

Dynamic Coding of Vertical Facilitated Vergence by Premotor Saccadic Burst Neurons

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Submitted 19 May 2008; accepted in final form 9 July 2008

Van Horn MR, Cullen KE. Dynamic coding of vertical facilitated vergence by premotor saccadic burst neurons. *J Neurophysiol* 100: 1967–1982, 2008. First published July 23, 2008; doi:10.1152/jn.90580.2008. To redirect our gaze in three-dimensional space we frequently combine saccades and vergence. These eye movements, known as disconjugate saccades, are characterized by eyes rotating by different amounts, with markedly different dynamics, and occur whenever gaze is shifted between near and far objects. How the brain ensures the precise control of binocular positioning remains controversial. It has been proposed that the traditionally assumed “conjugate” saccadic premotor pathway does not encode conjugate commands but rather encodes monocular commands for the right or left eye during saccades. Here, we directly test this proposal by recording from the premotor neurons of the horizontal saccade generator during a dissociation task that required a vergence but no horizontal conjugate saccadic command. Specifically, saccadic burst neurons (SBNs) in the paramedian pontine reticular formation were recorded while rhesus monkeys made vertical saccades made between near and far targets. During this task, we first show that peak vergence velocities were enhanced to saccade-like speeds (e.g., >150 vs. <100°/s during saccade-free movements for comparable changes in vergence angle). We then quantified the discharge dynamics of SBNs during these movements and found that the majority of the neurons preferentially encode the velocity of the ipsilateral eye. Notably, a given neuron typically encoded the movement of the same eye during horizontal saccades that were made in depth. Taken together, our findings demonstrate that the brain stem saccadic burst generator encodes integrated conjugate and vergence commands, thus providing strong evidence for the proposal that the classic saccadic premotor pathway controls gaze in three-dimensional space.

INTRODUCTION

To quickly and accurately redirect our gaze between near and far targets, we typically combine saccadic and vergence eye movements. During such eye movements, termed *disconjugate saccades*, the eyes rotate by different angles and with different trajectories to precisely realign the two visual axes on the new target of interest. Traditionally, disconjugate saccades were thought to be controlled by linear summation of premotor commands from two distinct neural control pathways that separately encode the conjugate and vergence components of eye motion: 1) a *conjugate* saccadic subsystem, which commands a rapid but yoked movement of the two eyes in a given direction; and 2) a separate *vergence* subsystem, which rotates the eyes in opposite directions to ensure accurate binocular positioning (Hering 1977; Mays 1984, 1998). Accordingly, the premotor circuitry involved in generating horizontal saccades (e.g., the saccadic burst neurons [SBNs] of the paramedian

pontine reticular formation [PPRF]) was generally assumed to provide the command to drive the horizontal conjugate component of such movements, whereas a specific subpopulation of neurons in the mesencephalic reticular formation (MRF), which encode a signal proportional to viewing distance, were thought to produce the required vergence command (Busetini and Mays 2005b; Gamlin 2002; Gamlin et al. 1989; Mays et al. 1986; Zhang et al. 1992).

The summation of commands from two distinct premotor pathways, however, cannot account for a number of observations that have been made regarding disconjugate saccades. Notably, vergence velocities reach values greater during disconjugate saccades than would be predicted by the linear summation of commands from separate saccadic and vergence premotor pathways (Busetini and Mays 2005b; Collewijn et al. 1997; Enright 1984, 1992; Maxwell and King 1992; Ono et al. 1978; Oohira 1993; van Leeuwen et al. 1998; Zee et al. 1992). Thus it is now generally recognized that the commands driving conjugate saccades and vergence eye movements are not generated by strictly independent neural subsystems. To date, however, the mechanism responsible for the facilitation of vergence during disconjugate saccades remains controversial.

Two general classes of models have been proposed to account for the facilitation of vergence during disconjugate saccades (Busetini and Mays 2005b; Gamlin 2002; King and Zhou 2002; Kumar et al. 2006; Mays 1998; Mays and Gamlin 1995; Scudder et al. 2002; Van Horn et al. 2008; Zhou and King 1998). In one model, the premotor saccadic pathway drives the conjugate component of the saccade, whereas changes in vergence are exclusively driven by a premotor command from vergence neurons. In this view, projections from the “conjugate” saccadic pathway to the “vergence” pathway play a pivotal role in enhancing the premotor vergence command during disconjugate saccades (Busetini and Mays 2005b; Kumar et al. 2005). Alternatively, it has been proposed that classically assumed “conjugate” saccadic structures in the oculomotor brain stem underlie vergence facilitation by providing monocular saccade commands to the abducens nuclei during saccades (Cova and Galiana 1996; King and Zhou 2000, 2002). In this view, the vergence pathway is used to adjust ocular alignment following the saccadic component of the movement. Consistent with this latter proposal, we and others have reported that the premotor burst neurons in the PPRF that drive horizontal saccades do not encode conjugate commands (King and Zhou 2000; McConville et al. 1994;

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Sylvestre et al. 2003; Zhou and King 1996, 1998). Indeed, we have recently shown that the vergence-related information dynamically encoded by the premotor brain stem saccadic circuitry alone is sufficient to shape the activity of the abducens motoneurons during horizontal disconjugate saccades (Van Horn et al. 2008). In the present study we tested the proposal that vergence is facilitated by the classical horizontal saccadic pathway using a combination of complementary behavioral and recording approaches in rhesus monkeys. Although prior single-unit studies had exclusively focused on neural correlates during horizontal disconjugate saccades (Van Horn et al. 2008; Zhou and King 1998), there is evidence suggesting that vergence might be similarly facilitated during vertical saccades (Busetini and Mays 2005a; Enright 1984; Kumar et al. 2005; Maxwell and King 1992; van Leeuwen et al. 1998; Zee et al. 1992). Understanding how the brain drives vertical saccades between near and far targets is particularly interesting in terms of the current debate regarding the premotor control of vergence during saccades. Although these saccades require a vertical conjugate command, which would originate from the vertical burst neurons of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) (Büttner et al. 1977; Crawford and Vilis 1991, 1992; King and Fuchs 1979; Missal et al. 2000; Moschovakis et al. 1991a,b) they do not require the simultaneous production of a horizontal conjugate command. Instead, a command to generate horizontal movements of the two eyes in equal and opposite directions (i.e., vergence) is needed. Thus by recording the discharges of horizontal SBNs during this dissociation task, we were able to address whether neuronal commands from the horizontal saccadic pathway dynamically encode the movement of an individual eye even when no horizontal conjugate saccade command is required. Our results provide firm evidence that vergence is facilitated during vertical saccades and that integrated conjugate-vergence information encoded by the classical horizontal saccadic pathway is appropriate to drive the observed facilitation.

METHODS

The neurons in this study were obtained from three rhesus monkeys (*Macaca mulatta*). The monkeys were prepared for chronic extracellular recording using the aseptic surgical procedures described previously (Sylvestre and Cullen 1999). Briefly, a stainless steel post was attached to the animal's skull with stainless steel screws and dental acrylic, permitting complete immobilization of the animal's head. Two stainless steel recording chambers, oriented stereotaxically toward the abducens nucleus on the right and left sides of the brain stem, were also secured to the implant. To record binocular eye position an eye coil (three loops of Teflon-coated stainless steel wire, 18- to 20-mm diameter) was implanted in each eye (Judge et al. 1980). All procedures were approved by the McGill University Animal Care Committee and complied with the guidelines of the Canadian Council on Animal Care.

Behavioral paradigms

Monkeys were trained to fixate targets for a juice reward. The timing and location of target illumination, data acquisition, and on-line data displays were controlled using REX (real-time experimentation), a UNIX-based real-time acquisition system (Hays Jr et al. 1982). Neuronal responses were recorded during 1) horizontal and vertical conjugate saccades, 2) oblique saccades, 3) saccade-free

symmetric vergence, 4) vertical saccades combined with vergence, and 5) horizontal saccades combined with vergence.

First, to elicit conjugate movements a red HeNe laser target was projected onto a cylindrical screen located 55 cm away from the monkey's eyes (isovergent, $\approx 3.5^\circ$ convergence). Ipsilaterally and contralaterally directed conjugate saccades were elicited by stepping the laser target between horizontal positions (± 5 – 30°), in 5° increments, in predictable and unpredictable sequences and vertical saccades were elicited by stepping the laser target between vertical positions (± 5 – 30°). Oblique saccades were generated by stepping the laser target between a central target to a sequence of targets that had varying vertical and horizontal components within this same range.

Next, to elicit changes in vergence a horizontal array of 16 red light-emitting diodes (LEDs), with intensities comparable to that of the laser target, was positioned between the screen and the monkey. Symmetric vergence was elicited by sequentially illuminating LEDs located along the midline (convergence angles: 17, 12, 8, and 6°). To generate vertical saccades with vergence, two specific paradigms were used, similar to those previously described in humans (Kumar et al. 2005; van Leeuwen et al. 1998).

1) A far laser target was located higher than a central near LED (i.e., Up).

2) A far laser target was located lower than a central near LED (i.e., Down).

The near LED target was located 8 cm in front of the monkey's nose and the upper and lower targets (Up and Down, respectively) were located 20° above and below the near target, respectively (Fig. 1). These paradigms generated vertical saccades with a horizontal vergence amplitude of about 10° . For example, when the monkey looked from a "far-up" target to a "near" LED the monkey made a downward

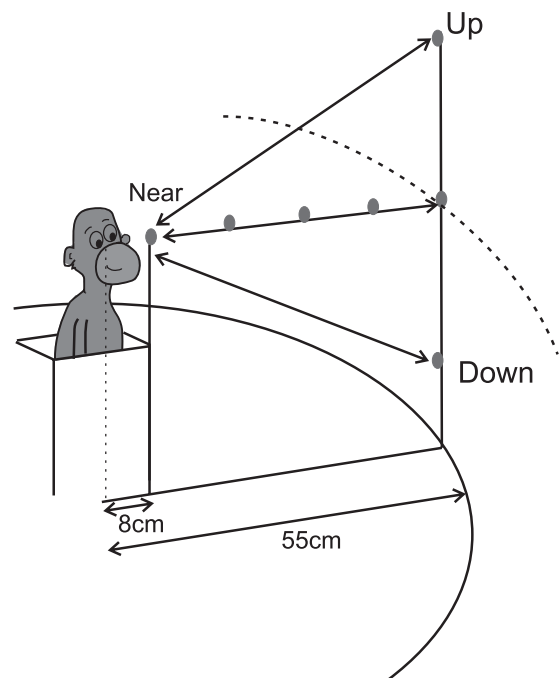


FIG. 1. Schematic representation of paradigms used to generate combined vertical-vergence movements. Light-emitting diodes (LEDs) located between the far screen and monkey's nose are used to generate vergence movements. Specifically, LEDs lit up along the midline were used to generate pure symmetric vergence (convergence angles: 17, 12, 8, and 6°). To elicit combined vertical vergence movements a near target was located 8 cm in front of the monkey's nose and the upper and lower targets (Up and Down, respectively) were located 20° above and below the near target. Abbreviations: An eye movement made from an "Up" target to a central near LED is denoted "Converge-Down" and a movement from a near LED to "Up" laser target would be "Diverge-Up."

converging movement (Converge-Down), whereas when the monkey looked from a “near” LED to a “far-up” laser target the monkey made an upward diverging movement (Diverge-Up). Notably, the two eyes moved in opposite directions such that the change in the horizontal conjugate [i.e., (left eye + right eye)/2] component was negligible.

Finally, to compare our sample of SBNs to those previously described (Sylvestre and Cullen 2002; Van Horn et al. 2008) neurons were also characterized during horizontal saccades combined with vergence (i.e., horizontal disconjugate saccades). The paradigms to elicit horizontal disconjugate saccades have been described previously (Sylvestre and Cullen 2002; Sylvestre et al. 2003; Van Horn et al. 2008). Briefly, an illuminated target changed from one of the close midsagittal LEDs to an eccentric (i.e., right or left of the midsagittal plane) laser target. During this paradigm, monkeys made saccades with horizontal components of 5–30° in amplitude in both directions and vergence components with amplitudes of approximately 4–13°. In addition, some LEDs were positioned in a configuration similar to the Müller paradigm (see Ramat et al. 1999 for examples) to elicit disconjugate saccades in which the movement of the right eye or left eye was minimized.

Data acquisition procedures

During experiments monkeys were seated in primate chairs located within the center of a 1-m³ magnetic eye coil system (CNC Engineering). Horizontal and vertical eye position signals were measured using the magnetic search coil technique (Fuchs and Robinson 1966; Judge et al. 1980). Each eye coil signal was calibrated independently by having the monkey fixate, with one eye masked, a variety of targets at different horizontal and vertical eccentricities and different depths. Position signals were low-pass filtered at 250 Hz (analog eight-pole Bessel filter) and sampled at 1 kHz. Since ocular saccades include very little power at >50 Hz (Cullen et al. 1996; Van Opstal et al. 1985; Zuber et al. 1968) eye position signals were further digitally filtered (with a 51st-order finite-impulse-response filter with a Hamming window and a cutoff at 125 Hz), before being differentiated to obtain eye velocity signals (using zero-phase forward and reverse digital filtering to prevent phase distortion).

Extracellular single-unit activity was recorded using enamel-insulated tungsten microelectrodes (2- to 10-MΩ impedance, FHC; for details, see Sylvestre and Cullen 1999). Saccadic burst neurons ($n = 57$) were identified on-line by their stereotypical discharge properties during eye movements (Cullen and Guitton 1997). Excitatory and inhibitory burst neurons (EBNs and IBNs, respectively) were distinguished based on their recording location relative to the abducens nucleus. EBNs were recorded in a small region extending 1–2 mm rostral to the abducens nucleus and 0.5–1.5 mm from the midline. IBNs were recorded in a region extending 0–2 mm caudal to the abducens nucleus and 0.5–1.5 mm from the midline. Both areas correspond to previous anatomical characterizations (Strassman et al. 1986a,b). When a neuron was isolated, unit activity, horizontal and vertical positions of the right and left eyes, and target position were recorded on a digital audio tape. The isolation of each neuron was reassessed off-line during playback. A burst neuron was considered to be adequately isolated only when individual action potential waveforms could be discriminated using a windowing circuit (BAK Industries) during saccades (e.g., see Fig. 1 in Sylvestre and Cullen 1999) and during fixation. Subsequent analysis was performed using custom algorithms (Matlab, The MathWorks).

Definitions and conventions

Eye movements are described in terms of conjugate [conjugate = (left eye + right eye)/2] and vergence [vergence = (left eye – right eye)] coordinates (where the left eye and right eye inputs could be either position or velocity signals), such that positive and negative

vergence velocity signals denote convergence and divergence, respectively. In addition, we report the movements of each eye as either ipsilateral or contralateral based on their location relative to the recording site. Note, positive and negative values indicate eye positions that are to the right and left or up and down of the central position (i.e., straight ahead), respectively.

Data analysis

The onset and offset of all saccades was determined using a 20°/s saccade velocity (i.e., horizontal or vertical) criterion. Horizontal saccades were defined as movements for which changes in vertical eye position were <10% of the change in horizontal position; vertical saccades were defined as movements for which changes in horizontal eye position were <10% of the change in vertical position. Saccades were categorized as conjugate if the change in vergence angle was <3.0° and further categorized as vertical, horizontal, or oblique. The onset and offset of slow, saccade-free vergence were determined using 10°/s vergence velocity criteria. Symmetrical vergence was defined as movements with a change in vergence >2.5° that were not accompanied by saccades.

The preferred direction for each neuron was determined by fitting a Gaussian function to the relationship between the number of spikes in a unit's discharge and saccade direction for saccades ranging in amplitude from 20 to 25°. A spike density function, in which a Gaussian function was convolved with the spike train (SD of 5 ms), was used to estimate neuronal firing rate (Cullen and Guitton 1996; Sylvestre and Cullen 1999). Linear optimization techniques were used to quantify each neuron's dynamic sensitivity to eye movements, during conjugate (Cullen and Guitton 1996, 1997; Sylvestre and Cullen 1999) and disconjugate saccades (Sylvestre et al. 2002, 2003; Van Horn et al. 2008), as described previously. Briefly, for each neuron we estimated the sensitivity to ipsilaterally directed conjugate saccades using the following dynamic model, which we have previously shown is an accurate description of both EBNs and IBNs (Cullen and Guitton 1997; Sylvestre and Cullen 2006; Van Horn et al. 2008).

CONJUGATE-ESTIMATION MODEL

$$FR(t) = b + r_{\text{horiz}} C J(t - t_d) \quad (1)$$

where $FR(t)$ is the neuron's instantaneous firing rate; b and r_{horiz} are constants that represent the bias and the neuron's horizontal eye velocity sensitivity, respectively; t_d refers to the dynamic lead time; and $C J(t)$ refers to the instantaneous horizontal conjugate eye velocity.

The specific linear regression models used for the analysis of neural responses during disconjugate saccades are elaborated in RESULTS. The goodness of fit of a given model to neuronal data was quantified using the variance-accounted-for value $\{VAF = 1 - [\text{var}(\text{mod} - \text{fr}) / \text{var}(\text{fr})]\}$, where mod represents the modeled firing rate and fr represents the actual firing rate. Note, that when estimating linear models, the VAF is mathematically equivalent to the correlation coefficient R^2 . Accordingly, a VAF value of 1 indicates a perfect fit to the data, whereas a value of 0 indicates a fit that is equivalent to the mean value of the firing rate models. The dynamic lead time of individual neurons (t_d) was computed during conjugate saccades as previously described by Sylvestre and Cullen (1999).

For each model parameter, which was estimated in our analysis of neuronal firing rates during disconjugate saccades, we computed 95% confidence intervals using a nonparametric bootstrap approach (Carpenter and Bithell 2000) and used these confidence intervals to identify nonsignificant or identical model parameters (Sylvestre and Cullen 2002; Sylvestre et al. 2003; Van Horn et al. 2008). Notably, equal numbers of converging and diverging saccades were included in

the disconjugate data set to prevent biasing the parameter estimates. If a confidence interval overlapped with zero the model was rerun with the nonsignificant term removed. The Bayesian information criterion (BIC), which served as a “cost index,” was calculated for each model estimation to quantitatively determine whether removing the term was justified (Schwartz 1978).

Quantification of ocular preference

The ocular preference of each neuron was quantified as previously described (Sylvestre and Cullen 2002; Sylvestre et al. 2003; Van Horn et al. 2008). Briefly, for a given neuron the velocity sensitivity of each eye was used to compute a Ratio index

$$\text{Ratio}_{\text{dyn}} = \frac{\text{Smaller estimated parameter value}}{\text{Larger estimated parameter value}}$$

Then, to indicate which eye provided the larger parameter value (i.e., the neuron’s “preferred eye”), each Ratio index was assigned an “i” or a “c” for the ipsilateral or contralateral eye, respectively. Using this approach, neurons were assigned to one of five categories: monocular ipsilateral, monocular contralateral, binocular ipsilateral, binocular contralateral, or conjugate [see Table 1 in Van Horn et al. (2008) for specific criteria for each category].

Statistical analysis

Data presented in the RESULTS are described as means \pm SDs. A one-way ANOVA followed by a Tukey–Kramer multiple-comparison test was used to compare results across behavior and neuron types.

RESULTS

The goals of this study were twofold. To establish that vertical saccades—like horizontal saccades—are effective in facilitating vergence in monkeys, we first compared vergence velocities during saccades and slow movements that required a comparable change in vergence angle. In addition, we determined whether, during such vertical saccades, peak vertical saccadic velocity and vergence velocities were temporally aligned. Our second goal was to characterize SBN firing rates during combined vertical–vergence movements to determine whether they dynamically encode vergence-related information (i.e., monocular signals) in a manner appropriate to facilitate vergence during vertical saccades. We then compared the command provided by a given SBN when vergence is facilitated during vertical versus horizontal saccades.

Characterization of vergence facilitated by vertical saccades

Figure 2 shows average traces of the four vertical–vergence movements studied. Position and velocity traces are shown for monkey D making saccades from a central near target to a higher far target (*A*: Diverge-Up), from the higher far target to the lower central near target (*B*: Converge-Down), from a lower far target to the higher near target (*C*: Converge-Up), and from the near target to a lower far target (*D*: Diverge-Down). In each example, fixation of the LED that was positioned 8 cm from the monkey’s nose required a vergence angle of about 10°. Note that since the velocities of the two eyes were equal and opposite in all four conditions, the horizontal conjugate velocity associated with each eye movement was virtually zero. During each of the four

paradigms vergence velocities were 1) substantially greater than expected for saccade-free vergence movements and 2) peak vergence velocities were relatively synchronized with peak vertical velocities (see arrows in Fig. 2). In the following text, we further quantify each of these findings.

We first compared the peak vergence velocities generated during each paradigm with those produced during pure symmetric vergence tasks requiring comparable changes in vergence angle. As illustrated in Fig. 3 vergence velocities were much faster when combined with a vertical saccade ($P < 0.05$) in all four of the paradigms and in all three monkeys. Average peak vergence velocities for each of the paradigms are quantitatively compared in Table 1. In addition, we found that vergence velocities during downward convergence were significantly slower in all three monkeys ($P < 0.05$) compared with the other vertical–vergence paradigms.

Temporal alignment of peak vertical and vergence velocities

Next, we evaluated the temporal alignment of peak vertical and vergence velocities. Figure 4, A_1 and A_2 illustrates typical examples of eye movements in which vertical and convergence movements were combined (Converge-Down and Converge-Up, respectively). As shown for these example movements, vergence and vertical velocities peaked at approximately the same time. This result was typical for all four behavioral conditions with only small differences in temporal dissociation between monkeys (see Table 1). On average, vergence velocities peaked approximately 3–4 ms after peak vertical velocity. Recently, Kumar et al. (2005) observed that significant temporal dissociations (≤ 320 ms) could occur when humans made self-paced shifts between far targets and higher near targets (i.e., Converge-Up). A similar dissociation pattern was not observed in the monkeys evaluated in this study. As illustrated in Fig. $4B_1$, during the Converge-Up condition the temporal dissociation was < 40 ms in the majority of trials ($> 95\%$). On the very rare occasion that peak vergence velocity was markedly delayed compared with peak vertical velocity in this condition (closed star in Fig. $4B_1$) the peak vergence velocity associated with the overall eye movement was relatively small ($\sim 50^\circ/\text{s}$). Indeed, the dynamics of the vergence components of these eye movements were similar to those of saccade-free vergence. As illustrated in Fig. $4B_2$ peak vergence velocities were generally $> 100^\circ/\text{s}$ when combined with a vertical saccade (Fig. $4B_2$, black bars). However, when peak vergence velocity was delayed, the resulting vergence velocity was in the range of vergence velocities observed during symmetric vergence (Fig. $4B_2$, dark gray vs. light gray, respectively).

These behavioral findings show that when monkeys make vertical saccades between near and far targets, vergence velocities are significantly facilitated. Furthermore, a robust temporal alignment of peak vertical and vergence velocities was observed, suggesting that the synchronization of saccadic and vergence velocities is an important determinant of vergence facilitation.

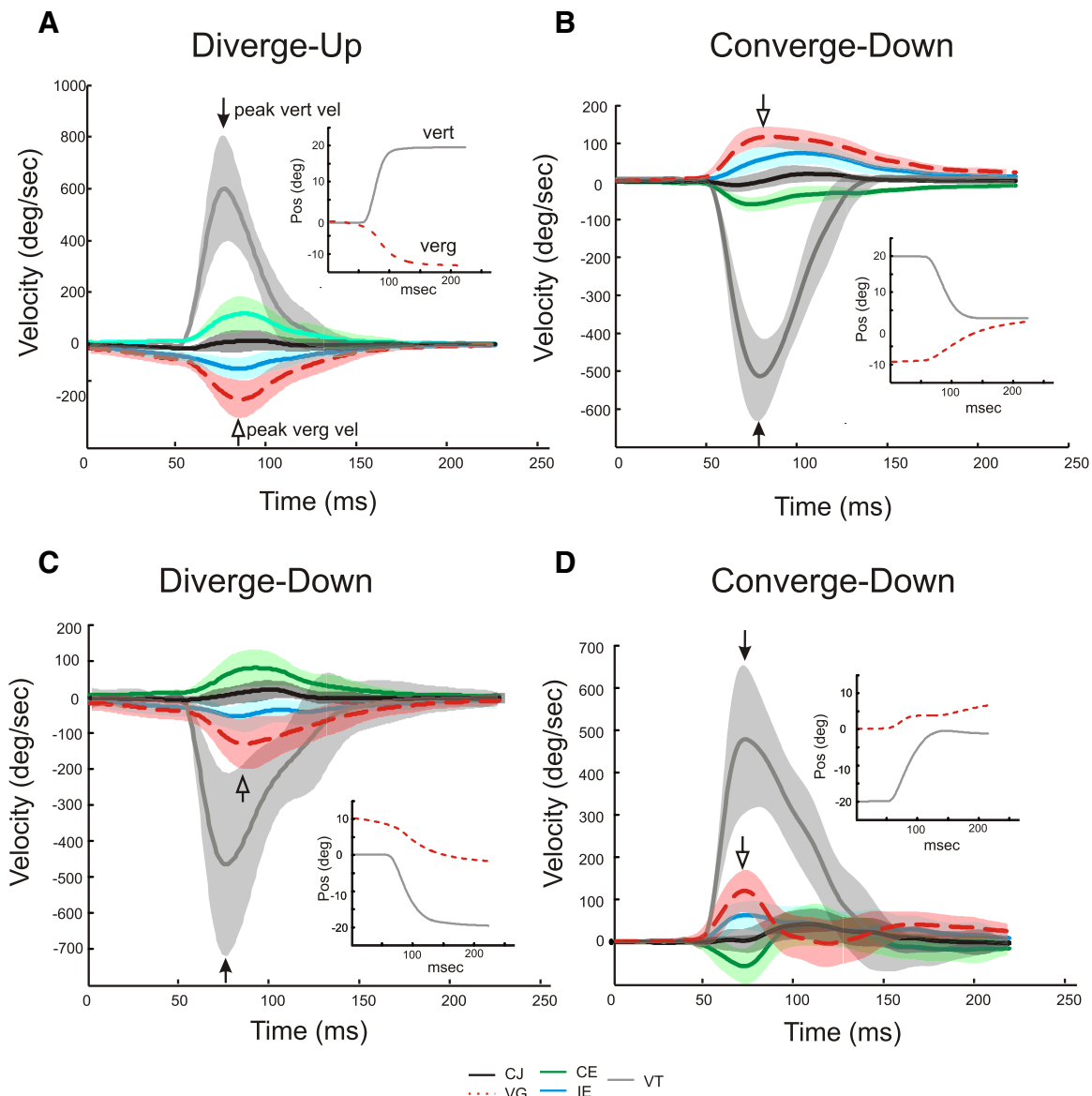


FIG. 2. Typical examples of behavior during disconjugate saccades made from a far up vertical target to a central near LED (Converge-Down), from a central near LED to a far up vertical target (Diverge-Up), from a far down vertical target to a central near LED (Converge-Up), and from a central near LED to a far down vertical target (Diverge-Down). Average individual eye velocity [i.e., ipsilateral (IE) and contralateral (CE), blue and green traces, respectively] and vertical (VT), conjugate (CJ), and vergence (VG) velocities (gray, black, and red traces, respectively) are plotted as a function of time for each paradigm. Average traces are superimposed on SDs. Corresponding vertical and vergence positions are shown in the insets for each paradigm. Closed and open arrows are used to mark peak vertical and vergence velocities, respectively.

Test of the hypothesis: vergence is facilitated by the classical saccadic pathway during disconjugate saccades

The second goal of this study was to determine whether the premotor burst neurons, which drive horizontal saccades, discharge in a manner appropriate to facilitate vergence velocities during vertical saccades between near and far targets. To address this question, we characterized the command signal that was dynamically encoded by the horizontal SBNs during vertical saccade-facilitated vergence. Notably, these saccades would also require a vertical conjugate command, which would originate from the vertical burst neurons of the riMLF (Büttner et al. 1977; Crawford and Vilis 1991, 1992; King and Fuchs 1979; Missal et al. 2000; Moschovakis et al. 1991a,b).

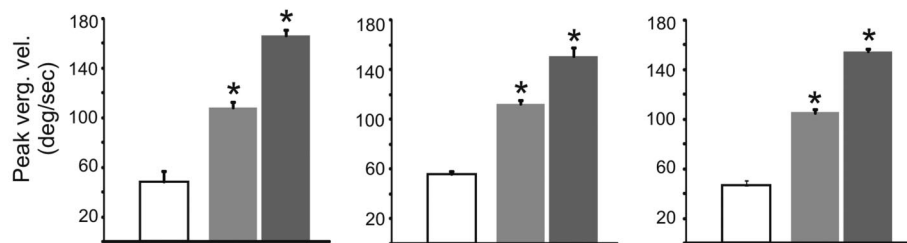
In all, 57 SBNs were recorded in the paramedian pontine reticular formation (PPRF), the majority of which ($n = 38$) were recorded with sufficient behavior during vertical-facilitated vergence to determine the neuron's ocular sensitivity (see METHODS). Neurons were classified as excitatory (EBNs; $n = 22$) or inhibitory (IBNs; $n = 35$) based on their anatomical location (see METHODS) and further categorized as short- or long-lead neurons depending on whether the mean period between the onset of the first spike and the onset of eye velocity was ≤ 15 or > 15 ms, respectively, during conjugate saccades (25 long-lead IBNs; 10 short-lead IBNs; 9 long-lead EBNs; 13 short-lead EBNs) (Cullen and Guitton 1997; Scudder et al. 1988). As shown in a recent comparison of short- and long-lead EBNs and IBNs during disconjugate saccades (Van

Convergence

Monkey M

Monkey R

Monkey D

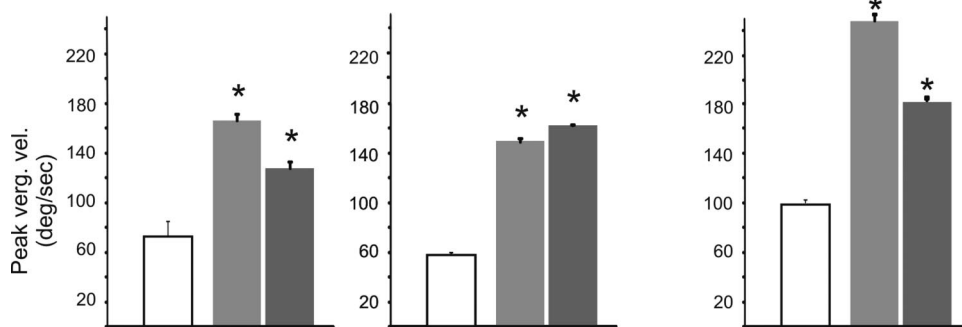


Divergence

Monkey M

Monkey R

Monkey D



□ Symmetric vergence ■ Up ■ Down

FIG. 3. Average horizontal peak vergence velocities ($^{\circ}/s$) during converging (*top*) and diverging (*bottom*) for symmetric vergence and vertical disconjugate saccades in monkeys M, R, and D. Stars indicate average vergence velocities that are significantly greater than saccade-free symmetrical vergence ($P < 0.05$).

Horn et al. 2008), we found no major differences (with the obvious exception of the burst lead times) between the two groups of neurons. Thus for simplicity, short- and long-lead EBNs and IBNs are discussed as a pooled population and are referred to as SBNs.

We first tested whether the command signal encoded by SBN correlates to the increase in vergence velocity that is observed when vertical saccades are made between far and near targets (i.e., Fig. 3). Our logic was the following: if SBNs provide a saccadic monocular command to the extraocular motoneurons, their responses should preferentially encode the movement of an individual eye during vertical as well as horizontal disconjugate saccades. Alternatively, if SBNs provide only a conjugate command to the extraocular motoneurons, then their firing patterns should be unaffected when compared with that generated when vertical saccades are made between two far targets. Overall, our results support the former proposal. Specifically, the movement of an individual eye was required to accurately describe the burst activity of the majority (84%) of the SBNs when vertical saccades were made between near and far targets. An example SBN illustrating this main finding is presented in Figs. 5 and 6.

Figure 5 shows the discharge of a typical neuron during four conjugate saccades. Notably, as further illustrated in the polar plot representing the average discharge for many vertical, oblique, and horizontal saccades, this neuron burst rigorously for ipsilaterally directed conjugate saccades but was completely silent for contralateral and vertical saccades made between two far targets. In contrast, when a vertical saccade was made simultaneously with a vergence movement to shift gaze between near and far targets, this same neuron was not silent (Fig. 6A). This is a striking result, given that the accompanying conjugate component of the horizontal eye movement was close to zero. Indeed, we found that this neuron fired action potentials only when the ipsilateral eye moved in the “on” (i.e., ipsilateral) direction, consistent with the proposal that SBNs preferentially encode the movement of a single eye during saccades. Notably, no neural activity was associated with vergence velocities that were not accompanied by saccades. For example, SBNs were silent during symmetric vergence and during the Converge-Up paradigm when vergence velocities were temporally delayed compared with the vertical saccade.

We next tested whether we could predict the firing rate of the neuron based on its sensitivity to eye movements during

TABLE 1. Temporal alignment of vertical and vergence peak velocities

Variable	Convergence		Divergence	
	Up	Down	Up	Down
<i>Monkey M</i>				
<i>n</i>	87	225	129	97
Peak vergence	107.6 (4.9)	165.8 (5.5)	165.7 (5.1)	120.8 (5.1)
Temporal alignment	9.3 (8.7)	8.5 (6.0)	9.56 (6.0)	-3.05 (2.8)
<i>Monkey R</i>				
<i>n</i>	80	82	110	109
Peak vergence	112.62 (6.9)	150.6 (2.2)	149.1 (9.2)	161.8 (16.9)
Temporal alignment	-25.8 (14.8)	8.4 (3.4)	8.7 (3.6)	-1.3 (16.9)
<i>Monkey D</i>				
<i>n</i>	133	80	119	107
Peak vergence	105.3 (2.3)	154.2 (3.7)	242.6 (7.9)	178.74 (7.3)
Temporal alignment	10.4 (2.6)	-7.7 (2.1)	7.1 (0.79)	12.8 (2.3)
<i>Averages</i>				
Peak vergence	108.5 (1.2)	156.6 (2.7)	185.8 (16.6)	155.8 (8.6)
Temporal alignment	-1.8 (6.7)	3.0 (0.4)	8.4 (3.1)	1.55 (2.2)

SE values are given in parentheses. *n* = number of movements; peak vergence in deg/s; temporal alignment = peak vertical velocity - peak vergence velocity (ms).

horizontal conjugate saccades using the following dynamic model.

Horizontal-prediction model

$$FR(t) = b + r_{est-hori} \dot{E}(t - t_d) \quad (2)$$

where $FR(t)$ is the predicted firing rate of the neuron; b is the bias; $r_{est-hori}$ is the neuron's horizontal eye velocity sensitivity estimated during horizontal conjugate saccades, respectively; t_d is the dynamic lead time; and $\dot{E}(t)$ represents either 1) conjugate velocity ($C\dot{J}$), 2) ipsilateral eye velocity ($I\dot{E}$), or 3) contralateral eye velocity ($C\dot{E}$) (for a comparable approach in the analysis of horizontal disconjugate saccades, also see Van Horn et al. 2008). The distribution of horizontal velocity sensitivities for the population of SBNs is shown in Fig. 7A and average parameters estimated during conjugate saccades are provided in Supplemental Table S1.¹ For the example neuron illustrated in Fig. 6, we found that neuronal discharge dynamics were most accurately predicted when we used the movement of the ipsilateral eye to estimate firing rate (Fig. 6, blue trace superimposed on firing rate). When conjugate or contralateral eye velocity was used in the estimation, we obtained much poorer predictions of neuronal firing (black and red traces superimposed on the firing rate, respectively).

Consistent with previous studies (Cullen and Guitton 1997; Hepp and Henn 1983; Kaneko 2006; Scudder et al. 1988; Strassman et al. 1986a,b), approximately half of the SBNs in our population were not completely silent during vertical saccades made between two far targets but instead produced a small discharge of action potentials. For these neurons ($n = 22/38$) we also characterized the firing rates during vertical saccades using a vertical-eye velocity-based version of Eq. 1 and found that they were dynamically

related to vertical eye velocity (mean VAF = 0.39 ± 0.15 and 0.28 ± 0.25 obtained for vertical up and down saccades, respectively; see Supplemental Table S1 for average parameters estimated during vertical saccades). Furthermore, we could well predict the firing rate of a given neuron in this subpopulation during oblique saccades by simply accounting for its sensitivity to horizontal and vertical velocity during horizontal and vertical saccades, respectively (mean VAF = 0.51 ± 0.17). Note this quality of fit is comparable to that obtained during conjugate saccades (see Supplemental Table S1). The tuning and discharge of an example neuron during oblique saccades are shown in Supplemental Figs. S1 and S2, respectively. Thus to fully describe the discharge dynamics of these neurons when vertical saccades were made between near and far targets (i.e., vertical saccades combined with vergence) we used a model that also accounted for each neuron's sensitivity both to horizontal and to vertical eye velocity during saccades. (Supplemental Fig. S3 shows this approach applied to the same example neuron that was shown in Supplemental Figs. S1 and S2.)

A neuron-by-neuron comparison of horizontal and vertical sensitivities estimated during ipsilateral versus vertical saccades is shown in Fig. 7B. Because we found no major differences (other than obvious exception of their tuning to saccade direction) between neurons with or without vertical sensitivities, they are discussed as a pooled population in the following text. Overall, we found that the discharges of the majority of the neurons in our population (27/38) were best predicted by the horizontal velocity of an individual eye, rather than the conjugate velocity, during vertical-facilitated vergence (~25% average relative improvement in VAF). Table 2 summarizes the average VAFs for conjugate versus individual eye predictions for the population of SBNs.

Estimation of the vergence-related signal encoded by horizontal SBNs during vertical disconjugate saccades

We next investigated whether estimating a more complex model, specifically a binocular expansion of the conjugate model, might provide an improved description of neuronal discharges during vertical saccades that are made between near and far targets using the following model.

Binocular-estimation model

$$FR(t) = b + r_{IE} \dot{I}E(t - t_d) + r_{CE} \dot{C}E(t - t_d) \quad (3)$$

where $FR(t)$ is the estimated firing rate; r_{IE} and r_{CE} are constants that represent the neuron's ipsilateral and contralateral velocity sensitivity, respectively; and $\dot{I}E(t)$ and $\dot{C}E(t)$ refer to the instantaneous velocity of the ipsilateral and contralateral eye, respectively. Note that for neurons that were not completely silent during vertical saccades made between two far targets, an addition term was included in Eq. 2 to account for their sensitivity to vertical saccadic eye motion. Model fits using this expanded binocular model (Eq. 2) for the example neuron are shown in the second row of Fig. 6 (black trace superimposed on firing rate). To determine whether both eye velocity parameters in the binocular model (i.e., $r_{IE} + r_{CE}$) were necessary to describe the firing rate of this neuron, we estimated the 95% confidence intervals using a bootstrapping technique described in METHODS and in previous studies (Syl-

¹ The online version of this article contains supplemental data.

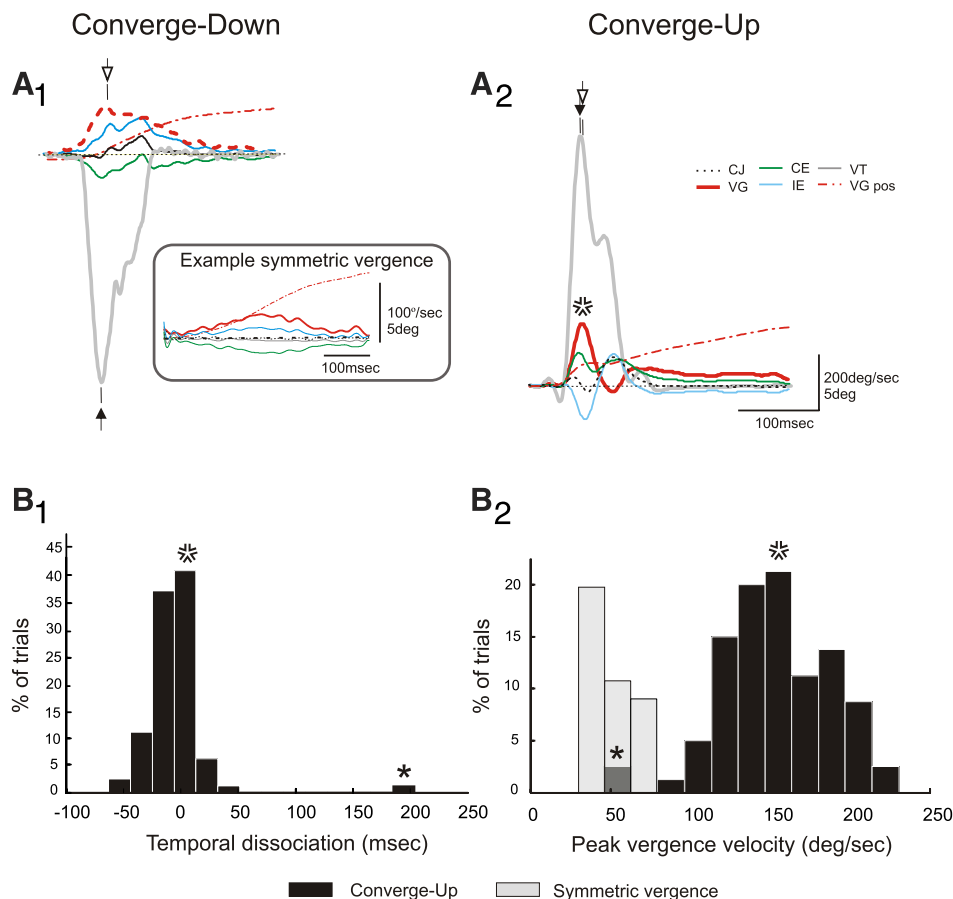


FIG. 4. A: individual examples of typical behavior observed when a vertical saccade is combined with a convergence movement (A₁: Converge-Down; A₂: Converge-Up). Closed arrows indicate peak vertical velocity and open arrows indicate peak vergence velocity. Typically peak vertical velocity peaked at approximately the same time as vergence velocity and very rarely was peak vergence velocity temporally dissociated from peak vertical velocity. B₁: distribution of temporal dissociations (i.e., time of peak vertical velocity – time of peak vergence velocity) calculated during the Converge-Up paradigm. The majority of the behavior resulted in velocities that have a temporal dissociation of <40 ms (black histograms), whereas an atypical example resulted in a dissociation of ≤ 200 ms (gray histogram). B₂: distributions of vergence velocities recorded during Converge-Up (black and gray bars) and symmetric vergence (light gray). The majority of the behavior resulted in peak vergence velocities greater than vergence velocities associated with saccade-free symmetrical vergence (see A₁ inset). Open and closed asterisks correspond to vergence velocities and dissociations calculated in the typical Converge-Up example (A₂) and an atypical example (data not shown), respectively. Notably, the vergence velocities associated with the atypical examples (dark gray histograms) resulted in overlapping with saccade-free vergence.

vestre and Cullen 2002; Sylvestre et al. 2003; Van Horn et al. 2008). Figure 6B shows the values of the original parameter estimates (vertical arrows) as well as the distributions of the estimates obtained using the bootstrapping approach (histograms). For each of the two parameter estimates, the 95% confidence interval is denoted by the heavy horizontal line below the distribution. Two important observations can be made from this figure: 1) the confidence intervals of the two eyes were statistically different (i.e., they do not overlap with each other and could therefore not be replaced with a single term proportional to conjugate eye velocity) and 2) the confidence interval for the sensitivity of the contralateral eye velocity was not statistically different from zero (i.e., the confidence interval overlaps with zero).

Accordingly, we removed the contralateral eye velocity term from the estimation model such that only ipsilateral eye velocity was used to estimate the firing rate using the following model.

Ipsilateral-estimation model

$$FR(t) = b + r_{IE} \dot{E}(t - t_d) \quad (4)$$

As expected, the resulting fit was nearly identical to that of the full binocular model (Fig. 6, second row, dotted blue trace superimposed on firing rate, $\Delta BIC = 0$), confirming that the contralateral eye velocity parameter played no significant role in describing the discharge of this neuron.

Similar results were obtained for the majority of neurons in our population of SBNs. Overall, the 95% confidence intervals

for most neurons ($n = 34/38$) did not overlap with each other, confirming that individual eye velocity terms should not be replaced with a single conjugate term. Moreover, in about two thirds ($n = 24/38$) of the neurons the 95% confidence interval for one eye velocity parameter overlapped with zero and the fits resulting from the full binocular model (Eq. 3) were nearly identical to the fits using the preferred individual eye (Eq. 4) (i.e., the eye for which the eye velocity parameter did not overlap with zero, mean population $VAF_{\text{binocular}} = 0.47 \pm 0.07$ vs. $VAF_{\text{reduced}} = 0.44 \pm 0.07$). Thus these results suggest that horizontal SBNs facilitate vergence during vertical saccades between near and far targets by preferentially encoding the horizontal movement of an individual eye.

Ocular sensitivities across of the population of SBNs

For each SBN, a $\text{Ratio}_{\text{dyn}}$ index was computed based on the parameters estimated for the binocular model to objectively assign each neuron to one of five ocular categories (for details, see METHODS and Van Horn et al. 2008). The distributions obtained for $\text{Ratio}_{\text{dyn}}$ during vertical saccades between near and far targets for all SBNs ($n = 38$) are shown in Fig. 8. We found that the majority of the SBNs could preferentially encode the movement of either eye (e.g., monocular ipsilateral, $n = 15$; monocular contralateral, $n = 9$). Table 2 summarizes the average VAFs and changes in BIC provided by the complete binocular versus reduced models for each of the five categories during vertical-facilitated vergence. This distribution is comparable to that previously described for a separate

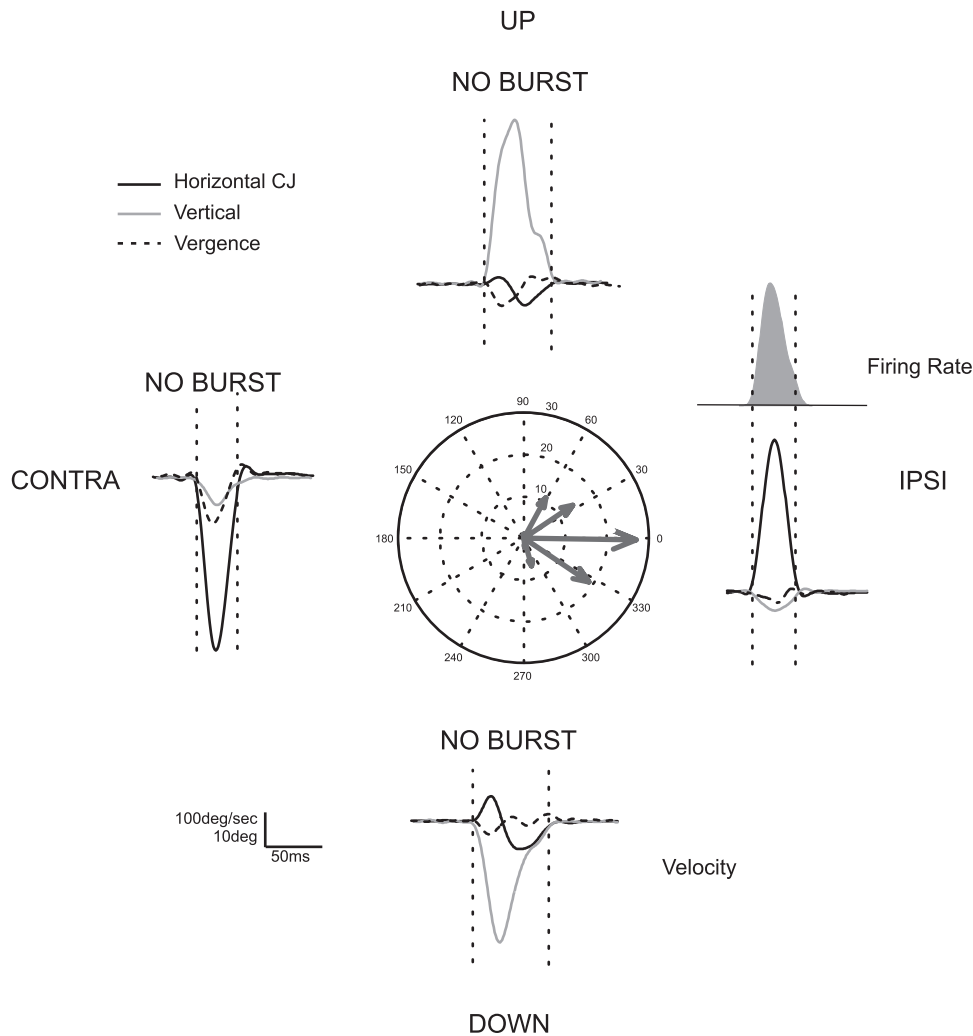


FIG. 5. Neural responses of a typical saccadic burst neuron (SBN) during four 10° saccades in the left, up, right, and downward directions. A polar plot representing average discharge for this neuron during numerous ipsilateral, oblique, and vertical saccades is shown in the middle of the 4 movements. Note that this neuron was completely silent (i.e., no burst) during saccades in the contralateral direction and during vertical saccades.

population of SBNs during horizontal disconjugate saccades (Van Horn et al. 2008).

Comparison of ocular preference during horizontal and vertical disconjugate saccades

To more directly relate our present results with those previously described (Van Horn et al. 2008) a subset of SBNs ($n = 16$) were also recorded during horizontal disconjugate saccades. Approximately an equal number of SBNs with and without vertical sensitivities ($n = 9$ and 7 , respectively) were tested. An analysis comparable to that described earlier was then used to determine whether, on a neuron-by-neuron basis, SBNs had similar ocular preferences when vergence was facilitated by either horizontal or vertical saccades. Figure 9 illustrates the neuronal discharge of the same example neuron shown in Figs. 5 and 6 during four example horizontal disconjugate saccades (converging and diverging are shown in Fig. 9, A_1 and A_2 , respectively). Note the large differences in dynamics for the two eyes during these movements: in the converging case (Fig. $9A_1$) the contralateral eye moved, whereas the ipsilateral eye was relatively stationary; in the diverging case (Fig. $9A_2$) the ipsilateral eye moved, whereas the contralateral eye was

relatively stationary. The conjugate component of the movements was comparable in the two conditions. Consistent with the results found during vertical-facilitated vergence, we found that the neuron's activity preferentially encoded the velocity of the ipsilateral eye (Fig. 9, *blue trace* superimposed on firing rate). In particular, an ipsilateral-based prediction most accurately predicted the firing rate (*blue trace* superimposed on firing rate), whereas conjugate- and contralateral-based predictions tended to overshoot the firing rate when the ipsilateral eye moved less (i.e., during the diverging movements for this example neuron; Fig. $9A_1$) and to undershoot when the ipsilateral eye moved more (Fig. $9A_2$; *black* and *red traces* superimposed on the firing rate). Confidence intervals obtained using the bootstrapping technique further confirmed that the neuron's sensitivity to contralateral eye velocity was not statistically different from zero (Fig. $9B$). Furthermore, when we removed the contralateral eye velocity term from our dynamic model such that only ipsilateral eye velocity was used to estimate the firing rate, the resulting fit was nearly identical to that of the full binocular model (Fig. 9, *second row, dotted blue trace* superimposed on firing rate, $\Delta\text{BIC} = 0$).

To directly address whether the command provided by a given SBN similarly facilitates shifts of vergence during

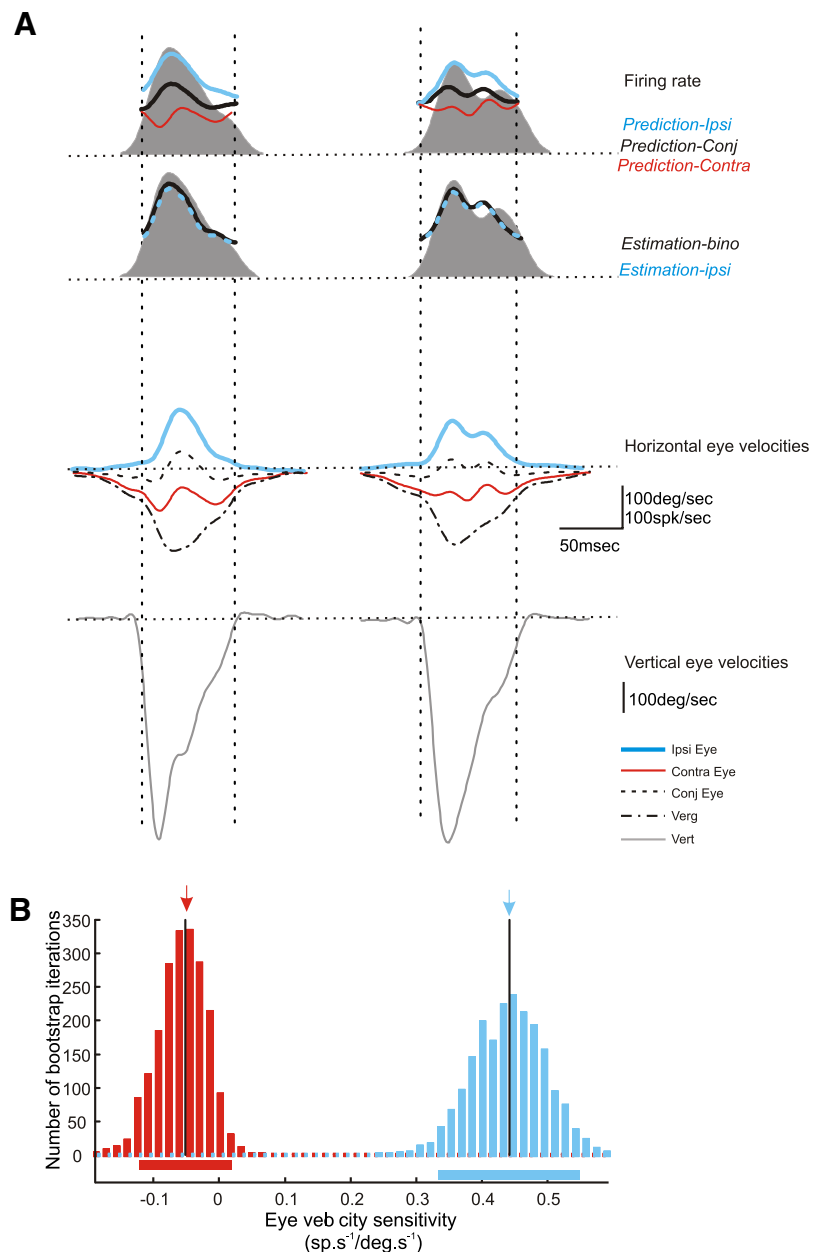


FIG. 6. *A*: neuronal responses and model fits for the same neuron shown in Fig. 5 when a vertical saccade is combined with a vergence movement (Diverging-Down). The *left* and *right* columns illustrate 2 example movements. The firing rate of the neuron is shown as the gray shaded area (*top row*, and reproduced in *2nd row* for clarity). Predicted model fits using ipsilateral, conjugate, and contralateral eye velocities are shown in the *top row* in blue, black, and red, respectively [variance-accounted-for (VAF) values: $VAF_{\text{ipsi}} = 0.60$; $VAF_{\text{conj}} = 0.53$; $VAF_{\text{contra}} = 0.33$]. Note the poor fits obtained when the conjugate and contralateral parameters are used to predict the firing rate of this neuron compared with the prediction using the ipsilateral eye. Estimated model fits using the binocular model and reduced ipsilateral model are shown in the *2nd row*. Note, VAF values indicated here were calculated when fitting the entire data set. Conjugate, vergence, and vertical velocities (*bottom row*) are also shown. Dotted vertical lines represent vertical saccade onsets and offsets of 20°/s. *B*: bootstrap histograms and 95% confidence intervals (thick horizontal bars) for this neuron. Note the 95% confidence interval for the contralateral eye (red bar) overlaps with zero.

both horizontal and vertical saccades, we calculated the $\text{Ratio}_{\text{dyn}}$ during horizontal saccades between near and far targets for this subset of neurons ($n = 16$) that were fully characterized during horizontal disconjugate saccades (e.g., Fig. 9). The ocular preference of a given neuron was typically the same when vergence was facilitated during either vertical or horizontal saccades. This result is shown in Fig. 10 where the preferred eye during vertical-facilitated vergence is plotted against the preferred eye during horizontal-facilitated vergence. For the majority of the neurons in our population ($\sim 75\%$), ocular sensitivities were identical during horizontal and vertical disconjugate saccades (black, red, and blue columns). Taken together, our analyses of vertical and horizontal disconjugate saccades suggest that the premotor burst neurons of the brain stem saccade burst generator functions to facilitate vergence when saccades are made between near and far targets by preferentially encod-

ing the horizontal movement of a specific eye. The implications of this finding are further explored in the DISCUSSION.

DISCUSSION

The saccadic burst neurons of the paramedian pontine reticular formation project to the extraocular motoneurons and provide the primary command that drives horizontal saccades. The results of recent studies suggest that these neurons do not encode conjugate commands during saccades but instead preferentially encode the movement of an individual eye (King and Zhou 2000; McConville et al. 1994; Sylvestre et al. 2003; Zhou and King 1996, 1998), thereby mediating the facilitation of vergence as well as horizontal conjugate velocity during horizontal disconjugate saccades (Van Horn et al. 2008). Here we investigated whether the monocular commands coded by SBNs are suitable for facilitating vergence when vertical saccades are

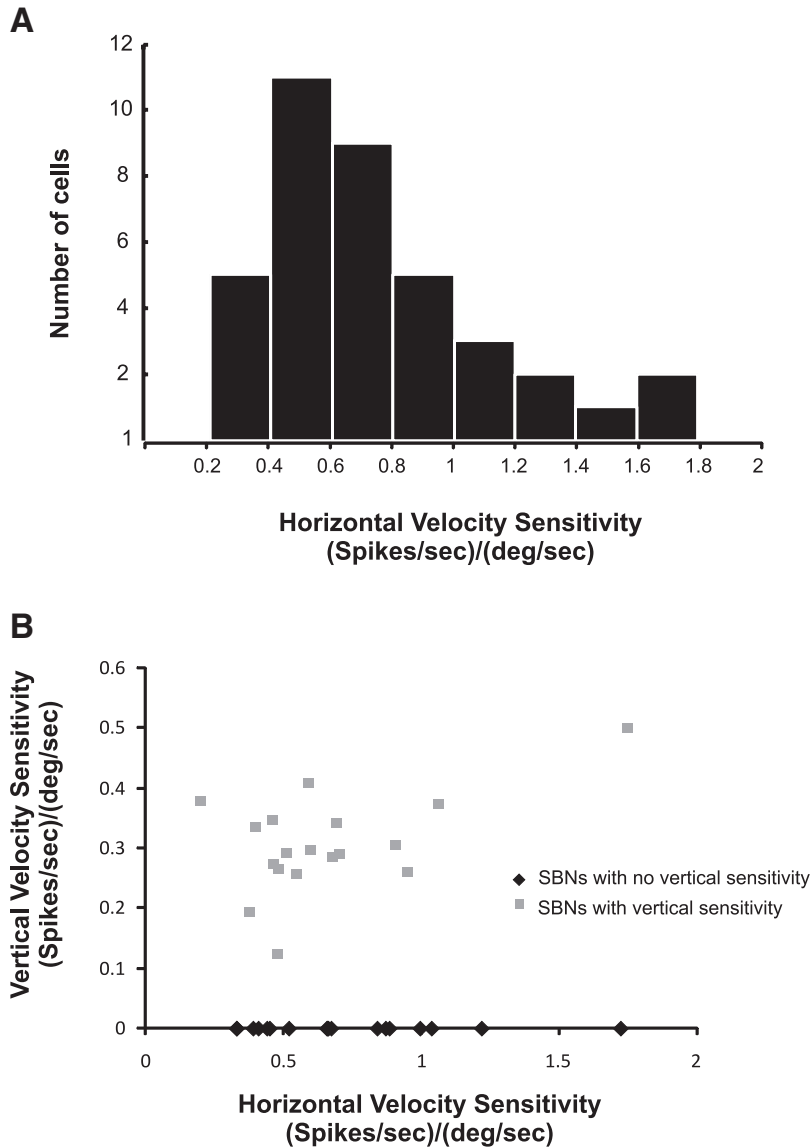


FIG. 7. *A*: distribution of horizontal sensitivities of SBNs estimated during conjugate saccades. *B*: a neuron-by-neuron comparison of horizontal and vertical sensitivities estimated during ipsilateral and vertical saccades, respectively. Neurons that were silent (i.e., no neuronal discharge) during vertical saccades are represented by filled circles and neurons that burst during vertical saccades are represented by gray squares.

made between near and far targets. Notably, such saccades require the generation of commands to make a vertical conjugate saccade, which would originate from vertical SBNs in the riMLF (Büttner et al. 1977; Crawford and Vilis 1991, 1992; King and Fuchs 1979; Missal et al. 2000; Moschovakis et al. 1991a,b) and vergence (but not horizontal conjugate) eye movements. Thus we could more directly test the hypothesis that the vergence information encoded by the classical hori-

zontal saccadic pathway is consistent with the vergence facilitation that occurs during saccades.

We first established that vergence velocities are significantly facilitated when vertical saccades are made between targets located at different distances. Next, we tested whether horizontal SBNs encode monocular commands that are appropriate to account for the facilitation of vergence during these vertical saccades, even though the commanded saccade had no signif-

TABLE 2. Average predictions: VAFs and Δ BIC

Ocular Category	<i>n</i>	VAF _{Pred-CJ}	VAF _{Pred-Pref}	VAF _{Est-Bino}	VAF _{Est-Pref}	Δ BIC
Monocular						
Ipsilateral eye preference	15	0.39 \pm 0.27	0.45 \pm 0.25	0.50 \pm 0.20	0.50 \pm 0.20	0.007 \pm 0.08
Contralateral eye preference	9	0.38 \pm 0.25	0.42 \pm 0.28	0.37 \pm 0.18	0.36 \pm 0.18	0.020 \pm 0.04
Binocular						
Ipsilateral eye preference	6	0.27 \pm 0.20	0.37 \pm 0.18	0.47 \pm 0.24	0.44 \pm 0.19	0.350 \pm 0.40
Contralateral eye preference	4	0.20 \pm 0.21	0.25 \pm 0.18	0.51 \pm 0.18	0.41 \pm 0.25	0.210 \pm 0.42
Conjugate	4	0.38 \pm 0.43	0.38 \pm 0.43	0.49 \pm 0.05	0.49 \pm 0.05	0.000 \pm 0.00

Values are averages \pm SDs. *n*, number of neurons; VAF, variance-accounted-for; BIC, Bayesian information criterion; Pred, prediction; Est, estimation; CJ, conjugate; Pref, preferred eye; Bino, binocular model. For example, VAF_{Pred-CJ} is the VAF resulting from predicting the firing rate using the conjugate velocity; VAF_{Est-Pref} is the VAF resulting from estimating the firing rate using the preferred eye velocity. Δ BIC = BIC binocular model – BIC preferred eye model.

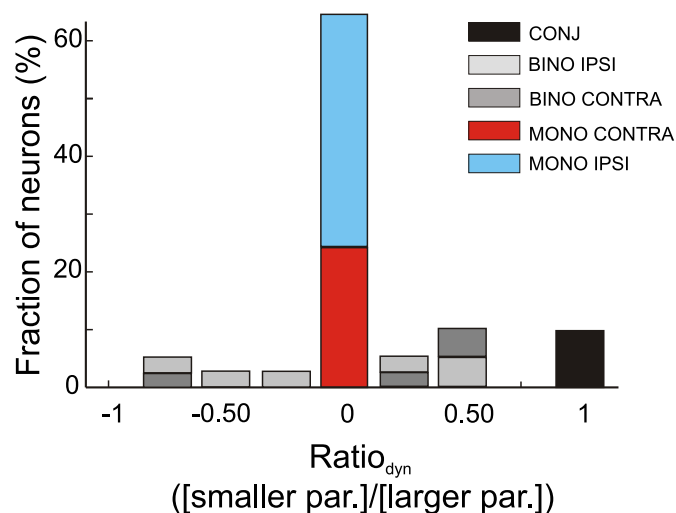


FIG. 8. Distribution of $\text{Ratio}_{\text{dyn}}$ indexes for SBNs. For each neuron, a $\text{Ratio}_{\text{dyn}}$ index was calculated using: [smaller parameter value]/[larger parameter value], where the smaller and larger parameter values are yielded by the nonpreferred and preferred eyes, respectively. The majority of the SBNs encoded the velocity of the ipsilateral eye.

icant horizontal conjugate component. We find that the majority of the SBNs preferentially encode the movement of a specific eye during both vertical and horizontal saccades that are made in depth. Thus our results are consistent with the proposal that the monocular command generated by the brain stem saccadic burst generator is for facilitating all shifts of vergence.

Vergence velocity is facilitated during vertical disconjugate saccades

In everyday life, we typically combine saccades and vergence to look between near and distant objects in three-dimensional space. During these orienting eye movements, there is general agreement that vergence velocity is facilitated (i.e., vergence velocities are greater than expected relative to saccade-free vergence of comparable amplitudes), whereas conjugate saccade velocities are slowed. Although most previous studies have focused on the facilitation that occurs when vergence movements are made in combination with horizontal saccades (Busetini and Mays 2005a; Collewijn et al. 1997; Enright 1984, 1992; Maxwell and King 1992; Ono et al. 1978; Oohira 1993; Van Horn et al. 2008; van Leeuwen et al. 1998; Zee et al. 1992), there had been some evidence for the facilitation vergence velocity during vertical saccades (Busetini and Mays 2005a; Enright 1984; Kumar et al. 2005; Maxwell and King 1992; van Leeuwen et al. 1998). However, because these studies characterized vertical saccades with nonnegligible horizontal components (Busetini and Mays 2005a) or did not methodically examine changes in horizontal conjugate position (Enright 1984; Ono et al. 1978; van Leeuwen et al. 1998), the possibility that the observed facilitation might be, at least in part, due to horizontal saccadic interactions, had been left open.

In the present study we limited our analysis to saccades for which vertical component of the movement was $\geq 90\%$ of total movement amplitude and found that during vertical saccades vergence velocities reached values as large as $300^\circ/\text{s}$ compared with saccade-free movements where ve-

locities were generally $< 100^\circ/\text{s}$. Our findings were consistent with those of prior reports, although in our study downward convergence was slower than upward convergence, whereas van Leeuwen et al. (1998) found the opposite tendency in humans.

Vergence and vertical velocities are temporally aligned during vertical saccades in monkeys

Horizontal gaze shifts between targets located at different depths are characterized by the synchronized occurrence of saccadic and vergence movements (Busetini and Mays 2005a; Enright 1984; Kumar et al. 2005; Maxwell and King 1992; van Leeuwen et al. 1998; Zee et al. 1992). This finding has been used as evidence for the proposal that the neural circuitries commanding horizontal saccades and vergence interact (Collewijn et al. 1997). In the present study we further show that when vertical saccades are made between far and near targets, the peak vergence and vertical velocities are generally temporally aligned in monkey. Specifically, peak vergence velocity peaked roughly 3–4 ms after peak vertical velocity. This finding was consistent regardless of whether gaze was shifted to/or from a lower or higher more distant target.

Similar temporal alignments have also been recently reported for humans during comparable tasks (Kumar et al. 2005; van Leeuwen et al. 1998; Zee et al. 1992). For example, most recently, Kumar et al. (2005) reported dissociation intervals that were on the order of about 4–20 ms for the majority of the trials. Notably, however, Kumar and colleagues (2005) did observe that in trials where human subjects shifted their gaze from a lower distant target to a near higher target (i.e., Converge-Up), the occurrence of peak convergence velocity could be considerably delayed relative to peak vertical velocity (delays generally > 40 and as large as 320 ms). In the present study, we rarely (e.g., $< 5\%$) observed such delays. Moreover, the few trials that had larger dissociation intervals were characterized by vergence movements that began after the onset of the vertical saccade and had velocity profiles resembling those of saccade-free vergence velocity ($\sim 50^\circ/\text{s}$). Thus the results indicate that the synchronized occurrence of a saccade is important for the facilitation of vergence velocities in monkey.

Dynamics of SBNs during horizontal and vertical conjugate saccades

Previous studies, which have used system identification techniques to characterize SBN discharge during horizontal conjugate and disconjugate saccades, have demonstrated that SBNs encode saccade trajectories in their spike trains. In particular, a clear relationship between EBN and IBN firing rates and eye movement dynamics has been described (Cullen and Guitton 1997; Sylvestre and Cullen 2006; Van Horn et al. 2008). Here, we demonstrate that this approach can be extended to describe the responses of SBNs during vertical and oblique saccades.

Although all neurons recorded in this study discharged primarily for ipsilaterally directed saccades the directional tuning differed between neurons. In particular, approximately half of the neurons in our sample were broadly tuned and were not completely silent during vertical saccades. This result is in

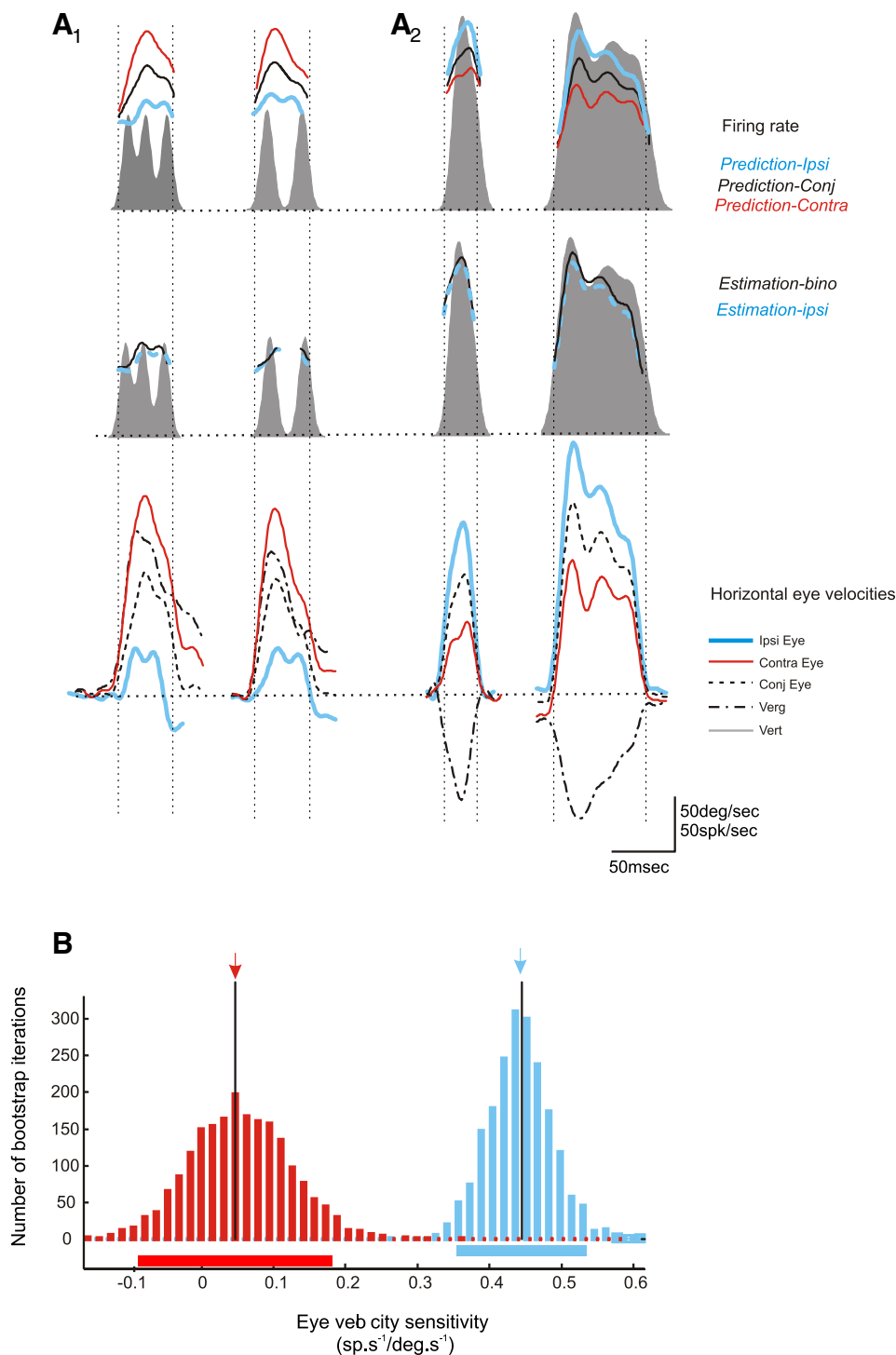


FIG. 9. Neuronal responses and model fits for the same neuron shown in Figs. 5 and 6 when a horizontal saccade is combined with a vergence movement (A_1 : converging disconjugate saccade when the contralateral eye moves more; A_2 : diverging disconjugate saccades when ipsilateral eye moves more; 2 example movements are shown for each behavior). Predicted model fits using ipsilateral, conjugate, and contralateral eye velocities are shown in the *top row* in blue, black, and red, respectively ($VAF_{\text{ipsi}} = 0.46$; $VAF_{\text{conj}} = 0.39$; $VAF_{\text{contra}} = 0.15$). Estimated model fits using the binocular model and reduced ipsilateral model are shown in the *2nd row*. *B*: bootstrap histograms and 95% confidence intervals (thick horizontal bars) for this neuron. Note the 95% confidence interval for the contralateral eye (red bar) overlaps with zero.

agreement with many previous studies that have also reported SBNs with broad tuning curves (Cullen and Guitton 1997; Hepp and Henn 1983; Kaneko 2006; Scudder et al. 1988; Strassman et al. 1986a,b). Although a metric-based analysis performed by Scudder et al. (1988) did report that the number of spikes generally increased for larger vertical movements this is the first study to describe the dynamic relationship between SBN discharge and eye velocity during vertical and/or oblique saccades. We found that for SBNs that were not completely silent during vertical saccades, the firing rates during vertical sac-

cades were dynamically related to vertical eye velocity (see Supplemental Table S1). Furthermore, the discharge characteristics during horizontal and vertical saccades could be used to accurately predict the firing rate of all SBNs during oblique saccades that had varying vertical and horizontal components.

SBNs contribute to increasing vergence velocities during disconjugate saccades

We have previously shown that the saccadic burst generator in the PPRF, which was commonly thought to encode horizon-

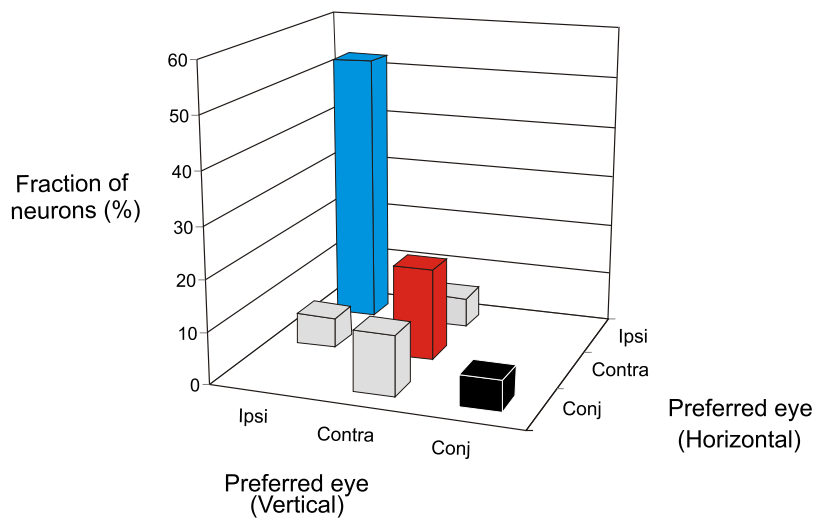


FIG. 10. Coherence of the preferred eyes for vertical and horizontal facilitated vergence. The *x*- and *y*-axes plot the 3 preferred eye categories (Ipsi, ipsilateral; Contra, contralateral; Conj, conjugate) and the *z*-axis plots the fraction of neurons. Solid blue, red, and black columns indicate coherence between the 2 behaviors and gray bars indicate the absence of coherence.

tal conjugate saccades (Busettini and Mays 2005b), in fact provides temporally appropriate vergence information to facilitate vergence during horizontal disconjugate saccades (Van Horn et al. 2008). In particular, the information was encoded in terms of an individual eye, where the majority of the neurons encoded the movement of the ipsilateral eye. In the present study, we tested the prediction that if the monocular commands issued by the SBNs are important for facilitating vergence during horizontal saccades they should also contribute to facilitating vergence associated with a vertical saccade when the conjugate component of the movement is negligible. As predicted, we found that SBNs are also well suited for facilitating vergence during a vertical saccadic eye movement. In particular, SBNs contribute to generating increased vergence velocities by dynamically encoding the movement of an individual eye rather than the conjugate component of the movement.

To directly compare our present results with those previously described (Van Horn et al. 2008), we recorded a subset of SBNs during both horizontal- and vertical-facilitated vergence. On a neuron-by-neuron basis, we found that SBNs have similar ocular preferences during both conditions. For example, a neuron that was found to dynamically encode the movement of the ipsilateral eye during horizontal disconjugate saccades was also found to encode the movement of the ipsilateral eye during vertical-facilitated vergence. Taken together with previous findings (Van Horn et al. 2008), this implies that the command provided by a given SBN is appropriate for facilitating shifts of vergence during disconjugate saccades by encoding integrated conjugate and vergence commands.

Interestingly, a number of neurons in this study were found to encode the movement of the “wrong” eye (e.g., the contralateral eye) or a combination of both eyes (e.g., binocular cells). This finding is consistent with the results of previous studies that have evaluated the responses of neurons in other premotor and motor nuclei. For instance, individual neurons in both the nucleus prepositus and abducens nucleus can preferentially encode the movement of either the contralateral or ipsilateral eye (McConville et al. 1994; Sylvestre and Cullen 2002; Sylvestre et al. 2003; Van Horn et al. 2008; Zhou and King 1998). Although at first glance this observation might appear surprising, it can be easily reconciled with the existing

circuitry. First, the abducens nucleus consists of both internuclear and motoneurons and neurons. Thus a premotor neuron (such as an EBN) that preferentially encodes information about the contralateral eye may in fact project to the appropriate eye through internuclear neurons. Second, although neurons are generally assumed to have equal synaptic weights, unequal weighting of the projections most certainly exists. For example, premotor neurons that encode the movement of the ipsilateral eye may provide stronger synaptic inputs to the motoneurons. Finally, inappropriate signals that are sent to abducens nuclei could be both cancelled out by additional premotor inputs such that the final drive to the lateral rectus muscle is correct and/or offset by a cocontraction of the antagonist muscle (i.e., medial rectus; see DISCUSSION of Sylvestre and Cullen 2002).

Premotor circuits for the control of changes in vergence angle

Although SBNs have been shown to carry vergence-related (e.g., monocular) information during disconjugate saccades, two important questions remain when considering the neural control of gaze in three-dimensional space: 1) What is the source of the vergence-related information to the horizontal SBNs? and 2) What additional vergence commands are required to drive nonsaccadic vergence movements (i.e., when the saccadic burst generator is silent)?

First, although it is well recognized that information about an individual eye is available throughout most of the visual and visual-motor cortex the source of monocular information to the SBNs remains unknown (Gnadt and Beyer 1998; Hubel and Wiesel 1962, 1970). Two possible candidates are the mesencephalic reticular formation (MRF) and superior colliculus (SC) (Ferraina et al. 2000; Genovesio and Ferraina 2004; Gnadt and Beyer 1998; Gnadt and Mays 1995; Mimeault et al. 2004). Both of these structures receive inputs from disparity-sensitive cortical and subcortical regions and stimulation of both the MRF (goldfish: Luque et al. 2006; monkey: Waitzman et al. 2008) and SC (monkey: Chaturvedi and Van Gisbergen 1999, 2000; Suzuki et al. 2004; cat: Suzuki et al. 2004) have clear effects on vergence. Moreover, neurons in the SC (cat: Jiang et al. 1996; monkey: Walton and Mays 2003) and the

MRF (Gamlin et al. 1994; Judge and Cumming 1986; Mays et al. 1986; Waitzman et al. 2008) are modulated during vergence eye movements. Notably, a recent report has shown that saccade-related burst neurons in the central MRF dynamically encode the movement of an individual eye during disjunctive saccades (Waitzman et al. 2008). These findings further support the proposal that inputs from the MRF and SC to the saccadic premotor neurons function in parallel with the cortico-pontine-cerebellar-midbrain loop, which has traditionally been viewed as the main pathway for the control of vergence (reviewed in Gamlin 1999). Although the traditional view describes the vergence and saccadic pathways as two distinct neural systems, our results, taken together with those of other recent studies, support the proposal that changes in vergence angle are controlled by means of a more distributed network.

Second, although we have clearly demonstrated that SBNs carry important vergence-related information to control saccades in three-dimensional space, SBNs are silent during slow vergence movements. For example, we have previously shown that the saccadic burst generator does not fire any action potentials during symmetric vergence as well as during periods of slow vergence that precede or follow disconjugate saccades (Van Horn et al. 2008). Thus this suggests that, whereas the SBNs function to rapidly drive the eyes to a new position, an additional vergence command is required to ensure accurate binocular realignment of gaze (King and Zhou 2000). Notably, neurons encoding slow vergence, which have been described near the abducens nucleus (Gnadt et al. 1988) and oculomotor nucleus (Judge and Cumming 1986; Mays 1984; Zhang et al. 1991, 1992), are likely candidates to drive such eye movements. Further work will be required to understand how neural circuits in the brain stem and cerebellum interact with descending control pathways to ensure the accurate control of gaze in three dimensions.

ACKNOWLEDGMENTS

We thank S. G. Sadeghi, C. Massot, J. Brooks, and M. Jamali for critically reading the manuscript and S. Nuara, W. Kucharski, and J. Knowles for excellent technical assistance.

GRANTS

This study was supported by Canadian Institutes of Health Research, Natural Science and Engineering Research Council of Canada, and Fonds de la Recherche en Santé du Québec.

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