CHAPTER 3

Single cell signals: an oculomotor perspective

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Abstract: We examine the activity of individual neurons in three different brain areas where firing rate, number of spikes (the integral of discharge rate), and the location of the active cell within a motor map are used as coding schemes. The correlations between single cell activity and the parameters of a movement range from extremely tight (motoneurons) to non-existent (superior colliculus). We argue that the relationship between the activity of single cell activity and global aspects of behavior are best described as coarse coding for all three types of neuron. We also present evidence, in some cases in a preliminary and suggestive form, that the distribution of spikes in time, rather than average firing rate, may be important for all three neuron types, including those using a place code. Finally, we describe difficulties encountered in obtaining an estimate of the motor command when more than one oculomotor system is active.

Introduction

Many investigators have approached the problem of sensorimotor integration by asking how the activity of single sensory neurons in various subcortical and cortical regions contribute to neural representations of the environment. Complementary studies have addressed the question of how the activity of individual neurons residing at various locations in motor pathways contribute to the planning and execution of sensory initiated movements. Recently there has been renewed interest in the questions of what the activity of a single cell represents and which features of cellular activity are important (see, for example, Britten et al., 1992; Britten and Newsome, 1998; Shadlen and Newsome, 1998; Borst and Theunissen, 1999; Deneve et al., 1999; DeCharms and Zador, 2000; Kara et al., 2000; Movshon, 2000; Reinagel and Reid, 2000). Are perceptual and motor decisions based on the activity of a small number of neurons (sparse coding) or is it necessary to compile

inputs from a large population of neurons in order to make accurate perceptual and/or motor decisions (coarse coding)? Are sensory and motor signals conveyed by the average rate of firing over some short time period sufficient (rate coding), or is the precise placement of the spikes in time (temporal or interval coding) critical? Is knowing the location of the active neurons within a sensory or motor map (place coding) sufficient or does the rate of discharge of neurons in the active population provide additional information? Recent discussions of these and related questions have focused on the activity of cortical neurons. In this chapter we consider the same issues from the perspective of single cell activity observed in the oculomotor brainstem. The activity of motoneurons in the abducens nucleus, short-lead burst neurons in the paramedian pontine reticular formation, and saccade-related burst neurons in the superior colliculus will be examined in the context of coding schemes (rate, interval and place codes) and the relative importance of the activity of individual neurons (coarse vs. sparse coding). We will also explore the conditions in which the activity of a single neuron is a valid measure of motor performance by examining cellular activity from measurement and statistical perspectives. Reflecting on the properties

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of subcortical neurons involved in the control of movement could provide a different perspective on the significance of single cell signals in other sensory and motor systems.

Abducens neurons

Fig. lA illustrates recordings from a single neuron in the right abducens nucleus. The top two traces plot horizontal and vertical eye position as a function of time. The next trace is a plot of instantaneous spike frequency, the reciprocal of interspike interval. The steady rate of action potentials observed while the eye is stationary near the center of the orbit is followed by a vigorous burst of activity before and during the rightward saccade. The burst of activity of motoneurons provides the innervation required to overcome the viscous resistance of the muscles and other orbital tissue and move the eye at a high speed. At the end of the saccade, there is a new, higher,

rate of firing that helps to overcome the elastic properties of the orbital tissue and hold the eye in the new position. As illustrated for two motoneurons in panel B, the relationship between tonic discharge rate and orbital position is linear. Motoneurons differ in the slope of the linear relationship and the orbital position at which they are recruited into action. Neurons that are recruited early have lower slopes than those that are recruited later (e.g., Robinson, 1970; Mays and Porter, 1984; Fuchs et al., 1988).

A measurement perspective

Table 1, modified from Stevens (1951), lists the different types of measurement scales, major defining features of each scale, and some of the types of statistical operations that are permissible with each type of measurement scale. For example, in *nominal scales,* numerals are merely used to label or classify numbers; words or letters would have been equally
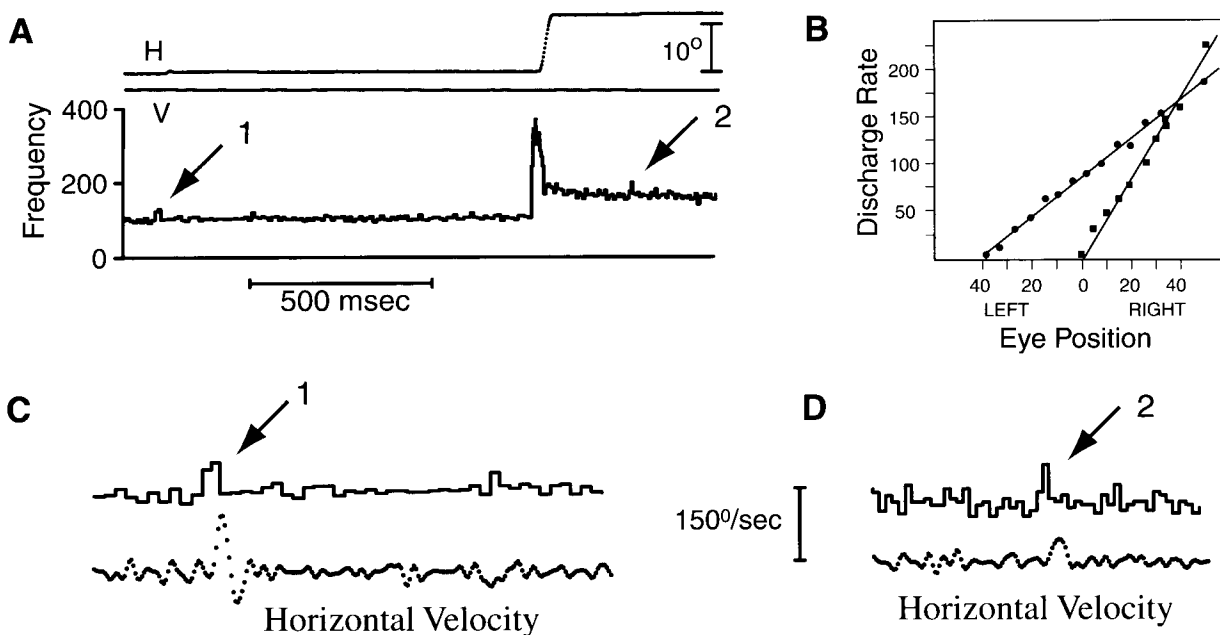

Fig. I. Coding mechanisms used by the extraocular motoneurons. Horizontal and vertical eye position traces and the corresponding instantaneous spike rate of a motoneuron in the right abducens nucleus are plotted as a function of time (A). The motoneuron discharges at a constant rate during fixation, generates a burst to produce a rightward (on-direction) saccade and stabilizes at a higher, tonic rate during the post-saccadic fixation. The discharge rate recorded during fixation is a function of eye position, as illustrated for two motoneurons (B). While this result is suggestive of a rate-coding mechanism, a closer examination of the traces in (A) suggests that interval or temporal coding scheme is also prevalent. The instantaneous spike rate around arrows marked I and 2 in (A) are plotted with the corresponding horizontal eye velocity in (C) and (D), respectively. Note that the extra spike(s) above the tonic rate results in a momentary rightward deflection of the eye.

TABLE I

Scales of measurement (modified from Stevens, 1951)

Scale	Empirical operations	Permissible statistics	Examples
Nominal	Determination of equality	Number of cases Mode Contingency correlation	`Numbering' of football players Assignment of type or model numbers to classes
Ordinal	Determination of greater or less	Median Percentiles Order correlation	Hardness of minerals Pleasantness of odors
Interval	Determination of equality of i ntervals or differences	Mean Standard deviation Order correlation Product-moment correlation	Temperature (Fahrenheit and Celsius) Energy Calendar dates
Ratio	Determination of equality of ratios	Geometric mean Coefficient of variation Decibel transformations	Length, weight, density resistance, etc. Loudness scale (sones)

effective. If classes containing several members have been formed it is possible to determine the mode or most numerous class. A number in an *ordinal scale* indicates the ranking of an item based upon some criterion, but the difference between rankings of I and 2 is usually not the same as the difference between rankings of 2 and 3. Review group ratings of grant applications are an example. An application assigned the score of 100 has a greater probability of being funded than an application assigned a score of l 50. However, the difference between scores of 100 and 150 signify quite different things than the difference between scores of 300 and 350. The zero point on an *interval scale* is a matter of convention; the classic examples are the Fahrenheit and centigrade scales of temperature. Equal intervals of temperature are determined by measuring equal volumes of expansion, but lacking an absolute zero, it would be meaningless to state that 20°C is twice as hot as 10°C. Physical measurements of height, weight, and length are examples of measurements that meet the criteria for a *ratio scale* of measurement. It is meaningful to say that 10 m is twice as long as 5 m.

We examine the activity of brainstem neurons from this `scales of measurement perspective' because only certain mathematical and statistical operations can be performed on each scale of measurement. For example, product moment correlations are permitted for data meeting the criteria of an interval scale, but not for data only meeting the criteria of an ordinal scale. Why are these scales of measurement relevant to the activity of neurons? As will become apparent when the activity of neurons in the superior colliculus is discussed, measures of the activity of neurons residing in a motor map may not meet the criteria for any useful scale of measurement of the various attributes of a movement. Consequently, conventional statistical procedures may not be useful when trying to determine which aspect of a movement is coded by the activity of a cell.

For motoneurons, the tonic eye-position-related activity meets the criteria for an interval scale of measurement of horizontal eye position, at least under the experimental conditions used to obtain the slope and intercept of the linear regression line of best fit. The change in number of spikes/s when eye position changes from 10 to 20° is the same as when eye position changes from 20 to 30°. Because, the activity of these cells is a valid measure of a particular motor parameter, descriptive and inferential statistics such as mean, standard deviation and product moment correlations can be employed in additional analyses of the properties of these neurons.

Place, rate or interval coding?

In terms of the candidate coding schemes being considered, motoneurons appear to be coding eye position using a rate code. Periods of regular discharge rate are associated with stable eye positions

and rapid changes in the rate of firing are associated with rapid changes in eye position (e.g., Fuchs et al., 1988). However, during slow movements of the eye, an additional increase or decrease in the instantaneous discharge rate is observed as the eye passes through a particular orbital position (Keller, 1981). A linear relationship is obtained when plotting instantaneous discharge rates as the eye passes through a fixed point at different velocities and the value of the slope, r, of the rate-velocity relationship has been used to construct a first-order differential equation relating each motoneuron's instantaneous firing rate to eye position and velocity (Keller, 1981). In a recent quantitative analysis of abducens neuron discharge dynamics during saccades and slow eye movements, Sylvestre and Cullen (1999) found that a single set of parameters could not be used to describe neuronal firing rates during both slow and rapid eye movements. The coefficients for eye velocity and position parameters consistently decreased as a function of the eye velocity that was generated.

DeCharms and Zador (2000) argue that the apparent distinction between the rate-coding hypothesis and the temporal-coding hypothesis is just one of time scale rather than of category. They note that the difference between rate coding and temporal coding for an individual spike train is based upon the interval chosen for counting the spikes and that the choice of interval is often based upon time scales believed to be relevant to a particular circumstance. According to this hypothesis, small variations in the exact timing of each spike could be important if we consider motoneuron activity during 5-10 ms periods rather than 200-400 ms intervals. Studies measuring motoneuron discharge with high temporal precision found the standard deviation of the interspike interval variability to be typically only about 6% of the mean discharge rate (Robinson, 1970; Keller and Robinson, 1972). However, in these experiments no attempt was made to relate small variations in the exact timing of each spike with minute changes in eye velocity or position. In our data archive we found recordings from several motoneurons in which small, brief deviations from the average firing rate were often *associated with* small, but observable, eye movements. As shown in Fig. 1C, the brief increment in the firing rate produced by two additional spikes was associated with a small eye movement having a

peak velocity of about 100°/s. In Fig. ID, a small increment in discharge rate produced by one additional spike was associated with a small movement having a peak velocity of 60°/s. The prevalence of such correlations is unknown.

Coarse or sparse coding?

The coding scheme(s) employed (place, rate, or interval) need not determine whether the activity of a small number of neurons (sparse coding) or a large population of neurons (coarse coding) is used to make accurate perceptual decisions or to control accurate movements. The high correlations observed between the firing rate of individual motoneurons and eye position could be interpreted as evidence that the activity of a small number of motoneurons controls the position of the eye. However, consideration of a number of factors indicates that the contribution of each abducens motoneuron to the control of the orbital position of the eye is relatively small. The abducens nucleus contains approximately 1 100 motoneurons (Steiger and Buttner-Ennever, 1978; Baker and Spencer, 1981). In terms of the steady firing rates observed during stable fixation intervals, most motoneurons have already been recruited into action when the eyes are in the center of the orbit (Robinson, 1970; Keller, 1977; Dean, 1996) and, accordingly, many motor units contribute to the muscle tension generated by the agonist muscle when the eye is in this position. It is likely that all the motoneurons have been recruited and all motor units participate in the generation of the tension required to hold the eye at a 25° eccentric position (in the pulling direction of the muscle). Furthermore, during the normal range of eye positions, motoneurons in the antagonist muscle motoneuron pool are also active and produce an innervation signal of opposite sign. Thus, as illustrated in Fig. 2A, horizontal eye position is controlled primarily by the ratio of motoneuron activity in the agonist and antagonist motoneuron pools. In theory, an infinite number of patterns of agonist and antagonist activity can maintain the eye in the same position. Three hypothetical examples are shown. In all three, the ratio of agonist and antagonist activity is the same and the eye is deviated 15° to the right. For the two cases shown on the left, the total output from the agonist and antago-
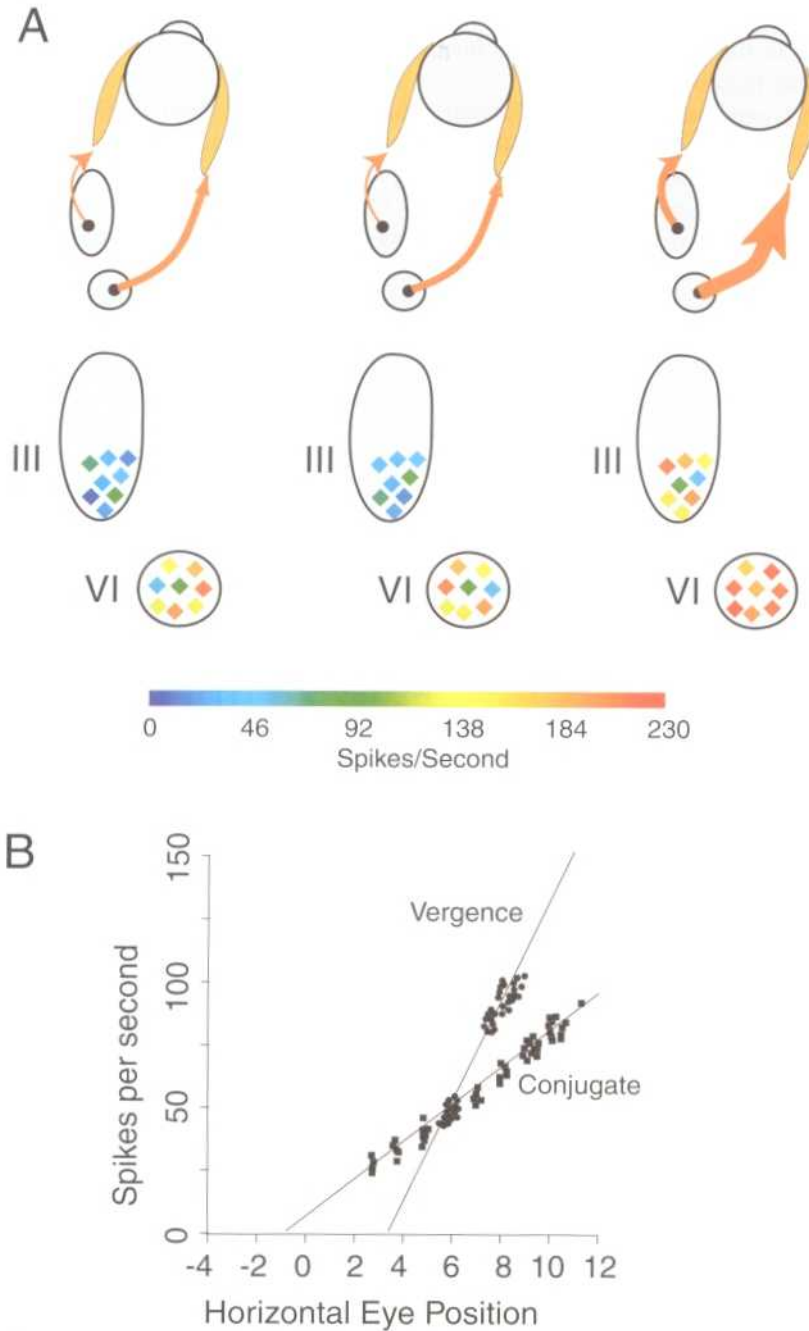
Fig. 2. Eye position is controlled by the ratio of activity in agonist and antagonist motoneuron pools. (A) The panel shows three schematics of the right globe connected to the lateral and medial recti muscles, their innervations from the abducens and oculomotor nuclei, respectively, and the level of activity in the representative motoneurons. The firing rates of the individual motoneurons in the three scenarios are different, as represented by the color scale, but the ratio of activity in the agonist and antagonist motoneuron pools is critical to maintain the eye in the same position. Thus, by recording the neural activity of any given neuron, we may not he able to determine the eye position. A perfect example is illustrated in the bottom panel (B), which demonstrates that the spike rate associated with the same eye position reached after a conjugate. saccadic eye movement and a disconjugate. vergence movement can be sig nificantly different.

nist motoneuron pools is the same but the contribution of each of the neurons is different. In the third panel, the overall innervation level of both motoneuron pools is higher, but the same agonist/antagonist ratio is maintained. These patterns of activity constitute a motor equivalence class or 'motomere' (after the term 'metamere' used in color vision to describe two stimuli that are physically different but exactly matched perceptually).

What is the evidence that the eye may, in fact, be maintained in the same position by different patterns of motoneuron activity? Panel B of Fig. 2 illustrates one well-documented case (Mays and Porter, 1984). The firing rate of an abducens motoneuron is plotted as a function of horizontal eye position for eye positions reached by yoked movements of the two eyes during saccades and for the same positions reached by a convergence movement in which the two eyes move in opposite directions. Note that the same motoneuron fires at quite different rates, even though the eye is in the same orbital position. Henn and colleagues (Henn et al., 1984a) reported that the patterns of motoneuron activity associated with the same orbital eye position are different during alert waking behavior and light sleep.

To summarize, when the line of sight is shifted from one location to another at a fixed depth plane, the discharge rate of individual motoneurons is highly correlated with the steady position of the eye in the orbit. Under these specific conditions it is possible to accurately predict orbital eye position knowing only the firing rate of a single neuron. These correlations could be misinterpreted to suggest that the activity of a few neurons controls the orbital position of the eye when, as illustrated above, the sustained steady eye positions observed during fixation intervals are maintained by a large population of cells distributed throughout the motoneuron pools innervating the agonist and antagonist muscles. The same orbital position can be achieved by an infinite number of patterns of motoneuron activity. The relationship between firing rate and eye position obtained during fixation intervals in one depth plane cannot be used to accurately predict eye position during fixations in a different depth plane or to accurately predict when a particular eye position is reached during slow eye movements.

Short-lead burst neurons in paramedian pontine reticular formation

Accumulated evidence obtained from clinical, microstimulation, lesion, anatomical, and chronic single unit recording data indicates that neurons in the paramedian zone of the pontine reticular formation (PPRF) generate motor command signals responsible for the changes in the horizontal positions of the eyes during saccades and the quick phases of nystagmus (for reviews see Raphan and Cohen, 1978; Henn et al., 1984b; Fuchs et al., 1985; Hepp et al., 1989; Moschovakis and Highstein, 1994; Moschovakis et al., 1996). Fig. 3 illustrates the activity of a short-lead burst neuron (SLBN) in the PPRF. These neurons display extremely low rates of spontaneous activity and generate a vigorous burst of activity shortly before the onset of ipsilateral saccades. A series of horizontal saccades of different amplitudes and instantaneous frequency records of the associated bursts of activity are illustrated in panel A. For SLBNs burst duration is approximately the same as the saccade duration and, as illustrated in panel B, the number of spikes in the burst is highly correlated with the amplitude of the horizontal component of the saccade (Luschei and Fuchs, 1972; Keller, 1974; King and Fuchs, 1979; Van Gisbergen et al., 1981; Scudder et al., 1988). Also (not illustrated), the peak firing rates of SLBNs is highly correlated with peak saccadic velocity (Keller, 1974; Van Gisbergen et al., 1981). A subset of pontine SLBN, the excitatory burst neurons (EBNs) have monosynaptic connections with motoneurons in abducens nucleus and the timing and intensity of the discharge of EBNs are appropriate for producing the saccadic modulation in the motoneurons (Strassman et al., 1986).

Scales of measurement

From a measurement point of view, the number of spikes in the burst of a SLBN meets the criteria for an interval scale of measurement of the change in horizontal eye position, for the conditions under which the data were obtained. For the horizontal component of ipsilateral saccade, the difference in the number of spikes generated for 4° and 8° saccades, for example, is the same as the difference observed when saccades of 10° and 14° are observed. Thus, the statistical
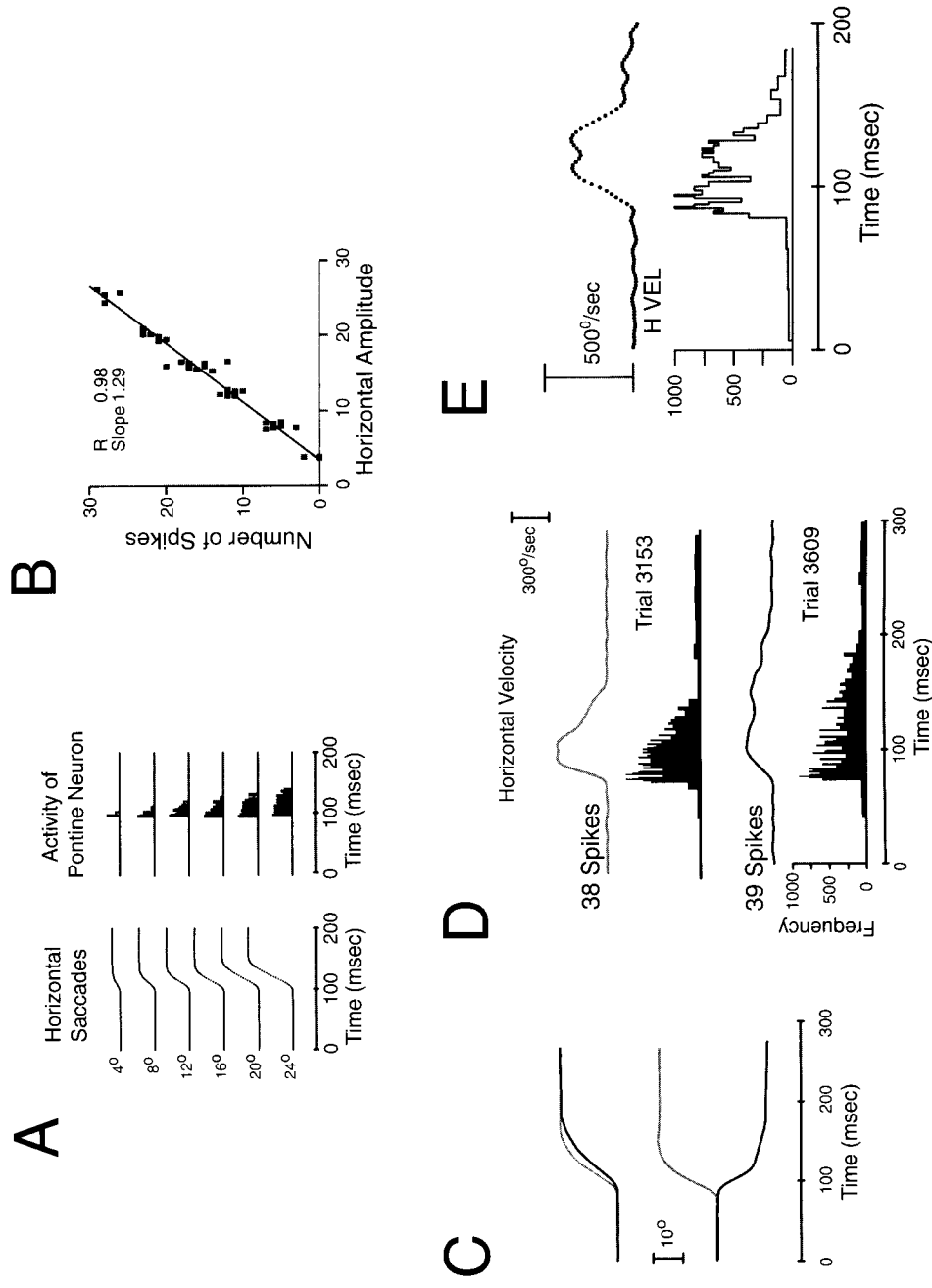
Fig. 3. Coding mechanisms of the short-lead burst neuron (SLBN). (A) Horizontal saccades of various magnitudes and the corresponding instantaneous spike rate of a SLBN are plotted as a function of time. (B) For this typical SLBN, the number of spikes in the burst is linearly related to the horizontal amplitude. Similarly, the burst duration is also linear related to the saccade duration (data not shown). These relationships lend support for a rate-coding mechanism. (C) Two oblique saccades with similar horizontal (top traces) but different vertical (bottom) components and (D) their corresponding horizontal velocities and instantaneous frequency records are plotted. As required by a rate code, the number of pulses is similar for the matched horizontal amplitude. However, the dynamics of the movements are influenced by the temporal distribution of the spike discharge, suggestive of a temporal code. (E) This observation is further illustrated for another neuron that dropped a spike during its burst and, consequently, resulted in a drop in the eye velocity. Therefore, like the motoneurons, the SLBNs may exhibit both rate and interval coding features.

analyses researchers have used to characterize these cells (see above) are appropriate.

Rate, interval, or place coding?

The time integral of firing rate, number of spikes, is highly correlated with the horizontal amplitude of saccades. Moreover, the distribution of spikes in time is also important, as indicated by the high correlation between the frequency of firing during the saccade-related burst and the velocity of the associated eye movement (Keller, 1974; King and Fuchs, 1979; Van Gisbergen et al., 1981; Cullen and Guitton, 1997a). Another example of the importance of the distribution of spikes in time is illustrated in panels C-E of Fig. 3. Panel D plots horizontal and vertical change in eye position as a function of time for the two oblique movements illustrated in panel C. Note that the horizontal amplitude of the two movements is the same but the movements have different durations because of variations in the amplitude of the vertical component of the movement. Beneath each velocity trace in panel D is a plot of the instantaneous discharge rate of the cell before and during that movement. Note that the cell generates 38 and 39 spikes in association with the top and bottom movements, respectively. The 38 spikes are distributed over about 80 ms and peak horizontal velocity is about 300°/s. The 39 spikes are distributed over about 150 ms; the peak velocity is much reduced and the movement duration is greater.

If, as suggested by DeCharms and Zador (2000), we examine the distribution of spikes over a shorter time period, does the exact placement of individual spikes become critical? We found no pertinent published data but were able to locate in our data archive recordings from cells in the medial vestibular nucleus indicating that this issue needs to be examined more carefully in future experiments. These neurons generate saccade-related bursts of activity and the number of spikes in the burst is highly correlated with the amplitude of the horizontal component of the saccade. For a few cells in our sample, the exact distribution of spikes in the burst was related to the velocity profile on a trial-by-trial basis. An example is shown in Fig. 3E. The close correspondence between the temporal pattern of activity of individual neurons and the profile of saccadic velocity on

a millisecond time scale suggests that either a few neurons have special effects upon the execution of saccades or, perhaps more likely, that the activity of some burst neurons can be synchronized.

Coarse or sparse coding?

Little is known about the relative contribution of individual EBNs to the generation of a saccade. Plots of number of spikes vs. saccade amplitude suggest that most EBNs are active before and during saccades larger than 5°. However, some SLBNs do not discharge before small (2-3° or smaller) saccades (see Fig. 3B). Based upon the information available, we conclude that a large population of pontine burst cells contributes to the generation of each saccade and that, despite the tight relationships between measures of spike activity and the parameters of the saccade, the contribution of each neuron to the movement is small. Other observations support this general conclusion. Strassman et al. (1986) found that the axonal terminals of individual EBNs were distributed in discrete patches in the abducens nucleus, covering a relatively small area of the nucleus. Local microstimulation at the site of putative EBNs rarely produces movements with saccadic velocity (Cohen and Komatsuzaki, 1972), suggesting that activation of a small number of EBNs does not recruit sufficient motoneurons to generate the innervation signal needed for a movement with saccadic velocity. Reversible inactivation of a small region of the pontine reticular formation produces reductions in saccadic velocity but does not prevent the occurrence of visually guided eye movements (Sparks et al., 2002). Collectively, these observations suggest that a large population of EBNs, spread over several millimeters, is active before and during each saccade and that the contribution of individual EBNs to the movement is small.

Saccade-related burst neurons in the superior colliculus

Fig. 4 illustrates properties of saccade-related burst neurons (SRBN) in the superior colliculus (SC). These cells generate a burst of action potentials before saccadic eye movements. The high frequency burst may reach instantaneous rates of 1000 or more
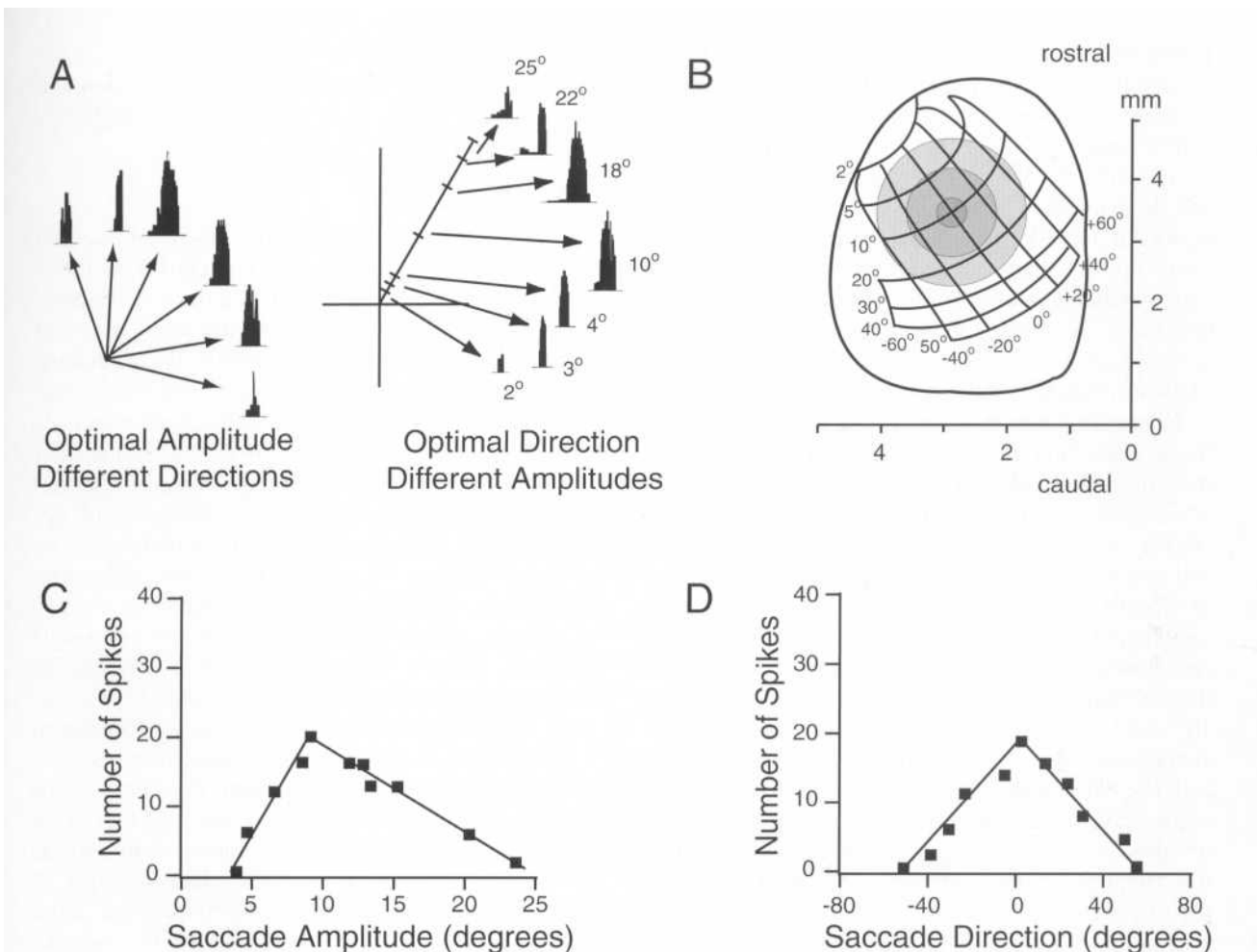
Fig. 4. Coding mechanisms and organization of the saccade-related burst neurons (SRBNs) in the superior colliculus. (A) The presaccadic discharge of a typical SRBN is plotted for eye movements of various amplitudes and directions to illustrate the properties of the movement held. The SRBN discharges a high frequency burst prior to onset of a saccade of optimal amplitude and direction. For movements of optimal amplitude but different directions and of variable amplitudes but in the optimal direction, the SRBN activity is later and weaker. (B) The motor map for saccadic eye movements, as constructed by Robinson (1972) is shown in the schematic. Neurons with small, optimal amplitudes reside in the rostral portion of the SC whereas cells discharging vigorously for large amplitudes are found in the caudal region. Similarly, neurons preferring saccades with upward (downward) components are localized within the medial (lateral) areas of the SC. The distribution is logarithmic along the rostral-caudal dimension (amplitude axis) but approximately linear along the medial-lateral extent (direction axis). A corollary of the observation that SRBNs are active for a large range of movements is that a large region of the superior colliculus is active during any given saccade. The shaded region depicts the spatial extent of activity for a horizontal 10° saccade. The gray scale indicates that neurons in the darkest region (center) discharge most vigorously while increasingly distant neurons (lighter shades) emit a later and weaker burst. This organization of neurons to form a motor map is a prime example of a place code. However, similar to the motoneurons and SLBNs, variability in the discharge rate for any given saccade often alters the dynamics of the movement (data not shown). In this sense, temporal coding features can also superimpose on a place code organization. (C.D) The plots quantify the qualitative assessment gathered from the format presented in (A). The data are from another SRBN. The number of spikes is plotted against amplitude for saccades in the optimal direction (C) and against direction for saccades of optimal amplitude (D). Neurons organized in a place code exhibit non-monotonic relationships between their spike count and saccade metrics, unlike the linear relationships observed for neurons (SLBNs and motoneurons) operating based on rate code. Thus, any given spike count of neurons in the SC does not reveal the amplitude of the executed saccade because each neural measure is associated with at least two saccade vectors. This trait of SRBNS does not meet the criteria for any useful scale of measurement, thereby preventing meaningful statistical measures on their activity (see text for details).

spikes per second. Each of these cells discharges maximally before movements of a particular direction and amplitude, but also discharges in association with a large range of eye movements. The activity of a typical SRBN is illustrated in panel A. This cell discharged most vigorously before upward and rightward saccades that were 14-18° in amplitude. Less vigorous activity was observed in association with movements of the same amplitude, but different directions. Similarly, for movements in the optimal direction, a weaker burst occurred for movements smaller or larger than the optimal amplitude.

Neurons of this type are organized according to the optimal amplitude and direction, and form a map of motor space. Fig. 4B illustrates the map of saccadic eye movement developed by Robinson (1972) (see figure legend for details). Because each cell discharges in association with a large number of saccades of different amplitudes and directions, a large population of cells is active before and during each saccade. The gray circles represents the hypothetical region of cellular activity associated with a 10° horizontal saccade. The population activity is characterized by a spatial and temporal gradient of activity: cells in the center of the active population (dark gray) discharge earliest and most vigorously whereas cells on the fringe of the active population (light gray) discharge later and less vigorously (Sparks and Mays, 1980).

The plots in panels C and D are sections through the movement field of a collicular cell. In panel C the number of spikes in the saccade-related burst is plotted as a function of the amplitude of the saccade for movements in the optimal direction. In panel D, the number of spikes in the burst is plotted as a function of saccade direction, for movement of the optimal amplitude. Note that the number of spikes, or peak frequency of the burst, or average frequency of the burst, or any other measure that we have considered is not linearly related to the amplitude - horizontal, vertical or vectorial component - or the direction of a saccade.

Thus, we observe a fundamental change in the relationship between spike activity and the metrics of movements when we move from motoneurons and pontine reticular formation to neurons in the SC. This change occurs because at the level of the SC, neurons are organized in a motor map and it is primarily the location of the cells in the map, not their rate of firing, that codes saccade direction and amplitude.

Scales of measurement

The non-monotonic relationships observed between measures of spike activity and the metrics of movements for neurons in superior colliculus is fundamentally different from the linear relationships observed for motoneurons and cells in PPRF. We postulated that the contribution of a single motoneuron or a single pontine EBN cell to the amplitude of a saccade or to the maintained position of the eye in the orbit is small. Nevertheless, because of the linear relationships between spike activity and measures of eye position and velocity, it is possible to make accurate predictions about the position of the eye in the orbit or changes in orbital position based upon the activity of a single neuron. In contrast, the activity of a single collicular neuron cannot be used to make accurate judgments about the direction or amplitude of a saccade. Referring to panel D, what could be concluded if it were known that two saccades occurred and the cell generated 5 spikes before the first saccade and 15 spikes before the second saccade? It is likely that 1 of 4 sequences of movements occurred: (a) a 5° saccade followed by a 7° saccade; (b) a 5° saccade and a 14° saccade; (c) a 20° saccade and a 7° saccade; or (d) a 20° saccade and a 14° saccade. Conclusions are limited because the activity of collicular neurons is ambiguous with respect to saccade direction and amplitude. As noted earlier, the same number of spikes is generated in association with a large range of movements having quite different directions and amplitude.

The activity of collicular neurons does not meet the criteria for any useful scale of measurement when used as a measure of the metrics of a saccade. Cell activity does not meet the criteria for an interval scale; equal changes in number of spikes do not indicate that equal changes in saccade amplitude have occurred. Measures of spike activity do not meet the criteria for an ordinal scale of measurement. A larger number of spikes does not mean that a movement with a larger (or smaller) amplitude has occurred. The practical consequences of this observation are that no useful statistics are permitted when using

C

Firing Rate (spikes/s)

800

400

0

-30   -20   -10   0   10

Initial Eye Position (deg)

B

gaze   eye   head

a

b

c

A

Amplitude (deg)

90
75
60
45
30
15
0

Gaze

Head

Eye

a   b   c

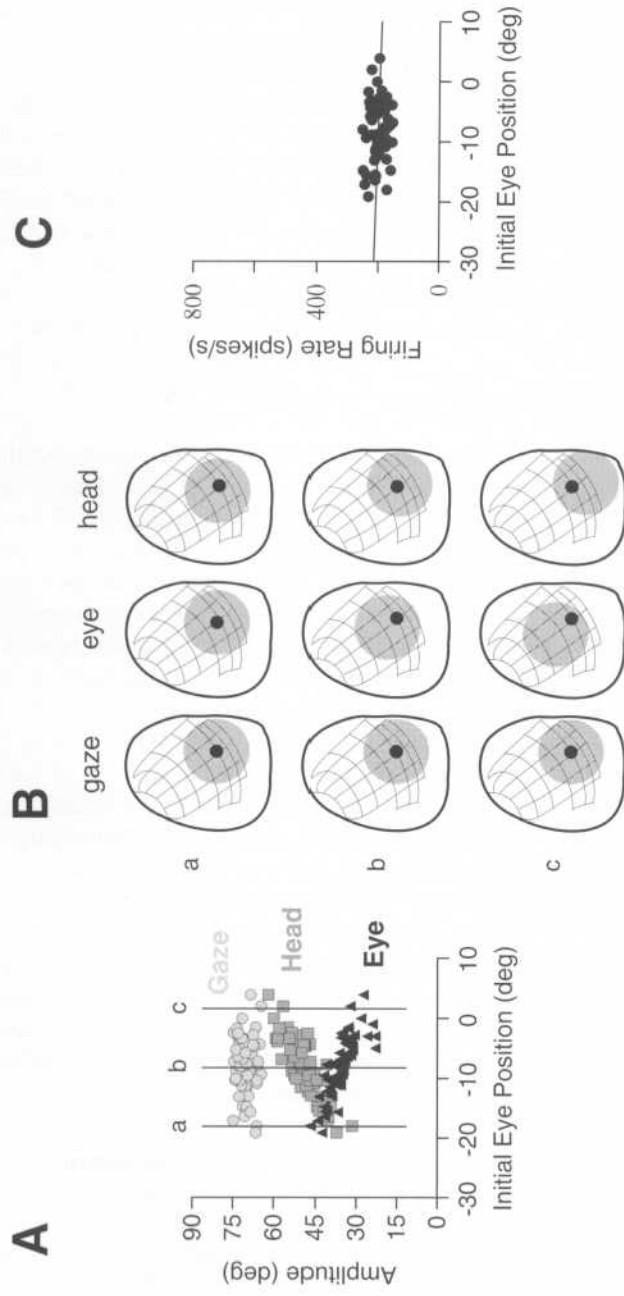-30   -20   -10   0   10

Initial Eye Position (deg)

Fig. 5. Determining the role of superior colliculus neurons in the control of coordinated eye and head movements. Based on traditional head-restrained experiments in primates, the SRBNs are considered to encode saccadic eye movements. Recent studies have demonstrated that SRBNs also discharge during head-unrestrained gaze shifts. Is the activity of neurons that discharge before saccades in the head-restrained monkey coding for eye displacement or for a gaze displacement that is accomplished by an eye movement? If the head were free, would the activity correlate better with the ocular component, the head movement or the coordinated eye-head change in gaze? Constraints placed by scales of measurements principles prevent the use of statistical tests, such as multiple linear regression analysis, to address these questions. To circumvent these limitations, Freedman and Sparks (1997) analyzed activity of SC neurons recorded during gaze shifts of similar amplitude but starting from different initial eye position in the head (IEP). (A) Behavioral data: gaze amplitude (circles), eye contribution (triangles) and head contribution (squares) are plotted as a function of IEP. Note that for a group of amplitude-matched gaze shifts, the eye and head contributions vary inversely as the IEP changes. The eye (head) contributions increase (decrease) as the IEPs are increasingly more contralateral (negative values) to the direction of the gaze shifts. (The initial head position in space was not controlled in the study.) (B) Predictions regarding the spatial locus of activity in the SC (gray shade) depend on whether the SC encodes gaze (left column), eye (middle column) or head (right column). The three rows refer to the three vertical lines from panel (A) and indicate the active population of SC neurons during similar amplitude gaze shifts starting from three different IEPs. The black, filled circle corresponds to the site on the motor map encoding the executed *gaze* shift (see Fig. 4B). If SC neurons encode gaze shifts (left column) without regard to the individual eye and head contributions, the spatial distribution of active SC neurons (gray shade) remains the same across all initial eye positions. Furthermore, the black and gray circles remain concentric. If SC neurons encode only the ocular component (middle column), the population of active neurons will shift from caudal to rostral sites of the SC as the IEP becomes increasingly ipsilateral (top to bottom, sequentially). Also, the locus of the most intense activity will not correspond with the black circle. If SC neurons encode the head contribution (right column), the ensemble of active neurons will shift from rostral to caudal sites as the IEP becomes increasingly ipsilateral (top to bottom, sequentially). (C) Firing rate, averaged over the duration of each movement, from one SRBN is plotted against IEP for a set of similar-amplitude gaze shifts. The observation, that the firing rate is independent of IEP supports the hypothesis that SC neurons encode gaze shifts.

the activity of a collicular SRBN as measure of movement parameters. Consequently, in their study of collicular activity in head-unrestrained animals generating coordinated movements of the eyes and head, Freedman and Sparks (1997) were not able to use statistical methods such as multiple regression techniques to determine if the activity of the cell was more related to eye, head, or gaze. As illustrated in Fig. 5, they were forced to use a more laborious experimental strategy to determine if the activity of a cell was specifying a movement of the eye, a movement of the head, or a change in gaze.

Rate, interval, or place coding?

As summarized above, although the vigor of discharge of a particular saccade-related burst cell varies for different movements within the movement field, information concerning saccade direction and amplitude is not contained within the discharge of a single cell. Unlike the primary vestibular afferents, for example, that encode head velocity by firing rate, the SC does not generate specific rates of firing to specify the direction or amplitude of a saccade. Saccade direction and amplitude are specified by the location of active neurons within the topographical map of movement fields, not their frequency of firing. Nonetheless, the level and temporal pattern of collicular activity does influence the velocity, duration, and amplitude of a saccade. A small number of stimulation pulses delivered to the SC during an on-going movement produces transient increases in the gaze velocity of cats (Munoz et al., 1991). Stanford et al. (1996) noted that stimulation trains must be continued until the site-specific maximal amplitude was obtained, otherwise the stimulation-evoked movement was truncated. They also observed, as previously reported in other animals (Du Lac and Knudsen, 1990; Pare et al., 1994) systematic effects of varying the frequency of stimulation upon the velocity of the evoked movements, indicating that the level of collicular activity is a determinant of saccade velocity. Results of experiments activating or inactivating the SC are consistent with this conclusion. The velocity of visually guided saccades is greatly reduced following inactivation of collicular neurons by local injections of muscimol or lidocaine (Hikosaka and Wurtz, 1985, 1986; Lee et al., 1988).

Manipulations in brain areas projecting to SC that indirectly affect the level or duration of collicular activity affect the speed and duration of saccades. Visually guided saccades are slowed or halted following electrical or pharmacological activation of areas that directly, or indirectly, inhibit saccade-related collicular activity (Munoz and Wurtz, 1993; Keller and Edelman, 1994). Inactivation of some of these same brain areas produces increases in saccade velocity (Munoz and Wurtz, 1993).

In summary, existing data are compatible with the hypothesis (Stanford et al., 1996) that a signal of desired displacement (amplitude and direction) is derived from the spatial location of collicular activity (a place code), the level of collicular activity influences movement velocity (a rate code), and ongoing collicular activity sustains the movement until the desired displacement is accomplished.

Sparse or coarse coding?

The case for coarse coding in the superior colliculus is strong. A large population of cells is active before and during each saccade and experiments in which a small subset of the active population was reversibly inactivated support the hypothesis that each member of the active population contributes to the movement (Lee et al., 1988). Saccadic accuracy results from the averaging of the movement tendencies produced by the entire active population (Lee et al., 1988; Sparks et al., 1990; Hanes and Wurtz, 2001). Small changes in the direction or amplitude of saccades are produced by slight shifts in the location of the large population of active cells. Interestingly, the large movement fields of collicular neurons may contribute to, rather than detract from, the accuracy of saccadic eye movements. The simulations of Baldi and Heiligenberg (1988) produced the apparently paradoxical result that, over a fairly large range, the wider the tuning curve of individual elements, i.e., the less precise they are, the more robust and precise the overall computation.

Single cell signals as estimates of commands being issued

According to traditional views of PPRF function, the excitatory burst neurons (EBNs) issue a sac-

cadic eye movement command that is delivered, monosynaptically, to the extraocular motoneurons. More specifically, the number of spikes in the saccade-related burst generated by the EBNs is tightly correlated with saccade amplitude. However, during coordinated eye-head movements, the spike count of EBNs is better correlated with gaze amplitude than with the amplitude of the eye component (Ling et al., 1999). This observation also holds for the inhibitory burst neurons (Cullen et al., 1993; Cullen and Guitton, 1997b), which are thought to reflect the activity of EBNs. There is disagreement about the interpretation of these findings, but some investigators find these data consistent with models (e.g., Galiana and Guitton, 1992) in which a reference signal of desired gaze displacement, derived from the superior colliculus (SC), serves as the input to a single gaze motor error comparator that controls both eye and head movements (see Guitton et al., 2003, this volume).

To distinguish between the traditional and recently suggested roles of the EBNs in the control of gaze, we exploited the antagonistic relationship of EBN and omnipause neurons (OPNs). Located within nucleus raphe interpositus, OPNs form a discrete collection of cells that discharge tonically during fixation and are silent during saccades. They gate the output of EBNs through a monosynaptic inhibitory connection (Curthoys et al., 1984). Microstimulation can be used to selectively activate OPNs and interrupt ongoing saccades or delay their onset (Keller, 1977, 1977; King and Fuchs, 1977). If EBNs encode eye movements only, then stimulation of the OPNs during a gaze shift will perturb only the eye component; the head movement will be unattenuated. If, on the other hand, the EBN output is relayed to both eye and neck motoneurons, stimulation of the OPNs should attenuate both eye and head movements.

We found that OPN microstimulation triggered on the onset of a gaze shift halted the change in gaze, typically until the end of stimulation, but had little, if any, effect on the head movement (Gandhi and Sparks, 2001). The interruption in gaze was mediated via a perturbation in the eye movement: the ocular component of the gaze shift stopped in mid-flight and the eyes immediately began to counter-rotate to stabilize gaze (the gain of the vestibulo-ocular reflex was approximately 1). Stimulation

prior to the onset of the gaze shift delayed the onset of gaze, but not the onset of the head movement. Head movements were typically initiated during the microstimulation and, therefore, led gaze onset. The direction of gaze was stable during the stimulation because the eyes counter-rotated compensating for the ongoing head movement. At the end of the microstimulation train, the gaze shift was initiated by a saccadic eye movement in the same direction as the ongoing head movement (Gandhi and Sparks, 2001; Sparks et al., 2002). These results provide strong support for the hypothesis that the EBNs participate in the eye pathway and that commands to motoneurons innervating the neck muscles originate from structures upstream of the EBNs. This raises the question of why, in head unrestrained animals the number of spikes generated by pontine burst neurons is more highly correlated with the amplitude of the gaze shift than it is with the amplitude of the eye movement.

One possibility that has been suggested (Sparks, 1999; Sparks et al., 2002) is illustrated in Fig. 6. Panels B and C represent the output of a Simulink (Mathworks, Inc.; Natick, MA) model that simulates the commands illustrated in panel A. The model utilizes local gaze feedback (Laurutis and Robinson, 1986; Guitton and Volle, 1987; Pelisson et al., 1988; Galiana and Guitton, 1992) and assumes that EBNs generate commands for eye movements whereas commands for moving the head originate in an independent, parallel pathway, as illustrated in panel A. Movements of the head can influence the command signals reaching extraocular muscles via the vestibulo-ocular reflex (VOR) which, in the simulations shown, has a gain of 1. In panel B, gaze (bold, solid lines), eye (dashed lines), and head (thin, solid lines) position are plotted as a function of time for 9 gaze shifts. Three sets of movements are shown. In each set, independent commands to move the eye and head were issued. Eye movement commands were either 25, 30, or 35°. Associated head movement commands were 20% smaller than the eye movement command (20, 24, or 28°). Variations in the amplitude of the head contribution to gaze were introduced by having the head movement begin 50 ms before the eye movement or 10 or 50 ms after the eye movement. Note the accuracy of the gaze shifts. Despite differences in the commands sent to
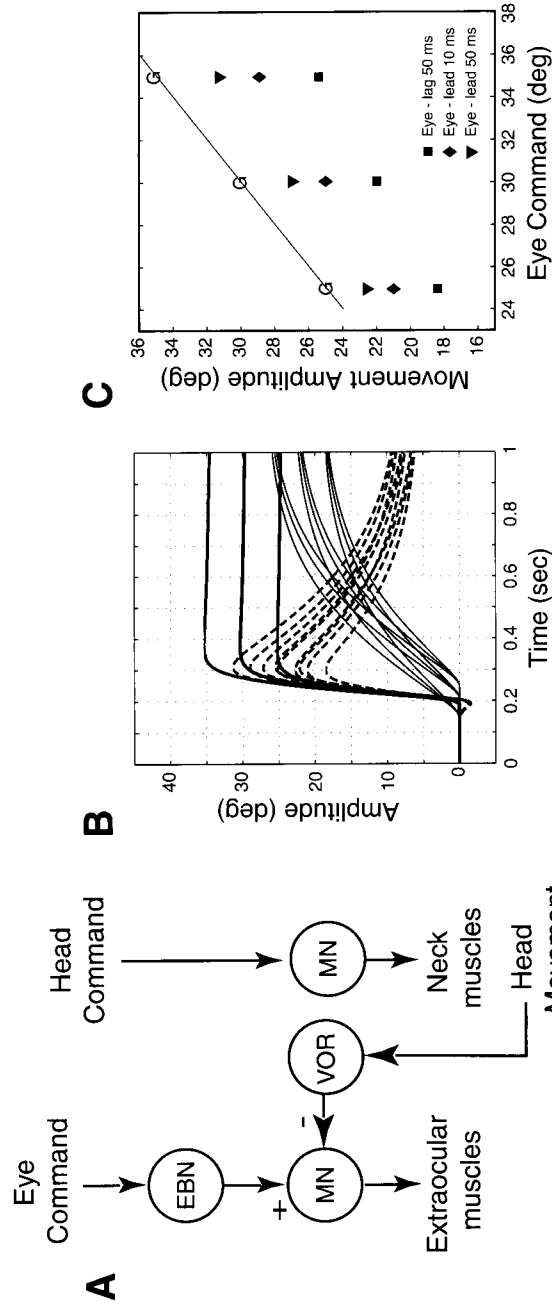
Fig. 6. Illustration of dissociations between motor commands and executed movements. (A) The schematic describes one possible version of the neural circuit that can implement coordinated movements of the eyes and head. The eye and head pathways receive separate inputs for desired eye and head movements, respectively. Furthermore, the gain of the vestibulo-ocular reflex is assumed to equal 1 during all gaze shifts and, therefore, the activity of the extraocular muscle motoneurons is reduced by an amount proportional to the amplitude of the head movement. This model was simulated on Simulink (Mathworks, Inc.). (B) The panel plots gaze (thick, solid lines), eye-in-head (dashed traces) and head (thin, solid curves) amplitudes as a function of time for a total of 9 simulations based on changing two variables: eye command and relative latency of eye with respect to head onset. Eye command was 25, 30 or 35°. Eye onset lagged head by 50 ms, led head onset by 10 ms or led head onset by 50 ms. The head command was always 80% of the eye command. (C) A quantification of the movements showed that gaze amplitude (G) always equaled the eye command. The slope of the best-fit line was one. Similarly, the total head amplitude equaled the head command (data not shown). In contrast, the eye component of the gaze shift was significantly less than the requested eye movement. Moreover, the perfect correlation between the eye command and the gaze amplitude wrongly leads to the suggestion that the EBNs encode gaze shifts (i.e., both eye and head movements), even though the EBNs encode the eye component only. See text for a discussion of the consequences of reducing the gain of the VOR during active gaze shifts.

the eye and head, changes in the relative timing of eye and head movements, and variations in the eye and head contributions to gaze, the change in gaze was exactly the displacement requested by the eye movement command. This occurred in the absence of an explicit gaze command. The changes in eye position were not those requested by the EBN signal. In this model, gaze, not eye, obeys the eye command. These observations are illustrated graphically in panel C. The amplitude of the gaze shift (G) and the eye movement (filled symbols) observed during the movements illustrated in panel B are plotted as a function of the command issued to the EYE. The thin solid line represents the unity gain slope. The points representing the amplitude of the gaze shift fall on the line representing unity gain for the eye movement command. The points representing the amplitude of the eye movement fall short of the unity gain line, depending upon the amplitude of the head movement occurring during the time period when the EBNs are active. Thus, if we were recording the activity of EBNs during these simulations, we would observe that the correlation between number of spikes in the burst and gaze amplitude was higher than the correlation between number of spikes and the amplitude of the eye movement. But, as demonstrated by examples, it would be incorrect to conclude that the output of the EBNs were relayed to motoneurons innervating neck muscles.

Motor physiologists would like to know how the activity of cortical and subcortical neurons is related to the motor command being issued. How do we know which motor command is being issued? In the absence of a head movement, measures of executed eye movements provide accurate estimates of the saccadic commands transmitted to the extraocular motoneurons. The estimates of the motor command are accurate because the motoneurons receive no additional inputs from other oculomotor subsystems (e.g., vergence, pursuit, vestibular) during the time when the saccade command is being implemented. Under these conditions, the amplitude of the movement is tightly correlated with the number of spikes ¡n the saccade-related burst of pontine EBNs, and the peak velocity of the movement is tightly coupled to the peak frequency of the burst. However, when the motoneurons are receiving inputs from parallel oculomotor subsystems while a saccade is being

generated, measures of the amplitude, direction or velocity of the executed saccade provide unreliable and potentially misleading estimates of the saccadic command issued to the motoneurons. Correlations of activity of premotor neurons with the amplitude, velocity, and duration of the executed eye movement cannot be used to make solid inferences about the motor signals being generated by the cells because of the dissociation between the command that is issued and the movement that is executed. This dissociation is illustrated by the simulated eye movements shown with dashed lines (Fig. 6B). The EBNs generated commands for a 25, 30, or 35° movement. Because the head was moving and the vestibulo-ocular reflex (VOR) was active with a gain of 1, the executed eye movements had amplitudes smaller than the movements that would have occurred if the head had not been moving. Because of the dissociation between the issued command and the executed movement, relationships between movement parameters and the activity of any neuron issuing an oculomotor command above the level of the motoneurons are misleading *in the absence of accurate information about other influences on motoneuron activity.* When more than one oculomotor subsystem is active (e.g., during combined eye-head gaze shifts or during static changes in the orientation of the head relative to gravity; Scherberger et al., 2001), the data obtained by correlating the activity of neurons above the level of motoneurons with various movement parameters must be interpreted cautiously.

The simulations illustrated in Fig. 6 were based upon the assumption that the gain of the vestibulo-ocular reflex was I during the executed movements. Numerous studies have shown that the gain of the VOR is reduced during gaze shifts and that the amount of the attenuation increases as the amplitude of the gaze shift increases (for references, see Roy and Cullen, 1998). However, large individual differences in the VOR attenuation observed during perturbations in head position occurring during large combined eye-head gaze shifts have been reported (Huterer and Cullen, 2001) and there is disagreement about the exact time course of the changes in VOR gain during the gaze shift (for references, see Roy and Cullen, 1998). Nevertheless, because the gain of the VOR is reduced during large gaze shifts, the actual differences between executed eye movements

and the commands to move the eye will be smaller than those illustrated in Fig. 6C. Nonetheless, when there is a significant head contribution to the gaze shift, the executed eye movement will be an unreliable estimate of the command signal sent to the motoneuron because the VOR gain is not reduced to 0 during the entire time course of the gaze shift. Interpretation of the data correlating the activity of EBNs or other pre-motoneuron signals with changes in eye, head, and gaze position is difficult because, at this time, methods of measuring the instantaneous state of VOR gain during a single gaze shift or of estimating trial-to-trial variability in VOR gain are not readily available.

Summary and conclusions

Contemporary conceptual considerations of the role of the activity of individual neurons in the representation of sensory and perceptual phenomena and in the control of movements is largely restricted to data obtained from cortical neurons. In this chapter we have made an initial attempt to include data obtained from the oculomotor brainstem in our thinking about the significance of single cell activity. Our major conclusions and conjectures are summarized below.

For oculomotor motoneurons, a tight linear relationship (correlation coefficients in the 0.9 to 0.99 range) is observed between firing rate during fixation intervals and the orbital position of the eye. It would be possible to make extremely accurate estimates of eye position based upon the rate-position curves of a small number of motoneurons selected to cover the normal oculomotor range of eye position (see Fig. I B). The ability to make accurate predictions of global behavior on the basis of a small number of cells does not constitute strong evidence for sparse coding. The number of neurons required to generate accurate predictions about motor outcomes is not necessarily an accurate estimate of the number of neurons required to implement the action. Indeed, in terms of the relative importance of individual neurons (coarse or sparse coding), we argue that the motoneuron control of orbital position is a coarse code. Each motoneuron innervates a small number of muscle fibers. The twitch and tetanic tension of each motor unit is small compared to total tension required to hold the eye in eccentric positions (see,

for example, Goldberg et al., 1998; Goldberg and Shall, 1999). Moreover, it is the ratio of the activity of neurons in the agonist and antagonist motoneuron pools that controls eye position. Finally, the question of coarse or sparse coding depends upon the level of analysis. The tension generated by individual extraocular muscle fibers is sparsely coded but, at a more global level, the position of the eye in the orbit is coarsely coded.

The relationship between motoneuron activity and eye position is not static. The firing rate associated with a given orbital position depends upon how that position was obtained (conjugate or disjunctive movements) and upon whether the eye is stationary or slowly moving through that position. We also presented preliminary data suggesting that rate and interval coding may coexist, depending upon the time scale being considered. In a few cells, small variations in the exact distribution of spikes were associated with minute changes in eye position. The prevalence of this phenomenon is unknown and if it occurs frequently, it will be important to determine if the relationship is due to synchronous activity in a subset of the neurons in the motoneuron pool.

The activity of SLBNs in PPRF also constitutes a rate code. The integral of spike rate (number of spikes) is correlated with saccade amplitude and it would be possible to make accurate predictions about the horizontal amplitude of a movement based upon a small number of pontine neurons. We spec-, ulate, however, that the representation of saccade amplitude by the activity of pontine neurons should be labeled coarse coding, not sparse coding. This speculation is based upon the large number of these cells located in a widespread region of pontine reticular formation, and upon the restricted effects of local microstimulation and reversible inactivation of a small subset of pontine cells. We also reported preliminary data suggesting that the exact distribution of spikes in the saccade-related burst of premotor neurons is associated with fine changes in the details of the velocity profile of a saccade. This result seems to contradict the coarse coding argument presented above, but that is not a necessary conclusion. Should further investigations indicate that small variations in the exact timing of each spike in the saccade-related burst are tightly coupled to measurable changes in saccadic velocity, the possibility that subgroups of

pontine burst neurons have a tendency to discharge synchronously would need to be examined.

In the superior colliculus information about saccade direction and amplitude is represented as a place code, the location of the active population within the motor map. Yet, the duration and level of activity are important determinants of saccade duration and velocity. This indicates that the spatial and temporal pattern of activity within the collicular motor map is `read out' by more than one mechanism, as previously suggested (Stanford et al., 1996).

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