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RESEARCH ARTICLE

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Temporal characteristics of neurons in the central mesencephalic reticular formation of head unrestrained monkeys

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Abstract The accompanying paper demonstrated two distinct types of central mesencephalic reticular formation (cMRF) neuron that discharged before or after the gaze movement: pre-saccadic or post-saccadic. The movement fields of pre-saccadic neurons were most closely associated with gaze displacement. The movement fields of post-saccadic neurons were most closely associated with head displacement. Here we examine the relationships of the discharge patterns of these cMRF neurons with the temporal aspects of gaze or head movement. For pre-saccadic cMRF neurons with monotonically open movement fields, we demonstrate that burst duration correlated closely with gaze duration. In addition, the peak discharge of the majority of pre-saccadic neurons was closely correlated with peak gaze velocity. In contrast, discharge parameters of post-saccadic neurons were best correlated with the time of peak *head* velocity. However, the duration and peak discharge of post-saccadic discharge was only weakly related to the duration and peak velocity of head movement. As a result, for the majority of post-saccadic neurons the discharge waveform poorly correlated with the dynamics of head movement. We suggest that the discharge characteristics of pre-saccadic cMRF neurons with monotonically open movement fields are similar to that of direction long-lead burst neurons found previously in the paramedian portion of the pontine reticular formation (PPRF; Hepp and Henn 1983). In light of their anatomic connections with the PPRF, these pre-saccadic neurons could form a parallel pathway that participates in the transformation from the spatial coding of gaze in the superior colliculus (SC) to the temporal coding displayed by excitatory burst neurons of the PPRF. In contrast, closed and non-monotonically open movement field pre-saccadic neurons could play a critical role in feedback to the SC. The current data do not support a role for *post*-saccadic cMRF neurons in the direct control of head movements, but suggest that they may serve a feedback or reafference function, providing a signal of current head amplitude to upstream regions involved in head control.

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Introduction

The central mesencephalic reticular formation (cMRF) is a region of the midbrain that is anatomically and physiologically positioned to directly participate in the control of gaze (Chen and May 2000; Waitzman et al. 2002). The accompanying paper demonstrated that the cMRF harbors two distinct groups of neurons, pre- and post-saccadic, that have spatial properties related to the displacement of gaze and head movements, respectively (Pathmanathan et al. 2005). The objective of the current paper was to test the idea that the discharge of each group of cMRF neurons also carries temporal signals that could direct gaze or head movement.

The instantaneous discharge rate of the oculomotor neuron burst preceding saccades encodes eye velocity (Robinson 1975). As a result, the integral of this burst (i.e., change in spike number) correlates closely with saccade displacement (Luschei and Fuchs 1972; Henn

and Cohen 1976). While the discharge rate of active SC neurons has been correlated with the velocity of the gaze or eye movement (Berthoz et al. 1986; Munoz et al. 1991; Waitzman et al. 1991; Stanford et al. 1996), most studies are in agreement that single superior colliculus (SC) neurons do not carry a monotonically increasing signal that encodes eye, head, or gaze displacement (Sparks and Gandhi 2003). This has the question of how an instantaneous eye velocity/saccade displacement signal is developed from the spatially coded signals found in the SC and frontal eye fields. To further complicate matters, recent experiments have demonstrated that neurons in the intermediate and deep layers of the SC begin to discharge in advance of *gaze* movements (eye + head movement) and are organized in a topographic map of contraversive desired *gaze displacement* (Sparks et al. 1976; Freedman and Sparks 1997a). Thus, the collicular output must be utilized to generate pre-motor, temporal signals to move both the eyes *and* the head. The details of how the skeletal motor system specifies the signals required to move the head during voluntary gaze movements are poorly understood (Peterson 2004).

The question then arises as to whether the requisite temporal activity needed to command eye and head movements could be generated in the course of a single tectofugal synapse. This could occur via collicular projections to the paramedian portion of the pontine reticular formation (PPRF) and nucleus reticularis gigantocellularis (NRG), to drive eye and head movements, respectively. It has been proposed that signals from the colliculus could be transformed into a temporal code as a result of the specific anatomic distributions of collicular efferents in these tecto-recipient structures (Moschovakis et al. 1998; Grantyn et al. 2002). In such a schema, the arrangement of tectal efferent pathways (which provide a higher density of projections from the caudal than rostral SC) could generate the higher discharge rates, which are observed for larger/faster saccades. However, the distribution density could not completely account for the transformation from spatial encoded gaze displacement to the rate code needed to move the eyes (Moschovakis et al. 1998; Grantyn et al. 2002).

A number of other physiological mechanisms have been invoked to augment the graded projection hypothesis. A shift of activity across the collicular map from caudal to rostral was suggested as one possibility (Munoz and Wurtz 1995b). A similar concept displaced the location of this shifting process from the SC to the cerebellar vermis (Quaia et al. 1999). Both of these ideas suffer from a lack of physiological evidence in primates to support the necessary shift in activity across the SC (Anderson et al. 1998; Moschovakis et al. 2001; Soetedjo et al. 2002a) or the vermis (Robinson and Fuchs 2001).

It has been even more difficult to describe a specific neuronal mechanism for transforming spatially coded gaze information at the level of the SC into the temporal pattern of activity required to move the *head*. Electromyographic (EMG) data from cervical muscles has demonstrated activity throughout the head movement including when gaze in space is stable (Corneil et al. 2001). Since head amplitude (Freedman and Sparks 1997b) and final head position (Bizzi et al. 1976; Phillips et al. 1995; Freedman and Sparks 1997b) are independently controlled variables that are not believed to be encoded by SC neurons, these signals must arise co-operatively from a different source (King et al. 1991; Corneil et al. 2002). The observation that deafferentation of neck musculature has little effect on either final head position or head displacement (Bizzi et al. 1976) strongly implies that these signals originate within the brainstem (Tweed et al. 1998). Moreover, once gaze is stable during voluntary gaze shifts the head continues to move while the eyes recenter in the orbit. As a result, the temporal signals controlling such head movements must outlast those required to shift gaze. Thus, the SC gaze signals could provide activity to the NRG that would *initiate* head movement, but could not be responsible for guiding the head's final trajectory once gaze is stable. Taken together, these findings suggest that the neurons and the distribution of projections of the SC *alone* do not generate the prolonged activity necessary to move the head, nor the correct activation sequence necessary to develop the spatial to temporal transformation required to move the eyes.

Naturally, the observation that the cMRF contains two groups of neurons, one associated with gaze movements and the other associated with head movements (Pathmanathan et al. 2005), raised the possibility that these neurons could participate in the transformation of SC spatial signals into the temporal patterns of discharge required to control gaze or head movements. This hypothesis is supported by the close coupling of the cMRF both anatomically and physiologically with the SC, as well as its projections to the eye and putative head pre-motor regions (e.g., the NRG). To explore this possibility, we examined the relationships of these neurons to gaze or head movements in specific temporal domains. Initially we posed the broad question of whether the discharge of each group of cMRF neurons was more closely associated with temporal parameters of the gaze or head movement. We then examined three specific temporal relationships: (1) Is there a relationship between burst duration and either the duration of the gaze or head movement; (2) Is there an association between peak gaze or head velocity and peak discharge rate; and (3) Is the cMRF discharge pattern correlated with the movement dynamics (e.g., velocity waveform) of gaze or head movements? If the cMRF provides input to the pre-motor structures involved in gaze or head control we would expect these relationships to be evident. Preliminary reports of this data have appeared previously (Pathmanathan et al. 2002; Pathmanathan and Waitzman 2003).

Methods

The same monkeys and neurons that were reported in the previous paper served as the data sample for the current paper. Therefore, the methods of preparation and recording were exactly the same as in the accompanying paper (Pathmanathan et al. 2005). The following additional methods were used to analyze the temporal aspects of the neuronal data.

Data analysis

Neuronal bursts were detected using an automated computational algorithm. A spike density function was generated by convolving the neuronal spike train with a Gaussian curve ($\delta = 4$ ms) to provide an estimate of discharge rate (Silverman 1986). The start and end of neuronal bursts were determined by smoothing the spike density function using a moving average filter (30 point parabolic, center-weighted). Possible bursts were considered to be periods when the discharge exceeded two standard deviations above the mean spontaneous discharge rate (as described in the accompanying paper, Pathmanathan et al. 2005). We then determined the peak discharge during these intervals. The start and end of the burst were considered as the times when the smoothed spike density function exceeded or returned to within 10% of the peak discharge minus the mean level (Waitzman et al. 1996). Note that the smoothing process was used *only* to establish the times of burst onset and offset. Once these analytic endpoints were established, spike counts were obtained. Traces of spike density used for data analysis or display in figures were not smoothed. This approach was verified both visually and using the modified Poisson spike train analysis technique (Hanes et al. 1995), which uses inter- spike interval to determine burst onset and offset.

To determine if parameters of the burst (i.e., burst onset, peak discharge, or the end of the burst) were temporally related to aspects of the movement (i.e., gaze or head onset, gaze or head peak velocity, or the end of the gaze or head movement), we correlated the latency to burst parameters with the latency to individual movement parameters. For example, we would expect that a neuron whose discharge was related to gaze velocity should demonstrate a correlation between the time of peak discharge and the time of peak gaze velocity. Movements selected for this analysis were directed along the neuron's preferred direction ($\pm 15°$) and had a burst detected within 50 ms of any movement parameter. Note that these criteria could include movements for which there was no head movement, in which case the trial was not used to determine correlation to head movement parameters. Eight pre-saccadic neurons were not recorded with a sufficient number of head movements in the optimal direction to generate correlations to head movement parameters. We classified these neurons as having no significant correlations to head movement parameters.

Latency measurements were calculated as the time of the event from a specified zero point (origin). To be useful, the origin must occur within a short time of the parameters of interest and must be measured reliably for each trial recorded for each neuron. Thus, an origin such as target onset could not be chosen, because it occurred a variable and long period of time before the primary events of each trial (i.e., the burst and gaze or head movement parameters). Had target onset been selected, correlations between these parameters would have been artificially inflated by the long interval to the burst and movement events (Rodriguez 1982). Furthermore, use of target onset would have precluded inclusion of spontaneous movements made in darkness. As a result, we used parameters of the gaze and head movement as the zero point. For the primary analysis, gaze onset was chosen as the origin (as shown in Fig. 1a) for three reasons: (1) It occurred in every trial for both pre- and post-saccadic neurons; (2) It occurred within a short time span that included the movement and burst; and (3) It could be measured reliably. In order to calculate the latency to gaze onset, the analysis was repeated using the *end* of gaze movement as the origin. This repeat approach permitted the calculation of correlations between burst parameters and the onset of gaze. It also brought the origin closer to the head movement parameters and post-saccadic discharge, and served as a check for correlations obtained with gaze onset as the origin.

We were most interested in deciding whether a particular neuron was temporally more closely associated with gaze or head parameters. The above analytic approach generated 18 correlations for each neuron (nine gaze-related and nine head-related, shown in Supplementary Electronic Table 3). Because of the large number of correlations and relatively small number of neurons in our sample, we do not discuss the relevance of significant correlations observed for a single neuron. Instead, only broad relationships in the population of pre- and post-saccadic neurons were analyzed. Therefore, to decide if a neuron was better correlated with gaze or head parameters, the correlations were paired into 9 gaze/head sets (e.g., time of burst onset versus time of gaze or head onset, time of peak discharge versus time of peak gaze or head velocity, etc., see Fig. 4c). For each set, we counted the neurons with statistically significant correlations to the gaze and head parameter, as shown Fig. 4a for latency to peak burst versus peak movement velocity. A McNemar test of paired proportions was used to calculate the probability that the observed distribution of significant correlations (to either gaze or head parameters) could have been generated by chance alone (McNemar 1947). A p value was determined from the chi-square distribution:

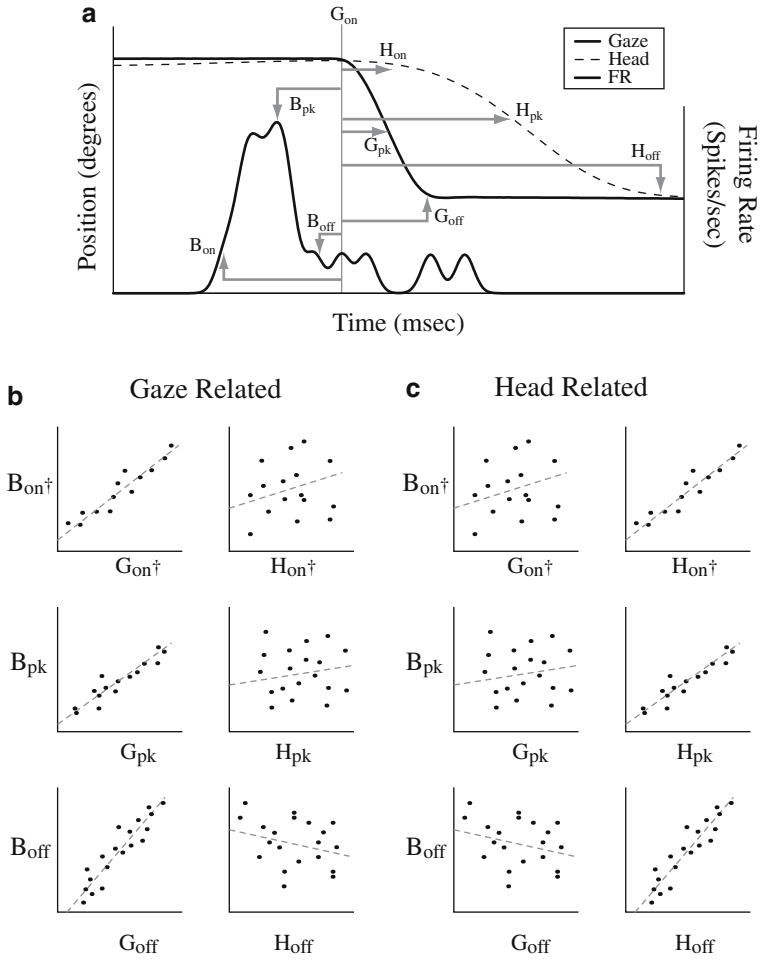

Fig. 1 Relationships between discharge and gaze or head movement. **a** the occurrence of each time interval is shown relative to gaze onset (G_{on}) for a single trial. For each trial, the times from gaze onset (G_{on}) to burst onset (B_{on}), peak discharge (B_{pk}), and burst offset (B_{off}) were measured. These times were correlated with times from gaze onset to peak gaze velocity (G_{pk}), end of the gaze movement (G_{off}), head movement onset (H_{on}), peak head velocity (H_{pk}), or end of the head movement (H_{off}). In this illustration, gaze onset is taken as the zero point (*vertical line* from which latencies are measured). Therefore, the correlation between burst parameters and latency to gaze onset could not be calculated. In order to compare the time of gaze onset to burst parameters, the calculations were repeated using gaze end (G_{off}) as the zero point (not shown). **b** if a neuron's discharge were gaze-related, we would expect that the time between bursts and gaze events would be consistent between trials. Therefore, we would expect strong correlations between the timing of burst and gaze parameters (e.g., B_{on} highly correlated with G_{on}, B_{pk} with G_{pk}, and/or B_{off} with G_{off}) (*left column*). No such relationship would be expected with head parameters (*right column*). **c** conversely, neurons related to the head movement would be expected to demonstrate strong correlations between burst and head movement event timings (*right column*), but little correlation to gaze movement timings (*left column*). *Dagger* indicates that the latencies were calculated using gaze offset rather than gaze onset as the zero point

$$\chi^2 = \frac{(|b-c|-1)^2}{b+c} \quad (1)$$

where χ^2 is the chi-square test statistic with one degree of freedom, b is the number of neurons with statistically significant correlations to the gaze (but not head) parameter ("Block B" in Fig. 4a, b), and c is the number of neurons with statistically significant correlations to the head (but not gaze) parameter ("Block C" in Fig. 4a, b). For this test, the null hypothesis states that a particular group of neurons (e.g., pre- and post-saccadic) would demonstrate, on average, an equal number of significant correlations to gaze or head parameters. Because nine pairings were subjected to repeated statistical testing (as shown in Fig. 4c), the Bonferroni correction for multiple comparisons was applied (Miller 1985). Using this correction, the null hypothesis was rejected at p values less than 0.0056 (0.05 divided by 9) and the probability of falsely rejecting any of the nine null hypotheses was maintained at the desired level of 0.05. A significant p value indicated that the population tested was better related to parameters of either gaze or head movement.

Dynamic analysis

To determine if movement-related information was encoded within the temporal pattern of the spike train, we

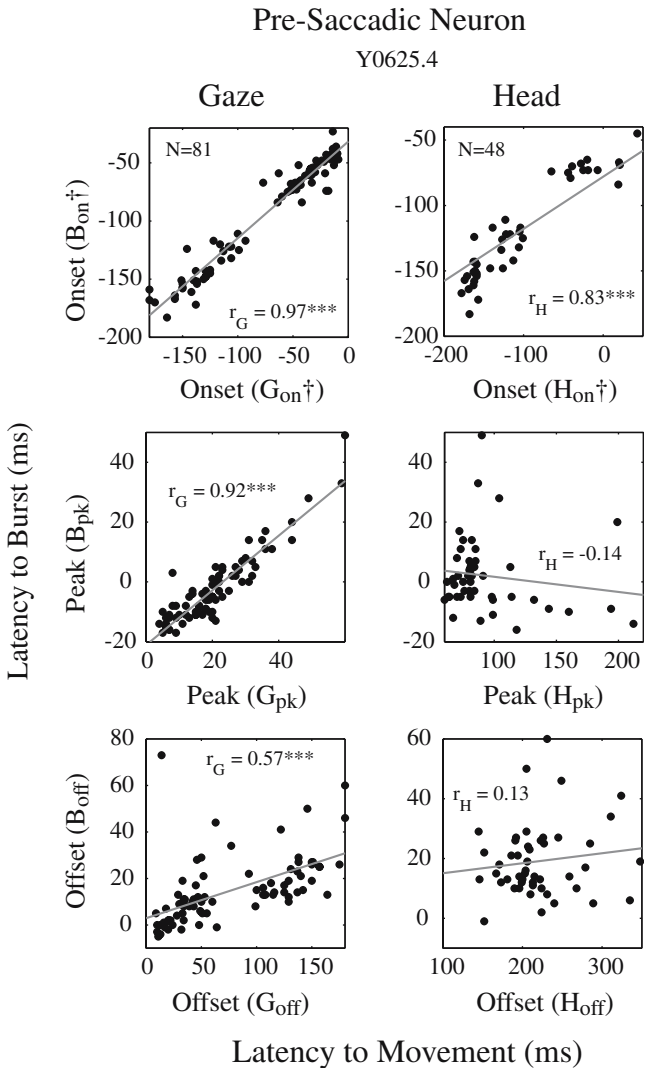

Fig. 2 Correlation of burst and movement latencies for a pre-saccadic neuron. Pre-saccadic neurons demonstrated strong correlations between burst and gaze parameters (*left column*), but not to head parameters (*right column*). Such a pattern suggests that pre-saccadic neurons participate in gaze, but not head movement control. The significance of the correlation coefficients is indicated by *asterisks* (* represents $p < 0.05$; ** represents $p < 0.01$; and *** represents $p < 0.001$). Note that more gaze than head movements were analyzed because some trials did not include a head movement. Therefore, the *right column* only includes trials with head movements. *Dagger* indicates that the latencies were calculated relative to gaze offset rather than gaze onset.

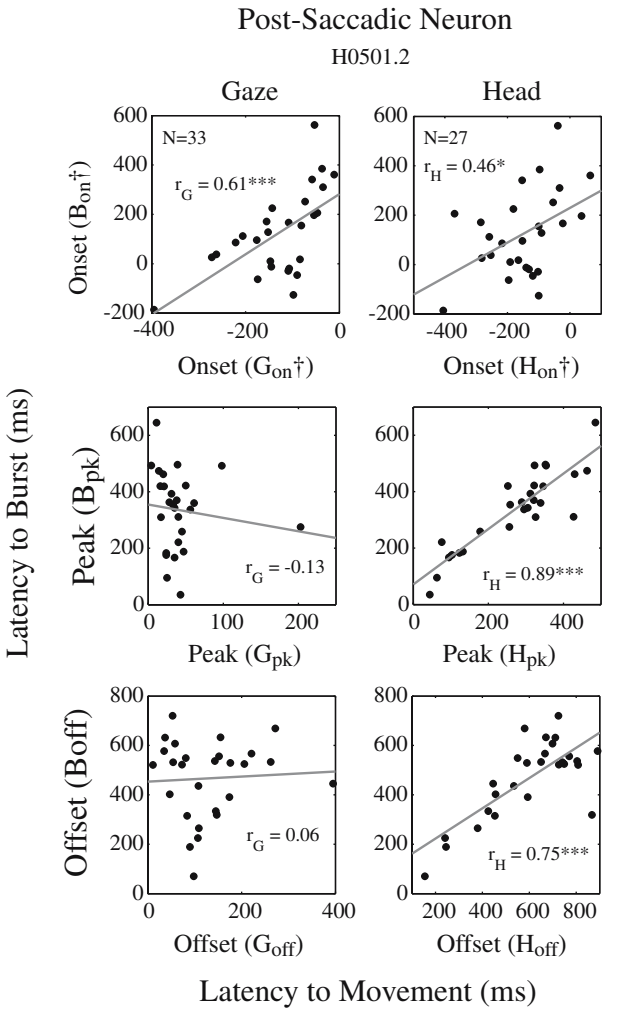

Fig. 3 Correlation of burst and movement latencies for a post-saccadic neuron. Post-saccadic neurons demonstrated stronger correlations between burst and *head* parameters (*right column*), but not to gaze parameters (*left column*). Note that this cell had the best correlations between peak burst (B_{pk}) and peak *head* velocity (H_{pk}) and between burst offset (B_{off}) and *head* offset (H_{off}). Conventions are exactly the same as in Fig. 2.

used a previously described system identification technique (Cullen et al. 1996). Briefly, this method fit the actual neuronal firing rate (as measured by the spike density function) with a mathematical model based on dynamic components of the eye, head, or gaze movement. For example, a model predicting that the neuronal firing pattern encodes gaze position, velocity, and acceleration would be:

$$\mathrm{FR}_{\mathrm{Est}}(t) = a \times G(t+td) + b \times \dot{G}(t+td) + c \times \ddot{G}(t+td) + \mathrm{bias} \quad (2)$$

where $\mathrm{FR}_{\mathrm{Est}}(t)$ is the estimated neuronal firing rate at time t; $G\ (t+td)$, $\dot{G}(t+td)$, and $\ddot{G}(t+td)$ are gaze position, velocity, and acceleration, respectively, at time $t+td$(where td is the time delay, or latency, from neuronal activity to movement); a, b, and c are constant gain terms for the position, velocity, and acceleration, respectively; and bias is a constant offset. Note that a model based exclusively on velocity would retain the bias but not include position or acceleration terms. The estimated firing rate was then compared to the actual neuronal firing rate to determine how well the model matched the real discharge. Goodness of fit was determined by the percentage of the variance of the actual firing rate accounted for (VAF) by the selected parameters (e.g., position, velocity, and acceleration) of the model:

a Pre-Saccadic Neurons

Relationship Between B_{pk} and H_{pk}	Relationship Between B_{pk} and G_{pk}: Not Significant	Relationship Between B_{pk} and G_{pk}: Significant
H_{pk} Not Significant	Block A: 1	Block B: 23
H_{pk} Significant	Block C: 0	Block D: 3

b Post-Saccadic Neurons

Relationship Between B_{pk} and H_{pk}	Relationship Between B_{pk} and G_{pk}: Not Significant	Relationship Between B_{pk} and G_{pk}: Significant
H_{pk} Not Significant	Block A: 12	Block B: 0
H_{pk} Significant	Block C: 10	Block D: 0

c

	Burst Parameter	Movement Parameter	Significant Gaze Only	Significant Head Only	p
Pre-Saccadic Neurons	B_{on} †	G_{on}/H_{on} †	14	0	<0.001*
	B_{on}	G_{pk}/H_{pk}	20	0	<0.001*
	B_{on}	G_{off}/H_{off}	13	0	<0.001*
	B_{pk} †	G_{on}/H_{on} †	13	0	<0.001*
	B_{pk}	**G_{pk}/H_{pk}**	**23**	**0**	**<0.001***
	B_{pk}	G_{off}/H_{off}	20	0	<0.001*
	B_{off} †	G_{on}/H_{on} †	14	0	<0.001*
	B_{off}	G_{pk}/H_{pk}	20	0	<0.001*
	B_{off}	G_{off}/H_{off}	14	0	<0.001*
Post-Saccadic Neurons	B_{on} †	G_{on}/H_{on} †	1	1	0.48
	B_{on}	G_{pk}/H_{pk}	0	11	0.003*
	B_{on}	G_{off}/H_{off}	2	2	0.62
	B_{pk} †	G_{on}/H_{on} †	1	1	0.48
	B_{pk}	**G_{pk}/H_{pk}**	**0**	**10**	**0.004***
	B_{pk}	G_{off}/H_{off}	3	4	1
	B_{off} †	G_{on}/H_{on} †	2	1	1
	B_{off}	G_{pk}/H_{pk}	0	7	0.02
	B_{off}	G_{off}/H_{off}	2	5	0.45

Fig. 4 McNemar analysis for pre- and post-saccadic neurons. A McNemar analysis was used to statistically quantify the relationship between each population of neurons and gaze or head movement. If the population of pre-saccadic neurons was truly gaze-related, we would expect to observe more statistically significant correlations to parameters of gaze than parameters of head. The converse is true for post-saccadic neurons. **a** the number of significant and non-significant correlations between the latency to peak movement velocity and peak discharge is tabulated for the population of pre-saccadic neurons. There was one neuron that demonstrated no significant relationship between latency to peak discharge (B_{pk}) and either peak gaze (G_{pk}) or head (H_{pk}) velocity ("Block A"). Twenty-three neurons demonstrated a significant correlation between B_{pk} and G_{pk} but not H_{pk} ("Block B"). No pre-saccadic neuron demonstrated a significant correlation between B_{pk} and H_{pk} but not G_{pk} ("Block C"). Three neurons demonstrated significant correlations to both G_{pk} and H_{pk} ("Block D"). **b** the same tabulation is shown for the population of post-saccadic neurons. In this case, no post-saccadic neuron demonstrated a significant correlation to G_{pk} only ("Block B"), while ten neurons were significantly correlated to H_{pk} only. **c** for each of the nine burst and movement latency pairings, we tabulated the number of neurons with significant correlations to either gaze or head parameters only (third and fourth columns, respectively). A McNemar test (see Methods) was used to determine the probability of observing such a distribution if there was no relationship to either gaze or head movement (*p* value in *fifth column*). The *bolded entries* indicate the tabulations shown in **a** and **b**. Note that *p* values were considered significant (indicated by *) at a level below 0.0056 because nine pairings were examined. Pre-saccadic neurons demonstrated significant relationships to gaze parameters for all nine pairings, while only two pairings were significant for post-saccadic neurons (both correlated with *head* parameters). *Dagger* indicates that the latencies were calculated relative to gaze offset rather than gaze onset.

$$\mathrm{VAF} = 1 - \left[\frac{\mathrm{var}(\mathrm{FR}_{\mathrm{Est}} - \mathrm{FR})}{\mathrm{var}(\mathrm{FR})}\right] \quad (3)$$

where var is the variance over the analysis interval, FR_{Est} is the estimated firing rate, and FR is the actual firing rate. Higher VAF values (with a maximum of 1.00) suggest a better fit for that particular model for a particular cell. The constant parameters (e.g., *a, b, c*, bias, and *td*) were chosen so that the VAF was maximized. Note that the VAF provides a measure of the goodness of fit of the selected model to the neuronal firing rate and *not* a measure of the variance of the cell discharge.

To carry out this dynamic analysis, we compared movement data with an identical interval of the spike density function offset by the latency, *td*. When examining gaze models, the duration of the spike density trace equaled the duration of the gaze movement. When

Table 1 Correlations between burst and gaze parameters

Pre-saccadic neurons				Post-saccadic neurons			
Cell	Optimal	*r*	*p*	Cell	Optimal	*r*	*p*
h0915.5	NA	—	—	h0501.2	$B_{on}\_H_{pk}$	0.9	< 0.001
h0915.6	$B_{pk}\_G_{pk}$	0.96	< 0.001	h0915.3	$B_{off}\_H_{off}$	0.61	0.05
h0918.3	$B_{pk}\_G_{pk}$	0.9	< 0.001	h0929.1	$B_{pk}\_H_{off}$	0.5	0.003
h0918.4	$B_{pk}\_G_{pk}$	0.86	< 0.001	p0408.3	NA	—	—
h0919.1	$B_{pk}\_G_{pk}$	0.78	< 0.001	p0426.2	$B_{pk}\_H_{pk}$	0.39	0.01
h0919.2	$B_{pk}\_G_{pk}$	0.72	< 0.001	p0426.3	NA	—	—
h0929.2	$B_{pk}\_G_{off}$	0.49	< 0.001	r0609.1	NA	—	—
p0408.2	$B_{pk}\_G_{pk}$	0.85	< 0.001	r0609.2	NA	—	—
p0410.1	$B_{pk}\_G_{pk}$	0.57	< 0.001	r0609.4	$B_{on}\_H_{pk}$	0.78	< 0.001
p0417.1	$B_{off}\_G_{off}$	0.88	< 0.001	r0609.5	$B_{on}\_H_{pk}$	0.7	< 0.001
p0418.1	$B_{pk}\_G_{pk}$	0.9	< 0.001	r0609.6	NA	—	—
p0419.5	$B_{pk}\_G_{pk}$	0.91	< 0.001	r0610.3	NA	—	—
p0422.1	$B_{off}\_G_{off}$	0.75	< 0.001	r0616.23	$B_{on}\_H_{off}$	0.44	0.004
p0503.3	$B_{pk}\_G_{pk}$	0.62	< 0.001	r0622.6	NA	—	—
p0503.6	$B_{off}\_G_{off}$	0.58	< 0.001	r0623.3	$B_{pk}\_H_{pk}$	0.59	0.001
p0507.3	$B_{pk}\_G_{pk}$	0.9	< 0.001	r0804.6	$B_{pk}\_H_{pk}$	0.88	< 0.001
p0507.5	$B_{pk}\_G_{pk}$	0.78	< 0.001	r0805.3	$B_{pk}\_H_{pk}$	0.92	< 0.001
p0509.3	$B_{on}\_G_{off}$	0.59	0.006	r0805.4	$B_{on}\_H_{pk}$	0.9	< 0.001
r0616.4	$B_{pk}\_G_{pk}$	0.34	< 0.001	r0805.56	$B_{off}\_H_{pk}$	0.97	< 0.001
r0622.4	$B_{pk}\_G_{pk}$	0.88	< 0.001	y0614.1	$B_{pk}\_H_{pk}$	0.97	< 0.001
r0624.3	$B_{pk}\_G_{pk}$	0.88	< 0.001	y0618.1	NA	—	—
y0625.4	$B_{pk}\_G_{pk}$	0.92	< 0.001	y0618.4	$B_{on}\_H_{pk}$	0.38	0.01
y0904.1	$B_{pk}\_G_{pk}$	0.77	0.009				
y0904.2	$B_{pk}\_G_{pk}$	0.77	< 0.001				
y0906.1	$B_{pk}\_G_{pk}$	0.9	< 0.001				
y0906.2	$B_{pk}\_G_{pk}$	0.84	< 0.001				
y1009.hf	$B_{off}\_G_{pk}$	0.75	< 0.001				

NA indicates no correlation achieved statistical significance; B_{on} indicates latency to burst onset; B_{pk} indicates latency to peak discharge; B_{off} indicates latency to burst offset; G_{on} indicates latency to gaze onset; G_{pk} indicates latency to peak gaze velocity, G_{off} indicates latency to gaze offset; H_{on} indicates latency to head onset; H_{pk} indicates latency to peak head velocity; H_{off} indicates latency to head offset; $B_{pk}\_G_{pk}$ indicates the correlation between latency to peak discharge (B_{pk}) and latency to peak gaze velocity (G_{pk}); $B_{on}\_H_{pk}$ indicates the correlation between latency to burst onset (B_{on}) and latency to peak head velocity (H_{pk}).

examining head models, the duration of the spike density trace equaled the duration of the overall head movement. Latency values between ± 50 ms were tested in 1 ms increments. This analysis was initially performed on movements that best activated the neurons (i.e., the movements to within 5° of the optimal location). For pre-saccadic neurons, we also extended the analysis to include all movements along the preferred direction of each neuron (i.e.., movements directed to within ± 15° of the optimal direction, as in the cross-sections of Fig. 8 in the accompanying paper, Pathmanathan et al., 2005). We tested six different models: gaze velocity ($\dot{G} + b$); head velocity ($\dot{H} + b$); gaze velocity plus gaze position ($\dot{G} + G + b$); head velocity plus head position ($\dot{H} + H + b$); gaze acceleration + gaze velocity + gaze position ($\ddot{G} + \dot{G} + G + b$); and head acceleration + head velocity + head position ($\ddot{H} + \dot{H} + H + b$). We did not examine models that combined gaze and head velocity. The validity of additional terms was estimated using a cost index (Bayesian Information Criteria, BIC) (Schwartz 1978; Cullen et al. 1996). This index imposes a penalty for the addition of modeling terms. If the improvement in the model outweighs the "cost," the index decreases. Therefore, lower BIC values justify additional terms and suggest that they are valid.

Results

In the first paper of this series, we provided strong evidence that there are two distinct classes of neurons in the cMRF: pre- and post-saccadic. We found that the discharge of pre- and post-saccadic cMRF neurons generated movement fields based upon the direction and amplitude of gaze or head movements, respectively. In the present paper, we focus on determining whether the cMRF discharge also encodes temporal information about gaze or head movement. If this hypothesis were true, we would expect that features of the burst (onset, peak, or offset) would predict temporal aspects of the movement. For example, a cell associated with gaze movements should demonstrate close correlations between the onset of the burst and gaze onset (B_{on} to G_{on}, Fig. 1a), time of peak discharge and time of peak gaze velocity (B_{pk} to G_{pk}), and/or the end of the burst and gaze end (B_{off} to G_{off}). We would not expect such a neuron to have similar relationships to parameters of the head movement (compare right and left columns of Fig. 1b). In contrast, a neuron associated with head movements would be expected to show a strong correlation between temporal characteristics of the burst (e.g., B_{on}, B_{pk}, and B_{off}) and the onset of head movement (H_{on}), time of peak head velocity (H_{pk}), or the end of the head movement (H_{off}). We would not expect such a neuron to demonstrate similar correlations to temporal aspects of the gaze movement (Fig. 1c, compare columns). We hypothesized that pre-saccadic cMRF neurons would be more closely associated with gaze movement parameters, while post-saccadic cMRF neurons would be more closely correlated with head movement parameters.

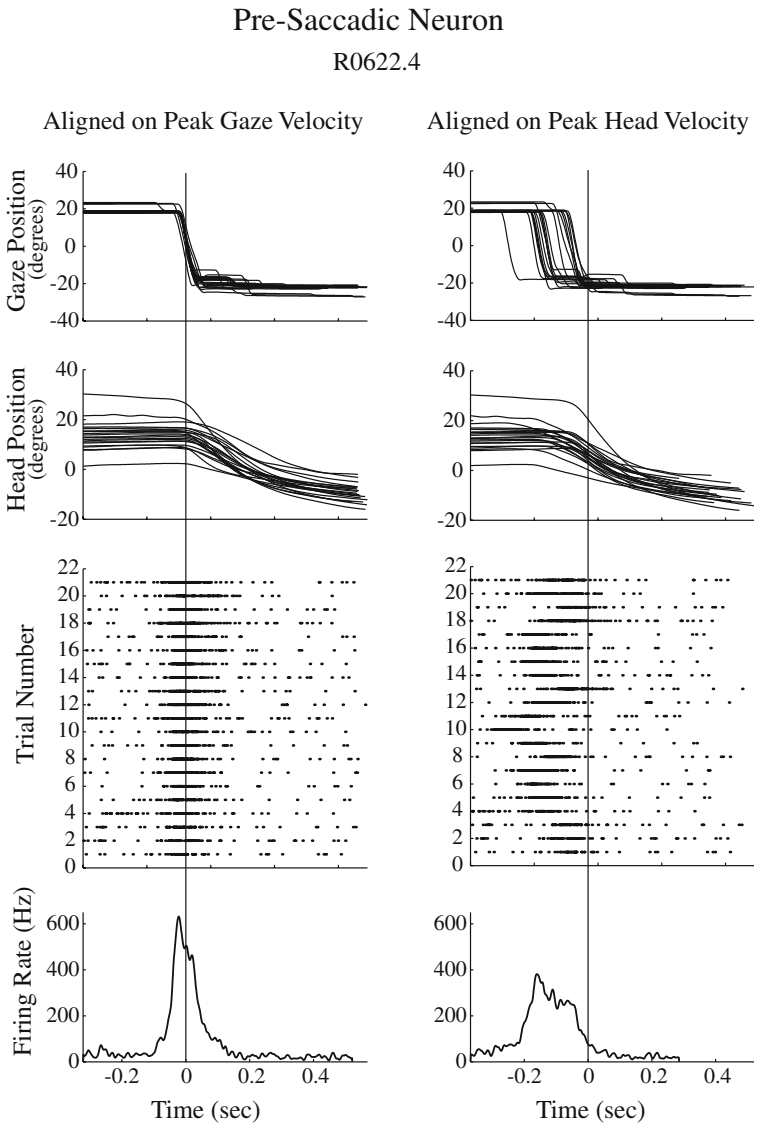

Fig. 5 A comparison of the activity of a pre-saccadic cMRF neuron aligned on peak gaze (*left column*) and peak head (*right column*) velocity. The *top* and *second rows* show the horizontal gaze and head position for 21 trials. The *third row* shows a raster of the neuronal activity during these trials, while the *fourth row* shows the average spike density trace for the rasters above. The alignment point (peak gaze or head velocity) is indicated by the *solid vertical line* passing through each panel. Note that the discharge for pre-saccadic neurons was better aligned on peak gaze than peak head velocity.

Using gaze onset as the origin (Fig. 1a), we examined the relationships between the burst parameters and gaze or head movement for every cMRF neuron in our sample. Recall that using gaze onset as the zero point precluded the examination of relationships to gaze onset (see Methods and Fig. 1a). Therefore, we repeated the analysis using the *end* of the gaze movement as the origin to examine relationships between the burst and movement onset (e.g., relationships to G_{on} or H_{on}). An example of this analysis for a pre-saccadic neuron (Fig. 2a) demonstrated close correlations between the pre-saccadic discharge and parameters of gaze, but not head movement. Most (20/27) pre-saccadic neurons demonstrated the highest statistically significant correlation coefficient (which we define as the "optimal correlation") for latency to peak discharge (B_{pk}) and peak gaze velocity (G_{pk}) (see Table 1 and Supplementary Electronic Table 3). One neuron demonstrated an optimal correlation between burst end and time of peak gaze velocity (e.g., B_{off} to G_{pk}). Five pre-saccadic neurons were optimally correlated with gaze end (G_{off}), but demonstrated correlations to various aspects of the burst (Table 1). No pre-saccadic neurons were optimally correlated with head parameters, although many did show statistically significant correlations between burst onset and head movement onset (Supplementary Electronic Table 3). One pre-saccadic neuron (H0915.5) was not well correlated with either gaze or head parameters. These findings support our hypothesis that the overwhelming majority of pre-saccadic neurons are best associated with parameters of the gaze movement.

The post-saccadic neurons demonstrated more variability in their temporal characteristics. The most common optimal correlation (i.e., highest statistically significant correlation coefficient) was to the time of peak head velocity (11/22 neurons, Fig. 3). Of these 11 neurons, five had optimal correlations between burst onset and peak head velocity (B_{on} and H_{pk}), five had optimal correlations between time of peak discharge and peak head velocity (B_{pk} and H_{pk}, like the neuron shown

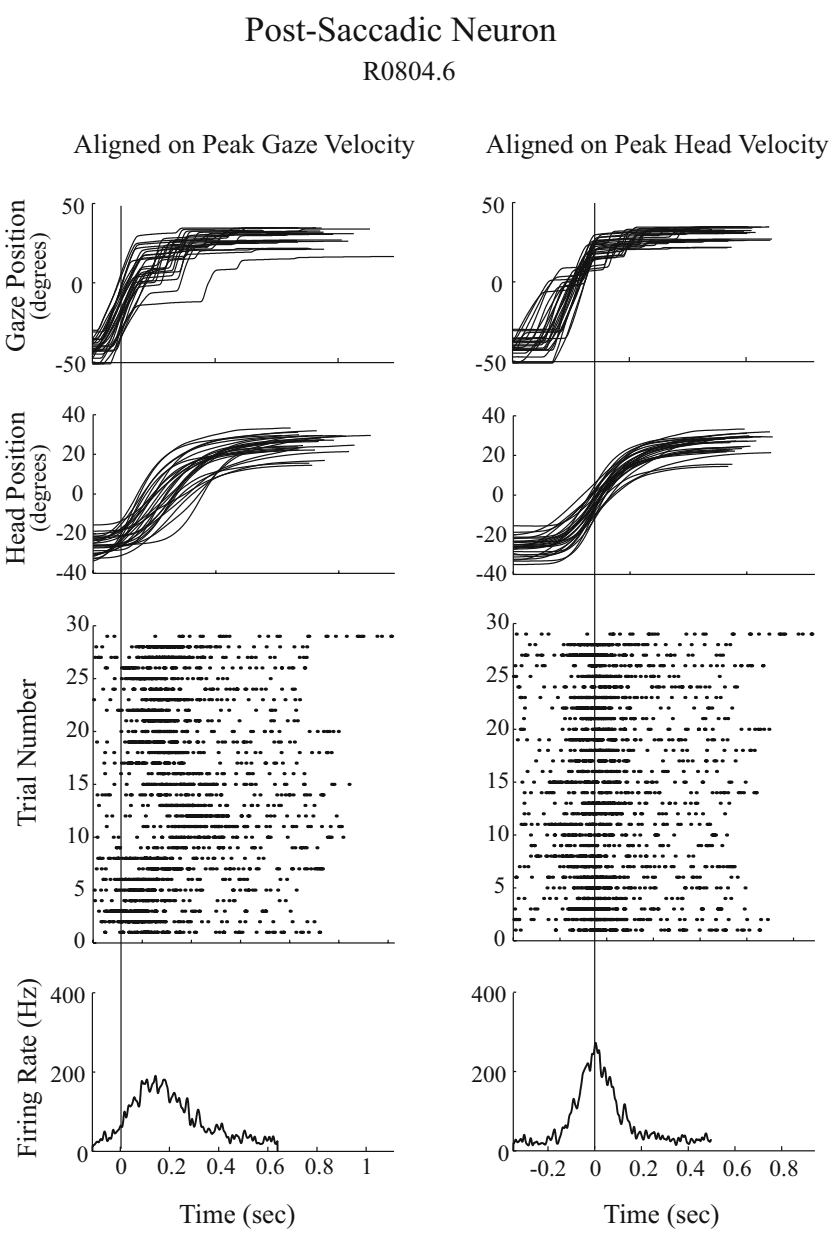

Fig. 6 A comparison of the activity of a post-saccadic cMRF neuron aligned on peak gaze (*left column*) and peak head (*right column*) velocity. The conventions are as in Fig. 5. Note that the activity was better aligned and demonstrated a higher peak discharge when the time of peak head (*right column*) not gaze velocity (*left column*) was used as the point of alignment.

in Fig. 3), and one neuron had an optimal correlation between burst offset and peak head velocity (B_{off} and H_{pk}). Three neurons were optimally correlated to head movement offset. The correlation coefficients of eight neurons did not reach statistical significance for any movement parameter. This variability demonstrates the heterogeneity of the post-saccadic population. Nevertheless, note that no post-saccadic neuron demonstrated an optimal correlation to a gaze parameter (Table 1 and Supplementary Electronic Table 3). These findings suggest that the majority of post-saccadic neurons were related to parameters of the head (but not gaze) movement.

To quantitatively determine if pre- and post-saccadic neurons were more closely associated with either gaze or head movement parameters we tabulated the number of neurons with significant correlations for each pairing of gaze and head parameters (e.g., B_{on} vs G_{on} and H_{on}, B_{pk} vs G_{pk} and H_{pk}, etc.). For each pairing, we constructed a table consisting of four categories of neurons: (1) Number of neurons with no significant correlations to either gaze or head (Block A, Fig. 4a, b); (2) Number of neurons with a significant correlation to gaze, but not head (Block B, Fig. 4a, b); (3) Number of neurons with a significant correlation to head, but not gaze (Block C, Fig. 4a, b); and (4) Number of neurons with a significant correlation to both gaze and head (Block D, Fig. 4a, b). The tabulations (McNemar's Test, see Methods Eq. 1) for the pairing of latency to peak discharge versus the latency to peak gaze and head velocity (B_{pk} vs G_{pk} and H_{pk}) of pre- and post-saccadic neurons is shown in Fig. 4a, b, respectively. Using this comparison, we found that 23 pre-saccadic neurons were significantly correlated with latency to peak gaze velocity, but not to peak head

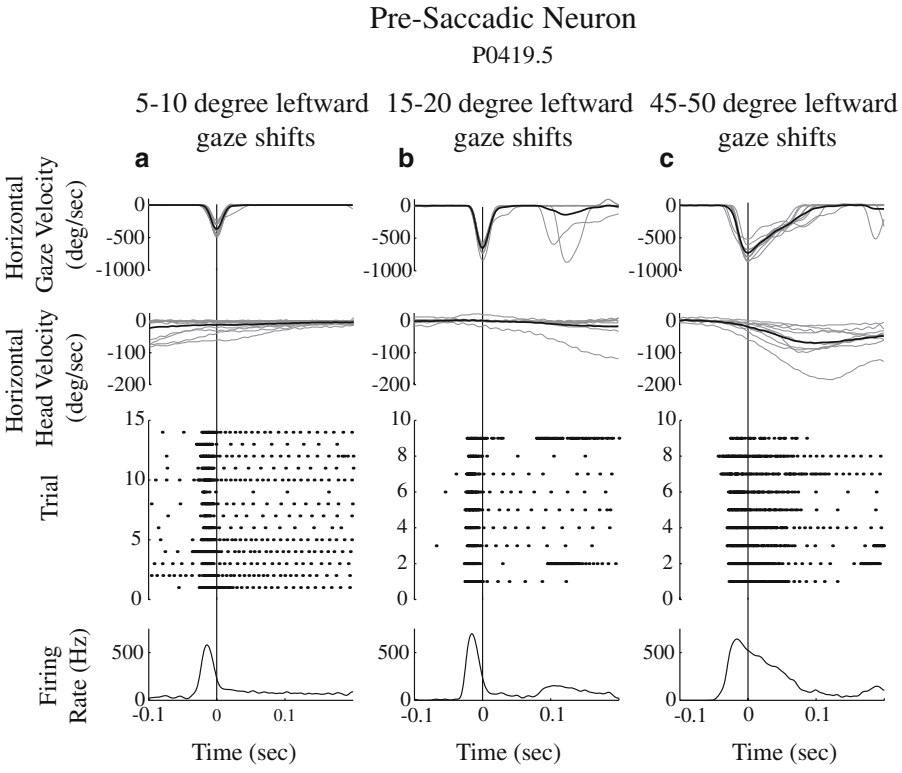

Fig. 7 A pre-saccadic cMRF neuron whose burst duration increased with saccade duration. This cMRF neuron had a monotonically open movement field and discharged before all contraversive (leftward) gaze shifts. For small saccades (5–10°, column **a**, 14 trials) the burst duration was short. Discharge duration and peak frequency increased for larger saccades of 15–20° (Panel **b**, 9 trials) and 45–50° (panel **c**, 9 trials) amplitude. The *top two rows* show horizontal gaze and head velocity, respectively, with individual velocity traces indicated by *grey lines* and the average velocity traces for all trials indicated by *bold lines*. A raster of the cell discharge and the average spike density are shown in the *third* and *fourth rows*. All trials are aligned on peak gaze velocity.

velocity (Fig. 4a, ''Block B''). No pre-saccadic neuron satisfied the converse criteria, that is, a significant correlation with the latency to peak head velocity, but no significant correlation with peak gaze velocity (Fig. 4a, ''Block C''). Such a distribution strongly suggests that the null hypothesis (that there should be an equal number of significant correlations between peak discharge and both peak gaze and head velocity) had to be rejected. In fact, the McNemar Test supported the hypothesis that the occurrence of the peak pre-saccadic discharge was

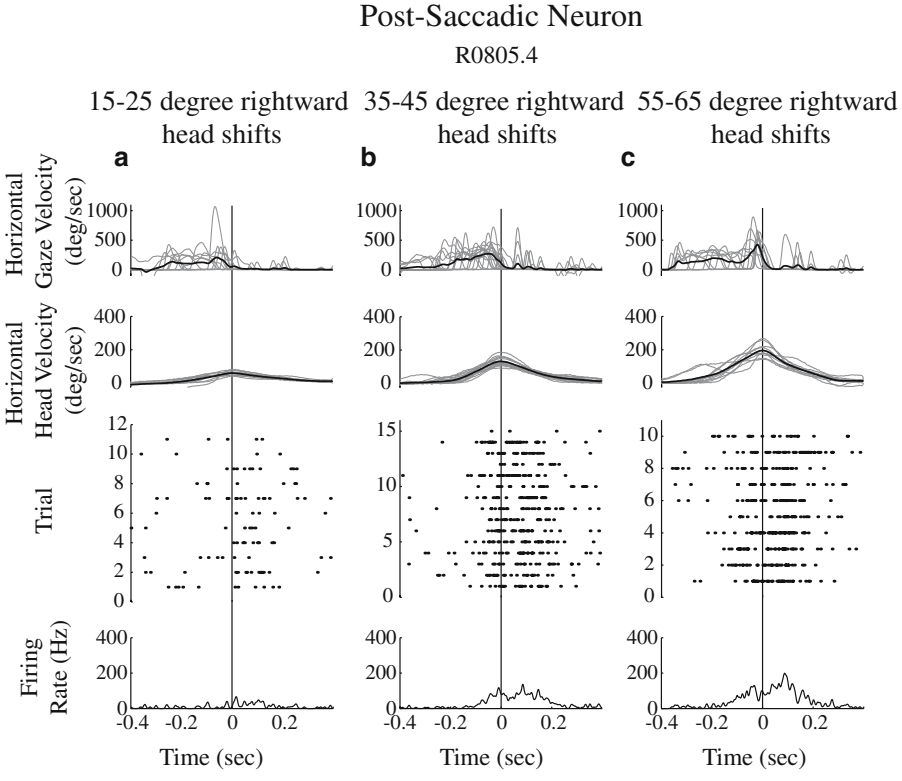

Fig. 8 Temporal characteristics of a post-saccadic cMRF neuron. This post-saccadic cMRF neuron had an open movement field. While the peak discharge increased with larger head movements (compare column **c** spike density to columns **a** and **b**), the duration of the discharge of this neuron did not increase with increased duration of head movement. Same conventions as in Fig. 7. All trials are aligned on peak head velocity.

Table 2 Temporal characteristics of cMRF neurons

	Correlation: peak discharge to peak gaze velocity	Correlation: peak discharge to peak head velocity	Correlation: burst to gaze duration	Correlation: burst to head duration	Gaze Vel VAF	Head Vel VAF
Pre-saccadic cells						
C ($N=10$)	0.09 ± 0.40	0.06 ± 0.37	0.16 ± 0.14	0.10 ± 0.17	0.28 ± 0.21	0.10 ± 0.11
NMO ($N=10$)	0.09 ± 0.24	−0.15 ± 0.26	0.43 ± 0.16	0.11 ± 0.12	0.39 ± 0.16	0.11 ± 0.12
MO ($N=7$)	0.43 ± 0.22	0.18 ± 0.18	0.55 ± 0.18	0.08 ± 0.24	0.60 ± 0.18	0.09 ± 0.08
Post-saccadic cells						
C ($N=6$)	0.00 ± 0.31	−0.15 ± 0.22	−0.25 ± 0.16	0.12 ± 0.33	0.04 ± 0.04	0.06 ± 0.05
O ($N=16$)	0.07 ± 0.29	0.11 ± 0.39	0.03 ± 0.23	0.13 ± 0.23	0.06 ± 0.06	0.19 ± 0.16

Abbreviations C indicates neurons with closed movement fields; *NMO* indicates neurons with non-monotinically open movement fields; *O* indicates neurons with open movement fields.

related to the time of peak gaze velocity ($p < 0.001$, B_{pk} vs G_{pk}/H_{pk} in Fig. 4c). Analysis of the remaining burst and movement parameter pairings (e.g., B_{on} to G_{on} or H_{on}, B_{off} to G_{off} or H_{off}, etc.) confirmed a significant association between *all* of the the burst and gaze pairings (see Fig. 4c, all p values less than 0.0056). This suggested that the pre-saccadic cMRF neurons were most closely associated with parameters of gaze and not head movement.

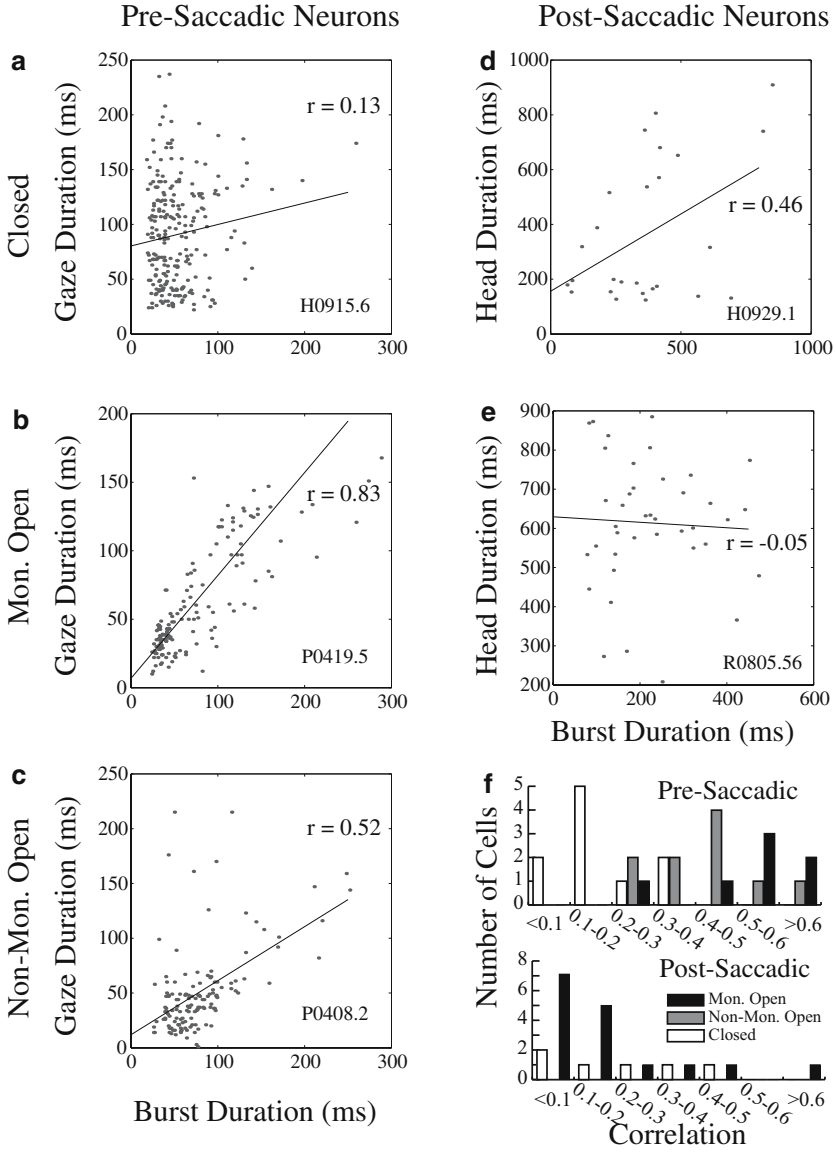

Fig. 9 Relationship of cMRF neuron burst duration to movement duration. The burst duration of pre-saccadic neurons was plotted against gaze duration (*left column*), while the burst duration of post-saccadic neurons was plotted against head duration (*right column*). **a** a pre-saccadic cMRF neuron with a closed movement field shows a poor correlation between burst and saccade duration, demonstrating a cluster of activity for saccades of particular amplitude and duration. **b, c** cMRF neurons with monotonically and non-monotonically open movement fields demonstrated stronger correlations between burst and saccade duration. **d, e** no significant relationships between burst and head duration were found for post-saccadic cMRF neurons. **f** the correlations for all of the pre- (*top*) and post-saccadic (*bottom*) neurons are shown separated by movement field type. Pre-saccadic cMRF neurons (*upper bar graph*) with monotonically open movement fields (*black bars*) tended to have higher correlations between burst and saccade duration than did closed movement field neurons (*white bars*). A similar relationship was not found for the post-saccadic cMRF neurons (*lower bar graph*). *Abbreviations*:*Non-Mon.Open*—non-monotonically open; *Mon.Open*—monotonically open.

Post-saccadic neurons also demonstrated a significant difference between the relationship to gaze and head parameters. Ten post-saccadic neurons had a statistically significant correlation between latency to peak discharge and latency to peak head velocity (i.e., B_{pk} to H_{pk}), but not gaze velocity (not B_{pk} to G_{pk}) (Fig. 4b, "Block C"). No post-saccadic neuron satisfied the converse criteria, that is, a significant correlation with the latency to peak gaze, but not head velocity (e.g., Fig. 4b "Block B"). As a result, the null hypothesis that post-saccadic neurons were equally well correlated with the latency to peak gaze and head velocity had to be rejected (Fig. 4c, McNemar Test, $p < 0.0056$). However, in contrast to the pre-saccadic neurons, the McNemar test found no significant relationships between the discharge of post-saccadic neurons and the onset or offset of gaze or head movement (Fig. 4c, post-saccadic neurons). Therefore, the McNemar analysis demonstrated that the only statistically significant pairing for the post-saccadic neurons was between burst parameters (B_{on} and B_{pk}, Fig. 4c) and peak head velocity (H_{pk}), when compared to similar relationships with peak gaze velocity (G_{pk}). This statistical analysis supports the hypothesis that post-saccadic neurons are related to head movement. Unfortunately, the small number of post-saccadic neurons collected limited our ability to characterize the apparent heterogeneity of the post-saccadic population and investigate significant relationships to other individual head parameters.

Based on the results of the above analysis, the discharge of most pre- and post-saccadic neurons was best correlated with peak movement velocity. Therefore, a

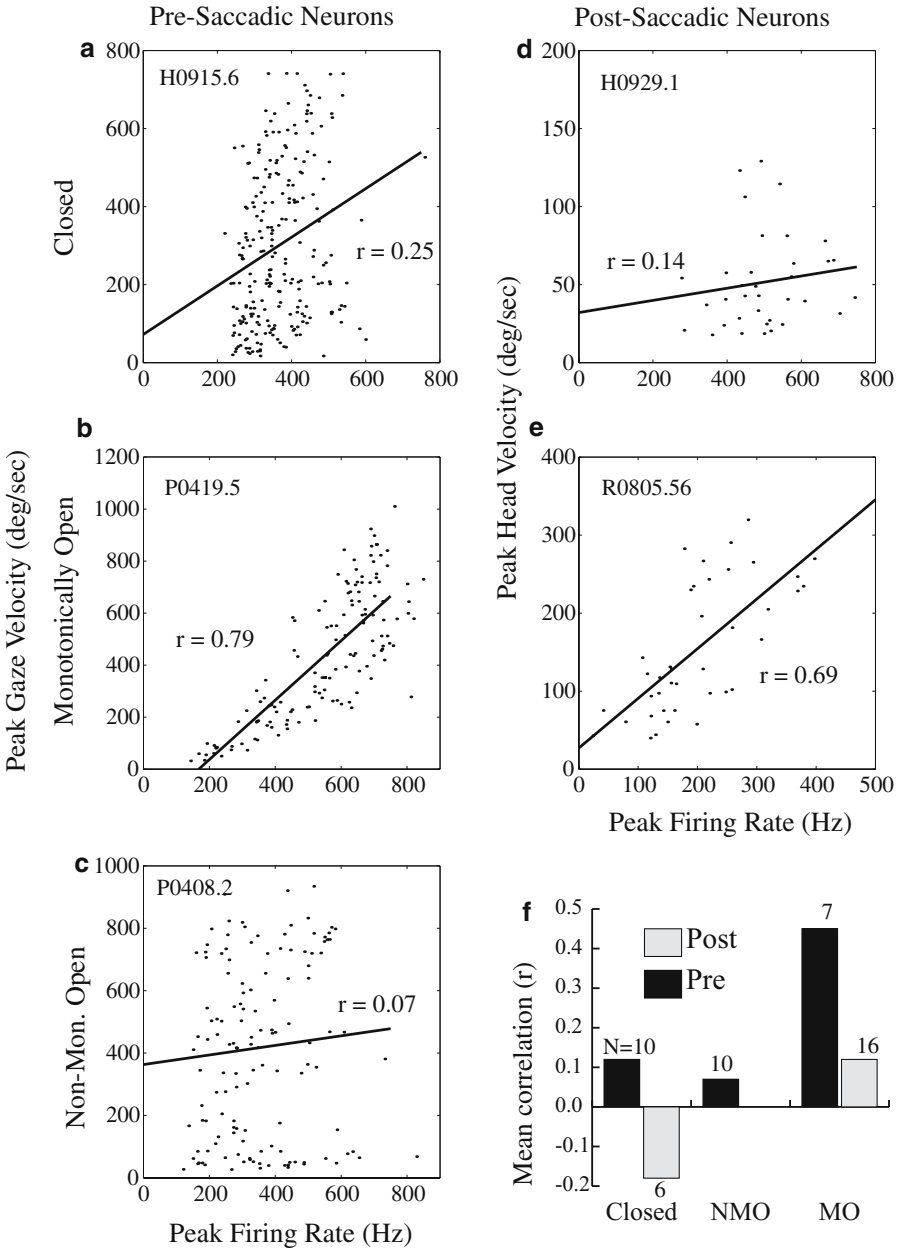

Fig. 10 Relationship between the peak discharge and peak movement velocity for cMRF neurons. The peak discharge of pre-saccadic neurons was plotted against peak gaze velocity (*left column*), while the peak discharge of post-saccadic neurons was plotted against peak head velocity (*right column*). **a** a pre-saccadic neuron with a closed movement field demonstrated little correlation between peak discharge rate and peak gaze velocity. **b** the correlation was much stronger for a pre-saccadic neuron with a monotonically open movement field. **c** Pre-saccadic neurons with non-monotonically open movement fields were found to have low correlations between peak discharge rate and peak gaze velocity. **d, e** in general, post-saccadic neurons with both closed and open movement fields had poor correlations between peak discharge rate and peak head velocity, but some post-saccadic neurons (such as the one shown in **e** with an open movement field had relatively strong correlations. **f** the average correlation is shown, separated by movement field type. *N* indicates the number of neurons in each category. *Abbreviations*: *NMO*—non-monotonically open; *MO*—monotonically open.

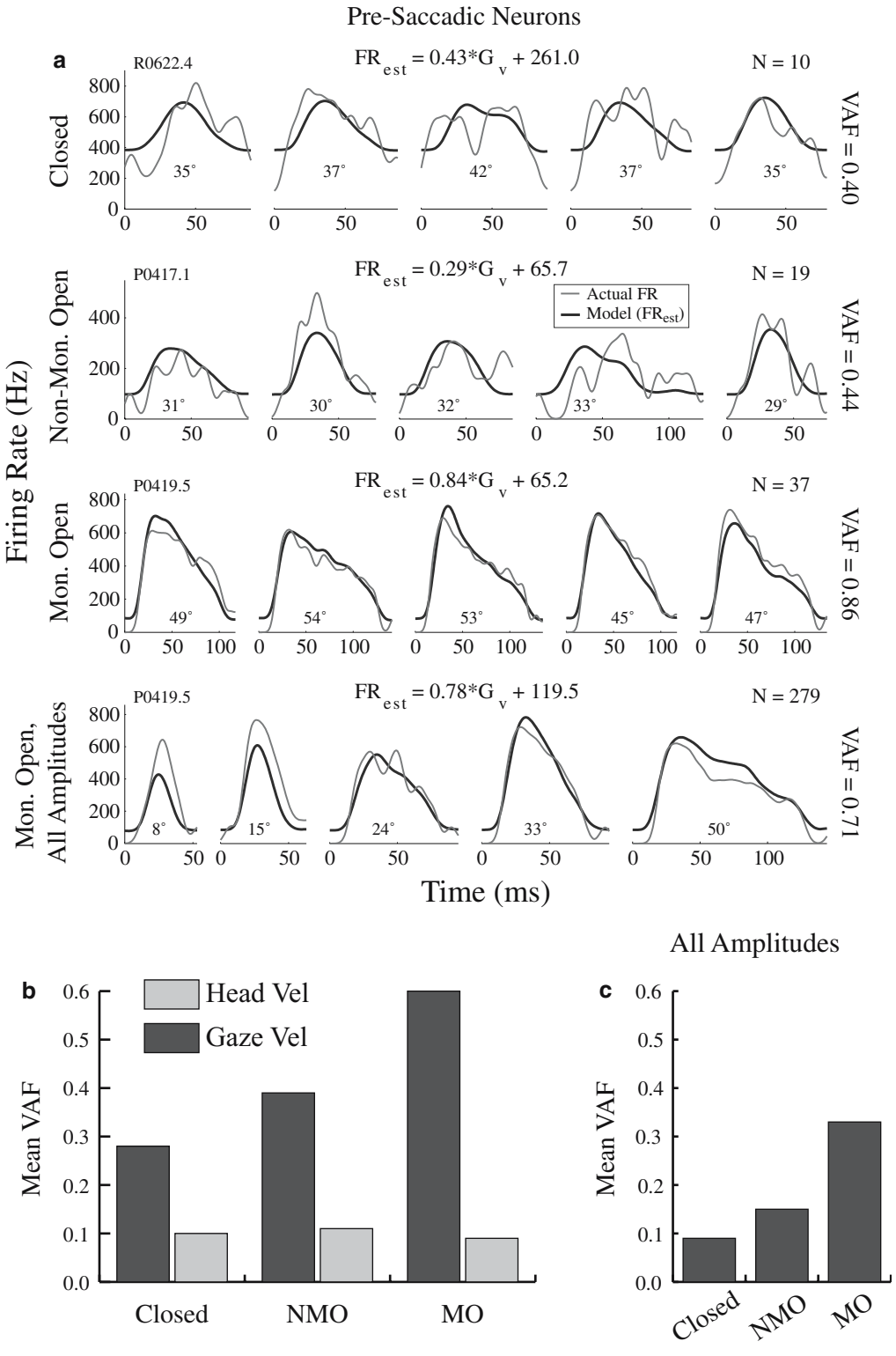

Fig. 11 Relationship between discharge profile and gaze velocity for pre-saccadic cMRF neurons. **a** The *top three rows* illustrate the activity of closed, non-monotonically open, and monotonically open pre-saccadic cMRF neurons (*grey lines*), respectively, during gaze shifts of the preferred amplitude and direction. Individual discharges are superimposed on an estimate of the activity based on a function of gaze velocity (*black line*, calculated from the equation shown above the row). The *bottom row* shows the same comparison for the monotonically open neuron shown in the *third row*, but using gaze shifts in the optimal direction of all amplitudes. The total number of trials used to calculate the VAF is shown in the *upper right corner* of each panel, although only five selected gaze shifts are illustrated in each row. **b** the discharge of monotonically open movement field neurons was best correlated with gaze velocity models (i.e., had the highest VAF values). For all pre-saccadic neurons, gaze velocity models were a better predictor of neuronal discharge than head velocity. **c** the mean VAF values were lower when gaze shifts of all amplitudes were considered. However, neurons with monotonically open movement fields were still the most strongly associated with gaze velocity models. *Abbreviations*: *C*—closed movement field; *NMO*—non-monotonically open movement field; *MO*—monotonically open movement field.

more logical approach to the display of raster data (e.g., Figs. 3 and 4 from the accompanying paper, Pathmanathan et al. 2005) would be to align trials on peak gaze and head velocity. As might be expected, the average spike density was higher and the latency was less variable when pre-saccadic data was aligned on peak *gaze* than head velocity (Fig. 5); compare the left column, average spike density aligned on peak gaze velocity, to the right column, aligned on peak head velocity. On an average, the discharge of pre-saccadic neurons occurred 18.5 ± 2.9 ms before peak gaze velocity (Supplementary Electronic Table 1). In contrast, the responses of post-

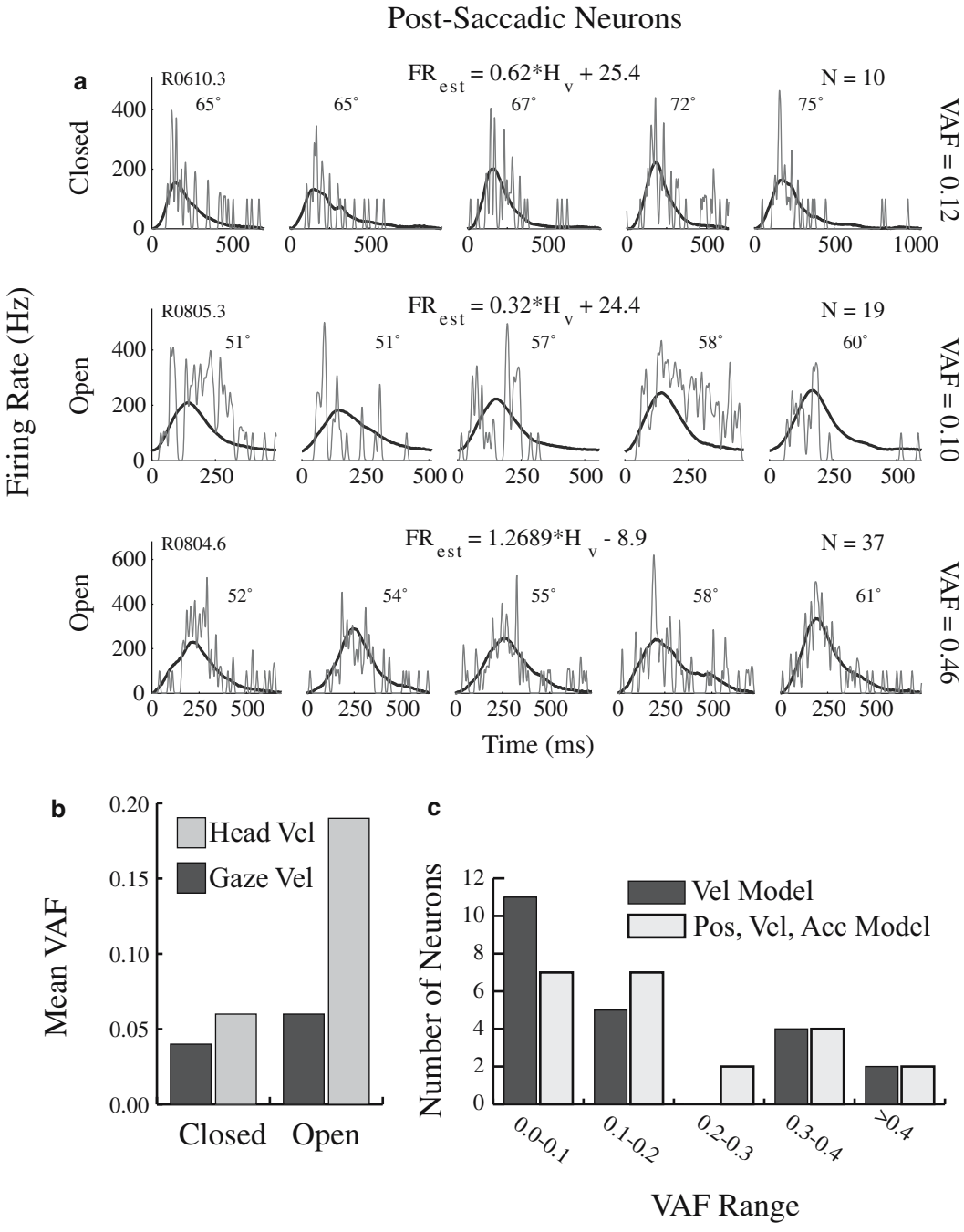

Fig. 12 Relationship between discharge profile and head velocity of post-saccadic neurons. Same conventions as in Fig. 11. **a** each row shows the activity of a post-saccadic neuron during five sample movements (*grey lines*), superimposed on the estimate of the discharge based on head velocity (*black lines*, determined from the equations shown above each row). The *top row* shows the comparison for a post-saccadic neuron with a closed movement field, while the *middle* and *bottom rows* show neurons with open movement fields. **b** in general, post-saccadic neurons had lower VAF values than pre-saccadic neurons. Nonetheless, head velocity models were consistently better than gaze velocity models and open movement field post-saccadic neurons had higher VAF values than closed movement field neurons. **c** the majority of post-saccadic neurons had VAF values < 0.1 for head velocity models. However, a small subset of post-saccadic cMRF neurons had higher VAF values.

saccadic cMRF neurons were more variable (Fig. 6). While post-saccadic neurons had a higher peak discharge when aligned on head than gaze parameters (compare right column, Fig. 6, average spike density aligned on peak head velocity, to the left column, aligned on peak gaze velocity), the choice of which head parameter for optimal alignment varied. The previous latency correlation analysis suggested that post-saccadic neurons were most often significantly correlated with peak head velocity, and that this parameter was the only

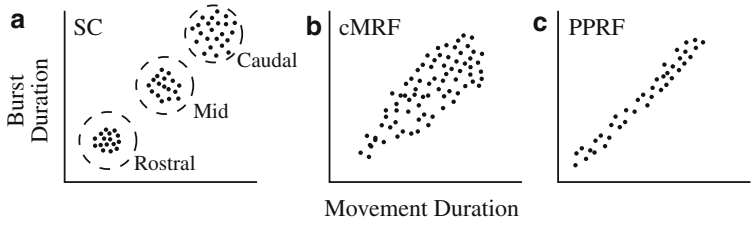

Fig. 13 Theoretical comparison of the gaze duration/burst duration relationship found in the pre-saccadic cMRF neurons with the relationships found in neurons of the SC and PPRF. **a** the duration of the discharge of neurons in the SC does not individually encode the amplitude or duration of all gaze shifts, although they may encode the duration of a subset of movements (*dotted circles*). **b** in contrast, the discharge duration of some cMRF neurons (particularly monotonically open movement field cells) was well correlated with movement duration for a wider range of movement amplitudes. **c** PPRF medium-lead burst neurons have similar, although stronger, correlations between burst and movement duration.

one capable of distinguishing head and gaze relationships (see Fig. 4). On average, the post-saccadic discharge occurred 11.6 ± 23.8 ms *after* peak head velocity (Supplementary Electronic Table 2). These findings confirm our hypothesis that pre-saccadic neurons were most closely associated with gaze shifts, while post-saccadic neurons were most closely related to head movements.

Temporal characteristics of the cMRF discharge

We next addressed the more specific hypothesis that the temporal pattern of discharge of cMRF neurons could encode dynamic aspects of the gaze shift. The primary model we used for comparison was the temporal relationships found in the excitatory and inhibitory burst neurons of the PPRF (Luschei and Fuchs 1972; Van Gisbergen et al. 1981; Hepp and Henn 1983; Scudder et al. 1988; Cullen and Guitton 1997b). In particular, we tested whether there was a correlation between (1) Duration of discharge and gaze or head duration (2) Peak discharge rate and peak gaze or head velocity and (3) Discharge pattern and gaze or head velocity profile. We would expect that the discharge of cMRF neurons would reflect these properties if their activity was used to drive PPRF medium lead burst neurons related to gaze or the purported head-related pre-motor neurons in the NRG.

Some of these temporal characteristics could be observed in the firing patterns of pre- and post-saccadic neurons (Figs. 7, 8). First, we observed a moderate increase in peak discharge associated with increased peak velocity for most pre-saccadic neurons with open movement fields (compare peak discharge for saccades shown in Fig. 7a with b). Furthermore, the discharge profile in shape, timing, and magnitude of this neuron closely resembled the velocity waveform. Another distinguishing feature was that increased gaze duration was correlated with increased discharge duration (compare the discharge profile with the velocity profiles for each column of Fig. 7). These results are quantified below and are consistent with our initial observation that the pre-saccadic latencies to discharge onset and offset were well correlated with gaze onset and offset, respectively (Figs. 2, 4c). Such relationships were less apparent for post-saccadic neurons. The post-saccadic neuron shown in Fig. 8 had a moderate increase in peak discharge rate as head movement amplitude (and hence head velocity) increased (Fig. 8, compare head velocity, 2nd row, with the spike density, 4th row). The discharge duration was shorter than the duration of the head movements, and the association between discharge and movement duration was far less robust than that observed for pre-saccadic cMRF neurons.

We directly compared discharge duration with gaze and head movement duration for both pre- and post-saccadic neurons (Fig. 9). Overall, a wide range of responses was observed. Figure 9a–c show the relationships found for three pre-saccadic neurons and Fig. 9d–e show the associations for two post-saccadic neurons. The closed movement field pre-saccadic (Fig. 9a, f, white bars, top panel) and post-saccadic (Fig. 9d, f, white bars, bottom panel) neurons had poor correlations between burst and either gaze (mean closed pre-saccadic correlation: 0.16 ± 0.14; mean closed post-saccadic correlation −0.25 ± 0.16) or head movement duration (mean closed pre-saccadic correlation: 0.10 ± 0.17; mean closed post-saccadic correlation 0.12 ± 0.33). In contrast, pre-saccadic neurons with monotonically open movement fields displayed a stronger relationship between burst and gaze duration (mean correlation: 0.55 ± 0.18), but not head duration (mean correlation: 0.08 ± 0.24) (Fig. 9b, f, black bars, top panel). The strength of this burst duration/gaze duration relationship did not reach that observed for PPRF neurons (Cullen et al. 1993; Cullen and Guitton 1997b). The relationship for non-monotonically open pre-saccadic neurons (Fig. 9c, f, gray bars, top panel) was intermediate to that found for monotonically open and closed movement field pre-saccadic neurons (mean gaze correlation: 0.43 ± 0.16; mean head correlation 0.11 ± 0.12). The burst duration of open movement field post-saccadic neurons showed little correlation to either head or gaze duration (mean gaze correlation: 0.03 ± 0.23; mean

head correlation 0.13 ± 0.23) (Fig. 9e, f, black bars, bottom panel). Results for individual neurons are found in Supplementary Electronic Table. 1 and 2.

For pre-saccadic cMRF neurons (Fig. 9f, top panel), the distribution of correlation coefficients shifted as a function of movement field type. Neurons with monotonically open movement fields (black bars) had the highest correlation coefficients, while those with closed movement fields had the lowest (white bars). Therefore, we conclude that the relationship to *gaze* shift duration improved as the movement field type became "monotonically open." On the other hand, little correlation was found between the duration of post-saccadic discharge and either gaze or head movement duration, even for neurons with open movement fields (Fig. 9f, bottom panel). For post-saccadic neurons, we also examined the relationship between discharge duration and the duration of either the accelerating or decelerating phases of the head movement. This analysis showed no correlation between discharge and movement duration (average correlation to duration of head acceleration = 0.09 ± 0.38; to duration of head deceleration = 0.03 ± 0.26) (see Supplementary Electronic Table 2).

Relationship between peak discharge rate and peak velocity

We next addressed the relationship between peak discharge rate of cMRF neurons and peak gaze or head velocity (Fig. 10). For both pre- and post-saccadic cMRF neurons with closed movement fields (Fig. 10a, d), peak discharge was poorly correlated with either peak gaze or head velocity (Table 2). Similarly, pre-saccadic neurons with non-monotonically open movement fields had poor correlations between peak discharge and peak gaze or head velocity (Fig. 10c). The relationship to peak gaze velocity was stronger for pre-saccadic cMRF neurons with monotonically open movement field characteristics (Fig. 10b). In contrast, a group of post-saccadic neurons with open movement fields did not demonstrate similar relationships to peak movement velocities (mean open movement field post-saccadic correlation to *gaze*: 0.07 ± 0.29; mean correlation to *head*: 0.11 ± 0.39). However, 5 of 16 post-saccadic neurons with open movement fields did have stronger correlations between peak discharge and peak head velocity (Fig. 10e). These results, summarized in Fig. 10f and Table 2 (with correlation coefficients for individual neurons listed in Supplementary Electronic Table. 1 and 2), suggest that the discharge of pre-saccadic monotonically open movement field cMRF neurons was most closely associated with gaze and not head velocity. On average, post-saccadic neurons had weaker relationships, but a subset of open movement field post-saccadic neurons had higher correlations between peak discharge and peak *head*, not gaze, velocity. These findings are consistent with the conclusion arrived at by using the McNemar analysis (Fig. 4).

Relationship between discharge pattern and movement dynamics

The analysis thus far has demonstrated evidence of relationships in sub-groups of cMRF neurons between discharge duration and gaze shift duration as well as peak discharge rate and peak velocity. Such characteristics are commonly found in the discharge of the premotor burst neurons in the PPRF for movements of the eyes. However, the pattern of discharge observed in PPRF neurons has also been shown to encode the dynamics of the gaze velocity profile (Van Gisbergen et al. 1981; Cullen and Guitton 1997b). If the cMRF participates in a relay of activity from the SC to neurons in the PPRF or NRG, we would hypothesize that the discharge profile of cMRF neurons should also closely match the gaze or head velocity profiles, respectively.

To test this possibility, we examined whether dynamic models could describe the firing patterns of cMRF neurons. Discharge rate of the neurons was estimated using scaled version of either gaze or head velocity. More complex models that included position and acceleration terms were also tested. Dynamic models were estimated for movements of the neuron's preferred amplitude and in its preferred direction (see Methods). Overall the discharge profile of pre-saccadic neurons was well described by models based on gaze velocity alone (VAF range: 0.10–0.86). The latencies predicted by dynamic models were comparable to, although slightly longer than, the peak discharge to peak velocity latency (mean peak to peak latency = 18.5 ± 2.9; mean dynamic model latency [*td*] = 22 ± 6 ms, individual latencies listed in Supplementary Electronic Table 4). Fig. 11a shows the discharge profiles and scaled gaze velocity profiles of five example gaze shifts for three pre-saccadic neurons (top three rows of data). Note that while only five specific examples are displayed, the overall VAF values reflect all movements whose amplitude and direction were within ±5° of the optimal movement. cMRF neurons with monotonically open movement fields had higher VAF values than non-monotonically open or closed movement field cells (e.g., compare the model of the neuron with the monotonically open movement field, 3rd row, to the non-monotonically open, 2nd row, and closed movement field neurons, 1st row in Fig. 11a). Thus, consistent with the previous parametric analyses shown in Figs. 9 and 10, temporal information was most strongly encoded in the discharge pattern of neurons with monotonically open movement fields.

On average, velocity models could account for 28 ± 21% of the variance of closed movement field pre-saccadic neurons, but could account for upto 39 ± 16% and 60 ± 18% of the variance of non-monotonically open and monotonically open movement field pre-saccadic neurons, respectively (Fig. 11b). Addition of gaze position to the gaze velocity model increased the VAF by an average of 0.06, while acceleration terms added only 0.01 (see Supplementary Electronic Table 4).

To determine if these additional terms were warranted, we calculated the BIC cost index (Schwartz 1978; see Methods, Dynamic analysis). The BIC cost indices were typically lowest for simple velocity models (velocity models had the lowest BIC indices for 19/27 neurons, see Supplementary Electronic Table 4), suggesting that the pattern of discharge of pre-saccadic cMRF neurons encodes gaze velocity and not gaze position or acceleration. Models using head velocity to characterize the pre-saccadic cMRF discharge were uniformly worse than models based on gaze velocity (see Supplementary Electronic Table 4).

Since pontine excitatory burst neurons may encode the velocity of a range of movement amplitudes, we also compared the discharge of pre-saccadic cMRF neurons to dynamic models of all amplitude gaze shifts to within ±15° of the optimal direction. The fourth row of Fig. 11a illustrates the activity of a pre-saccadic cMRF neuron with a monotonically open movement field during gaze shifts ranging from 5 to 60°. This pre-saccadic neuron demonstrated a relationship to the velocity and duration of all amplitude gaze shifts. However, the VAFs generated using all amplitude gaze shifts were always lower than the VAFs obtained using gaze shifts of the preferred amplitude (compare Fig. 11b, c). Monotonically open movement field neurons demonstrated the highest VAFs when all gaze shift amplitudes were used (average monotonically open movement field VAF: 0.33 ± 0.22, see Fig. 11c), while neurons with non-monotonically open or closed movement fields demonstrated relatively poor correlations with gaze shifts of increasing amplitude (average non-monotonically open and closed movement field VAF: 0.15 ± 0.07 and 0.09 ± 0.11, respectively).

Post-saccadic cMRF neurons were analyzed in a similar manner. In general, dynamic models accounted for only a small percentage of discharge variance, even when head velocity-based models were tested (Fig. 12a, top two panels). For head velocity-based dynamic models, the average optimal model latency (*td*) was similar to the average peak discharge to peak head velocity latencies previously described. For post-saccadic neurons with closed movement fields, the average peak to peak latency was −12 ± 29 ms (peak discharge occurring after peak head velocity), while the average optimal dynamic latency (*td*) was −8 ± 36 ms. For post-saccadic neurons with open movement fields, the average peak to peak latency was −11 ± 23 ms and the average dynamic latency (*td*) was 5 ± 33 ms. However, in a few instances the model latencies (*td*) were not similar to the peak to peak latency, especially for neurons with low VAFs (see Supplementary Electronic Table 5). A minority of open movement field post-saccadic neurons were well correlated with head movement dynamics (Fig. 12a, lower panel). On an average, head velocity models accounted for 19% of the variance in neuronal discharges in neurons with open movement fields and 6% of the discharge variance of neurons with closed movement fields (Fig. 12b). These models were better than those based on gaze velocity (Fig. 12b, c and Table 2). More complex models that combined head velocity with head position and acceleration improved the VAF by only 0.02 on an average. Despite the small improvement, the BIC cost indices were often lower for these more complex models (Supplementary Electronic Table 5), suggesting that position and acceleration terms were warranted.

Relationship of the discharge of pre-saccadic neurons to eye position

Eye-based models were also tested to determine how eye position influenced pre-saccadic cMRF discharge. It is well established that variations in the initial position of the eyes within the orbit influences the relative contribution of the eyes and head to the overall gaze shift (Freedman and Sparks 1997b). Therefore, neurons solely related to gaze should not be influenced by alterations in initial eye position during amplitude matched gaze shifts. Although initial eye position was not systematically varied, we did analyze natural variations in the position of the eyes at the start of gaze shifts. We compared the discharges preceding gaze shifts of the preferred amplitude and direction in which the initial position of the eyes was separated by at least 10° (eyes beginning 5° to the ipsilateral side vs 5° to the contralateral side). Unfortunately, only four neurons had sufficient data for analysis and none had an open movement field. For this very limited data set, we found no change in the discharge of the pre-saccadic burst if the eyes began ipsilateral or contralateral to the direction of the gaze shift (not shown). We also examined the effects of static eye position (eye position during periods when gaze was stable). Eye position models were compared with the background discharge for all pre-saccadic neurons in the study. Only two of 27 neurons displayed modest VAF values for eye position models (P0419.5, VAF = 0.18 and P0509.3, VAF = 0.11), although the average VAF value for eye position models was nearly 0 (average VAF = 0.015, ranging from 0 to 0.18). These results suggest that the high background discharge rates of pre-saccadic cMRF neurons were not modulated by eye position. Therefore, shifts of initial eye position could not account for the large bias term found for many pre-saccadic neurons (Supplementary Electronic Table 4).

Discussion

In this study we have shown that the discharges of pre- and post-saccadic cMRF neurons encode information spatially in the form of movement fields (Pathmanathan et al. 2005) and also carry information about the temporal characteristics of gaze and head movements. The discharge of pre-saccadic neurons lead gaze shifts (see Fig. 1, Pathmanathan et al. 2005), and the latency to

peak burst was highly correlated with the latency to peak gaze velocity. Furthermore, for many pre-saccadic neurons the latency to burst offset was well correlated with latency to gaze offset, as previously described (Waitzman et al. 1996). These correlations supported the hypothesis that pre-saccadic neurons were most closely correlated with gaze movement (McNemar analysis, Fig. 4c). A sub-population of pre-saccadic neurons with monotonically open movement fields had three temporal properties also observed in the pre-motor neurons of the PPRF: (1) Burst durations that were closely associated with gaze shift duration. (2) Peak firing rates that were well correlated with peak gaze velocity and (3) Discharge profiles that corresponded closely with gaze velocity waveforms. Pre-saccadic neurons with closed movement fields were poorly correlated with burst duration or movement velocity.

In contrast, post-saccadic neurons began to discharge after gaze movement onset and during the head movement. The latency of their discharge was well correlated with various *head*, rather than gaze parameters (although eight of the 22 neurons showed no statistically significant correlations to either gaze or head movement). The most common statistically significant correlations were between times of peak head velocity and either burst onset or time of peak discharge. The variability of the post-saccadic relationships to head movement most likely reflected the heterogeneity of this population. Because our sample size was too small to analyze the significance of relationships between individual burst and movement parameters, we concluded that the *population* of post-saccadic cMRF neurons was significantly correlated with head, as opposed to gaze movement parameters (McNemar analysis, Fig. 4c). With a few exceptions, the discharge of post-saccadic neurons was weakly correlated with head movement duration, peak head or gaze velocity, or the dynamics of head or gaze movement, suggesting that they do not encode the putative temporal characteristics necessary to drive head pre-motor neurons.

Our results suggest that cMRF neurons can be subdivided into different cell types whose neuronal discharges encode signals critical to the control of gaze or head movement. These signals include: (1) movement duration; (2) time of peak gaze or head velocity; (3) the gaze or head velocity waveform; and (4) head or gaze movement amplitude (see Fig. 8, Pathmanathan et al. 2005). The relationships of pre and post-saccadic cMRF neurons to these signals are discussed in the following sections.

Duration signals in cMRF neurons

If cMRF neurons directly participate in gaze or head control then their discharge would be expected to share the same close correlation to movement duration as has been observed in the excitatory burst neurons of the PPRF. Previous studies of a relationship between saccade and cMRF burst duration in head restrained monkeys have demonstrated either no relationship to duration (Moschovakis et al. 1988) or a relationship in association with other saccade metrics (Handel and Glimcher 1997). Those studies only examined saccade amplitudes upto 30°. The current experiments expanded movement amplitude to 70° and more precisely determined the onset and offset of the burst using strict statistical measures (see Methods). This approach showed that the majority of the cMRF pre-saccadic burst neurons with monotonically open movement fields and many pre-saccadic neurons with non-monotonically open movement fields had discharges that were strongly correlated with gaze duration. Similar movement field properties and relationships between burst duration and saccade duration have been documented in the direction long-lead burst neurons (DLLBNs) of the PPRF (Luschei and Fuchs 1972; Hepp and Henn 1983). Thus, the pre-saccadic cMRF neurons and the DLLBNs could provide parallel pathways for transforming the weak burst/duration relationship of SC neurons into the tightly coupled relationship observed in the excitatory burst neurons of the PPRF.

Pre-saccadic cMRF neurons with closed movement fields were poorly correlated with the duration of all gaze shifts in the preferred direction. However, this does not eliminate the possibility that these neurons could be correlated with the duration of a smaller subset of gaze shift amplitudes in the preferred direction, making them similar to closed movement field neurons in the SC (Waitzman et al. 1991; Keller and Edelman 1994; Anderson et al. 1998). If true, cMRF neurons with closed movement fields could provide feedback to the SC that would help generate the burst to saccade duration relationship found in some SC neurons (Waitzman et al. 1991, 2000; Munoz and Wurtz 1995a; Soetedjo et al. 2002b; Guitton et al. 2003).

On the other hand, the duration of the post-saccadic cMRF discharge was almost always shorter than the duration of the head movement and was poorly related to either the overall duration of the head movement or its accelerating or decelerating phases. None of the post-saccadic neurons demonstrated any relationship to the duration of the gaze movement. Nevertheless, these neurons discharged consistently during head movements and near the time the head movement reached peak velocity (Figs. 3 and 6). Since the discharge characteristics of the putative head pre-motor neurons have not been defined in the primates, it is difficult to relate the post-saccadic discharge to head movement control. However, given its limited duration and late onset, the post-saccadic cMRF discharge could not provide the sole drive to pre-motor neurons for moving the head. An alternative possibility, is that these neurons supply a portion of the temporal signal used to move the head (e.g., drive a particular group of cervical muscles that is active during a specific period of the overall head movement). This idea is expanded upon in the subsection that follows later (cMRF post-saccadic neurons: role in head control).

Velocity signals in cMRF neurons

Previous analysis of pre-saccadic cMRF neurons with the head restrained had demonstrated a clear relationship to saccade velocity (Waitzman et al. 1996). The current results confirm and extend the previous findings using larger gaze movements and a more precise parametric analysis. We found evidence of a clear relationship between the discharge profile of pre-saccadic cMRF neurons with monotonically open movement fields and gaze velocity that approached the relationship observed in PPRF pre-motor and abducens motoneurons (Van Gisbergen et al. 1981; Cullen and Guitton 1997a). For most pre-saccadic neurons, models based on horizontal gaze velocity produced the best VAF. For a small subset of neurons, a cost analysis function (BIC) supported the addition of a horizontal gaze position term to the horizontal gaze velocity model, although the improvement in the fit was small. Effects of initial eye position on the discharge of cMRF neurons could not be conclusively determined given that we did not systematically vary initial eye position, although our findings suggest that the background rate of cMRF neurons does not encode eye position. Moreover, we were unable to specifically test if cMRF neurons with monotonically open movement fields had a dynamic relationship to a combination of eye and head movement, as has been done for the medium lead burst neurons in the PPRF (Cullen and Guitton 1997b). Despite these caveats, we conclude that the majority of monotonically open movement field cMRF pre-saccadic neurons carry information about horizontal gaze velocity in the pattern of their discharge.

In contrast, the relationships between peak discharge and peak head velocity, and between instantaneous discharge and head velocity waveform of post-saccadic cMRF neurons were weaker than the comparable relationships observed in pre-saccadic neurons. Nevertheless, head velocity models provided stronger fits than gaze velocity models for post-saccadic neurons. This was consistent with the McNemar analysis that supported an overall relationship of post-saccadic neuron discharge to head and not gaze movement. We did find that a minority of neurons ($N = 4$), located in the medial portion of the cMRF, did have better correlations with either head velocity or some combination of head velocity, acceleration, and position (VAF $>$ 0.3 for h0501.2, r0804.6, r0805.4, and r0805.56) than neurons located elsewhere in the cMRF.

There are three reasons why we may not have detected similar relationships in other post-saccadic neurons. First, the sluggish dynamics of the head made it difficult to determine the precise onset and offset of head movement. Second, we measured horizontal and vertical head positions and not the activity of the individual cervical muscles driving the movement. Although we can only speculate as to why cMRF neurons were not active throughout the head movement, it is possible that cMRF neurons were actually best related to the activation of a single muscle or selected group of muscles rather than the overall head displacement. Recent evidence strongly suggests that different sub-groups of cervical muscles are activated during different portions and positions of the overall head movement (Corneil et al. 2001). Indeed, projections from the cMRF directly target the cervical spinal cord (Castiglioni et al. 1978). Thus, the discharge of post-saccadic cMRF neurons could be associated with activation of a *select* group of cervical muscles later in the head movement. If the same muscle group were activated at different times during both agonist and anatagonist movement, this would account for the evidence of bidirectional activity observed in eight post-saccadic cMRF neurons (Pathmanathan et al. 2005). The third, and final hypothesis was that our recording methods did not measure the torsional characteristics of either head or gaze movements. Thus, a relationship between eye or head torsion and the neuronal signal would have been overlooked.

cMRF post-saccadic neurons: role in head control

Despite the preliminary nature of the data obtained from the post-saccadic neurons, we suggest that the temporal and spatial characteristics of these cells supports a role in an updating network providing higher structures with an efference copy (corollary discharge) of the amplitude (or velocity) and direction of the previous head movement. While we found little relationship between the discharge of post-saccadic neurons and head movement duration, we did find evidence of a nearly linear increase in spike number for increasing head amplitude (Pathmanathan et al. 2005). The fact that the peak discharge of post-saccadic neurons typically occurred *after* peak head velocity but during the continuing head movement (Fig. 6 and Supplementary Electronic Table 2) suggests that these neurons could play a role in relaying information to higher regions of the oculomotor system about the occurrence, amplitude, or outcome of the head movement in progress.

The cMRF has been shown to receive afferent projections from the spinal cord (Fukushima et al. 1981) and NRG (Cowie et al. 1994) and distributes efferents to the SC, interstitial nucleus of Cajal (INC), intermedullary lamina (IML) of the thalamus, and the nucleus reticularis tegmenti pontis (NRTP) (Scheibel et al. 1954, 1955; Edwards and de Olmos 1976; Cohen and Buttner-Ennever 1984; Chen and May 2000). Therefore, we suggest that cMRF post-saccadic neurons could distribute feedback signals from putative "head plant" burst neurons (e.g., the NRG for horizontal head movements) and cervical spinal cord motoneurons to a number of critical gaze structures including the cerebellar vermis and rostral midbrain. Both experimental and clinical data have documented deficits in head control and posture following damage to the MRF (Mori et al. 1985; Lee and Marsden 1994; Ragge et al. 2003). Inactivation of the cMRF in monkeys can generate profound head tilts (Waitzman et al. 2000),

which could be the result of a loss of cMRF output to regions involved with maintenance of head position. For example, inactivation of the interstitial nucleus of Cajal (INC) produces profound disturbances in vertical and torsional head posture, suggesting that it plays a role as an "integrator" for the head movement system (Klier et al. 2002). Since the cMRF provides ascending input to the INC (Edwards and de Olmos 1976), cMRF inactivation could lead to the observed head tilts. Future measurements of three-dimensional head and gaze signals could address the question of whether the post-saccadic discharge of cMRF neurons could provide a torsional velocity or position signal to the INC.

cMRF pre-saccadic neurons: role in gaze control

Evidence that many pre-saccadic cMRF neurons have large, open movement fields and close relationships to the velocity and duration of gaze movement suggests that this subset of cells could play a role in the conversion of gaze signals coded spatially in the SC into the temporal (i.e., rate of discharge) signals found in the excitatory burst neurons of the pons. Although the discharge of both burst and build-up SC neurons may be related to the dynamics (e.g., velocity and/or duration) of gaze shifts (Berthoz et al. 1986; Waitzman et al. 1991; Keller and Edelman 1994; Munoz and Wurtz 1995a; Sparks 2002), this topic remains controversial because the discharge of most SC neurons is tuned to specific gaze amplitudes (Sparks and Gandhi 2003). Therefore, individual SC neurons could only encode the movement dynamics of a strict subset of gaze amplitudes. For example, if movement duration were encoded, one would expect that rostral SC neurons would encode the duration of small gaze shifts and caudal SC neurons would encode the duration of larger movements (Fig. 13a). In contrast, a sub-population of pre-saccadic cMRF neurons (those with monotonically open movement fields) was well correlated with the duration, peak velocity, and velocity profile of a wide range of gaze shift amplitudes (Fig. 13b). However, this correlation was not as strong as that observed in PPRF burst neurons (Van Gisbergen et al. 1981; Scudder et al. 1988; Cullen and Guitton 1997b) (Fig. 13c).

Since cMRF neurons have direct projections to the PPRF, we hypothesize that neurons with monotonically open movement fields could form part of a tecto-reticular-pontine pathway that parallels the direct tecto-pontine pathways (Harting 1977; Raybourn and Keller 1977; Huerta and Harting 1984). This pathway through the cMRF would work in concert with the direct tecto-pontine projections probably mediated by the DLLBNs in the pons (Keller 1979; Hepp and Henn 1983; Keller et al. 2000b). We suggest that output neurons of the SC have weighted projections to the pre-saccadic burst neurons in the cMRF (Edwards and Henkel 1978; Moschovakis et al. 1998). Appropriately weighted projections from SC units, each encoding the dynamics of a subset of gaze shift amplitudes, could also generate the properties observed in closed, non-monotonically open, and monotonically open pre-saccadic cMRF neurons. In turn, to generate the tightly coupled burst duration to movement duration relationship found for PPRF burst neurons, we propose that monotonically open cMRF neurons, which had the strongest relationships to gaze dynamics for a wide range of movement amplitudes, would project to PPRF burst neurons to provide information on desired velocity and duration. Recent theoretical insights suggest that multiple weakly associated neural signals can be combined to generate a more strongly correlated signal (e.g., Pouget et al. 2002). This would suggest that the strong correlation between burst duration and saccade duration found in the medium-lead burst neurons of the PPRF could arise from multiple less well-correlated inputs. Such inputs could be provided by a combination of activity from the population of pontine (DLLBNs) and mesencephalic (cMRF) long-lead burst neurons.

The idea that monotonically open movement field cMRF neurons function in a feed-forward role for the horizontal component of gaze movements does not preclude the possibility that other classes of cMRF neurons could participate in feedback control of saccades (Waitzman et al. 2000). As a result we suggest that the saccade hypermetria observed following muscimol inactivation of the cMRF was the result of the combined reduction of both the feed-forward activation of horizontal burst neurons in the pons and reduced feedback from the cMRF to the SC (Chen and May 2000; Waitzman et al. 2000). In a typical situation, loss of the feed-forward signal would be compensated by appropriate feedback. However, with the loss of both the horizontal feed-forward and feedback activity, the response should be observed in the unaffected vertical system. This would explain why the hypermetria was observed primarily in the vertical component of oblique movements, and why saccade direction deviated toward the earth vertical (Waitzman et al. 2000). The feedback pathway from the cMRF to the SC could also account for the evidence that some SC neurons also reflect saccade duration, as observed following stimulation or inactivation of the OPNs (Keller and Edelman 1994; Keller et al. 2000a; Soetedjo et al. 2002b). Therefore, we conclude that cMRF neurons not only provide feedback to the SC and higher supranuclear regions, but also participate in the feed-forward pathway from the SC to downstream pre-motor structures.

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