

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

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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 steps in disparity dichoptically at 40 cm while eye movements were recorded with infrared oculography. First- and second-order phasic and slow-tonic convergence response properties increased linearly with disparity demand ($p < 0.01$), whereas divergence responses did not ($p > 0.05$). Phasic divergence responses were slower than convergence ($p = 0.012$) and were associated with a higher frequency of saccades ($p < 0.001$). The average rate of slow-tonic change was correlated to the average peak velocity of phasic vergence at the same vergence demand in both directions, $r = 0.78$, $p < 0.0001$. Clear directional asymmetries were observed in phasic and tonic vergence responses. The response properties of the slow-tonic mechanism varied directly with the peak velocity of the complementary phasic system. 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 divergence mechanism but did not directly influence the response behavior of the slow-tonic mechanism.

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 1A; Stark, Kenyon, Krishnan, & Ciuffreda, 1980; Westheimer & Mitchell, 1956). Optical blur and proximity also stimulate vergence through synkinetic neural cross-links in the “near-triad” (Maddox, 1886; Schor, 1980; Westheimer & Mitchell, 1956). These reciprocal cross linkages between accommodation and vergence have been identified as accommodative vergence (Alpern, Kincaid, & Lubeck, 1956) and vergence accommodation (Fincham & Walton, 1957). 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 (Schor, 1979a; Schor, 1980). 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 1A; Schor, 1992). 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 (Fincham & Walton, 1957; Jiang, 1995; Schor, 1986; Schor & Kotulak, 1986). When fixation is prolonged, a slow change in the underlying tonic levels of vergence innervation occurs via the “slow-tonic” vergence (SV) mechanism (Figure 1B; Schor, 1979a; Sethi, 1986). SV has been modeled to

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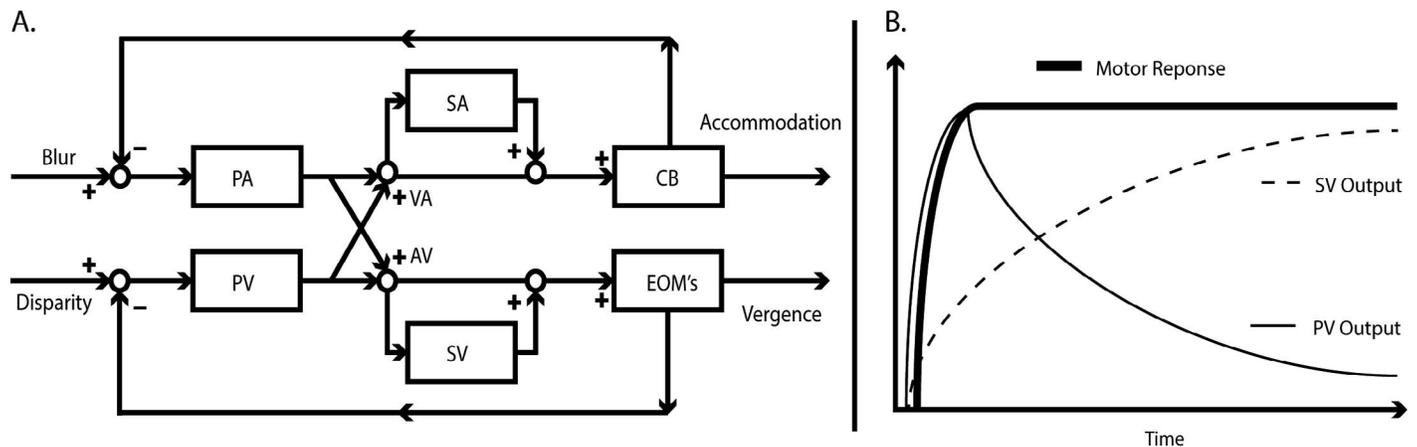


Figure 1. (A) Simplified vergence model adapted from Schor, 1992. (PV = phasic vergence; PA = phasic accommodation; SV = slow-tonic vergence; SA = slow-tonic accommodation; VA = vergence accommodation; AV = accommodative vergence; EOMs = extraocular muscles; CB = ciliary body. (B) Graphical illustration of the replacement of PV by SV as fixation time increased adapted from (Schor, 1979b), reprinted with permission from Erkelens, I. M., Thompson, B., Bobier, W. R., & Munoz, D. (2016). Unmasking the linear behaviour of slow motor adaptation to prolonged convergence. *European Journal of Neuroscience*, 43(12), 1553–1560.

replace PV output over time (Figure 1B). This has been based upon changes in tonic levels of vergence that follow sustained viewing at increased levels of convergence (Schor, 1979b). 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 (Jiang, 1996; Schor, 1979a, 1979b; Sreenivasan & Bobier, 2014). 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 (Howard, 2012).

The “main sequence” is the common analysis tool applied to saccadic eye movements (Bahill, Clark, & Stark, 1975). In this analysis, the peak velocity of an individual movement is plotted against their respective response amplitudes. The plot is then regressed, with the slope of this function providing a behavioral correlate for the degree of neural recruitment (Bahill et al., 1975; Gamlin & Mays, 1992). Previous work has demonstrated that this main sequence relationship is upheld in phasic vergence responses (Alvarez, Semmlow, Yuan, & Munoz, 1999; Hung, Ciuffreda, Semmlow, & Horng, 1994; Rashbass & Westheimer, 1961; Semmlow, Hung, Horng, & Ciuffreda, 1994); however, significant directional asymmetries have been reported between convergent and divergent phasic vergence main sequences (Hung et al., 1994; Hung, Zhu, & Ciuffreda, 1997). This directional asymmetry extends to the latencies (Hung et al., 1997; Semmlow & Wetzel, 1979; Tyler, Elsaid, Likova, Gill, & Nicholas, 2012) and dynamics (Hung et al., 1997; Tyler et al., 2012) of

disparity-driven vergence responses. These data, along with neurophysiological evidence derived from primates (Mays, 1984; Mays & Gamlin, 1995; Nitta, Akao, Kurkin, & Fukushima, 2008) 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 (Brautaset & Jennings, 2005; Sethi & North, 1987). In addition, recent evidence has indicated a strong relationship between peak velocity and short-term sensorimotor adaptations within the PV mechanism (Alvarez et al., 2009). Current models predict similar directional asymmetries and adaptive relationships *should* exist in SV, if PV is truly the driving stimulus for tonic vergence innervation change. The current study will test these hypotheses by quantifying and comparing the behavioral function of PV and SV with convergent and divergent disparities separately, using a main sequence analysis of each in healthy adults.

Methods

Participants

Four males (25–32 years old) 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

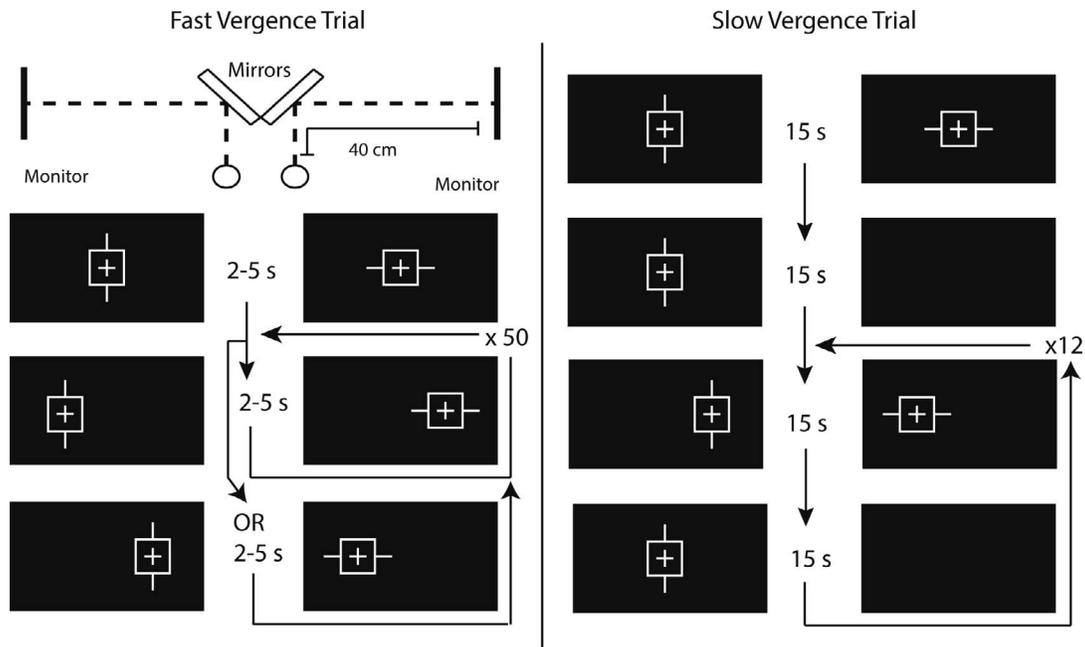


Figure 2. PV trials: PV was elicited from horizontal disparities created dichoptically. Phasic vergence responses were defined by the initial reflexive motor response (above left). Note: Dichoptic disparity presentation clamps the accommodative demand. Slow trials: SV was measured as the rate and amplitude of heterophoria change (sampled every 15 s) during 3 min of disparity viewing. Heterophoria was measured by extinguishing the right stimulus to simulate occlusion, above right reproduced with permission from Erkelens, I. M., Thompson, B., Bobier, W. R., & Munoz, D. (2016). Unmasking the linear behaviour of slow motor adaptation to prolonged convergence. *European Journal of Neuroscience*, 43(12), 1553–1560.

optometrist screened each participant to ensure normal binocularity. This was defined as greater than 6/7.5 corrected monocular visual acuity, stereoacuity better than 40 arc seconds, with a near point of convergence greater than 9 cm. Each subject's heterophoria was within two prism diopters of orthophoria as measured objectively via the eye-tracker and confirmed with the alternating cover test. Two subjects were slight esophores (0.9 PD, S2 and 0.1 PD, S3) whereas the other two subjects were slight exophores (0.7 PD, S1 and 1.4 PD, S4). Subjects with small heterophorias were recruited to control for the suggested effects of heterophoria amplitude and direction on phasic vergence responses (Alvarez, 2015; Kim, Granger-Donetti, Vicci, & Alvarez, 2010).

Apparatus, eye-tracking and 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 (three at each stimulus amplitude) and six PV trials on separate days. Stimuli were presented dichoptically at 40 cm on two 7-inch LCD monitors (Lilliput®, Wolverhampton, UK) within a haploscope (Figure 2). Each eye's visual stimulus subtended $2.73^\circ \times 2.73^\circ$, with a line width of 0.08° (Figure 2) and had two

vertical or horizontal lines unique to each eye's stimulus, which served as 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 ($\pm 40^\circ$) of the eye tracker, which has a spatial resolution of 0.03° and an average accuracy of 0.5° or less.

Dichoptic stimuli and 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 2), where both accommodation and proximity are held constant while disparity vergence is varied. In this “noncongruent” 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 noncongruent disparity (Rosenfield, 1997; Thiagarajan, Lakshminarayanan, & Bobier, 2010); 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 (Alpern & Ellen, 1956; Kenyon, Ciuffreda, & Stark, 1978). 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 noncongruent and cue-congruent, depending the disparity step sizes used (Alvarez, Semmlow, & Pedrono, 2005; Hung et al., 1997; Scheiman, Talasan, Mitchell, & Alvarez, 2017). This variation is likely due to the difficulty found in eliciting saccade-free divergence responses to larger uncrossed disparities (Hung et al., 1994). 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 40 cm viewing distance. PV and SV responses were then generated by creating a symmetric, noncongruent change in disparity only. These conditions were designed to ensure that each system's responses were generated using an identical type of disparity stimuli. A single testing distance of 40 cm was selected for this study to provide optimal conditions to elicit purely 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 40 cm or 2.5 MA), while convergence responses were unaffected by testing distance (Alvarez, Bhavsar, Semmlow, Bergen, & Pedrono, 2005). 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 (Banks, Kim, & Shibata, 2013). 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. Accordingly, a test distance of 40 cm was selected, as any asymmetries between convergence and divergence are expected to increase if the same procedures were performed at greater distances.

PV trials

Detailed descriptions of the methods used to measure PV have been reported in previous studies (Alvarez et al., 2005; Hung et al., 1997). 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 noncongruent disparity steps (2° , 4° , 8° , 12° convergent; -2° , -4° , -6° divergent) at 40 cm. A total of 30-step stimuli at each amplitude were presented over the course of six separate visits (210 total step stimuli). The order of step amplitude presentation and the time delay (2–5 s) 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 (Alvarez et al., 2005). All responses were visually inspected for blinks or saccades within the vergence responses.

SV trials

A detailed description of the SV trial procedures is published in previous work (Erkelens, Thompson, & Bobier, 2016), which was based on work in other laboratories (Han, Guo, Granger-Donetti, Vicci, & Alvarez, 2010; Satgunam, Gowrisankaran, & Fogt, 2009). In each trial the subject first viewed a fixation cross (Figure 2B) binocularly for 2 s at an initial vergence demand of 2.5 meter angles (8.44°), which was cue-congruent to the accommodative and proximal demand at 40 cm. The RE image was then extinguished for 15 s, 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 noncongruent disparity demand was fused for 15 s, followed by another 15 s of right eye (RE) image extinction to re-measure the heterophoria. This was repeated with the same disparity amplitude until a total of 3 min of adapting disparity had been viewed and 13 heterophoria measures were obtained (Figure 2). The change in heterophoria over the course of a single trial defined the input of the SV system.

Tonic accommodation trials

According to the model (Figure 1A), 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 (Schor, 1992). To confirm this, three additional experimental trials were completed by each subject to assess slow-tonic accommodation before and after prolonged noncongruent disparity viewing. The same procedures (Methods) were completed once for the

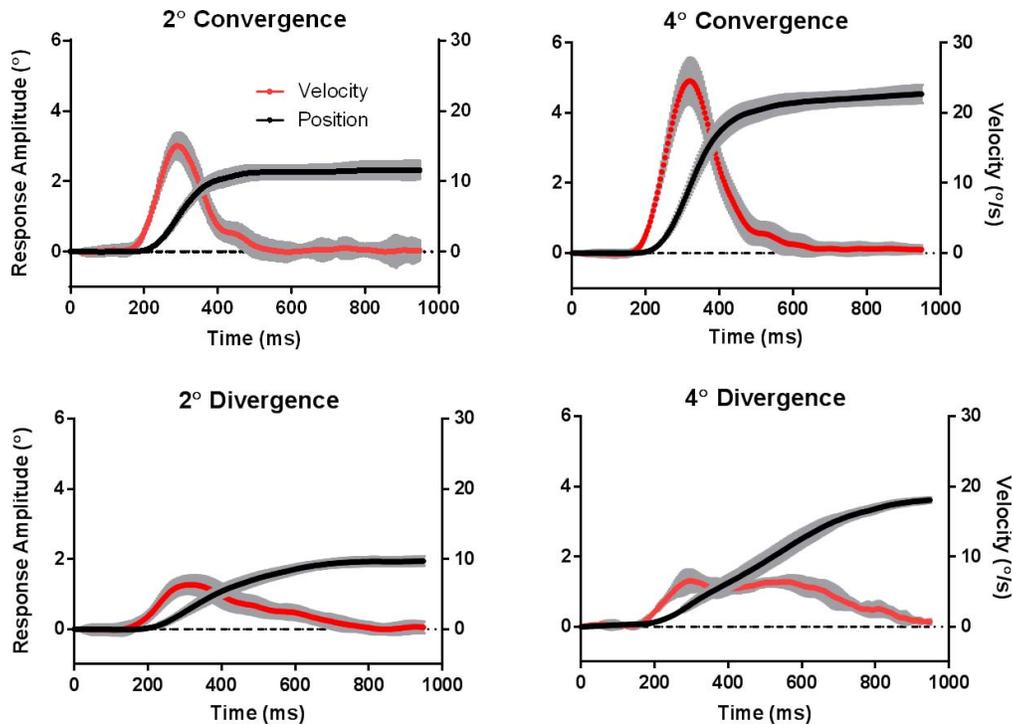


Figure 3. Average vergence responses (position – black, velocity – red, SD – gray) for phasic convergence ($A = 2^\circ$, $B = 4^\circ$) and divergence ($C = 2^\circ$, $D = 4^\circ$) responses to disparity step stimuli for one subject. The response amplitude and peak velocity are clearly different between convergence and divergence at a given stimulus size. 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.

-6° , 12° , and 0° of additional noncongruent disparity. After 5 min of dark adaptation, accommodation was measured continuously for 15 s by a commercially available photorefractor (PowerRefractor, Multichannel Systems, Reutlingen, Germany) at 25 Hz, while the individual monocularly fixating a $0.2\text{ c}/^\circ$ 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 (Schor & Kotulak, 1986). The average accommodative state of the last 3 s of monocular fixation defined the initial SA innervation. The same procedures as in Methods were then completed. Immediately after, SA was re-measured using the same protocol as aforementioned. Pre- and postmeasures of SA were subtracted and the difference compared across disparity adapting conditions. Absence of a change in pre- versus postmeasures between stimuli amplitudes would suggest these various cue-conflict stimuli have little to no effect on tonic accommodation.

Motor response classification (PV trials)

Pilot data of the PV trials revealed three general types of motor responses to the symmetric step stimuli; pure

vergence, saccades, and saccade vergence (Figure 4). This is not unexpected, as saccades often occur in conjunction with vergence and may facilitate the overall vergence response (Alvarez & Kim, 2013; Enright, 1992; Erkelens, Steinman, & Collewijn, 1989; Zee, Fitzgibbon, & Optican, 1992). “Pure vergence” responses were defined by the absence of a visible conjugate movement (Figure 4A). 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 400 ms of the response initiation (Figure 4B). The conjugate components were easily identified visually and were generally smaller than 1° to 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 4C). These responses were not analyzed, along with responses in which a blink occurred within ± 300 ms 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.

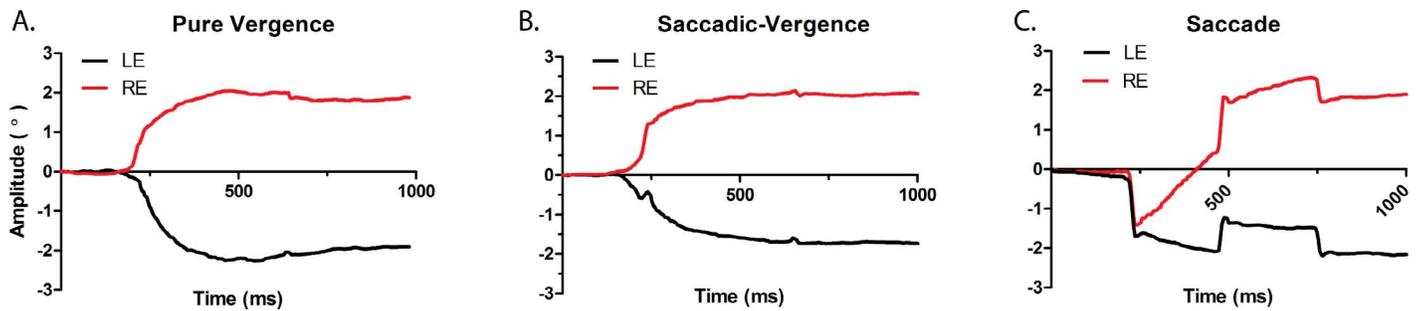


Figure 4. Examples of motor response type during the PV trials. (A) “Pure vergence” response, containing no significant conjugate components. (B) “Saccadic vergence” response, initiated by a vergence movement and containing a small ($<1.0^\circ$) but significant conjugate (saccadic) component within 300 ms of the response initiation. (C) “Saccade” response, whereby the initial motor response is dominated by a large ($>1.0^\circ$) conjugate component.

Data analysis

Eye position was recorded in screen pixel coordinates and analyzed offline in MatLab (MathWorks, Natick, MA) 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 participant’s 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 $2^\circ/s$ velocity threshold criterion, following the same analysis and smoothing criteria as previously published (Maxwell, Tong, & Schor, 2010). The amplitude, duration, peak velocity and latency of this step vergence change defined the PV response (Figure 3). Main sequence plots for PV were regressed based on the disparity stimulus direction (Figure 5).

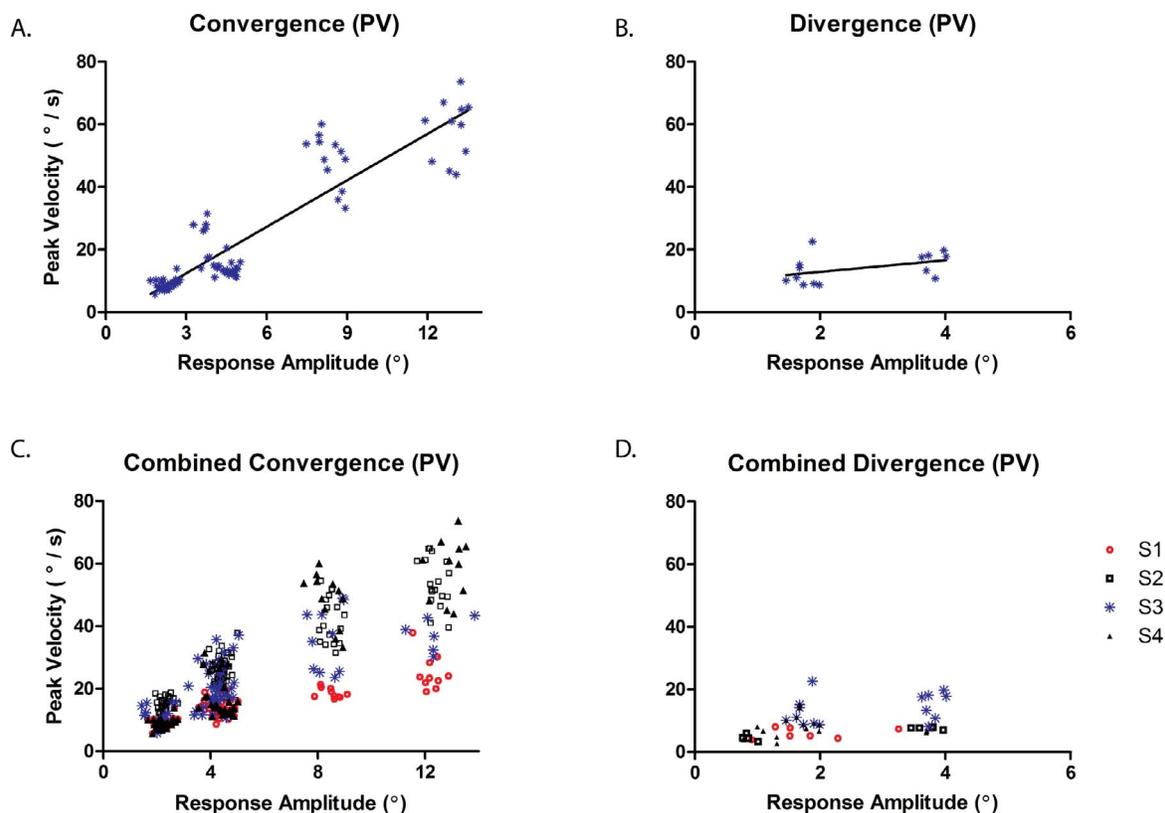


Figure 5. PV main sequence plots to convergence (A & C) and divergence (B & D) disparity for one subject (A & B) and all subjects combined (C & D). The linearity of the main sequence relationship in convergence is apparent, although not in divergence.

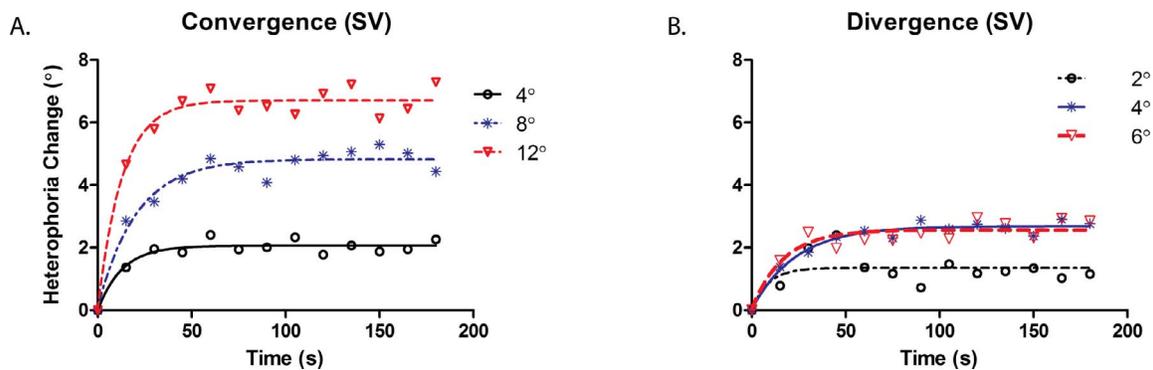


Figure 6. Plot of heterophoria measures for six SV trials of different disparity stimulus amplitudes (left convergence, right divergence) with exponential functions fit. The time constant, amplitude maximum velocity of heterophoria change was defined for each trial from these functions.

In the SV trials, heterophoria was defined as the average vergence angle of the last 3 s of the RE stimulus off periods (Erkelens et al., 2016; Han et al., 2010). 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 then used to calculate the maximum velocity (V_{max}) of SV by dividing span ($^{\circ}$) by the time constant (s) from each trial (Figure 6). The V_{max} ($^{\circ}/s$) 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.

Results

General observations

Each subject was able to fuse all noncongruent 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 change was correlated to the peak velocity of the phasic response to an equal disparity step amplitude.

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 3. 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 Tables 1 and 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.

Consistent with previous findings, larger step stimuli elicited a greater frequency of vergence responses containing at least one saccade within the first 250 ms of eye movement onset (Hung et al., 1997). At least five pure vergence responses were elicited from each convergence step stimuli amplitude, whereas there were no pure vergence responses generated to the 6° divergence stimuli by any subject. A repeated-measures ANOVA compared the frequency of each movement

Stimulus	Direction	Response amplitude ($^{\circ}$)	Peak velocity ($^{\circ}/s$)	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 1. Summary of averaged (SD) PV characteristics taken from pure vergence response data across all subjects. Although the reported phasic divergence response amplitude appears to fall short of the stimulus demand, this is based on the velocity threshold of $2^{\circ}/s$ 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 3A–D. Welch's unpaired t test p values are noted for the comparison of convergence versus divergence for each parameter.

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)
	<i>p</i> 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)
	<i>p</i> value	<0.001	<0.001	1.0	1.0

Table 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.

type and the effects of stimulus direction and amplitude for the two overlapping disparity stimuli amplitudes (Table 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, whereas 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.

Main sequence plots (Figure 5) and regression summaries (Table 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 (Hung et al., 1997; Lee, Granger-Donetti, Chang, & Alvarez, 2009). The two subjects that had previous experience with eye movement studies demonstrated the steepest slopes, as is also consistent with previous literature (Hung et al., 1997). No linear relationship was observed between response amplitude and peak velocity in phasic divergence main sequence regres-

sions, for any subject ($p > 0.09$, Table 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 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 4 outlines the average exponential functions fit to each SV trial. Figure 6 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 (*V*_{max}) for each stimulus direction separately. There was no main effect of subject or interaction effects in these analyses ($p > 0.05$). 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 heterophorias. A main effect was also found for convergence amplitude on *V*_{max}: $F(2, 4) = 29.3, p = 0.004$, 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 *V*_{max}: $F(2, 4) = 0.19, p = 0.83$, and time constants, $F(2,$

Subject	Convergence		Divergence		Slope comparison (<i>H</i> ₀ = no difference)
	Regression slope	<i>p</i> value (<i>H</i> ₀ = 0)	Regression slope	<i>p</i> value (<i>H</i> ₀ = 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 3. Main sequence bivariate regression slopes for each subject’s PV responses. Regression functions were tested against the null hypothesis of zero slope and then within subject, between stimulus directions (final column).

Stimulus	Convergence			Divergence		
	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 4. The average (SD) span, time constant (tau) and R² for the exponential curves fit to each SV trial as shown in Figure 6. The absolute values of the measured heterophoria were used to create the exponential functions.

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.

A Welch's t test comparison of the group average Vmax (mean difference: $0.077 \pm 0.1^\circ/\text{s}$, $p = 0.75$), amplitude (mean difference: $0.65 \pm 0.33^\circ$, $p = 0.11$), and time constants (mean difference 15.7 ± 13.3 s, $p = 0.24$) 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 7) and regression functions (Table 4) were analyzed. Although 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 3). This result highlights the different motor response properties of the SV mechanism to prolonged convergent and divergent disparities.

PV and SV relationship

Figure 8 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 (Tables 3 and 5).

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), $p = 0.01$,

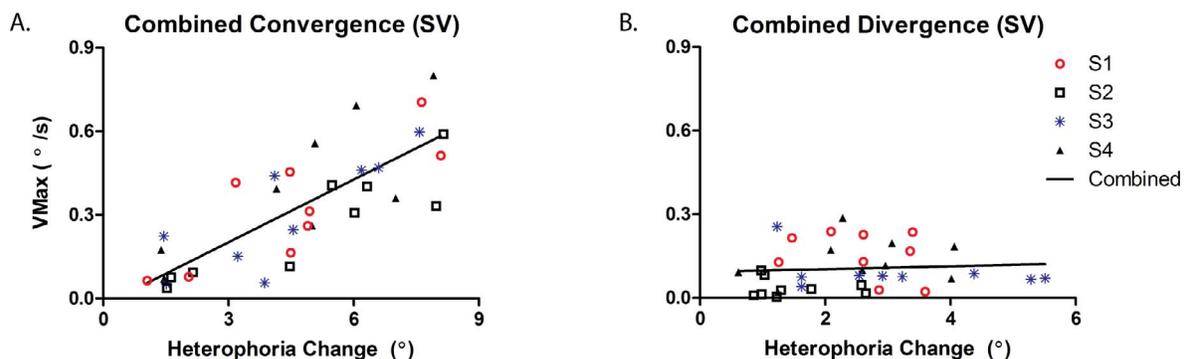


Figure 7. SV main sequence plots and regressions of the combined data from all trials in all subjects. Heterophoria change and Vmax represent the amplitude and rate of SV change. Linear main sequence effects are seen to convergent (A) stimuli in each subject, while no relationship was found in the main sequence regressions to divergent (B) disparity stimuli.

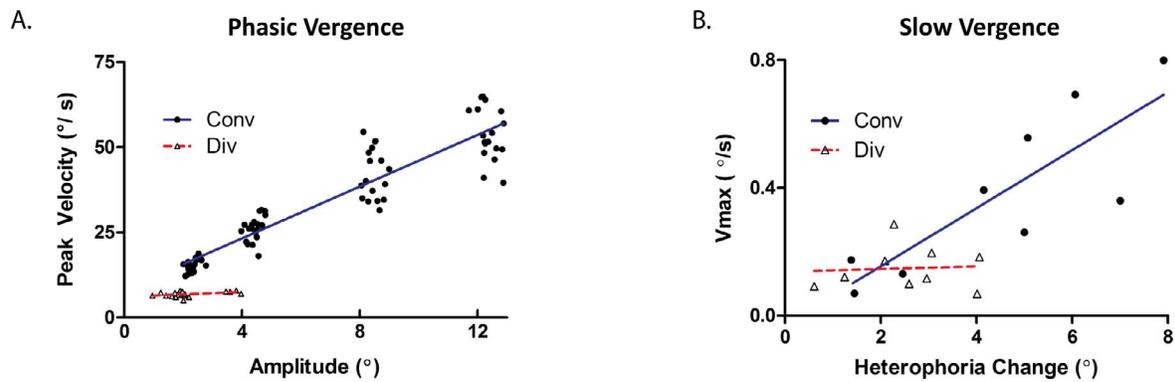


Figure 8. Main sequence plots and regressions for both PV (A) and SV (B) to both convergent and divergent disparities. All subjects demonstrated linear main sequence effects to convergent disparity stimuli in PV and SV responses, whereas no such relationship was noted in PV or SV to divergent disparities.

whereas 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 (Fisher, 1921) indicated these correlations may be 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 already mentioned, as statistically they appear similar. This Pearson 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.

Slow-tonic accommodation and 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) 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, (mean \pm SEM; $0^\circ = 0.06 \pm 0.13$ D, $p = 0.65$; 6° divergence = -0.05 ± 0.18 D, $p = 0.78$; 12° convergence = 0.08 ± 0.11 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 (Thiagarajan et al., 2010). 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 noncongruent conditions.

Subject	Convergence		Divergence		Slope comparison ($H_0 = \text{no difference}$)
	Regression slope	p value ($H_0 = 0$)	Regression slope	p value ($H_0 = 0$)	
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 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 compared between stimulus directions for each subject (null hypothesis, slopes were equal).

Discussion

Directional asymmetries and relationship between PV and SV

Clear directional asymmetries were present in disparity-driven vergence responses. The positive slope in the 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 (Mays, Porter, Gamlin, & Tello, 1986). 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 each 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 (Alvarez et al., 2005; Hung et al., 1997) was defining convergence and divergence with respect to a cue-congruent accommodative, vergence, and proximal starting position. We felt this to be important since SV has been shown to influence PV response dynamics (Kim & Alvarez, 2012; Lee et al., 2009; Satgunam et al., 2009). 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 3). 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 (Alvarez et al., 2005; Hung et al., 1997; Patel, Ögmen, White, & Jiang, 1997; Tyler et al., 2012; Vaegan & Pye, 1979). 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 1A; Maxwell et al., 2010; Schor, 1992). Our results provide novel evidence for this PV-SV 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.

Stimulus cue-congruency

There is greater variance in the phasic divergence response and main sequence regression data between studies and subjects when compared with phasic convergence (Chen, Lee, Semmlow, & Alvarez, 2010). 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 (Alvarez et al., 2005; Hung et al., 1997). The results of the present study have demonstrated that, under these specific conditions, there is negligible 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 noncongruent starting demands were used. This was especially the case when larger divergence responses were required (Alvarez et al., 2005; Hung et al., 1997). 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 noncongruent (more convergence required than accommodation). Our results indicate that large (>4°) 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 noncongruent starting stimulus as “convergence relaxation” (Westheimer & Mitchell, 1956). 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 (Alvarez et al., 2005; Hung et al., 1997; Scheiman et al., 2017).

Saccadic interactions

The recruitment of small saccades is significantly greater in divergence responses compared to convergence in our data (Table 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 versus saccadic vergence responses. Phasic vergence peak velocities were not different between pure convergence (2° : $11.06 \pm 2.3^\circ/\text{s}$, 4° : $23.57 \pm 3.08^\circ/\text{s}$), and saccadic convergence responses (2° : $10.38 \pm 1.4^\circ/\text{s}$, 4° : $23.70 \pm 2.95^\circ/\text{s}$); (mean difference at 2° stimulus: $0.68^\circ/\text{s}$, $p = 0.63$; and at 4° : $0.13^\circ/\text{s}$, $p = 0.86$). Whereas saccadic divergence peak velocities (2° : $9.31 \pm 1.5^\circ/\text{s}$, 4° : $11.06 \pm 2.3^\circ/\text{s}$) were significantly higher than in pure divergence (2° , $p = 0.021$; 4° , $p = 0.023$); (mean difference at 2° stimulus: $2.83^\circ/\text{s}$, $p = 0.03$; and at 4° : $3.62^\circ/\text{s}$, $p = 0.02$). 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 (Kenyon et al., 1978). 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 (Alvarez & Kim, 2013). 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 (Alvarez et al., 2010; Alvarez & Kim, 2013; Daftari, Alvarez, Chua, Demarco, & Ciufieda, 2003; Semmlow, Chen, Pedrono, & Alvarez, 2008). This group also identified a strong inverse relationship between the frequency of saccadic vergence interactions in the presbyopic patient’s ability to adapt to multifocal progressive lenses, as well as the peak velocity of the pulse component of the PV mechanism (Alvarez et al., 2009; Tsang, Kim, Granger-Donetti, Semmlow, & Alvarez, 2010). Consistent with these studies, 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 in our data. 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 and the nonadapting presbyopes studied by Alvarez. If divergence is limited by the size of its dedicated neuronal substrate in our sample population, as we speculate as follows, 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 (Sreenivasan & Bobier, 2014; Thiagarajan et al., 2010). 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.

Neural recruitment and model predictions

Linear main sequence effects in saccades and phasic convergence responses reflect increased neural recruitment in the premotor and motor areas (Bahill et al., 1975; Gamlin & Mays, 1992; Patel et al., 1997). 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 identi-

fied 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 with the number of convergence neurons in similar areas, the populations of divergence neurons are less (Mays et al., 1986; Mays & Gamlin, 1995; Nitta et al., 2008), with the exception of the posterior interposed nucleus (Zhang & Gamlin, 1998). The anatomical vergence resting position is parallel or slightly divergent when measured under general anesthesia (Toates, 1974). Tonic vergence, measured in absolute darkness, is slightly convergent (Fisher, Ciuffreda, Tannen, & Super, 1988; Owens & Tyrrell, 1992; Rosenfield, 1997; Toates, 1974). If the orbital mechanics naturally drive the vergence position toward 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 study's 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.

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 noncongruent 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.

Keywords: oculomotor, disparity vergence, convergence, direction asymmetry, adaptation

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