Published in final edited form as:

Exp Brain Res. 2011 October ; 214(2): 225–239. doi:10.1007/s00221-011-2823-8.

Gaze shift duration, independent of amplitude, influences the number of spikes in the burst for medium-lead burst neurons in pontine reticular formation

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Abstract

Abstract Changes in the direction of the line of sight (gaze) allow successive sampling of the visual environment. Saccadic eye movements accomplish this goal when the head does not move. Medium-lead burst neurons (MLBs) in the paramedian pontine reticular formation (PPRF) discharge a high frequency burst of action potentials starting ~12 ms before the saccade begins. A subgroup of MLBs rostral of abducens nucleus monosynaptically excites oculomotor neurons. The number of spikes in the presaccadic burst is correlated with the amplitude of the horizontal component of the saccade, and the peak discharge rate is correlated with peak eye velocity. During head-unrestrained gaze shifts, a linear relationship between the number of action potentials in MLB bursts and gaze (but not eye) amplitude has been reported. The anatomical connection of MLBs to motor neurons and the similarity between the phasic motor neuron burst and MLB discharge have raised questions about the usefulness of counting spikes in MLBs to determine their role in eye-head coordination. We investigated this issue using a behavioral technique that permits a dissociation of eye movement amplitude and duration during constant vector gaze shifts. Surprisingly, during gaze shifts of constant amplitude and direction, we observe a nearly linear, positive correlation between saccade duration and spike number associated with a negative correlation between spike number and saccade amplitude. These data constrain models of the oculomotor controller and may further define the time-dependence of hypothesized neural integration in this system.

Keywords

Gaze; Saccade; Primate; PPRF; Head unrestrained

Introduction

When the head does not move, saccadic eye movements are characterized by a set of stereotyped relationships between peak velocity, duration and amplitude (Bahill et al. 1975;

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Conflict of interest

The authors declare that they have no conflict of interest.

Bahill and Stark 1977; Baloh et al. 1975a,b; Becker 1989). Single unit recordings in paramedian pontine reticular formation (PPRF) in head-restrained monkeys have identified a group of neurons, referred to as medium-lead burst neurons (MLBs), whose discharge is proportional to horizontal saccade velocity (Hepp and Henn 1983; Kaneko et al. 1981; Keller 1974; Luschei and Fuchs 1972; Scudder et al. 1988; van Gisbergen et al. 1981). Models describing the saccadic control system (Becker and Jürgens 1990; van Gisbergen et al. 1981) propose that a copy of the MLB velocity command is mathematically integrated and compared with a reference signal of desired eye displacement. Thus, these models predict that the number of spikes in the burst will be directly related to saccade amplitude. Consistent with this prediction, when the head is restrained, the number of spikes can account for ~95% of the variance in the amplitude of saccades (Cullen and Guitton 1997a; Kaneko et al. 1981; Ling et al. 1999; Scudder et al. 1988; Strassman et al. 1986a,b). However, when the head is restrained, movement parameters (velocity, amplitude and duration) are correlated. For example, saccade amplitude is linearly correlated with movement duration. For this reason, the previously published data from head-restrained monkeys could easily have supported the hypothesis that spike number is related to movement duration, as well as saccade amplitude.

When the head is free to move, the relative contributions of the eyes and head can vary, depending on the initial positions of the eyes in the orbits (Freedman and Sparks 1997; Freedman 2008). For gaze shifts of a particular vector, eye amplitude and duration can be anti-correlated (Freedman 2008). Several studies have demonstrated that, when the head is free to move, the number of spikes in the burst is better correlated with the gaze component amplitude than the eye component amplitude of the gaze shift (Cullen and Guitton 1997b; Ling et al. 1999, 2003; Sylvestre and Cullen 2006). The same has been reported for abducens motoneurons, even when the spike count is adjusted to compensate for changes in eye position during the saccade (Ling et al. 1999; Ling et al. 2003). These data suggest that the relationship between the number of spikes and amplitude may be more complex when the head is unrestrained, but the reason for this is not well understood. Ling et al. (2003) proposed that more spikes might be required to attain a movement of the same amplitude when the duration is long. If this is true, then the linear relationship between the spike count and component gaze amplitude might reflect the combined influences of amplitude and duration, rather than encoding gaze amplitude, per se. The present study sought to directly test this hypothesis.

Hypotheses posit that the duration of the saccade (or gaze shift) is not controlled directly, but is governed by the rate at which motor error declines to zero. This is determined by the desired size of the movement and the burst generator equation (Becker and Jürgens 1990; Robinson 1973; van Gisbergen et al. 1981) that converts motor error into a signal proportional to velocity. As long as the burst generator equation is unaltered, movement duration will be inextricably linked to movement amplitude. However, some models propose that the burst generator equation is modulated by a signal proportional to head velocity (see Eq. 4, Freedman 2001). This hypothesis predicts that, for gaze shifts of a given vector, as head velocity increases, the firing rate of MLBs will decline. By varying the initial positions of the eyes in the orbits, we were able to dissociate saccade duration and amplitude during constant amplitude and direction gaze shifts (Freedman 2008). This made it possible to ask

whether the number of spikes in the MLB burst is uniquely predictive of component amplitude, as is commonly assumed. The present data indicate that the number of spikes is correlated with both the duration of movements and the amplitude.

Methods

Preparation of subjects and data acquisition

Three female Rhesus monkeys (*Macaca mulatta*) were used in this study. Two sterile surgeries were used to prepare animals for experiments. In the first, a stainless steel post was affixed to the skull with bone screws and a scleral search coil implanted under the conjunctiva of one eye (Judge et al. 1980). After recovery, subjects were trained to make gaze shifts to visual targets (details below). Once the animals had become proficient at the required tasks, a second surgery was performed to place a recording chamber over a trephine craniotomy. The chamber was positioned on the midline at stereotaxic zero (monkeys U and P) or 1 mm caudal to zero (monkey Q). All surgical and experimental procedures were approved by the University of Rochester Animal Care and Use Committee and were in compliance with the National Institutes of Health Guide for the Care and Use of Animals.

During experiments, animals were seated in a custom-designed chair that permitted the head to rotate freely and without obstruction, but prevented movements of the torso. A small, lightweight cam-lock device was attached to the head post at the beginning of each experimental session. Once the micropositioner and electrode were in place, the head post was removed but the cam-lock device remained on the head. This allowed the head to rotate freely in any direction.

The cam-lock device served as a mount for three red (650 nm) diode lasers and a coil for monitoring head position. The central laser was directed along the midsagittal plane of the subject. A second laser was directed 18° to the left, while the third was pointed 18° to the right of the mid-sagittal plane. The monkey was then placed in the center of a cube that contained 3 pairs of magnetic field coils (CNC Engineering, Seattle, WA). The 4 vertical faces of the cube contained two pairs of Helmholtz coils in spatial and phase quadrature (Collewyn 1977). The current generated in the coils was linearly related to the horizontal rotational position of the scleral and head-mounted coils within ~2% over 360°. The top and bottom faces of the cube contained a third pair of Helmholtz coils that were used to measure the vertical angle of the coils. Signals from the gaze and head coils were sampled at 1 kHz, filtered and saved for offline analysis. All aspects of the experiment were controlled through the use of custom software running on a PC with an extended PCI bus (National Instruments, Austin, TX). Targets were presented on a flat LED board that spanned $\pm 48^\circ$ horizontally and $\pm 40^\circ$ vertically and contained LEDs every 2°. In a second apparatus, targets were presented on the inside surface of a 1.5 m diameter hemisphere (0.5-in. acrylic; Capital Plastics, Beltsville, MD) using two lasers attached to independent, two-axis motorized gimbals (RGV 100 rotation stages; Newport, Irvine, CA). These gimbals position visual targets with better than 0.01° accuracy.

Single neurons in PPRF were isolated using standard amplification (Bak Electronics, Mount Airy, MD) and filtering techniques. PPRF was identified by the characteristic high frequency

bursts associated with ipsiversive gaze shifts and by the proximity of the recording site to other known neurophysiological landmarks, such as omnipause neurons, superior colliculus (SC), trochlear nucleus, and abducens motoneurons. In addition to recording the digitized spike times, the analog signal from the electrode was digitized at 25 kHz and used offline to confirm the isolation of each neuron.

Behavioral tasks

Subjects were trained to perform a delayed gaze shift task. An additional head alignment contingency was imposed in order to control the positions of the eyes in the orbits at the beginning of gaze shifts. Task features are presented schematically in Fig. 1. At the start of each trial, a visual target was illuminated. At the same time, one of the three head-mounted lasers was selected at random by behavioral control software and was switched on. Subjects were required to fixate the illuminated target and simultaneously align the lit head-mounted laser on the same target. Because the leftmost laser (for example) was aimed 18° left of straight ahead, aligning the spot with the target required the monkey to turn the head to the right, resulting in an initial eye-in-head position of ~18° left. The animals were then required to maintain the gaze and head alignment for a variable period (500–1,000 ms, in 100 ms increments). If this was accomplished successfully, a second visual target was switched on at a new location. Monkeys were required to maintain gaze and head positions for an additional period (the “delay period”). The head-mounted laser and the fixation target were then switched off. This was the cue to initiate a gaze shift to the location of the still illuminated second target. The temporal sequence of illumination of targets and head-mounted lasers is shown in Fig. 1. Below are representative gaze, eye, and head positions plotted as functions of time illustrating the performance of the task. Subjects were rewarded if they maintained fixation of the second target for 500–1,000 ms (100 ms increments). There were no task requirements for head alignment with the second target.

The location of the second target was randomly chosen to elicit gaze shifts with horizontal components ranging from 10° contralateral to 70° ipsilateral. In general, the increments were 10°, with the exception that an additional target was sometimes used to elicit 4° ipsiversive gaze shifts. One of the goals of this study was to determine, for each cell, the relationship between neural activity and the horizontal and vertical components of gaze shifts with a wide range of amplitudes. For some analyses, however, it was necessary to have a large number of trials to the same target location. To achieve both of these ends, on most recordings, 50% of the trials required gaze shifts with no vertical component. On the other 50% of trials, the vertical component of the target shift was 10°, 20°, 30°, or 40° up or down. However, for nine cells, 50% of the trials were to a single oblique target location, usually (40, 40).

Data analysis

All data analyses were conducted using Matlab (Math-Works, Natick, MA). Eye position was computed by subtracting head position from gaze position. Gaze, eye, and head movements were identified using a sliding window algorithm based on velocity criteria (Walton et al. 2007, 2008). In the text below, “eye amplitude” will be used to refer to the amplitude of the eye-in-head saccade. “Gaze amplitude” will refer to the amplitude of the

eye-in-space saccade. The term “head amplitude” will be used to refer to the total amplitude of the head movement, including the portion before (if any) and after the end of the gaze shift. This is distinct from “head contribution” which was computed by subtracting the head position at gaze shift onset from the head position at gaze offset.

For a small minority of trials, the eyes began to counter-rotate in the orbits before the end of the gaze shift (possibly because the head velocity and VOR gain were sufficient to overcome the saccade-related eye velocity). All MLBs continued to discharge during this period, suggesting that the saccadic command was still active. For this reason, duration was always taken to be the duration of the gaze shift.

Two methods were used to identify MLBs and distinguish them from long-lead burst neurons (LLBNs). The first was based upon the criteria established by Hepp and Henn (1983) and marked the start of phasic activity as the time that spike frequency first rose to 50% of the peak value. However, because spike frequency sometimes fell below 50% of peak value in the middle of the burst for large gaze shifts, burst offset was defined as the last spike associated with the high frequency burst. The second method defined the start and end of a burst as the times of the first and last spikes, respectively, associated with the high frequency burst. In each case, burst lead was defined as the time between burst onset and gaze onset, and a cell was classified as an MLB if the mean burst lead (for all ipsiversive gaze shifts) was less than 12 ms. Because the bursts of MLBs began and ended abruptly, these two approaches identified the same group of neurons as MLBs. In subsequent analyses, burst onset and offset were defined using the latter criteria. The number of spikes was defined as the number of action potentials identified within a window beginning at burst onset and ending with burst offset. Within the burst, spike frequency was computed in two ways. First, instantaneous spike frequency was computed by taking the inverse of each interspike interval. In addition, a five point moving average was used to obtain a smoothed estimate of spike frequency. An analysis of the relationship between the number of spikes in the burst and eye/gaze amplitude was only performed if the cell’s isolation was maintained for at least 50 trials. Other analyses, however, required a larger number of trials (see “Results”).

Results

Electrical isolation of 244 individual neurons was maintained for a minimum of 50 and a maximum of 1,396 trials. Sixty-three of the 244 neurons from 6 hemispheres of 3 subjects (monkeys U, Q, and P) were classified as Medium-Lead Burst neurons (see “Methods”). Of the others, 121 were classified as LLBNs (using Hepp and Henn 1983 criteria), 17 as burst-tonic cells, and 10 as vertical burst neurons. The remainder were task-related neurons that were difficult to classify. Here, we focus on MLBs; other cell types will be described elsewhere. Movement fields of three MLBs are illustrated in Fig. 2. These example neurons were selected because electrical isolation was maintained for more than 400 trials, and the range of movement amplitudes and directions was large. In each panel, vertical gaze shift amplitude is plotted as a function of horizontal amplitude. The color axis (shown in panel b, applies to all examples) displays the number of action potentials in the movement-associated phasic activity (referred to below as the MLB burst) for each trial. As expected from MLBs,

there is a systematic increase in the number of spikes as a function of horizontal movement amplitude. The neurons in A (subject P) and B (subject U) were recorded from the left PPRF, and the example in panel c was from the right PPRF (subject P). In each case, discharge increased systematically as horizontal amplitude increased from 10° to 70°.

Figure 3 plots a movement field of a fourth MLB in the right PPRF recorded during 833 trials. This neuron was selected to illustrate several key points about MLB discharge during head-unrestrained gaze shifts. First, consider movements directed along the horizontal meridian (gray band). This group of movements was selected to demonstrate the duration effect in a group of trials with horizontal gaze shifts, elicited from different initial eye positions. This means that, for each position along the x -axis, this data set includes trials with varying contributions of the eyes and head. For this subset of trials (shaded region in Fig. 3a), horizontal gaze shift amplitude is plotted as a function of the number of spikes in the burst (Fig. 3b). As previously demonstrated (Cullen and Guitton 1997b; Ling et al. 1999; Sylvestre and Cullen 2006), there is a linear relationship between gaze amplitude and the number of spikes in MLB bursts. In this example, the number of action potentials in the selected 450 trials accounted for 92% of the variance in gaze shift amplitude. For comparison, the amplitude of the eye movement component of gaze from the same trials is plotted as a function of number of spikes in the burst (Fig. 3c). In this case, a linear fit accounted for 66% of the variance in saccade amplitude. However, in spite of the correlation between the number of spikes and gaze amplitude, there was still a considerable range of movement amplitudes associated with a given number of spikes. For example, trials having between 80 and 82 spikes (vertical shading in 3B) were associated with horizontal gaze shifts having amplitudes ranging from 37° to 68°. During the same set of trials associated with ~81 spikes, eye movement amplitudes had a similar 30° range. Conversely, during horizontal gaze shifts having the same amplitude (e.g. ~40°; horizontal bar in Fig. 3b), the number of MLB spikes varied from 50 to >80.

The seemingly high variability of MLB discharge may be surprising given the hypothesized correlation between the number of spikes in MLB bursts and movement amplitude. When the head does not contribute to the accomplishment of a gaze shift, saccade kinematics (velocity profiles, movement duration etc.) depend only on movement amplitude. This link between saccade duration and amplitude can be uncoupled during constant vector gaze shifts. When the initial positions of the eyes vary, saccade duration-amplitude relationships can be anti-correlated (Freedman 2008). Constant vector gaze shifts were selected from the movement field illustrated in Fig. 3 (black rectangle in 3a). These gaze shifts were all directed along the horizontal meridian and had amplitudes between 40° and 42°. Eye velocity is plotted as a function of time for 9 movements meeting these criteria (d–f). These 9 trials are separated into 3 sets of 3 based on the amplitude of the head movement on each trial. In panel d, these 3 eye movements were coupled with head movements that were ~8° in amplitude. In e, head movements were ~15°, and in F, they were nearly 42°. As is clear in this figure, eye movement velocities declined as the head contribution increased. In addition, the duration of the saccadic component of these constant vector gaze shifts increased with increasing head contribution. Below each velocity profile are vertical lines indicating the spike times during the selected movements. The duration of the MLB burst was prolonged during longer eye movements. The key point, however, is that as head contribution

increased, eye movement amplitude decreased from 39° for the movements in panel d to 22° during the movements in F. At the same time that eye amplitude decreased, spike number appeared to increase. So while gaze amplitudes were constant, the number of spikes in the burst increased by ~25% (from 61 to 76) as eye movement amplitudes decreased. These relationships are illustrated in Fig. 4 for the 31 constant vector gaze shifts highlighted in Fig. 3a. Figure 4a recapitulates the reversal of the duration-amplitude relationship during constant vector gaze shifts (Freedman 2008). The number of spikes in the burst is plotted as a function of saccade amplitude (4b) and illustrates the inverse relationship outlined above. The positive correlation between the number of spikes and the duration of the eye movement is illustrated in Fig. 4c.

These data show that the number of spikes in the burst is not a reliable predictor of gaze shift or of eye movement amplitude. However, by including movement duration, burst variability can be accounted for. In Fig. 5, for the example cell shown in Figs. 3 and 4, the number of spikes is plotted as a function of horizontal eye amplitude and horizontal saccade duration. Data were fit with the following planar model:

$$\text{Number of Spikes} = a + b * EH_{amp} + c * EH_{dur}$$

where EH_{amp} is the horizontal amplitude of the eye movement, EH_{dur} is the duration of the horizontal component, and a , b , and c are constants. The plane fits were performed using all ipsiversive gaze shifts, including those with vertical components. The inclusion of duration in the model improved the R^2 value from 0.63 to 0.95. The slopes were significantly different from zero for both horizontal eye amplitude ($b = 0.61 \pm 0.05$) and duration ($c = 0.38 \pm 0.01$). As Table 1 shows, all cells showed a significant relationship between the number of spikes and duration, independent of horizontal eye amplitude. The distribution of slopes for the duration-number of spikes relationship is shown in Fig. 7a. The mean slope was 0.217. A comparison was performed between the linear model that included only horizontal eye amplitude and the model that included duration. For the model that employed only horizontal eye amplitude as a predictor of the number of spikes, the mean R^2 across all cells was 0.506. Adding duration to the model, however, increased the mean R^2 to 0.826. Figure 7c shows the distribution of R^2 values for the planar fits across all cells. We also tried fitting the data to a model that used head contribution and eye amplitude to predict the number of spikes. For 51/63 cells (81%), the variance accounted for was higher when duration was used in the model than when head contribution was used. For 9/63 cells (14%), the variance accounted for was higher for the model that included head contribution. Three cells (5%) showed no difference. Overall, the variance accounted for was lower when head contribution was used in the model (mean R^2 was 0.765). The duration model, therefore, clearly performed better than the head contribution model.

One might suggest that the duration dependence described above is simply a consequence of the VOR and the fact that the number of spikes in the burst is linearly correlated with horizontal gaze amplitude, a fact that has been demonstrated in several previous studies (Cullen and Guitton 1997b; Ling et al. 1999; Ling et al. 2003; Sylvestre and Cullen 2006). Because VOR signals are added downstream from the MLBs, if the gain of the VOR during

the gaze shift is greater than 0, then the measured eye amplitude will be smaller than what was requested by the MLBs. For a particular gaze vector, the larger the head contribution, the greater would be the discrepancy between actual and requested eye amplitude. Since larger head contributions are also associated with longer durations, this would mean that the number of spikes would be correlated with duration in addition to eye amplitude.

For example, a 20° saccade that contributes to a 40° gaze shift would have a longer duration, and a larger number of spikes, than a 20° saccade that occurs in the absence of a head movement. In this example, if the number of spikes in the burst uniquely encodes horizontal gaze amplitude, then there would be more spikes associated with the 20° saccade that contributes to a 40° gaze shift— but that would not necessarily have anything to do with duration, per se. It might merely be a secondary effect attributable to the fact that the VOR reduces the measured amplitude of the saccade by an amount that is correlated with movement duration. Of course, the larger the VOR gain during the gaze shift, the more it would contribute to a correlation between the number of spikes and duration when horizontal eye amplitude is used in the model. If the duration effect is due *solely* to the VOR, then it should disappear when one uses horizontal gaze amplitude instead of horizontal eye amplitude in the model, even if one assumes that the VOR gain is 1 for the entire duration of the gaze shift. In the example above, if 40° gaze shifts with long durations are associated with more MLB spikes than 40° gaze shifts with short durations, then one cannot dismiss the effect as due solely to the VOR. We tested this idea by repeating the above planar fits, using horizontal gaze amplitude instead of horizontal eye amplitude:

$$\text{Number of Spikes} = d + e * GH_{amp} + f * GH_{dur}.$$

When this was done on the example cell shown in Fig. 5, the coefficients of the planar fit were significantly different from zero for both gaze amplitude ($e = 0.65 \pm 0.06$) and duration ($f = 0.27 \pm 0.02$) (Fig. 6). When horizontal gaze amplitude was used in the model, a significant effect of duration was found for 46/63 cells (73%). The distribution of slopes for this relationship across all cells is shown in Fig. 7b. The mean slope for duration was 0.115. A comparison was performed between the linear model that included only horizontal gaze amplitude and the model that included duration. When the model employed only horizontal gaze amplitude as a predictor of the number of spikes, the mean R^2 across all cells was 0.758. Adding duration to the model increased the mean R^2 to 0.845. The distribution of R^2 values for the planar fits is shown in Fig. 7d. Results of this analysis are given for all cells in Table 2. Thus, more spikes were required to attain the same amplitude if the duration was long, regardless of whether eye or gaze amplitude was used in the model.

Discussion

Several previous studies have reported that, for MLBs, the number of spikes in the burst is better correlated with gaze amplitude than eye amplitude (Cullen and Guitton 1997b; Ling et al. 1999, 2003; Sylvestre and Cullen 2006). It has also been reported that the same is true of abducens motoneurons, even when the spike count is corrected for the position signal (Ling et al. 1999, 2003). Ling et al. (2003) proposed that the number of spikes in the burst might

be related to movement duration in addition to amplitude. To our knowledge, the present study is the first to directly test this hypothesis. Activity of medium-lead burst neurons rostral of the abducens nucleus was recorded during head-unrestrained gaze shifts made with the eyes in different starting positions relative to the head. As shown previously, during constant amplitude gaze shifts directed along the horizontal meridian (for example), the relationship between saccade amplitude and duration can be reversed under these conditions (Freedman 2008). Here, we show that MLB discharge depends not only on saccade amplitude, but also on the duration of the saccade. This can lead to an inverse correlation between the number of MLB spikes and eye amplitude. While the number of spikes in the MLB burst is perhaps not the critical parameter to assess in considering the role of these neurons in generating eye movement commands (Cullen et al. 2000; Ling et al. 1999, 2003; Sparks et al. 2002), most hypotheses of saccadic and gaze shift control make implicit assumptions about the number of spikes in MLB bursts. These assumptions arise primarily from the proposed integration of MLB output that is used both as tonic input to the eye motor neuronal pools and as feedback to the comparator. In most models (head restrained: Becker and Jürgens 1990; van Gisbergen et al. 1981; head unrestrained: Freedman 2001), the burst generator's velocity signal is integrated to obtain a feedback signal related to current displacement. Mathematically, this operation implicitly assumes that the number of spikes in the burst encodes amplitude. If our sample of MLBs is representative of the population, however, then this assumption is incorrect, because a given sum total of MLB spikes does not uniquely encode a particular horizontal eye amplitude or a particular horizontal gaze amplitude. This observation precludes true integration in either the feedback or feedforward pathways.

As noted above (see "Results"), one might argue that the correlation between the number of spikes and duration is due merely to the fact that, for some head-unrestrained gaze shifts, the VOR influences the eye velocity. If the VOR during gaze shifts has any nonzero value, the measured saccade amplitude will be less than what was "requested" by the MLBs. Because gaze shifts with large head contributions tend to have longer durations than amplitude-matched gaze shifts with small head contributions, a positive value for the VOR during gaze shifts might produce a correlation between duration and the number of spikes in the burst for movements with a given eye saccade amplitude (see "Results"). It is possible that, when horizontal eye amplitude is used in the model, the slope along the duration axis is partly attributable to the VOR. However, the "VOR hypothesis" cannot *fully* account for our data, for several reasons. First, most recent studies have reported that the VOR gain is decreased during gaze shifts (Cullen et al. 2004; Guitton and Volle 1987; Lauritis and Robinson 1986; Péliisson et al. 1988; Tabak et al. 1996; Tomlinson and Bahra 1986; Tomlinson 1990). Second, the present data clearly show that the duration effect is still significant even when the model employs horizontal gaze amplitude as a predictor instead of horizontal eye amplitude.

A close examination of the existing literature suggests the possibility that the duration effect reported in the present study may be an indirect consequence of the velocity signals carried by these cells. A number of studies have examined the relationship between firing rate and saccade velocity in head-restrained preparations (Hepp and Henn 1983; Kaneko et al. 1981; Keller 1974; Luschei and Fuchs 1972; Scudder et al. 1988; van Gisbergen et al. 1981). A

close examination of the regression analyses in these studies suggests that the efficacy of a given spike for driving the eyes may be related to the firing rate. That is, a given number of spikes at a high firing rate will move the eyes farther than the same number of spikes at a low firing rate. This can be confirmed by a straightforward calculation based on the regression coefficients reported in these studies. For example, Cullen and Guitton (1997a) reported a y -intercept of 177.3 and a slope of 0.96 for their model 2d. This predicts that a firing rate of 800 spikes/s should lead to an eye velocity of 650°/s. A decrease in firing rate to 400 spikes/s (50%) leads to an eye velocity of only 250°/s (38.5%). Thus, a given number of spikes at 800 spikes/s will move the eyes farther than the same number of spikes at a frequency of 400 spikes/s. When the head is restrained, the tight coupling of amplitude with peak and average velocity means that a given number of spikes will still uniquely predict horizontal saccade amplitude. When the head is free to move and the initial positions of the eyes in the orbits are variable, amplitude and duration become decoupled. In this case, movements of a given amplitude can be achieved by bursts with a wide range of average firing rates. This exposes the fact that the number of spikes is not uniquely predictive of amplitude. For movements of a particular amplitude, the average firing rate decreases as the duration increases, which means that it takes more spikes to achieve the same eye displacement. It is important to note that this can be deduced by a straightforward calculation based on the *head-restrained* data. Thus, although the slope of the duration effect may be influenced by the VOR if it has any nonzero gain, the duration effect reported in the present study is not *solely* a consequence of the VOR.

The same concept applies for the relationship between eye velocity and the firing rate of abducens motor neurons (for example, see Fig. 7c, d in Sylvestre and Cullen 1999). This implies that the “extra” spikes associated with long-duration movements are needed to overcome firing rate-dependent effects at the level of eye muscle activation and/or the plant itself. Perhaps, low firing rates activate the eye muscles less effectively than high firing rates.

Cullen and Guitton (1997b) performed a dynamic analysis of MLB firing rates, using a system identification approach. These authors concluded that MLBs carry a velocity signal and that the VOR influences the actual eye velocity at the level of the motoneurons. The present data are consistent with the idea that MLB discharge is probably best regarded as a dynamic velocity signal and that amplitude is not explicitly encoded by the number of spikes.

What, then, are we to make of models that compute the eye displacement by integrating the MLB velocity signal? As noted above, these models implicitly assume that the number of spikes in the burst encodes amplitude. If long-duration movements require more spikes, then the area under the MLB firing rate curve will be greater for these movements and, therefore, the integrated value will differ. As a result, the output of a perfect integrator at any one time will no longer uniquely represent a particular current displacement. This may lead to an inappropriate feedback signal to the comparator and, possibly, an inappropriate tonic eye position signal to the motoneurons. Although vestibular input may partially offset this effect, it seems likely, for the reasons stated above, that this would not be sufficient by itself.

It is possible that the answer may relate to the way that actual neurons achieve integration. It is likely that the integrator that provides feedback to the comparator is different from the one that produces the step component of motoneuron discharge (i.e., the “feedforward integrator”) because the former would need to reset after each saccade and the latter must maintain its value to keep the eyes from drifting away from the current target. In either case, the firing rate of a perfect integrator cell, at any given time, should depend only upon the cumulative number of input spikes, regardless of the frequency of the input. It may not be realistic, however, to assume that real neurons would behave in this way. For example, it has been suggested that neural integration is a result of synaptic effects, such as short-term potentiation, that enhance the excitability of the postsynaptic cell as a function of the number of input spikes (Navarro-López et al. 2004, 2005; Shen 1989). Navarro-López et al. (2004) recorded intracellularly from nucleus prepositus hypoglossi (NPH) neurons and reported a sustained depolarization of the membrane potential in response to stimulation of PPRF. In addition, Navarro-López et al. (2005) reported short-term potentiation in NPH neurons in response to PPRF stimulation. Shen (1989) created a model neural integrator based on short-term potentiation. With respect to feedback integration, an important question is whether such synaptic mechanisms could reset fast enough to account for the data suggesting a resettable integrator (Breznen and Gnadt 1997; Nichols and Sparks 1995). The decay time constants of these synaptic processes vary widely, with some having time constants of only tens of ms (Shen 1989).

Such an increase in the excitability of a cell, however, would not change the fact that it would fire at a higher rate in response to high frequency input than for low frequency input, even if the cumulative spike count is the same. That is, these synaptic effects would increase the output frequency that results from a given input frequency but, like almost any neuron, they should also output a higher frequency when the input frequency is higher. Thus, the response of the cell is, perhaps, best understood as having two components: (1) an integrative component, driven by changes in the excitability of the cell (i.e., the firing rate resulting from a given input frequency increases as the cumulative number of input spikes increases) and (2) a frequency component, which is due simply to the fact that most neurons will fire at a higher rate in response to higher frequency input. The firing rate at a given point in time would be related to *both* the cumulative spike count and the input frequency in a manner that could be described as follows:

$$FR(t) = a \int f(t) + b f(t)$$

where FR is the output firing rate, f is the input frequency, and a and b are constants. When the head is restrained, the additional term would act only as a gain factor, because the frequency, duration, and the number of input spikes increase together as saccade amplitude increases. For head-restrained data, the behavior of these cells may approximate that of a perfect integrator and it is appropriate to model it as such. However, the present data show that, when the head is free to move and the initial positions of the eyes in the orbits are varied, the firing rate of MLBs is not tightly coupled with amplitude or duration. Indeed, the peak and average firing rates *decrease* as the duration of the movement increases and as gaze amplitude increases. A low frequency input for a longer duration should not activate the

integrator neurons as effectively as a high frequency input for a shorter duration, even if the number of input spikes is the same. Because of the frequency term in the above equation, it will take more spikes to attain the same output firing rate when the input is a lower frequency over a longer duration. Thus, the frequency term will tend to decrease the amplitude of short duration saccades and increase the amplitude of long duration saccades. This would tend to cause dysmetria if the number of spikes were the same. However, when the saccade duration is long and the MLB firing rate is low, the slope and bias terms in the firing rate—velocity equations (see, for example, Cullen and Guitton, 1997b) mean that the MLB firing rate will be higher than a simple spike count would predict. This, in turn, causes the integrator output to rise at a faster rate, which balances out the frequency term in the above integrator equation. In this way, the feedback loop can still produce normometric movements, despite the fact that the efficacy of a given spike for driving the eyes declines as firing rate declines.

We suggest that the more complex kinematic characteristics of head-unrestrained gaze shifts expose the fact that the feedback is not mediated by a true integrator. If the firing rate of integrator neurons is a key signal in the feedback loop, the “extra” MLB spikes observed for longer-duration movements may simply compensate for the lower frequency input. To accurately model the behavior of the burst generator when the head is unrestrained, movement duration must also be considered.

Acknowledgments

We thank Ginger Parker and Dr. Gil Rivlis for technical assistance. This work was supported in part by National Eye Institute Grant EY 13239 (EGF), and the Center for Visual Science and Center for Navigation and Communication Sciences and the University of Rochester.

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Fig. 1.

Schematic representation of experimental setup and behavioral task. (A) At the start of the trial, the monkey must look to, and align a head-mounted laser with, a visual target (*T1*). (B) During the delay period, a second target (*T2*) appears, but the monkey must maintain gaze and laser alignment on *T1*. (C) After a variable fixation period, *T1* and the head-mounted laser are extinguished, and the monkey must look to *T2*. Representative eye (*thin solid line*), gaze (*thick solid line*), and head (*dashed line*) traces are shown below

Fig. 2.

Movement field plots for three representative MLBs. *Horizontal* and *vertical* gaze amplitude are shown on the *x* and *y* axes, respectively. The number of spikes in the burst is indicated by the *color* (*scale bar* shown in panel **b** applies to all). Note the increased variability for larger amplitudes

Fig. 3.

Example data from cell P21. **a** Movement field plot showing the subsets of data used in other panels. The *horizontal shaded region* shows the subset of trials used in panels **b** and **c**; the small rectangle shows the trials used in panels **d–f**. **b** Horizontal gaze amplitude is plotted as a function of the number of spikes in the burst. Note that trials with 80–82 spikes (*vertical shaded region*) could have horizontal gaze amplitudes of anywhere from 37° to 68°. Trials with gaze amplitudes of 40°–42° (*horizontal shaded region*) could have anywhere from 50 to 80 spikes. **c** Horizontal eye amplitude is plotted as a function of the number of spikes. Note the large variability. **d–f** Velocity traces and rasters are shown for three groups of 3 trials, all with the same gaze vector. Trials were grouped based on the initial eye position. Panel **d** shows rightward gaze shifts with initial eye positions of ~18° *left*. In this case, the head contributed ~1°–3°. In panel **e**, the eyes begin approximately centered in the orbits. For these trials the head contributed between 5° and 8°. In panel **f**, the eyes begin ~18° to the *right* in the orbits. This translated to a head contribution of approximately 18°–22°. For these constant vector gaze shifts, as the initial eye position becomes more rightward, saccade amplitude decreases, while the movement duration and the number of spikes increases

Fig. 4.

Relationships between saccade amplitude, duration and the number of spikes for trials with the same gaze vector for cell P21. All panels are based on the subset of trials indicated by the *rectangle* in Fig. 3a. **a** For gaze shifts of a particular vector, the relationship between saccade duration and amplitude can have a negative slope. **b** For the same subset of trials shown in **a**, the number of spikes is negatively correlated with horizontal saccade amplitude. **c** In contrast, the number of spikes is positively correlated with saccade duration

Fig. 5.

A plane was fit to the data for horizontal saccade amplitude, gaze duration, and the number of spikes in the burst. The *data* shown are from cell P21, the same cell shown in Figs. 3 and 4. Although the variability is high when the number of spikes is plotted as a function of horizontal saccade amplitude, much of this variability can be accounted for by including duration in the model (R^2 rose from 0.63 to 0.95 when duration was included in the model)

Fig. 6.

A plane was fit to the data for horizontal gaze shift amplitude, gaze duration, and the number of spikes in the burst. The *data* shown are from cell P21. Evidence of a slope along the duration axis shows that spike number is correlated with gaze duration, independent of horizontal gaze amplitude

Fig. 7.

Results of the planar fits for all cells. Panels **a** and **b** show *histograms* of the distributions of slopes for the relationship between duration and the number of spikes in the burst when horizontal eye amplitude (**a**) or horizontal gaze amplitude (**b**) were included in the model. Panels **c** and **d** show the distribution of R^2 values for the planar fits when horizontal eye amplitude (**c**) or horizontal gaze amplitude (**d**) were included in the model

Table 1

Results of analyses involving eye amplitude

Cell	N	Regression statistics for horizontal eye amplitude versus saccade duration for constant vector gaze shifts			Statistics for plane fit for number of spikes, horizontal eye amplitude, and saccade duration			
		Eye Amp-Dur slope	Eye Amp-Dur R square	Eye Amp-Dur intercept	Eye Amp NumSpikes slope	Eye Dur NumSpikes slope	R square using Hor Eye Amp only	R square using EHamp and duration
U1	53			4.93	-0.35*	0.13*	0.15	0.79
U2	593	-0.28	0.05	6.06*	-0.48*	0.15*	0.25	0.92
U3	159			-1.87	-0.7*	0.36*	0.68	0.92
U4	104			-3.37	0.52*	0.23*	0.61	0.84
Q1	281	-1.25	0.14	-0.3	0.47*	0.28*	0.21	0.55
Q2	143	-2.03*	0.23	11.1*	-0.65*	0.17*	0.32	0.85
Q3	175			4.76*	-0.48*	0.09*	0.30	0.63
Q4	82			10.19*	-0.29*	0.05*	0	0.54
Q5	175	-1.64*	0.42	1.01	-0.2*	0.08*	0.37	0.83
Q6	52			3.81	-0.59*	0.15*	0.19	0.76
Q7	192	-1.83*	0.31	5.17*	0.5*	0.23*	0.06	0.79
Q8	333	-2.61*	0.45	-7.73*	0.36*	0.18*	0.37	0.73
Q9	77			8.63*	0.55*	0.13*	0.32	0.66
P1	160	-2.83*	0.20	12.85*	0.36*	0.18*	0.33	0.92
P2	282	-1.96*	0.49	4.89*	-0.34*	0.31*	0.60	0.95
P3	177	-2.31*	0.42	-0.46	-0.46*	0.41*	0.22	0.93
P4	228	-2.01*	0.42	-1.17*	-0.14*	0.11*	0.60	0.83
P5	177	-2.52*	0.47	-8.4*	-0.7*	0.31*	0.67	0.90
P6	189	-1.15*	0.20	-4.7*	0.54*	0.18*	0.68	0.88
P7	344	-1.01*	0.13	-5.6*	0.55*	0.16*	0.66	0.88
P8	237	-1.18*	0.26	5.7*	0.02*	0.05*	0.33	0.69
P9	87			0.8	0.36*	0.1*	0.34	0.61
P10	157			3.71*	0.59*	0.18*	0.62	0.93
P11	347	-1.91*	0.29	-3.38*	0.55*	0.43*	0.49	0.98
P12	376	-1.41*	0.31	-8.04*	0.32*	0.31*	0.47	0.77
P13	145			-9.11*	0.33*	0.21*	0.60	0.89

Cell	N	Regression statistics for horizontal eye amplitude versus saccade duration for constant vector			Statistics for plane fit for number of spikes, horizontal eye amplitude, and saccade duration			
		Eye Amp-Dur slope	Eye Amp-Dur R square	Eye Amp-Dur intercept	Eye Amp NumSpikes slope	Eye Dur NumSpikes slope	R square using Hor Eye Amp only	R square using EHamp and duration
P14	278	-3.44*	0.58	0.71	0.37*	0.39*	0.50	0.89
P15	413			4.78*	0.49*	0.22*	0.71	0.83
P16	132			9.16*	0.57*	0.09*	0.72	0.86
P17	58			8.44*	0.24	0.26*	0.31	0.73
P18	121			-11.69*	0.83*	0.19*	0.75	0.89
P19	52			10.98*	0.46*	0.13*	0.59	0.85
P20	366	-2.22*	0.29	-1.15	0.49*	0.29*	0.58	0.89
P21	833	-4.8*	0.42	2.64*	0.61*	0.38*	0.63	0.95
P22	86			7.3*	0.46*	0.16*	0.63	0.82
P23	673	-4.23*	0.57	7.76*	0.37*	0.16*	0.62	0.78
P24	91			0.97	0.78*	0.28*	0.66	0.91
P25	59			27.02*	1.28*	0.56*	0.68	0.26
P26	352			9.2*	0.21*	0.05*	0.19	0.59
P27	331	-0.7	0.10	-0.74	0.06	0.26*	0.54	0.5
P28	532	-3.34*	0.45	-2.66*	0.57*	0.15*	0.81	0.95
P29	67			-3.32	0.32*	0.14*	0.43	0.75
P30	368	-4.56*	0.68	-7.43*	-0.54*	0.32*	0.67	0.94
P31	245			-1.39	0.84*	0.18*	0.67	0.89
P32	433	-1.94*	0.29	-2.37*	0.74*	0.12*	0.84	0.93
P33	110			-4.54*	-0.65*	0.20*	0.82	0.96
P34	166			-2.93*	0.43*	0.11*	0.84	0.96
P35	235	-2.9*	0.28	-3.54*	0.63*	0.21*	0.72	0.88
P36	355	-1.06*	0.53	-5.44*	0.17*	0.25*	0.35	0.90
P37	196	-3.01	0.18	-0.38	0.69*	0.24*	0.67	0.95
P38	162			-6.35*	0.62*	0.25*	0.64	0.95
P39	158			3.83*	0.82*	0.11*	0.80	0.92
P40	916	-1.43*	0.42	8.38*	0.35*	0.07*	0.44	0.69
P41	155			11.3*	0.48*	0.11*	0.59	0.80
P42	271	-0.94*	0.30	5.12*	0.29*	0.07*	0.53	0.71

Cell	N	Regression statistics for horizontal eye amplitude versus saccade duration for constant vector gaze shifts			Statistics for plane fit for number of spikes, horizontal eye amplitude, and saccade duration				
		Eye Amp-Dur slope	Eye Amp-Dur R square	Eye Amp-Dur intercept	Eye Amp NumSpikes slope	Eye Dur NumSpikes slope	R square using Hor Eye Amp only	R square using EHamp and duration	
P43	374	-1.36*	0.33	-6.7*	0.56*	0.14*	0.68	0.91	
P44	322	-1.25*	0.47	-7.77*	0.63*	0.42*	0.51	0.95	
P45	192	-1.98*	0.53	-9.02*	0.29*	0.3*	0.31	0.86	
P46	413	-1.98*	0.62	-3.1*	0.57*	0.2*	0.51	0.88	
P47	571	-0.69*	0.21	-7.28*	0.85*	0.21*	0.65	0.94	
P48	82			-13.54*	0.53*	0.42*	0.46	0.95	
P49	147	-1.84*	0.79	-11.9*	0.60*	0.37*	0.16	0.75	
P50	290	-1.28*	0.58	-12.58*	0.63*	0.55*	0.25	0.91	

The leftmost column gives the cell ID for all cells analyzed for this report. Bold text indicates the cell used as an example in Figs. 3, 4, 5. Column 2 gives the total number of good trials analyzed. The next three columns show the regression coefficients for the relationship between horizontal eye amplitude and saccade duration for one selected gaze vector (usually 50, 0). Data are not shown for some cells because this analysis was only performed on a given cell if at least 15 trials were found for the selected vector. The rightmost three columns show the coefficients for a plane fit that predicts the number of spikes in the burst as a function of horizontal eye amplitude and duration. Asterisks indicate coefficients that were significantly different from zero. Note that, for all cells, the number of spikes in the burst was significantly positively correlated with duration, independent of horizontal eye amplitude

Results of plane fit that predicted the number of spikes in the burst as a function of the horizontal gaze amplitude and duration

Table 2

Cell	N	Statistics for plane fit for number of spikes, horizontal gaze amplitude, and saccade duration			
		Gaze Amp NumSpikes slope	Gaze Dur NumSpikes slope	R square using Hor gaze Amp only	R square using GHamp and duration
U1	53	-0.29*	0.10*	0.33	0.83
U2	593	-0.36*	0.08*	0.73	0.95
U3	159	-0.51*	0.12*	0.78	0.88
U4	104	0.38*	0.14*	0.85	0.88
Q1	281	0.35*	0.22*	0.30	0.54
Q2	143	-0.49*	0.07*	0.67	0.84
Q3	175	-0.33*	0.06*	0.43	0.65
Q4	82	-0.29*	0.05*	0.20	0.54
Q5	175	-0.25*	0.12*	0.67	0.79
Q6	52	-0.39*	0.09*	0.62	0.84
Q7	192	0.39*	0.15*	0.39	0.81
Q8	333	0.28*	0.13*	0.68	0.77
Q9	77	0.35*	0.10*	0.32	0.61
P1	160	0.36*	0.18*	0.84	0.92
P2	282	-0.42*	0.23*	0.90	0.95
P3	177	-0.67*	0.28*	0.84	0.94
P4	228	-0.14*	0.09*	0.97	0.97
P5	177	-0.92*	0.11*	0.89	0.90
P6	189	-0.67*	0.04*	0.87	0.87
P7	344	-0.55*	0.16*	0.91	0.88
P8	237	-0.01	0.05*	0.61	0.68
P9	87	-0.36*	0.10*	0.36	0.60
P10	157	-0.66*	0.05*	0.86	0.93
P11	347	-0.65*	0.29*	0.93	0.98
P12	376	-0.32*	0.31*	0.67	0.77
P13	145	-0.52*	0.10*	0.91	0.92
P14	278	-0.37*	0.39*	0.77	0.89

Cell	N	Statistics for plane fit for number of spikes, horizontal gaze amplitude, and saccade duration			
		Gaze Amp NumSpikes slope	Gaze Dur NumSpikes slope	R square using Hor gaze Amp only	R square using GHamp and duration
P15	413	-0.55*	0.08	0.93	0.82
P16	132	-0.61*	-0.06*	0.85	0.85
P17	58	0.51*	0.17*	0.69	0.76
P18	121	1.15*	0	0.95	0.95
P19	52	0.29*	0.10*	0.74	0.77
P20	366	0.63*	0.18*	0.86	0.89
P21	833	0.65*	0.27*	0.89	0.94
P22	86	0.51*	0.07*	0.78	0.79
P23	673	0.28*	0.13*	0.71	0.75
P24	91	0.84*	0.14*	0.86	0.88
P25	59	1.89*	1.1*	0.95	0.30
P26	352	-0.16*	0.05*	0.35	0.64
P27	331	-0.15	0.22*	0.74	0.5
P28	532	0.62*	0.03*	0.90	0.93
P29	67	0.44*	0.04	0.63	0.77
P30	368	-0.67*	0.15*	0.92	0.95
P31	245	1.01*	-0.01	0.84	0.91
P32	433	0.92*	-0.08	0.91	0.95
P33	110	-0.71*	0.03	0.95	0.96
P34	166	-0.48*	0	0.95	0.96
P35	235	0.85*	-0.03	0.87	0.91
P36	355	-0.27*	0.16*	0.84	0.91
P37	196	0.91*	0.04*	0.92	0.95
P38	162	0.95*	0.02	0.97	0.97
P39	158	1.02*	-0.12*	0.81	0.88
P40	916	0.45*	-0.04*	0.56	0.68
P41	155	0.58*	-0.01	0.73	0.78
P42	271	0.24*	0.03*	0.56	0.64
P43	374	0.59*	0.02	0.84	0.88
P44	322	0.95*	0.17*	0.93	0.95

Cell	N	Statistics for plane fit for number of spikes, horizontal gaze amplitude, and saccade duration				
		Gaze Amp NumSpikes slope	Gaze Dur NumSpikes slope	R square using Hor gaze Amp only	R square using GHamp and duration	
P45	192	0.51*	0.15*	0.84	0.88	
P46	413	0.71*	0	0.84	0.87	
P47	571	1.03*	-0.06*	0.83	0.87	
P48	82	0.94*	0.12*	0.94	0.96	
P49	147	1.1*	0.04	0.69	0.77	
P50	290	0.72*	0.35*	0.89	0.90	

Asterisks indicate coefficients that were significantly different from zero. Bold text indicates the cell used as an example in Figs. 3, 4, 5. Note that, for 46/63 cells (73%), the number of spikes was significantly positively correlated with duration, independent of horizontal gaze amplitude