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Directional Asymmetry During Combined Saccade–Vergence Movements

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Kumar, Arun N., Yanning Han, Louis F. Dell’Osso, Dominique M. Durand, and R. John Leigh. Directional asymmetry during combined saccade–vergence movements. *J Neurophysiol* 93: 2797–2808, 2005. First published December 29, 2004; doi:10.1152/jn.00858.2004. We investigated relationships between saccadic and vergence components of gaze shifts as 10 human subjects switched visual fixation between targets aligned in the midsagittal plane that lay in different vertical directions and at different distances. When fixation was shifted between a higher distant target and a lower near target, peak convergence velocity followed peak vertical saccadic velocity by a median interval of 12 ms. However, when fixation was shifted between a lower distant target and a higher near target, peak convergence velocity followed peak vertical saccadic velocity by a median interval of 76 ms. For the 2 stimulus arrangements, the median intervals by which peak divergence velocity followed the peak vertical saccadic velocity were 4 and 20 ms, respectively. The dissociation interval between the peak velocities of convergence and upward saccades increased with vertical saccade size, required convergence angle, and elevation of the endpoint of the movement. Velocity waveforms of vergence responses were more skewed when peak velocity was closely associated with saccadic peak velocity than when the vergence responses were delayed. Convergence peak velocities did not vary in any consistent pattern, but divergence peak velocities were generally smaller with responses that were delayed. Vergence movements were accompanied by small, high-frequency conjugate oscillations, suggesting that omnipause neurons were inhibited for both types of responses. In conclusion, the present findings indicate that the dynamic properties of horizontal vergence movements depend on the direction and timing of vertical saccades; these findings suggest experimental tests for current models of saccade–vergence interaction.

INTRODUCTION

Binocular, single vision requires that the foveal region of each eye, which contains the highest photoreceptor density, be pointed at the object of interest (Carpenter 1991). Under natural conditions, we frequently move our point of visual fixation between objects that lie in different directions and at different distances in the environment. The ability to voluntarily change the line of sight (gaze angle) of each eye from one object to another is achieved by 2 distinct types of eye movements: saccades and vergence (for reviews, see Carpenter 1988; Leigh and Zee 1999; Mays 2003).

Saccades are rapid movements that carry the eyes in the same direction (conjugate or versional movements). The premotor signals for saccades are generated by medium-lead burst neurons in the reticular formation (Sparks 2002; van Gisbergen et al. 1981) that project monosynaptically to ocular motoneurons. Premotor burst neurons for horizontal saccades lie in the

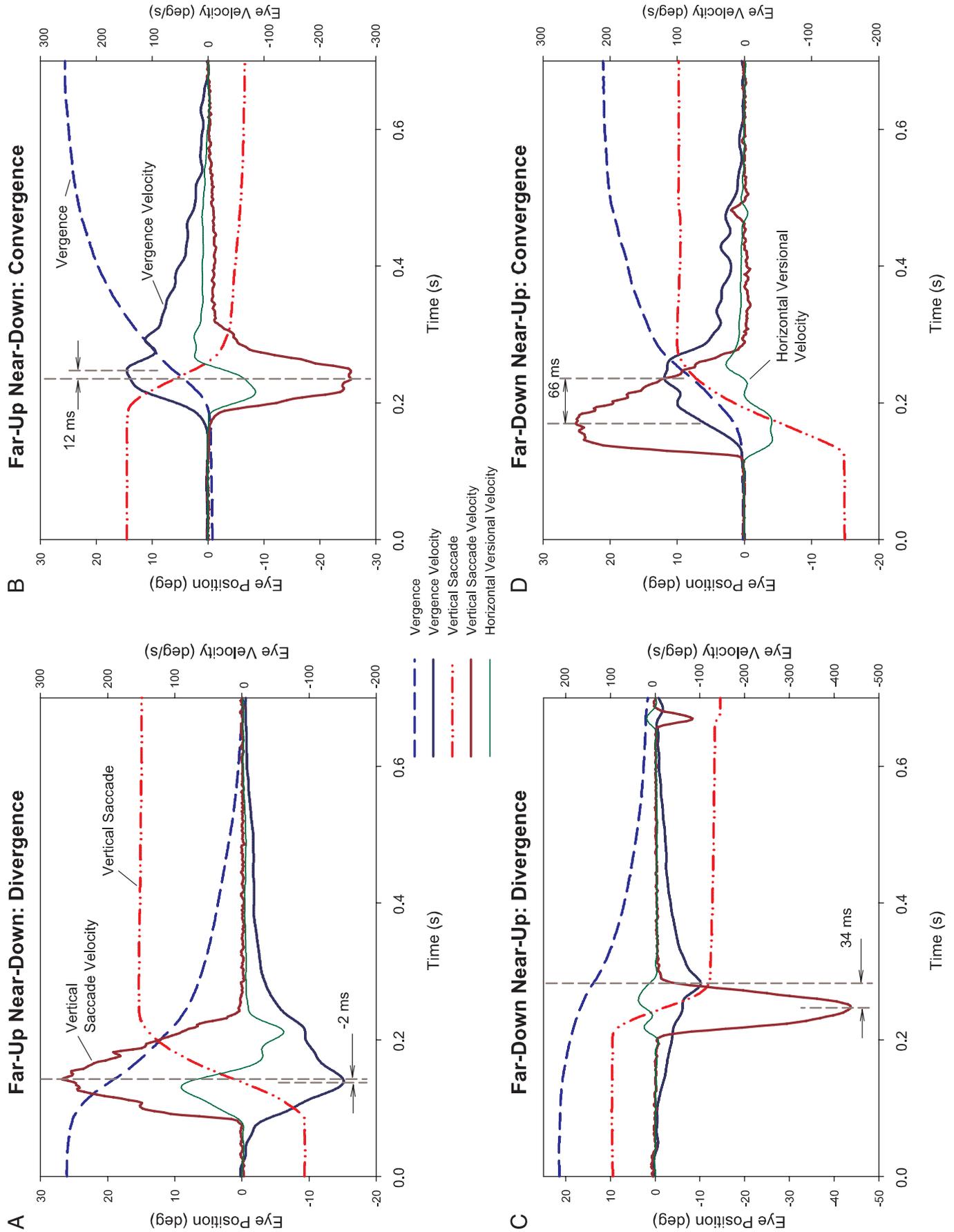
paramedian pontine reticular formation (PPRF) (Horn et al. 1997). Premotor burst neurons for vertical saccades lie in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the midbrain (Horn and Büttner-Ennever 1998). The activity of both sets of burst neurons is gated by omnipause neurons, which lie in the pontine nucleus raphe interpositus (Horn et al. 1994), and are tonically active except during saccades (Yoshida et al. 1999).

Voluntary shifts of the line of sight between objects lying at different depths in the environment require vergence movements, during which the eyes rotate in opposite directions (disjunctive rotations). Electrophysiological evidence indicates that the premotor signals for vergence shifts between 2 targets lying at different depths are generated by midbrain “vergence burst neurons” (Mays 1984; Mays and Gamlin 1995; Mays et al. 1986); these cells receive weak inhibition from the omnipause neurons during the movement.

Most natural shifts of the fixation point are made between objects lying at different gaze angles and in different depth planes in the visual environment, requiring both saccadic and vergence components. Saccades are brief (often <100 ms), ballistic movements, whereas vergence movements may last as long as 500 ms in humans. Thus during combined saccade–vergence movements, the vergence component often outlasts the saccade and, during this period, small (about 0.2°), high-frequency (10–35 Hz) conjugate oscillations occur (Ramat et al. 1999; Zee et al. 1992). It is postulated that these oscillations are saccadic in origin because, in humans, the high-gain properties of the saccadic system make it potentially unstable, and saccadic oscillations have been frequently reported in health and disease (Leigh and Zee 1999; Ramat et al. 1999, 2004; Zee et al. 1992). Thus similar high-frequency oscillations occur, for example, with blinks (Hain et al. 1986) and some normal subjects can induce them voluntarily with a convergence effort (Yee et al. 1994). Although electrophysiological evidence from macaque suggests that some omnipause neurons are modulated during convergence (Busetini and Mays 2003), it is difficult to extrapolate from monkey to human because the former species does not show the propensity for the saccadic system to oscillate that humans do. Nonetheless, in humans, it is proposed that these small-amplitude, high-frequency conjugate oscillations can be used as a behavioral marker that omnipause neurons are inhibited, although not necessarily silent, during combined saccade–vergence movements (Ramat et al. 2004; Zee et al. 1992).

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For most combined saccade-vergence movements, the peak velocities of saccadic and vergence components occur at almost the same time (Zee et al. 1992). Saccades made in combination with vergence are slowed down (compared with conjugate movements), whereas vergence movements are accelerated if they are made with a saccade (Collewijn et al. 1995; Zee et al. 1992). This codependency of the dynamic properties of saccades and vergence is preserved even if a vertical saccade is made with a horizontal vergence movement (Enright 1984). Because vergence movements are horizontal but the saccade is vertical, it seems unlikely that an interaction of vergence and saccadic commands in the ocular motor plant could account for the acceleration of vergence. More likely, a central interaction between saccadic and vergence systems is responsible. Such findings have led to the development of models for saccade-vergence interactions in which pulse generators for the saccadic and vergence components are coupled. Thus in a "saccade-related vergence burst neuron" (SVBN) model described by Zee and colleagues (1992), vergence movements are accelerated when combined with a saccade because the discharge of the omnipause neurons is silenced, removing inhibition from both vergence and saccadic burst neurons.

The present study was motivated by the serendipitous finding that when subjects shift gaze between a lower distant target and a higher near target (Far-Down Near-Up), peak vergence velocity is delayed compared with peak saccadic velocity; this delay is more pronounced for convergence than for divergence (Kumar et al. 2003). Our goals were to study this phenomenon and characterize how the vergence velocity waveforms during such dissociated saccade-vergence responses differ from the waveforms when the 2 components occur in close temporal succession.

The work reported in this paper constitutes research performed by A. N. Kumar as part of the Doctoral Dissertation requirements.

METHODS

Subjects

We studied 10 healthy human subjects (8 male, 2 female) whose ages ranged from 25 to 57 yr. Six subjects were naïve as to the purpose of the experiments, and all gave informed, written consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center.

Measurement of eye movements

We measured horizontal and vertical movements of each eye using the magnetic search-coil technique, with 6-ft. field coils that used a rotating magnetic field in the horizontal plane and an alternating magnetic field in the vertical plane (CNC Engineering, Seattle, WA). The SD of system noise was $<0.02^\circ$ and cross talk between horizontal and vertical channels was $<2.5\%$. Search coils were calibrated using a protractor device before each experimental session. The curve relating coil rotation on a protractor to the signal measured from the system over a range of $\pm 20^\circ$ was within 98.5% of a straight line.

During all experiments, subjects sat in a vestibular chair, with their heads braced against a headrest; head stability was monitored using a search coil attached to their foreheads.

Visual stimuli

Two visual targets were presented: 1) a red laser spot projected onto a tangent screen at a viewing distance of 1.2 m (the "far target"); 2) a green light-emitting diode (LED) that was positioned at a distance of 10 or 20 cm (the "near target"). Both near and far targets were positioned on the midsagittal axes of subjects' heads, unless specified otherwise. The location of the far target on the tangent screen was determined by X-Y mirror galvanometers, under computer control. The location of the near target was determined by a flexible arm that was attached to the headrest of the chair.

Experimental paradigms

Paradigms were of 2 main groups: (A) with the far target located lower than the near target: Far-Down Near-Up (FDNU); and (B) with the far target located higher than the near target: Far-Up Near-Down (FUND). We analyzed responses to these stimuli and systematically studied the effects of the following factors: 1) target distance and direction; 2) visually guided versus self-paced responses; 3) target alignment on one eye versus the subject's midline; 4) binocular versus monocular viewing.

(A) FAR-DOWN NEAR-UP (FDNU) 1. *Self-paced shifts—Midline.* Subjects were asked to make self-paced shifts between the far and near targets, which were both continuously illuminated. The direction of the near target was at 0° , up 10° , and up 20° . The far target was located 10, 20, and 25° below the near target.

2. *Visually guided shifts—Midline.* Subjects switched fixation between the far and near targets, which were illuminated alternately, the timing of target appearance being randomized in the range 1.75–2.75 s. The direction of the near target was at 0° , and the far target was located 10° and 20° below the near target.

3. *Self-paced shifts—Dominant eye aligned, binocular viewing.* In this set of trials, the far and near targets were both aligned on the subject's dominant eye (determined by a simple "sighting" procedure). The subject viewed the targets with both eyes. The placement of targets was similar to Paradigm 2.

4. *Self-paced shifts—Dominant eye aligned, nondominant eye occluded.* This set of trials was similar to Paradigm 3, except that the subject viewed the targets with the nondominant eye occluded.

(B) FAR-UP NEAR-DOWN (FUND) 5. *Self-paced shifts—Midline.* Subjects were asked to make self-paced shifts between the far and near targets, which were both continuously illuminated. The direction of the near target was at 0° , down 10° , and down 20° . The far target was located 10, 20, and 25° above the near target.

6. *Visually guided shifts—Midline.* Subjects switched fixation between the far and near targets, which were illuminated alternately, the timing of target appearance being randomized in the range 1.75–2.75 s. The direction of the near target was at 0° , and the far target was located 10 and 20° above the near target.

The complete protocol (Paradigms 1–6) was tested on 4 subjects to systematically study the effects of the various factors, with near targets located at 10 and 20 cm. We then tested 6 more subjects using Paradigms 1 and 5 for one of the following arrangements of targets: with the near target located 10 cm away at an elevation (or depression) of 20° and the far target located 20° below (or above) the near target. We also measured responses with the near target located at 7.5 cm in 2 subjects who were able to focus on it at this distance.

FIG. 1. Representative records from one subject of self-paced convergence and divergence movements made in concert with vertical saccades for the Far-Up Near-Down (FUND) and Far-Down Near-Up (FDNU) paradigms. Dashed gray vertical lines indicate timing of peak vertical eye velocity and peak vergence velocity; dissociation periods are specified. Note that high-frequency conjugate oscillations occurred during both FDNU and FUND responses.

Data analysis

To avoid aliasing, coil signals were passed through Krohn-Hite Butterworth filters (bandwidth, 0–150 Hz) before digitization at 500 Hz with 16-bit resolution. Version (conjugate position) was calculated from (right eye horizontal gaze + left eye horizontal gaze)/2. The vergence angle was obtained by subtracting the right horizontal gaze from the left horizontal gaze. Thus positive values indicate convergence and negative values indicate divergence. The vergence and the vertical eye position signals were differentiated (Ramat et al. 1999) to yield vergence velocity and vertical eye velocity signals, respectively, with noise typically $<0.5^\circ/\text{s}$. With this differentiator, and a digitization frequency of 500 Hz, the bandwidth for the first derivative was 0–170 Hz and for the second derivative was 0–148 Hz.

All responses studied constituted combined saccade–vergence movements. The onset of the vergence (or saccadic) movement was defined as the time when vergence (or saccade) speed exceeded $10^\circ/\text{s}$, and the end as the time at which the speed dropped below $10^\circ/\text{s}$. All responses were analyzed interactively using programs written in MATLAB (The MathWorks, Natick, MA). The following were noted for each response: the peak vergence velocity, the peak vertical saccade velocity, the times of peak vergence and vertical saccade velocities, the duration and size of the vergence movement, and the duration and size of the vertical saccade. Transient, small-divergence movements preceded most convergence responses in Paradigms 1–4; the peak velocity of this transient divergence was also recorded. For visually guided shifts (Paradigms 2 and 6), latency of the vertical saccade (defined as the time interval between the target jump and saccade) and latency of the vergence movement (time interval between target jump and vergence) were also noted. In analyzing the vergence velocity waveforms, we found that the skewness of responses varied according to the stimulus (see RESULTS). We defined skewness as the ratio D_{acc}/D , where D_{acc} is the duration from onset of vergence movement to peak velocity and D is the total duration of the vergence movement (van Opstal and van Gisbergen 1987).

RESULTS

First, we summarize the general features of responses to the stimuli that we used. Second, we show how different stimulus conditions affected the temporal dissociation of peak velocities of saccadic and vergence components for the FDNU paradigm. Third, we summarize how the dynamic features of the conver-

gence response were affected when it was dissociated from the saccadic component. Finally, we compare these results with those obtained during control experiments. It should be noted, throughout the paper, that temporal relationships of the saccadic and vergence components are based on the timing of respective peak velocity values and do not refer to time delays in pathways hypothesized to be generating these gaze shifts.

General features of saccade–vergence responses

Figure 1 shows representative responses from one subject who switched fixation between near and far targets that were positioned with either the far target higher (FUND: *A* and *B*) or the near target higher (FDNU: *C* and *D*). With the FUND paradigm, the peak velocities of the saccade and vergence components were similarly timed for both convergence and divergence movements (temporal dissociation was <15 ms). With the FDNU paradigm, peak velocity of the divergence response followed peak saccadic velocity by 34 ms (*C*) and the peak velocity of the convergence response followed peak saccadic velocity by 66 ms (*D*). This was a robust phenomenon: all 10 of our subjects showed temporal dissociation of peak velocities of vergence and saccadic components similar to Fig. 1, *C* and *D* when the near target was higher, but in the other 2 cases (corresponding to Fig. 1, *A* and *B*), peak velocities of vergence components occurred soon after peak saccadic velocity. Note that high-frequency conjugate oscillations occurred during both FDNU and FUND responses.

Delay of the peak velocity of the vergence component after the peak velocity of the saccadic component, with specified positions of the near and far targets, is summarized for the group of 10 subjects in Fig. 2. For convergence responses, median delay was 12 ms for the FUND paradigm and 76 ms for the FDNU paradigm; this delay interval was significantly different (Mann–Whitney rank-sum test, $N_1 = 186$, $N_2 = 135$, $P < 0.001$). For divergence responses, median delay was 4 ms for the FUND paradigm and 20 ms for the FDNU paradigm; although there was substantial overlap of data (Fig. 2), this delay interval was significantly different (Mann–Whitney rank-

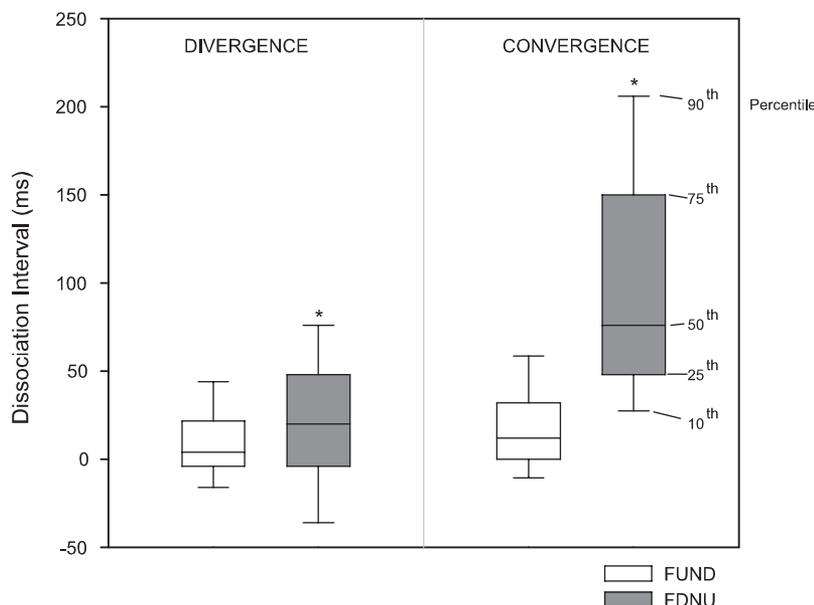


FIG. 2. Comparison of the dissociation interval between the peak velocity of vertical saccades and the peak velocity of vergence movements made during self-paced shifts for the 2 test paradigms, with the near target located at 10 cm from the subjects. For the FDNU paradigm, the near target was placed at an elevation of 10° and the far target was projected 25° below the near target. For the FUND paradigm, the near target was placed at a depression of 10° and the far target was projected 25° above the near target. Asterisks indicate that dissociation interval is significantly greater for the FDNU paradigm for both convergence and divergence movements ($P < 0.001$, Mann–Whitney rank-sum test). Boxes show 10th, 25th, 50th (median), 75th, and 90th percentiles.

sum test, $N_1 = 168$, $N_2 = 139$, $P < 0.005$). Because the dissociation between the peak velocities of vergence and saccadic components was much more pronounced for convergence than divergence components, our analysis is mainly focused on saccade-convergence movements.

Factors influencing temporal dissociation of saccadic and convergence components

Figure 3, A–C shows representative saccade-convergence movements from the FDNU paradigm from one subject, illustrating how the range of temporal dissociation between the 2 components was influenced by change in vergence angle. This dissociation, measured as the interval between the peak velocity of the saccadic and convergence components, ranged between 124 and 320 ms. Note how vertical saccades were of similar size in the 3 records, but temporal dissociation of saccadic and convergence peak velocities increased as the final convergence angle increased. Figure 3, D–F shows an increase

of the dissociation interval with increase in size of the saccade, even though convergence size was kept constant.

Consistent with prior studies (e.g., Sylvestre et al. 2002), we noted how conjugate upward saccades are associated, in many normal subjects, with a transient divergence movement. We sought to determine whether this transient divergence could be the explanation for the delayed occurrence of convergence when combined with an upward saccade. The transient divergence is identified by an asterisk in the responses of Fig. 3; it is evident that they are small and stereotyped, and invariant with respect to the convergence response that follows. We addressed this issue quantitatively in 2 subjects, by attempting to correlate the peak velocity of the initial divergence movement and the dissociation interval between peak saccadic and peak convergence velocity; we found no significant correlations.

Figure 4A summarizes the influence of vertical saccade size, end position of vertical saccades, and required convergence

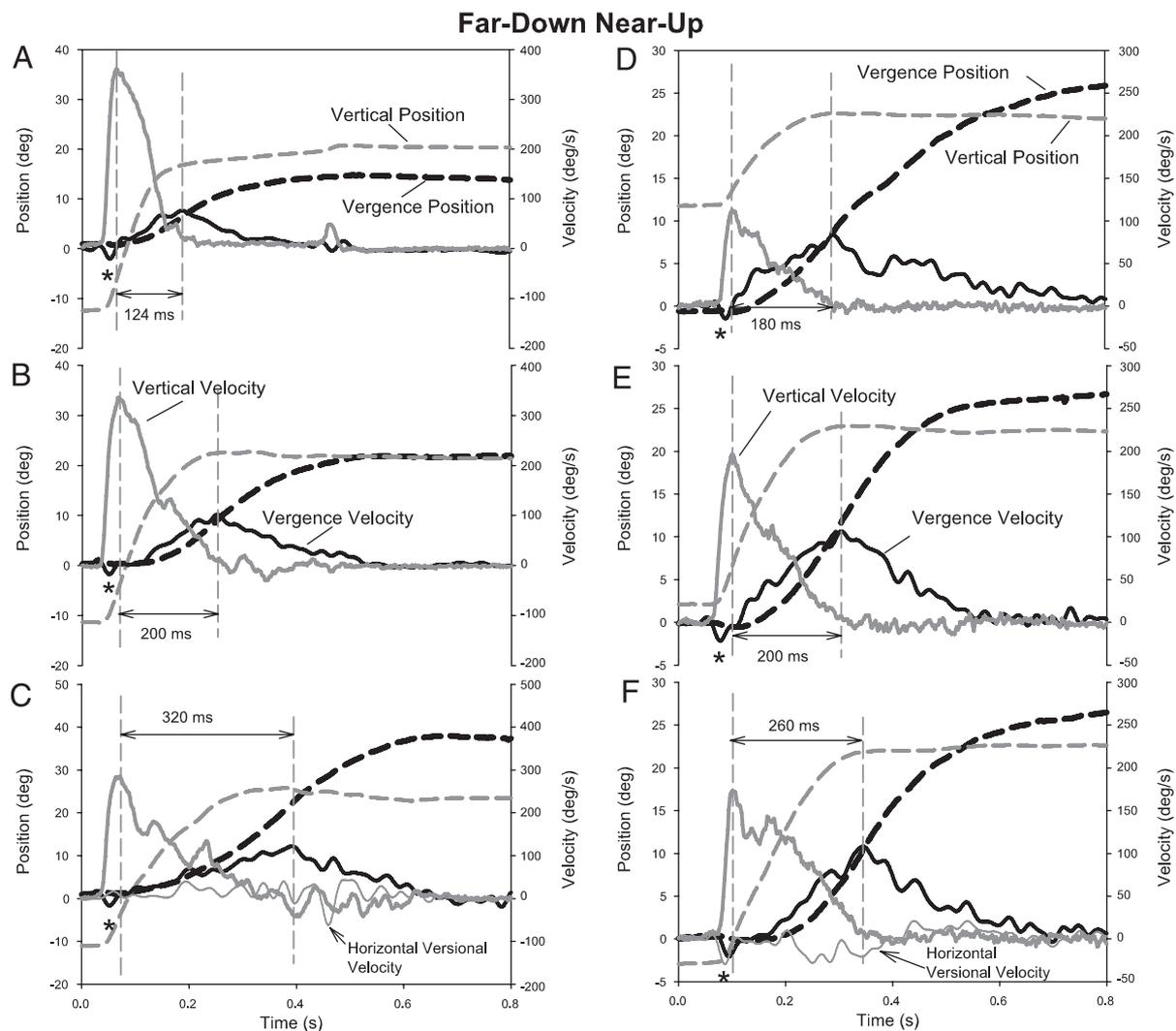


FIG. 3. A–C: responses of one subject showing the range of dissociation of vertical saccadic and convergence responses as he made self-paced shifts of fixation during the FDNU paradigm, with a constant vertical separation of the targets. Note that the temporal dissociation increased to 320 ms as required vergence angle increased. D–F: responses from the same subject showing increase of temporal dissociation when the convergence angle was kept constant and the vertical saccade size was increased. Dashed vertical lines indicate timing of peak vertical eye velocity and peak convergence velocity. Asterisk indicates the transient divergence associated with vertical saccades (e.g., Sylvestre et al. 2002), which remains similar for all responses. Horizontal versional velocity (shown in C and F) showed high-frequency, low-amplitude oscillations throughout the response, suggesting that the omnipause neurons remain inhibited (Ramat et al. 1999).

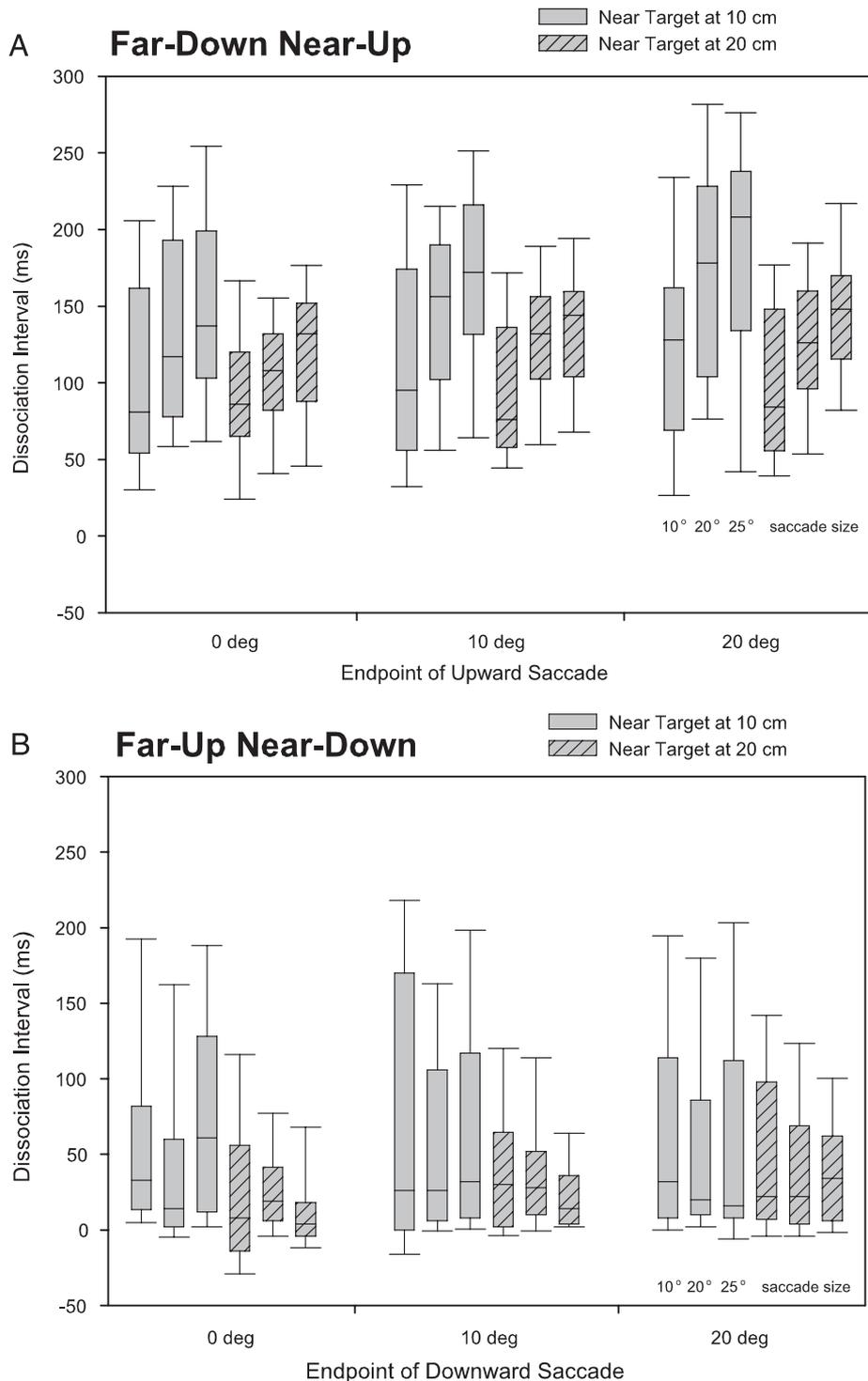


FIG. 4. Box plots showing variation of the dissociation interval between the peak velocity of vertical saccades and the peak velocity of vergence movements with changes in saccade size, convergence angle, and endpoint of the vertical saccade during self-paced shifts for the (A) FDNU and (B) FUND paradigms. All 3 factors contributed to an increase in the dissociation interval for A, whereas there was no significant effect of the 3 variables on responses in B. Percentiles are as in Fig. 3. See text for details.

angle on temporal dissociation between saccadic and convergence peak velocity (convergence amplitude) during shifts of the fixation point for the FDNU paradigm in 4 subjects. Statistical comparisons using an ANOVA model indicated that all 3 factors had significant effects on saccade–convergence dissociation: vertical saccade size ($P < 0.0005$, $F = 34.9$), convergence amplitude ($P < 0.0005$, $F = 29.8$) and to a lesser extent, the endpoint of the vertical saccades ($P < 0.003$, $F = 5.9$). Interaction terms did not have a significant effect on the dissociation interval. Figure 4B shows that none of these

experimental conditions produced significant dissociation of peak velocities of saccadic and convergence components during the FUND paradigm ($P > 0.1$).

Effect of dissociation of saccadic and convergence components on the dynamic features of the convergence response

We analyzed response from 4 subjects to determine whether the peak velocity of vergence responses differed during FUND versus

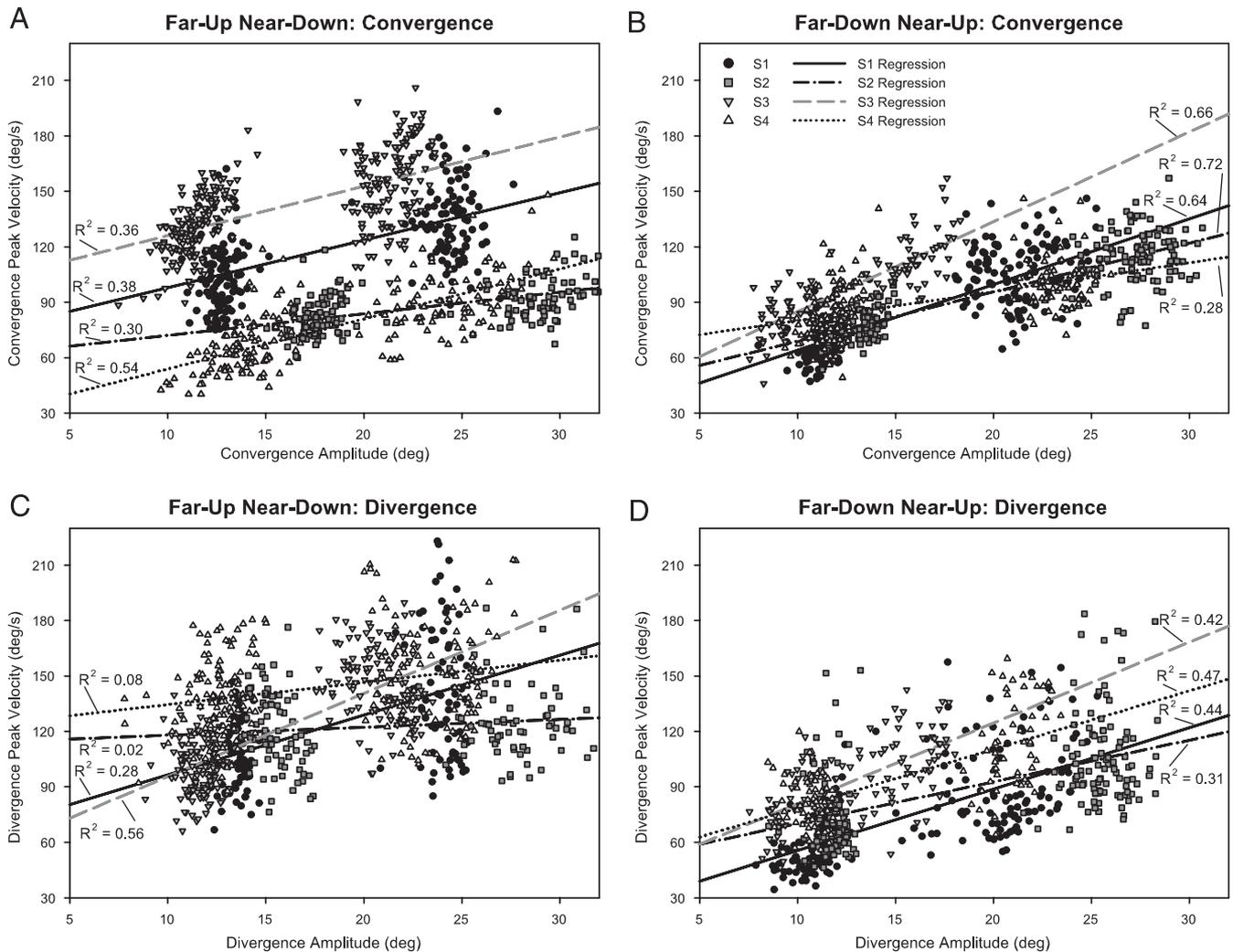


FIG. 5. Comparison of vergence peak velocities vs. vergence amplitude from 4 subjects. Vergence responses are summarized for (A, C) FUND and (B, D) FDNU paradigms when the near target was placed at a viewing distance of 10 or 20 cm. Regression coefficients (R^2 values) are specified for each subject. For convergence responses, slopes as deg/s/deg (intercepts as deg/s) of the regression lines were (A) S1: 2.57 (72.1); S2: 1.17 (60.3); S3: 2.67 (99.4); S4: 2.70 (26.8); (B) S1: 3.55 (28.6); S2: 2.65 (42.4); S3: 4.86 (36.3); S4: 1.56 (64.5). For divergence responses, slopes (intercepts) of the regression lines were (C) S1: 3.23 (64.3); S2: 0.43 (113.7); S3: 4.49 (50.6); S4: 1.20 (122.5); (D) S1: 3.32 (22.4); S2: 2.26 (47.6); S3: 4.37 (37.1); S4: 3.16 (47.0).

FDNU paradigms for similar near-target distances. Figure 5 plots vergence peak velocity versus vergence amplitude for the 2 paradigms for both convergence and divergence. The 2 clusters of data points for each subject indicate the 20-cm target (smaller vergence angle) and the 10-cm target (greater vergence angle), respectively. The different ranges of vergence amplitudes shown by each subject could be attributed to 2 factors. The first was differences in interocular distance between subjects, requiring different vergence angles. The second (and most important for Subject 3, who showed the smallest vergence amplitudes) was vergence drifts that preceded and followed the “saccadic” component (Kumar et al. 2002). Note, as described in METHODS, that we measured that component of the vergence response when velocity exceeded 10 deg/s.

For convergence responses (Fig. 5, A and B) vergence peak velocity was positively correlated with convergence amplitude in all 4 subjects for both paradigms (coefficient of regression, $R^2 > 0.28$). For divergence responses, 2 subjects showed a weak positive correlation of divergence peak velocity with amplitude for FUND (Fig. 5C), but all showed strong relation-

ships between divergence amplitude and peak velocity for FDNU (Fig. 5D). We compared peak velocity values for each subject and near target, for FUND or FDNU using a Kruskal-Wallis one-way ANOVA on ranks; results are summarized in Table 1. For convergence, subjects showed no consistent differences between the 2 paradigms. However, for divergence, subjects generally showed peak velocities that were greater during the FUND paradigm than during the FDNU paradigm.

We also compared the durations of vergence movements during FUND and FDNU paradigms (Fig. 6). Each subject showed substantial variance of data but vergence amplitude and vergence duration showed strong correlations. We compared duration values for each subject and near target, for FUND or FDNU using a Kruskal-Wallis one-way ANOVA on ranks; results are also summarized in Table 1. Subjects showed no consistent differences with respect to convergence movements between the 2 paradigms. However, divergence movements during the FDNU paradigm were generally longer than those during the FUND paradigm.

TABLE 1. Comparison of peak velocity and duration for FDNU and FUND paradigms

Variable	20-cm Convergence		10-cm Convergence		20-cm Divergence		10-cm Divergence	
	FUND	FDNU	FUND	FDNU	FUND	FDNU	FUND	FDNU
	<i>S1</i>							
PV	103	66*	132	106*	105	55*	138	82*
Dur	299	365*	437	452	290	364*	470	537*
<i>N</i>	(115)	(108)	(99)	(125)	(77)	(111)*	(72)	(103)
	<i>S2</i>							
PV	80	77	93	115*	117	69*	124	99*
Dur	399	387	585	547*	406	445*	582	658*
<i>N</i>	(91)	(83)	(87)	(103)	(82)	(80)	(70)	(102)
	<i>S3</i>							
PV	131	83*	156	111*	80	101*	145	105*
Dur	195	249*	296	300	323	391*	459	468
<i>N</i>	(144)	(50)	(133)	(55)	(43)	(133)	(121)	(65)
	<i>S4</i>							
PV	63	82*	90	99	138	80*	149	111*
Dur	401	379	551	607*	328	410*	541	582*
<i>N</i>	(105)	(128)	(90)	(70)	(122)	(78)	(120)	(58)

Values given are median (number of data points); PV, peak velocity (deg/s); Dur, duration (ms). * $P < 0.05$ by Kruskal–Wallis one-way ANOVA on ranks (see text).

Figure 7 compares vergence peak velocity versus vertical saccade peak velocity for each combined saccade–vergence movement. The figure shows pooled data from each subject for both 10- and 20-cm target distances and 3 saccade amplitudes. In Fig. 7, *A* and *B*, R^2 was < 0.10 for both paradigms, indicating that for the limited range of vergence movements that we studied, the peak velocity of the convergence component was not related to the speed of the vertical saccade. In the case of divergence movements (Fig. 7, *C* and *D*), there was a weak dependency of divergence peak velocity on the saccadic peak velocity for the FUND paradigm. For the FDNU paradigm, divergence peak velocity showed no correlation or negative correlation with saccadic peak velocity. These results show some similarities with those reported by van Leeuwen et al. (1998) for vertical saccades, but may not be comparable with studies in which vergence movements were combined with horizontal saccades (e.g., Walton and Mays 2003), when intrasaccadic vergence transients probably influence peak vergence velocity.

For each of the 4 subjects, we investigated whether there was a relation between the timing of the peak vergence velocity and the end of the saccade. However, there was no consistent pattern between the 2 events; the median time interval (quartiles) between saccade end and vergence peak velocity was 100 ms (70 to 137 ms) for Subject 1, 16 ms (–10 to 52 ms) for Subject 2, 48 ms (26 to 79 ms) for Subject 3, and –25 ms (–56 to 18 ms) for Subject 4.

Figure 8 compares the shape of the convergence velocity waveforms from one subject for the FUND paradigm (Fig. 8*A*) and for the FDNU paradigm (Fig. 8*B*). A qualitative difference is evident in the 2 convergence velocity waveforms shown: either strong positive skewing (skewing ratio 0.22 in *A*) or minimal skewing (skewing ratio 0.34 in *B*); a ratio of 0.5 indicates an unskewed response. Although the vergence veloc-

ity waveforms did show some oscillations (Fig. 8, *A* and *B*), interactive measurement of the skew ratio of $> 1,000$ individual responses revealed consistent differences according to whether response occurred during FUND or FDNU conditions. Figure 8*C* compares the skewing ratios for vergence responses using pooled data from 4 subjects. For the FDNU paradigm, convergence responses were significantly less skewed than convergence responses made for the FUND paradigm (Mann–Whitney rank-sum test, $N_1 = 356$, $N_2 = 414$, $P < 0.001$). For convergence responses, the median skew ratio was 0.27 for the FUND paradigm and 0.38 for the FDNU paradigm. For divergence responses, the median skew ratio was 0.19 for the FUND paradigm and 0.24 for the FDNU paradigm; these skew ratios were significantly different (Mann–Whitney rank-sum test, $N_1 = 169$, $N_2 = 139$, $P < 0.001$).

Results of control experiments

All of the results presented so far concern self-paced shifts of the fixation point. We compared each of the main findings—dissociation of saccadic and convergence components and effects on dynamic properties of convergence responses—with corresponding properties of visually stimulated gaze shifts. We found no systematic or significant differences between self-generated or visually stimulated responses. During self-paced shifts of the fixation point between near and far targets aligned on subjects' dominant eye, the dissociation between peak velocities of the vertical saccade and convergence movement was still present for the FDNU paradigm, even though it was the nondominant eye that generated the vergence movement. For control trials in which the subject was viewing only with the dominant eye (other eye occluded), subjects made mainly vertical saccades and a small or undetectable vergence component.

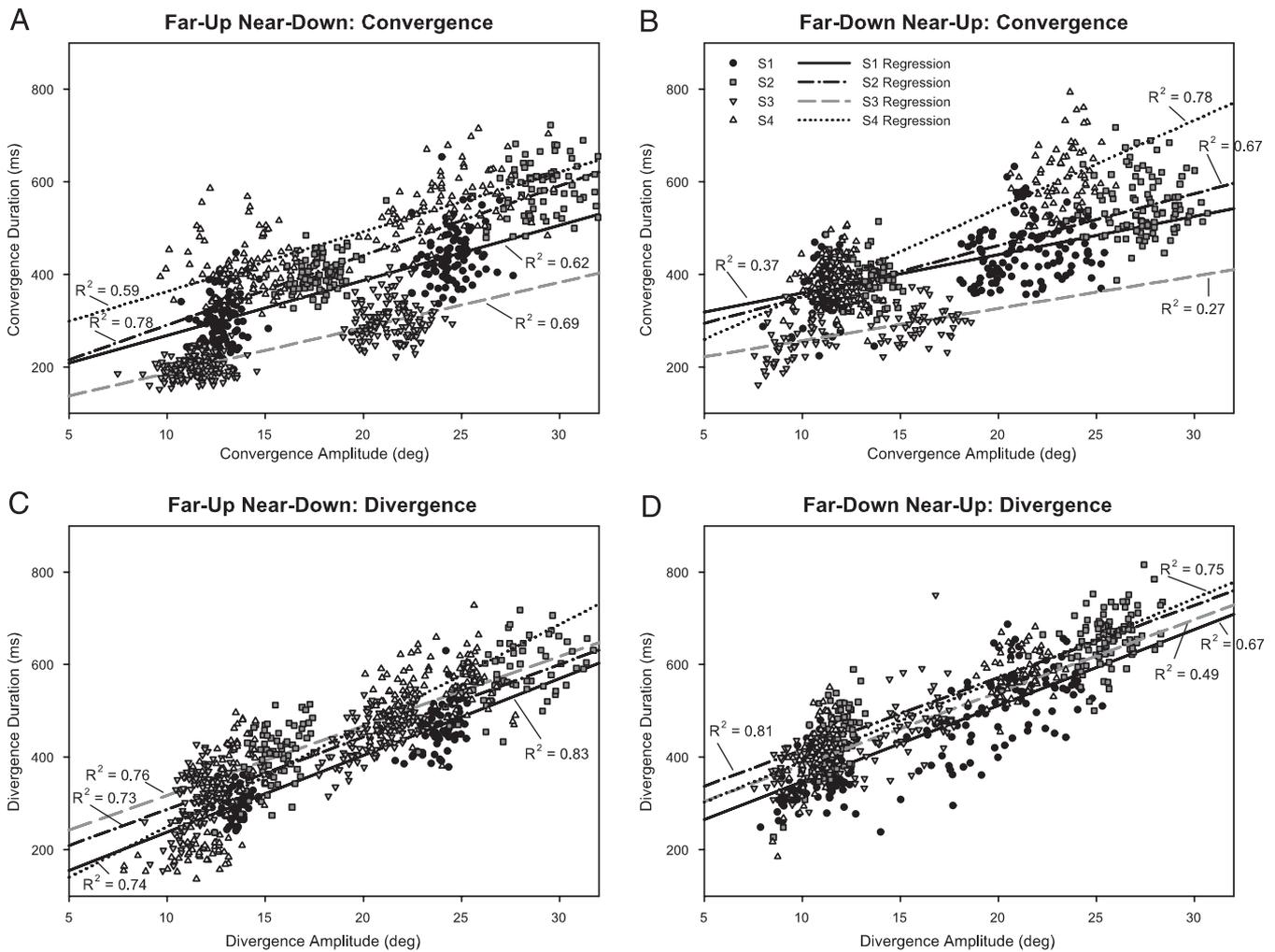


FIG. 6. Comparison of the duration of vergence components vs. vergence amplitude from 4 subjects; similar test conditions and display of data as in Fig. 5. For convergence responses, slopes as ms/deg (intercepts as ms) of the regression lines were (A) S1: 12 (149); S2: 15 (140); S3: 9.8 (88); S4: 13 (234); (B) S1: 8.3 (277); S2: 11 (238); S3: 7 (187); S4: 19 (165). For divergence responses, slopes (intercepts) of the regression lines were (C) S1: 17 (72); S2: 16 (131); S3: 15 (167); S4: 22 (31); (D) S1: 16 (183); S2: 16 (259); S3: 16 (226); S4: 18 (214).

DISCUSSION

The present study has focused on an exception to the close timing of the vertical saccadic and the horizontal vergence components of combined saccade-vergence movements (Collewijn et al. 1995; Enright 1984; Zee et al. 1992). On the one hand, we confirm that when the far stimulus lies above the near stimulus (FUND paradigm), convergence peak velocity follows vertical peak velocity by a median interval of 12 ms. On the other hand, we have demonstrated that when the far target is positioned lower than the near target (FDNU paradigm), convergence peak velocity follows the saccadic velocity peak by a median interval of 76 ms (Fig. 2). We also report increased separation between the timing of peak velocity of vertical saccades and divergence movements for FDNU movements (median 20 ms) when compared with FUND movements (median 4 ms). This behavior was a consistent and robust finding in 10 normal subjects. A similar dissociation of saccadic and vergence components is evident in the version-vergence plots of FDNU responses reported by van Leeuwen et al. (1998; their Fig. 7), although they did not measure the temporal dissociation of the 2 components.

In discussing these findings, first, we review the experimental conditions that favor dissociation of the 2 components; second, we consider possible mechanisms by which saccades may influence the dynamic properties of vergence movements; and finally we suggest possible implications of our findings for current models for saccade-vergence interaction.

Factors favoring temporal dissociation of saccadic and convergence components

We systematically studied FDNU responses in 4 subjects and showed that the delay of the convergence peak velocity increased with larger vertical saccades, larger convergence movements, and, to a lesser extent, with higher end positions of the saccade (Fig. 4). Most natural shifts of the point of fixation are between objects that are located nearer and lower versus farther and higher. This is partly a result of our hands usually being held below our heads during most behaviors (e.g., during reading). Only occasionally do we view close objects that lie above our eyes, and most subjects find it somewhat of a strain to sustain such a gaze angle, whereas divergence from this position is relatively effortless. Thus the behavior that we

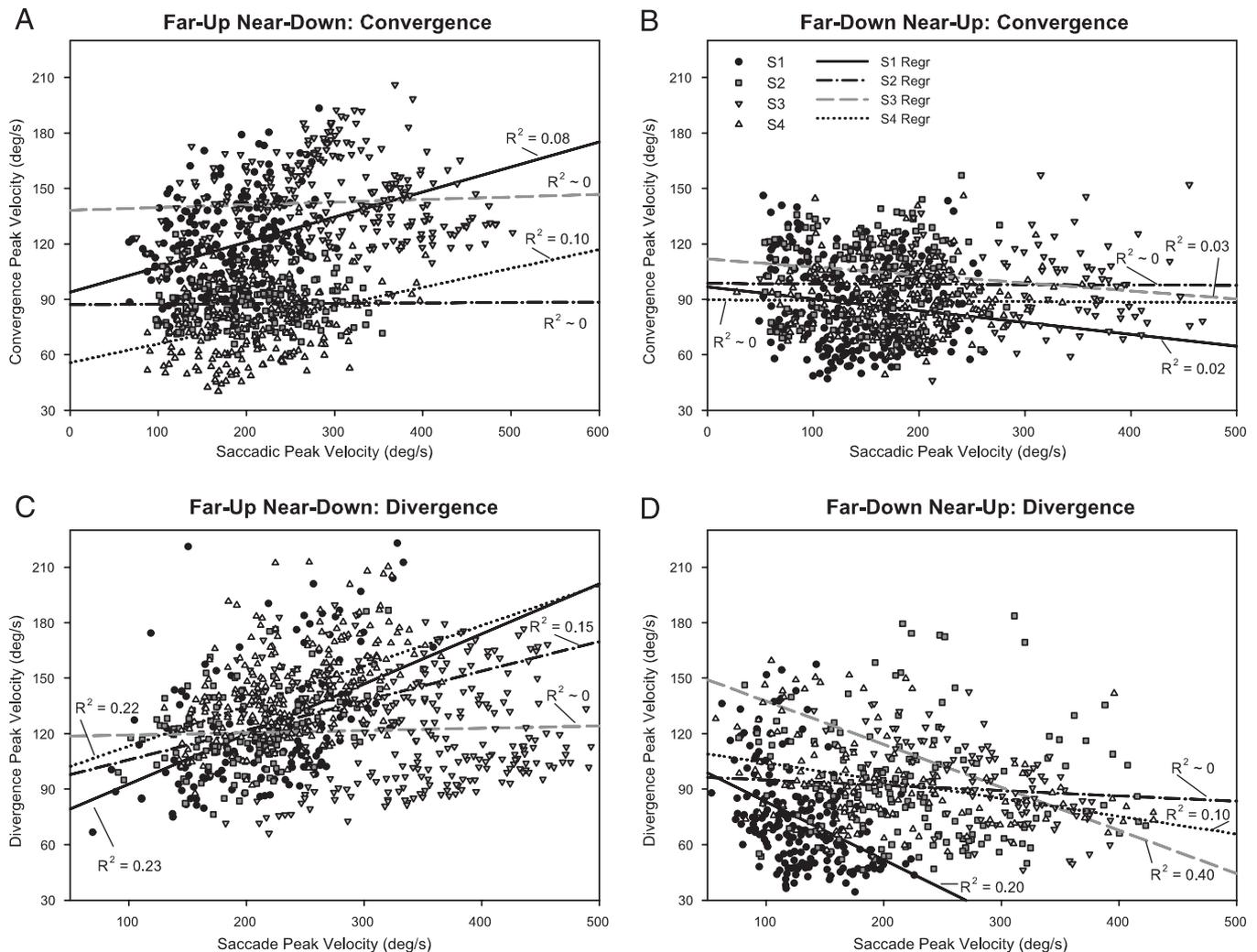


FIG. 7. Relationship between vertical saccadic peak velocity and vergence peak velocity for corresponding movements in 4 subjects; similar test conditions and display of data as in Fig. 5. Regression lines are flat and have poor correlation ($R^2 < 0.10$) for both the (A) FUND and (B) FDNU paradigms, indicating no dependency of convergence peak velocity on the speed of the vertical saccade. Peak divergence velocities showed a weak dependency on peak saccadic velocities ($R^2 > 0.15$, except for Subject 3) for the FUND paradigm (C), whereas there was no correlation or negative correlation between divergence peak velocities and saccadic peak velocities for the FDNU paradigm (D).

mainly studied is somewhat unusual, although no subject had any difficulty in performing the gaze shifts. When asked to perform such gaze shifts, in all of our subjects, the peak velocity of the saccadic component preceded the peak velocity of the convergence component. We wondered whether this response could be attributable to a nonlinearity of orbital mechanics when the eye was in “near-up” gaze. However, the dissociation occurred even when the ending position corresponded to the middle of the orbital range, provided the starting point for the saccade was lower. Indeed, we found that dissociation of the peak velocity of the 2 components was influenced more by vertical saccade size and convergence amplitude than by saccade endpoint (Fig. 4). It seems possible that the dynamic properties of convergence components during FDNU movements may be different because these movements are seldom used during natural behavior. Further experiments might establish whether these dynamic properties adapt during systematic FDNU training.

We also considered whether temporal dissociation of saccadic and convergence responses could be attributable to the

transient divergence that accompanies upward saccades in some subjects (Maxwell and King 1992; Sylvestre et al. 2002; Zee et al. 1992). However, as indicated by the asterisks in Fig. 3, such divergence movements are quite small and occur much earlier than the delayed convergence. Moreover, we found no correlations between the peak velocity of the initial divergence movement and the dissociation interval (time between peak saccadic and peak convergence velocity).

Divergence from a high, near target also produced dissociation of saccadic and vergence components, but this was not as pronounced as for convergence movements. Divergence responses that were delayed after the saccadic component were generally slower and lasted longer, unlike the speed and duration of convergence responses, which did not vary in any consistent pattern between the 2 paradigms (Fig. 5). Divergence movements also remained skewed (Fig. 8C), unlike convergence responses to the FDNU paradigm. These different behavioral properties are consistent with the electrophysiological findings of separate populations of divergence and convergence burst neurons (Mays 1984).

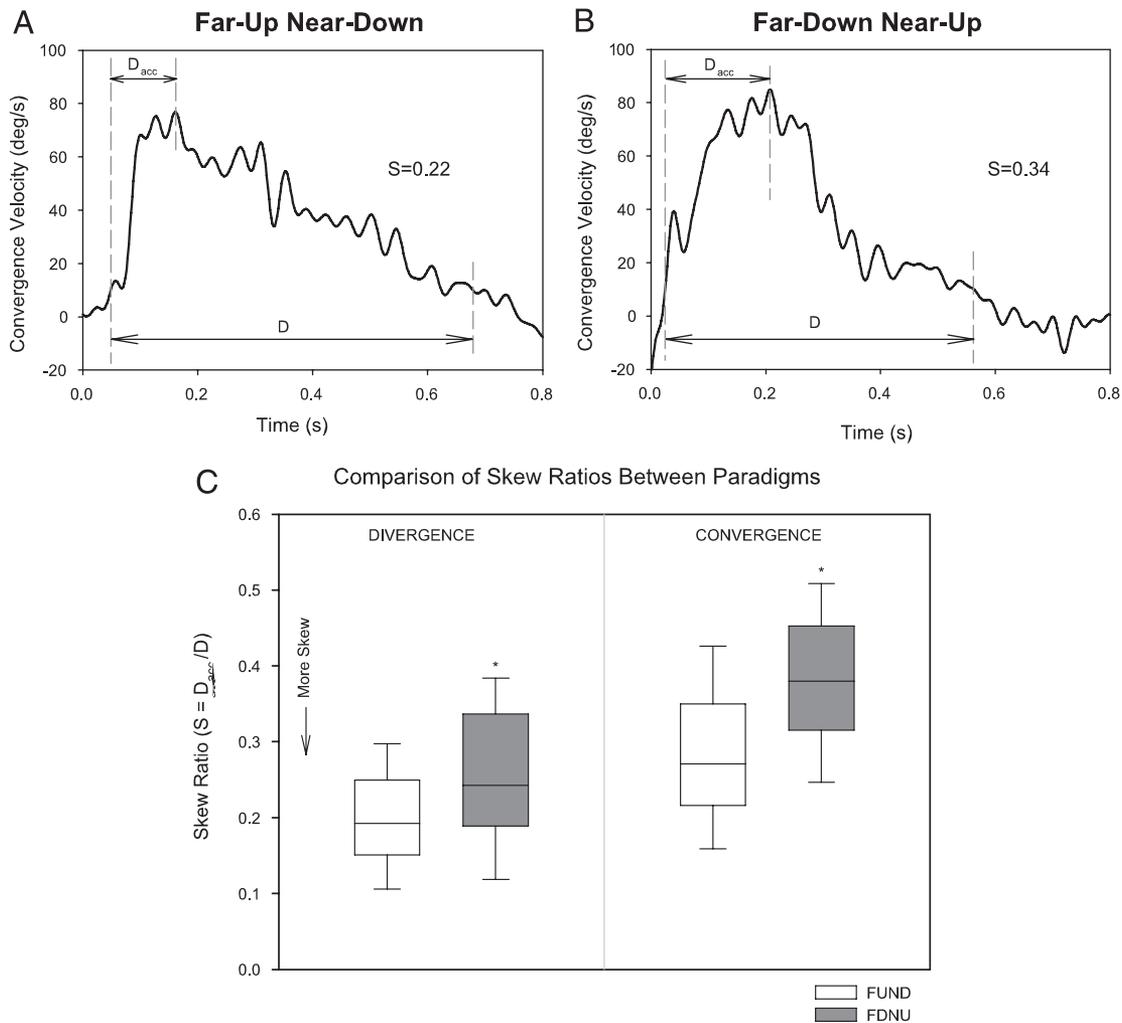


FIG. 8. Representative responses highlighting the difference in convergence velocity waveform profiles for (A) FUND and (B) FDNU paradigms. Waveform in A is positively skewed, whereas that in B is much more symmetric. D_{acc} : time from onset of convergence movement to peak velocity; D: total duration of the vergence movement; S: skewness ratio computed as D_{acc}/D . Data traces in A and B are representative responses from Subject 4 to the arrangement of targets described in Fig. 3. C: comparison of skew ratios, for both convergence and divergence, for the FUND and the FDNU paradigms. Boxes represent pooled data from 4 subjects for the arrangement of targets described in Fig. 3. Percentiles are as in Fig. 3. Asterisk indicates $P < 0.001$ (Mann-Whitney rank-sum test).

Possible mechanisms for interactions between saccades and vergence

Our findings indicate that the dynamic properties of convergence and divergence are influenced by the direction and timing of the associated saccadic component. In fact, saccades are known to speed up a variety of types of eye movements, including disparity or radial-flow-induced vergence movements (Busetini et al. 1996, 1997; Zee et al. 1992), ocular following of large-field moving stimuli (Gellman et al. 1990; Kawano and Miles 1986), and the onset of smooth pursuit (Lisberger 1998). Other examples of “enhancement” of one eye movement by another are reported, such as increased vestibuloocular reflex gain by a prior saccade (Das et al. 1999; Tabak et al. 1996). Such effects might arise from a population of neurons that encodes both types of eye movements, such as the velocity-to-position neural integrator for eye movements (Cannon and Robinson 1985; Goldman et al. 2002). One possibility is that when saccade and vergence movements occur together, the saccadic pulse can transiently change the parameters of the vergence-generating neurons. In this way, discharge properties of vergence burst

neurons would change to produce more or less velocity waveform skewing, depending on the timing and direction of an associated saccade. Similar to this mechanism, the occurrence of a saccade might have a “multiplicative” effect on the output of the convergence-burst neurons, as suggested by Mays and Busetini (2003).

At present, an anatomical substrate by which saccadic commands could influence vergence neuron activity cannot be firmly identified, although one possibility is neurons of the nucleus reticularis tegmenti pontis (NRTP). The NRTP contains vergence-related neurons in close proximity to saccade-related neurons (Gamlin and Clarke 1995). Other possible sites where saccade and vergence commands might influence each other include the superior colliculus (Chaturvedi and van Gisbergen 2000; Walton and Mays 2003), and the lateral intraparietal (LIP) area (Gnadt and Mays 1995). Through these or similar connections, the high-frequency discharge of burst neurons in riMLF might influence horizontal convergence by changing the properties of midbrain vergence-generating neurons, when both systems are active at the same time (van Leeuwen et al. 1998). Further studies are required to provide a

firmer neurobiological substrate for the interaction between the saccadic and vergence systems.

These issues also prompt reexamination of current models for saccade–vergence interactions. Thus a key premise of the SVBN model of Zee et al. (1992) is that the omnipause neurons are the only link between the saccade and vergence systems. We found that small, high-frequency conjugate oscillations occurred irrespective of stimulus paradigm (FUND or FDNU) (Figs. 1 and 3), suggesting that omnipause neurons were continuously suppressed for both types of responses. Nonetheless, some dynamic properties of the vergence movement, such as velocity wave skewing (Fig. 8) were affected by the direction and timing of the accompanying vertical saccade. Thus our findings seem more in line with the hypothesis of Collewijn et al. (1997) that the vergence system and the saccadic system act separately, but interact with each other whenever they occur at the same time. Our current results provide the opportunity to systematically test these 2 models for saccade–vergence interaction.

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