems involves a combination of fast (reflexive) and slow (recalibration) mechanisms. Here we used the oculomotor vergence system as a model to investigate the mechanisms underlying slow motor adaptation. Unlike reaching with the upper limbs, vergence is less susceptible to changes in cognitive strategy that can affect the behaviour of motor adaptation. We tested the hypothesis that mechanisms of slow motor adaptation reflect early neural processing by assessing the linearity of adaptive responses over a large range of stimuli. Using varied disparity stimuli in conflict with accommodation, the slow adaptation of tonic vergence was found to exhibit a linear response whereby the rate ($R^2 = 0.85$, $p < 0.0001$) and amplitude ($R^2 = 0.65$, $p < 0.0001$) of the adaptive effects increased proportionally with stimulus amplitude. These results suggest that this slow adaptive mechanism is an early neural process, implying its fundamental physiological nature that is potentially dominated by subcortical and cerebellar substrates.

6.2 Introduction

6.2.1 Background

Motor adaptation allows for the recalibration of physical responses to changing environmental or sensory demands. This process is essential for maintaining optimal motor control and is present in both the skeletal and oculomotor systems. Deficits in motor adaptation result in inaccurate reaching and saccadic eye movements in disorders such as Parkinson's disease [189]. Converging evidence from human studies suggest that the cerebellum plays a central role in adaption of both the skeletal and oculomotor systems [190,191]**.** Recently, multiple neural processes have been discovered in the adaptation of reaching movements. These different processes, 'fast' and 'slow', occur simultaneously during adaptation [145]. When a reaching movement is perturbated by an external force during its execution, errors occur. 'Fast' adaptive mechanisms provide an immediate, but transient response to these errors, while 'slow' mechanisms generate a long-term recalibration of the movement. Motor adaptation has generally been considered a basic physiological process due to its linear generalizability across differing stimuli and motor tasks [192,193]. However, deviations in this linearity to larger perturbations have recently been identified in both reaching and eye movements

[194]. Complex computational models have been designed to explain these non-linear behaviours; however, this likely reflects the behaviour of both fast and slow adaptive mechanisms combined. Given the complexity of these statistical models, this non-linear behaviour likely represents cognitive, higher level processing. It is reasonable then to assume that non-linearity's would exist within such an assessment of motor adaptation due to the cognitive inputs. Separating the contributions of each mechanism from the final adapted response is difficult, which has impeded the study of the slower, more elementary neural adaptive processes. To accomplish this, it becomes necessary to look for adaptive mechanisms in motor systems with the least complicated neural circuitry.

Eye movements have provided an appropriate model for exploring motor systems. Adaptations of eye movements can be classified as adjustments in the ballistic neural response driving the eye movement, or by a subsequent change in the levels of tonic innervation that follow the completed movement and hold the eyes in the new position [195]. Saccades and vergence eye movements demonstrate a linear relationship between peak velocity and amplitude of the ballistic (fast) portion of the movement [34,101] This is defined as the systems 'main sequence' (MS) [35]. It is well established that these responses can be quickly adapted using double-step paradigms [50,95,196]. This adaptation is non-linear to large stimulus amplitudes and the saccadic data [197] seems to also best fit the error relevance model [194]. This implies that adaptation of the fast system involves a cognitive component [50,196]. In contrast, there is little evidence characterizing the adaptive behaviour of the underlying tonic innervations, in isolation, within these motor substrates. It remains unclear if the slower, more basic adaptations of tonic innervations [155] are susceptible to similar cognitive influences seen in the fast systems. The aim of this study was to objectively characterize the properties of a slow adaptive mechanism using the adaptation of tonic vergence within the oculomotor system.

6.2.2 Vergence

Ocular vergence is the rotation of the eyes in opposite directions in response to retinal disparity. Vergence movements are controlled by both fast and slow neural mechanisms with synkinetic cross-links to ocular accommodation (Figure 6-1). 'Fast-Phasic vergence' (PV), comprising both pulse and step innervation, is responsible for generating the complete motor response to disparity. Vergence also demonstrates resting amount of 'tonic vergence' (TV) innervation, which is seen as the angle between the two visual axes after a prolonged period in absolute darkness [195]. During extended near fixation the PV response fatigues, resulting in errors in the vergence position [78]. To avoid this, PV also stimulates the 'slow vergence' system (SV) [43]. SV is responsible for adapting the underlying amount of TV innervation to better match the new fixation distance, which reduces the required PV output (Figure 6-1) [79]. When one

eye is occluded for a short period of time the PV response decays quickly (Schor, 1979a). The resulting open-loop vergence position, known clinically as the "phoria", is the sum of the TV innervation and the cross-link driven accommodative-vergence. Changes to the phoria over time, in the absence of a change in accommodation, indicate the adaptation of TV innervation via the SV system. A similar interaction occurs when binocular fixation through a base out optical prism is prolonged. Optical prism does not alter the accommodative demand, which creates a non-congruent, conflicting visual stimulus due to the near triad linkage of vergence and accommodation (Figure 6-1). This non-congruency generates a much stronger SV response in order to maintain a balance between the accommodation and vergence systems (Figure 6-1) [42,102]. SV can be considered a slow adaptive process based on its longer decay time constants, which can be in the order of minutes to hours [45]. The ability to easily assess SV behaviour in the absence of PV via occlusion, combined with the large SV response generated under prismatic viewing conditions provide an ideal environment for investigating the response properties of this slower adaptive mechanism.

6.2.3 Purpose

PV has been shown to demonstrate positive, linear main sequence effects [34,195]. To date, no study has objectively quantified the main sequence characteristics of SV innervation or a slow adaptive process in general, despite the fact that SV is modelled as replacing PV [43,79]. We hypothesize that SV will demonstrate linear adaptive effects over a large range of disparity stimuli based upon model predictions of PV, which demonstrates linear MS effects, as the stimulus input to SV [43]. Strong linear MS effects in SV over a large stimulus range would suggest this type of adaptation is predominantly an early neural process, whereby cognitive processing is limited. This would suggest this type of adaptation is a fundamental physiological process, likely controlled by the midbrain and cerebellum [185].

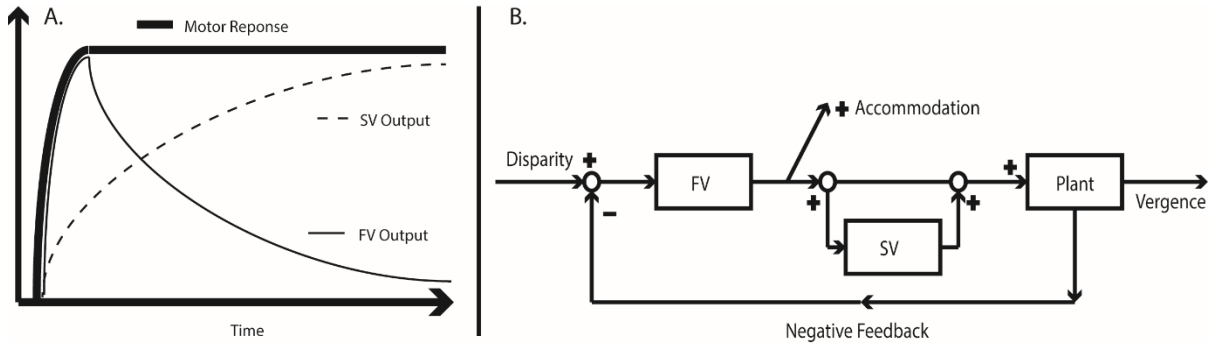

Figure 6-1: A) Simplified model of vergence control; Fast-Phasic Vergence (PV) responds to disparity (error in vergence angle) to generate a convergence response. The convergence response also stimulates the accommodative system to increase the ocular focus. TV adaptation is achieved by replacement of the FV controller output by SV. The reduction of PV then uncouples the vergence driven accommodative response. Errors in the vergence position are fed back into the system. (Adapted from Schor; 1979a) **B):** Graphical representation of a convergence response (bold line) and the contributions of Fast and Slow mechanisms. The Fast response initially drives the movement and then decays as it is gradually replaced by the slow system. The overall response shows little change. (Adapted from Schor; 1992).

6.3 Materials & Methods

6.3.1 Overview & Statement of Ethics

Participants were recruited from the graduate student population at the School of Optometry and Vision Science, University of Waterloo. Informed consent was obtained after verbal and written explanations of the study procedures. The study protocol was approved by the University of Waterloo ethics review board and adhered to the tenets of the Declaration of Helsinki.

6.3.2 Participants:

4 individuals participated. Each was screened by an optometrist to ensure normal binocular vision [94,102]. The average of 3 clinical phoria measures via the alternating cover test are defined in table 1 for each subject. Visual acuity was 6/6 in each eye and stereopsis was at least 40 seconds of arc. There was no history of ocular surgeries, amblyopia or vision training in any of the participants.

6.3.3 Instrumentation:

Vergence stimuli were presented dichoptically via a haploscope. One 7" LCD monitor was placed at each end of the haploscope arm, 28cm from infrared-passing cold mirrors, which were placed orthogonally, 12 cm from the observer's cornea (Figure 6-2). The stimuli to each eye were controlled using Experiment Builder® via a host computer. Each eye received a separate white-on-black stimulus with total dimensions of 2.73° x 2.73 ° and a 0.08° line width (Figure 6-2). Each arm of the haploscope was aligned vertically and horizontally to provide a total convergence stimulus of 8.44° at the cyclopean screen center, with no vertical disparity. This convergence demand is congruent to the accommodative demand at the 40cm working distance, with an assumed interpupillary distance of 60mm. This congruent disparity and accommodative stimulus limits any adaptive responses from occurring initially. Additional convergent demands of 4, 8, and 12° were stimulated by changing the relative position of each target on the monitor, while the accommodative stimulus was held constant. This simulates the same non-congruent disparity provided by base-out prism (Figure 6-2). Head movements were controlled using a custom chin rest. The apparatus was enclosed in order to control any extraneous peripheral or proximal cues which can affect vergence responses [4].

6.3.4 Eye Tracking and Data Analysis:

Horizontal eye movements were recorded at 250Hz and analyzed offline using a video-based, infrared eye-tracking system (EyeLink2®, SR Research®, Ottawa). All eye movements were in the linear range of the eye-tracker (±40°). Eye movements were calibrated monocularly at the beginning of each trial using a custom 9-point calibration sequence [198]. Left eye and right eye positions were normalized to the screen center as the zero position and converted to degrees from pixel position. The vergence position was taken as the difference between the right and left eye positions relative to the screen center. Blinks and saccades were identified using the Engbert-Klegil criterion in Data Viewer® and removed before the data was exported to Microsoft Excel® for further analysis.

6.3.5 Experimental Protocol

Each participant wore the same corrective lenses, if required, for all sessions. 9 trials were completed, 3 at each non-congruent disparity stimulus amplitude (4° 8° and 12°), which was selected randomly at the beginning of each trial. A trial began with 5 minutes of dark adaptation to decay any SV innervation induced by previous visual tasks. The trial was initiated by the researcher, beginning with a brief (2s) presentation of the stimulus to each eye at screen center. The stimulus presented to the right eye

was then extinguished to simulate occlusion for 15 seconds, providing a baseline phoria measure which was used to define baseline TV innervation [188]. The right eye's stimulus then reappeared and both left and right stimuli were stepped to an additional 2°, 4° or 6° convergent position, providing a total retinal disparity of either 4°, 8° or 12°. The subject then viewed this disparity for 15 seconds, before the target of the right eye was extinguished for 15 seconds providing an 'adapted' phoria measure. This pattern of binocular fusion interleaved with an adapted phoria measure was repeated for 6 minutes using the same non-congruent disparity amplitude for a single trial. This design provided a total of 3 minutes of converged binocular viewing with 12 adapted TV measures (Figure 6-2). Only one trial condition was completed within an 8 hour period to prevent fatigue or contamination of any TV adaptation between trials [81]. Based on previous work, these binocular intervals were selected in order to sufficiently stimulate the SV system [45,95].

6.3.6 Assessing Slow Vergence (SV):

Measurement of SV innervation was obtained from the change in phoria measures. A convergent change in the phoria indicated an increase SV innervation output. The SV output was characterized by the change in phoria over time in each trial (Figure 6-3). Previous research has indicated that the decay of PV occurs completely within the first 10 seconds after occlusion [42,188]. Therefore, the phoria was taken as the average of the last 3 seconds of this open-loop period. The change in phoria over time defined the change in TV innervation via SV[188].

6.3.7 Data & Statistical Analysis:

In each trial for a given convergence stimulus, the TV positions were plotted over time (Figure 6-3) and fit with an exponential function using GraphPad 5®. An expected asymptotic pattern of TV change resulted, allowing a final amplitude (plateau of the function) and time constant (τ) to be defined for the change in TV due to SV innervation (Figure 6-3). Maximum velocity (V-max) of this SV innervation output was calculated for each trial by dividing the plateau amplitude by the time constant [94,96]. Each V-max was then plotted against the amplitude of TV change. The linear regression of these data defined the main sequence of slow vergence. The amplitude of SV innervation was plotted over the corresponding disparity stimulus amplitude and a linear regression function was fit for each subject. The amplitude and MS functions of SV innervation were compared between participants using a one-way ANOVA. Linear regressions were fit to each participant's data. The R^2 values of these functions were taken as an indicator of the degree of linearity within the system.

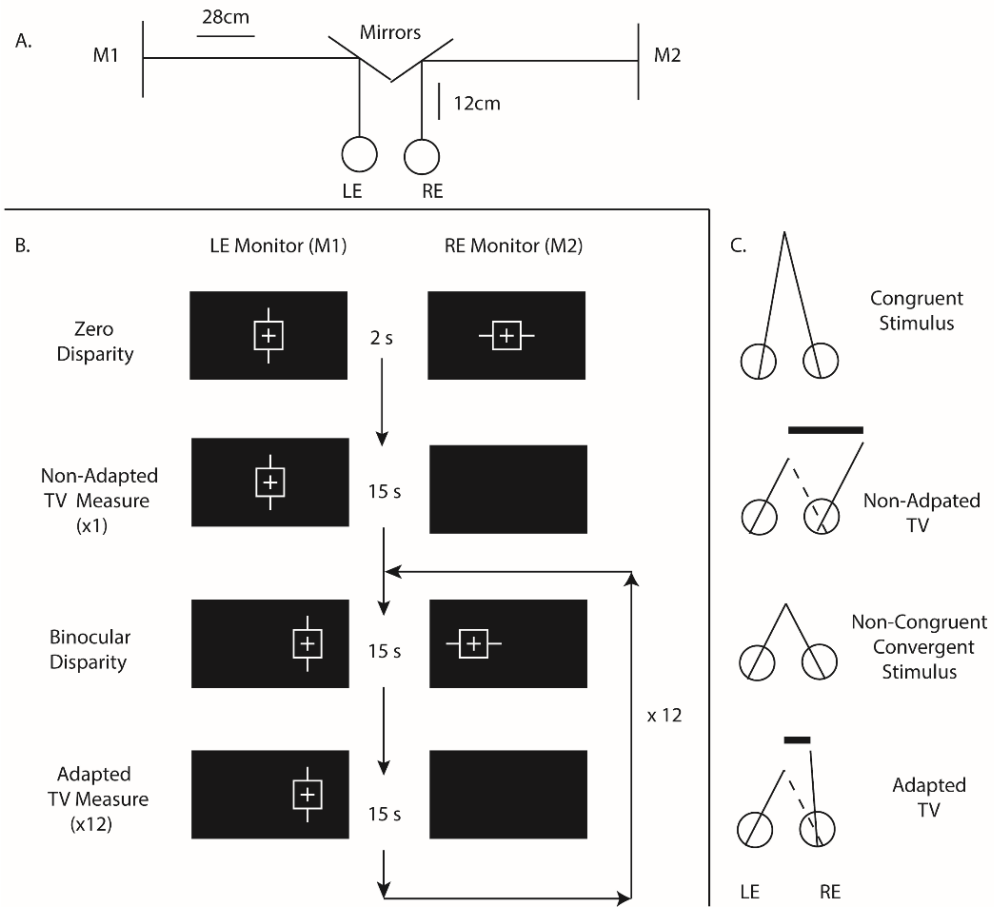

Figure 6-2: A) Schematic view of the Haploscope (Top, LE = Left Eye, RE = Right Eye). **B):** Block diagram outlining the stimulus presentation procedure for each trial. **C):** Schematic of eye position at each stimulus presentation. Solid lines indicate actual eye position. Dashed lines indicate where the fused position of the LE would be during occlusion periods. The angular difference between the dashed and solid line represents the TV position during occlusion. Thick horizontal lines indicate the magnitude (and change) TV due to increased SV output.

6.4 Results

6.4.1 Vergence Responses:

Subjects were able to fuse all disparity amplitudes using PV. This was shown by a fast vergence movement within 300ms of the onset of the disparity stimulus (RE image turned on) and the subject reporting no diplopia. Each time the RE target was extinguished, that eye underwent a fast, divergent movement, indicating a decay of FV output, while the left eye remained stationary. The amplitude of this fast-divergent movement reduced over time, indicating an adaptation of the TV position via SV. Figure 6-3A demonstrates a typical vergence response trace for one complete trial for S1 to a 12° disparity stimulus. Figure 6-3B shows the same trial (red) when plotted using only TV measures every 15 seconds. The solid line represents the exponential function fit to the data and demonstrates the adaptation of TV via increased output of SV innervation.

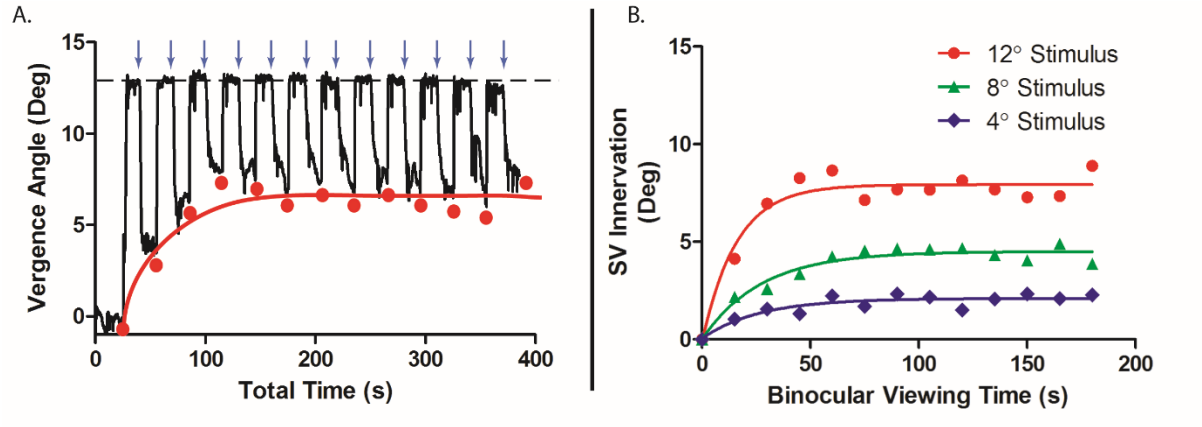

Figure 6-3: A) Convergence response trace of 1 trial to a 12° disparity stimulus. The disparity demand of 12° (dashed line) indicates the fused-adapting position. The TV measurements (circles) rapidly become more convergent after each period of occlusion (arrows), indicating increased SV output. **B)**: The graphical representation of the SV output for the same 12°trial in 3A (red) and 2 other trials of different stimulus amplitudes (green and blue). Each point represents the average (last 3s) TV position after 15s of occlusion. The exponential function fit to the data is shown, indicating the increased output of SV that is responsible for the convergent adaptation of the TV position.

Subject	ACT (PD)	Baseline Phoria (˚)	Stimulus (˚)	Span (˚)	Tau (s)	R^2
S1	-1	-0.08 (0.37)	4	2.09 (1.06)	20.66 (6.03)	0.80 (0.05)
			8	4.78 (0.25)	16.83 (9.42)	0.87 (0.09)
			12	6.73 (1.97)	12.16 (3.18)	0.83 (0.18)
S2	0	0.43 (0.64)	4	1.77 (0.33)	28.68 (10.97)	0.48 (0.10)
			8	5.33 (0.79)	24.05 (13.33)	0.84 (0.16)
			12	7.48 (1.01)	17.89 (5.45)	0.89 (0.10)
S3	0	0.09 (0.55)	4	2.28 (1.38)	46.44 (20.73)	0.39 (0.24)
			8	3.96 (0.67)	16.38 (6.26)	0.36 (0.21)
			12	6.79 (0.71)	13.40 (0.69)	0.69 (0.18)
S4	-2	-0.82 (0.65)	4	1.43 (0.04)	16.52 (7.41)	0.30 (0.09)
			8	4.74 (0.51)	12.94 (5.42)	0.65 (0.25)
			12	6.99 (0.92)	12.71 (5.88)	0.81 (0.11)

Table 6-1: Alternating cover-test (ACT) phoria values by subject in prism diopters (PD). Mean and (standard deviation) values for the baseline phoria at the start of each trial (˚), span/plateau (˚), time constant (s) and R2 of the exponential curves fit to each trial's data.

6.4.2 Exponential Curve Fits

Summary data for the baseline phoria and exponential curve fits are listed in Table 6-1. Repeated measures ANOVA indicated no influence of trial number on the initial baseline phoria value at the start of each trial $F(8,24) = 0.99$, $p = 0.47$. This confirms that assumption that 5 minutes of dark adaptation before the start of each trial was sufficient to decay any previous adaptations in SV. Repeated measures ANOVA analysis of the remaining variables found a significant effect only between subject variability in the R^2 values of the curve fits ($p = 0.004$). Qualitative analysis of the data and raw eye movement traces indicated this effect was due to one subject (S3) blinking more throughout the trials; however, mean fits for each trial were still well correlated ($R^2 > 0.3$). Significant effects of amplitude on the R^2 values ($p = 0.01$) indicate the fits were better for the larger stimuli amplitudes. This is attributable to the smaller adaptive effects expected at smaller stimulus amplitudes, resulting in larger apparent variance in the curve

fits. The effects of stimulus amplitude on the TV change (curve span) and time constants were also significant ($p < 0.001$). Larger stimulus amplitudes resulted in larger changes in TV (span) and slightly shorter time constants. Interaction effects were not significant for any variables in table 1 ($p > 0.1$), and thus the effects of stimulus amplitude were consistent in each of these variables across all subjects.

6.4.3 Amplitude of TV Adaptation:

All 4 subjects showed an increase in the amplitude of SV innervation with increasing disparity amplitudes, indicating that SV adapted the TV position in a linearly proportional manner to the amplitude of the disparity demand (Figure 6-4). This positive linear relationship was significant for all 4 subjects (Table 6-1). Comparison of the individual regression functions did not demonstrate a significant difference between the slopes, $F(3,28)=0.67$, $p=0.58$, or the y-intercept, $F(3,31)=0.59$, $p=0.63$; therefore a combined regression function was defined Table 6-2).

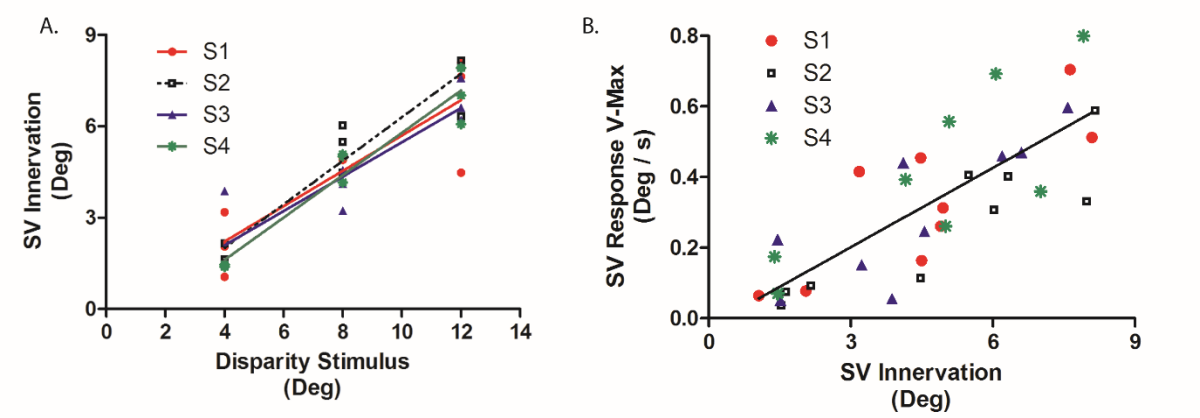

Figure 6-4: A) Plot of amplitude of SV Innervation output vs. disparity stimulus amplitude for each trial. Y-axis indicates the total change in TV position, indicating the total output of the SV system. Linear regressions are plotted for each subject's data. **B):** Combined Main Sequence plot of V-max of SV vs. SV output amplitude. Each subject demonstrated a significant ($p < 0.05$) positive linear relationship and a strong correlation ($r2 > 0.65$) between rate and amplitude of TV adaptation.

Subject	SV Innervation Amplitude (Figure 4A)			SV Main Sequence (Figure 4B)		
	Slope & Intercept	R^2	p-value	Slope & Intercept	R^2	p-value
S1	0.57x – 0.12	0.76	0.0023	0.075x – 0.012	0.67	0.0074
S2	0.71x – 0.85	0.92	<0.0001	0.066x – 0.057	0.80	0.0013
S3	0.56x – 0.17	0.83	0.0007	0.076x – 0.031	0.68	0.0065
S4	0.70x – 1.2	0.94	<0.0001	0.090x - 0.020	0.72	0.0038
Combined	0.64x – 0.046	0.85	<0.0001	0.75x – 0.023	0.65	<0.0001

Table 6-2: Summary of linear regression analysis of each subject's data and the combined functions for SV Innervation Amplitude and SV innervation Main Sequence (MS).

6.4.4 Main Sequence:

In all subjects the rate (V-max) of SV innervation output increased linearly with respect to response amplitude (Figure 6-4B). This is demonstrated by the significant positive linear relationship in the MS plots (Figure 6-4B & Table 6-1). Comparison of the individual regressions functions did not demonstrate a significant difference in the slope values, $F(3,28)=0.33$, $p=0.80$ or y-intercept, $F(3,31)=2.32$, $p = 0.094$; therefore a combined MS regression function was calculated (Table 6-1) and plotted (Figure 6-4B).

6.5 Discussion & Summary:

6.5.1 Discussion

This study provides a novel, objective analysis of the static and dynamic properties of a slow adaptive process in a motor system. Using vergence eye movements and video-based eye tracking, the adaptation of TV via SV was found to exhibit strong linear effects in both its amplitude and rate functions (MS) in all subjects. The significant strength of these linear effects is reflected in the high R^2 values for the individual and combined functions detailed in

Table 6-2. No significant difference was found in these functions between individuals, indicating that a commonly functioning neural mechanism is likely responsible for this adaptive response in binocularly normal individuals. The linear effects seen in SV when compared to previous PV findings [28,34], suggest that the amplitude of the initial disparity error and subsequent motor response of the FV system significantly influence the behaviour of this slow adaptive mechanism. This behaviour of SV is consistent with a number of models that implicate PV as the input signal to the SV system [28,43]. In broader motor terms, the (slow) recalibration of this motor system appears to be a function of the initial error amplitude and the subsequent strength of the (fast) corrective movement innervation.

The clear linearity seen in SV innervations adaptive effects on the TV position provides new evidence supporting early processing of this type of slow motor adaptation. Unlike short-term adaptations of subsequent movements to transiently disturbed environments, such as when trying to catch a ball that is randomly blown laterally by a gust of wind, the adaptive responses studied here are generally considered to be reflexively-driven [195]. Motor adaptation involving cognitive processes would be expected to distort the expected linearity of the adaptation, especially to large perturbations. Sensory prediction of error has been shown in saccades and limb movements to be central to the learning or adaptation of responses immediately preceding the perturbation induced error [133,199]. It has also been shown that the magnitude of the perturbation and cognitive processing of the error relevance have varying effects on the linearity of the adaptation of the preceding movements [194]. These transient adaptive effects have been used to characterize the fast adaptive processes and are known to demonstrate non-linearity to larger error stimuli [194,197]. The strong linearity seen with SV provides empirical evidence supporting the fundamental nature of these slow adaptive mechanisms. The size of the disparity perturbations, with respect to the conflict with accommodation, in this study are significantly larger than what would be experienced naturally at a working distance of 40cm. If the slow adaptation of TV via SV was to exhibit non-linear effects due to cognitive weighting of the errors relevance to the motor system, we would have expected to see this in both the 8 and 12° stimuli amplitudes; however, no such deviations from the linear patterns were found in any of the subjects tested. The linearity is then further taken to imply that higher-level cognitive processes are of minimal influence and the relevance of the error is of limited importance to this slow adaptive mechanism.

The linear behaviour of this type of slow adaptation suggests primary influences from subcortical and cerebellar areas. The MS of the slow adapting element in vergence follows a similar MS relationship already established in saccades and PV, but with much lower velocity values [34,35]. The cerebellar vermis

has been shown to contribute significantly the fast adaptation of saccades to double-step stimuli [183,200]. Various regions of the cerebellum are also known to have significant influence on the dynamic, static and adaptive properties of saccades [200–202]. Further, cell recordings from the posterior interposed nucleus of the cerebellum show adaptive responses to targets incongruent to demands of accommodation and vergence [203]. Therefore, it would not be unreasonable to speculate that the fast and slow adaptive mechanisms of the vergence response result from similar cerebellar activity in conjunction with the midbrain [204]. Cell recording studies in of the midbrain and cerebellar vermis in primates have also identified 3 distinct cell types that fire specifically for vergence eye movements [47,183,203]. These cells could provide a viable substrate for this adaptation. A simultaneous measure of these neuronal responses patterns with that of FV and SV in future studies could provide empirical evidence to support this hypothesis and would further implicate the cerebellum as a primary site for the modulation of slow adaptive mechanisms.

Clinically, disorders in the motor control of vergence are quite common. Convergence insufficiency (CI) results in poor convergence responses to target step changes in depth and is estimated to exist in up to 12% of the general population and roughly 50% of patients suffering from a traumatic brain injury [12]. Research has shown that patients with CI possess weak PV and SV responses [49,139]. Our data supports the models that indirectly suggest CI is a malfunction in the generation of the fast corrective movement in response to disparity [28,43]. Which then results in a weakened SV response. Further research exploring the relationship between PV and SV behaviour in patients with CI can provide an understanding how these and other adaptive processes fail to develop, malfunction or are impaired such as in CI cases resulting from TBI's.

6.5.2 Study Limitations

Attributing the adaptation of the heterophoria exclusively to slow vergence innervation assumes that tonic accommodation was stable over time. If not, an increase in tonic accommodation could lead to an attenuation of accommodative-convergence and an overall reduction of the vergence response (Figure 6-1). Such a reduction could underestimate the measurement of tonic vergence adaptation. Tonic accommodation was not measured before and after vergence adaptation in this experiment; however, we expect its effect to be small or negligible. Previous work has demonstrated that changes in accommodative-convergence from prolonged blur driven-accommodation produced only small reductions (less than 1˚) on the measurements of tonic vergence[205]. Our laboratory has recently reported that tonic accommodation, measured while monocularly viewing a difference of Gaussian's target, was not altered

after prolonged convergence was stimulated using optical prism at 40cm[48]. Furthermore, another group employed a similar dichoptic design and non-congruent convergence disparities as ours to adapt TV and reported no change in tonic accommodation when measured in a dark, empty field. In this case, the result may have been confounded by the finding that opening the accommodative-loop using darkness may have partially masked accommodative adaptation[206]. Combined, these studies suggest that the influence of the cross-linked neural innervation on tonic innervation levels within the near-triad is minor. Therefore, although we cannot definitively rule out an effect of tonic accommodation on our results, any effects were likely to be minimal.

6.5.3 Summary

Our data provides a novel assessment of slow motor adaptation measured in ocular vergence. Strong linearity was found in the amplitude and rate of TV adaptation via SV innervation, suggesting this mechanism is a basic physiological function, reflecting early processing that has limited cognitive inputs. The data also suggests that clinical adaptive disorders are an expression of a weak reflexive response that fails to generate an appropriate slow recalibration of the motor system. We suggest a theoretical neural origin for these slow adaptive processes based on previous neurophysiological data. Further research utilizing the techniques described within this study can further expand our neural understanding of how different types of motor adaptation occur and how they dysfunction or are impaired through injury.

Chapter 7

Isolating the adaptive element of tonic convergence & divergence

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7.1 Overview

Eye movements have provided an excellent substrate with which to explore the neural control of motor systems. The simplicity of the neural circuitry and physical plants, in comparison to visually directed limb movements, allow for much easier analysis and extrapolation. The adaptive capabilities of eye movements are robust and reflect the significant neural plasticity within these systems. Although crucial for optimal motor function, these adaptive properties and the neural mechanisms responsible are only beginning to be understood. While limb and saccadic adaptations have been intensively studied, the adaptive response is measured indirectly as a change in the original response. Vergence, however, appears to provide the opportunity to measure the adaptive response in isolation. The following are preliminary results of a study investigating the adaptive properties of vergence eye movements using a main sequence analysis. The effects of stimulus directionality and amplitude are investigated and compared to the reflexive vergence innervation patterns known to exist to similar stimuli.

7.2 Introduction

Vergence is a unique class of binocular eye movements that are disjunctive in nature and serve to shift the depth of fixation. The reflexive control of vergence in response to retinal disparity is the product of two separate neural processes, phasic and tonic, with different time constants [43] (Figure 6-1A). Phasic vergence (PV) provides the initial pulse-step innervation required to obtain binocular alignment and also generates a coupled shift in ocular focus (accommodation). If a disparity stimulus is viewed for a prolonged period, a slow change in the tonic vergence (TV) innervation shifts the resting vergence posture closer to the new viewing distance and replaces the phasic systems output [79] (Figure 6-1B). This tonic adaptation is vital to maintaining a balanced response with the accommodative system by shutting off the cross-linked interaction [207].

7.2.1 Research Objective

Current models of vergence predict the stimulus for TV adaptation is the PV output (Figure 6-1A) The PV system follows a defined linear relationship between the peak velocity and amplitude of its responses, known as the main sequence (MS) [101]. This research isolates and objectively quantifies this MS relationship within the TV system for the first time and compares it with the known behavior of the PV system.

7.2.2 Hypothesis

PV is known to demonstrate different main sequence effects to convergent or divergent disparities. Model predictions assume the stimulus for TV adaptation is the PV output. Therefore, we hypothesize that TV adaptation will demonstrate similar MS effects seen in the corresponding PV system, but of an order of magnitude slower.

7.3 Methods

7.3.1 Participants, Apparatus & Eye Tracking

4 visually normal subjects (20-35 years) completed 18 experimental trials each. Only one trial was completed in a 24-hour period. Subjects wore a head-mounted eye tracker while viewing images presented dichoptically on two 7-inch LCD monitors placed at 40cm within a haploscope. This apparatus allows disparity to be varied in isolation while holding all other stimuli (accommodation and proximity) constant. Eye movements were recorded binocularly by an infrared video-based system at 250 Hz (EyeLink 2, SR Research), which is well above the required Nyquist frequency. All movements fell within the linear range (+/- 40°) of the eye tracker, which has a RMS resolution of 0.01°. Data was stored as screen pixel coordinates and analyzed offline.

7.3.2 Procedures

Each trial began with a custom monocular 9-point calibration. The subject then viewed a fixation cross with suppression checks binocularly for 2 seconds. The initial binocular convergence demand of 8.44° (at screen center) was congruent to the accommodative demand at 40cm, in order to minimize any initial TV adaptation. The RE image was then extinguished for 15 s, which removed the disparity stimulus for PV, allowing it to decay and the TV to be manifest. The RE image then reappeared and both left and right images shifted laterally to induce 4,8,12° of additional convergence or 2,4,6° of divergence. This non-congruent disparity (unequal to accommodation) was then viewed for 15 s, followed by another 15 s of RE image extinction to re-measure TV innervation. This was repeated with the same disparity amplitude until a total of 3 minutes of adapting disparity had been viewed and 13 TV measures obtained.

7.3.3 Data Analysis

The LE and RE pixel positions were converted to degrees and then normalized to each screen center. Vergence angle was defined as the LE - RE position, (convergence = positive, divergences = negative). TV innervation was defined as the average vergence angle of the last 3 s of the RE stimulus off

periods (Figure 7-1) [188]. Each TV measure was plotted overtime for a single trial and the change overtime defined the adaptation of TV innervation. An exponential curve fit to these points to produce a time constant and span (amplitude) value (Figure 7-1). The maximum velocity (Vmax) of TV adaptation was calculated by dividing span (°) by the time constant (s) from each trial. The Vmax (°/s) was then plotted over the adapting response amplitude (span) to define the main sequence. TV plots to divergence and convergence trials were then regressed separately to determine the MS relationship for each system (Figure 7-1).

7.4 Results & Discussion

All subjects were able to fuse the additional non-congruent disparity stimuli at all amplitudes without reporting diplopia, actively engaging accommodation (no perceived blur), or a visual loss of suppression checks.

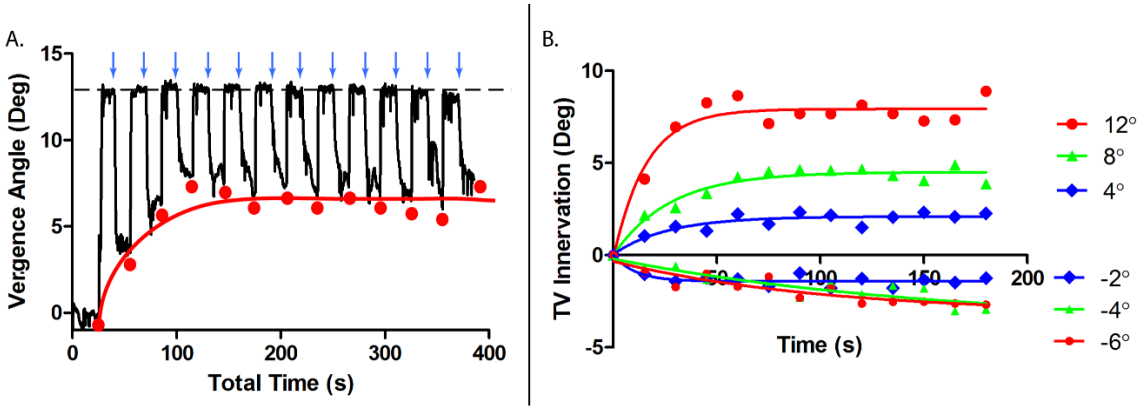

Figure 7-1: A) Vergence trace for one (12° convergence) trial. Arrows indicate RE image off. Red dots indicate TV measurement area. Red line is exponential curve fit to TV measures. **B):** Plot of TV measures for 6 different disparity stimulus amplitudes with curve fits.

The combined MS regression plot of all subjects' convergence data (Figure 7-2) reveals a significant positive linear relationship ($R^2 = 0.65$, $p < 0.001$). The regressions of each individual's convergence data demonstrate similar properties. Comparisons of the individual regression slopes showed no statistical differences among the participants, $F(3,28) = 0.33$, $p = 0.80$.

Divergence MS regressions were different than convergence (Figure 7-2). The combined divergence MS regression analysis showed no significant relationship ($R^2 = 0.006$, $p = 0.65$). Similar

trends were found in the individual regression data ($R^2 < 0.20$, $p > 0.30$). The slope of each individuals function was not significantly different from zero and were not different between subjects, $F(3,28) = 0.68$, $p = 0.57$.

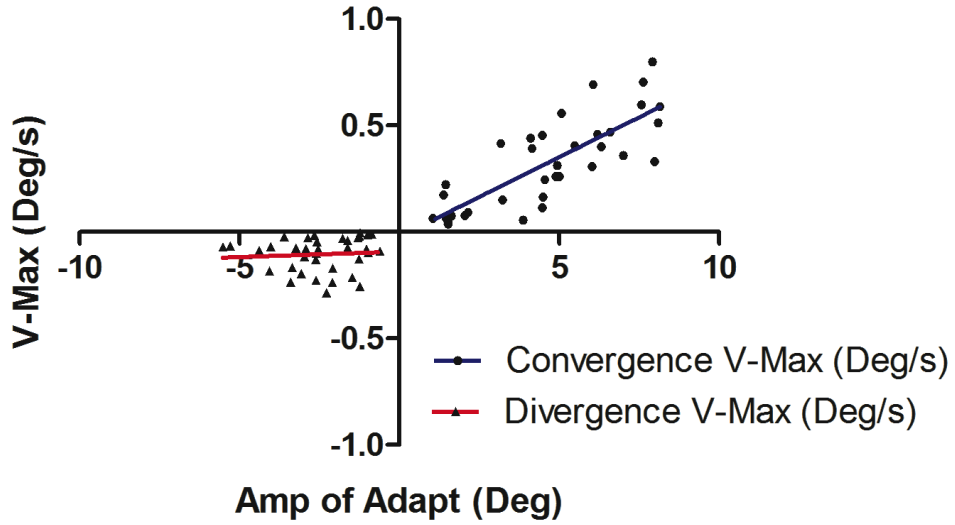

Figure 7-2 Main sequence analysis and regression functions for convergence (+) and divergence (-) of the pooled participants data.

Phasic vergence is known to demonstrate linear MS effects to convergence stimuli [34,86]. Similar linear effects seen here in TV adaptation indicate that the PV and TV systems share a common motor control strategy to convergent disparities and confirm model predictions. In contrast, published MS analysis of phasic divergence is variable [57]. The variability of phasic divergence is reflected in the non-linear MS relationship between TV adaptation and divergent stimuli. These results provide further evidence that vergence responses to convergent and divergent disparity reflect two separate neural processes. It is possible then, that the non-linear MS in divergence reflects a saturated neural response. This implies that divergence is more passive in nature (a relaxation of convergence), potentially relying more on the elastic forces of the anatomical orbital mechanics to move the eyes, as opposed to a burst of neural innervation. This type of relationship in the PV system to divergent stimuli would provide evidence for this and explain the lack of a MS relationship between the rate of adaptation and the amplitude of the stimulus.

7.5 Future Work

This study provides the first objective analysis of TV adaptation to both convergent and divergent non-congruent disparity stimuli. This method leverages the unique adaptive qualities of the vergence system to isolate the underlying mechanisms contributing to the total motor response. The results of this study highlight the different adaptive behaviors that can exist within a single motor unit to differing stimuli. Future work will apply this method to different clinical populations with abnormal binocular vision systems and compare the results to the binocularly normal controls studied here.

Chapter 8

Asymmetries between convergence and divergence reveal tonic vergence is dependent upon phasic vergence.

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8.1 Overview

Horizontal vergence eye movements are controlled by two processes, phasic and slow-tonic. Slow-tonic responses are hypothesized to be stimulated by the faster, pulse-step neural output of the phasic system. This suggests that the general behavior of each system should be similar; however, this relationship has yet to be investigated directly. We characterize the relationship between phasic and tonic vergence by quantifying directional asymmetries in the response properties of each mechanism to the same disparity amplitudes.

Four subjects viewed symmetric disparity steps dichoptically at 40cm while eye movements were recorded with infrared oculography. Phasic and slow-tonic convergence response properties increased linearly with disparity demand ($p < 0.01$), while divergence responses did not ($p > 0.05$). Phasic convergence responses were faster ($p = 0.012$) than divergence, where unnecessary saccades occurred more frequently. The average rate of slow-tonic change was correlated to the average peak velocity of phasic vergence at the same vergence demand, $r = 0.78$, $p < 0.0001$.

Clear directional asymmetries are observed in phasic and tonic vergence responses. The motor behavior of the phasic mechanism is retained within the slow-tonic response properties to both divergent and convergent disparities. These results provide empirical evidence of the relationship between phasic and slow-tonic vergence, suggesting that the latter depends on the motor function of the former, specifically the peak velocity. The recruitment of additional oculomotor mechanisms, such as saccades, improved the phasic response properties of the slower phasic divergence mechanisms but did not affect the response behavior of the slow-tonic system.

8.2 Introduction

Horizontal vergence eye movements align the two visual axes to the appropriate fixation depth. This alignment is a critical first-step for binocular vision and stereopsis. The primary sensory stimulus for horizontal vergence is retinal disparity (Figure 1-2) [103,208]. Optical blur and proximity also stimulate vergence through synkinetic neural cross-links in the 'near-triad'[20,103,209]. These reciprocal cross linkages between accommodation and vergence have been identified as accommodative-vergence [210] and vergence-accommodation [7]. Both vergence and accommodation are characterized by flexible, tonic neural innervation to their respective plants. This tonic innervation adjusts in the direction of newly adopted fixation distance to reduce the neural load on the reflexive fusion mechanism [42,209]. Control models of the horizontal disparity vergence system identify the reflexive and tonic changes in vergence as two separate

neural processes, 'phasic' and 'slow-tonic' respectively. These mechanisms combine to provide the required extraocular muscle innervation for binocular alignment (Figure 1-1A) [43]. Phasic vergence (PV) reflexively moves the two visual axes in opposite directions toward a new fixation distance in response to retinal disparity. This response also generates a cross-coupled change in accommodation via vergence accommodation [7,39,211,212]. When fixation is prolonged, a slow change in the underlying tonic levels of vergence innervation occur via the 'slow-tonic' vergence (SV) mechanism (Figure 1-1B) [42,81]. SV has been modelled to replace PV output over time (Figure 1-1B). This has been based upon changes in tonic levels of vergence that follow sustained viewing at increased levels of convergence (Schor 1979). This replacement of PV with SV innervation, in turn, modulates the cross-linked vergence-accommodation response in order to maintain a balance between accommodation and vergence [42,49,79,213]. Such is the case when viewing through base out prism; the vergence and accommodative stimuli are not cue-congruent (convergence is increased and accommodation is unchanged). The mechanisms through which SV and PV interact are unclear, as is the means by which SV, along with other oculomotor, vestibular and extra ocular muscle inputs influence the level of tonic vergence innervation [3].

The 'main sequence' is common analysis tool applied to saccadic eye movements [35]. In this analysis the peak velocity of individual movements are plotted against their respective response amplitude. The plot is then regressed, with the slope of this function providing a behavioral correlate for the degree of neural recruitment [29,35]. Previous work has demonstrated that this main sequence relationship is upheld in phasic vergence responses [34,56,86,143]; however, significant directional asymmetries have been reported between convergent and divergent phasic vergence main sequences [101,143]. This directional asymmetry extends to the latencies [101,157,174] and dynamics [101,174] of disparity-driven vergence responses. These data, along with neurophysiological evidence derived from primates [37,38,183] has provided the foundation for the hypothesis that disparity driven phasic divergence and convergence responses are controlled by separate neural substrates. The effects of stimulus direction on SV responses on the other hand, remains unclear [102,107]. Current models predict similar directional asymmetries ***should*** exist in SV, if PV is truly the driving stimulus for tonic vergence innervation change. The current study will test this hypothesis by quantifying and comparing the behavioral function of PV and SV to convergent and divergent disparities separately, using a main sequence analysis of each in healthy adults.

8.3 Methods

8.3.1 Participants

4 males (25-32y/o) completed the study. Subjects 2 and 3 had previous experience in oculomotor studies involving eye tracking. Informed consent was obtained after verbal and written explanations of the study procedures. The study protocol was approved by the University of Waterloo ethics review board and adhered to the tenets of the Declaration of Helsinki. An optometrist screened each participant to ensure normal binocularity. This was defined as greater than 6/7.5 corrected monocularly visual acuity, stereoacuity better than 40 arc seconds, with a near point of convergence greater than 9cm. Each subject's heterophoria was within 2 prism diopters of orthophoria as measured objectively via the eye-tracker and confirmed with the alternating cover-test. 2 Subjects were slight esophores (0.9 PD, S2 and 0.1 PD, S3) while the other two subjects were slight exophores (0.7 PD, S1 and 1.4 PD, S4). Subjects with small heterophoria's were recruited to control for the suggested effects of heterophoria amplitude and direction on phasic vergence responses [91,214].

8.3.2 Apparatus, eye-tracking & general procedures

Each trial began with 5 minutes of dark adaptation where the participants were instructed to relax their eyes. Each participant completed 18 SV experimental trials each (3 at each stimulus amplitude) and 6 PV trials on separate days. Stimuli were presented dichoptically at 40 cm on two 7-inch LCD monitors (Lilliput, UK) within a haploscope (Figure 8-1). Each eyes visual stimulus subtended 2.73° x 2.73°, with a line width of 0.08° (Figure 8-1) and had two vertical or horizontal lines unique to each eye's stimulus, which provided subjective suppression checks. Eye movements were recorded binocularly using video-based infrared oculography at 250 Hz (EyeLink 2; SR Research, Ottawa, Canada). All eye movements fell within the linear range (+/- 40°) of the eye tracker, which has a spatial resolution of 0.03° an average accuracy of 0.5° or less.

8.3.3 Dichoptic stimuli & test distance

Objects that physically shift in depth along the midline produce an equal (congruent) change in proximity, disparity and blur. Isolating disparity vergence mechanisms for study requires controlling the blur and proximal stimuli. This can be achieved dichoptically, using a haploscope (Figure 8-1), where both accommodation and proximity are held constant while disparity vergence is varied. In this "non-congruent" design, a much stronger SV response is required to prevent blur that would be generated via the PV driven vergence-accommodation cross-link. Because of this, SV function has typically been

characterized using base-in or base-out optical prism to create non-congruent disparity [155,215]; however, monocular optical prism creates a condition where fusion can be gained theoretically by a monocular movement and yet experimentally both eyes move, which invokes a complex vergence and saccadic interaction [216,217]. In contrast, symmetric disparities, created dichoptically, have typically been used to study PV. Interestingly, in these studies, the congruency of the initial stimulus from which PV is measured is not consistent and varies between non-congruent and cue-congruent, depending the disparity step sizes used [90,101,140]. This is likely due to the difficulty found in eliciting saccade-free divergence responses to larger uncrossed disparities [143]. Because the main goal of the current study was to examine the interaction between PV and SV responses, all stimuli began from an initially cue-congruent fixation position of 2.5 MA (8.44° based on a 60mm interpupillary distance) of convergence at a 40cm viewing distance. PV and SV responses were then generated by creating a symmetric, non-congruent change in disparity only. These conditions were designed to ensure that each system responses were generated using an identical type of disparity stimuli. A single testing distance of 40cm was selected for this study to provide an optimal environment for maximum divergence responses. Previous work has demonstrated a starting position bias for divergence, with larger and faster responses being elicited from closer testing distances (up to 40cm or 2.5MA's), while convergence responses were unaffected by testing distance [90]. Therefore, differences between phasic convergence and divergence responses would be expected to increase as the testing distance increases. Additionally, subjective ocular discomfort ratings for uncrossed disparities have been reported to be significantly higher at farther working distances [218], this information further supports the assumption that the fastest and most optimal divergence response would occur when the initial fixation distance was nearer to the observer, resulting in less symptomology when presented with uncrossed disparity. Since the purpose of this study was to characterize asymmetries between divergence and convergence responses, the testing distance of 40cm was chosen as any asymmetries between convergence and divergence at this distance would be expected to increase if the same procedures were performed at greater distances.

8.3.4 PV trials

Detailed descriptions of the methods used to measure PV have been reported in previous studies [90,101]. What is unique in this study is that every PV response measured was generated from an initially cue-congruent starting stimulus. Briefly, PV was stimulated by randomly presenting non-congruent disparity steps (2, 4, 8, 12° convergent; -2, -4, -6° divergent) at 40cm. A total of 30 step stimuli at each amplitude were presented over the course of 6 separate visits (210 total step stimuli). The order of step

amplitude presentation and the time delay (2-5s) between stimulus steps was randomized in Experiment Builder® (SR Research, Ottawa, Canada). These criteria have been shown to minimize predictive changes in vergence motor behavior [127]. All responses were visually inspected for blinks or saccades within the vergence responses.

8.3.5 SV trials

A detailed description of the SV trial procedures is published in previous work [55], which was based on work in other laboratories [82,188]. In each trial the subject first viewed a fixation cross (Figure 8-1) binocularly for 2 seconds at an initial vergence demand of 2.5-meter angles (8.44°), which was cue-congruent to the accommodative and proximal demand at 40cm, based on a 60mm interpupillary distance. The RE image was then extinguished for 15s, which resulted in a rapid decay of PV innervation, allowing the underlying tonic innervation to manifest in what is clinically defined as the near heterophoria. The RE image then reappeared and both left and right images were stepped inward to induce an additional (symmetric) 4, 8, 12° of convergence demand or outward by 2, 4, 6° to increase the divergence demand. This non-congruent disparity demand was fused for 15s, followed by another 15s of RE image extinction to re-measure the heterophoria. This was repeated with the same disparity amplitude until a total of 3 minutes of adapting disparity had been viewed and 13 heterophoria measures were obtained (Figure 8-1). The change in heterophoria over the course of a single trial defined SV.

8.3.6 Tonic accommodation trials

According to the model (Figure 1-1), attributing changes in heterophoria solely to the SV mechanism assumes that slow-tonic accommodation (SA) was unchanged; otherwise, accommodative-vergence would decrease, reducing the vergence output during monocular viewing [43]. To confirm this, 3 additional experimental trials were completed by each subject to assess slow-tonic accommodation before and after prolonged non-congruent disparity viewing. The same procedures (section 8.3.5) were completed once for the -6, 12 and 0° of additional non-congruent disparity. After 5 minutes of dark adaptation, accommodation was measured continuously for 15s by a commercially available photorefractor (PowerRefractor®, Multichannel Systems, Reutlingen, Germany) at 25Hz, while the individual monocularly fixating a 0.2 cycle per degree difference of Gaussian target at 4 meters. This target mitigates blur-driven accommodation and any vergence driven accommodation is eliminated via occlusion allowing SA to be isolated [212]. The average accommodative state of the last 3s of monocular fixation defined the initial SA innervation. The same procedures as in methods section 2.4 were then

completed. Immediately after, SA was re-measured using the same protocol as above. Pre and post measures of SA were subtracted and the difference compared across disparity adapting conditions. Absence of a change in pre vs post measures between stimuli amplitudes would suggest these various cue-conflict stimuli have little to no effect on tonic accommodation.

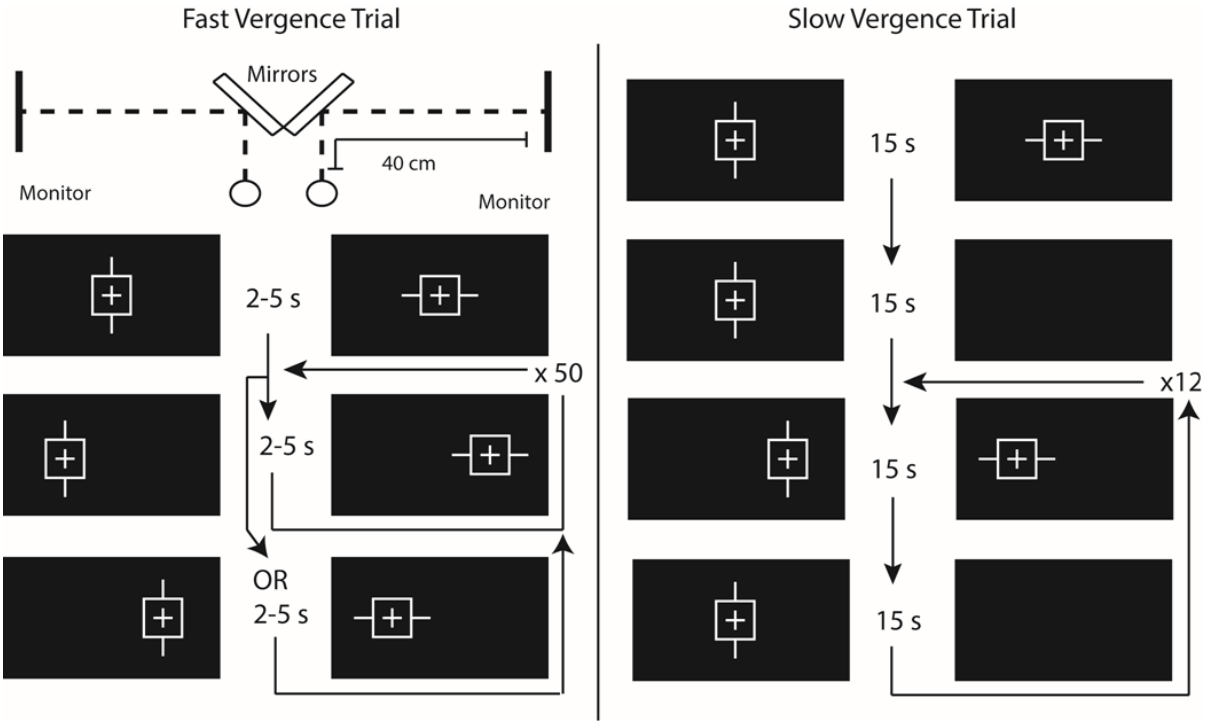

Figure 8-1: PV trials: PV was elicited from horizontal disparities created dichoptically. Fast vergence responses were defined by the initial reflexive motor response (above left). Note, dichoptic disparity presentation clamps the accommodative demand. Slow Trials: SV was measured as the rate & amplitude of heterophoria change (sampled every 15s) during 3 minutes of disparity viewing. Heterophoria was measured by extinguishing the right stimulus to simulate occlusion, above right.

8.3.7 Motor response classification (PV trials)

Pilot data of the PV trials revealed 3 general types of motor responses to the symmetric step stimuli; pure vergence, saccades and saccade-vergence (Figure 8-3). This is not unexpected, as saccades

often occur in conjunction with vergence and may facilitate the overall vergence response [66,89,144,219]. "Pure vergence" responses were defined by the absence of a visible conjugate movement (Figure 8-3 Left). The majority of the analysis pertains specifically to these movements, as they are most representative of an isolated disparity driven vergence response. "Saccadic-vergence" responses were initiated by a vergence movement and contained a small conjugate component within 400ms of the response initiation (Figure 8-3 Center). The conjugate components were easily identified visually and were generally smaller than 1-2° in amplitude. "Saccade" responses were initiated by a large conjugate movement, always exceeding 1° in amplitude and were subsequently followed by a vergence movement combined with multiple other saccades (Figure 8-3 Right). These responses were not analyzed, along with responses in which a blink occurred within +/- 300ms of the stimulus step change or during a response. Because the number of each movement type varied between individuals, statistical tests conducted on these data utilized the appropriate corrections for unequal variances and sample sizes.

8.3.8 Data analysis

Eye position was recorded in screen pixel coordinates and analyzed offline in MatLab® (Math Works, USA) using a custom analysis package. Vergence was defined as left minus right eye position. Statistical analysis was comprised of either repeated measures analysis of variance, with Greenhouse-Geisser correction, two-tailed Welch's unequal variance t-tests, or bivariate regressions (individual x - response amplitude and y - peak velocity variance was calculated for each participants dataset). All reported average data are given with their respective standard deviation (SD)

In the PV trials, the start and end of each phasic step response was identified using a 2°/s velocity threshold criterion, following the same analysis and smoothing criteria as previously published [28]. The amplitude, duration, peak velocity and latency of this step vergence change defined the PV response (

Figure 8-2). Main Sequence plots for PV were regressed based on the disparity stimulus direction (Figure 8-5).

In the SV trials, heterophoria was defined as the average vergence angle of the last 3s of the RE stimulus off periods [55,188]. Each heterophoria measure was plotted as a function of time and an exponential curve was fit to this plot for a single trial. The change in heterophoria defined the change in underlying tonic vergence innervation and the magnitude of the adaptive change of SV. The time constant and span (amplitude) of these exponential functions was used to calculate the maximum velocity (Vmax) of SV by dividing span (°) by the time constant (s) from each trial (

Figure 8-6). The Vmax (°/s) was then plotted over the amplitude of heterophoria change (span) to define the SV main sequence plot. SV main sequence plots to divergence and convergence trials were separately regressed to determine the main sequence relationship for each system.

8.4 Results & Discussion

8.4.1 General observations

Each subject was able to fuse all non-congruent disparity stimuli without reporting sustained diplopia, blur or a visual loss of the suppression checks. As expected, directional asymmetries were observed in PV response characteristics and main sequence regressions. Consistent with model predictions, these directional asymmetries were retained within the SV response properties and main sequence regressions. The rate of tonic innervation change is correlated to the peak velocity of the phasic response to an equal disparity step amplitude.

8.4.2 PV motor behavior

PV function to convergence and divergence stimuli was initially characterized from the two similar step stimuli (2° & 4°). The averaged response and velocity profile for one subject's 4° PV data is illustrated in

Figure 8-2. Clearly, pure divergence and convergence responses are different in this subject and this finding was consistent across all participants. A summary of the pooled average PV response parameters can be found in Table 8-1 & Table 8-2. The average response amplitude, peak velocity and latency for divergence and convergence were compared. In all cases, pure phasic convergence responses were faster, larger and had a shorter latency than divergence.

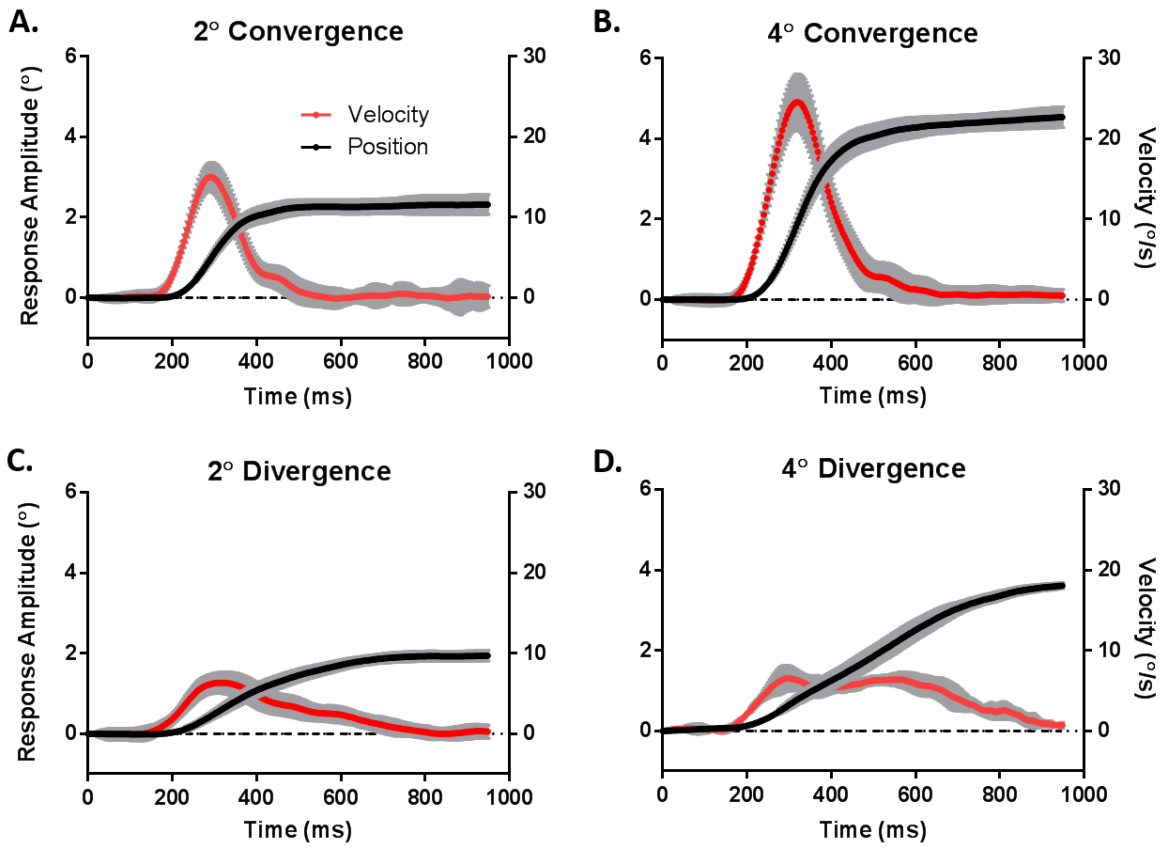

Figure 8-2: Average vergence responses (position - black and velocity - red) and SD for phasic convergence (A = 2°, B = 4°) and divergence (C = 2°, D = 4°) responses to disparity step stimuli for one subject. The response latency, amplitude and peak velocity are clearly different between convergence and divergence. The peak velocity clearly increases in convergence responses between 2° and 4° stimuli, resulting in increased response amplitude. In divergence, the vergence response peak velocity does not change for larger step stimuli amplitudes. Instead, to increase divergence response amplitude, the width of the velocity waveform is increased, resulting in increased response duration, resulting in larger movement amplitude.

Stimulus	Direction	Response Amplitude (˚)	Peak Velocity (˚/s)	Latency (ms)
2˚	**Convergence**	2.08 (0.2)	11.06 (2.3)	130 (7.3)
	Divergence	1.39 (0.4)	6.49 (1.3)	172 (22.7)
	p-value	< 0.001	< 0.001	< 0.001
4˚	**Convergence**	4.03 (0.3)	23.57 (3.08)	129 (9.4)
	Divergence	2.53 (0.8)	7.21 (2.1)	174 (24.0)
	p-value	< 0.0012	< 0.001	0.002

Table 8-1: Summary of averaged (SD) PV characteristics taken from pure vergence response data across all subjects. While the reported phasic divergence response amplitude appears to fall short of the stimulus demand, this is based on the velocity threshold of 2˚/s set to define the phasic response. The final divergence response amplitude closely matched the stimulus amplitude, but this was due to a very slow visually guided drift at the end of the movement, after the 'end' velocity threshold had been reached, as can be seen in Figure 8-3. Welch's unpaired t-test p-values are noted for the comparison of convergence vs. divergence for each parameter.

Consistent with previous findings, larger step stimuli elicited more vergence responses containing at least one saccade within the first 250ms of eye movement onset [101]. At least 5 pure vergence responses were elicited from each convergence step stimuli amplitude, while there were no pure vergence responses generated to the 6˚ divergence stimuli by any subject. A repeated-measures ANOVA was used to compare the frequency of each movement type and the effects of stimulus direction and amplitude for the two overlapping disparity stimuli amplitudes (Table 8-2). A main effect of movement type was significant, $F(3,18) = 33.6$, $p < 0.001$. Significant interaction effects were noted between movement type and stimulus amplitude, $F(3, 18) = 3.58$, $p = 0.03$, and movement type and stimulus direction, $F(3,18) = 111.2$, $p < 0.001$. A Tukey post-hoc analysis demonstrated that divergence stimuli elicited a greater number of saccadic-vergence responses at each stimulus amplitude, while convergence stimuli elicited a greater number of pure vergence responses. This result indicates that both the stimulus direction and amplitude of the target influenced the resulting motor response within this group of individuals. The number of blinks and saccade dominated responses were not significantly different at either stimulus amplitude.

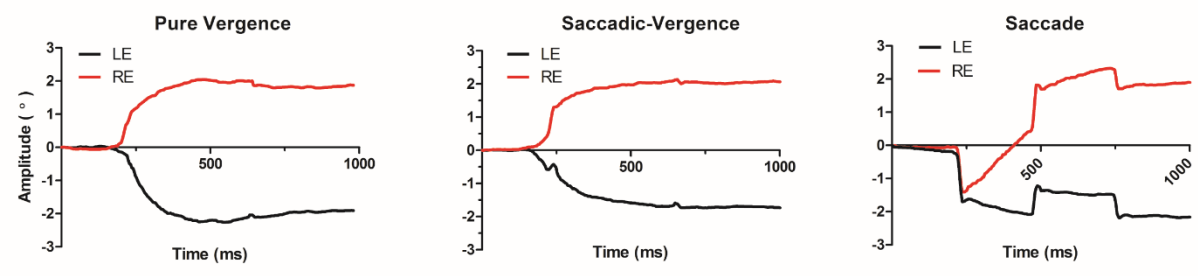

Figure 8-3: Examples of motor response type during the PV trials. Left: "Pure vergence" response, containing no significant conjugate components. Center: "Saccadic-vergence" response, initiated by a vergence movement and containing a small (< 1.0˚) but significant conjugate (saccadic) component within 300m/s of the response initiation. Right: "Saccade" response, where by the initial motor response is dominated by a large (>1.0˚) conjugate component**.**

Stimulus	Direction	Pure Vergence	Saccadic-Vergence	Saccade	Blink
2˚	**Convergence**	24 (5.8)	1.25 (0.9)	0.75 (0.9)	4 (4.6)
	Divergence	15 (6.7)	9.5 (5.9)	1.5 (1.7)	4 (4.2)
	p-value	< 0.001	< 0.001	1.0	1.0
4˚	**Convergence**	25.3 (5.1)	2.3 (3.3)	0.3 (0.5)	2.3 (2.1)
	Divergence	2.8 (1.5)	22.5 (4.4)	0.8 (0.9)	4.0 (4.1)
	p-value	< 0.001	< 0.001	1.0	1.0

Table 8-2: Average (SD) count of each movement type made during the 30 PV trials to the 2˚ and 4˚ disparity step stimuli. Significance values listed in red denote the post-hoc Tukey HSD corrected p-values.

Main sequence plots (Figure 8-4) and regression summaries (Table 8-3) were generated from the pure vergence responses to all stimuli amplitudes presented. Directional asymmetries were clearly visible when the data was plotted for each main sequence. In each subject, a significant linear relationship was seen in the main sequence of PV to convergence disparities. These convergence PV regression functions were significantly different between subjects, $F(3, 161) = 8.55$, $p < 0.0001$. The slopes of these regression function are similar to what was previously reported for convergence stimuli [101,160]. The two subjects that had previous experience with eye movement studies demonstrated the steepest slopes, as is also consistent with previous literature [101]. No linear relationship was observed between response amplitude and peak

velocity in phasic divergence main sequence regressions, for any subject ($p > 0.09$, Table 8-3). When compared within each subject, the slope of the phasic convergence main sequence regression was significantly different from the slope of the phasic divergence main sequence regression ($p < 0.05$, Table 8-3).

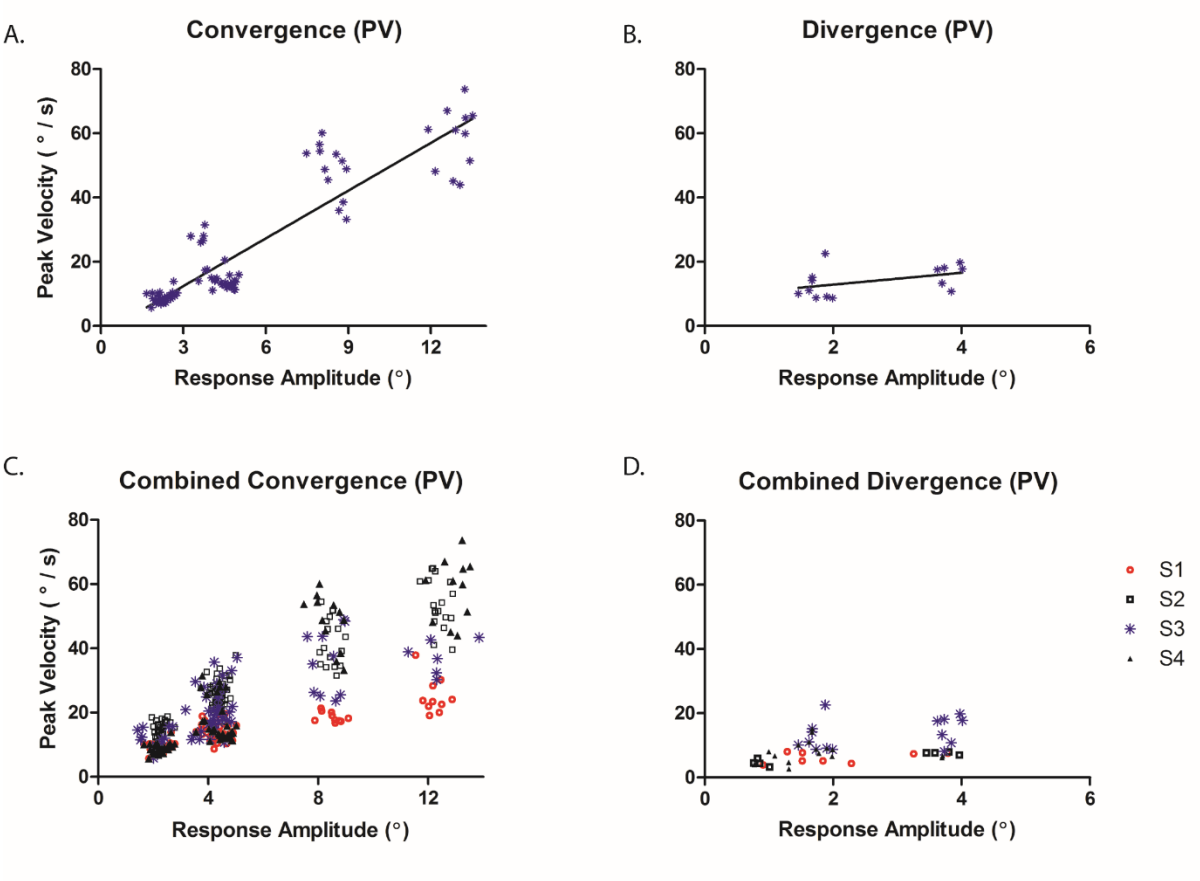

Figure 8-4: PV main sequence plots to convergence (A&C) and divergence (B&D) disparity for one subject (A&B) and all subjects combined (B&D). The linearity of the main sequence relationship in convergence is apparent, while not in divergence.

Subject	Convergence		Divergence		Slope Comparison (H_o= no difference)
	Regression Slope	p-value (H_o= 0)	Regression Slope	p-value (H_o= 0)	
S1	2.75 (± 0.1)	0.0003	0.46 (± 0.2)	0.13	0.02
S2	3.90 (± 0.2)	< 0.0001	0.54 (± 0.3)	0.09	0.03
S3	4.44 (± 0.2)	< 0.0001	1.12 (± 0.5)	0.17	0.009
S4	2.68 (± 0.2)	< 0.0001	-0.72 (± 0.6)	0.25	0.03

Table 8-3: Main sequence bivariate regression slopes for each subject's PV responses. Regression functions were tested against the null hypothesis of zero slope (no relationship) and then within subject, between stimulus direction.

8.4.3 SV motor behavior

Consistent with the results of the PV trials, directional asymmetries between convergence and divergence were clear in the SV trial data. Table 8-4 outlines the average exponential functions fit to each SV trial. Figure 8-5 depicts these functions fit to the averaged trial data at each stimulus amplitude for one subject. Repeated measures ANOVA was used to assess the effect of stimulus amplitude on the amplitude of SV change (span), time constant (tau) and maximum velocity of adaptation (Vmax) for each stimulus direction separately. There was no main effect of subject or interaction effects in these analysis' ($p > 0.05$). A main effect of stimulus amplitude on the amplitude of SV innervation change was significant for both convergence; $F(2,4) = 36.0$, $p = 0.003$, and divergence $F(2,4) = 99.2$, $p < 0.001$. Therefore, increasing the amplitude of the disparity increases the amount of SV innervation change in these participants with minimal heterophoria's. A main effect was also found for convergence amplitude on Vmax; $F(2,4) = 29.3$, $p = 0.004$ and the time constant $F(2,4) = 31.5$, $p = 0.004$. This demonstrates that as the amplitude of the convergence disparity increased, so did the rate of SV innervation change in these individuals. In contrast, there was no main effect of stimulus amplitude on the Vmax; $F(2,4) = 0.19$, $p = 0.83$, and time constants, $F(2,4) = 5.4$, $p = 0.08$ for divergence, indicating that the rate of SV change was not affected in these participants by the prolonged disparity stimulus amplitude.

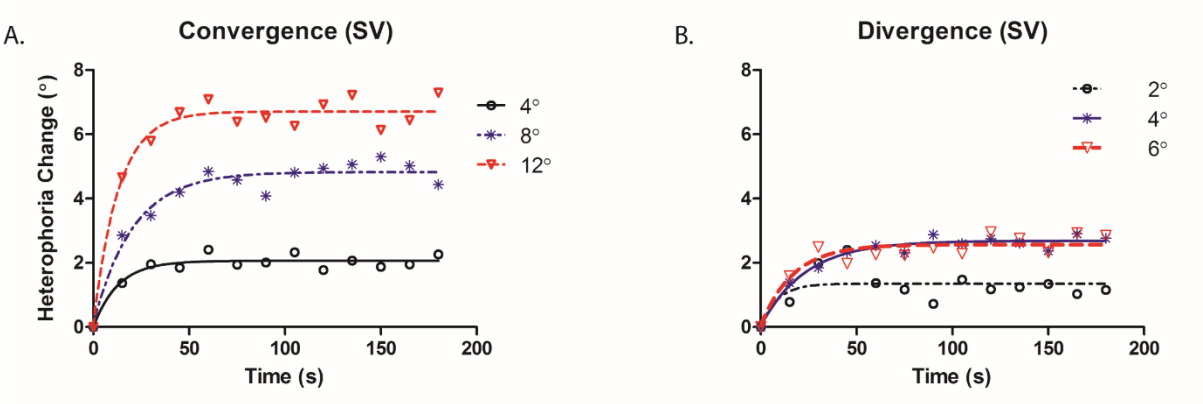

Figure 8-5: Plot of heterophoria measures for 6 SV trials of different disparity stimulus amplitudes (left convergence, right divergence) with exponential functions fit. The time constant, amplitude maximum velocity of heterophoria change was defined for each trial from these functions.

	Convergence			Divergence		
Stimulus	**4˚**	**8˚**	**12˚**	**2˚**	**4˚**	**6˚**
Span (˚)	1.82 (0.9)	4.53 (0.8)	7.25 (1.1)	1.38 (0.4)	2.57 (0.79)	3.27 (1.5)
Tau (s)	27.12 (16.9)	19.10 (8.5)	13.39 (4.1)	26.34 (25.6)	42.82 (42.8)	85.03 (98.2)
Vmax (˚/s)	0.12 (0.04)	0.31 (0.07)	0.53 (0.07)	0.11 (0.08)	0.11 (0.07)	0.09 (0.08)
R^2	0.48 (0.2)	0.68 (0.3)	0.81 (0.1)	0.42 (0.3)	0.59 (0.3)	0.58 (0.3)

Table 8-4: The average (SD) span, time constant (tau) and R^2 for the exponential curves fit to each SV trial as shown in Fig. 6. The absolute values of the measured heterophoria were used to create the exponential functions.

A Welch's t-test comparison of the group average Vmax (mean difference: 0.077 ± 0.1°/s, p = 0.75), amplitude (mean difference: 0.65 ± 0.33°, p= 0.11) and time constants (mean difference 15.7 ± 13.3s, p = 0.24) of heterophoria change to the 4° stimulus were not significantly different. This result was consistent across subjects and demonstrates that, at this stimulus amplitude, SV behavior is similar in each direction.

Directional asymmetries were most notable in SV when the main sequence plots (Figure 8-6) and regression functions (Table 8-5) were analyzed. While positive slopes of main sequence regressions were significant in each subject to convergence stimuli ($R^2 > 0.65$, $p < 0.001$), no such linear relationships were present in any subject to divergence stimuli ($R^2 < 0.20$, $p > 0.30$). In all subjects, the slope of the convergence SV main sequence regression was significantly different from divergence regression slopes ($p < 0.05$, Table 8-3). This result highlights the different motor response properties of the SV mechanism to prolonged convergent and divergent disparities.

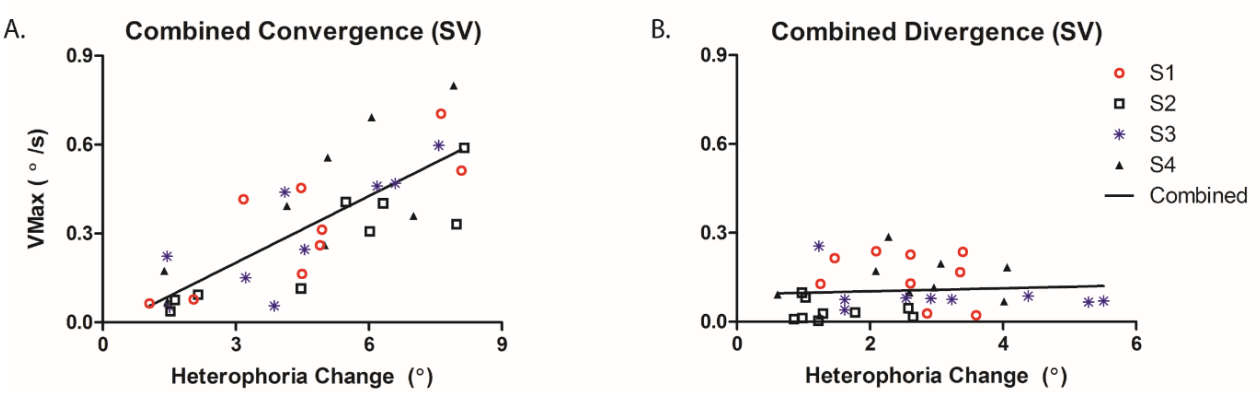

Figure 8-6: SV main sequence plots and regressions of the combined data from all trials in all subjects. Heterophoria change and Vmax represent the amplitude and rate of SV change. Linear main sequence effects are seen to convergent (A) stimuli in each subject, while no relationship was found in the main sequence regressions to divergent (B) disparity stimuli.

Subject	Convergence		Divergence		Slope Comparison (H_o = no difference)
	Regression Slope	p-value (H_o= 0)	Regression Slope	p-value (H_o= 0)	
S1	0.088 (± 0.01)	0.0003	- 0.011 (± 0.03)	0.74	0.01
S2	0.073 (± 0.01)	0.0005	- 0.007 (± 0.02)	0.70	0.03
S3	0.091 (± 0.02)	0.007	- 0.017 (± 0.02)	0.30	0.004
S4	0.095 (± 0.02)	0.001	0.0053 (± 0.02)	0.84	0.02

Table 8-5: Main sequence bivariate regression slopes for each subject's SV responses and the combined data function. Regression functions were tested against the null hypothesis of zero slope (no relationship) and then compare between stimulus directions for each subject (null hypothesis, slopes are equal).

8.4.4 PV and SV relationship

Figure 8-7 depicts the relationship between PV and SV mechanisms to the different disparity directions for one participant. The trends exhibited were consistent across participants. In both PV and SV, positive linear slopes of main sequence regressions were observed to convergence stimuli in all subjects. No such relationship was observed in the divergence condition for either vergence mechanism, as well as any subject (Table 8-3 & Table 8-5).

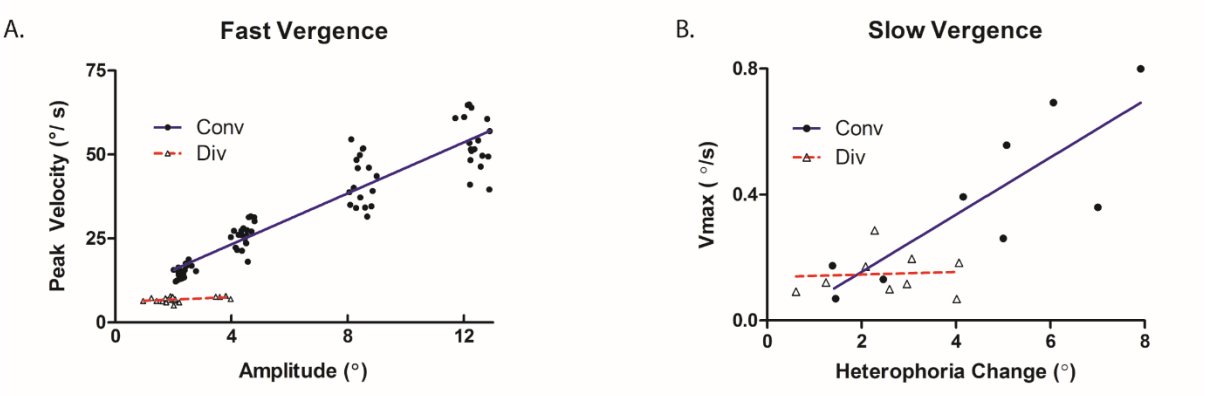

Figure 8-7: Main sequence plots and regressions for both PV (A) and SV (B) to both convergent and divergent disparities. All subjects demonstrated linear main sequence effects to convergent disparity stimuli in PV and SV responses, while no such relationship was noted in PV or SV to divergent disparities.

A within subject one-way comparison was conducted between the slope of each PV and SV main sequence regression. Divergence exhibited no significant difference between each regression slope in all subjects ($P > 0.15$). This result would be expected, as all divergence main sequence regression slopes were not significantly different from zero to begin with. In contrast, every participant's convergence PV and SV main sequence regression slopes were significantly different ($P < 0.01$). The slopes of the PV regressions were always significantly steeper than SV. These results imply a direct relationship between the PV and SV mechanism for both convergence and divergence. In the latter case, the flat main sequence of each mechanism implies a saturation of the PV response peak velocity, which then translates to a similar saturation of the SV Vmax. To explore this relationship between each mechanism further a Pearson correlation analysis of the pooled data was conducted. The average Vmax of SV was correlated to the average peak velocity of PV responses at each stimulus amplitude. There was a statistically significant correlation between SV and PV velocities in convergence, $r = 0.69$ (95% CI = 0.20 - 0.91), $p = 0.01$, while no significant correlation was demonstrated in divergence, $r = -0.14$ (95% CI = -0.74 – 0.58), $p = 0.72$. A direct comparison of these different correlations using a method first described by Fisher [220] indicated these correlations are different from one another ($z = 1.67$, $p = 0.05$). This difference is clearly the result of the variance within the divergence correlation and the range of data available, which is much smaller than that of convergence due to the lack of pure vergence responses to larger (6°) uncrossed

disparity steps. The same correlation analysis was then conducted on the pooled data from above, as statistically they appear similar. This person correlation demonstrated a much stronger relationship between PV peak velocity and SV Vmax, $r = 0.78$ (95% CI = 0.52 - 0.91), $p < 0.0001$. This result clearly highlights the relationship between the motor function of the reflexive PV mechanism and the subsequent rate of tonic vergence innervation change via the SV mechanism.

8.4.5 Slow-Tonic accommodation & zero disparity

Attributing changes in heterophoria solely to the SV mechanism assumes that SA was unchanged. A repeated measures analysis of variance of the tonic accommodation trials (Methods 8.3) revealed no significant effect of stimulus amplitude on tonic accommodative levels, $F(2,9) = 0.23$, $p = 0.77$**.** A Welch's t-test comparing the average change in tonic accommodation in each stimulus condition against a null hypothesis of zero change was also not significant, ($0^\circ = 0.06 \pm 0.25$ D, $p = 0.65$; 6° divergence = -0.05 ± 0.35 D, $p = 0.78$; 12° convergence = 0.08 ± 0.22 D, $p = 0.52$). Combined, these results confirm the assumption that tonic accommodation was not significantly altered after prolonged viewing of both cue-congruent and non-congruent disparity stimuli of fixed accommodative demand. This is consistent with previous findings [215]. The heterophoria was unchanged after prolonged viewing of the zero disparity (cue-congruent) condition (mean change $0.07 \pm 0.39^\circ$, $p = 0.74$). Further to this, a regression analysis of each heterophoria measurement in the zero-disparity condition did not demonstrated a significant trend in any of the participants, (slope = 0.001 ± 0.009, $p > 0.2$). This confirms the assumption that prolonged viewing of cue-congruent accommodative-disparity demands induces little change in SV and, therefore, any changes in SV measured were not attributable to the experimental apparatus and are solely driven by the non-congruent conditions.

8.5 Discussion

8.5.1 Directional asymmetries & relationship between PV and SV

Clear directional asymmetries were present in disparity driven vergence responses. The (positive) linear relationship between stimulus amplitude and response peak velocity exhibited by the PV mechanism to convergent stimuli is reflective of increased neural recruitment in the motor and premotor vergence areas [47]. This differed drastically from phasic divergence responses, which showed no significant relationship between these parameters, suggesting either early saturation or passivity of this mechanism. Most noteworthy is the fact that the motor behavior expressed by the different phasic mechanism was retained within the respective SV mechanisms response properties. In other words, when

the response amplitude and peak velocity of PV was reduced, so was SV response amplitude and Vmax. This conclusion is supported by the strong correlation between the reflexive fusional vergence movement (PV – peak velocity) to step disparity stimuli and the subsequent rate of tonic innervation change to the same stimuli (SV - Vmax). A key difference between this study and previous investigations [90,101] was defining convergence and divergence with respect to a cue-congruent accommodative, vergence and proximal starting position . We felt this important since SV has been shown to influence PV response dynamics [82,96,160]. Defined this way, disparity driven divergence differs significantly from convergence in both the PV and SV neural mechanisms. Unlike convergence, the velocity of divergence does not vary significantly with response amplitude for both phasic and slow-tonic vergence (Figure 8-2). Thus the degree of neural recruitment with increasing demands differ between the two response directions. These results are consistent with the existence of separate neural substrates for each directional motor (vergence) response [58,90,101,174,221]. The results support current models of disparity driven vergence, which predict that SV innervation is driven by the response output of the phasic vergence mechanism as demonstrated by the aforementioned correlations (Figure 1-1A). Our results provide novel evidence for this relationship using identical stimuli and similar analytical metrics. While divergence and convergence are clearly the result of two different patterns of neural innervation, the main sequence effects exhibited by each PV mechanism are retained within the respective SV response properties. The positive correlation between PV peak velocity and SV Vmax suggests that increasing neural recruitment within the PV mechanism results in a similar increase in recruitment within the SV mechanism.

8.5.2 Stimulus Cue-Congruency

There is greater variance in the phasic divergence response and main sequence regression data between studies and subjects when compared to phasic convergence [57]. Previous investigations have reported main sequence regression slopes in phasic divergence that were significantly less than convergence, although a direct comparison was not made in these studies between each regression [90,101]. The results of the present study have demonstrated that, under these specific conditions, there is a negligible if any relationship between the amplitude and velocity of phasic divergence responses. This implies limited, if any, neural recruitment within the divergence motor substrate to increasing uncrossed disparity demands. In the two other independent investigations cited, phasic divergence responses initiated from both cue-congruent and non-congruent starting demands were used. This was especially the case when larger divergence responses were required [90,101]. In order for each of these studies to obtain purely divergent responses (with no saccades) to 6° or 8° disparity steps, the initial starting stimulus was

non-congruent (more convergence required than accommodation). Our results indicate that large (> 4º) divergence step responses from a cue-congruent starting demand are next to impossible to make without involving other oculomotor motor systems (saccades). We suspect that the divergence responses elicited by presenting disparity steps from a vergence demand greater than accommodation (over-converged) in each of these studies also includes an additional relaxation of the initial convergence neural drive and is not exclusively a disparity driven divergence response. Mitchell and Westheimer first defined such divergence responses from a non-congruent starting stimulus as 'convergence relaxation'[103]. This additional convergence relaxation, when added to the underlying phasic divergence drive, may be responsible for increasing the response peak velocity to larger divergent disparity stimuli, as previously reported in each of these studies [90,101,140].

8.5.3 Saccadic Interactions

The recruitment of small saccades is significantly greater in divergence responses compared to convergence in our data (Table 8-1). We speculate that these conjugate, saccadic-like movements within divergence responses reflect the recruitment of additional oculomotor networks (proximity, accommodation, saccades) to compensate for the slower divergence mechanism. This additional recruitment may provide two specific advantages; the first being faster monocular foveal fixation and the second being faster binocular fusion. The latter is investigated by a post-hoc analysis of the grouped average peak velocity of pure vergence vs. saccadic-vergence responses. Phasic vergence peak velocities were not different between pure convergence (2˚**:** 11.06 ± 2.3˚/s, 4˚**:** 23.57 ± 3.08˚/s), and saccadic-convergence responses (2˚**:** 10.38 ± 1.4˚/s, 4˚**:** 23.70 ± 2.95˚/s); (mean difference at 2˚ stimulus: 0.68˚/s, p = 0.63; and at 4˚: 0.13˚/s, p = 0.86). Whereas saccadic-divergence peak velocities (2˚**:** 9.31 ± 1.5˚/s, 4˚**:** 11.06 ± 2.3˚/s) were significantly higher than in pure divergence (2˚, p = 0.021; 4˚, p = 0.023); (mean difference at 2˚ stimulus**:** 2.83˚/s, p = 0.03; and at 4˚: 3.62˚/s, p = 0.02). More directly, this increase in divergence peak velocity due to saccades was significantly greater than convergence at both 2˚ (p = 0.03) and 4˚ (p = 0.02) disparity amplitudes. These results indicate that divergence responses benefit from the addition of these small conjugate movements, whereas convergence does not.

These saccadic-vergence movements bear a strong resemblance to the accommodative-vergence movements described as 'Type III' vergence movements in an earlier study of vergence dynamics to accommodative stimuli [217]. This response type in our data may reflect the effects of additional accommodative influences as well. The Alvarez group has demonstrated that patients with convergence insufficiency (CI) have slower phasic convergence responses than controls [219]. These slower responses

were strongly associated with increased saccades within convergence responses. After successful orthoptic therapy, the number of phasic convergence responses containing saccades significantly decreased when the peak velocity of the PV response normalized[139,141,219,222]. Consistent with this result, a correlation analysis of the frequency of saccadic-vergence with the phasic peak velocity revealed a strong inverse correlation for both 2° ($r = -0.75$, $p = 0.03$) and 4° ($r = -0.89$, $p = 0.003$) step vergence responses. This result indicates that larger peak velocities of the phasic response result in reduced frequency of saccadic-vergence interactions. The phasic divergence motor behavior presented herein shows many similarities to the response properties of the CI's studied by Alvarez. If divergence is limited by the size of its dedicated neuronal substrate in our sample population, as we speculate below, it is possible that the phasic convergence responses of CI patients reflect an underdeveloped convergence mechanism. Reduced (slow) phasic divergence responses result in slowed slow-tonic vergence change in the data presented in the current study. This reduced rate of replacement of PV with SV has been shown to increase the cross-linked vergence-accommodation response due to the prolonged output of the PV response needed to acquire and maintain binocular fusion and is strongly correlated to the symptoms of eye strain and fatigue experienced by individuals with CI [49,215]. The results of this study indicate that the size of these neural substrates and thus the strength of the PV output dictates the subsequent function of the SV mechanism. Therefore, rehabilitative therapies, such as orthoptics, for conditions such as CI should aim to strengthen the phasic convergence response, which, in turn, should result in improved SV response dynamics and lead to the desired reduction in symptomology. In the broader context of motor adaptation these results suggest that slow adaptive processes, such as SV innervation change, are modulated by the strength and function of the reflexive motor response that drives the initial movement.

8.5.4 Neural Recruitment & Model Predictions

Linear main sequence effects in saccades and phasic convergence responses reflect increased neural recruitment in the premotor and motor areas [29,35,58]. The linear main sequence relationships seen across subjects and vergence mechanisms (PV & SV) to convergent disparities would therefore imply an increased neural response via increased recruitment. When the same logic is applied to the divergence results, the opposite conclusion can be drawn. Negligible linear effects in the main sequence regression plots for PV and SV to divergent disparities suggests a lack of an enhanced neural response and recruitment to incrementally larger disparities. Poor or absent recruitment would imply this system is saturated. Vergence neurons that respond preferentially to divergent disparities have been identified in many premotor and motor areas in previous cell-recording studies in primates. The existence of such

neurons suggest disparity driven divergence does have a dedicated neural circuit. However, when compared to the number of convergence neurons in similar areas, the populations of divergence neurons are less [37,47,183], with the exception of the posterior interposed nucleus [203]. The anatomical vergence resting position is parallel or slightly divergent when measured under general anesthesia [104]. Tonic vergence, measured in absolute darkness, is slightly convergent [104,155,223,224]. If the orbital mechanics naturally drive the vergence position towards a divergent posture (such as a spring pulling back to its resting state), a strong active neural drive would not be required for divergence in response to uncrossed retinal disparities. In contrast, convergence must overcome these orbital mechanics to move fixation closer in the presence of crossed disparity. The closer the fixation distance, the stronger the response required to overcome these increasing elastic forces. It is then sensible to expect to see larger pools of convergence neurons available to recruit, which would then result in the linear main sequence effects seen in both PV and SV to convergent disparities. The common clinical reporting that divergence is much less amenable to change with orthoptics can be understood as ceiling effect for an already saturated response having a differing neuron pool than convergence. In terms of model predictions in relation to this studies primary objective, the preservation of linear main sequence effects from phasic convergence to slow-tonic convergence and limited if any main sequence relationship in both divergence mechanisms combined with the strong correlation between PV and SV velocities support the hypothesis that the pulse-step output of the PV system provides the required stimulus for the SV mechanism.

8.6 Conclusions

The current study adds to the growing evidence from human oculomotor studies and neurophysiological studies in primates that convergence and divergence responses exhibit significantly differing motor response behavior and differing patterns of neural recruitment. This study provides direct empirical evidence that adaptive, slow-tonic vergence responses to non-congruent accommodative-vergence demands are underpinned by the response properties of the reflexive PV. This interaction is not equal between convergence and divergence and is strongly correlated to the peak velocity of the phasic vergence response.

Chapter 9

Sensorimotor adaptation of reflexive vergence eye movements is directionally biased.

This chapter has been submitted to Vision Research and is currently under review.

Manuscript #: VR-18-42

9.1 Overview

Divergence is known to differ from convergence across a wide range of clinical parameters. We have postulated that a limited neural substrate results in reduced fusional divergence velocities and subsequently a reduced capacity to adapt tonic vergence to uncrossed disparities. We further investigated this hypothesis by characterizing the degree of plasticity in reflex vergence to repetitive end-point errors using a disparity-based double-step paradigm.

10 adults (26±3.8y/o) completed 4 study visits. Reflexive convergence or divergence was measured (250Hz infrared oculography) to a 2° disparity step and then lengthened or shortened via a repeated double-step (2°±1.5°). Stimuli were presented dichoptically at 40cm.

Adaptive modification of vergence responses was similar between directions for the shortening conditions ($p>0.69$), suggesting a common neural mechanism responds to overshooting errors. In comparison, adaptive lengthening of convergence was slower ($p<0.01$), but of equal magnitude, suggesting a second neural mechanism with a longer time constant for undershooting errors. Divergence response velocities were slower at baseline ($p<0.01$) and did not increase after adaptive lengthening ($p=0.22$). Instead, increases in divergence response amplitudes were a result of increased response duration ($p<0.02$), implying saturation of the reflexive, preprogrammed pulse response.

Adaptive responses serving to increase or decrease reflexive vergence recruitment were asymmetric. Adaptive lengthening of convergence and divergence identified further directional asymmetries. The results support the hypothesis that the neural substrate underlying divergence is attenuated, resulting in reduced reflexive plasticity when compared to convergence. The clinical implications of these results are discussed.

9.2 Introduction

9.2.1 Overview

Plasticity in motor systems allows us to maintain accurate and precise movements throughout our lives. Changes in the sensory-motor environment create errors and uncertainty in movement execution. These errors stimulate the neural mechanisms that underlie plasticity. These mechanisms recalibrate future movements with the purpose of maintaining optimal function[145]. This plasticity, generally referred to as sensorimotor adaptation, can respond to both internal error sources (fatigue, growth, and physical injury) and external error sources (catching a Frisbee on a windy day, walking on an uneven surface).

Virtual and augmented reality head mounted displays constitute a very drastic change in our sensory-motor environment. New prescription spectacle lenses can alter the magnification and distort of our visual environments as well. Such changes demand a robust adaptive response from the eye movements that sub-serve binocular alignment and allow for stereopsis; yet we are only just beginning to understand the function and limits of these adaptive capacities. The current study aims to quantify the directional effects of error signals on the adaptive capacity of reflexive vergence eye movements.

Vergence eye movements shift our binocular fixation point in depth and provide the fundamental motor alignment required for stereopsis[60]. These responses are coupled with accommodation (and pupil size) making up the near-triad[4]. Plasticity within the mechanisms controlling ocular vergence and its synkinetic interactions with accommodation are vital to user satisfaction with new spectacle lenses[8,10,180] and virtual or augmented reality systems[225,226]. The behavior and underlying neural mechanisms of these vergence adaptive processes are only just beginning to be understood.

The study of saccadic eye movements has been central to the development of our current models of sensorimotor adaptation[124,145,227]. The robust adaptive properties exhibited by reactive saccades and the availability of accurate, non-invasive eye-tracking systems with which to measure these effects has made oculomotor systems an attractive substrate to study sensorimotor adaptation. In addition, visual stimuli for oculomotor systems can be easily manipulated to simulate various end-point execution errors. McLachlan first demonstrated this using the classic ‘double-step’ paradigm[112], where the position of a visual target is repeatedly altered during the execution of the primary saccade, inducing an error at movement completion and activating rapid changes in subsequent saccades. Building on this experimental design, current models identify at least two distinct, overlapping neural processes that underlie the adaptation of oculomotor systems to such repetitive end-point errors[228–232]. One mechanism displays a rapid onset but

poor temporal retention and transference to other motor and sensory systems[196,233], while a second has a much slower rate of onset but appears to possess a longer period of retention and greater transference [147,228,230]. These two mechanisms appear to be arranged in parallel, at least in humans[231]. The former mechanism, known as 'short-term' sensorimotor adaptation[145], is the focus of the following investigation where we aim to characterize the behavior of short-term sensorimotor adaptation in reflexive vergence responses in order to provide a greater understanding of the mechanisms that drive this form of motor adaptation.

9.2.2 Background

Reflexive vergence responses occur to step changes in retinal disparity and have been characterized behaviorally[38,103,158] and neurally[38,47] by a 'pulse-step' drive of innervation, similar to that of saccades[123]. The pulse component is a transient, open-loop response that initiates a ballistic inward (convergence) or outward (divergence) rotation of the two eyes and is best characterized by peak velocity[32,34,58,234]. The visually-guided step mechanism controls the latter stages of the reflexive response, providing the precise binocular alignment required for sensory fusion[27,158]. Short-term sensorimotor adaptations of reflexive vergence responses have recently been identified using a disparity-based version of McLaughlin's original saccadic double-step experiment[50,51,95]. In these studies, repetitive errors resulted in significant adjustments to the peak velocities and amplitudes of subsequent responses. The majority of this work has focused on short-term sensorimotor adaptations in reflexive convergence responses to repeated under-shooting end-point errors, where subsequent convergence response amplitudes and peak velocities are significantly increased[10,50,51,95,117,118,235].

Vergence also possesses an additional adaptive mechanism that slowly alters the degree of tonic vergence innervation during prolonged near viewing[42,78]. This adaptive process, referred to clinically as 'heterophoria' adaptation, reduces the neural load on the reflexive vergence system required to maintain binocular motor fusion and allows vergence to act independently of accommodation[49]. This form of vergence plasticity has received a considerably more attention in the literature[81,180] when compared to sensorimotor adaptation in reflexive vergence[50,51,95]. Heterophoria, or simply 'phoria', adaptation plays a critical role in adjusting to viewing conditions where demands between accommodation and vergence become unequal, such as when viewing binocularly through ophthalmic prisms[155]. A pattern has recently evolved showing that phoria adaptation is directionally asymetric[57]. Specifically, we have demonstrated that the rate and magnitude of phoria adaptation varies based on the direction of the prolonged disparity[236]. It is unclear whether similar patterns exist within short-term sensorimotor adaptations of

reflexive vergence to double-step disparity stimuli[10,117]. A primary aim of the current study was to determine if such a relationship exists.

In saccadic adaptation to double-step stimuli, the direction of the error signal created by the second step influences the adaptive behavior observed[114,237–239]. In gain increasing conditions, where the second step is in the same direction as the original stimulus (under-shooting error signal), changes in the subsequent saccadic amplitude and peak velocity occur at a slower rate and are less complete in magnitude when compared to saccadic recalibrations to gain decreasing paradigms (over-shooting error signal). This result has been taken to imply the existence of two separate adaptive neural mechanisms, each responding to a specific directional error signal, with over-shooting errors being a stronger stimulus to adaptation[115,121]. Currently, there is a paucity of data that characterizes the directional effects of the error signal in reflexive vergence adaptation. One study has identify differences in the dynamic properties of adapted convergence responses after gain decreasing versus increasing double-steps; however the temporal effects of such stimuli were not addressed nor were the normalized differences in the magnitude of adaptive changes compared[51]. In line with this open question, a second aim of the current study was to characterize the effects of error signal direction on the temporal effects and final magnitude of adaptive modifications in both reflexive convergence and divergence adaptation.

Saccadic adaptation is also known to be vector specific, with a sharp roll-off of adaptation for saccades directed more than 45° from the primary adapted vector[196,240,241]. While normal reflexive saccades demonstrate minute directional asymmetries, bias toward the side of motor dominance[242], the effects of these baseline dynamic asymmetries on adaptive responses is not clear. In contrast, large directional asymmetries have been noted between reflexive divergence and convergence responses[58,90,101]. The effects of these large baseline dynamic asymmetries on the adaptive responses to double-step paradigms has yet to be explored. A single previous study has indicated that both reflexive divergence and convergence responses were amendable to gain increasing adaptation; however, no comparisons between directions were provided, possibly due to the sample size and variable adaptive effects observed[50]. In this particular study, the condition stimulus was a step-ramp and not a true double-step. This has led others to argue the adaptive effects are more demonstrative of explicit motor learning and predictive processes[127]. We have hypothesized that reflexive divergence responses saturate at low disparity step-stimulus amplitudes under specific experimental conditions[236]. This saturation is observed as a plateau of the divergence response peak velocity as disparity step-stimulus amplitudes exceed 3°. This reflexive saturation also appears to result in a saturated phoria adaptation response to prolonged

uncrossed disparities[236,243]. If this hypothesis of reflexive divergence saturation is correct, one would expect that divergence responses at or near this natural saturation limit would be unable to adapt to double-step gain increasing stimuli, at least not in the typical increase in peak velocity and response amplitude expected. Accordingly, the current study will address this assumption of divergence saturation and the corresponding effects of reflexive motor response asymmetries on short-term sensorimotor adaptation in vergence.

The neural source of sensorimotor adaptation in reflexive vergence is also an open question. Behavioral evidence suggests that reflexive saccadic adaptation occurs upstream of the saccadic burst generator in the brainstem[115]. The main sequence ratio relationship represents the neural integration of the vergence velocity signal by the premotor neural machinery in the brainstem. The preservation of the main sequence relationship between saccade peak velocity and saccade amplitude after double-step adaptation implies the velocity signal is altered upstream of the subcortical saccadic-burst generator [244]. In reflexive vergence adaptation, there are conflicting reports regarding changes in the ratio of peak velocity to movement amplitude, also known as the 'main sequence' ratio. One study demonstrated large changes in main sequence ratios of both convergence and divergence after gain increasing adaptation[50]; however, as previously mentioned, these effects may be due to use of a step-ramp condition stimulus[127]. A second study identified main sequence ratio changes in convergence after gain increasing, but not gain decreasing adaptation. These effects were inconsistent however, and varied amongst the small pool of participants[51]. Another series of modelling studies, based on behavioral data, contradicts these results and has suggested that the main sequence ratio would be unaltered after convergence gain increasing adaptation[52,125]. In order to clarify these effects an additional goal of the present study was to determine whether or not the main sequence ratio of vergence is affected by gain increasing and decreasing double-step paradigms in both divergence and convergence systems. This will provide additional insight to the potential neural loci of short-term sensorimotor adaptation in reflexive vergence.

9.2.3 Study Aims

Clearly there is a need to better define the behavior, limits and potential neural mechanisms underlying short-term sensorimotor adaptation in disparity-driven reflexive vergence. Such information would provide valuable insights into potential determinates of oculomotor plasticity with real-world clinical and technological applications. This study was designed to characterize the short-term sensorimotor adaptive behavior of reflexive convergence and divergence in naïve, binocularly normal participants using both adaptive lengthening and shortening double-step disparity stimuli.

9.3 Methods

9.3.1 Participants

10 subjects (5 males, 25.6 ±4 y/o) completed the study. Participants were recruited from the University of Waterloo undergraduate student population. Informed consent was obtained after verbal and written explanation of the study procedures. The study protocol was approved by the University of Waterloo ethics review board and adhered to the tenets of the Declaration of Helsinki. An optometrist assessed each participant for normal oculomotor and binocular function at the first study visit. This was defined as monocular best corrected visual acuity of 6/6, local stereoacuity better than 60' arc seconds, with a near point of convergence greater than 6cm. Each subject's heterophoria was determined with an alternating cover test[187]. Fusional vergence ranges were tested in free-space using prism bars and were at least twice the magnitude of the heterophoria[59]. The study participants had varied levels of heterophoria at near, with four exophores (maximum 8 prism diopters), three esophores (maximum 3 prism diopters) and three orthophores.

9.3.2 Apparatus & Stimulus

Images were presented dichoptically on two 7-inch LCD monitors (Lilliput, UK) at a constant 40cm viewing distance via a haploscope. This apparatus has been described in detail in previous work[55,236]. Each subject's interpupillary distance was set in the haploscope before testing. Monocular eye movements were recorded at 250Hz using infrared oculography via the EyeLink2 system (SR Research, Canada). This instrument has a spatial resolution of 0.03°, with an average accuracy of 0.5°. Eye movements analyzed fell within the linear range of the instrument (±40°**).** The visual fixation stimulus was controlled using Experiment Builder (SR Research, Canada) and consisted of an identical white central fixation cross (0.5° x 0.5°**,** 0.08° line width) surrounded by a white box (2.75° x 2.75°, 0.08° line width) on a black background[55]. Each monitor's image had a unique feature attached to one edge of the surrounding box. This allowed the participant to subjectively monitor for suppression during the experiment. All participants were able to complete the procedures at each visit without suppression in any trial. Head movements were limited by a custom chin and forehead restraint.

9.3.3 Procedures

Participants completed 1 screening and 4 experimental trials. Each experimental trial tested a single vergence direction and contained only one type of double-step conditioning stimulus. During the first visit participants were shown the baseline test stimulus for both the divergence and convergence

stimuli to familiarize them with the experimental set-up and ensure they could adequately obtain fusion. Only the 4 experimental trials contained the double-step conditioning stimuli in order to preserve each participant's naivety. One trial was completed per day, with at least 5 days (maximum 12) between trials. The order of these conditions was randomized for each individual. The four double-step conditions were; convergence gain increasing (CGI), convergence gain decreasing (CGD), divergence gain increasing (DGI) and divergence gain degreasing (DGD), Figure 9-1.

All disparity step stimuli were presented from an initially congruent accommodative-vergence-proximity position based on the participant's interpupillary distance and a viewing distance of 40cm (Figure 9-1B). For a 60mm interpupillary distance, this corresponded to an initial angular vergence demand of 8.44°**.** From this position, two different disparity step-stimuli were used in each trial. The single-step stimulus consisted of a single disparity gap step of 2°**.** The double-step stimulus consisted of the same initial 2° gap step, followed 175ms later by a second gap step of ±1.5°, forming a modified version the classic double-step stimuli first described by McLaughlin for saccades[112]. For the gain decreasing conditions, the second step was reversed from the direction of the initial fixation position, whereas the second step in the gain increasing trials was in the same direction as the first step (Figure 9-1B).

Each experimental trial was separated into 4 phases; calibration, baseline, adaptation and recovery (Figure 9-1A). Each phase was separated by a 120s break to avoid fatigue. A trial began with the participant placed in complete darkness for 5 minutes and instructed to keep their eyes open and their vision relaxed during this time in order to allow tonic levels of vergence and accommodation to reset to their resting levels. Each trial began with a 9-point monocular calibration procedure spanning 48° horizontally and 16° vertically. The baseline phase contained 25 single-step test stimuli in one direction. The time between disparity steps was randomized between 3s and 6s to impair prediction[127] (Figure 9-1B). Participants were instructed to keep the image single and clear at all times. During the adaptation phase the double-step stimuli were presented in the same direction as the baseline stimuli. In this phase, 25 double-step stimuli were presented sequentially after which single-step stimuli were randomly interspersed between every 4-6 double-step stimuli until a total of 75 double-step and 10 single-step stimuli were presented. The recovery phase was identical to the baseline phase and consisted of 25 single-step stimuli (Figure 9-1B).

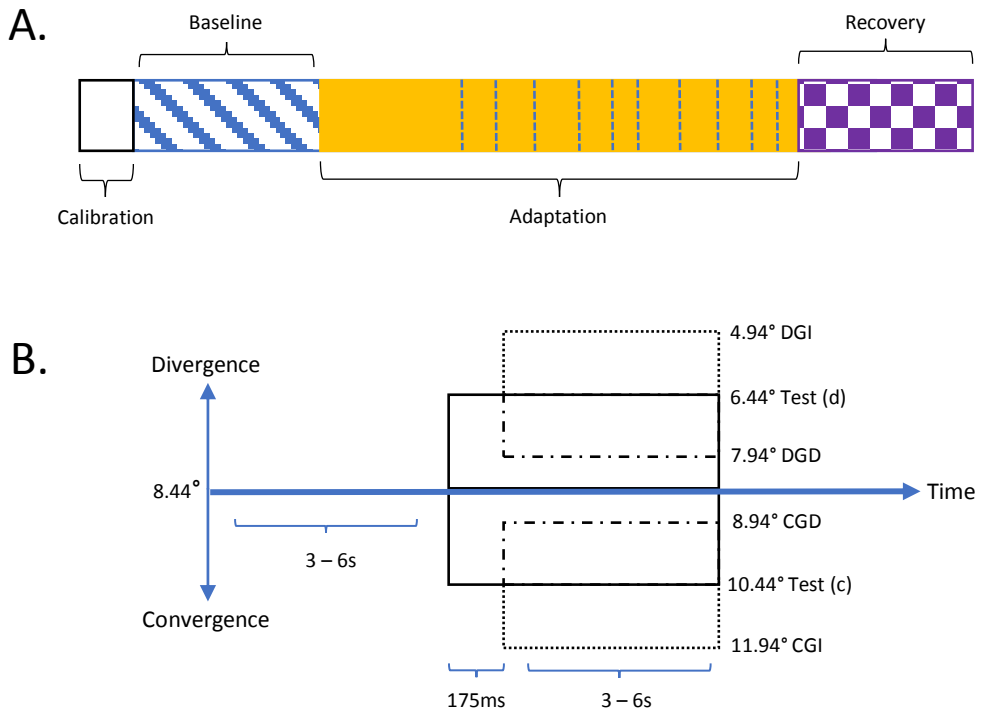

Figure 9-1: A) Schematic representation of a single complete trial. The dashed vertical lines illustrate where the single-step stimuli are interleaved with the double-step stimulus in the adaptation phase. Note these single-step stimuli began only after 25 double-step stimuli were presented in the adaptation phase. There was a 120s break given between each phase (not depicted). **B)**: Schematic of the different step stimuli used. The thick blue solid line represents the congruent vergence-accommodation-proximity demand from which all disparity steps began. The thinner black solid line illustrates the single-step stimuli (c = convergence, d =divergence). The even dashed line represents the gain increasing double-step stimulus and the uneven dashed line the gain decreasing double-step stimulus.

Saccadic eye movements lend well to the study of reflexive sensorimotor adaptation due to saccadic suppression, whereby visual input during the execution of each saccade is suppressed[245,246]. This prevents visual feedback of additional target movement (double-steps) during a given saccade. Because vergence movements are slower and have longer durations than saccades, visual feedback from the second step in the 'double-step' may be integrated into the latter portion of the vergence response. This

makes assessing alterations in the initial open-loop vergence motor command difficult, as a second vergence command can be issued and executed before the first command has reached its completion. This especially confounds the quantification of vergence response amplitude and duration to the double-step stimuli. In order to ascertain adaptive changes in the open-loop vergence motor command in response to the double-step stimuli, two different strategies were employed. The first method follows previous study designs where the baseline single-step 'test' stimuli are added randomly near the end of the adaptation phase[117]. Vergence responses to the 'test' stimuli in the current experiment defined the overall change in response amplitude and duration. The second approach mathematically estimated the open-loop response amplitude using a modified phase-plane analysis applied by other groups[34,51] and described in the next section.

9.3.4 Data Analysis

Monocular eye positions were recorded, digitized as screen pixel position and analyzed off-line using a custom analysis package in MatLab (Waltham, MA, USA). Vergence was defined as the difference between right and left eye position and vergence responses were identified using a 1.5°/s start-stop velocity threshold. Movement settling time was defined as the time from the onset of the movement to when the vergence velocity fell at or below 0°/s for 40ms. The responses in each trial phase were separated temporally into blocks of 10. Within each block, vergence responses containing saccades or with latencies less than 80ms and response amplitudes or peak velocities outside 2 standard deviations of the block mean were excluded[174]. The average number of responses used for statistical analysis in each block were 8.12 ± 1.1 baseline phase, 7.63 ± 1.5 adaptation phase and 7.96 ± 1.4 recovery phase.

A phase-plane analysis was employed to determine the amplitude of the initial open-loop vergence response, henceforth referred to as 'pulse amplitude'[§§§§§]. A graphical illustration of the time-domain trace and this analysis can be found in Figure 9-2. Briefly, this analysis assumes that the velocity profile of a completely open-loop, ballistic response is symmetrical[174]. Therefore, the velocity profile following the peak velocity was modified to be symmetric to the first half[86,174]. In the phase-plane, the end of this symmetric velocity profile was used to determine the amplitude of the open-loop response in the absence of visual feedback. The total response amplitude was defined by the start-stop velocity threshold and represented the combined pulse and step mechanism input.

[§§§§§] See 0 for background on pulse-step model and 0 for phase-plane analysis description

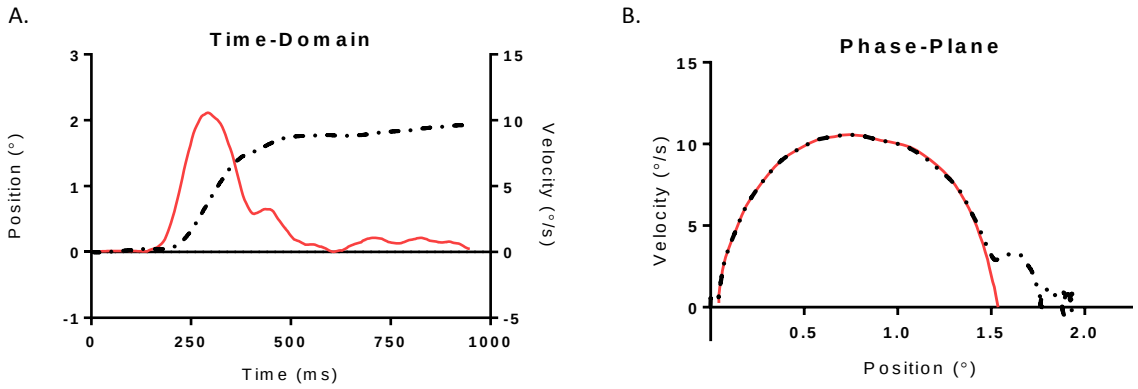

Figure 9-2: A) Time domain plot of a single convergence movement. Red solid line represents the velocity profile, while the black hashed line depicts vergence position. **B)** The same convergence movement in A, depicted in the phase-plane. The black hashed line represents the empirical velocity profile of the actual movement. The red solid line represents the predicted symmetric velocity profile. The ordinate intercept of this symmetric velocity waveform defines the open-loop 'pulse amplitude'. In this example the open-loop 'pulse amplitude' was approximately 1.6° while the total vergence response amplitude is just under 2.0°.

9.3.5 Statistical Analysis

Results were tested for normality using a Shapiro-Wilk test preceding any statistical analysis. All parameters satisfied the assumption of normality ($p>0.05$) and therefore parametric statistics were used throughout. Greenhouse-Geisser or Welch's corrections were applied were variances between groups differed significantly.

To assess directional asymmetries and the potential effects of block-time bias in the baseline vergence responses a two-way repeated measures ANOVA model was applied to the total response amplitude, pulse response amplitude (obtained via phase-plane analysis), peak velocity, peak acceleration, movement duration, settling time and latency with the 4 stimulus conditions as the first factor and block-time as the second. Adaptive changes in vergence dynamics in the adaptation and recovery phases were individually compared against the null-hypothesis of zero change using a two-way t-test. To compare the total magnitude of adaptation the vergence responses to the single-step stimuli interlaced during the adaptation phase were binned as the 'test response' block and analyzed separately. The normalized change in these

responses was compared using a one-way repeated measure ANOVA, with the 4 different stimulus conditions as the factor. To investigate the temporal characteristics of adaptation in the different conditions, a two-way repeated measures ANOVA model was constructed for the normalized change in the vergence pulse amplitude, peak velocity, duration and total response amplitude with block-time as the first factor and stimulus condition as the second factor. The main sequence ratio was calculated for each participant's baseline and test stimuli vergence responses by dividing the averaged response amplitude of the open-loop pulse mechanism by the averaged peak velocity of these movements[50,116] and compared with a one-way ANOVA. Post-hoc analyses were carried out using Bonferroni corrections to control for multiple comparison false discovery rate.

9.4 Results

9.4.1 Baseline Vergence Asymmetries

The averaged data for all subjects within a stimulus condition for the last baseline block is detailed in

Table 9-1. There was no effect of block-time in any of these parameters, $F(1,9) < 0.4$, $p > 0.1$, indicating that vergence behavior was stable between blocks in the baseline phase. There was a significant main effect of stimulus condition in each of the following parameters; total response amplitude F $F(1.6, 14.9) = 12.5$, $p = 0.001$; pulse amplitude $F(2.1, 19.3) = 14.7$, $p < 0.001$; peak velocity $F(1.8, 16.6) = 15.8$, $p < 0.001$, peak acceleration $F(1.4, 12.3) = 17.9$, $p < 0.001$ and settling time $F(1.3, 11.5) = 19.75$, $p < 0.001$. Post-hoc comparisons identified differences between the convergence and divergence directions ($p < 0.01$), but not within a given response direction ($p > 0.6$). There was no main effect of stimulus direction on the latency, $F(1.5, 13.3) = 1.1$, $p = 0.35$, or response duration $F(1.9, 17.4) = 3.43$, $p = 0.07$.

Baseline Responses	CGI	CGD	DGI	DGD
Total Response Amplitude (°)	1.92 (0.1)	1.91 (0.2)	1.61 (0.3)	1.57 (0.3)
Pulse Amplitude (°)	1.69 (0.2)	1.72 (0.3)	1.35 (0.3)	1.29 (0.2)
Peak Velocity (°/s)	11.99 (1.8)	12.53 (2.0)	8.33 (2.1)	7.82 (2.2)
Peak Acceleration (°/s^2)	124.2 (29.2)	136.1 (35.3)	76.5 (26.3)	71.3 (21.1)
Duration (ms)	367.1 (55.5)	349.5 (47.0)	402.4 (66.3)	408.9 (53.9)
Settling Time (ms)	450.7 (76.5)	430.5 (87.2)	634.4 (110.5)	620.9 (106.2)
Latency (ms)	140.6 (13.5)	132.6 (15.8)	147.1 (22.2)	152.2 (23.8)

Table 9-1: Mean (SD) response parameters in each of the 4 different conditions baseline phase (2° single-step stimulus); CGI = convergence gain increasing, CGD = convergence gain decreasing, DGI = divergence gain increasing, DGD = divergence gain decreasing. Differences were only significant between convergence and divergence directions.

Given that there were systematic differences between the response properties of convergence and divergence in the baseline phase, the raw values of any change after adaptation were normalized using Equation 1 below in order to provide valid comparisons of adaptation effects. This normalization is commonly used in oculomotor experiments when such differences in the baseline movement properties are encountered[247].

Equation 1: $\% \boldsymbol{Change} = (\boldsymbol{Baseline\ Parameter} - \boldsymbol{Adapted\ Parameter}) \div \boldsymbol{Baseline\ Parameter}$

9.4.2 Temporal effects of adaptation

The adaptation of the open-loop pulse response properties followed an exponential pattern, plateauing between the third and fourth blocks in the adaptation phase. Figure 3 and 4 illustrate the temporal effects of each stimulus condition during the adaptation phase in each trial. Responses to test stimuli were not included in this analysis.

Figure 9-3 depicts the mean response position and velocity traces of the last baseline block (0) as well as the second (2) and last (7) blocks in the adaptation phase for each condition. The adaptive behavior of the two gain decreasing conditions (Figure 9-3 B&D) is similar, with significant reductions in the initial open-loop response from baseline leading to a reduction the in dynamic overshoots created by the second stimulus step. In contrast, the gain increasing condition produced different adaptive behavior for convergence and divergence stimuli. For convergence (Figure 9-3A) the large initial undershoots created by the second step resulted in a second corrective vergence motor command that occurred before the initial response was complete. By the last adaptation block the initial open-loop response was significantly increased, resulting in a much smaller second corrective movement (Figure 9-3A). Figure 4 illustrates that as the pulse response amplitude and peak velocity of convergence began to increase the response duration and settling time gradually reduced throughout the adaptation blocks**.** In the DGI condition the large undershooting errors observed during the adaptation phase (Figure 9-3D) resulted in a gradual increase in the response duration and settling time over the course of adaptation blocks (Figure 9-4); however, there was a negligible increase in the open-loop motor pulse amplitude or peak velocity. In this condition, a second corrective movement is not seen during adaptation (Figure 9-3D), as it blends directly into the slow initial pulse response. Because the second corrective movement occurs before the first is completed, the total response amplitude and duration of the DGI responses in Figure 9-4 remain unchanged across each trial block. As stated in the methods section, such artifacts precipitate the use of single-step stimuli within the adaptation phase as well as a phase-plane analysis to isolate the initial, open-loop vergence motor command.

There was a significant main effect of block-time for each of the following parameters; pulse amplitude $F(10, 90) = 62.2$, $p < 0.0001$ and peak velocity $F(10,90) = 56.7$, $p < 0.0001$. The changes plateau between the second and third blocks in all conditions. This justifies binning all the single-step stimuli intersperse within the adaptation phase together. A main effect of stimulus condition was also significant for pulse amplitude $F(3,27) = 44.5$, $p < 0.0001$ and peak velocity $F(3,27) = 63.8$, $p < 0.0001$. Interaction effects were significant for both parameters $F(30,270) > 5.0$, $p < 0.0001$. Post-hoc analysis indicated both gain decreasing conditions exhibited a greater change than the gain increasing conditions in the first adaptation block ($p < 0.04$, Block 1, Figure 9-4). In this first block, adaptive changes in the two gain increasing conditions were not significantly different ($p > 0.11$). In the second adaptation block (Block 2, Figure 9-4), the CGI condition had significantly greater changes than the DGI condition ($p < 0.03$), while these changes were still significantly less than the two gain decreasing conditions ($p < 0.01$). In the third adaptation block-time (Block 3, Figure 9-4), the degree of adaptation was the same between

the CGI condition and the two gain decreasing conditions (CGD, $p = 0.29$; DGD, $p = 0.37$) and remained the same for the rest of the adaptation phase ($p > 0.60$). Additionally, the change in each of these 3 conditions (CGI, CGD & DGD) was significantly greater than the DGI condition for all of these blocks ($p < 0.001$). When the gain decreasing parameters where compared between directions, there was no difference within any block-time ($p > 0.49$). Finally, the changes in the open-loop component responses were not significantly different from zero at any time in the DGI condition ($p > 0.43$).

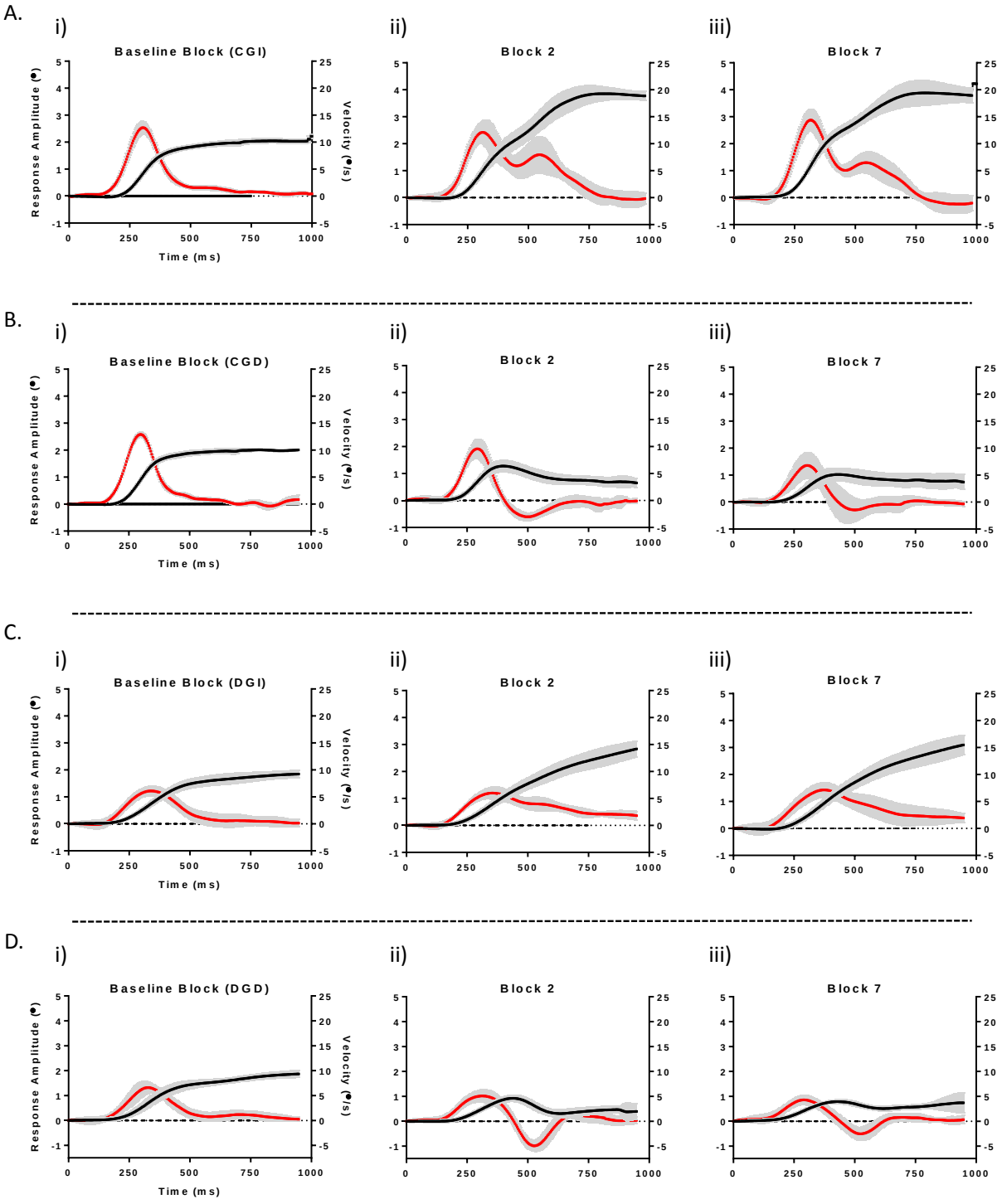
A.
i)
Baseline Block (CGI)
ii)
Block 2
iii)
Block 7
B.
i)
Baseline Block (CGD)
ii)
Block 2
iii)
Block 7
C.
i)
Baseline Block (DGI)
ii)
Block 2
iii)
Block 7
D.
i)
Baseline Block (DGD)
ii)
Block 2
iii)
Block 7
Response Amplitude (°)
Velocity (°/s)
Time (ms)

Figure 9-3: Mean and SEM response amplitude and velocity traces resulting from each of the 4 different stimulus conditions for one subject (A = CGI, B = CGD, C= DGI, D = DGD; i = last baseline block, ii = second block in the adaptation phase, iii = last block in the adaptation phase). The mean position trace (black line) is plotted on the left y-axis, the mean velocity trace (red line) on the right y-axis and the standard deviation is plotted in grey for each. Individual responses were smoothed using a 40ms (10 sample) moving average before being combined and plotted. Absolute values are plotted for divergence.

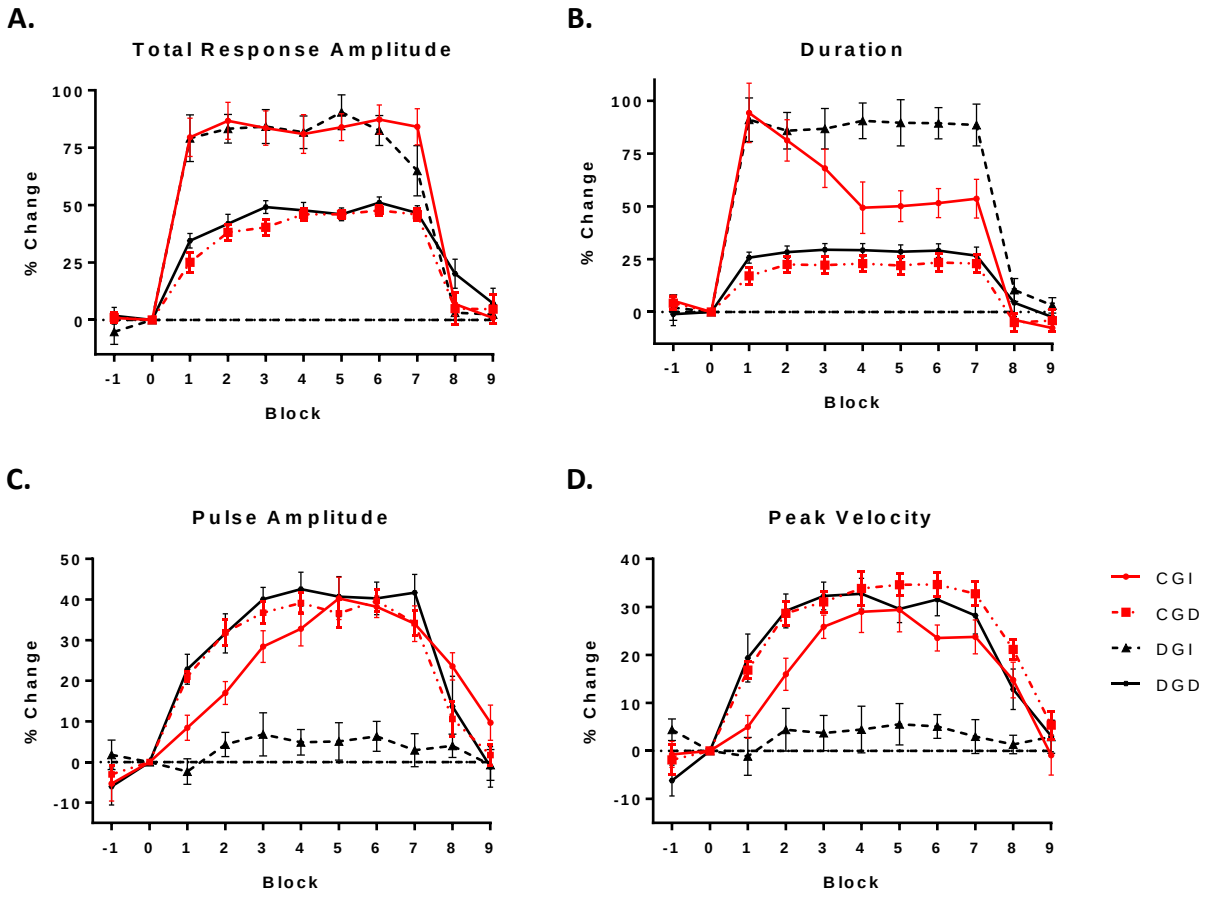

Figure 9-4: Mean and standard deviation of the temporal effects of the different double-step stimuli during each of the 3 different phases. The absolute value of the percentage change in each parameter when compared to the last baseline block (0) are plotted (**A**= total response amplitude, **B** = total response duration, **C** = pulse response amplitude, **D** = response peak velocity). Block numbers -1 & 0 represent the baseline phase, 2-7 the double-step adapting phase, and 8-9 the recovery phases.

9.4.3 Modulation of open-loop vergence response.

A summary of the change in each parameter for each condition is detailed in Table 9-2 and Figure 9-5. A main effect of stimulus condition for the absolute value of the adaptive changes was significant in the following parameters; total response amplitude $F(2.3, 20.8) = 8.0$, $p = 0.002$; pulse amplitude $F(2.2, 21.1) = 21.2$, $p < 0.0001$; peak velocity $F(2.1, 19.0) = 24.4$, $p < 0.0001$; peak acceleration $F(2.2, 19.8) = 15.3$, $p = 0.0002$; duration $F(1.8, 16.3) = 7.2$, $p = 0.007$; and settling time $F(2.2, 20.1) = 16.1$, $p < 0.0001$. Post-hoc comparisons showed that the adaptive modifications of the pulse amplitude, peak velocity and acceleration in the DGI condition were significantly less than all 3 of the other double-step conditions ($p < 0.02$). Changes in these parameters for the DGI condition were not significantly different from zero ($p > 0.15$, Table 9-2). An overall increase in response duration was significant for the DGD, CGD and DGI conditions. In the CGI condition the opposite effect was observed, where the total movement duration and decreased significantly. In both increasing conditions, the settling time was reduced, while the opposite was found for the decreasing conditions. This reduction in total response duration and settling time in the CGI condition was the result of a larger, faster open-loop pulse response to the test stimuli in this condition. The DGI condition resulted in significantly larger total response amplitudes after adaptation (Table 9-2, $p = 0.001$); however, Figure 9-5A demonstrates this was mainly a result of an increase in the total duration of the response velocity profile. More specifically, the peak velocity is maintained for a longer period of time, resulting in greater initial response duration but shorter settling times. Importantly, this change in divergence responses to the test stimuli was not a result of an increase in the preprogrammed response parameters of pulse amplitude, peak velocity and peak acceleration ($p > 0.68$, Table 9-2). In other words, the width of the pulse response increased in the DGI condition, while the height of the pulse response was modified in the other 3 conditions. This effect was more pronounced in the participants with the slowest initial open-loop response. Interestingly, when the individual datasets are considered for the DGI condition, there were two participants who exhibited noticeable increases in the divergence pulse amplitude, peak velocity and peak acceleration to the single-step ('test') stimuli (Figure 9-5C). These participants were also found to have the largest and fastest baseline divergence pulse response properties (Figure 9-6). In these individuals, the baseline divergence and convergence response properties were roughly equal. Pearson correlation analysis of these data demonstrated a significant relationship between the baseline pulse response properties and their degree of adaptive change in the gain increasing conditions (CGI pulse amplitude: $r = 0.74$, $p = 0.02$ and peak velocity $r = 0.62$, $p = 0.04$; DGI pulse amplitude: $r = 0.88$, $p < 0.001$ and peak velocity $r = 0.78$, $p = 0.01$). The strength of this correlation in the DGI condition is influenced by the two subjects that showed reductions in these

parameters after adaptation. This same relationship was of limited significance in the gain decreasing data (CGD pulse amplitude: $r = 0.41$, $p = 0.21$ and peak velocity $r = 0.37$ $p = 0.15$; DGD pulse amplitude: $r = 0.28$, $p = 0.54$ and peak velocity $r = 0.49$, $p = 0.08$).

In regards to latency changes between conditions, there was no main effect in the original one-way ANOVA described above, $F(2.5, 22.7) = 0.14$, $p = 0.91$. In order to rule out the influence of prediction on these results, the latency change from baseline to test stimuli responses was tested against the null-hypothesis of zero for each condition with a two-tailed unpaired t-test. As detailed in Table 9-2**,** the latency change was not significant for any condition ($p > 0.16$).

% Adaptive Change (Baseline vs Test)	CGI	CGD	DGI	DGD
Total Response Amplitude	21.6 (9.6) t(9) = 7.3 p < 0.0001	-27.8 (16.5) t(9) = 3.3 p < 0.0001	10.3 (9.1) t(9) = 3.3 p = 0.001	-24.6 (17.4) t(9) = 4.6 p < 0.0001
Pulse Amplitude	30.1 (11.4) t(9) = 7.8 p < 0.0001	-38.4 (12.9) t(9) = 12.3 p < 0.0001	-2.6 (17.1) t(9) = 0.51 p = 0.68	-32.5 (13.2) t(9) = 7.7 p < 0.0001
Peak Velocity	25.4 (9.8) t(9) = 8.2 p < 0.0001	-36.1 (10.0) t(9) = 12.0 p < 0.0001	-0.8 (12.9) t(9) = 0.20 p = 0.85	-32.5 (13.1) t(9) = 7.6 p < 0.0001
Peak Acceleration	27.3 (8.8) t(9) = 12.3 p < 0.0001	-34.9 (13.3) t(9) = 11.4 p < 0.0001	-0.06 (12.1) t(9) = 0.02 p = 0.98	-25.7 (13.7) t(9) = 16.7 p = 0.0001
Duration	-12.5 (7.9) t(9) = 5.5 p = 0.004	23.3 (23.2) t(9) = 3.2 p = 0.01	8.06 (7.3) t(9) = 3.0 p = 0.02	19.1 (21.2) t(9) = 2.3 p = 0.05
Settling Time	-22.8 (16.1) t(9) = 4.4 p = 0.002	32.6 (18.4) t(9) = 5.7 p = 0.0003	-2.4 (7.6) t(9) = 0.87 p = 0.40	29.1 (20.1) t(9) = 4.6 p = 0.001
Latency	-1.8 (5.5) t(9) = 1.1 p = 0.32	-2.6 (5.5) t(9) = 1.7 p = 0.16	2.5 (6.2) t(9) = 1.5 p = 0.24	-1.4 (8.5) t(9) = 0.5 p = 0.63

Table 9-2: Normalized mean (SD) percentage change in the vergence response parameters to the test stimuli for a given adapting paradigm. The mean change of each parameter was tested against the null-hypothesis of zero change with a two-tailed t-test (p-values given highlighted in red indicate no significant change).

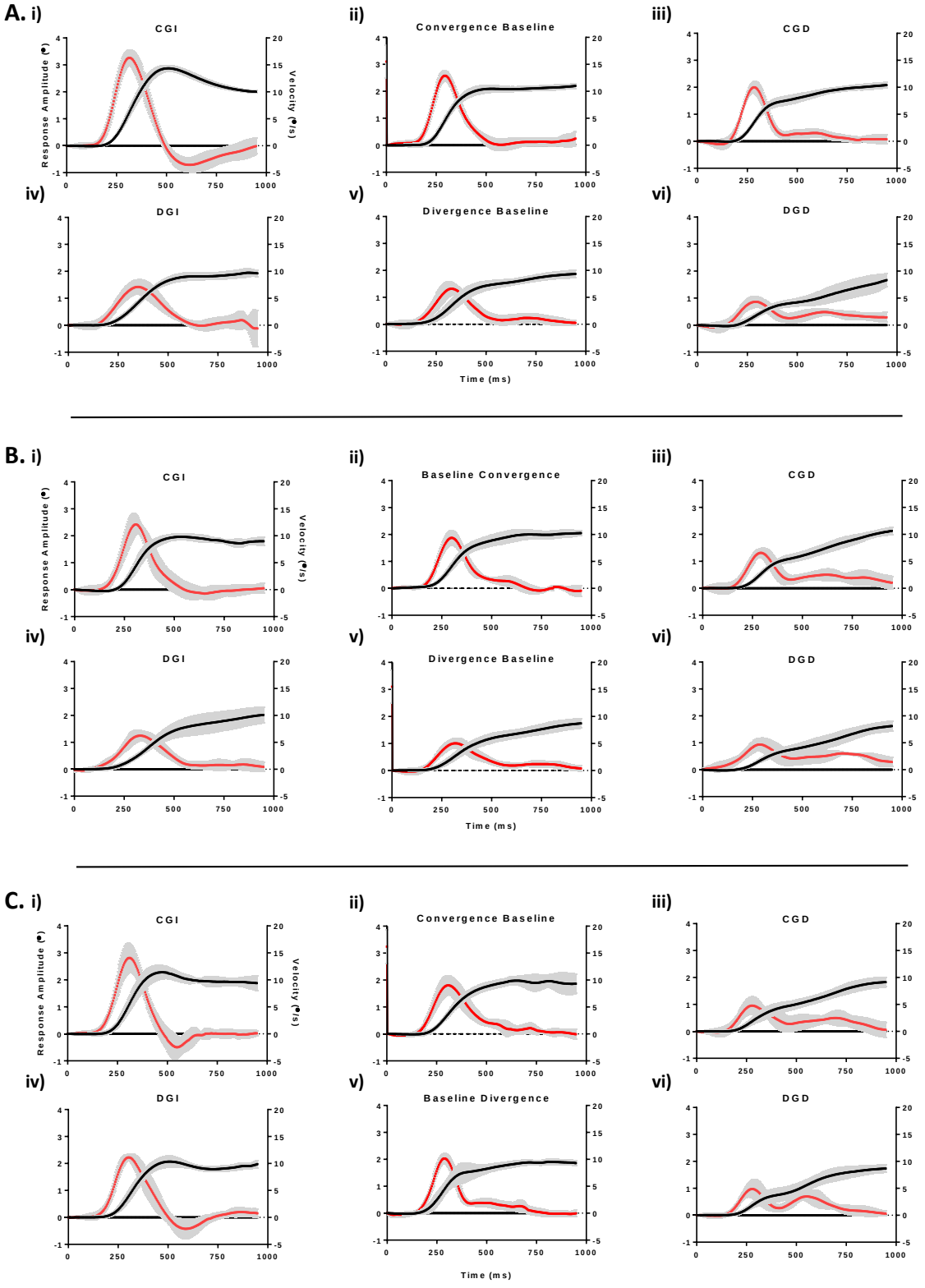
A. i)
CGI
ii)
Convergence Baseline
iii)
CGD
iv)
DGI
v)
Divergence Baseline
vi)
DGD
Response Amplitude (°)
Velocity (°/s)
Time (ms)
B. i)
CGI
ii)
Baseline Convergence
iii)
CGD
iv)
DGI
v)
Divergence Baseline
vi)
DGD
Response Amplitude (°)
Velocity (°/s)
Time (ms)
C. i)
CGI
ii)
Convergence Baseline
iii)
CGD
iv)
DGI
v)
Baseline Divergence
vi)
DGD
Response Amplitude (°)
Velocity (°/s)
Time (ms)

Figure 9-5: Mean and standard deviation (gray) of the position (black) and velocity (red) traces of the last 10 baseline phase responses (convergence = ii, divergence = v) and test responses in the adaptation phase (gain increasing = i & iv, gain decreasing = iii & vi). Data in **A**) is from the participant with greatest difference between baseline convergence and divergence responses. Data in **B)** is the most representative of the entire group's responses, while data in **C)** is from the subject with the fastest baseline divergence responses. Individual responses were smoothed using a 40ms moving average. Absolute values are plotted for divergence.

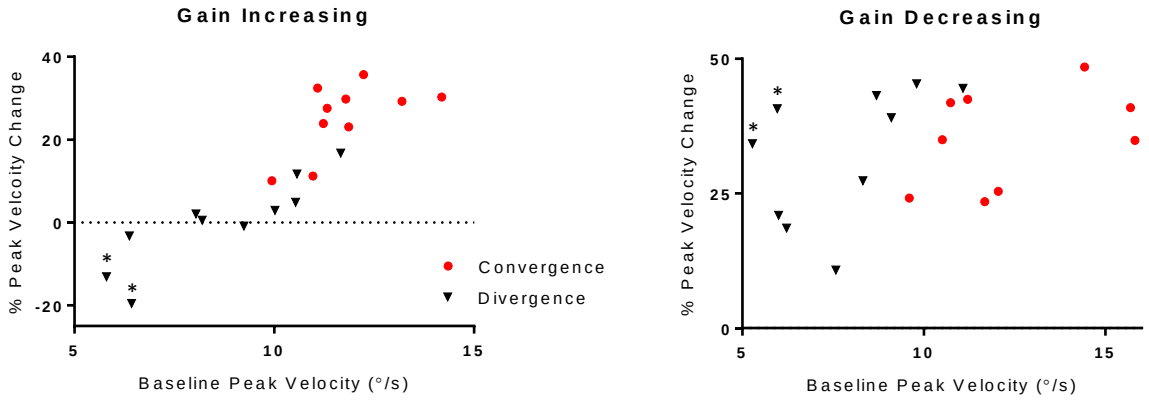

Figure 9-6: Scatter plots of the mean percent change in response peak velocity after adaptation (test stimuli) plotted against the mean baseline response peak velocity for the gain increasing conditions (left panel) and gain decreasing conditions (right panel, absolute values of change plotted). Convergence and divergence are shown separately for each. There were two subjects (* above their data points) that demonstrated a significant reduction in their divergence response peak velocities after gain increasing adaptation (left). The same two participant's data can be seen in the right panel as the slowest baseline response velocities with large reductions in peak velocity after gain decreasing adaptation that were atypical when compared to the remaining participants data.

9.4.4 Fatigue & Retention

Previous research has indicated that fatigue may affect vergence response dynamics after as little as 200 consecutive trials[69]. To avoid fatigue, our participants were given a break between each phase. In addition, we limited the number of vergence step stimuli to 150 per trial/day. To rule out fatigue as a confounding factor, the last block of recovery responses was compared to the baseline block using a two-tailed t-test with a null hypothesis of zero change. Results are detailed in Table 9-3**.** In both divergence conditions there is no significant difference between baseline and recovery phases in any parameter measured. Convergence pulse amplitude and peak velocity remained larger after adaptive lengthening (CGI), while the opposite effect as seen after adaptive shortening (CGD). If fatigue was a factor, a consistent reduction of all these parameters would be expected, regardless of the adaptive condition.

When the individual data sets were considered, there were two participants that exhibited a consistent decrease in the open-loop divergence response parameters to the test stimuli (Figure 9-6) and the recovery blocks after both gain increasing and decreasing adaptation conditions. Interestingly, these participants had the slowest baseline divergence response peak velocities. This result could indicate that the baseline divergence mechanism fatigued in these subjects, resulting in a generalized decrease in open-loop divergence response characteristics in both the gain increasing and gain decreasing conditions.

% Change Retained (Baseline vs Recovery)	CGI	CGD	DGI	DGD
Pulse Amplitude	9.8 (11.4) t(9) = 2.7 p = 0.02	-5.2 (6.5) t(9) = 2.6 p = 0.03	-0.7 (11.9) t(9) = 0.2 p = 0.85	-7.4 (11.4) t(9) = 2.1 p = 0.07
Peak Velocity	8.4 (7.3) t(9) = 4.2 p = 0.003	-7.0 (5.0) t(9) = 4.5 p = 0.002	4.7 (8.2) t(9) =1.8 0.10	-5.5 (9.2) t(9) = 1.9 p = 0.09
Peak Acceleration	5.6 (8.3) t(9) = 2.0 p = 0.08	-6.1 (9.3) t(9) = 1.9 p = 0.09	3.1 (11.7) t(9) = 0.78 p = 0.46	-7.2 (11.6) t(9) = 1.9 p = 0.10
Duration	-6.1 (8.2) t(9) = 2.4 p = 0.04	-0.8 (6.9) t(9) = 0.23 p = 0.82	0.08 (12.2) t(9) = 0.02 p = 0.98	-0.4 (14.9) t(9) = 0.08 p = 0.94
Latency	0.7 (7.8) t(9) = 0.30 p = 0.77	-2.2 (7.4) t(9) = 0.93 p = 0.38	1.9 (8.5) t(9) = 0.72 p = 0.49	-0.03 (12.1) t(9) = 0.01 p = 0.99

Table 9-3: Mean (SD) of the normalized percent change in the vergence response parameters at the end of the recovery phase compared to the last baseline block. The mean change was tested against the null-hypothesis of zero change. Test statistic for each are given in the cell, with p-values indicating a significant amount of retention highlighted in red.

9.4.5 Main sequence effects

The baseline main sequence ratio of our convergence responses was 7.65 ± 0.65 (gain increasing trials) and 7.60 ± 1.1 (decreasing trials). For divergence these values were 6.22 ± 0.82 (gain increasing) and 6.03 ± 0.63 (gain decreasing). The change in this ratio after adaptation was as follows; convergence gain increasing: +0.12 ± 0.47, convergence gain decreasing: -0.38 ± 0.8, divergence gain increasing: +0.001 ± 0.3 and divergence gain decreasing: -0.001 ± 1.6. A one-way repeated measures ANOVA of these changes demonstrated no main effect of condition, $F(3,27) = 0.49$, $p = 0.69$. When tested against the null-hypothesis of zero change using a two-tailed t-test, all were not significantly different from zero ($p>0.15$), indicating that the main sequence ratio is preserved after adaptive modification under the given conditions, regardless of the condition or direction of stimulus.

9.5 Discussion

The purpose of the study was to characterize sensorimotor adaptation in reflexive vergence eye movements and explore the effects of disparity direction on this behavior. Overall, the contribution of the open-loop pulse response was significantly smaller in divergence than convergence in the baseline, non-adapted recordings. This confirms behavior found in previous studies, which is believed to reflect fundamental differences in the underlying neural substrates controlling each of these motor responses[101,157,174]. The majority of the adaptive response to double-step disparity stimuli were observed in the open-loop component in CGI, CGD and DGD conditions. Gain decreasing double-step stimuli elicited a more rapid modulation of dynamic vergence response parameters when compared to the gain convergence increasing double-steps. In the DGI condition, most (8) of the participants exhibited limited, if any modification of the open-loop response after the adaptation phase. Participants with the largest and fastest open-loop vergence responses in the baseline phase demonstrated the greatest amount of sensorimotor adaptation overall. In line with our tonic vergence adaptation findings[236], the behavior of sensorimotor adaptation in reflexive vergence was directionally asymmetric in the gain increasing condition.

The main sequence ratio was not affected during and after double-step adaptation in this study. This result suggests that sensorimotor adaptation of reflexive vergence is not a result of changes in the brainstem vergence burst generators integration of the velocity command. Rather the source of these adaptive effects is likely then upstream of the subcortical saccadic machinery. This is consistent with saccadic literature, where the main sequence relationship has been shown to be preserved across a variety of different adaptive conditions[115,202,204,230,239,244]. A consistent response latency throughout each experiment also suggests that higher level, explicit cognitive processes (such as prediction) did not play a role in the adaptation observed. In reflexive saccades, this form of sensorimotor adaptation has been shown to be cerebellar based[201,248–250]. The similarities between previous reflexive saccadic data and vergence adaptation observed in the current study may also then suggest a role for the cerebellum in reflexive vergence adaptation.

The adaptive behavior observed to the gain decreasing conditions was, on average, similar between convergence and divergence directions. This implicates a common adaptive mechanism that responds to overshooting disparity errors, irrespective of the vergence response direction. Adaptive changes in the open-loop pulse response to both gain decreasing conditions was faster, but roughly equally in final amplitude when compared to the convergence gain increasing condition. This common

adaptive plateau between the CGI, CGD and DGD conditions suggests a common error-signal input and adaptive strategy to repetitive end-point errors, regardless of disparity direction. This is consistent with saccadic literature as outlined in the introduction[237,239]. Our data further demonstrates that overshooting errors are a much stronger stimulus to modify future responses, resulting in faster adaptive changes. Taken together, these results demonstrate the presence of potentially 3 distinct mechanisms underlying the sensorimotor adaptation of disparity-driven vergence responses. One mechanism responds to overshooting errors (gain decreasing condition), a second to undershooting errors (gain increasing condition) and potentially a third mechanism that is engaged if the reflexive pulse-generating motor substrate is unable to expand its response contribution further. It is not clear from the results if the latter mechanism is universal to all types of disparity errors, or if it is further subdivided based on error direction, as it was observed only in the DGI condition. It is also unclear if this behavior represents a distinctly separate neural process or if it is an extension of the 2 former adaptive mechanisms.

We have previously postulated that the pulse mechanism of reflexive divergence saturates at low stimulus amplitudes in observers with small heterophoria's[236]. In this model, the saturation of the reflex generating motor substrate results in saturation in the adaptive mechanisms responsible for altering tonic vergence neural innervation (phoria adaptation). The current study would support this hypothesis of reflexive divergence saturation, which in turn then limits the recruitment of a larger, faster, preprogrammed vergence response in the presence of consistent under-shooting error signals. Extending this, it can be reasoned that a large reflexive divergence system would be unnecessary, given that the anatomical and physiological vergence resting angle is generally equal to or greater than parallel in humans[104]. Even in cases of esotropia, strabismus surgeons have consistently noted divergent tonic vergence postures when these patients are sedated[251,252]. In contrast, convergence innervation would be required to exceed the naturally divergent orbital mechanics and thus develop a much larger and more robust reflexive response to crossed disparities. Anatomically, this could explain the disproportionate size of the medial recti when compared to the lateral recti[253]. Cell-recording studies in primates have shown the profile of neuronal firing rates in the pre-motor neural circuitry is strongly correlated with the velocity profile of the resulting vergence responses and is demonstrative of the degree of neural recruitment available within the motor substrate[37,47]. The inability of our participants to increase divergence peak velocity and pulse response amplitude implies that the system is unable to recruit a greater neuronal response. When this situation is encountered, the system resorts to increasing the duration of neuronal firing, thus increasing total movement duration and total response amplitude. It is possible that such saturation effects are the result of saturation at the extraocular muscles or cranial nerves; however,

saccadic movements are much faster than vergence responses in both the adducting and abducting eye. A limitation in abduction is therefore unlikely to responsible for the saturated behavior observed. In addition, when saccades are combined with vergence in response to uncrossed disparities, significant increases in the divergence response properties occur[66,68].

The adaptive plateau reached in all conditions is incomplete when compared to the error size induced by the double-step. Such a result could imply a saturation limit to the adaptive mechanism or saturation in the recruitment of additional reflexive vergence neural resources. Since it has been shown by numerous groups that convergence does not saturate beyond 4° disparity steps[34,43,86,101], the latter explanation is unlikely. The dual-rate state space model of sensorimotor adaptation would suggest the remainder of the adaptive changes required to restore optimal response function would result from an additional neural mechanism, acting at a much slower rate[228–231]. In the case of vergence, alterations in tonic vergence innervation have been shown to increase the response dynamics of reflexive vergence responses to additional changes in disparity[82,94,96,160]. While we did not assess tonic vergence during each experimental trial, it is likely that, overtime, a gradual shift in tonic vergence would result in further adaptive changes in the reflexive vergence response, especially when undershooting errors are experienced. It is also unclear if the saturation limit of the adaptive changes observed is affected by the end-point error size. Saccadic research demonstrates linear adaptive effects when the end-point error is less than 30% of the initial motor command[194]. There is little evidence exploring the adaptive effects of smaller end-point vergence errors on sensorimotor adaptation. Additional work assessing tonic vergence and using differing double-step amplitudes would clarify these dimensions of reflexive vergence plasticity.

The interpretation of the current study results shed light on the on-going discussion of the role of accommodation-vergence cue-conflicts in VR environments and overall user-experience. It is well known that VR requires strong adaptive responses from a multitude of sensory and motor systems, including vergence, for optimal user immersion[254]. Previous work has indicated that the visual symptoms of general fatigue, headaches and ocular discomfort in VR environments are the greatest when uncrossed disparities are viewed and when adaptation in vergence is compromised[11,136]. The results of the current study provide an oculomotor hypothesis for these observations. The symptoms experienced may be the result of reduced vergence plasticity due to a saturated reflexive vergence mechanism, especially in the uncrossed/divergent direction. Defining the limits and differential effects of proximity on these saturation levels may help define the acceptable levels of disparity in order to mitigate adverse user symptoms. The

results of this study also provide an explanation for why divergence responses are much less amendable during oculomotor training than convergence[59]. The natural orbital mechanics require less active divergence response mechanism is less important in order to acquire binocular fusion than is convergence. If the neural substrate underlying divergence is naturally small, it would lend much less to expansion and modification after perceptual learning tasks. The development of new VR technologies and rehabilitative therapies for vergence dysfunctions should take into account the insights developed from the present results.

9.6 Summary

The results provide novel insight into the different neural mechanisms underlying sensorimotor adaptation in reflexive disparity-driven vergence. The differential effects of error signal type on convergence and divergence responses highlight the different strategies that are employed to compensate for repetitive end-point errors. The adaptive response observed in reflexive vergence is related to the underlying function of the open-loop preprogrammed response and the subsequent architecture of the underlying motor substrate, as is also the case in phoria adaptation. The preprogrammed response characteristics. These results have important implications for oculomotor training and virtual reality environment design.

Chapter 10

Sensorimotor adaptation of reflexive fusional vergence is impaired in Convergence Insufficiency

This chapter has been prepared in the form of a manuscript that will be submitted to Investigational Ophthalmology and Vision Science upon the successful publication of the preceding chapter.

10.1 Overview

Patients with convergence insufficiency (CI) exhibit reduced reflexive fusional convergence response dynamics and reduced tonic (phoria) adaptation to crossed disparities. Reflexive vergence, like saccades, exhibits a rapid adaptive response to double-step paradigms; however, tonic and reflexive adaptations are likely rooted in different neural pathways. The effects of CI on the latter form of oculomotor adaptation in vergence is currently unknown. We contrast the adaptive capacities of both reflexive fusional convergence and divergence in patients with CI to aged match controls.

10 adults with CI (26±3.8y/o) and 10 aged-matched controls completed the study. At 2 separate visits reflexive convergence or divergence was measured to a 2° disparity step and then adaptively lengthened via a repeated double-step disparity stimulus (2° ± 1.5°, 175ms inter-step delay). Stimuli were presented dichoptically from 40cm. Eye movements were monitored binocularly at 250Hz using video-based infrared oculography.

The results confirm that reflexive convergence responses are significantly slower in CI; mean and SE are given (CI: 7.4°/s ± 3 vs Control: 12.0°/s ± 2, $p<0.001$). Baseline reflexive divergence response velocities were similar between groups (CI: 8.3°/s ± 2 vs Control: 7.5°/s ± 3, $p= 0.81$). Importantly, individuals with CI exhibited a limited capacity to adaptively lengthen their reflexive convergence response gain (CI: -11.1% ±22 vs Control: 30.1% ±11, $p<0.001$). Reflexive divergence gain lengthening was similar between groups (CI: 9.1% ±21 vs Control: 10.3% ±9, $p>0.99$) and significantly less robust when compared to the degree of convergence gain adaptation in controls ($p<0.01$)

The condition of CI leads to weakened vergence adaptive capacities. This now includes reflexive adaptive lengthening as well as tonic vergence adaptation. Symptomology for CI is then expected to reflect more than a reduced ability to converge. The results support the hypothesis that the adaptive capacities of vergence are related to the strength of the underlying reflexive fusional response mechanisms and highlight directional asymmetries in vergence control amongst both clinical and general populations. The evidence suggests the neurophysiological under-pinning of CI is rooted in an underdeveloped or perturbated reflexive fusional vergence mechanism.

10.2 Introduction

When we shift our gaze to different distances, our eyes move in opposite directions. These disjunctive, ‘vergence’ eye movements are an essential building block for the sensory perception of stereopsis[3].

The primary stimulus for vergence is retinal disparity[208]; while perceived proximity changes[255] and retinal blur[7,256] and can also drive vergence responses. Step changes in retinal disparity generate reflexive inward (convergence) or outward (divergence) rotations of the eyes that are controlled by separate neural substrates[33,58]. Like saccades, vergence is characterized by a 'pulse-step' of neural innervation[28,30,32,34,158]. The 'pulse' component generates a reflexive, preprogrammed response to a step change in retinal disparity, while the step component integrates this preprogrammed response with visual feedback, guiding the eyes to the new desired vergence angle and holding them there[28]. These control mechanisms exhibit robust adaptive properties that allow us to maintain efficient and precise binocular alignment through-out our lives[257].

Convergence insufficiency (CI) is the most common non-strabismic oculomotor dysfunction[12]. Individuals diagnosed with CI demonstrated reduced capacities to conformably converge their eyes to obtain binocular motor fusion at typical reading distances (40cm)[258]. These oculomotor control deficits result in visual fatigue, headaches and blurred vision[109,258]. In more severe cases, patients report intermittent or even constant diplopia when attempting to fixate at near. The diagnosis of CI in adolescences has been associated with deficits in reading abilities[259] and potentially even impairments of visual attention and behavior deficits[260–263]. Furthermore, recent investigation revealed adults with CI perform worse on tests of higher level cortical integrative functions than aged-matched controls[264]. CI can be developmental or acquired in nature, being one of the most common visual diagnoses after a closed-head traumatic brain injury[13,265]. The impact of CI on other cognitive processes and the appropriate rehabilitative therapies for CI is the source of much debate. This due to our limited understanding of the neural basis of convergence insufficiency.

Sensorimotor adaptation defines a set of neural processes that maintain a high degree of accuracy and precision in a specific set of movements in the face of changing internal or external environmental conditions[120]. These processes are always active, comparing the result of a motor command to a theoretical 'internal model' of the sensorimotor environment[145,194]. If errors or bias are encountered in the expected results, such as when walking on a sloped surface, these adaptive processes recalibrate future movements. Experimentally, these adaptive processes are studied in saccadic eye movements by shifting the target stimulus before the eyes arrive at the intended location, also known as the 'double-step'[112,115]. In this error-based motor adaptation paradigm, the second shift in target location creates a perceived error in the initial preprogrammed motor response. If this double-step stimulus is continually repeated in the same direction, the amplitude and peak velocity of subsequent saccades is altered in order to compensate. These

adaptations occur and decay at rapid rates and are therefore referred to as short-term sensorimotor adaptations[115].

Short-term sensorimotor adaptations have been identified in reflexive vergence control using a disparity based version of the double-step paradigm[50,51,53,95,117,119]; however, they remain largely unexplored when compared to saccades. Sensorimotor adaptation in reflexive convergence has been strongly associated with our ability to comfortably adjust to new spectacle prescriptions[257]. This is especially the case in multifocal lens designs, where the degree of optical magnification is not uniform across the visual field and differs between eyes[10]. Recently, we have demonstrated that directional asymmetries between reflexive convergence and divergence responses in healthy, binocularly normal controls also extend into their adaptive capacities[266,267]. In addition to being slower at baseline than convergence, reflexive divergence movements demonstrated limited recruitment of larger, faster responses after completing an adaptive lengthening paradigm[236]. This finding was suggestive of saturation in the underlying preprogramed pulse generating divergence neural mechanism in certain individuals, as the subsequent divergence responses show little to no increases in their peak velocities. Beyond this limit, the sensorimotor adaptive mechanisms increase the duration of the initial divergence response in order to increase the overall initial response amplitude; however, the overall efficacy of this alterative process in reducing the initial reflexive errors is significantly reduced[236].

One of the hallmark laboratory signs of CI is reduced reflexive convergence responses to step changes in retinal disparity when compared to binocularly normal controls[13,97,105,139,140]. Ground breaking neural imaging data has recently demonstrated a reduction in the functional activity in the cortical and subcortical convergence regions in participants with both acquired and developmental CI[141,268]. Such data would suggest the neural basis of CI is a reduced or limited reflexive convergence substrate. Similar then to our proposed model in divergence, it would be expected that sluggish reflexive convergence responses in the CI population should then demonstrate a reduced capacity to adaptively lengthen their responses in an error-based motor learning task, such as the double-step paradigm.

The following study aims to test two separate but dependent hypotheses. First, that individuals with convergence insufficiency should demonstrated reduced capacities to adaptively lengthen their convergence responses when compare to binocularly normal controls. This is based on the assumption that their baseline reflexive convergence responses are slower and more variable than controls[97,139]. The second being that a limited or potentially saturated reflexive (convergence) neural substrate should lead to

alterations in the adaptive behavior and a reduction in the efficacy of the sensorimotor adaptation observed.

10.3 Methods

10.3.1 Participants

A total of 10 binocularly normal controls and 12 age-matched participants with convergence insufficiency were recruited from the undergraduate and graduate student population at the University of Waterloo, ON, Canada. The data from the control participants has been published previously[269]**.** To be included in either study group, subjects were required to have monocular visual acuities greater than 6/7.5 and at least 70 arc seconds of local (contour) stereopsis. A history of previous ocular injuries, surgeries, or diagnosed traumatic brain injuries were also exclusion criteria. All screening tests were completed through the subject's habitual refractive correction. The results of the screening tests are detailed in Table 10-2. Global stereopsis was assessed with the TNO random-dot stereoscopic vision test. Vergence facility was measured over the course of 60 seconds using the standard 3 base-in, 12 base-out prism procedures at 40cm while viewing a single line of 0.2 Log Mar vertical text[270]. This target was the same used to measure positive (PFV) and negative (NFV) fusional reserve blur points (or break if no blur was reported) at 40 cm using a prism bar in free space[271]. Heterophoria's were measured using the alternating cover test at 6M and 40cm[59]. Sheard's ratio was defined as the difference between the near heterophoria and the compensating fusional vergence reserve, divided by the near heterophoria amplitude[59]. Near point of convergence (NPC) was measured using a single letter 0.2 LogMar target, moved directly along the midline at a constant speed until the subject reported diplopia or the examiner observed one eye losing fixation and taking up an exotropic vergence posture.

10.3.2 Convergence Insufficiency Classification

Convergence insufficiency was primarily defined using the CITT groups criteria[110,111]. The main diagnostic criteria is a heterophoria exo-deviation that was at least 4-PD greater at 40cm than 6m[12,111]. Additionally, CI participants had to exhibit two or more of the following signs to be included; a receded near-point of convergence (NPC) beyond 6cm, PFV reserves less than twice the amplitude of the near exophoria (failing Sheard's criterion, Sheard's ratio < 2), a CISS score of equal to or greater than 20, and/or vergence facility reduced below 13cpm[270]. Two CI participants (S7 and S9) had been previously diagnosed with CI and prescribed oculomotor therapies; however, neither completed the prescribed treatment and both remained symptomatic at the time of recruitment. An additional 2 participants that met

the CI inclusion criteria were excluded because they were unable to obtain motor fusion of the convergence stimuli in the dichoptic apparatus described above. These two participants also demonstrated the largest degree of exophoria at near. A summary of the clinical screening results for both CI and control groups can be found in Table 10-2 below**.**

10.3.3 Apparatus

Images were presented dichoptically via a haploscope on two 7-inch LCD monitors placed at 40cm (Lilliput, UK). Each subject's interpupillary distance was set in the haploscope at each visit in order to provide a congruent accommodative-vergence stimulus when the binocularly fused target was placed at the center of each monitor. This was the starting position for each step change in disparity. Head movements were limited by a custom chin and forehead restraint. Monocular eye movements were recorded at 250Hz, digitized and stored for off-line analysis using infrared oculography (EyeLink2 - SR Research, Canada). The complete experimental apparatus and visual stimulus parameters have been described in detail in previous work[236,269] (see Figure 6-2 and Figure 9-1).

Controls											
	MSRE	**Age**	**Stereopsis ('arc)**	**Facility (cpm)**	**Phoria (6 m)**	**Phoria (40 cm)**	**NPC (cm)**	**PFV**	**NFV**	**CISS Score**	**Sheard's Ratio**
S1	-7.25	28	120	12	-2	-2	2	40	-16	2	19
S2	0	21	30	20	-0.5	-3	0	16	-14	7	4.3
S3	-0.5	27	60	16	1	2	2	20	-8	14	11
S4	-1.75	32	30	21	1	3	0	35	-18	0	12.7
S5	-1.5	22	120	18	-3	-5	0	35	-25	0	6
S6	-4.5	23	30	25	2	4	0	40	-14	2	11
S7	0	31	60	16	-4	-7	3	45	-25	16	5.4
S8	-4.5	23	60	15	0	-2	4	30	-14	10	14
S9	-1	22	30	17	0	-1	0	35	-20	3	34
S10	-5	30	60	14	-2	-4	0	40	-16	2	9
Mean (SD)	*-2.6 (2.5)*	*25.9 (4.2)*	*60.0 (34.6)*	*16.1 (2.9)*	*-0.75 (1.9)*	*-1.5 (3.6)*	*1.1 (1.4)*	*33.6 (9.2)*	*-17.0 (5.2)*	*5.6 (5.9)*	*12.6 (8.7)*

Table 10-1: A) Clinical assessments of the control group. Exo (divergent) values are negative and eso (convergent) are positive. All phoria and fusional reserve values are in prism diopters (PD). "s" denotes suppression in the absence of diplopia. MSRE = Mean sphere refractive error, NPC = near point of convergence, PFV = positive fusional vergence, NFV = negative fusional vergence, CISS = convergence insufficiency symptom survey, cpm = cycles per minute**.**

Convergence Insufficiency											
	MSRE	**Age**	**Stereopsis ('arc)**	**Facility (cpm)**	**Phoria (6 m)**	**Phoria (40 cm)**	**NPC (cm)**	**PFV**	**NFV**	**CISS Score**	**Sheard's Ratio**
S11	-2	22	120	9	-3	-12	8	16	-18	22	0.33
S12	-0.75	27	60	5	0	-6	4	10	-18	26	0.25
S13	-1.75	26	240	9	-1	-8	9	14	-12	23	0.75
S14	-0.25	34	120	6 (s)	-1	-10	15 (s)	6 (s)	-12 (s)	20	0.2
S15	-3	21	60	8	0	-8	11	10	-14	23	0.25
S16	0	22	240	0 (s)	-4	-9	11 (s)	6 (s)	-10 (s)	30	0.33
S17	-6.25	24	60	5	0	-6	6	10	-14	27	0.67
S18	-1.75	34	30	12	0	-4	25	14	-18	6	0.5
S19	0	20	120	6	-1	-10	7	12 (s)	-14	28	0.2
S20	-1.75	24	60	12	0	-5	9	14	-12	22	0.17
Mean (SD)	*-1.75 (1.9)*	*25.4 (4.7)*	*111.0 (74.9)*	*7.6 (3.7)*	*-1.2 (1.4)*	*-9.1 (1.9)*	*10.5 (5.9)*	*11.4 (3.2)*	*-15.2 (3.4)*	*23.8 (6.6)*	*0.36 (0.3)*

Table 10-2: B) Clinical assessments of the convergence insufficiency group. Exo (divergent) values are negative and eso (convergent) are positive. All phoria and fusional reserve values are in prism diopters (PD). "s" denotes suppression in the absence of diplopia. MSRE = Mean sphere refractive error, NPC = near point of convergence, PFV = positive fusional vergence, NFV = negative fusional vergence, CISS = convergence insufficiency symptom survey, cpm = cycles per minute.

10.3.4 Procedures & Stimuli

A summary of the basic protocols is provided here; however, a complete description of experimental procedures with schematic illustrations has been described elsewhere[95,117] and in our previous work[46]. Briefly, participants completed 1 screening and 2 experimental visits. One trial was completed per day, with at least 5 days (maximum 15) between trials. The order of the experimental conditions was randomized. The two experimental conditions were; convergence gain increasing (CGI) also referred to as 'adaptive lengthening' and divergence gain increasing (DGI), or 'adaptive shortening'.

Each experimental trial contained a baseline, adaptation and recovery phase and was confined to a single vergence direction (convergence or divergence). After completion of each phase, the participant was given a break, of up to 3 minutes, before continuing.

The baseline and recovery phases were identical and consisted of 25, 2° symmetric step changes in disparity (single-step) that were presented with a randomized delay to prevent prediction[127]. The adaptation phase was comprised of 75 double-step stimuli and 10, 2° single-step, 'test' stimuli (identical to that of the baseline and recovery phases). The double-step stimuli began with the same 2° disparity step, followed 175ms later by an additional 1.5° step in the same direction. The 'test' stimuli began only after 25 consecutive double-step stimuli had been presented and were randomly interleaved with the remaining 50 double-step stimuli at an average rate of 5:1[117]. The use of single-step test stimuli is required to elucidate the adaptive changes in the dynamic vergence responses to the initial 2° disparity error signal presented in the baseline and recovery phases.

A 2° step amplitude was chosen in order to limit the number of responses containing saccadic interactions and maximize the volume of quality vergence response data, since larger step changes in disparity tend to generate more vergence responses that contain significant conjugate components[65]. These mixed movements have significantly increased vergence response amplitudes and peak velocities when compared to responses that are more disjunctively symmetric[68,84,144,222,272] and are therefore excluded from analysis.. Furthermore, in CI, they are encountered much more frequently and at lower step amplitudes[219].

10.3.5 Data Analysis

Monocular eye positions were analyzed off-line using a custom analysis package designed in MatLab (Waltham, MA, USA) and used in previous work[269]. The difference between right and left eye positions defined the vergence angle and a two-point central difference algorithm defined vergence velocity. Step vergence response amplitudes were identified using a 1.5°/s start-stop velocity threshold applied at the onset of each step-stimulus. The settling time was defined by the difference between the time of movement onset and the time at which the vergence velocity was equal to or less than 0°/s for 16ms consecutively. The responses in each baseline and recovery phase were binned sequentially into blocks of 10. In the adaptation phase, the 10 single-step 'test' stimuli were binned separately and were used to define the adaptive changes in vergence response properties. Vergence responses containing saccades or with latencies less than 80ms and response amplitudes or peak velocities outside 2 standard deviations of their respective block means were also excluded[174].

The degree of adaptation within each subject's vergence system was defined as the percent difference between the mean of the last baseline bin response metric and corresponding measurement mean in the test response bin. Previous work has demonstrated that the majority of reflexive vergence adaptation under these circumstances occurs within the first 20-30 double-step stimuli[117,269].

To mathematically isolate the initial, open-loop, reflexive vergence command of each response analyzed (hence forth known as the 'pulse') a phase-plane analysis was employed. This type of analysis and its application to vergence responses has been summarized numerous times elsewhere[33,51,269]. It provides a means to estimate the amplitude of this open-loop pulse response if visual feedback were unavailable.

Two-way ANOVA models were used to assess the effect of the test conditions (CGI vs DGI) and group (control versus CI) on the vergence response parameters measured in the baseline, adaptation ad recovery phases of the experiment. Bonferroni corrected post-hoc testing was then used to compare differences between groups on specific conditions. The results of these post-hoc tests are detailed in each table in the results section. In the adaptive and recovery analysis the group means within a condition were tested against the null hypothesis of zero change using a two-tailed t-test. An insignificant change at the end of the adaptive phase would indicate no effect of the double-step stimuli, while a significant change from zero at the end of the recovery phase would indicate retention of any response parameter modifications acquired in the adaptive phase. For each vergence parameter tested in this way the p-values were corrected to account for the appropriate number of multiple comparisons.

10.4 Results

10.4.1 Clinical Screening Differences

Control and CI participants did not differ statistically in age ($t = 0.9$, $p = 0.4$), mean sphere refractive error ($t = 0.1$, $p = 0.96$), distance heterophoria ($t = 0.59$, $p = 0.55$) or negative fusional vergence ($t = 1.7$, $p = 0.11$). CI participants had significantly higher levels of exophoria at near ($t = 5.4$, $p < 0.001$), greater NPC's ($U = 0.5$, $p < 0.001$) and CISS symptom scores ($U = 2.5$, $p < 0.001$); while having significantly lower vergence facility ($U = 0.5$, $p < 0.001$), positive fusional vergence ($U = 7.3$, $p < 0.001$) and Sheard's ratio ($U = 0$, $p < 0.001$). Global stereopsis was better in the control group, but the difference did not reach statistical significance ($U = 27$, $p = 0.09$) in part due to the greater variation in the CI group Table 10-2.

10.4.2 Baseline Vergence Response Differences

As expected and consistent with previous work[97,139–141], the control group exhibited significantly faster and larger convergence (pulse) responses to the baseline 2° disparity steps compared to the CI group

Table 10-3 and

Figure 10-1**.** The only convergence response parameter that demonstrated no significant effect in the two-way ANVOA was total response amplitude. This can be attributed to the large degree of variation in the CI population data where two participants struggled to consistently and fully fuse the baseline convergence steps and showed markedly reduced initial response amplitudes. In addition, reduced divergence response amplitudes in both groups and convergence responses in the CI group were partially a result of the 1.5 °/s velocity criterion used to define the initial total response amplitudes end point. This is reflected in the larger settling times required to obtain fusion in the group as a whole. The convergence response latency in the CI group was also significantly greater than controls convergence in the baseline blocks.

In contrast, no significant differences were found between the two group's baseline divergence responses, Table 10-3 and Figure 10-2. While the variability of the baseline convergence responses was clearly larger in the CI group, there did not appear to be any systematic differences in the variability of divergence responses between the two groups. The mean number of movements analyzed from the baseline phase was not different between groups for a given direction (convergence: Control 84.5% ± 9 vs CI 76.2% ± 14, $p = 0.11$; divergence: Control 81.4% ± 7 vs. CI 73.8% ± 14; $p = 0.13$).

Baseline mean convergence response properties from the CI group were also compared to the divergence responses of the control group**.** In general, there were no significant differences identified between the group means for this comparison, with the exception of latency, which was significantly greater for the convergence responses of the CI group when compared to the convergence responses of the control group.

Vergence Direction	Group	Response Amplitude (°)	Pulse Amplitude (°)	Peak Velocity (°/s)	Peak Acceleration (°/s^2)	Latency (ms)	Duration (ms)	Settling Time (ms)
Convergence	Control	1.92 (0.2)	1.69 (0.2)	11.99 (1.8)	124.2 (29.1)	140.6 (13.5)	367.1 (55.5)	450.7 (76.5)
	CI	1.60 (0.5)	1.11 (0.5)	7.38 (2.5)	70.67 (38.3)	169.7 (26.8)	460.1 (84.8)	660.6 (143.8)
Divergence	Control	1.61 (0.3)	1.35 (0.3)	8.33 (2.1)	76.5 (26.3)	147.1 (22.2)	402.1 (63.1)	604.4 (95.9)
	CI	1.50 (0.5)	1.28 (0.6)	7.48 (2.7)	61.58 (24.9)	156.9 (27.5)	444.9 (95.6)	637.2 (158.2)
ANOVA Results F(1,34)	Interaction	F = 0.7 p = 0.42	F = 3.9 p = 0.05	F = 6.4 p = 0.02	F = 3.9 p = 0.05	F = 1.7 p = 0.21	F = 1.1 p = 0.3	F = 5.1 p = 0.03
	Group	F = 2.9 p = 0.99	F = 5.7 p = 0.02	F = 13.5 p < 0.001	F = 11.9 p = 0.002	F = 6.8 p = 0.01	F = 7.7 p = 0.009	F = 9.5 p = 0.004
	Condition	F= 2.6 p = 0.12	F = 0.4 p = 0.54	F = 5.8 p = 0.02	F = 8.2 p = 0.007	F = 0.2 p = 0.70	F = 0.2 p = 0.68	F = 2.7 p = 0.11
Convergence Control vs. CI		NA	p = 0.02	p < 0.001	p = 0.002	p = 0.03	p = 0.04	p = 0.002
Divergence Control vs. CI		NA	p = 0.98	p = 0.85	p = 0.73	p = 0.80	p = 0.81	p = 0.93
Control Divergence vs CI Convergence		NA	p = 0.56	p = 0.78	p = 0.97	p = 0.14	p = 0.15	p = 0.73

Table 10-3: Group means (SD) of vergence response properties to the 2° disparity step stimulus in the final block of the baseline phase. Two-Way ANOVA results are given along with post-hoc analysis (bottom 3 rows) if appropriate. NA (not applicable) is given where there were no significant main effects or interactions in the initial ANOVA.

10.4.3 Sensorimotor Adaptation of Reflexive Vergence

10.4.3.1 Convergence Lengthening

Table 10-4 summarizes the normalized percent change of vergence responses to the test stimuli during the adaptation phase for both stimulus directions in each group. The same results for a sample of individual subjects are depicted graphically in

Figure 10-1**.** As detailed in previous work[269], the control group convergence responses were significantly larger and faster after adaptive lengthening, which resulted in the total movement duration and settling time being reduced. In the CI group, there was no significant change in mean response amplitude, pulse amplitude, peak velocity or peak acceleration during the adaptation phase.

When compared to controls, the mean adaptive changes in the CI group were significantly less across all response parameters (Table 10-4). The exception to this was the change in response latency, which was not significantly different from zero in either group. The average number of convergence responses that were free of blinks or significant saccadic-intrusions to the test stimuli in the adaptation phase was significantly different between groups (82.2% ± 9 Control, 59.5% ± 21 CI; $p = 0.009$). This was due to an increase in the number of convergence responses containing saccadic-intrusions in the CI group during adaptation (12.7% ± 10 increase from baseline, $p = 0.01$).

There was a large degree of variation within the CI group's adaptation data, especially when compared to controls. Three participants in the CI group demonstrated noticeable reductions in the dynamic properties of their convergence responses during and after adaptive lengthening. A significant increase in the time to peak velocity in these individuals was also noted during these phases. These three subjects also had the slowest baseline convergence responses. An example of their convergence datasets is depicted in the top row of

Figure 10-1B**.** This was not observed in the remaining 7 CI participants, where small increases in response amplitude were accompanied by increases in response duration with no significant changes in the reflexive pulse response amplitude or peak velocity & acceleration. Figure 10-2 provides a graphical illustration of the general relationship between mean baseline reflexive convergence peak velocity and the (mean) degree of adaptive increases that were observed within a subject. A Pearson correlation analysis was performed on the mean baseline response peak velocity and the normalized mean % change in this parameter after adaptation. In both groups, there was a significant positive relationship between these two properties (control group: $r = 0.62$, $p = 0.04$; CI group: $r = 0.75$, $p = 0.01$; one-tailed). This same correlation analysis was also performed on the mean baseline pulse response amplitude and mean

normalized % pulse amplitude change after adaptation. Again, there was a significant positive relationship between this baseline response parameter and its degree of adaptive change (control group: $r = 0.74$, $p = 0.02$; CI group: $r = 0.86$, $p = 0.001$; one-tailed).

From Figure 10-2 it can be seen that the slowest baseline reflexive responses exhibited a decrease in the pulse response amplitude and peak velocity after adaptation. Such a finding could be the result of fatigue in the neural substrate or the physical plant (medial recti). To ensure that these 3 CI subject's data were not responsible for the between groups effects reported, their data was excluded and the between group analysis described above was re-run. The results of this re-analysis were still significantly different across the same parameters, stated earlier in this section ($p < 0.02$). Importantly, the overall change in the pulse response dynamics after adaptation was still not significantly different from zero in this subgroup of CI subjects ($p > 0.15$).

Vergence Direction	Group	Response Amplitude	Pulse Amplitude	Peak Velocity	Peak Acceleration	Latency	Duration	Settling Time
Convergence % Change	Control	21.61 (9.6) t(9) = 7.3 p < 0.0001	30.12 (11.4) t(9) = 7.8 p < 0.0001	25.43 (9.8) t(9) = 8.2 p < 0.0001	27.31 (8.8) t(9) = 12.3 p < 0.0001	-1.88 (5.5) t(9) = 1.1 p = 0.32	-12.54 (7.9) t(9) = 5.5 p = 0.004	-22.87 (16.1) t(9) = 4.4 p = 0.002
	CI	-9.64 (18.6) t(9) = 1.7 p = 0.13	-11.08 (22.1) t(9) = 1.6 p = 0.15	-14.61 (20.6) t(9) = 2.2 p = 0.06	-18.22 (27.3) t(9) = 1.0 p = 0.33	2.49 (8.2) t(9) = 0.53 p = 0.61	6.72 (10.9) t(9) = 1.9 p = 0.08	0.13 (16.4) t(9) = 0.02 p = 0.97
Divergence % Change	Control	10.30 (9.1) t(9) = 3.3 p = 0.001	-2.64 (17.1) t(9) = 0.51 p = 0.68	-0.82 (12.9) t(9) = 0.20 p = 0.85	-0.06 (12.1) t(9) = 0.02 p = 0.98	2.51 (6.2) t(9) = 1.1 p = 0.24	8.06 (7.3) t(9) = 3.0 p = 0.02	-2.45 (7.6) t(9) = 0.87 p = 0.40
	CI	9.02 (20.9) t(7) = 1.2 p = 0.47	10.3 (19.1) t(7) = 1.5 p = 0.18	0.51 (20.7) t(7) = 0.07 p = 0.95	1.67 (20.9) t(7) = 0.2 p = 0.82	6.10 (10.6) t(7) = 1.6 p = 0.14	15.51 (16.8) t(7) = 1.2 p = 0.04	8.76 (33.8) t(7) = 0.4 p = 0.50
ANOVA Results F(1,34)	Interaction	F = 9.3 p = 0.005	F = 21.8 p < 0.001	F = 14.9 p < 0.001	F = 15.2 p < 0.001	F = 0.02 p = 0.87	F = 2.7 p = 0.11	F = 0.8 p = 0.37
	Group	F = 10.9 p = 0.002	F = 5.9 p = 0.02	F = 13.1 p = 0.001	F = 13.1 p = 0.001	F = 2.5 p = 0.12	F = 14.1 p < 0.001	F = 7.1 p = 0.01
	Condition	F = 0.6 p = 0.46	F = 1.0 p = 0.33	F = 1.1 p = 0.31	F = 0.4 p = 0.54	F = 2.6 p = 0.12	F = 16.9 p < 0.001	F = 5.1 p = 0.04
Convergence Control vs. Convergence CI		p < 0.001	p < 0.001	p < 0.001	p < 0.001	NA	p = 0.002	p = 0.05
Divergence Control vs. Divergence CI		p = 0.99	p =0.43	p = 0.99	p = 0.99	NA	p = 0.49	p = 0.63
Control Divergence vs CI Convergence		p = 0.03	p = 0.72	p = 0.27	p = 0.15	NA	p = 0.99	p = 0.99

Table 10-4: Mean and (SD) of the normalized percent change in vergence response properties to the test stimuli in the adaptation phase compared to the last baseline block. The p-values within each cell represent the result of a one-sample two-tailed comparison, where the normalized percent change was tested against the null hypothesis of zero change. Two-Way ANOVA results are given along with post-

hoc analysis (bottom 3 rows) if appropriate. NA (not applicable) is given where there were no significant main effects or interactions in the initial ANOVA.

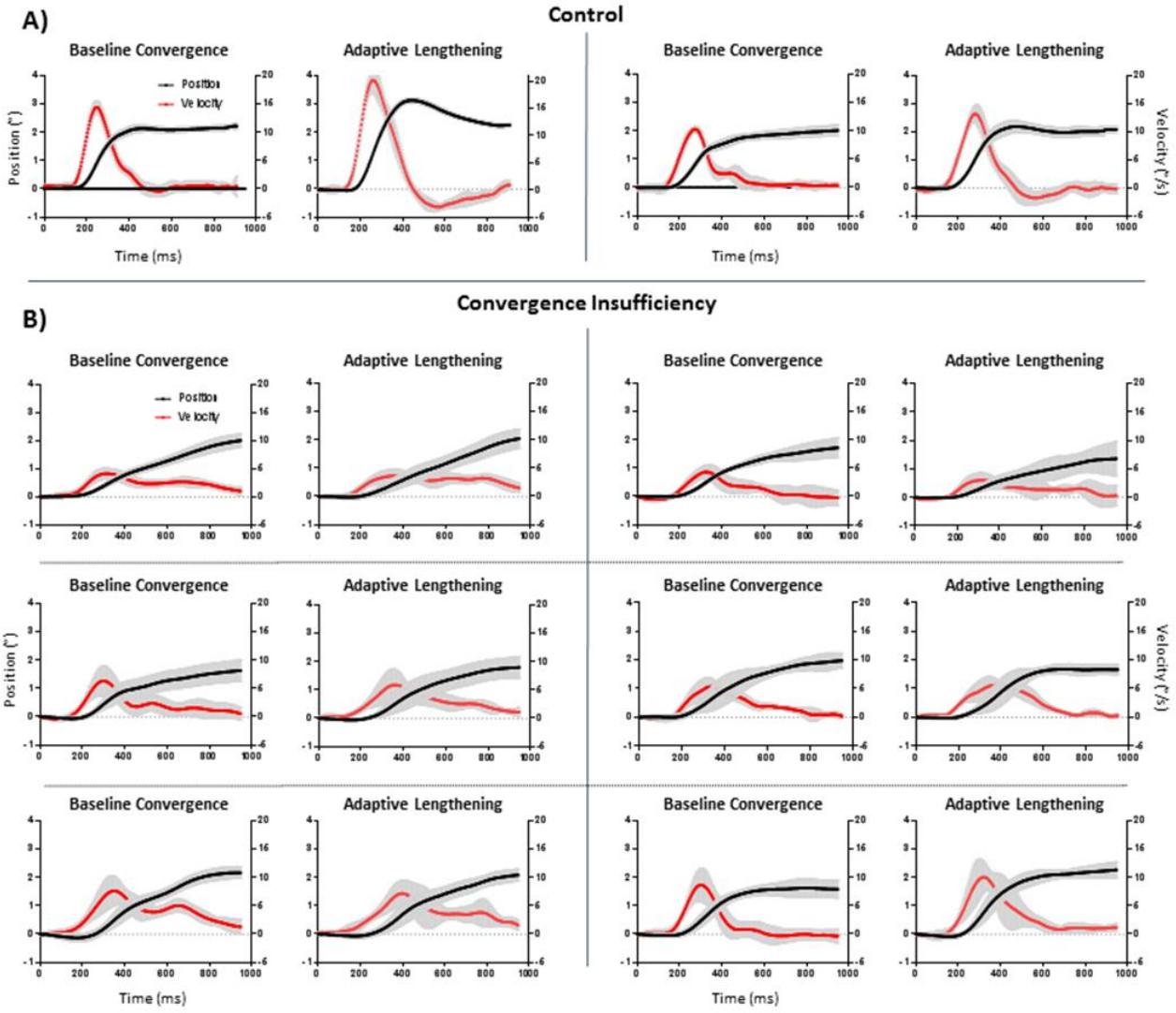

Figure 10-1 Mean position (black) and velocity (red) convergence response traces for 2 control (A) and 4 CI (B) participants. SD of each dataset is plotted in grey. Baseline convergence plots are formed from the last block of 10 single-step stimuli in the baseline phase. Adaptive lengthening plots are the combined convergence responses to the single-step test stimuli during the adaptation phase. The baseline convergence pulse amplitudes and peak velocities are significantly greater in the control participants

when compared to the CI group. Controls also demonstrated increases in these parameters after double-step adaptation, while in CI participants, little if any increase in the pulse response amplitude or peak velocity are noted in the adaptation phase.

10.4.3.2 Divergence Lengthening

During divergence adaptive lengthening, there were two CI participants who became diplopic and were unable to obtain fusion to any of the step stimuli (S14 & S16). Their data were excluded from analysis. In the remaining CI subjects, the adaptive effects on divergence responses were similar to that of the control group[269]. The CI group demonstrated a limited capacity to adaptively increase the amplitude or peak velocity of their reflexive divergence responses to the double-step stimuli. This observation was the same in the control and CI groups and is summarized in the bottom half of Table 10-4 with a sample set of the CI subject data depicted in

Figure **10-3**.

There were an additional 2 participants in the remaining CI subgroup who exhibited large reductions in their divergence peak velocities and pulse response amplitudes during and after adaptation. In keeping with the same observation made in the convergence responses in the CI group, these individuals' responses had increases in their time to peak velocity, suggestive of fatigue. An example of such data is given in the top left panel of

Figure **10-3**B.

Control participants had significantly more divergence responses to the test stimuli that were free from saccades and blinks when compared to CI's (76.6% ± 9 vs. 61.4% ± 14; $p = 0.01$); however, the number of responses excluded due saccadic intrusions was not significantly increased from baseline in the CI group (7.4% ± 15, $p = 0.16$).

The bottom row in Table 10-3 summarizes the comparison of adaptive changes observed in the control group's divergence responses and the CI group's convergence response. With the exception of overall response amplitude change being slightly greater in controls adapted divergence responses, the adaptive effects of the double-step stimulus are not significantly different from each other in these conditions.

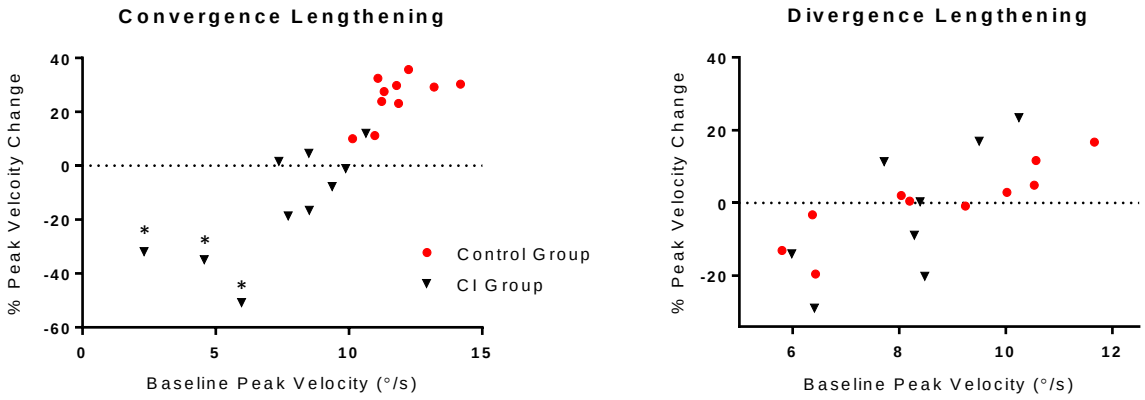

Figure 10-2: Scatter plots of the mean normalized % peak velocity change after adaptation compared to the mean baseline vergence response peak velocity for each participant. Within each dataset there is a significant correlation between the normalized peak velocity change during adaptation and the peak velocity measured at baseline. (*) in the right panel are placed above the CI participants data where large reductions in peak velocity were observed after adaptive lengthening of their convergence responses.

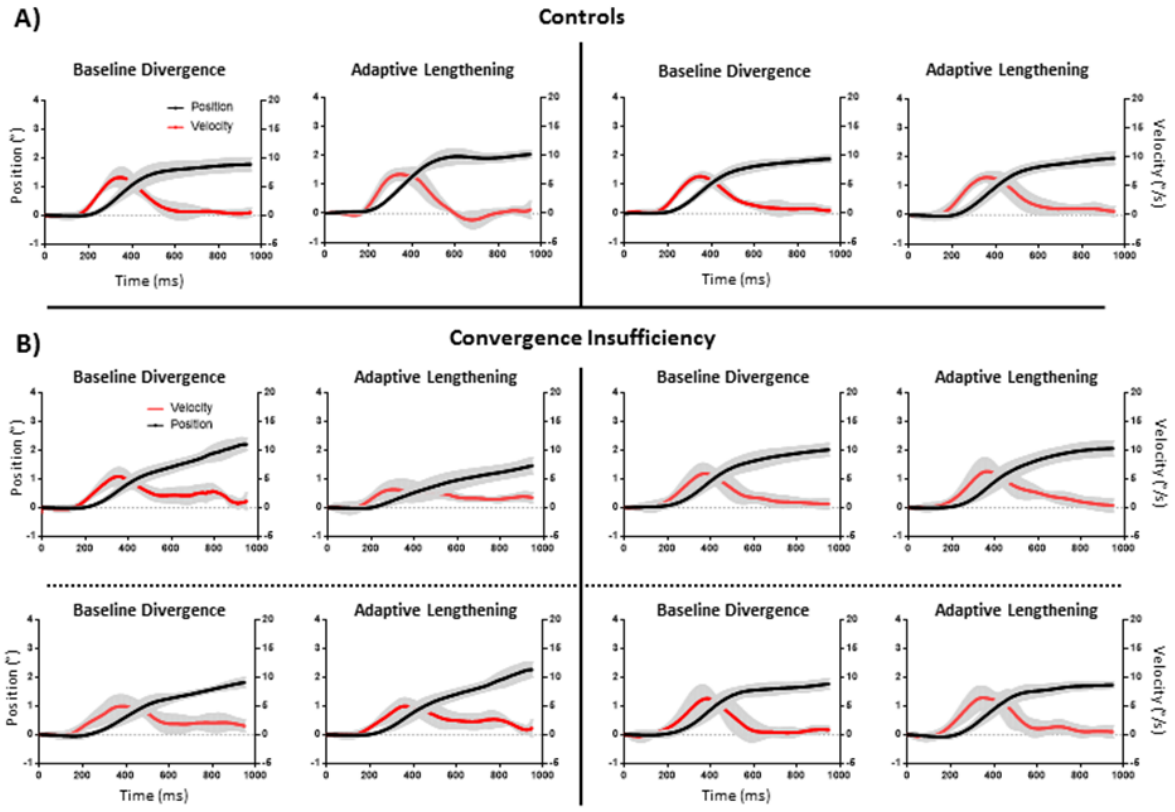

Figure 10-3: Mean position (black) and velocity (red) divergence response traces for 2 control (A) and 4 CI (B) participants (absolute values plotted). SD of each dataset is plotted in grey. Baseline divergence plots are formed from the last block of 10 single-step stimuli in the baseline phase. Adaptive lengthening plots are the combined divergence responses to the single-step test stimuli during the adaptation phase. The baseline divergence pulse amplitudes and peak velocities are similar between the control and CI group. In both groups, little if any increase in the pulse response amplitude or peak velocity are noted in the adaptation phase. Instead, the duration of the initial pulse response increases, resulting in increases in the overall response gains. Importantly, this was not due to recruitment of a larger, faster open-loop pulse response in either group.

10.4.3.3 Recovery Post-Adaptation

The normalized mean change between the final block (last 10 responses) of the recovery phase and the last baseline block are summarized in

Table 10-5. The results of the control data are discussed at length in other work[269]. In the CI group, there was an overall reduction in all of the convergence response properties. This effect was significant for only the peak velocity and peak acceleration. In contrast, the control group retained a small but significant increase in their reflexive pulse response amplitudes and peak velocities from the adaptation phase, resulting in slightly shorter movement durations and settling times. In the divergence direction, neither group mean demonstrated significant changes from baseline.

Vergence Direction	Group	Pulse Amplitude	Peak Velocity	Peak Acceleration	Latency	Duration	Settling Time
Convergence	Control	9.8 (11.4) t(9) = 2.7 p = 0.02	8.35 (7.3) t(9) = 4.2 p = 0.003	5.62 (8.3) t(9) = 2.0 p = 0.08	0.73 (7.8) t(9) = 0.30 p = 0.77	-6.07 (8.2) t(9) = 2.4 p = 0.04	-11.23 (13.4) t(9) = 2.6 p = 0.03
	CI	-5.84 (18.3) t(9) = 1.2 p = 0.35	-11.15 (14.7) t(9) = 2.4 p = 0.04	-15.84 (15.3) t(9) = 4.7 p = 0.009	1.92 (7.0) t(9) = 0.9 p = 0.41	-6.36 (14.6) t(9) = 1.8 p = 0.11	-5.16 (18.7) t(9) = 1.0 p = 0.34
Divergence	Control	-0.74 (11.9) t(9) = 0.2 p = 0.85	-4.67 (8.2) t(9) =1.8 0.10	-3.12 (11.7) t(9) = 0.78 p = 0.46	1.91 (8.5) t(9) = 0.02 p = 0.98	0.084 (12.2) t(9) = 0.72 p = 0.49	-8.29 (22.86) t(9) = 1.1 p = 0.28
	CI	-9.15 (12.8) t(7) = 2.0 p = 0.09	-2.78(23.6) t(7) = 0.3 p = 0.75	-7.52 (19.9) t(7) = 1.1 p = 0.32	7.87 (11.4) t(7) = 2.2 p = 0.07	4.13 (20.4) t(7) = 0.4 p = 0.67	4.54 (14.8) t(7) = 0.92 p = 0.38
ANOVA Results F(1,34)	Interaction	F = 0.6 p = 0.45	F = 5.3 p = 0.03	F = 3.5 p = 0.07	F = 0.7 p = 0.41	F = 0.2 p = 0.64	F = 0.3 p = 0.56
	Group	F = 6.8 p = 0.01	F = 3.6 p = 0.07	F = 7.9 p = 0.008	F = 1.6 p = 0.21	F = 0.2 p = 0.68	F = 2.6 p = 0.12
	Condition	F = 2.5 p = 0.13	F = 0.3 p = 0.62	F = 0.002 p = 0.97	F = 1.6 p = 0.22	F = 3.3 p = 0.08	F = 1.2 p = 0.29
Convergence Control vs. Convergence CI		p = 0.08	p = 0.02	p = 0.009	NA	NA	NA
Divergence Control vs. Divergence CI		p = 0.58	p = 0.99	p = 0.91	NA	NA	NA
Control Divergence vs CI Convergence		p = 0.87	p = 0.74	p = 0.20	NA	NA	NA

Table 10-5: Mean and (SD) of the normalized percentage change in vergence response properties in final recovery block compared to the last baseline block. The p-values within each cell represent the result of a one-sample two-tailed comparison, where the normalized percent change was tested against the null hypothesis of zero change. Two-Way ANOVA results are given along with post-hoc analysis (bottom 3

rows) if appropriate. NA (not applicable) is given where there were no significant main effects or interactions in the initial ANOVA.

10.5 Discussion

The central aim of this study was to investigate the effects of convergence insufficiency on the short-term sensorimotor adaptive capacities of reflexive fusional vergence. Using a novel error-base motor learning paradigm (double-step disparity stimuli) we tested the hypothesis that reduced reflexive vergence response dynamics would lead to a reduction in the overall efficacy of the underlying adaptive mechanism responsible for maintaining optimal vergence kinematics. This hypothesis was predicated on our previous findings[269] and the assumption that reflexive fusional convergence responses would be reduced in CI when compared to controls[97,119,139,140].

Consistent with this previous literature, our results demonstrated markedly reduced baseline reflexive convergence response dynamics, accompanied by increases in response duration, settling times and overall response variability to step changes in retinal disparity in our CI group. These reduced convergence response dynamics in the CI group were subsequently associated with reduced sensorimotor adaptive capacities and demonstrate a functional impairment of a neural mechanism that is fundamental to the maintenance of bi-foveal fixation, motor fusion and stereopsis. The results are consistent with what other have reported previously regarding the function of both the reflexive convergence mechanism[97,110,139,141,142,219] and the tonic adaptive mechanisms[48,106–108,207,214,273].

In general, the sensorimotor adaptive capacities of reflexive convergence responses were significantly reduced in the CI group when compared to controls. Adaptive lengthening of convergence responses in the CI group resulted in limited, if any increase in future movement dynamics. Instead, increases in convergence response amplitudes in the CI group after adaptation came as a result of increased response durations in some CI participants and not because a greater recruitment of the open-loop reflexive vergence response. This convergence adaptive behavior in CI was similar to their adaptive capacities in the divergence direction. Interestingly, these effects in the CI group were no different from the control groups divergence responses and adaptive capacities. Additionally, an increased recruitment of saccadic influences in convergence responses was noted in the CI group after adaptation. The was evidence by an increase in the amount of saccadic-vergence responses and decreased frequency of pure vergence responses as the experimental trial progressed. Similar to what others have reported in patients with CI[219,274], slower convergence dynamics tend to result in greater recruitment of saccadic-vergence

responses in our patient cohort. These effects have also been reported in binocularly control subjects, with a greater frequency in the slower divergence responses[84,88,89,222].

The second aim of this study was to test the hypothesis that sluggish reflexive vergence responses are the result of a smaller reflexive vergence neural substrate that is unable to recruit larger motor responses to increased stimulus demands. The use of a double-step adaptive paradigm to investigate this question allows us to test the saturation hypothesis without having to use a sequence of larger disparity steps, where saccadic intrusions are significantly greater and make most the data unusable. The similarities between the divergence data in each subgroup and the convergence data in the CI group support this hypothesis. Overall, the participants with the smallest and slowest reflexive convergence pulse responses demonstrated the least amounts of adaptive modulation, regardless of the group or disparity direction. The opposite was also true for participants with larger, faster initial baseline vergence response properties (Figure 10-2). This relationship was significant for both the peak velocity and pulse response amplitude.

It is unclear whether the recruitment of more saccadic-vergence responses in the CI group was a separate adaptive mechanism in response to the double-step stimuli, or the result of central fatigue in the motor substrate. Because the frequency of these saccadic-vergence responses increased with experimental phase in the CI group, it is likely that central fatigue may have played a role. Others have shown these type of saccadic-vergence responses to be more frequent in CI[219,275]. Their frequency reduces as symmetric vergence response dynamics increase with rehabilitation treatment[219]. It would be interesting to explore the facilitatory effects of such saccadic-vergence interactions on adaptive behavior in future work; however, they would be difficult to compare with controls, given their relative scarcity in our current data set.

We found no significant differences in baseline reflexive fusional divergence parameters between groups. This is consistent with previous literature that has reported reflexive divergence responses in both CI and control groups pre and post orthoptic vision therapy were not significantly different[141,214]. These findings suggest that while the CI group's heterophoria was more exophoric at near (and this was not compensated for in the dichoptic apparatus) a significant facilitation of the divergence responses did not occur as a result. Taken together, these studies confirm that convergence and divergence are truly separate neural substrates and that a motor impairment in one mechanisms does not impair or facilitate the development or response mechanics of the opposing vergence substrate. Furthermore, it suggests that convergence insufficiency is not merely a shift in the distribution of motor neurons responsible for convergence and divergence.

Cell-recordings in primate vergence motor and premotor areas have indicated that vergence response amplitudes are well correlated with the duration of neuronal firing and that vergence velocity was well correlated with the neuronal firing rates[37,38,47]. Based on these neurophysiological data, one interpretation of our results is that limited increases in the peak velocity of reflexive vergence responses after adaptive lengthening adaptation are demonstrative of a ceiling effect in the neural firing and recruitment rates. Neural imaging data from participants with CI have also shown an overall reduction in the functional activity of the cortical and subcortical vergence regions when compared to healthy controls[141,268]. Taken together, the results suggest that CI is, at a basic level, an underdeveloped or impaired reflexive (disparity-driven) convergence response mechanism. This reduced reflexive convergence response capacity then leads to an impairment in the overall efficacy of sensorimotor adaptation in this neural substrate. As is often the case then, attempts to adjust to the impairments result in increased recruitment of other oculomotor systems, in this case, saccades. By extension then, rehabilitative therapies targeting the pre-programmed reflexive fusional response mechanisms should result in the most efficacious outcomes, where adaptive responses improve as a result of improvements in reflexive response dynamics. Furthermore, objective measurements of reflexive fusional vergence dynamics can further serve as diagnostic biomarkers of CI and its resolution through treatment.

An unexpected finding in the baseline vergence data was the longer reflexive convergence response latencies in the CI group. And while the CI group data was indeed more variable, the overall effect was quite large. There is a paucity of data providing similar comparisons between CI and control group convergence response latencies in the literature. The studies that provide the most detailed analysis of convergence response dynamics either fail to report response latencies [139,141,214,219] or do not compare the findings between groups[97,140]. One study did find differences between traumatically induced CI's and control groups convergence latencies[13]. The authors of this study also reported greater divergence latencies in their triatic CI group than controls. This was not the case in our results. The latency differences reported in the previous works cited are likely more representative of the different etiologies of CI (traumatic vs. *presumed* developmental). It is possible that the greater reflexive convergence response latencies in our CI group represent an up-stream sensory processing issue with retinal disparity. The larger and more variable global random-dot stereoacuity thresholds in our CI population could be taken to support such a conclusion. Others have not reported differences between groups on these stereoacuity parameters[276] and our limited sample size may reduce the external validity of the stereoacuity findings reported within this study. Future work in such patient groups should focus on characterizing

stereoacuity thresholds in greater detail with more rigorous psychophysical protocols to provide a greater understanding of the sensory status of such populations.

The capacity to adaptive lengthen convergence responses is strongly related to successful adaptation multifocal lens wear during presbyopia[10]. Intuitively, these two functions can be directly related, as multifocal lenses induce acute non-uniformities in the magnification of perceptual space across the visual field. This altered sensory input would command rapid recalibrations of binocular alignment and motor control systems, as we have demonstrated here. Failure of such adaptive mechanisms, such as that observed in our small sample of CI subjects, would be expected to result in negative user experiences and mal-adaptation. Taking this into account, the clinician should then be aware of significant differences in optically induced spectacle magnification created by anisometropic refractive errors in patients with reduced convergence function.

10.6 Future Directions

The generalizability of these results and the conclusion of this study would be validated by additional data characterizing the effects of convergence therapy on these adaptive responses in CI. We would expect that improved reflexive convergence response dynamics during and after therapy would occur in lock-step with their adaptive capacities. Others have provided evidence that this would be the case; however, this study used the same error-based disparity double-step paradigm as both the rehabilitation therapy and the outcome measure, such task-specific explicit learning mechanisms could not be ruled out.

10.7 Summary

This study was designed to characterize the adaptive capacities of reflexive vergence in patients with convergence insufficiency and contrast it with that of binocularly normal controls. The results confirm that reflexive convergence responses to step changes in retinal disparity are significantly reduced in CI. Importantly, these individuals also exhibited a limited capacity to adaptively lengthen their reflexive convergence responses through the recruitment of faster reflexive responses, as is the case in controls. Reflexive divergence adaptive responses were less robust when compared to convergence in controls and found to be similar between groups. These results add to the growing body of behavioral and neural imaging data that suggests convergence insufficiency is the result of a generally reduced or impaired reflexive convergence neural substrate. The data provide the first assessment of short-term sensorimotor adaption of vergence in convergence insufficiency and provide new insight into the

functional oculomotor deficits in these patient populations and the neurophysiological under-pinning's of convergence insufficiency.

Chapter 11
General Discussion & Future Work

11.1 General Discussion

The purpose of this dissertation was to examine the adaptive elements of vergence in terms of their relationship with reflexive vergence and their directional asymmetries. Two adaptive elements have been identified in the tonic and reflexive control mechanisms. The latter appears similar in nature to sensorimotor saccadic adaptation, while the former is specific to vergence and may have a different neural pathway. That said, both elements exhibited the same directional asymmetries in their dynamic behavior. Convergence plasticity was significantly greater than divergence in healthy, binocularly normal controls. A consistent finding was that when greater recruitment was observed within the reflexive PV mechanism, as evidence by greater open-loop response amplitudes and peak velocities, faster (rate) and larger (gain) adaptive changes were observed in both the PV adaptive and SV adaptive mechanisms. The combined results of this work suggest the plasticity in both adaptive vergence elements are dependent on the structure (size) and function (speed and accuracy) of the reflexive system. The results have important implications for VR/AR environment design, understanding the basic mechanisms of CI and by extension the most appropriate treatments, as well as our general understanding of motor adaptation.

11.1.1 Mechanisms and models of disparity-driven vergence adaptation

The data provide insight into the underlying control mechanisms responsible for disparity vergence plasticity. The behavioral strength of the reflexive vergence mechanism appears to dictate the degree of plasticity within the system. Specifically, the data suggest that larger, faster reflexive response characteristics result in greater adaptive changes when the system is subjected to prolonged accommodative-vergence cue-conflicts or repetitive, systematic errors in the execution of reflexive responses to step changes in retinal disparity. The baseline vergence response peak velocity and pulse response amplitude then may provide a suitable biomarker with which to indirectly estimate the general plasticity within the system.

Importantly, reflexive and adaptive divergence responses demonstrated little behavioral evidence of increased neural recruitment as the amplitude of the input stimulus (disparity step size) increased. This is suggestive of a saturation limit within these control mechanisms. The effect may stem from a reflexive divergence neural substrate that is significantly smaller in comparison to convergence. This finding is not

surprising, given that the elastic forces of the orbital tissues and EOM's generally drive the vergence angle to a parallel, if not diverged position. The neurophysiological data, although limited, does supports these hypotheses.

Interestingly, the facilitation of saccades on the reflexive vergence response velocities does not appear to influence the adaptive behaviors. More simply, the increased peak velocities of saccadic-vergence responses do not enhance the adaptive gain of TV via the SV mechanism. The frequency of saccadic-vergence responses appears inversely proportional to the reflexive vergence peak velocity and open-loop response amplitude, suggesting additional recruitment of other oculomotor systems when the PV mechanism reaches saturation limits. These limits of PV output also then broadly define the limits of the adaptive responses, while the facilitation of binocular alignment via saccadic recruitment has little to no influence on the gain within each adaptive element. A summary of these theoretical relationship are illustrated in Figure 11-1.

These results run parallel to what has recently been reported in non-human primate cell recordings from premotor vergence neurons in the superior colliculus. According to Van Horn et al. the neural signal for the change in vergence that occurs during a saccadic-vergence response (asymmetric vergence) is almost entirely encoded in the difference between the saccadic burst generating neurons[64,68]. This conclusion assumes that each saccadic burst neuron encodes a specific eye velocity (Helmholtz hypothesis) and position and not a binocular conjugate signal (Herring hypothesis). Interestingly, within this recording data there is still a much slower vergence change at the very beginning and end of each saccadic-vergence movement during which the saccadic burst neurons are silent, indicating that an additional vergence signal is also at play[63,68]. This additional vergence signal is likely the pure-vergence signal we have been focused on during this dissertation. Our behavioral data then suggests that the saccadic-vergence signal carried solely by the saccadic burst neurons does not feed into the adaptive mechanisms that underlie tonic and phasic vergence plasticity. Future work should focus on characterizing the difference between symmetric and asymmetric vergence demands on the adaptive responses measured in both vergence systems. The data here would hypothesize similar adaptive effects measured to symmetric and asymmetric disparity demands.

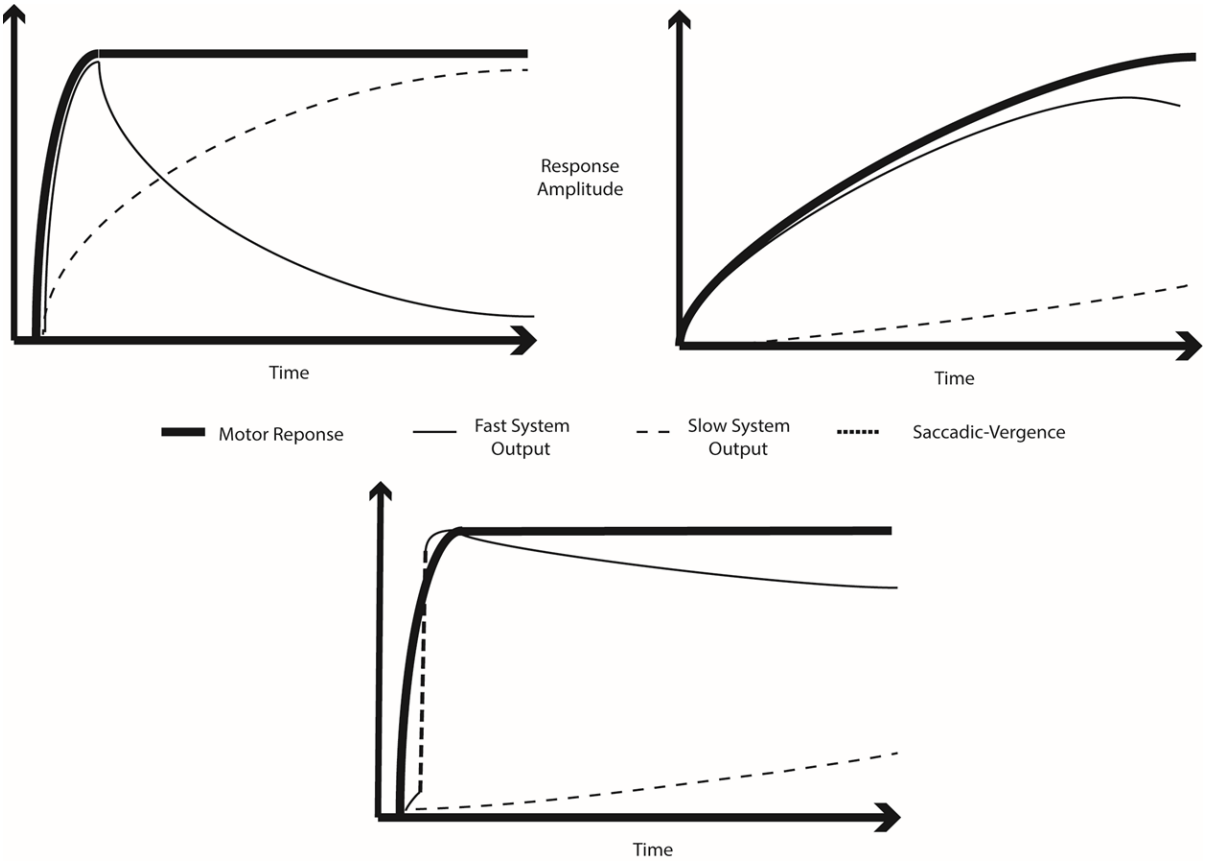

Figure 11-1: Schematic of individual mechanisms output over time in vergence control. The thick solid line represents the vergence response angle measured. The thin solid line (fast system) depicts the combined pulse-step output of the PV system. The thin dotted line illustrates the adaptation of TV/heterophoria by the SV mechanism. Top Left) Schematic model represents the control group convergence data. Top Right) Model of divergence responses in control groups and convergence responses in CI groups. Bottom) Additional saccadic-vergence (thick dotted line) facilitates the measured response velocities of the PV systems, but does not enhance the adaptive changes associated with the SV system. This behavior was most often observed when PV responses were the slowest. Y-axis is theoretical response amplitude.

11.1.2 Clinical Implications

The data provide empirical evidence and explanations for the clinical differences that have long been observed between convergence and divergence. The limited reflexive and subsequent adaptive

divergence substrates explains why divergence is much less amendable to orthoptic therapy in clinical populations, whereas, convergence therapy can be very successful. In addition, the sluggish divergence responses when compared to convergence shed light on the mechanisms underlying differences in positive and negative fusional reserve measures. The data also then support using smaller values of base-in prism compared to base-out during vergence facility testing[270].

11.1.2.1 Convergence insufficiency

Observations of the data in Chapter 10 suggest that CI may be, at its neurophysiological roots, an underdeveloped or impaired convergence substrate. It is not clear whether these deficits are subcortical or cortical in nature from the current data, although the functional imaging data from Alvarez et al. would indicate it is both a cortical and cerebellar dysfunction.

In terms of the clinical diagnosis of CI, the results of this dissertation suggest that the best clinical metric would be a test that directly assesses the reflexive fusional vergence response. Currently, vergence facility is the closest (validated) clinical test of such function, as it assesses the rate (cycles per minute) of disparity vergence change from base-in viewing to base-out viewing. Since there does appear to be a strong fatigue component within the CI population during convergence testing (increased saccades), assessing vergence facility in blocks of time as opposed to an average over one minute may provide an additional diagnostic variable to increase the sensitivity of this test in terms of diagnosing asymptotic CI. If fatigue plays a significant role, as the data suggest, then the application of symptom surveys, like the CISS (convergence insufficiency symptom) survey should consider temporal factors as well. It is interesting that many patients with borderline CI score low on the CISS survey initially, but when the survey is given and the participant is told to consider their symptoms after ***prolonged*** reading, the scores tend to increase significantly. Chapter 10 was not powered to address the relationship between symptoms of CI, clinical metrics and experimental observations, therefore further work is needed to directly investigate these questions and hypotheses.

Fusional vergence ranges can also offer an indirect assessment of the tonic adaptive capacities and so are still a valuable tool in the clinical assessment of non-strabismic binocular vision/oculomotor dysfunctions. The literature and this dissertation strong suggest that the blur point in these tests is the most important, since this is the point where tonic adaptation is saturated and vergence-accommodation is engaged through the VA crosslink. The near point of convergence provides an assessment of the overall fusional capacities at near when all stimuli (blur, proximity and disparity) and so a system that has compensated well for reduced disparity driven-convergence by recalibrating accommodative-vergence or

proximal vergence responses may have a normal NPC. Further work is needed to address the influences of these other near-triad stimuli on the adaptive changes in tonic vergence. This is of greater importance to wearable technologies where these cues are not varied congruently, and so a system that has compensated in such a way for a reduced disparity driven vergence mechanism may function normally (and comfortably) in real-world environments, but may have extreme difficulty and discomfort when disparity is presented in conflict with accommodative and proximal stimuli in order to provide depth on a flat display. The factor of fatigue would then also be even more relevant in such artificial viewing environments.

If the root cause of developmental CI is an underdeveloped reflexive convergence system, then this should be the target of rehabilitation therapy. Procedures such as jump ductions via beads-on-a-string (Brock String) and base-out prism flippers would be the most appropriate therapies as they provide rapid step changes in retinal disparity. Activities that require the vergence system to function under increased convergence load (viewing through constant base-out prism demands) would then be expected to provide the least rehabilitative efficacy. The treatment therefore then must address the significance of the convergence deficient at outset and tailor the treatment to each individual patient.

One of the most common treatments for CI is the use of base-in prism with refractive correction at near. The theory behind this treatment is that base-in prism reduces the amplitude of convergence needed to maintain fixation at nearby correcting the large divergent (exo) heterophoria measured at 40cm. This heterophoria correction then should free up more reflexive fusional convergence that would be needed to maintain fixation at closer working distances. Evidence of the efficacy of this approach is limited and varied. One group reported symptomatic relief in a small sample of presbyopes, while another group found that base-in prism was ineffective at reducing symptoms associated with CI. A common fear with this treatment is the need to increase the magnitude of the base-in with time because the heterophoria adapts (and returns to baseline amplitudes). If this occurs the current amplitude of base-in prescribed would be then ineffective. It is very likely that some patients would rapidly adapt to the base-in prism and others may not. This would depend on the strength of their reflexive (and thus adaptive) divergence mechanisms, as the data herein suggest. Individuals with larger, faster reflexive divergence responses to base-in prism (uncrossed disparity) would then be expected to adapt rapidly to base-in and we would expect base-in spectacle treatment would least effective in these individuals.

Convergence evidence from this and other work then suggest that disparity-driven vergence peak velocity and pulse response amplitudes may offer effective biomarkers for the diagnosis of convergence

dysfunctions, indicators of appropriate treatment modalities and metrics useful in monitoring progression of rehabilitation.

11.1.3 Implications for Technology

The data presented here provide an explanation for the increased discomfort and fatigue associated with viewing prolonged uncrossed disparities (in reference to accommodation) in VR environments. Slower, less adaptable divergence responses would constantly recruit accommodative responses during uncrossed disparity viewing via divergence driven AV. This excessive accommodative response is precisely the mechanism by which CI is thought to induce symptomology in patients. Therefore, a similar explanation can be applied using the data herein and the increased discomfort induced by uncrossed retinal disparities.

The limitations imposed by the accommodative-vergence cue-conflict created in the current iterations of VR technologies has been well established. This has led to attempts in developing multifocal of displays aimed at increasing the availability of blur cues within the environments and decreasing the overall conflict between the near-triad systems[11,254,277,278]. Unfortunately, these displays are heavy, expensive and have low resolution, which limits their application in the immediate future. In the development of these new displays, priority should be given to providing greater congruency between uncrossed disparity and dis-accommodative blur cues for the general population.

Given the variance in vergence control across the general and population and the prevalence of dysfunctional vergence control, there is a need to customize the VR environment for the specific user in order to provide an experience that is comfortable and accessible for everyone. Newer iterations of VR designs use online eye-tracking as feedback for appropriate image rendering. Using this on-board technology developers should consider designing short calibration sequences, where the user makes simple vergence eye movements to different amplitudes and directions of retinal disparity. Defining where the response behavior of both reflexive convergence and divergence saturate would provide an estimation of the limits of disparities that may be presented comfortable to each individual user. While such reconstructed environments would have reduced immersive effects due to lower amounts of retinal disparity, the experience would be more comfortable for the user. In addition, as this process is repeated as wear time increases and the user gains experience, the system can be recalibrated until the full range of disparity can be utilized. This assumes a training effect during use, which is precisely the reason why VR is now being investigated as a platform with which to rehabilitate patients with poor binocular vision[279].

11.2 Limitations

The current work has several limitations that should be recognized. The main limitation is the generalizability of the results to different visual environments and the general population. The former is a result of a single, fixed accommodative and proximal distance being used in the haploscope. The latter is a result of the small sample size.

The sample size calculations suggest the experiments conducted were properly powered to detect the specific question being asked and the differences expected. However, others have pointed out a large degree of variance in the vergence response properties, even within what are assumed to be binocularly normal control participants. The strict and extensive inclusion criteria for the control groups in the studies conducted likely means a small subset of the general population considered to be 'binocularly normal' has been observed. There were participants who were excluded from the control group based on clinical and experimental metrics that were not symptomatic, aware of, or diagnosed with oculomotor deficits. These populations likely account for the diversity in data reported from experiments where binocularly normal control participants were defined with much laxer clinical inclusion criterion.

Using a single fixed display screen distance was partly by design in this work. The majority of the data available in the literature uses the exact same conditions to measure vergence behavior, therefore, this specific apparatus was chosen to allow for greater relatability to the current body of knowledge. Furthermore, the literature available suggests that convergence responses to disparity are minimally affected by changes in display distance and accommodative demands, while divergence response dynamics are inversely proportional to the display distance. Therefore, a near display distance would have provided the most optimal environment from which to observe the fastest and largest divergence responses and thus the least degree of directional asymmetries between the convergence and divergence systems. It is expected that if the same experiments were to be repeated with the dichoptic viewing distance (proximal and accommodative demands) increased, the adaptive capacities (and reflexive response dynamics) of divergence measure would be even further reduced from what was reported. These effects then would be expected to enhance the directional asymmetries in vergence plasticity observed.

In a similar vein, in order to measure SV behavior, one must interrupt fusion and allow PV to decay completely in order to measure the tonic/heterophoria position. This interruption of fusion for 15 seconds every 15 seconds would be expected to reduce the observed gain of adaptive changes in TV when compared to the condition where fusion was always maintained. Unfortunately, occluding one eye to eliminate fusion is currently the only direct method of assessing the change in TV. Future work may

consider using both the change in fixation disparity and the output of the vergence-accommodative crosslink as an indirect measure of changes in TV, as both of these measures indicate the output of the PV system. As technology improves, it may be possible to complete similar experiments while accurately measuring both vergence and accommodation simultaneously. It is expected that such methods would produce SV dynamics that are even faster and larger than what was observed herein and thus demonstrate an even stringer relationship between the adaptive capacities of TV and the dynamic behavior of reflexive PV.

11.3 Future Work

Clearly there is a need to repeat these same experiments over a larger range of display distances to confirm the previous assumptions. In addition, data on the proximal and accommodative effects on vergence plasticity under the same circumstances would provide a more complete picture of the different sensory inputs that may drive vergence adaptation. We focused on the influence of retinal disparity on vergence adaptation as this is the primary stimulus for the vergence oculomotor system. At the same time, accommodative measures would be of great interest to the understanding of the crosslinked interactions during different combinations of vergence stimuli. Unfortunately, the two measurements of each motor response (accommodative and vergence) simultaneously is very difficult to do with any degree of accuracy or precision. These technical limitations are being resolved by industry, as these questions have enormous relevance to the development and design of VR and AR environments.

The neural physiological loci of these different vergence adaptive processes remains to be identified. The cerebellum is known to be involved in almost every motor learning or adaptive process and thus is a likely suspect to be involved. Schor has referred to the oculomotor vermis as the ‘oculomotor repair shop’ in his clinical teachings, suggesting that it plays a major role in constantly recalibrating vergence control based on errors encountered. It is unclear whether the cerebellum houses the machinery for PV adaptation, SV, or both. The current brain imaging data from the Alvarez group suggests a role for the cerebellar oculomotor vermis during rehabilitation of CI[141,268]; however, the imaging data does not provide a causal role for this structure in either of the adaptive processes explored in this dissertation. Future investigations should aim to parse out the different roles this structure plays in the adaptive control of vergence. An interesting avenue with which to explore these questions would be through the use of non-invasive brain stimulation techniques, combined with the behavioral measures and experiments defined herein. It has been well established that certain repetitive forms of non-invasive brain stimulation can temporarily alter the plasticity of relatively focal neural networks. Combining such

stimulation protocols while observing the adaptive procedures used here would potentially allow for a more casual relationship between cerebellar structures and the different forms of vergence adaptation to be developed. Furthermore, such non-invasive brain stimulation techniques may also provide a mechanism with which to enhance cortical plasticity before rehabilitative therapies are introduced, in order to improve the efficacy of these treatments.

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Appendix A

Background Vergence Literature

Eye Movement Taxonomy

Eye movements are generated either voluntarily or involuntary in order to keep a visual stimulus centered on the fovea. In frontal eyed primates, the two eyes visual fields overlap significantly. Because of this shared visual field, the eyes must work together in order to keep the object of visual regard on each individual fovea[3].

Binocular eye movements can be broken up into two general classes by defining their conjugacy[56]. This refers to the overall effect on the angle of intersection of the two visual axes, known as the 'ocular vergence angle'. Conjunctive (version) eye movements result in a net ocular vergence angle change of zero. Pursuits and saccades are examples of slow-tracking and ballistic, gaze changing conjugate eye movements respectively. Disjunctive (vergence) eye movements result in either a positive or negative change in the ocular vergence angle, with positive angle changes referring to gaze shifts to nearer distances[103,172,280].

Vergence Eye Movements

The ocular vergence angle can be further dissected into the horizontal, vertical and torsional (cyclo) angle subcomponents[281]. Because the eyes are separated horizontally in humans, the vertical ocular vergence component is rarely changed, with the visual axes remaining on the same transverse plane for almost all visual tasks. The same can be said for rotational, cyclo-vergence planes, which are generally limited in their rotational abilities in the first place. The exact opposite effect is seen with horizontally along the mid-sagittal plane, where changes in horizontal ocular vergence are much more common. Horizontal vergence eye movements serve to change our distance of fixation in depth and will be referred to herein simply as vergence eye movements.

Vergence Direction

The disjunctive nature of vergence eye movements means that each visual axes rotate in opposite direction. Convergence occurs when the eyes rotate towards each other and the change in fixation distance is nearer to the observer (positive change in ocular vergence angle). In divergence, the eyes rotate away from each other and result in a change of fixation distance to a point further from the observer

(negative change in ocular vergence angle)[104]. These movements can be slow, tracking movements, or ballistic gaze-shifting movements. Physiologically, convergence is the product of bilateral media rectus contraction, and a simultaneous binocular relaxation of the antagonistic lateral recti muscles[195]. Divergence requires the exact opposite extraocular muscle effects.

Asymmetric vs. Symmetric Vergence

There exists a plane of fixation in both theoretical and visual space that defines where the angle of ocular vergence is equal. This 'isovergent' plane passes through the center of rotation of each eye and is not a flat surface. The isovergent plane varies in curvature based once again on IPD and fixation distance[3] (Figure 1-2).When a binocular eye movement begins and ends on this theoretical curved plane, it is considered 'isovergent' or purely conjugate. Vergence movements can be made in isolation (directly along the sagittal plane) or in conjunction with a horizontal conjugate component (Figure 1-2). The latter is a combination of both saccadic and/or pursuit motor commands and vergence motor commands, which are controlled by separate mechanisms. These movements are described as 'asymmetric' vergence[103,216]. The former is referred to as 'symmetric' or 'pure' vergence and is generally considered to be solely the generated by the vergence neural substrate(s)[68,282]. For this reason, we have focused this work completely on symmetric vergence stimuli (along the mid-sagittal plane) and their associated motor responses.

Units of Measure

Ocular vergence is universally defined as zero when the two eyes visual axes are parallel and gaze is directed towards a distant (>6 meter) image[56]. The scientific and clinical research literature use 3 very different metrics to describe ocular vergence; however, these 3 metrics are fundamentally relatable based on the knowledge of the working distance and the IPD of the specific individual. The following is a brief summary of each.

Degrees/Minutes of Arc

The simplest and most universal ways of defining horizontal ocular vergence is by the angular degree of convergence from an axis parallel to the midsagittal plane. This unit of measure requires the distance of fixation change and the monocular distance of the visual axes from the sagittal midline (monocular IPD). The inverse tangent of the monocular IPD (in cm) divided by the fixation distance (in cm) gives the monocular vergence angle in degree's. Total ocular vergence in degrees is estimated by multiplying this value by 2[104]. This assumes a symmetric monocular IPD. This work will mainly use

angular degrees when defining vergence metrics, as this has become the most common with the wide-spread use of non-invasive eye tracking systems and is more accessible to other motor sciences.

Prism Diopters

Clinically, ocular vergence is described by prism diopters (PD), which is also referred to as a 'centrad' in some literature. This unit is in reference to the optical displacement of an image by an ophthalmic prism; whereby one prism diopter is equal to a horizontal devotion of the light ray of 1 centimeter at a distance of 1 meter[59]. Prism diopters of vergence are calculated using the distance of the object and the IPD. The prismatic convergence demand from parallel (zero) is the calculated by multiplying the inverse of the working distance by the total interocular separation in centimeters. Where the IPD is assumed to be 6cm, the angular degrees of convergence can be multiplied by 1.75 to estimate the vergence change in prism diopters[281].

Meter Angles

Changes in fixation distance also require changes in the optical power of the eyes refractive structures in order to keep the image clear on each fovea. Because of the complex interactions between ocular vergence and ocular accommodation there is a need for a proportional unit of measure, from which comparisons can be made. Meter angles (MA) are defined by the inverse of the distance of the object of fixation and are roughly equal to the accommodative blur stimulus in diopters[283]. Meter angles do not directly account for differences in interocular separation; however, they can be converted to prism diopters by multiplying by the IPD (in cm).

Interocular Separation

A crucial component of ocular vergence angle is the effect of the horizontal separation between the two visual axes, also known as the interpupillary distance (IPD). The greater the distance between the two visual axes, the larger amount of convergence is required to align the eyes at near. As stated mentioned earlier, the slow increase in IPD with growth in infancy and childhood demands a recalibration of the ocular vergence response in order to maintain accurate bi-foveal fixation (Figure 1-2).

Components of Vergence

Under natural, real-world viewing conditions the neural controllers responsible for ocular vergence receive input from several different sensory systems. Maddox formally described four primary sensory inputs to vergence in 1893, where a hierarchal arrangement defined their relative importance to

the overall oculomotor response[284]. In the Maddox classification system that is still used today, the 4 inputs are retinal disparity, accommodative (blur), proximal and tonic vergence. Until now, vergence has been discussed in the context of objects physically shifting in space. The following gives a brief review of each of the Maddox subcomponents of vergence responses based on the type of sensory input.

Tonic Vergence

At the most basic level, the ocular vergence angle has a baseline resting position in the absence of any neural innervation[175]. This position is the result of the general mechanics of the extraocular muscles and other orbital tissues and defines the anatomical position of rest. This is much the same as how a spring has a resting state, depending on the load applied. In vergence, this anatomical resting angle is most accurately observed in cadavers[285,286] or when under general anesthesia[287], when the extraocular muscle electrical activity is zero[252]. Unlike skeletal muscle that is electrically silent when at rest, extraocular muscles always display some degree of neural innervation in the conscious individuals[252]. Various groups have reported that the anatomical vergence angle of rest is generally divergent from parallel, between 20-25° [252,285,286]. This varies widely among the populations examined, but is always at least parallel in non-strabismic patients. Differences in the anatomical position of rest have been hypothesized to arise from structural variations in the orbit[175].

There is additional basil neuromuscular tonus from the midbrain motor neurons to the extra ocular muscles, even at complete rest[252]. In an awake individual with no visual stimuli present this physiological vergence resting position represents the sum of the anatomical vergence angle and basil tonic neural innervation[104]. This additional 'tonic' vergence innervation results in a vergence resting angle that is slightly convergent from parallel to roughly 3° (range of 0.25-0.75MA)[155,288]. The difference then between the physiological position of rest (~20° divergent) and the physiological position of rest (~3° convergent) suggests that the total amplitude of tonic vergence is roughly 23° of convergence.

When tonic vergence is measured clinically in a vergence stimulus deprived environment it is known as 'dark vergence'. This measure encompasses the sum of the anatomical angle of rest and this basil neural innervation from the midbrain[155,252]. It is impractical to put all patients under general anesthesia to measure the true anatomical position of rest in order to define the absolute value of tonic vergence innervation. In the measurement of dark vergence both the blur and disparity cues to vergence are eliminated[289]. Dark vergence is an indirect measure of tonic vergence innervation since the individual is aware of their general surroundings and can be influenced by various proximal cues in different environments. Dark vergence has been shown to be quite stable throughout adult life[223], when measured

under similar environmental conditions. In infants, the dark vergence posture tends to be much more converged (35cm) than that of adults (~200cm)[289].

The degree of tonic vergence neural innervation is highly plastic and can be varied in response to altered viewing conditions[81,290,291]. This tonic vergence plasticity will be discussed in detail in subsequent sections and chapters.

Proximal Vergence

Proximity refers to physical distance in space. In visual space, proximity refers to the conscious awareness of nearness. This perceived distance drives vergence responses, even in the absence of visual stimuli[255,292]. Proximal vergence is one of the more difficult Maddox vergence components to measure, since it requires both blur and disparity driven vergence inputs to be eliminated. In dynamic vergence responses, proximal vergence gain has been reported to be roughly 0.4-0.7[293,294]. Interestingly, proximal vergence seems to have little influence on the steady state maintenance of the convergence angle during sustained fixation, instead playing a more significant role in the initial oculomotor response to large shifts in target distance[293]. The influence of proximity on the vergence angle is limited beyond roughly 3 meters, and increases proportionally with the change in distance from there[295].

Proximal vergence innervation can significantly influence the measurement of dark vergecne[296]. This explains why dark vergence is even more converged than the physiological position of rest measured under anesthesia[252]. Even the simple act of placing a hood over the subjects head in order to create complete darkness results in increasingly convergent measures od dark vergence, since the physical proximity of the hood in front of the eyes provides a perception of nearer distances[297]. Consequently, the size of the room can influence the measurement of dark vergence[288,296].

Disparity Vergence

Disparity in the retinal images occur when an object is located nearer or farther than the isovergent plane (Figure 1-2). The image of this object falls onto retinal points that lack a common visual direction cortically and results in double vision, or ‘diplopia’. The angular magnitude of retinal disparity is proportional to the distance the object of regard is from the isovergent plane. When the image/object is further than the isovergent plane, uncrossed retinal disparities are created. Uncrossed disparity triggers a divergence response. The opposite is true for objects or images nearer than the isovergent plane. In this case, crossed retinal disparities are created that trigger a convergence response[3]. It is important to keep in

mind that a large majority of studies focus mainly or solely on the convergence responses to crossed disparities. This will be a subtopic of a later chapter.

In 1956 Westheimer and Mitchell demonstrated, as Maddox first hypothesized, that vergence motor responses could be elicited by retinal disparity alone[103]. In their Wheatstone Stereoscope apparatus, different images are presented to each eye using a septum or mirrors. Such environments are classified as 'dichoptic', the instruments with mirrors are known as 'haploscopes'. VR and AR environments work on the same dichoptic principals. Lateral shifts (in opposite directions) of each image creates retinal disparity, while the accommodative and proximity demands are held constant. Similar effects can be achieved with horizontal optical prism. Since vergence responses to retinal disparity seemed to serve as the mechanism to eliminate this diplopia, they had been referred to conventionally as 'fusional' vergence responses. Subsequent research has shown that it is the retinal disparity and not the sensory perception of diplopia itself that is the true sensory stimulus for these vergence responses; hence they are referred to now as 'disparity vergence' responses[208].

Retinal disparity is considered to be the strongest and most influential input to vergence control[208,298], especially when large changes in ocular vergence angle are required. Disparity vergence responses are robust to blur artifacts[25,298] and can create reflexive vergence changes even when the image presented to each eye is not the same in texture, contours or luminance[26]. Large 'step' changes in retinal disparity generate reflexive, ballistic vergence responses; while slow, 'ramp' changes in retinal disparity produce slow, smooth changes in vergence angle[158]. These two separate vergence responses are analogous to slow-tracking pursuit and large ballistic saccadic movements along the isovergent plane[30,158].

Accommodative-Vergence

Retinal blur is the primary stimulus for ocular accommodation; a process by which the dioptric power of the crystalline lens changes in order to obtain a focused, clear image on the retina[299]. Retinal blur and the subsequent ocular accommodative change also drive a change in the horizontal vergence angle through a neural cross-linked interaction[7,256,300].

Blur-driven changes in vergence angle are known as accommodative vergence (AV)[5,6,210]. Since optical blur is a monocular sensory cue, accommodative-vergence occurs even when one eye is closed[216]. This observation led Johannes Muller to first hypothesize a theoretical crosslinked relationship between accommodation and vergence in strabismic esotropes in 1823 and in healthy controls in 1846. This blur-driven vergence response is referred to as the accommodative-vergence to accommodation (AV) ratio

and is defined by the magnitude of vergence change in prism diopters over the change in ocular accommodation in diopters[22,301].

Typically, the accommodative response gain is less than one based on the depth of focus, and therefore the stimulus AV ratio underestimates the actual AV response. When the accommodative response is measured directly, along with the change in vergence angle, the resulting AV/A ratio is known as the 'response AV' and is generally larger than the stimulus AV[210]. Clinically, the stimulus AC ratio is usually measured and reported. In general, the AV ratio is roughly 4PD/1D and is relatively stable throughout life[302].

The Near-Triad

When we shift our gaze in depth, 3 main motor responses occur in order to ensure each retinal image remains clear while also being bi-foveally fixated. Vergence alters the visual axes alignment, accommodation alters the refractive power of each eyes crystalline lens and the pupil dilates or constricts in order to alter the depth of focus. In order to properly coordinate these 3 responses, synkinetic neural-motor cross-links exist between these three motor systems[303]. The most important of which are the vergence and accommodative interactions.

Vergence-Accommodation

Retinal disparity generates both a vergence response directly and a synkinetic accommodative response through the vergence-accommodation cross-link[7,300]. When accommodative changes occur as a result of retinal disparity alone, the crosslinked response is termed vergence-accommodation (VA)[301]. The amount of accommodative change that accompanies a disparity-driven vergence response is known as the vergence-accommodation to vergence ratio. This synkinetic interaction will be the subject of further discussion in the modeling and neurophysiological sections that follow.

Vergence Metrics

Beyond the direct angular measurements of ocular vergence already discussed, there are other static and dynamic properties of vergence that are measured both clinically and experimentally. The following will review the most common of these metrics used to describe.

Clinical Measures

Fixation Disparity

When an object is bi-foveally fixated and single binocular vision is perceived, the ocular vergence angle is not precisely that of the calculated demand. This error in binocular fixation, known as the 'fixation disparity' is small, generally around 6 minutes of arc horizontally (0.1 degrees)[22,23] and falls within Panums' Fusional Area, which is why diplopia is not experienced[3].

Fixation disparity can be measured both objectively using an eye-tracker and subjectively using patient feedback[1]. Objective eye tracking measures of fixation disparity tend to be significantly larger than what is reported subjectively[1]. In the oculomotor models of vergence control, fixation disparity is said to be a purposeful error, providing feedback that allows for constant fusional vergence engagement[78].

Heterophoria

Heterophoria defines the vergence angle when retinal disparity inputs are eliminated[59]. It represents the summed inputs of tonic, proximal and accommodative vergence and their combined over action (esophoria) or under action (exophoria). Occluding one eye, such as in the alternating cover test, removes disparity information and allows for the clinical measurement of heterophoria using optical prsim[59]. Other methods of measuring heterophoria, like the Modified Thorington Technique (MTT), involve presenting dissimilar stimuli to each eye in order to eliminate the influence of disparity vergence[59]. In the case of the MTT, a Maddox Rod is placed in front of one eye to achieve dissociation between the two eyes ocular images and therefore rendering the disparity vergence system essentially open-loop. The compulsion to fusion of even dissimilar retinal images displayed by the reflexive fusional vergence system[25] can influence these measures. In order to avoid such effects, it is suggested that eye behind the Maddox Rod is occluded for up to 15 seconds and then briefly flashed the image in order to measure heterophoria[59].

Tonic vergence innervation is highly adaptable[8]. This plasticity has important implications for equilibrium in the near-triad and clear, comfortable binocular vision and will be the subject of discussion in later sections. One way to indirectly measure changes in the underlying tonic vergence innervation is to assess the heterophoria before and after an adaptive task is completed. The assumption being that when all other stimuli to vergence (blur and proximity) are kept constant; changes in the degree of heterophoria are the result of alterations in the underlying tonic vergence innervation[45].

Recently, heterophoria has been quantified objectively using dichoptic stimulus presentation and infrared oculography[188]. There appears to be good agreement between the objective eye-tracking assessments of heterophoria and the various clinical assessments.

Heterophoria varies greatly between individuals and between various working distances[177]. Typically, the distance heterophoria is close to zero (orthophoria) or slightly diverged (exophoria)[59]. As the working distance decreases, heterophoria tends to become more exophoric in the general population. Large heterophoria's require a greater neural input from the disparity vergence mechanism in order to maintain binocular fusion[304].

Fusional Vergence Reserves

While arguably not a simply a static measure of the vergence system, the fusional vergence reserves provide insight into the function of the disparity vergence control system. The fusional reveres define the amount of optical prism that binocular fusion can be maintained through. These values are much greater for the horizontal than vertical directions.

Horizontal fusional reserves can be measured at both distance and near. In both cases optical prism is systematically increased in one direction (via the rotary prisms in a phoropter or in free space with a prism bar) while an accommodative target slightly above threshold is viewed[59,305]. The objective is to obtain the amplitude of prism that first induces sustained blurring of the target, followed by the maximum amplitude through which binocular fusion can be maintained and finally the amount of prism required to re-obtain fusion once diplopia or suppression is reported.

The three outcome measures outline the different functions of the vergence system[59]. The blur point reveals where the AV ratio is engaged in order to help maintain fusion, while the break point defines the maximal output of both the reflexive disparity vergence system and any additional voluntary vergence in reserve. The recovery point indicates the greatest amount of prism that is likely able to be fused if not given in a small, step-wise manner. The repeatability of the break point and recovery is the highest, while the blur point is quite variable, especially in untrained participants[306,307].

The degree of fusional vergence reserve is used to gauge the degree of compensation of an existing heterophoria. Sheard argued that in order for a heterophoria to be considered well compensated at a particular viewing distance, the amplitude of the opposite fusional reserve blur point should be twice the heterophoria amplitude[308].

Fusional Vergence Facility

Fusional vergence facility defines, at a very basic level, the overall speed and stamina of the disparity vergence system. It tests the speed at which the vergence angle can be changed in response to retinal disparity while the accommodative cues remain clamped over a prolonged period of time. Clinically this is defined as the number of cycles per minute that can be completed with an altering base-in base-out prism flipper[59].

Near Point of Convergence

The near point of convergence, or simply 'NPC' defines the maximum amount of convergence that can be obtained using real world targets. To measure the NPC, a visual target is moved along the midline at a constant velocity while the patient is instructed to maintain fusion and report the first point of diplopia, while the clinician monitors of suppression and exotropia. The distance at which fusion is lost is measured 3 times and defines the NPC[59,309]. In this test, both accommodative, proximal and disparity cause are present. In addition, much like the break point of fusional reserves, voluntary vergence also plays a role in the measurement of NPC. Therefore, the NPC is not a specific test of one particular component of the vergence system and is more a generalized assessment of the maximal amplitude of convergence obtainable.

Laboratory Measures of Disparity Vergence

Commercially available and easy-to-use eye-tracking systems have led to an explosion of eye movement research focusing on the dynamic properties of various eye movements. In symmetric vergence, there are two response sub-types that are analogous to the conjugate pursuit and saccadic movements. A symmetric vergence response can either be a smooth, ramp-like to slow moving targets, or a larger step-like responses between two different targets or to a fast-moving ramp target (above roughly 4-5 °/s)[30,93]. The current dissertation addresses the step-like vergence behavior and its associated adaptive responses, so the slow-ramp vergence response mechanics will only be briefly discussed. The following will outline the most commonly used dynamic metrics used to assess vergence in general. It is also important to note that the majority of the work describing these attributes and their relationship to the neural-mechanical control mechanisms/strategies focus more on convergence than divergence responses.

Response Amplitude, Gain and Duration

The amplitude of the response, or the response gain, is a relative measure that defines the vergence response by its output to input ratio, where the input is the physical stimulus cue change. In either case the amplitude of the response must contain a start and stop point in time. This is most often achieved by applying a velocity threshold, where the first derivative of the vergence position is used to identify a specific limit with which the velocity must exceed for a minimum period of time. This limit in vergence is often between 1 and 2°/s for step vergence responses[28]. This threshold is an order of magnitude less than that typical of saccadic eye movements[123]. The end of the movement can then be defined by a fixed velocity parameter, as is the start, or, it can be defined as a percentage of the maximum velocity peak within the vergence response itself. This latter is less commonly used in vergence because of the slower response velocities when compared to saccades. The difference in time between the start and stop points defines the movement duration. If a fixed end-criterion of 0 °/s is used, the resulting duration from start to stop is considered the 'settling time'[97]. In ramp stimuli, the vergence response velocities are typically quite slow and so the gain or response amplitude is usually defined by the change in vergence angle within 200 milliseconds of the stimulus starting and stopping[30].

Velocity

In addition to being used to define the start and stop criterion, the peak velocity is a common metric of dynamic step vergence responses. Vergence responses to step changes in disparity saturate in velocity at between 40-60 °/s if they are purely symmetrical vergence[28,86,166]. When such responses contain saccadic components (asymmetric vergence), the response velocity can be two to three times greater[28,66,88,144]. It is unclear as to why such facilitatory effects occur. Some have hypothesized that the omni-pause neurons may also gate vergence responses indirectly[37,66]; however, this remains a topic of debate[68].

Vergence responses to step changes in blur, driven by the AV/A cross-link, are generally slower than those driven by retinal disparity. Proximal vergence responses have been reported to be both faster[294] and slower[28] than responses to retinal disparity; however the former study's reports of proximal response velocities was likely the sum of the blur, disparity and proximal responses, which the latter demonstrates significantly enhances the vergence response velocities.

Main Sequence Relationship

There exists a tight relationship between the vergence response amplitude and duration as well as the vergence response amplitude and peak velocity, known as the main sequence relationship. This relationship is well described in saccades[35] and has been more recently described in depth in disparity driven convergence responses[86,143]. It was originally demonstrated in one of the first control models of vergence created by Rashbass and Westheimer in 1961[56]. Originally, this relationship was developed in the field of astrophysics in order to describe the relationship between a hydrogen star's color and its brightness, which could then be indirectly used to estimate the stars temperature. In vergence eye movements, the main sequence characterizes a neurophysiological relationship between response amplitude and peak velocity, which is an indirect measure of neural recruitment in subcortical premotor vergence areas of macaque monkeys[29,38,47,310].

The plot of either response amplitude versus duration or peak velocity defines the main sequence plot[35] (Figure 0-1, Right). A linear model fit to this data defines the main sequence relationship. In eye movements, this relationship defines the subcortical integration of the movement velocity signal that is generated in the higher-level cortical area's[123]. In saccades, the peak velocity main sequence is linear between 2° and 16° degree disparity stimuli[35], after which the peak velocity plateaus, resulting an overall exponential shaped curve[311].

Typically, main sequence plots have used univariate regression analysis to define the slope and intercepts of the function[28,34,56,86,143]. However, in all actuality, there is variation in both the response amplitude and duration/velocity components of the function, which warrants the use of a bivariate regression model to properly describe the relationship. The main sequence of convergence is generally linear up to 8-12° response amplitudes. The slope of the main sequence has been reported to be between 4-7 °/s[28,34,86,166]. The slope of the function is taken as an indirect measure of neural recruitment and neural firing rates[35,36].

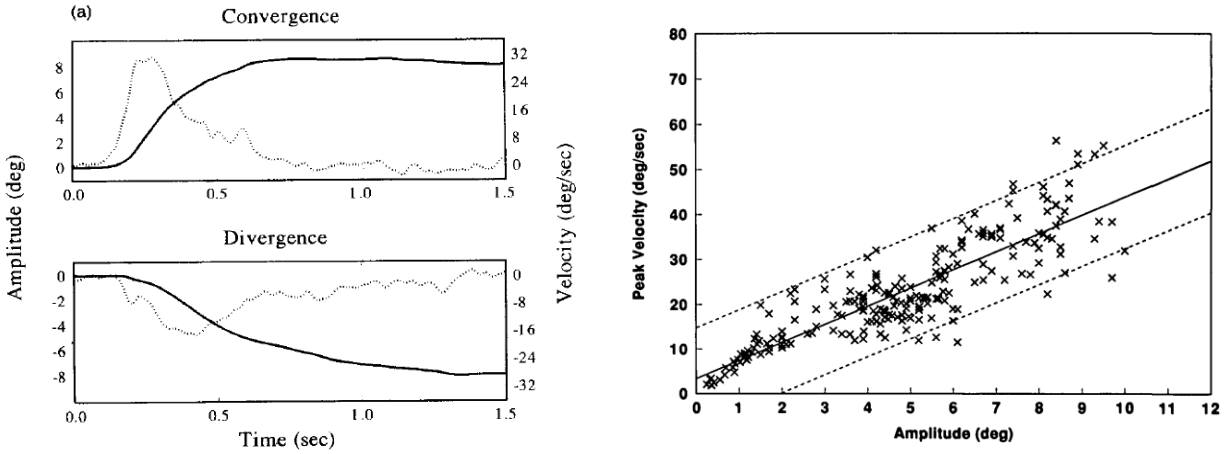


Figure 0-1: Left) Convergence (top) and divergence responses to an 8° step change in fixation distance. Solid line represents the vergence position trace (left y-axis), dotted lines depict the vergence velocity (right y-axis). Here, divergence is plotted as negative values. The stimulus onset occurs at time = 0ms. It should be noted from this data that convergence and divergence appear to exhibit very different response behaviors to the same stimulus amplitude. Right) The assembled convergence main sequence plot from the same subject, vergence peak velocity versus open-loop response amplitude. Clearly there is a positive linear relationship, indicating that large response amplitudes recruit a greater response peak velocity and is analogous with recruitment of neural firing (see Figure 0-3). Reprinted with permission from Elsevier (see Copyright Permissions).

Latency

The vergence response latency (to step changes in retinal disparity) is defined by the time interval between the change in object location/disparity and the initiation of the vergence response, beyond some set velocity criteria[173]. Vergence latency represents the total time required for sensory processing of the disparity errors and the generation of the appropriate motor command to reach the extraocular muscles. Vergence latencies are typically between 130-160ms[173], depending on the analysis criterion used[57]. This latency is slightly shorter than saccades and slightly longer than pursuits[195]. Blur driven vergence has a slightly greater latency than disparity driven vergence[28,161,281], likely reflecting the difference sensory processes underlying blur and disparity detection. The latency of proximal vergence remains unclear, but appears to be within the range (mainly on the low end, ~125-130ms) of what has been reported for disparity driven vergence responses[88,294]. The predictability of the stimulus is also known to affect

disparity-driven fusional vergence latencies. If the stimulus is predictable a decrease in overall convergence latency occurs[127,151,173].

Control Models of Disparity Vergence

Neural systems are often modeled as electrical circuits in order to help us better understand the functional organization, neural control mechanisms and potential dysfunctions of such systems. These models then guide the development of future technologies and treatments/rehabilitative interventions for dysfunctions when they occur. The development of wearable technology (Google Glasses) as well as augmented and virtual reality environments has commanded a greater understanding of all visual processes. This is especially true of vergence eye movements, since the perception of depth is a central sensory cue for a successful, fully-immersive experience. Treatment of oculomotor dysfunctions are also rooted in our models of their function, and thus treatments are targeted at specific neural functions/control deficiencies. Eye movements are one of the simplest motor systems in existence; therefore, they have provided a less complex neural substrate with which to study movement control in general. Observations of saccadic eye movements under a myriad of conditions are the basis for most neural-control models of any limb or body movement.

Control system models of disparity vergence have been in existence for almost 50 years. Numerous groups have contributed to the current models and have provided their own iterations of these in various works across the literature. Unfortunately, this has led to very confusing vernacular used to describe the neuro-motor components of vergence. The same wording has been used by to describe different control mechanisms under different experimental conditions. This has led to controversy, misinterpretations of model designs and incorrect deployment of these models[312,313]. The following will attempt to provide a clear review of the evolution of our current models of disparity-driven vergence control. It is also important to keep in mind that much of the data used to generate these models either failed to differentiate between convergence and divergence responses, or was based entirely on convergence response dynamics.

Fundamental Components

In all models of disparity-driven vergence an initial dead-zone is integrated to represent Panums' Fusional Area, where the physical retinal disparity is so small that perceptually the images are perceived as fused and singular[2]. Vergence responses are under constant visual feedback control, thus one or more negative feedback loops have been integrated into all models (Figure 0-2). Finally, every model contains

a physiological plant with which the neural inputs must act upon. The plant represents the extraocular muscles and is modeled as either a first or second-order system. Additionally, the cross-linked inputs to vergence (blur and proximity) as well as tonic vergence innervation are all factored into the current dynamic models of vergence control.

History & Evolution of Vergence Model's

The first model of vergence responses was proposed by Rashbass and Westheimer in 1961 and detailed the dependence on visual feedback for vergence to occur and be maintained. This was significantly different than what is observed in saccades, where a movement could be completed even when the stimulus was eliminated, suggesting no direct feedback control[56,172].

The model was then expanded to include 2 separate components based on additional observations. First, a 'transient' component responds to large changes in retinal disparity and provides a coarse adjustment in the vergence angle. This was based on the observation that dissimilar images (both contour, texture, illumination and blur/spatial frequency) presented to disparate retinal loci could still stimulate changes in vergence angle[25,26]. Second, a 'sustained' component provides the fine-tuning of the vergence response in order to obtain bi-foveal fixation and motor fusion[25,27,298]. It was argued early on within the Maddox model that the cross-linked accommodative response was responsible for this fine-tuning, sustained component. This was before the use of dichoptic stimuli presentations were used to isolate disparity-driven responses and when much of the vergence data was generated with targets shifting in space or with spherical lens induced changes in blur[5,20,256,300,302,314]. Such a conclusion was logical however, since the accommodative response was known to be driven by high spatial frequency[299], information that is not available in the retinal periphery, where resolution visual acuity is low. Thus, accommodative responses would not be triggered by large steps in retinal disparity when a target shifts in the physical world. While this still is likely true to an extent, later studies would show that indeed disparity was an independent input to this sustained, fine-tuning mechanism[56,103,298].

Using computer simulations in 1977, Krishnan and Stark proposed a model of vergence control to disparity stimuli using a parallel integral-derivative (PID) controller[21]. In this model, the fast derivative controller (transient component) was followed by the output of a slower integral controller (sustained component). These mechanisms were arranged in parallel, so the input signal is the same to both systems and the input to the plant mechanism is the sum of the two, fast and slow, components. A unity gain feedback mechanism was used; however, such a model would not predict the empirical finding of fixation disparity.

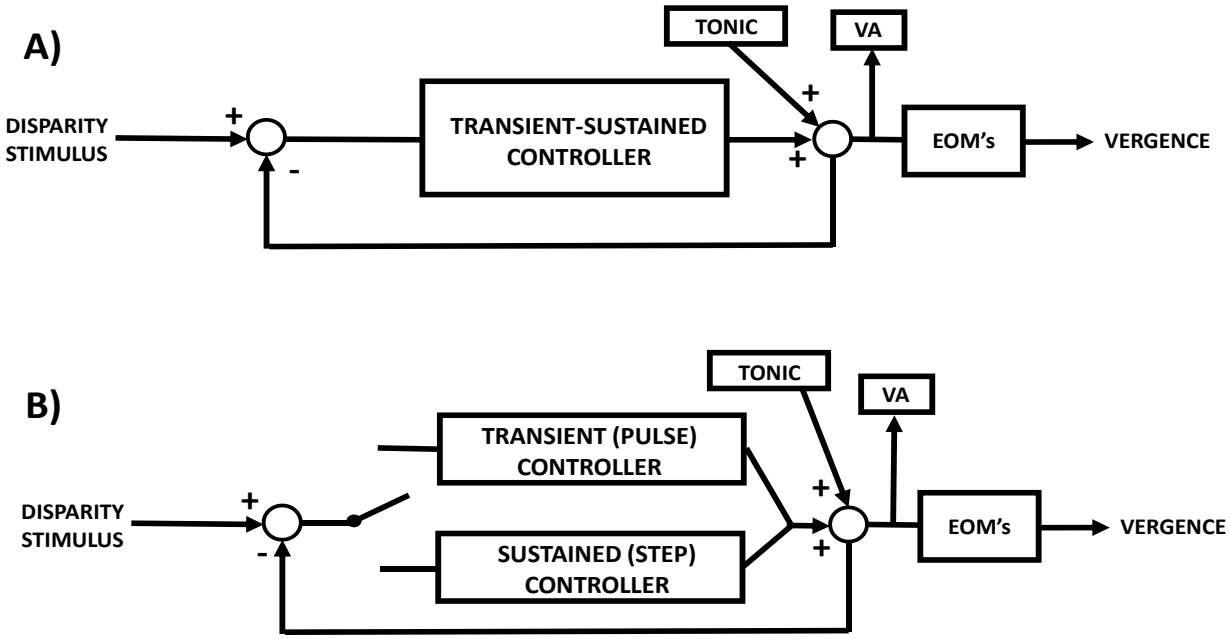


Figure 0-2: Schematic representations of the first vergence control models. A) The transient and sustained controllers are represented as a single subunit (modified from Krishnan, Stark 1977). In B) the transient and sustained components are separated in what was originally described as the dual-mode model and later as the pulse-step model of disparity vergence control (Modified from Hung et al, 1986). Here, the pulse component is not influenced by feedback. The switch represents the theoretical shift from the ballistic open-loop response to the visually guided sustained/step response in the later portions of the vergence movements execution. The adaptive components that will be discussed later are not included in this figure, nor are the accommodative inputs to vergence (see 0 for modeling discussion and Figure 0-4). VA = vergence-accommodation cross-link, EOM's = extraocular muscles.

Schor would later rectify this issue with his work on the relevance of fixation disparity in the control of the vergence angle[78]. Schor proposed that fast fusional vergence responses were the product of a 'leaky' neural integrator[78,79]. In this model, Schor introduced the 'slow' vergence mechanism that had a much longer time constant than the 'fast' leaky neural integrator. It was the longer decay time constant that was the basis for the adaptive changes observed in heterophoria[42,78]. The leaky neural integrator allowed for there to be a constant small angle error in the vergence response (fixation disparity), which

was then feedback in order to maintain the vergence posture. It is important to differentiate Schor's 'slow' controller from the (slow) sustained mechanism of Krishnan and Stark's model do not address the same thing.

Hung introduced the dual-mode model to address this specific issue in 1986. In this model, a 'slow' control mechanism was responsible for ramp changes of retinal disparity up to a specific velocity limit, after which, a 'fast' component would generate larger step changes in vergence angle to 'catch-up' to the moving target. As previously mentioned, this is much the same as saccades begin to occur when a pursuit movement cannot keep up with a fast-moving target along the isovergent plane. To add to the already redundant and confusing taxonomy, Schor also published his formal model of vergence control in 1986 that contain his original 'fast' and 'slow' control mechanisms, while also attempting to integrate the cross-linked influence of accommodation. While Schor's model was aimed at explaining the phenomenon of heterophoria or 'prism' adaptation, Hung's attempted to address the slow-ramp versus step like behavior of reflexive vergence responses to different velocity disparity ramp stimuli.

Slow and Fast Vergence Terminology

In total, there are 3 different 'slow' control mechanisms that have been described during the development of the vergence control models. The first is what we will now refer to as the *'slow-tracking'* mechanism, which Hung described as being responsible for the smooth-ramp behavior of vergence[158]. The second is the slow, 'sustained' component in the control of step changes in vergence angle[21]. We will refer to this now as the *'step'* component of the reflexive fusional vergence system. Finally, the 'slow' component described by Schor to explain heterophoria changes via tonic vergence adaptations will now be referred to as the *'slow-tonic'* mechanism[78,79].

The term 'fast' vergence is less liberally used in the literature but still not used consistently. There are 2 specific uses for the term 'fast vergence' and each describes two very different oculomotor responses. The term 'fast' vergence was applied to the initial reflexive change in vergence angle in the prior discussions[56,103,298]. This encompasses both the 'transient' and 'sustained' responses[21,27,78,158]. In these studies, vergence responses were symmetric and did not contain any significant conjugate (saccadic) component. 'Fast' vergence has also been used to describe step changes in vergence angle that contained large saccadic components and were usually elicited using an asymmetric disparity stimulus that moved both horizontal and in depth (asymmetric vergence)[65,68,222,315]. These vergence responses had significantly greater peak velocities. In this instance the latter form of vergence was referred to as the 'slow' vergence response, even though in the former work, this pertained to the 'fast' response mechanism when

responses were contained to be purely symmetric vergence. We will use the term ‘saccadic-vergence’ to describe the asymmetric vergence responses and ‘fast-phasic’ or simply ‘phasic’ vergence (PV) to describe the purely symmetric (disconjugate) step changes in vergence angle.

Current Vergence Control Model Components

Slow-Tracking Fusional Vergence

When objects move smoothly along the midline at slow enough velocities, the vergence responses mirror this behavior, as would a pursuit movement tracking an object moving along the isovergent plane[56]. The slow tracking mechanism responds to smooth, ramp changes up to a specific velocity[158]. Once the velocity threshold is surpassed and larger retinal disparities exist, the vergence responses changes to larger, sequential step-like responses[30,56,93,158]. The oculomotor mechanisms responsible for this ramp-like control area modeled independently from the step-like responses and the current body of empirical data is quite sparse, focusing more on the latter forms of vergence responses.

Current evidence suggests that the slow-tracking vergence mechanism can respond to smooth changes in disparity up to on average 5 °/s. This limit varies significantly among the population, being as low as 0.9 °/s to as high as 9 °/s[30,158]. Above this target velocity, all vergence responses were composed of a series of small step changes in vergence angle.

It has been shown that the accommodative response, driven by retinal disparity through the VA crosslink is velocity sensitive[212]. At low temporal oscillatory frequencies (<0.1Hz) vergence responses occurred in the absence of an accommodative change. When the frequency is increased (0.5Hz) a significant accommodative change was observed. This finding provided evidence that the ‘slow-tracking’ mechanism did not share in the synkinetic crosslinked interactions with accommodation.

Fast-Phasic Fusional Vergence

Beyond the velocity limit of the slow-tracking vergence mechanism, vergence responses are step-like and are generated by the ‘fast-phasic’ (reflexive fusional) vergence mechanism. This system has received considerably more attention in the literature than the ‘slow-tracking’ vergence mechanism. The initial transient component creates the reflexive change in vergence angle in response to retinal disparities, even if the retinal images are dissimilar[25,26]. It was Westheimer and Mitchell that first demonstrated this compulsion to fusional of the transient component. They also noted that this response was typically less than the required response (gain < 1) and that dissimilar images would not result in complete binocular alignment and motor fusion[103]. Jones & Stephens furthered this work by showing that

binocular alignment could only be maintained precisely if the disparity presented in the parafoveal field was less than 0.5°. This led them to conclude that the sustained component required similar, fusible images with small degrees of disparity in order to be engaged and produce a response[100].

Pulse-Step Mechanism of Fast-Phasic Fusional Vergence

Semmlow, Horng and Hung demonstrated that reflexive fusional vergence movements could be generated with retinal disparities that were presented for only 50ms and thus argued for a control mechanism that responds to retinal disparity and is not influenced by feedback[31]. This was similar to and based upon Jones' earlier model[27]. In this model of the PV system a 'pulse' generator was responsible for the initial, 'transient' response, and was not under feed-back control. In other words, the 'pulse' response was completely open-loop and had a very short major and minor time constant (>200ms). The slower, 'step' mechanism would then provide the final neural signal to obtain and maintain binocular motor fusion and was under constant feed-back control[32]. More recently Schor et al. have combined this 'pulse-step' configuration of the PV system into their original adaptive control models[43,316] of both accommodation and vergence. These models have since become known as the 'pulse-step' models for both accommodative control[162] and vergence control[28].

This approach to the design and control of the PV mechanism solves the two central challenges that binocular primates are faced with. The first is the need to rapidly acquire binocular alignment and the second is the degree of accuracy required in this binocular alignment in order to allow for fusion an eventually stereopsis[234]. Each problem requires a different control strategy and thus a bi-modal pulse-step mechanism is ideal for serving both purposes. The pulse (open-loop) response amplitudes tend to be quite variable but serve to rapidly and coarsely realign the two eyes, while the velocity signal integrating step mechanisms provides the precise and stable binocular alignment needed for sensory fusion.

Measuring PV responses

Different approaches have been used to untangle the contributions of the pulse and step mechanisms. Most obviously, a briefly flashed stimulus can be used in order to limit/eliminate visual feedback. Since the latency of reflexive vergence responses to step changes in retinal disparities runs in the range of 120-200ms, a step change in disparity that is present for 200m/s or less generally elicits a completely open-loop response. It is not always practical experimentally to provide briefly flashed stimuli and so others have used different mathematical modeling techniques to separate the pulse and step

components when visual feedback would have been present (non-flashed stimuli). These two different methods are based on two separate sets of assumptions.

The first method and assumption is that an open-loop response will have a velocity profile that is roughly symmetric on either side of the peak velocity. Using this, one can plot the vergence response in the phase plane (velocity vs position) and fit a model of the pre-peak velocity curve (or area under the curve) to the post-peak velocity curve to identify what the amplitude of the initial , symmetric, open-loop pulse response would have been[34,86,166]. This will be referred to as a 'phase-plane' analysis.

In a similar vein, others have characterized the degree of symmetry of the vergence velocity profile. This provides an indirect measure of the relative contribution of the open-loop and closed-loop responses. Tyler et al. first introduced this as the 'normalized temporal asymmetry index' (NTAI)[174]. The NTAI is the Weber contrast ratio of the area under the velocity curve before the peak velocity and the area after the peak velocity. If the total response amplitude is then multiplied by this ratio an estimate of the initial pulse response component can be inferred. Both of these methods are susceptible to misinterpretation in the case where a vergence response contains two or more high velocity components[125]. Therefore, when using such analysis, it is important to identify the first point the velocity profile peaks by findings the point in time of zero acceleration and not simply just the maximum velocity found between the start and stop velocity thresholds of the movement criterion.

The second method and set of assumptions rely on an analytical signal processing strategy known as the independent component analysis (ICA). In an ICA, a blind-source separation analysis attempts to disentangle the different basic signals that combined to form a complex signal. In this case, the input signal into the analysis is a series of at least 40 vergence responses. Initially, a principal component analysis (PCA) is applied to the data. The results of this analysis identify the number of components making up the signal, which ideally should be 2 in this case. Noise and variance always provide additional signals; however, their overall contribution is many orders of magnitude smaller than the first two. The ICA identifies the characteristics of the first and second components and scales them simultaneously to provide the best fit to the averaged input signal data. The first component is then assumed to be the pulse mechanisms output and the second smaller component the result of the step mechanism[54,130]. Clearly, this procedure is very abstract and less applicable to biological signals than others discussed. Furthermore, it cannot deal with single responses and instead provides an average based on multiple responses that are averaged before processing. This can be problematic since the same group has also demonstrated that the fast-phasic vergence mechanism fatigues significantly within 100 trails[69].

Neurophysiology of Fast-Phasic Vergence

The computational modelling of vergence control also relied heavily on neurophysiological recordings in primates. Mays was the first to demonstrate that vergence cells in the macaque monkey mesencephalon were generally specific to either divergence of convergence and that convergent neurons were found in a much greater quantity than divergence neurons[38]. Others have echoed similar results in other subcortical areas[62,185,317]. Only the posterior interposed nucleus of the cerebellum appearing to contain more divergence than convergence specific neurons[203].

Over a series of later studies Mays and Gamlin demonstrated that 3 distinct subgroups of vergence neurons existed for the control of convergence; 'burst', 'burst-tonic' and 'tonic' in macaques. The names corresponded to their frequency response profiles. It was shown that the velocity of a vergence response was well correlated to the firing frequency in burst cells and burst-tonic cells (Figure 0-3). The vergence response amplitude was best correlated with the number of spikes in the burst cells response. The tonic firing rate of the burst-tonic and tonic cells was also correlated with the overall vergence angle. These findings supported the earlier computational and control systems modelling work of Stark and Krishnan.

Recent imaging data has provided a clearer view of the cortical structures involved in the generation and control of vergence eye movements in humans. fMRI evidence has identified significant activity in the posterior parietal cortex, the frontal eye fields and the cerebellum during the execution of repetitive vergence movements in humans[141,148,151,268]. Similar neural regions were found to be active in the macaque monkey during disparity-driven vergence responses[149,154,318]. The fMRI data unfortunately does not differentiate between convergence and divergence responses.

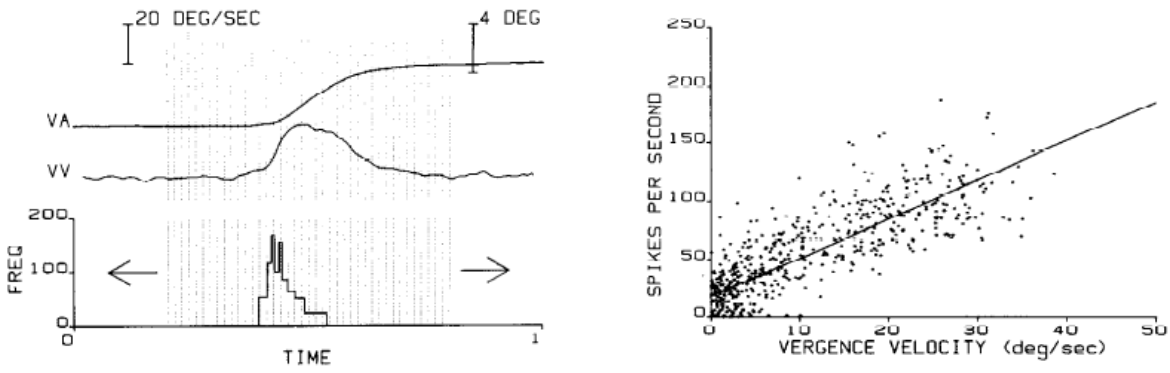


Figure 0-3: Left) Convergence response to a 4° step change in disparity (in a haploscope) from a macaque monkey. The left plot depicts the eye movement data with the firing frequency of a convergence cell along the bottom. VA = vergence angle, VV = vergence velocity. Right) Linear regression plot of the maximum firing frequency of the convergence cell on the left versus the peak velocity of the convergence response measured. This cell represents a 'burst' cell, as its firing frequency is well correlated to the peak velocity. "Burst-tonic" cells show similar behavior initially, but the steady state firing frequency does not return to zero. In these cells, the change in steady state firing frequency is related to the overall change in vergence angle. From this data the behavioral main sequence recorded from eye movements finds a neurophysiological correlate to cell firing frequency in the premotor areas. Reprinted from Mays 1986[47], with permission from the American Physiological Society (see Copyright Permissions)

Efference Copy of the Vergence Signal & the Cerebellum

Two different feedback mechanisms are incorporated into the pulse-step models of vergence control. The first feedback loop is the product of the fixation disparity error that arises from the subtle inaccuracies of the 'leaky' step mechanisms steady-state response. The second feedback loop is what is known as the efference copy in other motor literature[145,146,191,319] and is modeled to be the output of the pulse mechanism (Figure 0-4)[116,125]. A copy of the pulse motor command is compared to the expected/desired response to the disparity the stimulus encountered. If the actual response differs from the expected response, modifications to the on-going motor command can be made (feedforward modulation), or an additional motor command is generated based on the expected error (feedback

modulated). The feed-forward pathway appears to plays a greater role in vergence control because of its slower velocities and longer durations when compared to saccades. In this instance, the initial motor command is not modified, but the transition between the pulse response and the step responses appear to be modified to help elongate undershooting responses[116].

The 'internal model' to which the efference copy of a motor command is compared to is widely accepted to be housed mainly in the cerebellum[122]. In oculomotor systems, cerebellar vermis (oculomotor vermis) has been shown to be central to this process for saccades and vergence in both humans and non-human primates[320]. In non-human primates, lobule VI and VII of the OMV have cells that respond to both crossed and uncrossed disparities[182,200]. Cell recordings in macaque monkeys have demonstrated that vergence related cells are present in both the purkinje cell layer[183] and the deep cerebellar nuclei[203]. In the purkinje layer, convergence neurons were found in much larger proportion than divergence, while the convergence relate neurons firing rates demonstrated similar velocity and response amplitude relationships as reported by Mays and Gamlin in the 1980's[183]. When these cells are deactivated chemically the peak velocity of convergence movements was reduced. In studies on cerebellar patients, localized infarcts to the oculomotor vermis (OMV) of lobule 7 of the cerebellum did not impair any of the fast-phasic vergence response characteristics; however, the slow-tracking mechanism showed a dramatically reduced gain in both the divergence and convergence direction[321]. Differences between the animal and human data may be related to the species in question, or the extent of the cerebellar inactivation produced. It would be expected that localized chemical inactivation would have more specific effects; whereas cerebrovascular infarcts to this area would have consequences elsewhere in the brain, especially given the various periods of time between the injury and the data collection in most individuals. Regardless, the cerebellum plays a clear role in vergence control.

Inputs to Vergence-Accommodation

Schor originally suggested that accommodative responses driven by the disparity vergence system through the VA crosslink were driven by the fast-phasic mechanisms[43,316]. This conclusion was a result of the velocity sensitivity exhibited by the VA response[212]. The lack of a significant accommodative change to low frequency (slow changes) in vergence disparity ramps, below 0.1Hz. In retrospect, this data provided evidence that the slow-tracking vergence mechanism did not influence the VA response. Jiang et al. provided additional evidence that indeed, it was the PV mechanism responsible for driving the accommodative response[213]. It is still not clear which component of the PV system, pulse or step, drives the cross-linked changes in accommodation via the VA. The most comprehensive model published by

Bharadwaj, Maxwell and Schor places two crosslinks to accommodation, one for each mechanism (pulse and step)[28,162,322]. Empirical evidence for this design is incomplete.

Slow-Tonic Vergence

Tonic Vergence & Heterophoria

In all current models of vergence, a basic response bias is factored in as an input somewhere in the control system. This response bias represents tonic vergence innervation. Clinically, the levels of tonic vergence are approximated by assessing the heterophoria (vergence resting position in the absence of disparity inputs)[45]. In the measurement of heterophoria, monocular occlusion is used to remove any disparity feedback information. Typically, the monocular occlusion is maintained for 10-15 seconds before the heterophoria is measured. This is done in order to allow the output of the fast-phasic mechanism to decay completely. Krishnan et al. demonstrated that after occlusion, the vergence angle would change for up to 16 seconds before stabilizing[21], hence the length of time used in heterophoria measurements like the Alternating Cover Test and the Modified Thorington Technique (MTT) use 15 seconds as their suggested time of occlusion before measurements begin[59].

The measured amplitudes of tonic vergence innervation are highly adaptable. Behavioral evidence of this adaptive plasticity has been reported as early as the late 1800's, where Marlow noted that heterophoria's would become increasingly exophoric with prolong periods of occlusion; up to and including 27 days[323]. This was the basis for his prolonged occlusion test, where true tonic vergence innervation was measured after 1-2 weeks of monocular occlusion[77]. The slow decay of heterophoria to a more exophoric angle was later taken as evidence of an additional slower control mechanism that is responsible for varying the *apparent* levels of tonic vergence as measured by the heterophoria[78]. It was Sethi and North that formalized the hypothesis that the heterophoria measure was truly a reflection of the adapted state if tonic vergence innervation[45].

Slow-Tonic Vergence Latency

It seems as though binocular fusion is not required to engage the SV mechanism; however, binocular experience is. Larson had initially demonstrated that without binocular experience, heterophoria could still be altered in the presence of horizontal prism induced disparities. In this study an alternating image flashing technique was employed to monitor the heterophoria. In their 'no binocular experience' condition, where only one eye was ever viewing, they showed a small but significant change in the heterophoria[324]. At a later date, the authors realized that within the alternation between eyes there was

roughly 100ms between the opening of one eyes shutter and the closing of the other eyes that allowed for binocular experience[325]. Their conclusions were rectified later to indicate that while binocular experience is a requirement for slow-tonic vergence change, binocular fusion was not, since the 100ms binocular experience time was shorter than the latency of the reflexive fusional vergence movement required[326]. Others would go on to confirm such results in future studies and also exclude the saccades induced by alternating image presentations as inputs to the slow-tonic mechanism[327].

Neurophysiology of Slow-Tonic Vergence

While there is limited data characterizing the dynamic response properties of the slow-tonic system, there is even less neurophysiological evidence of its potential neural loci.

In the original cell-recording studies in the macaque monkey midbrain, Mays et al. did identify cells that appeared to modulate their response well after the dynamic vergence response was complet[38,47]. This phase-lag in the firing rate changes could be interpreted as the signal for tonic vergence, however no other groups have confirmed this finding. Morley et al. studied the adaptive changes in heterophoria to prolong prism viewing in 2 macaque monkeys (note that one monkey was strabismic while the other was moderately myopic). Recordings from separate vergence and accommodation relate neurons indicated that some of the adaptive response signal responsible for the changes in heterophoria's was observed in the neuronal firing rates in this area, the entirety of the response could not be reconciled with the cell recordings[46].

Given that the slow-tonic vergence response is assumed to be an adaptive one and the cerebellum plays a broad reaching and significant role in many forms of oculomotor adaptation[328], it is possible that some part of the slow-tonic vergence neural machinery is housed here. The evidence for this is limited however. In humans, 13 patients with generalized cerebellar dysfunctions demonstrated an impaired capacity to adapt their heterophoria to vertical prism-induced disparities when compared to controls[329]. Unfortunately, many of the patients in this study had other neurological comorbidities and exhibited large exophoria to being with, confounding the localization of the heterophoria deficit to the cerebellum alone. In a second study, the adaptive capacities of heterophoria to horizontal prism was shown to be reduced in 5 patients with diffuse and generalized cerebellar degenerations[72]. In this study the controls were not aged matched and differed significantly from the cerebellar patient group (mean almost 25 years younger control group). It was also not clear which direction the prism was given and it was reported to vary among the participants. Further, 2 of the 5 patients demonstrated no measurable stereopsis which may have severely impacted the processing of the disparity input. The former study of 13 cerebellar patients

neglected to assess stereopsis at all. In both studies it appears that data is skewed by a small percentage of participants showing a larger effect. Given the confounders reviewed, the conclusions that can be drawn from this data are limited.

At this point, the role of the cerebellum in the adaptive control of tonic vergence through the slow-tonic vergence system is unclear. Further, there is little additional evidence to suggest where, either cortically or subcortically the neural machinery responsible for slow-tonic vergence control may be.

Models of Cross-Linked Interactions

There are two competing models of disparity vergence control that have attempted to integrate the slow-tonic behavior into their control networks using adaptive loops. Each of these models was formalized in print in 1992 and came from two separate research groups. The biggest difference between the two models is the placement of the cross-linked interactions between the accommodative and vergence systems relative to the adaptive mechanisms.

The first model, proposed by Hung, described the sustained (step) controller time constant as variable. The output of the fast-phasic response was fed back into the step controller and served as the signal to modify its decay time constant. In this model, the longer the disparity stimulus was fused for, the greater the increase in the decay constant, thus resulting in changes in the vergence angle during occlusion (phoria adaptation). The tonic vergence innervation/bias was integrated into the system after the crosslinked interactions, while the adaptive mechanisms feedback loop was placed before the crosslinked interactions[181].

In the model published by Schor, a separate response controller was created in order to account for the effects of heterophoria adaptation[43,316]. This controller represented the slow-tonic mechanism and was placed after the cross-linked interactions between vergence and accommodation. This slow-tonic mechanism fed directly into the tonic bias. Schor argued that the slow-tonic mechanisms output should come after the cross-links based on two observations. The first was that both tonic accommodation and tonic vergence could be transiently altered through prolonged engagement of the opposite system[206].

The evidence across the literature generally supports the positioning of the slow-tonic mechanism after the cross-linked interactions between the two systems.

Saladin expanded Schor's model in 2005 to reflect the different response dynamics displayed by convergence and divergence. In this model, the controllers were named for specific anatomical structures and clinically observed behaviors. The cross-links in this model were positioned in a similar manner to Schor's original model[330].

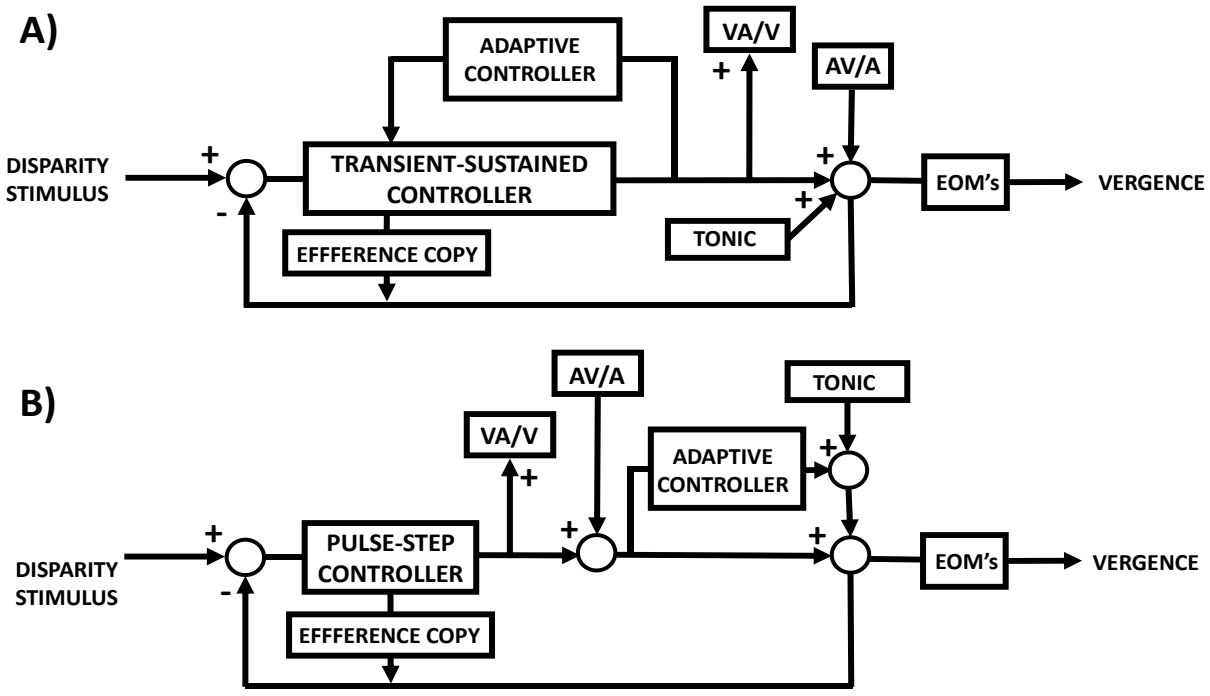


Figure 0-4: Two different adaptive control models of disparity driven vergence. A) The adaptive control model derived from the dual-mode model by Hung et al 1986. In this model, the adaptive controller responsible for changes in heterophoria observed after prolonged fixation modifies the decay time constant of the sustained components innervation output. The cross-linked interactions with accommodation occur after the adaptive control loop. Note that the tonic innervation is represented as a stand-alone bias input. B) The Adaptive control model put forward by Schor et al. Here, the adaptive control loop receives input from the pulse-step (fast-phasic) controller and is placed after the cross-linked inputs to and from accommodation. The adaptive control mechanism feeds directly into the tonic vergence bias and thus is modelled as an additional input from the tonic system, hence it is referred to as the 'slow-tonic' controller in this dissertation. The fast-phasic component in both A) and B) models is depicted as a single motor control for simplicity in both schematic representations. The efference copy is created by the initial pulse (transient) vergence response and is compared against the internal model's

prediction. Any errors that would be predicted from the original pulse/transient vergence command are feedback into the system, along with the visually guided feedback.

Clinical Dysfunctions of Vergence Control

There are four main categories of non-strabismic vergence control dysfunctions in the clinical literature. The most common vergence dysfunction is by far convergence insufficiency, followed by convergence excess. Non-strabismic Divergence anomalies are much less prevalent (<1%)[59].

Convergence Insufficiency

Convergence insufficiency is a dysfunction that prevents an individual from comfortably viewing (binocularly) at near distances. It has been reported in the literature as early as 1855 by von Graefe[331], and was a major component of the first classification system proposed by Duane in 1896[332]. The clinical diagnosis and treatment of CI remains controversial. This is more so true in terms of agreement for the most effective and appropriate therapies. While many different researchers have provided evidence that symptomology resulting from CI can be reduced through training, a consensus on the optimal training environment (home-based vs office based) and training tasks prescribed does not currently exist.

The following will briefly review the definition, epidemiology and pathophysiology of CI as well as its symptoms and suspected neurophysiological causes based on the previously outlined models of vergence control. Specific therapies will not be addressed here.

Definition of CI

Since Duane's first published his classification system, the definition of CI has revised by various groups. The initial definition from Duane outlined that CI was primarily a larger exophoria at near than distance, with either a remote near point of convergence (NPC) or a reduced capacity to maintain fusion through base-out prism at near (PFV)[332,333]. Recently, randomized clinical trials on CI treatments have provided a more concrete definition of the condition. The CITT group defines CI as patients who exhibit all of the following[111]; 1. Larger exophoria at near (>4PD). 2. A receded NPC (>6cm). 3. Positive fusional reserves at near that are less than twice the amplitude of exophoria (failing Sheard's criterion[308]). This group also devised and validated a survey with which to classify the degree of near point symptoms potentially caused by CI[110,334]. A symptom score greater than 20 (16 in children) on the Convergence Insufficiency Symptom Survey (CISS) was also required in order for a patient to be classified has having CI.

Prevalence of CI

The prevalence of convergence insufficiency varies greatly in the literature reports. A large amount of this variation is due to the large degree of variance in the way CI is defined in order to be diagnosed. While the CITT group defined CI by the presence of all 3 clinical findings and associated symptomology, others have used less strict criterion. In clinical studies, one sign of CI has been reported in between 25-55% of patients examined, while 2 symptoms were present in roughly half of these patients (~12.5% overall), and all 3 symptoms in up to 6% of the population[333,335,336]. It has been estimated in an extensive literature review of CI that symptomatic CI is present in roughly 5-10% of the general population[12].

In recent years CI has seen a renewed interest in the literature. This is partially due to the prevalence of the disorder, along with other anomalies of binocular vision, in patients suffering head injuries[337,338], specifically war-veterans with blast related injuries[13,339–341] and children[13,265]. Various reports cite a prevalence of almost half of blast injuries and mild traumatic brain injuries suffered in sports demonstrate some degree of CI (depending on the definition criteria)[13].

Etiology of CI

The root neurophysiological cause of CI is not clear, nor has this topic been explored in the research. Most of the literature surrounding CI focuses on the clinical definition, prevalence and treatment of CI[12].

According to a conglomeration of work, Schor suggests that disorders of binocular vision are rooted in anomalous function of the cross-linked interactions, as first suggested/defined by Duane[332] and further by Tait[5] and Wick[59]. Schor found an inverse relationship between the gain of the AV and VA crosslinks[342]. This led to the conclusion that the true root cause of CI may be in the adaptive mechanism responsible for managing the degree of cross-linked output[87]; specifically the slower-tonic mechanism. How or why these adaptive capacities become impaired is unknown, as is the specific neural dysfunctions that underlie these mechanisms.

It is questionable whether or not the type of CI exhibited in patients with traumatic brain injuries (TBI) is a different entity from that observed in children and adults without a history of brain injuries[13]. There is currently no evidence that suggests there is any differences between the two conditions. Some have speculated that CI in TBI patients could have potentially existed in some degree before the injury (remembering almost 50% of clinical populations have one sign of CI). A TBI would then serve as merely

an additional perturbing factor, potentially increasing the symptoms then expressed by a population already displaying one or more signs of CI.

Symptoms of CI

The most common symptoms reported by individuals with CI is discomfort and reduced vision quality during visual demanding tasks at nearer working distances, such as reading or working on a computer or laptop[12,109,258,333]. Other frequent symptoms include frontal headaches, eye strain (asthenopia), blurred vision, double vision (diplopia), excessive tearing, a pulling sensation in or around the eyes, eyelids that feel heavy or droopy and generally more tired eyes[109,258,333]. Less common symptoms include migraines, dizziness or vertigo[343,344], as well as motion sickness and poor depth perception[333].

The CITT group has validated a questionnaire that quantifies near-point related symptoms related to CI[110,334]. The survey includes a variety of other reading related symptoms that have also been reported by other groups in CI, such as frequently re-reading lines or paragraphs and losing one's place often while reading.

The effects of CI on user experience with new wearable technologies like VR and AR environments has not yet been investigated. It can be assumed that any dysfunction of vergence control would have a negative impact, since these environments rely heavily on the manipulation of retinal disparity to induce the perception of depth from a flat screen.

Clinical Signs of CI

As stated before there are 3 main clinical criterion used to define CI[12,333]. The first is an exophoria larger at near than distance (>4PD). This indicates that the overall contributions of proximity and accommodation to the vergence posture are not well matched to the stimulus demand; thus requiring additional input from the disparity vergence system to maintain fusion. This explains the additional finding of a low stimulus AV/A ratio when measured by the gradient and calculated techniques[59].

The second criterion is a receded NPC beyond 6cm[12,333]. The receded NPC indicates a reduction in the maximum amount of convergence that can be achieved when the presence of all vergence related motor cues are available. Taken in conjunction with the near versus distance heterophoria, an assumption can be made from the NPC about the strength of the disparity vergence and voluntary vergence systems. It is not completely clear if the NPC alone is of diagnostic value, since some report no association

between the NPC and visual symptoms[274] while other report the opposite[109,258]. This controversy likely emerges from the large degree of variation in the testing procedures and fixation targets used[12,345].

The third main criterion is a reduced ability to binocularly fuse sequential step changes in base-out prism at near[12,333]; specifically, the PFV amplitudes as they pertain to Sheard's criterion are used[308]. This additional criterion addresses the disparity driven vergence system more directly. The measurement of positive fusional vergence (PFV) is an indirect measure of the function of the SV controller[79,99]. In the diagnosis of CI the blur point obtained during PFV measurement is the most crucial, if it can be reliably obtained. It also proves to be the most elusive and variable based on the fact that subjective reporting of blur is quite variable depending on the instructions given and the pupil size and depth of focus can influence perceived blur a great deal. The first point of sustained blur indicates when the slow-tonic system is unable to completely replace the fast-phasic innervation needed to maintain fusion. At this point, a sustained accommodative response is generated through the VA crosslink. Others have demonstrated that the inability to rapidly engage the slow-tonic mechanism to alter the heterophoria while attempting to fusing base-out prism is a likely a root cause of the symptoms reported by individuals suffering from CI[107,177,276,346–349]. The stems from the same vein of reasoning, that the impaired ability to adapt the tonic vergence innervation through the slow-tonic controller results in excessive cross-link driven accommodation[207,348], resulting in the symptoms of asthenopia. When the function of the slow-tonic controller normalizes with therapy, the severity of the symptoms begins to reduce when the prolonged output of the VA/A cross-link in reduced[49]. The break point at which constant diplopia (or suppression) is reported illustrates the maximal amount of prism that can be fused while engaging voluntary vergence and while more repeatable than the blur point, provides significantly less diagnostic value.

There are two other main clinical findings in addition to the 3 stated above and reduced AC/A ratio's. The first is a reduced amplitude of vergence facility, particularly failing to fuse when the 12 base-out prism is in place[97,109,350,351]. Reduced vergence facility suggests that the slow-tonic mechanism's responses are susceptible to fatigue, which may also play a role in the symptomology reported, as suggested by Saladin in his control systems analysis of CI[273]. The second is reduced accommodative function, both facility and amplitudes[12,352]. While accommodative dysfunctions are not the topic of the current dissertation, it is important to recognize that the symptoms reported in CI are often found in the presence of accommodative dysfunctions as well[352].

Laboratory & Experimental Data from CI Patients

Recently, the use of video based high speed eye-tracking has allowed for further quantification of deficits in vergence control in CI. Specifically, deficiencies in the fast-phasic response mechanism to step changes in retinal disparity have been characterized in detail in the past 15 years.

In his original work, Grisham noted that the CI group demonstrated a reduced rate of tracking to ramp disparity stimuli presented dichoptically[304]. In a follow-up to this study, Grisham et al. then assessed the effect of vergence therapy/training on the tracking rates described in his first study. It was reported that the vergence tracking dynamics improved to near normal levels in the CI group that was treated versus not treated[353]. The effects seem to be retained 9 months after therapy was completed.

In 2003 Daftari et al. confirmed Grisham's observations. Here the main sequence ratio of convergence was significantly reduced when compared to controls. This could suggest a different/reduced recruitment pattern of convergence cells in patients with CI. Building on this work, Alvarez et al. confirmed that fast-phasic vergence responses to step changes in retinal disparity were slower[141]. After successful therapy, these parameters normalized along with the clinical findings of PFV and NPC. The reduced response velocities suggest that the overall function of the PV mechanism, specifically the pulse response is reduced in CI. Thiagarajan and Ciuffreda extended this work and reported that participants with a history of traumatic brain injury (TBI) had reduced convergence peak velocities and longer durations than controls.

Since Alvarez keynote publication in 2010 that also included functional magnetic resonance imaging (fMRI) data, there have been numerous reports that have confirmed the reduction of convergence peak velocity in patients with CI, whether traumatic[13,119,140,354] or non-traumatic[18,214,219,265,268] in etiology. From the evidence it is not clear at this point if there is an effect on the vergence latency and if the steady state vergence response is affected.

It has been known for some time that the vergence behavior of patients with CI often includes more saccadic interactions when compared with binocularly normal controls. In 1999 van Leewuan et al. demonstrated that CI's generally made more saccades with a much smaller vergence components when attempting to fixate from distance to near on real world targets[274]. It was reported that many of the participants become exotropic when trying to fixate at near. They showed that a skewed monocular preference drove the dominant eye to fix while the other eye was left to be strabismic. Interestingly, even subjects that were able to binocularly fuse at near produced vergence response with larger saccadic components and smaller vergence components than controls. Saccadic-vergence interactions serve to facilitate or speed-up vergence response dynamics in both directions[66,88,89,355]. It is possible then that the

saccadic influences of the non-strabismic CI patients was potentially helping to facilitate an already reduced fast-phasic convergence mechanism by recruiting other oculomotor systems (saccades). Alvarez provided evidence for this later when they observed a similar finding as van Leewuan pre-therapy and then reported a reduction in the number and amplitude for saccadic-vergence interactions after therapy[219]. This reduction in saccadic interactions/recruitment was subsequently associated with an improvement in the overall pure convergence response velocities. Such evidence would be taken to suggest that these interactions are malleable and that should sufficient vergence resources become available (therapy) or reduced (mTBI), the contribution of other oculomotor systems to facilitate the change in fixation distance can also be altered.

Broader Functional Effects of CI

It is controversial whether or not CI has broader impacts, beyond oculomotor symptoms and signs. While vertigo, nausea and motion sickness have been reported as less common findings in CI, other groups have found correlations between both academic performance and behavioral tendencies.

Shortly after Duane first proposed the classification system of oculomotor anomalies, two separate groups identified a potential relationship between reading abilities in the school aged populations and CI. It was reported that CI is more common in children with reading disabilities[356,357] and that low PFV may be a risk factor for reading deficiencies[358]. The cause and effect relationship here is weak and thus it has been contentious in the literature if such a relationship even exists.

In the more recent literature, Granet et al. found a 3-fold increase in the prevalence of attention deficient and hyperactivity disorder (ADHD) in children diagnosed concomitantly with CI[260]. In parallel work, Borsting et al. found that cognitive and attentional deficiencies (as measured by self and parent reporting scales) were significantly greater in the subpopulation diagnosed with CI [262]. In another follow-up study, the increased prevalence of ADHD in CI first reported by Garnet in 2005 was confirmed using a different symptom scale and patient population[359]. Additionally, it was shown in a sample of children with CI that successful therapy resulted in a reduction in the parent-reported symptoms of ADHD[261]. Unfortunately, this study lacked a control group or placebo therapy. A second, more recent study found similar improvements in the parent reported symptoms of behavioral dysfunctions after office-based therapy for CI[263]. Unfortunately, again, this study lacked a control group or placebo treatments. While the evidence presented certainly suggests some relationship between CI, learning, reading and behaviors (at least in school aged children) the lack of properly controlled studies has prevented a universal consensus

from other healthcare providers. The American Association of pediatrics to published a revised position statement in 2009 outlining the lack of evidence for a

In the review of the literature there is a paucity of data that characterizes other motor deficits that may be associated with CI. This is curious given that others have demonstrated a negative impact of the use of base-in and base-out prism on fine motor skills[360] as well as a relationship between fine motor skills and quality of visual acuity and binocular fusion[361–364]. One study has suggested that CI may even influence higher level cognitive processing and executive function, as evidenced by reduced Stroop-Test scores in participants with low PFV's and higher exophoria's[264]. An interesting vein of research would be to explore other motor and executive function deficiencies in patients with clinical significant CI. Such investigations would likely prove easier to design and complete than the previous investigations relating to attention, reading and behaviors.

Neurophysiology of CI

There is limited evidence in humans of the neural loci of CI. This is perhaps in part due to the incomplete understanding of the behavioral control mechanism deficiencies exhibited by these patients.

In non-human primates it has been shown that lesions of the deep cerebellar nuclei can result in reduced convergence response velocities[182,183]. Additionally, lesions of the oculomotor vermis of the cerebellum (lobules VI and VII) result in reduced capacities to adapt the heterophoria to prolonged prism, although these findings were variable amongst the three macaque monkeys studied[365]. Consistent with these findings in primates, studies of human patients with cerebellar degenerations or damage demonstrate effects on both the fast-phasic[321] and slow-tonic control mechanism responsible for heterophoria daptation[72,329]. For a more thorough review of this literature see previous neurophysiology sections.

Alvarez et al first provided evidence of the neural loci of CI when they compared the blood-oxygenation dependent response (BOLD) from fMRI scans in patients with CI to controls and before and after successful rehabilitative therapy[141,268]. They found decreased activity in the posterior parietal cortex, frontal eye fields and cerebellum when CI subjects completed convergence movements. This functional activity improved post-therapy to near normal levels and was seen in conjunction with improvements in both the convergence response velocities and PFV's. These studies provided the first imaging evidence of the effects of therapy. At the time of writing there are yet to be further publications; however multiple studies by this group have been initiated since the last publication in 2014 that should help provide a more

detailed understanding of the effects. Combined with the recent behavioral evidence characterizing the mechanistic deficiencies in CI, we are not far from a consensus on the actual root causes of CI.

Summary of Vergence Mechanism Function in CI

In summary, there are deficits in both the slow-tonic and fast-phasic control mechanisms in convergence insufficiency. This is not surprising given that all the various models of vergence control use the output of the fast-phasic transient component as the input to the adaptive mechanism that underlies heterophoria adaptation, however or wherever it is placed. A better understanding of how these two mechanisms interact and the changes in these relationships in clinical cases of dysfunctional vergence would provide much needed behavioral evidence in the search for a neurophysiological root causes of CI.

Other vergence Anomalies

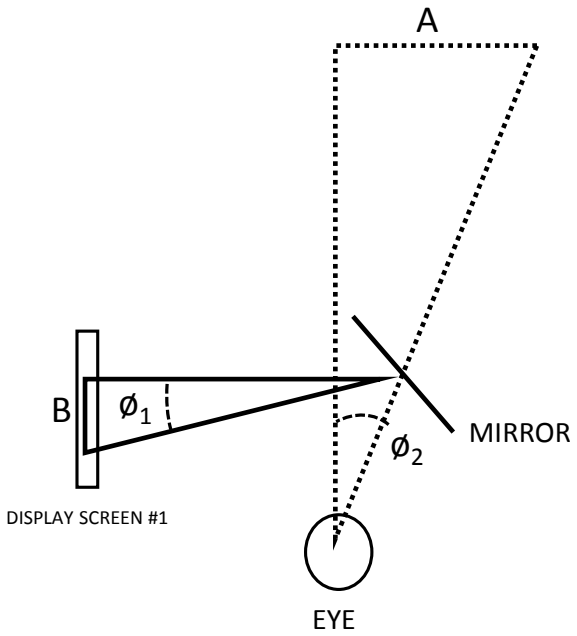
Under the Duane system of oculomotor dysfunctions the remaining 3 conditions of convergence excess, divergence insufficiency and divergence excess are much less common than that of CI[332]. Interestingly, it has been hypothesized by different groups that these clinical dysfunctions are also rooted in mismatched or imbalance cross-linked interactions between vergence and accommodation[207,366,367]. Due to the relative rarity of these conditions in comparison to CI, they will not be discussed in the context of this review.

Appendix B

Because the infrared passing mirrors are not coincident with the center of rotation of the eyes, a conversion must be made for both the lateral image movement on the haploscope monitors and the required IPD to be set at the mirrors. This appendix will cover the conversions made to determine the appropriate horizontal image shift on each haploscope monitor to create 1° of disparity for the viewer. The second section in this appendix will then deal with the necessary conversion to determine the appropriate IPD between the infrared passing mirrors in the haploscope and the angular vergence demand required to provide a congruent accommodative-proximity-vergence stimulus to the viewer. This is obviously based upon the IPD. This section provides the calculations based upon a 6cm IPD. The full conversion chart created for all IPD's used from these conversions can be found in the methods section.

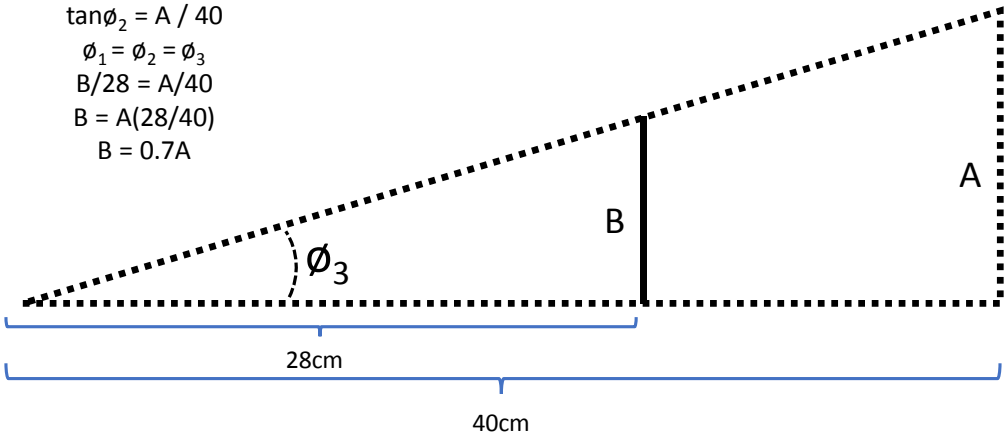
Figure 0-5 depicts the environment and conversion used to determine the appropriate distance the images must be shifted laterally on each monitor in order to stimulate the correct amount of retinal disparity. This distance is physically less on the monitors due to the mirrors reflection and Snell's law (angle of incidence = angle of reflection). Therefore, using similar triangles, one can determine the amplitude of horizontal movement (in both centimeters and screen pixels) required on the monitor to provide the same angular rotation that would occur if the target was shifted in real space.

MONOCULAR HAPLOSCOPE SCHEMATIC



MONOCULAR SIMPLIFIED TRIANGLES

$\tan\phi_1 = B / 28$
$\tan\phi_2 = A / 40$
$\phi_1 = \phi_2 = \phi_3$
$B/28 = A/40$
$B = A(28/40)$
$B = 0.7A$

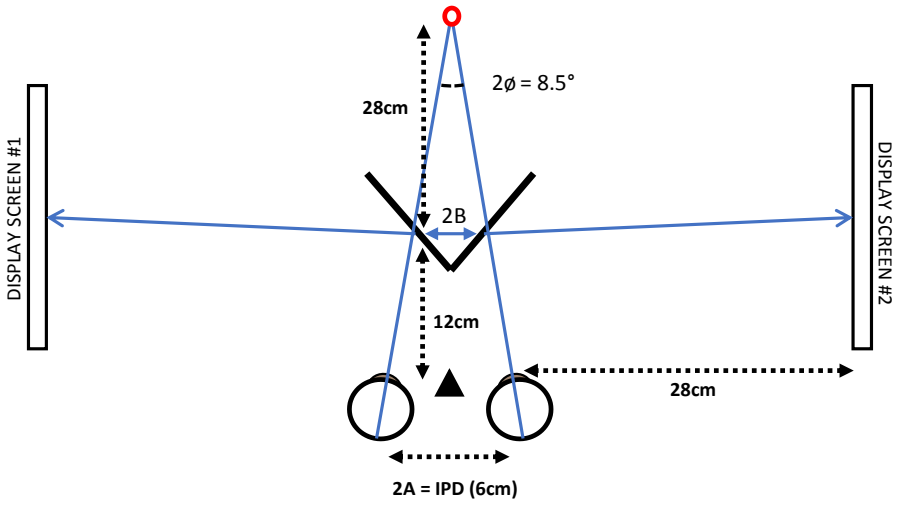


$\tan\phi_3 = B/28$
$\phi_3 = 1°$
$28 * \tan(1°) = B$
$B = 0.4889$ cm

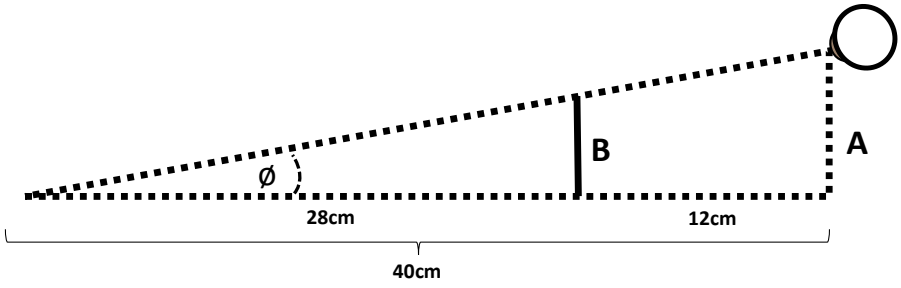
Display Screen Width = 15.3cm
Display Resolution Pixels (horizontal = 800, vertical = 480)
800/15.3 = 52.28 pixels/cm
1° Vergence Change = 0.4889cm = 25.56 pixels

Figure 0-5: Haploscope schematic and similar triangle conversion (all monocular) for lateral image shift on the haploscope monitors. The image must move less on the haploscope monitors (solid lines) than would be required in real-space (dotted lines) to provide the same angular demand for vergence/disparity. Since the angle of incidence on the monitor will be equal to the angle of reflection, similar triangles can be used to determine the required lateral shift on the monitor. When the mirrors are placed 28cm from the LCD monitors, this conversion factor becomes 0.7x the actual image shift required in free space. Using the display screen width and number of pixels (800 horizontal x480 vertical resolution) the number of pixels per degree or monocular disparity can be calculated. Shifting each eyes image by 25.56 pixels will create 1° of disparity to each eye, for a total of 2° of total disparity.

HAPLOSCOPE SCHEMATIC



MONOCULAR SIMPLIFIED TRIANGLES



Monocular Mirror IPD = B
Monocular IPD @40cm = A
tanø = A/40 = B/28
B/28 = A/40
B = A(28/40)
B = 0.7A

6cm IPD = 4.2cm Mirror PD

Ø = Monocular Convergence Demand @ 40cm
tanø = A/40
Ø = $\tan^{-1}$ (A/40)
When monocular IPD = 3cm (6cm binocular)
Ø = $\tan^{-1}$ (3/40)
Ø = 4.22 °
2Ø = 8.44°

6cm IPD = 8.5° Convergence

Figure 0-6: Haploscope schematic and similar triangle conversion of IPD for one eye. Since the infrared passing mirrors are not coincident on each eyes center of rotation, the IPD required between the mirrors (‘2B’) is different from that measured clinically at eth spectacle plane (‘2A’). The conversion factor of 0.7x the IPD measured is set between the haploscope monitors. In addition, to provide a congruent demand between accommodation and vergence the IPD must be taken into account. Provided in this diagram is the total convergence demand for an individual with a 6cm IPD when viewing at 40cm. As the IPD increases, the overall convergence demand required to retain a congruent stimulus increases (and visa versa).

The physical screen size and resolution can be used to determine the total number of pixels that span a specific angular distance. The example provided details this calculation for a 1 shift for one eye. Because symmetric disparity stimuli are being used in this experiment, this number must also be doubled. So if each eyes monitor has the image shift 25.56 pixels in opposite directions, the total binocular retinal disparity created would be 2 degrees. Therefore, a 1° binocular disparity stimulus requires a 12.78 pixel shift of each monitors image.

Figure 0-6 describes the conversion that must be made in order to provide the proper IPD at the infrared passing mirrors for the patient. Again, because the mirrors are not coincident with the center of rotation of the eyes, the separation between them is actually less than the intraocular separation measured clinically. The schematic demonstrates the monocular similar triangles calculation used.