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Activity of Mesencephalic Vertical Burst Neurons During Saccades and Smooth Pursuit

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Missal, M., S. De Brouwer, P. Lefèvre, and E. Olivier. Activity of mesencephalic vertical burst neurons during saccades and smooth pursuit. *J. Neurophysiol.* 83: 2080–2092, 2000. The activity of vertical burst neurons (BNs) was recorded in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF-BNs) and in the interstitial nucleus of Cajal (NIC-BNs) in head-restrained cats while performing saccades or smooth pursuit. BNs emitted a high-frequency burst of action potentials before and during vertical saccades. On average, these bursts led saccade onset by 14 ± 4 ms (mean \pm SD, $n = 23$), and this value was in the range of latencies (~ 5 – 15 ms) of medium-lead burst neurons (MLBNs). All NIC-BNs ($n = 15$) had a downward preferred direction, whereas riMLF-BNs showed either a downward ($n = 3$) or an upward ($n = 5$) preferred direction. We found significant correlations between saccade and burst parameters in all BNs: vertical amplitude was correlated with the number of spikes, maximum vertical velocity with maximum of the spike density, and saccade duration with burst duration. A correlation was also found between instantaneous vertical velocity and neuronal activity during saccades. During fixation, all riMLF-BNs and $\sim 50\%$ of NIC-BNs (7/15) were silent. Among NIC-BNs active during fixation (8/15), only two cells had an activity correlated with the eye position in the orbit. During smooth pursuit, most riMLF-BNs were silent (7/8), but all NIC-BNs showed an activity that was significantly correlated with the eye velocity. This activity was unaltered during temporary disappearance of the visual target, demonstrating that it was not visual in origin. For a given neuron, its ON-direction during smooth pursuit and saccades remained identical. The activity of NIC-BNs during both saccades and smooth pursuit can be described by a nonlinear exponential function using the velocity of the eye as independent variable. We suggest that riMLF-BNs, which were not active during smooth pursuit, are vertical MLBNs responsible for the generation of vertical saccades. Because NIC-BNs discharged during both saccades and pursuit, they cannot be regarded as MLBNs as usually defined. NIC-BNs could, however, be the site of convergence of both the saccadic and smooth pursuit signals at the premotoneuronal level. Alternatively, NIC-BNs could participate in the integration of eye velocity to eye position signals and represent input neurons to a common integrator.

INTRODUCTION

Primates and cats use a combination of saccades and smooth pursuit eye movements to follow objects moving in their environment. During pursuit initiation, the eyes accelerate in the direction of target motion, and eye velocity increases to match target velocity in ~ 200 ms. This avoids a deterioration of visual perception due to a “slip” of the visual image on the

retina. During the acceleration phase of the smooth eye movement, a saccade is usually generated to reduce the error between eye and target positions. It is not known how the saccadic and smooth pursuit systems interact to achieve that common purpose: catching-up and matching speed with that of the moving target. Saccadic and smooth movements are under the control of several different neural structures (for pursuit see review in Keller and Heinen 1991; for saccades see review in Moschovakis and Highstein 1994). Recently, it has been shown that the primate superior colliculus (SC), which plays an important role in the control of saccades (see review in Sparks and Hartwich-Young 1989), could also interact with the control of smooth eye movements (Krauzlis et al. 1997). The SC contains cells encoding the “motor error,” i.e., the direction and the amplitude of the movement required to bring the eye on the target. The rostral part of the SC is a region that contains cells encoding small motor errors and is active before small amplitude saccades (Anderson et al. 1998) and during fixation (Munoz and Guitton 1991; Munoz and Wurtz 1993; Paré and Guitton 1994). It has been suggested these small motor errors could be shared by the saccadic and smooth pursuit systems (Krauzlis et al. 1997). In agreement with this hypothesis, ongoing smooth pursuit in the monkey can be modulated by electrical stimulation of the rostral SC (Basso et al. 1997). Furthermore, in the cat, it has been shown that stimulation of the SC evokes saccades (Guitton et al. 1980; Roucoux and Crommelinck 1976) followed by slow, smooth eye movements when stimulation duration exceeds that of saccades (Coimbra et al. 1998; Grantyn et al. 1996; Missal et al. 1996). Along the same lines, it has been shown that, in the cat, some efferent collicular cells discharge during both saccades and the slow eye movements that sometimes follow them during orientation toward a stationary target (Olivier et al. 1993). The role of the SC in smooth movement control has been already hypothesized on theoretical grounds (Lefèvre and Galiana 1992).

One main target of efferent collicular cells in the brain stem are saccade-related brain stem neurons that emit a high-frequency burst of action potentials associated with saccades in their preferred direction; these cells are generically referred to as burst neurons (BNs). BNs form a heterogeneous population with different properties (see review in Moschovakis et al. 1996). One group of BNs, the so-called medium lead burst neurons (MLBNs), discharge a high-frequency burst of spikes ~ 5 – 15 ms before the beginning of all saccades in their preferred direction. Their discharge specifies the metrics and dynamics of the saccade. MLBNs with a horizontal preferred direction are found in the paramedian pontine reticular forma-

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tion (in the cat: Kaneko et al. 1981; in the monkey: Keller 1974; Luschei and Fuchs 1972) and make monosynaptic excitatory connections with the ipsilateral abducens motoneurons (in the cat: Igusa et al. 1980; Sasaki and Shimazu 1981; in the monkey: Strassman et al. 1986). MLBNs with a vertical preferred direction are found in the rostral mesencephalic reticular formation (in the cat: Delgado-Garcia et al. 1988; Nakao et al. 1986; in the monkey: Büttner et al. 1977; King and Fuchs 1979), more specifically in the rostral nucleus of the medial longitudinal fasciculus (riMLF) and in the interstitial nucleus of Cajal (NIC). In the cat, some MLBNs receive a monosynaptic input from the SC (Chimoto et al. 1996; Hikosaka and Kawakami 1977). If the SC plays a role in smooth pursuit, it is therefore possible that some BNs are active during both saccades and smooth pursuit. These neurons would be a convergence site for the two orienting systems that work in synergy during orientation toward a moving target.

The aim of the present study was to investigate the activity of MLBNs during *both* saccades and smooth pursuit and to assess their possible role in the control of these two types of movements. This study was restricted to vertical movements and vertical BNs. A preliminary account of these data has been published in an abstract form (Lefèvre et al. 1999).

METHODS

Experimental procedures

The results reported in the present study were gathered from recordings made in two adult cats trained to perform a saccade and smooth pursuit task. All procedures were approved by the Université Catholique de Louvain Ethics Committee and were in accordance with the American National Institutes of Health Guide for Care and use of Animals.

Each cat underwent two surgeries. Before training began, cats were surgically implanted, under deep general anesthesia (6–10 mg/kg im Ketamine and 0.1 mg/kg im Xylazine), with a scleral search coil to measure gaze position (Robinson 1963), and a plastic rod was cemented on the skull. This rod was tilted 24° anterior in the sagittal plane. After training was completed, cats underwent a second surgery, and a craniotomy was made to allow access to the mesencephalon with microelectrodes. This craniotomy was centered at stereotaxic coordinates A0–A2; a stainless steel recording chamber was cemented over the craniotomy.

Behavioral procedures

Cats were held in a restraining box and faced a tangent screen 1 m away that spanned about ± 35 deg of their visual field. They were trained to fixate 1° target spots back-projected onto the screen. When a trial started, cats were required to look at a fixation target either 10° above or below the center of the screen and to maintain steady fixation for 500 ms. The target then started to move at a constant velocity either downward if the initial target position was above the center of the screen or upward if the initial position was below. Total amplitude of target displacement was always 20°. Blocks of 20 trials consisted of 70% trials in the preferred direction of the cell recorded and 30% in the opposite direction. Target velocity varied from block to block and had one of the following values: 5, 10, 20, 30, or 40°/s. During fixation and pursuit, the position of the eye had to remain within a square window of $4 \times 4^\circ$ centered on the target. Animals received a food reward if they pursued the target to its final position.

Cats were also trained to keep pursuing the target when it was switched off for a short period of time (target blinks). The target was extinguished during its displacement in 10–50% of the trials, depend-

ing on the performance of the animal. The animals rapidly learned to continue pursuing the target during its temporary disappearance, predicting its reappearance after the target blink period (predictive smooth pursuit). Target blink lasted 350–400 ms, changing on a day-to-day basis, depending on the performance of the animal.

Data acquisition and recording methods

Vertical and horizontal eye position signals were low-pass filtered at 320 Hz and sampled at 2 kHz. They were stored on the hard disk of a PC for off-line analyses together with target position and neuronal data. MATLAB (Mathworks) was used to implement digital filtering, velocity, and acceleration estimation algorithms. MATLAB's zero-phase forward and reverse digital filtering (using a Butterworth designed 2nd-order low-pass, 35-Hz, cutoff filter) was applied to the position signals. The velocity and acceleration of horizontal and vertical components were derived from position signals using a central difference algorithm.

Spikes of single neurons were recorded using commercial tungsten microelectrodes (1 M Ω at 1 kHz; Frederick Haer). Cell activity was amplified and filtered using standard methods (Neurolog, Digitimer). Action potentials were discriminated on-line using a time-amplitude window discriminator system (BAK Electronics). The time of spike occurrence was stored on disk together with eye and target position signals.

Movements parameters

Saccade variables studied included amplitude, duration, and maximum velocity. Saccade onset or offset was defined as the time when eye velocity exceeded or fell below 15°/s, respectively. This criterion was combined with an acceleration criterion to determine saccade onset and offset during combined saccade and smooth pursuit eye movements. During saccades, eye acceleration in the direction of the measured component had to exceed a threshold fixed at 500°/s². Eye acceleration had to remain higher than the threshold value for at least 20 ms. Smooth pursuit eye movements were defined as prolonged saccade-free periods of slow eye displacement at an approximately constant velocity (acceleration close to or equal to the noise level, $\sim 180^\circ/\text{s}^2$) when the animals attempted to track a moving target. The velocity of smooth pursuit eye movements had to increase if target velocity was increased. Other kinds of slow eye movements, for example postsaccadic drifts or slow saccades, were discarded from this analysis. The smooth pursuit variables measured included amplitude of the movement, duration, and average velocity. Average smooth pursuit velocity was computed as the ratio of eye displacement amplitude to duration.

Estimation of neuronal firing rate

To transform a discrete spike train, $S = [ts_1 \cdots ts_i \cdots ts_N]$, where ts_i is the time at which the i th spike occurs, in a continuous function of time, each spike was replaced by a Gaussian function. The spike density function is then defined as the sum of the Gaussian functions. This function is also called the fixed-kernel estimation because the same standard deviation (s_0) is used for each Gaussian. The main problem is usually to select a good value for s_0 because the shape of the spike density function depends critically on s_0 . Classically ranging from 2 to 20 ms, s_0 should be large for a low firing rate to reduce the noise and small during bursts of activity to avoid filtering out the signal. This problem can be solved by varying the value of the kernel, s_0 throughout the trial, a method called the adaptive-kernel estimation. In the present study, this adaptive method was essential because we studied the discharge of neurons during both saccades and smooth pursuit movements, accompanied by strong and weak cell activity, respectively. The adaptive value of s_0 was estimated from the data following a procedure described by Richmond and Optican (1987).

Quantitative measures of neuronal activity

Burst variables analyzed included burst onset and offset, burst duration, maximum discharge rate estimated from the spike density function, and number of spikes in the burst. Burst onset was defined as the moment when the spike density function crossed a threshold fixed at 80 spikes/s for >30 ms (Fig. 1, time t_1). Burst offset was determined in a symmetric way (t_3). These criteria were defined empirically but match similar criteria established by Van Gisbergen et al. (1981) for MLBNs in the monkey (100 and 80 spikes/s for burst onset and offset, respectively). Burst duration was defined as the time elapsed between burst onset and offset. The latency of the response is the difference between saccade onset time and burst onset time, positive values indicating that the burst leads the saccade. Burst onset and offset associated with saccades were sometimes difficult to determine during combined saccadic and smooth pursuit movements because of the presence of an equivocal transition zone in the cell activity related either to the saccade or the smooth pursuit (see RESULTS). This very often led to an ambiguous identification of the burst onset and/or offset for saccades occurring during pursuit. Indeed, a discharge before a saccade during pursuit could be either a lasting smooth pursuit-related discharge or the rising activity related to preparation of the following saccade. Therefore the number of spikes in the burst was determined independently of the identification of burst onset and offset. The number of spikes was counted over a

period starting 40 ms before saccade onset and finishing 40 ms after the saccade, to include all possible spikes related to saccade occurrence (integration period, see double-headed arrow in Fig. 1). This measure of spike number yielded comparable results when applied for saccades of identical amplitude executed either toward stationary targets or during smooth pursuit. This method proved to give more reliable and less variable measurements than the method that consists of counting spikes occurring between burst onset and offset as determined with the aforementioned firing threshold technique.

Rise time is defined as the time elapsed between burst onset and maximum firing rate (rise time = $t_2 - t_1$, Fig. 1). It reflects the rate of increase of the initial firing period of the burst. A short rise time means that the burst was very sharp, reaching maximum firing rate over a few interspike intervals near saccade onset.

Neuronal activity during pursuit was measured on a period starting 40 ms after the end of the previous saccade and ending 40 ms before the beginning of the next saccade. The number of spikes was integrated over that period, and the mean firing frequency was computed (number of spikes/duration). This procedure avoids mixing saccade-related activity with smooth pursuit-related activity.

Cross-correlation method

To determine whether the instantaneous activity of burst neurons is related to the instantaneous velocity of the eye, we computed for each

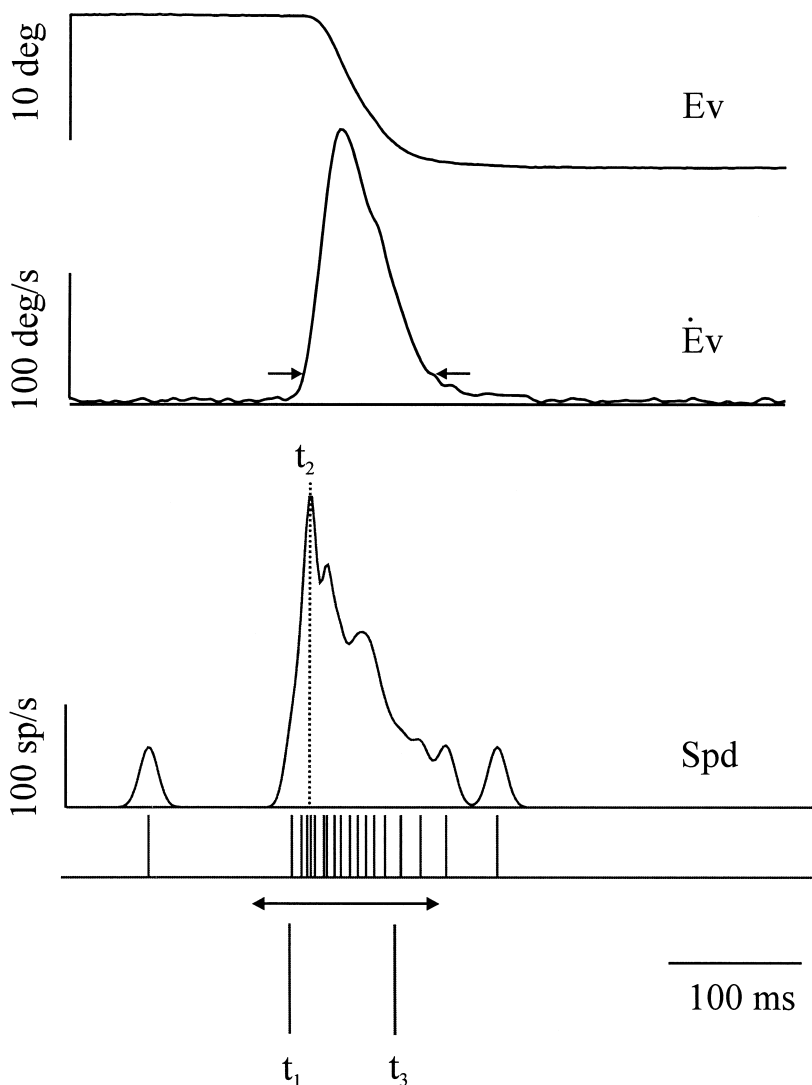


FIG. 1. Measures of saccade parameters and neuronal activity. From top to bottom: vertical eye position (E_v), vertical eye velocity (\dot{E}_v), spike density (Spd) and individual spikes (vertical lines). The 2 small arrows on the eye velocity profile indicate the saccade onset and offset. The horizontal double-headed arrow below individual spikes indicates the duration of the integration period during which spikes were counted. t_1 indicates the burst onset, t_2 the time of maximum of the spike density, and t_3 the burst offset.

saccade the cross-correlation function between the vertical velocity of the eye and the spike density waveform. This method relies on the basic assumption that the two signals, namely vertical eye velocity and spike density, share a common component. Therefore it should be possible to compute a correlation coefficient. However, the two signals may indeed have a common component (velocity), but that component in one signal may be delayed in time with respect to the same component in the other signal. Therefore the spike density waveform was shifted in time by steps of 2 ms, and the correlation with eye velocity was computed each time. The value of the correlation will increase and reach a maximum when the time delay between the two signals is equal to zero. If n is the number of data points in the signal, the result of that procedure is a cross-correlation function with $2 * n - 1$ elements. The maximum of the cross-correlation function is a good indicator of the dynamic correlation between the eye velocity and spike density function. Figure 2A shows the cross-correlation function for the saccade presented on Fig. 1. The maximum correlation was 0.97. The resulting cross-correlation function also allowed us to determine the delay of a neuron's activity with respect to the saccade because the position of the peak in the cross-correlation function depends on the number of steps necessary to bring the signals into register. In Fig. 2A, the position of the peak of the correlation function is at sample 120, whereas the middle of the

function is at sample 112 ($n = 112$). Figure 2B shows the two signals before (*left*) and after the spike density was shifted with respect to eye velocity by 16 ms (*right*). The cross-correlation method gives therefore a quantitative measure of the dynamic correlation between eye velocity and spike density and an alternative method of measuring burst latency. This estimation of burst latency is similar to the "dynamic lead time" proposed by Cullen and Guitton (1997).

Regression analysis and model estimation

The relationship between neuronal activity and eye velocity in one group of neurons reported in this study was quantified with a linear (Eq. 1) and a nonlinear model (Eq. 2)

$$\text{activity} = b * \text{velocity} + c \quad (1)$$

$$\text{activity} = b_0 * [1 - \exp(-\text{velocity}/b_1)] + b_2 \quad (2)$$

where *activity* is the average discharge rate during pursuit (number of spikes/duration) and the maximum firing rate during saccades and *velocity* is the average vertical velocity during pursuit and the maximum vertical velocity during saccades. Average velocity during pursuit was the ratio of eye displacement and duration. The constant b_0 corresponds to the maximum discharge level and b_1 is the time constant of the exponential. The constant b_2 corresponds to the activity when the velocity of the eye is zero.

The nonlinear estimation was performed using the nonlinear estimation procedures of a commercial software (STATISTICA, Stat-Soft). Estimation of the model was performed using the least-squares method. To find the minimum of the loss function (commonly known as least squares), to find the best fitting set of parameters, and the standard error of the parameter estimates, the quasi-Newton convergence method was selected. Other convergence methods tested yielded similar values of the parameters of the nonlinear function. To evaluate the fit of the model, the algorithm computes the total variance of the dependent variable (total sum of squares, SST), the proportion of variance due to the residuals (error sum of squares, SSE), and the proportion of variance due to the regression model (regression sum of squares, SSR = SST - SSE). The ratio of the regression sum of squares to the total sum of squares (SSR/SST) explains the proportion of variance accounted for (referred to as VAF in the text) in the dependent variable (y) by the model. This ratio is analogous to the r^2 ($0 < r^2 < 1$) or coefficient of determination.

Histological procedures

Recording sites of units reported here were verified by histological reconstruction of some recording tracks. For each animal, one to three lesions were made by passing 20 μA of anodal current for 20 s at recording sites of typical neurons. At the end of experiments, animals were deeply anesthetized (pentobarbital sodium) and perfused intracardially with saline followed by 10% Formalin. Serial 20- μm frozen sections were cut in the frontal plane and stained with the Nissl method. Recording sites were easily determined using a projection apparatus.

RESULTS

Twenty-three neurons showing a burst of activity related to vertical saccade occurrence were recorded in the mesencephalic reticular formation of two animals.

Location of recording sites

Vertical BNs were recorded in two different regions of the mesencephalon. Fifteen burst neurons were recorded in the region of the NIC and eight in the field H of Forel, in or near

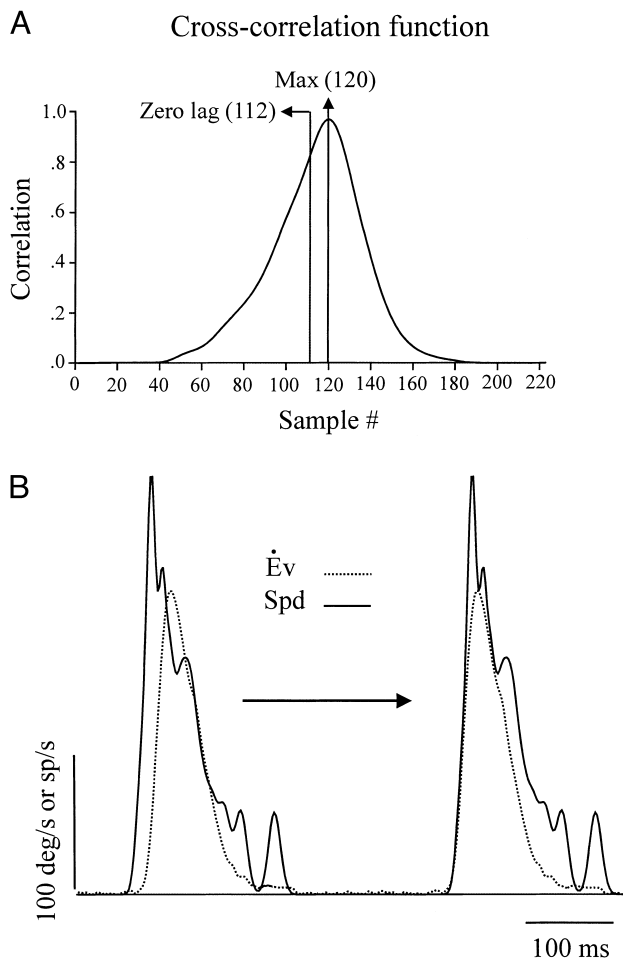


FIG. 2. Cross-correlation method. A: example of a cross-correlation function computed between vertical eye velocity and spike density. If the eye velocity and spike density were strictly synchronized, the maximum of the function (Max) should coincide with the zero lag position (Zero lag) at the middle of the function. The distance between these 2 positions shows that the burst preceded the saccade by 8 samples (16 ms). B: velocity profile and spike density function before (*left*) and after (*right*) they were shifted by the value given by the cross-correlation function. Same abbreviations as in Fig. 1.

the riMLF. Figure 3 shows schematic diagrams of recording locations of three cells. Figure 3A shows an electrolytic lesion made at a recording site most probably located in the NIC or in its immediate vicinity (see Fukushima 1987). Figure 3B shows two lesions that were probably situated in the riMLF according to Wang and Spencer (1996). Burst neurons recorded near or in the NIC will be referred to as NIC-BNs, whereas those recorded near or in the riMLF will be referred to as riMLF-BNs.

Activity during saccades

All BNs recorded ($n = 23$) were active before and during vertical saccades. Figure 4A shows the activity of a typical NIC-BN (*cell 15*) when the animal explored spontaneously its visual environment.

Downward saccades were associated with a high-frequency burst of action potentials whose maximum frequency varied with saccade amplitude (compare *S1* with *S2* in Fig. 4A). Upward saccades were associated with a weak burst containing solely a few spikes. Such a weak discharge during movements in the opposite direction was a feature of all BNs recorded and is a characteristic of MLBNs described in the literature (Van Gisbergen et al. 1981). A weak burst was also present during saccades in the orthogonal direction (horizontal saccades). During fixation periods, this NIC-BN was silent or emitted a

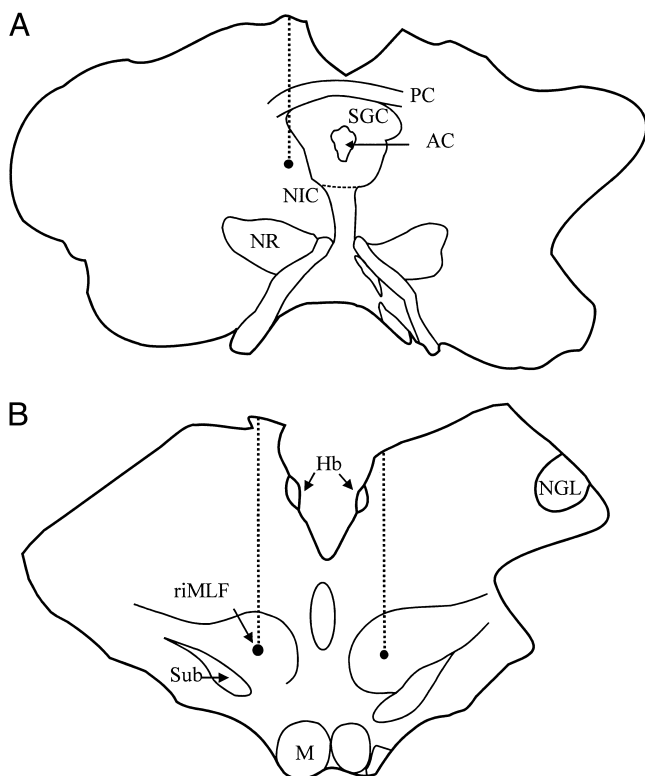


FIG. 3. Localization of recording sites shown on 2 frontal sections of the mesencephalon. Black dots show the positions of electrolytic lesions corresponding to recording sites. Vertical dotted lines show reconstructions of electrode tracks based on the serial sections. *A*: drawing of a section through the region of the interstitial nucleus of Cajal (NIC). *B*: drawing of a section through the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). AC, aqueductus cerebri; Hb, nucleus habenulae medialis; NGL, nucleus corporis geniculati lateralis; M, nucleus medialis mamillaris; NR, nucleus ruber; PC, commissura posterior; SGC, substantia grisea centralis; Sub, nucleus subthalamicus.

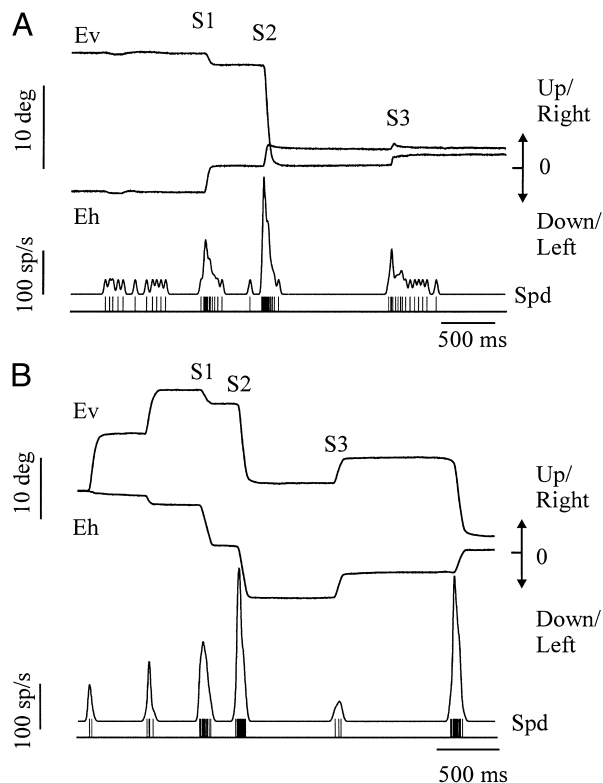


FIG. 4. Activity of burst neurons during saccades and fixation periods. *A*: example of the activity of a typical NIC-BN (*neuron 15*). This neuron emitted high-frequency bursts of action potentials before vertical downward saccades (*S1* and *S2*) and a weak burst associated with upward movements (*S3*). *B*: activity of a typical riMLF-BN (*neuron 17*). This neuron emitted high-frequency bursts before downward saccades (*S1* and *S2*) and a few spikes during upward movements (*S3*). The saccade-related activity in NIC-BNs and riMLF-BNs was apparently very similar. Eh, horizontal eye position. Other abbreviations as in Fig. 1.

few spikes. All NIC-BNs had a similar saccade-related activity. Figure 4B shows the activity of a downward riMLF-BN (*cell 17*) during fixation periods and saccades in the ON- (down) and OFF- (up) directions (up). A strong burst whose maximum spike density was apparently related to saccade amplitude accompanied all downward saccades (*S1* and *S2* on Fig. 4B). During upward saccades (*S3* in Fig. 4B), a weak burst was observed whose spike density apparently did not covary with movement amplitude. All riMLF-BNs had a similar saccade-related activity. During fixation periods, all riMLF-BNs recorded were silent.

All NIC-BNs recorded had a downward ON-direction. In the riMLF, BNs with an upward ON-direction were found intermixed with neurons with a downward ON-direction, sometimes along the same recording track (see Table 1).

Figure 5 shows rasters of activity for the same NIC-BN as illustrated in Fig. 4 (*cell 15*) for downward (Fig. 5A) and upward movements (Fig. 5B). Eye movement traces show the vertical component of saccades made toward a visual target or during exploration of the environment. The horizontal component during the selected movements was $<5^\circ$ on average. Rasters were aligned on saccade onset. Spontaneously and visually guided saccades of different amplitudes were pooled together, and each raster was ranked according to the amplitude of the vertical component of the associated saccade, from small (*top*) to large saccades (*bottom*). For downward saccades

TABLE 1. Value of the correlation coefficient

Cell	Ap/N _s	V _{max} /D _{max}	Du _s /Du _B	Fixation Activity	sl _s	sl _p	r _p	r ²	VAF
1	0.86	0.81	0.61	5.6 ± 6.8	0.47				
2	0.76	0.92	0.60	17.6 ± 12.3	0.72				
3	0.79	0.82	0.50	18.8 ± 9.7	0.76	10.90	0.59	0.79	0.88
4	0.63	0.82	0.58	0	0.56	5.70	0.50	0.81	0.81
5	0.83	0.93	0.47	0	0.65	3.70	0.72	0.84	0.95
6	0.83	0.70	0.59	9.5 ± 12.7	0.99	4.30	0.72	0.85	0.87
7	0.81	0.60	0.47	46.5 ± 9.4	0.23	1.80	0.49	0.67	0.82
8	0.89	0.92	0.62	0	0.76	1.70	0.71	0.85	0.94
9	0.46	0.37	0.19	0	0.17	4.10	0.89	0.54	0.79
10	0.86	0.65	0.52	37.5 ± 18.1	0.76	3.20	0.79	0.83	0.92
11	0.83	0.53	0.75	0	0.55	5.00	0.89	0.71	0.88
12	0.74	0.92	0.41	0	0.60	2.60	0.57	0.94	0.96
13*	0.85	0.83	0.63	0.4 ± 1.4	1.00	4.90	0.90	0.79	0.93
14	0.60	0.64	0.45	0	0.63	5.00	0.82	0.76	0.86
15*	0.90	0.87	0.67	8.3 ± 9.0	0.82	2.80	0.69	0.86	0.89
16	0.59	0.72	0.89	0	0.98				
17*	0.86	0.71	0.75	0	1.13				
18	0.83	0.68	0.62	0	1.13				
19	0.82	0.68	0.77	0	0.76				
20	0.81	0.76	0.60	0	0.74				
21	0.71	0.71	0.57	0	1.03				
22	0.78	0.79	0.63	0	1.13				
23	0.69	0.78	0.59	0	0.63				
Mean	0.77 ± 0.11	0.74 ± 0.13	0.58 ± 0.14	18.2 ± 16.1	0.64 ± 0.23	4.30 ± 2.30	0.71 ± 0.14		

Values in Fixation Activity and Mean are means ± SD. Cell, sequential number of the neuron recorded; Ap/N_s, correlation between vertical amplitude (Ap) and number of spikes in the burst (N_s); V_{max}/D_{max}, correlation between vertical maximum velocity (V_{max}) and maximum of the spike density (D_{max}); Du_s/Du_B, correlation between vertical saccade duration (Du_s) and burst duration (Du_B); Fixation Activity, mean activity during fixation; sl_s, slope of the relationship V_{max}/D_{max}; sl_p, slope of the relationship between average velocity during pursuit and average firing frequency; r_p, correlation coefficient of the relationship between average velocity during pursuit and average firing frequency; r², coefficient of determination of the relationship between eye velocity and neuronal activity; VAF, variance accounted for by the nonlinear model. Cells 1–15, interstitial nucleus of Cajal burst neurons (NIC-BNs). Cells 16–23, rostral interstitial nucleus of the medial longitudinal fasciculus burst neurons (riMLF-BNs). All correlations were significant at $P < 0.01$, except the correlation Du_s/Du_B for neuron 9 and neuron 12. * Cells selected as example in the paper.

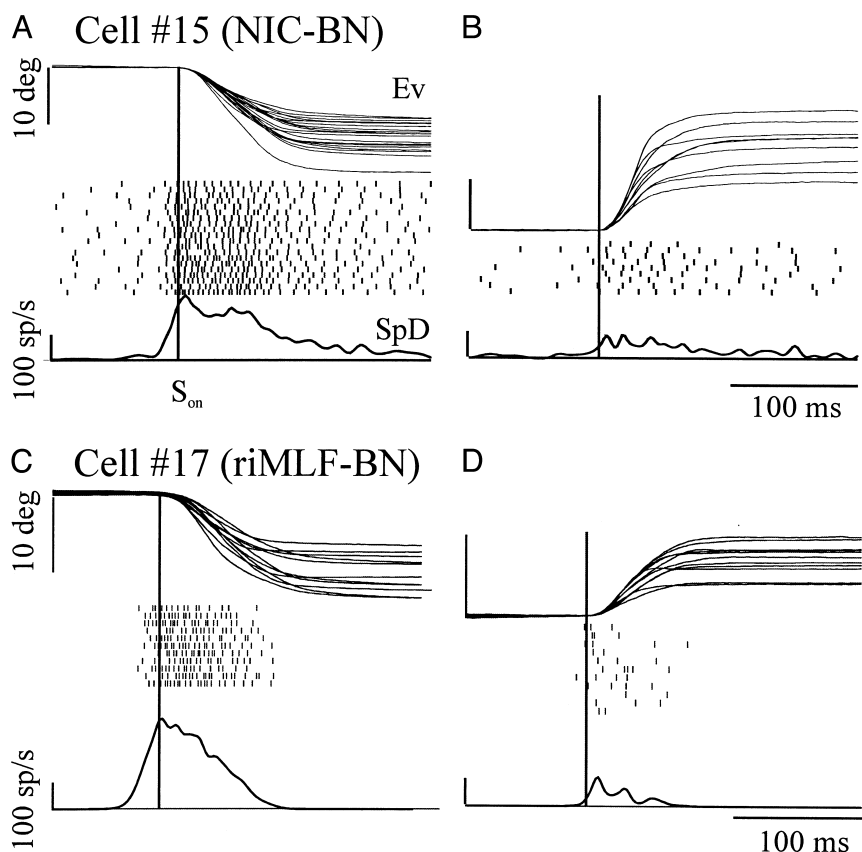


FIG. 5. Raster displays of the activity of a NIC-BN (neuron 15; A and B) and a riMLF-BN (neuron 17; C and D). A and C: activity associated with vertical downward saccades. B and D: activity associated with upward saccades. Vertical saccades of different amplitudes were pooled together and ranked according to the amplitude of the movement from top, small saccades, to bottom, larger saccades. Abbreviations as in Fig. 1.

(ON-direction, Fig. 5A), cell activity preceded saccade onset by 10 ± 2 ms (mean \pm SD, $n = 20$); this value was 15 ± 3 ms when determined with the cross-correlation method. As already mentioned, saccades in the OFF-direction were also accompanied by a weak burst, loosely related to saccade amplitude (Fig. 5B). Figure 5, C and D, shows two raster displays for the riMLF-BN illustrated in Fig. 4B (*cell 17*). For downward saccades, bursts led eye movement by 12 ± 2 ms in this example ($n = 11$); this value became 18 ± 4 ms when estimated with the cross-correlation method. As shown in Fig. 5D, during upward movements, this neuron also emitted only a few spikes loosely related to saccade amplitude.

The average latency of the vertical bursters with respect to saccade onset was 14 ± 3 ms for all NIC-BNs ($n = 15$) and 12 ± 3 ms for all riMLF-BNs ($n = 8$); this difference was not statistically significant (t -test for independent samples; $t = 1.4$; $P > 0.01$). The latency estimated with the cross-correlation method was not significantly different either (14 ± 8 ms for NIC-BNs and 18 ± 4 ms for riMLF-BNs; t -test for independent samples; $t = 2.4$; $P > 0.01$). We also computed the rise time of the burst (see METHODS) in the two groups of neurons. The rise time of NIC-BNs (29 ± 10 ms) was about twice the rise time of riMLF-BNs (16 ± 5 ms); this difference was statistically significant (t -test for independent samples; $t = 3.65$; $P < 0.01$).

To further study the coding of saccades by NIC-BNs and riMLF-BNs, the correlation between saccade and burst parameters was studied in each cell (see Table 1 for all data). Because BNs were the most active during vertical movements, only correlations between vertical component and burst parameters were analyzed in detail. Figure 6 shows the quantitative relationships between saccade and burst parameters for downward (negative values) and upward saccades (positive values) in a NIC-BN (*cell 15*). Figure 6A shows the relationship between saccade and the number of spikes in each burst accompanying a saccade. The correlations between these two variables was significant for downward saccades only (ON-direction). The slope of the linear regression fitted through these data points was close to one, meaning that the number of spikes in the burst increased by about one per degree of amplitude for downward saccades. There was a minimum of ~ 10 spikes in the burst (Y -intercept), and this value corresponds to the average number of spikes in the burst for saccades in the OFF-direction. Figure 6B shows the correlation between the maximum velocity of the vertical component of saccades and maximum of the spike density function for the same neuron. There was a significant correlation between these two variables for ON-direction (downward) but not for OFF-direction (upward) saccades. For downward movements, this cell increased its discharge by 0.8 (spikes/s)/(deg/s). This slope is similar to those previously reported in the literature for MLBNs (see review in Moschovakis et al. 1996). A significant correlation was also found between the downward vertical component duration and burst duration (Fig. 6C). However, this correlation was weak, and there was more scatter in the data. All NIC-BNs as well as all riMLF-BNs showed similar correlations between saccade parameters and burst parameters (see Table 1).

The average correlation between the peak saccadic velocity and the maximum of the spike density function was high (NIC-BNs: 0.7 ± 0.2 , $n = 15$; riMLF-BNs: 0.7 ± 0.1 , $n = 8$)

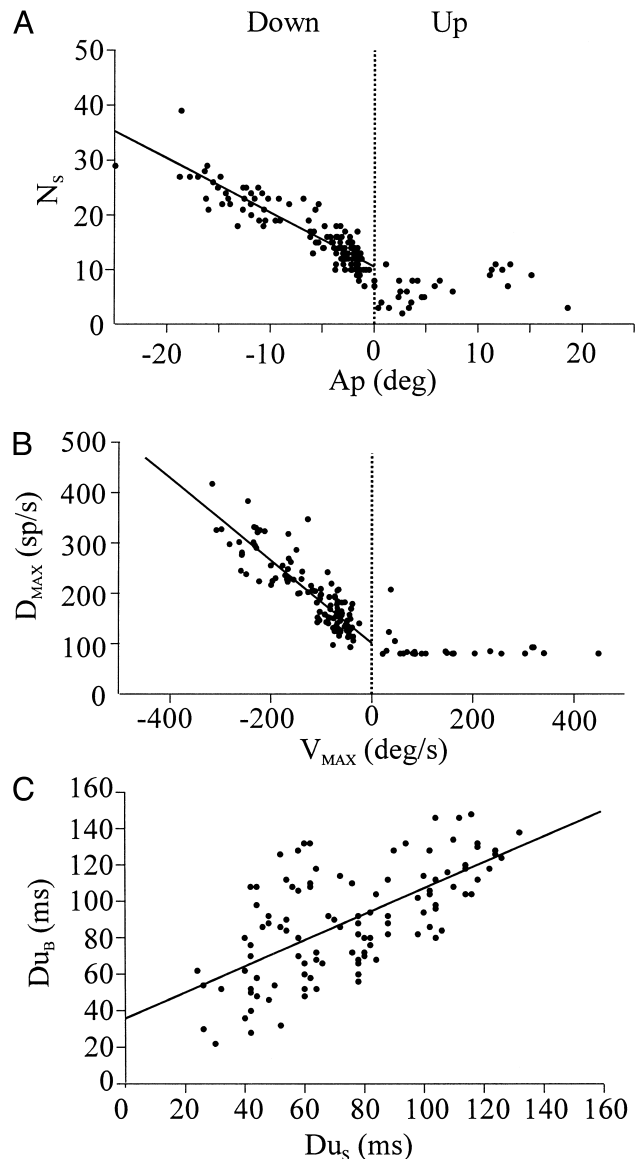


FIG. 6. Relationship between saccade parameters and burst parameters in a typical NIC-BN (*neuron 15*). A: relationship between vertical component amplitude (A_p) and number of spikes in the burst (N_s). Equation of regression line computed for downward saccades: $Y = 10.6 - 1.0 * X$; $n = 119$; $r = 0.9$. B: relationship between vertical component maximum velocity (V_{MAX}) and maximum of the spike density function (D_{MAX}). Equation of regression line for downward saccades: $Y = 101.1 - 0.8 * X$; $n = 119$; $r = 0.9$. C: relationship between vertical component duration (Du_s) and burst duration (Du_B). Equation of regression line for downward saccades: $Y = 0.04 + 0.7 * X$; $n = 111$; $r = 0.7$.

and suggests that there could be a dynamic correlation between saccadic eye velocity and the instantaneous firing rate. This question was investigated further by using the cross-correlation method. The cross-correlation function between instantaneous eye velocity and firing rate was computed on a sample of saccades of various amplitudes for each cell. The average value of the maximum of that correlation function was 0.7 ± 0.1 for NIC-BNs ($n = 15$) and 0.8 ± 0.1 ($n = 8$) for riMLF-BNs.

Activity during fixation

As already mentioned, riMLF-BNs were never responsive during fixation. In contrast, NIC-BNs were sometimes active in

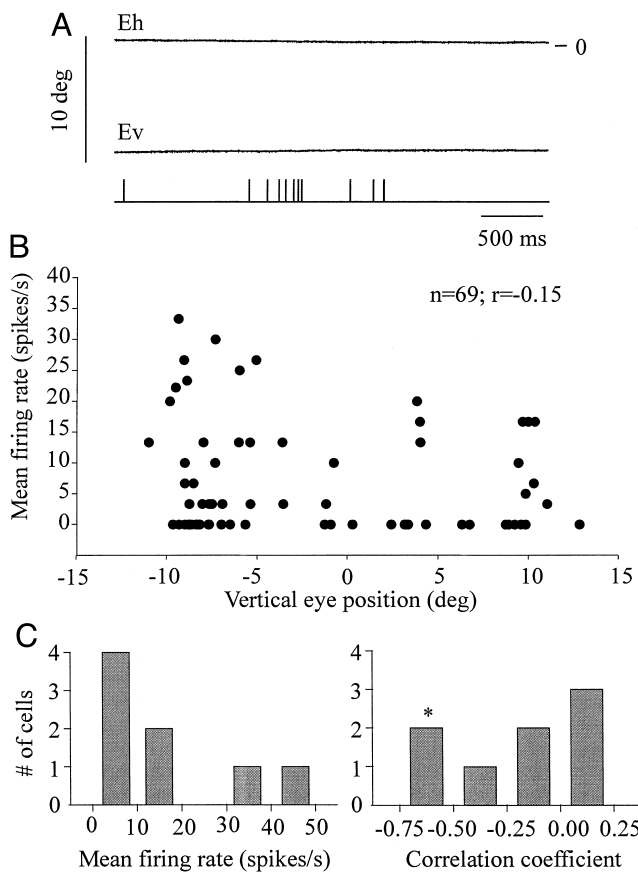


FIG. 7. Eye position-related activity of NIC-BNs. *A*: activity of *neuron 15* during fixation at a position $\sim 10^\circ$ below the horizontal meridian. Only a few spikes were occasionally observed. *B*: mean firing rate as a function of the vertical position of the eye for the same cell. Negative values represent downward eye positions, below the horizontal meridian. Each point represents the mean firing rate computed over 69 epochs of 300 ms for different vertical orbital positions. No significant correlation was found between the eye position and mean firing rate. *C*, *left histogram*: distribution of average firing rate for all NIC-BNs ($n = 8$) active during fixation. *Right histogram*: distribution of the correlation coefficients of the relationship between eye position and average firing rate computed for the same cell group. * Results from the only 2 cells showing a significant correlation.

the absence of eye movement. This activity during fixation, if related to eye position in the orbit, could give a critical information concerning the role of NIC-BNs. To quantify the activity of each NIC-BN during fixation, 300-ms fixation periods were selected between spontaneous or visually guided saccades. This values of 300 ms was chosen because it corresponds approximately to half the duration of the mean intersaccadic interval in cats. These periods were carefully selected so that the closest saccadic eye movements were separated in time by at least 100 ms. Average firing rate was computed for each cell during these 300-ms epochs. Seven NIC-BNs (47%) were completely inactive during fixation periods. Eight NIC-BNs (53%), including *cell 15*, were active during fixation. As can be seen in Table 1 (*column 5*), this fixation activity was on average very low (mean: 18.2 ± 16.1 spikes/s; $n = 8$), except for one neuron (*cell 7*), and quite variable as indicated by the large standard deviations. Figure 7*A* shows a typical example of fixation activity in *cell 15* when the eye was deviated downward, which corresponds to the ON-direction of this neuron. Figure 7*B* shows the average discharge of this cell related

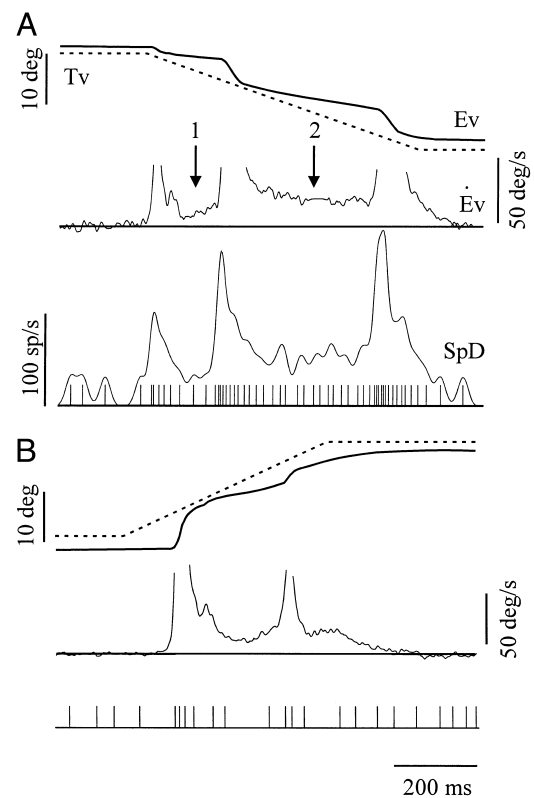


FIG. 8. Activity of a NIC-BN (*neuron 15*) during pursuit of a moving target. *A*: pursuit of a target moving at 20° /s from 10° up to 10° down. The animal used a combination of saccades and smooth movements to follow the target. During smooth pursuit epochs (*arrows 1 and 2*), the neuron discharged at an approximately constant frequency proportional to the velocity of the eye. A high-frequency burst accompanied downward saccades. *B*: activity during upward pursuit. The neuron was weakly active during both upward smooth pursuit and saccades. Tv, vertical position of the target (dashed line). Other abbreviations as in Fig. 1.

to different positions of the eye in the orbit. The cell activity during fixation was often equal to zero (33 of 69 measured periods of fixation) irrespective of the eye position in the orbit. However, in a few instances, when the eye was in more eccentric positions in the ON-direction, the discharge was higher than for symmetrical positions in the OFF-direction. This suggests that the activity of NIC-BNs during fixation periods could be related to the position of the eye in the orbit. To test

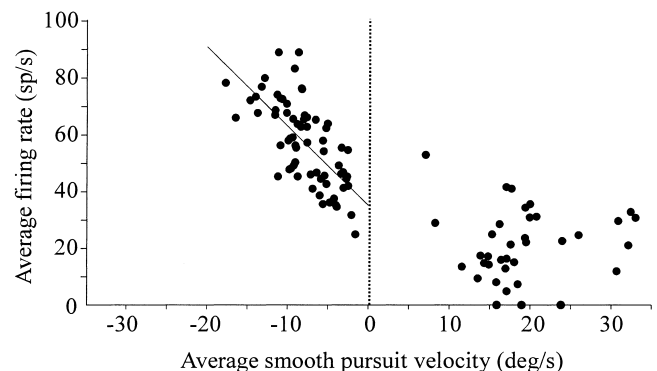


FIG. 9. Relationship between eye velocity and neuronal activity during smooth pursuit for a typical NIC-BN (*neuron 15*). There was a correlation between average smooth pursuit velocity and average firing rate for downward movements (negative values) but not for upward movements (positive values). Equation of the regression line: $Y = 35.3 + 2.8 * X$; $n = 67$; $r = 0.7$.

this possibility, we computed the correlation between average activity during the 300-ms fixation periods and vertical positions of the eye in the orbit in the ON- (down) or OFF-directions (up). For *cell 15*, there was not any obvious modulation of activity related to eye position, and the correlation between eye position and average firing rate was not significant ($n = 69$; $r = 0.15$; NS). This procedure was repeated for each NIC-BNs showing an activity in fixation periods. Within the range of vertical positions tested (-10 to $+10^\circ$), only two cells showed a significant correlation between average discharge and position of the eye in the orbit (Fig. 7C).

Activity during pursuit of a visual target

The activity of 21 BNs was also recorded during smooth pursuit along the vertical axis, in both directions. The large majority of riMLF-BNs (7/8) were not active during smooth pursuit. One riMLF-BN emitted a few spikes during fast pursuit, but this activity was not correlated with the velocity of the smooth movement. In contrast, all NIC-BNs were very active during head-restrained smooth pursuit of a visual target, as shown in Fig. 8 (*cell 15*). During the downward pursuit movement illustrated in Fig. 8A, the eye moved smoothly at an average velocity of $7.5^\circ/\text{s}$ (see *arrow 1*) and $14.4^\circ/\text{s}$ (see *arrow 2*) between saccades. During these two smooth pursuit epochs, this cell had a mean firing rate of 33 and 55 spikes/s, respectively, a frequency that varied apparently as a function of the eye velocity. This activity cannot be attributed to a sensitivity of NIC-BNs to eye position because we found a position-related activity for only two NIC-BNs. To test whether the ON-direction of NIC-BNs during pursuit was the same as during saccades, trials with an upward and downward target displacements were interleaved. As during upward saccades, during upward smooth pursuit this NIC-BN emitted only a few spikes, unrelated to the ongoing eye movement (Fig. 8B). It was found that the ON-direction was similar for saccades and smooth pursuit in all NIC-BNs.

Figure 9 shows the correlation between average smooth pursuit velocity and average firing rate during downward (*left*) and upward (*right*) smooth eye movements (*cell 15*). There was a linear increase of average firing rate with increase in smooth pursuit velocity but only for downward movements. The slope of the regression line was higher than that of the regression computed between saccadic maximum velocity and maximum of the spike density [2.79 (spikes/s)/(deg/s) vs. 0.82 (spikes/s)/(deg/s)]. Table 1 shows the value of the correlation coefficient for the velocity/average firing rate relationship for all NIC-BNs tested during smooth pursuit ($n = 13$). All correlations were significant ($P < 0.01$). No significant correlation was found between the eye velocity during smooth movements in the OFF-direction and average discharge frequency in any of the neurons recorded.

Because the activity of NIC-BNs during pursuit could at least partly reflect a visual stimulation caused by the slip of the target on the retina, a few trials with target disappearance were investigated for each cell. Target disappearance during pursuit led to predictive smooth pursuit as shown in Fig. 10. During predictive smooth pursuit, the neuron illustrated in Fig. 10A (*cell 15*) continued to discharge as long as the eyes were moving. Figure 10B shows the activity of another NIC-BN (*cell 13*) during three different types of eye movements: a visual fixation period (*arrow 1*), an anticipatory smooth eye movement at a low velocity (*arrow 2*), and a predictive pursuit during target extinction (*arrow 3*). This particular cell showed no activity during the fixation period. During the anticipatory eye movement (*arrow 2*), there was an induced retinal slip into upward direction. In spite of this retinal slip, the cell showed a discharge proportional to the eye velocity. The discharge then smoothly increased together with eye velocity until the first saccade occurred. During the temporary disappearance of the target (*arrow 3*), the cell remained active. The shape of the spike density closely matches that of the velocity profile with one important difference: the activity is proportionally stronger during pursuit than during saccades. This is due to the steeper

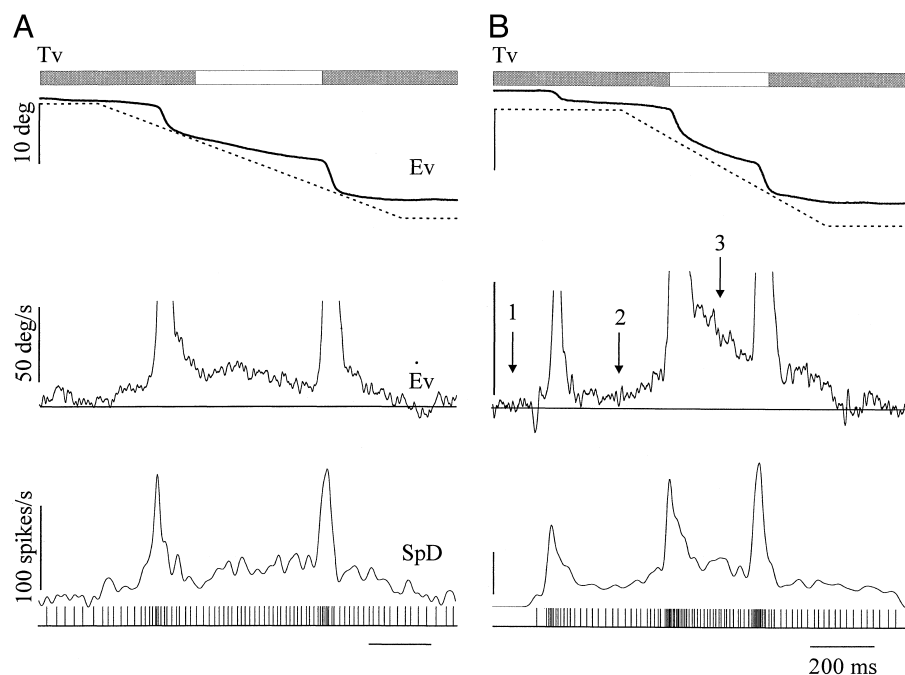


FIG. 10. Activity during predictive smooth pursuit in NIC-BNs. Horizontal bars show the periods when the moving target was present (filled bar) or temporarily extinguished (open bar). A: activity of *neuron 15* during pursuit of a target moving at $20^\circ/\text{s}$. The target was extinguished during a 400-ms period, but the eye continued to move smoothly until the target reappeared. During the period of predictive pursuit, the neuron activity did not drop to zero but remained at a sustained level. After the 2nd saccade, both neuronal activity and eye velocity decreased and dropped back to zero. B: activity of *neuron 13* during pursuit of a target moving at $30^\circ/\text{s}$. This neuron had no spontaneous activity during fixation (*arrow 1*). *Arrow 2* indicates an anticipatory smooth eye movement that was accompanied by a slow increase in the neuron activity. During disappearance of the target (*arrow 3*), the activity was sustained, showing that it was related to the movement of the eye, and not to a visual stimulation.

slope of the relationship between firing rate and velocity during smooth pursuit. All the thirteen NIC-BNs tested during smooth pursuit showed a sustained discharge proportional to eye velocity during temporary disappearance of the target. Therefore a visual origin of the activity during smooth pursuit can be excluded.

Coding of eye velocity during saccades and pursuit

It has been shown that the discharge of NIC-BNs was correlated with the velocity of the eye during saccades and that the average firing rate was equally well correlated to average velocity during smooth pursuit. The slope of the relationship between velocity and average firing rate during smooth pursuit is steeper than the slope of the relationship between maximum saccadic velocity and maximum of the spike density (see Table 1). As is particularly obvious on the example given in Fig. 10, A and B, the discharge is relatively more important during smooth pursuit than during saccades if compared with the difference in velocity between the two movements.

To compare the activity of NIC-BNs during saccades and smooth pursuit, we tried to identify a model that could describe the relationship between discharge and eye velocity during both saccades and smooth pursuit. These movements have very different dynamics, so if a single model could explain the relationship between velocity and cell activity, it is necessarily a nonlinear relationship between firing rate and eye velocity. Figure 11 shows plots for two cells (Fig. 11A, *cell 15*; Fig. 11B, *cell 13*). A nonlinear exponential function was selected to describe the relationship for both pursuit and saccade data sets (Eq. 2, see METHODS) and compared with a linear model (Eq. 1,

see METHODS). For *cell 15* (Fig. 11A), the variance accounted for (VAF) by the nonlinear model was 89% of the total variance, a value higher than the variance accounted for (r^2) by a linear model (86%). The nonlinear regression analysis shows that the activity during pursuit and saccades could be predicted from the eye velocity trace by using Eq. 2 as regression model. For *cell 13* (Fig. 11B), the nonlinear model explained 93% of the variance, a value higher than the prediction based on a linear model (79%). Note that for the cell shown in Fig. 11A, the range of velocities during pursuit was smaller than for the cell shown in Fig. 11B. For all cells tested during both saccades and smooth pursuit ($n = 13$), the curve described by Eq. 1 could fit the relationship between eye velocity and cell activity. Table 1 gives the values of the VAF by the nonlinear model and the variance explained by the linear model (r^2). For all cells, the variance explained was larger when the nonlinear model was used.

DISCUSSION

This study is the first report of smooth pursuit-related activity in any type of neuron in the cat. We analyzed the activity of vertical saccadic burst neurons with a downward ON-direction in the region of the interstitial nucleus of Cajal and in the rostral interstitial nucleus of the medial longitudinal fasciculus. It was shown that NIC-BNs were active during both saccades and smooth pursuit, whereas riMLF-BNs were responsive only during saccades. A nonlinear exponential model proved the existence of a relationship between NIC-BN firing rate and eye velocity, whatever the type of movements.

Are riMLF-BN vertical MLBNs?

In the cat, MLBNs discharge a high-frequency burst of spikes before the beginning of all saccades in their ON-direction and project to oculomotor neurons (Igusa et al. 1980; Kaneko et al. 1981; Sasaki and Shimazu 1981). Cat MLBNs discharge with a latency of 13.5 ± 3.5 ms with respect to saccade onset (Nakao et al. 1988), a value very close to what we found in this study. Correlations between burst parameters and saccade parameters are similar in riMLF-BNs and MLBNs. Therefore the riMLF-BNs of this study are probably vertical MLBNs described by Nakao et al. (1988) and are likely to be involved in generating the presaccadic burst of activity. The absence of spontaneous activity in between saccades suggests that riMLF-BNs are subject to the inhibitory control of omnipause neurons (OPNs), cells that are supposed to play a permissive role for saccades and to form a gate controlling movement duration (in the monkey: Keller 1974; in the cat: Kaneko and Fuchs 1982; Nakao et al. 1988; Paré and Guitton 1998).

Comparison of NIC-BNs with other groups of neurons active before saccades

NIC-BNs have a saccade-related activity very similar to that of MLBNs, especially NIC-BNs without spontaneous activity. However, their activity during smooth pursuit indicates that they form another category of BNs. Different groups of neurons have been shown to have activity sharing some aspects with that of NIC-BNs. Burst-tonic (BT) neurons in the NIC have a high-frequency burst of activity related to the saccade and a tonic activity during fixation periods that is tightly

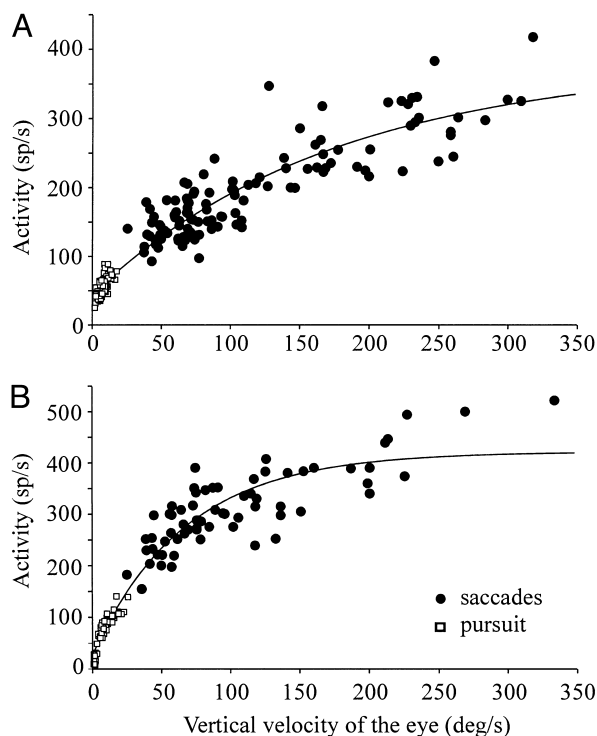


FIG. 11. Relationship between eye velocity and neuronal activity during saccades (●) and smooth pursuit (□). A: *neuron 15*. Equation of the curve: $Y = 335.9 * \{1 - \exp[-x/(175.1)]\} + 45.3$; variance accounted for (VAF) = 0.89; $n = 186$. B: *neuron 13*. Equation: $Y = 394.2 * \{1 - \exp[-x/(67.7)]\} + 27.5$; VAF = 0.93; $n = 120$.

correlated to the position of the eye in the orbit (correlation ~ 0.9) (in the cat: Fukushima et al. 1990). In the monkey, the discharge of BT neurons was shown to be correlated with eye velocity during smooth pursuit (King et al. 1981). However, the following observations rule out the possibility that NIC-BNs are BT neurons. 1) NIC-BNs were normally silent or emitted only a few spikes during upward pursuit when the eye crossed positions where the same cell was very active during downward movements at the same velocity (compare Fig. 8, A and B). 2) The activity of NIC-BNs during fixation was infrequent and not related to orbital eye position in most NIC-BNs. 3) A large proportion of NIC-BNs had no activity at all when the eye was immobile and nevertheless were very active during both saccades and smooth pursuit (7 cells of 15). 4) Some BT neurons paused for saccades in the OFF-direction, but NIC-BNs never did. 5) In cats, correlations between saccade parameters and burst parameters in BT cells are weak. The typical value of the amplitude/number of spikes correlation is between 0.4 and 0.6, a value much lower than what we observed here (0.8 on average). It is therefore very unlikely that NIC-BNs are BT neurons.

In the cat, neurons named vestibular and saccade neurons (VSNs), also located in the NIC, have been shown to discharge before vertical downward or upward saccades and during vertical vestibular stimulation (Fukushima et al. 1995). The metrics of the discharge of VSNs was usually weakly correlated with the metrics of saccades (range 0.5–0.6). Half of these neurons showed some eye position sensitivity. Primate VSNs have been shown to discharge during both saccades and smooth pursuit (Kaneko and Fukushima 1998), as NIC-BNs in this study. However, some differences between NIC-BNs and VSNs activity have to be noted. 1) In the monkey, vertical VSNs shows a bidirectional pursuit-related discharge, whereas in NIC-BNs, a consistent smooth pursuit-related discharge was observed only in the same direction as the ON-direction for saccades. 2) In the cat as well as in the monkey, the discharge of VSNs is only weakly correlated with saccade parameters, and they are broadly tuned, a burst being sometimes observed in the absence of any eye movement. 3) In both species again, the discharge frequency of VSNs during fixation period is higher than what we found for NIC-BNs, and all VSNs were spontaneously active. 4) In the cat, the onset of the burst in VSNs preceded saccade onset by 35 ms on average (Fukushima et al. 1995), a duration much longer than what we observed in the present study (13 ± 3 ms on average). Because the response of NIC-BNs to vestibular stimulation was not tested in this study, it cannot be ruled out that NIC-BNs and VSNs belong to the same group of neurons. Members of this group could share common properties varying continuously across neurons.

Possible role of NIC-BNs

One of the major findings of this study is that the activity of NIC-BNs during both saccades and pursuit can be described by the same exponential model. This model gives actually a better description of NIC-BNs behavior than linear models. It explains most of the variance by using only one independent variable, the velocity of the eye, whatever the type of movement actually executed. The fact that NIC-BNs were active

during both kinds of movements could be related to the results of electrical stimulation of the cat SC. It has been shown that when the collicular stimulation exceeds the duration of the saccade, constant velocity smoothlike eye movements are elicited (Coimbra et al. 1998; Grantyn et al. 1996; Missal et al. 1996). As the SC projects to the NIC, although weakly, and the surrounding reticular formation (Grantyn and Grantyn 1982; Grantyn et al. 1982), vertical smooth eye movements could be due to the activation of NIC-BNs at a lower level during intersaccadic periods. Comparison of the fastest pursuit and slower saccades (see Fig. 11B) shows that there could be a continuum between these two types of movements in the cat. Therefore stimulation of the same collicular region could potentially yield either a saccade or a smooth movement, depending on the internal state of the system. This internal state, saccadic or pursuit mode, is probably determined by higher level cortical structures. We suggest that NIC-BNs could be involved in the conjoint behavior of catching-up to a moving target with saccades and matching its speed with smooth movements. This hypothesis implies also that NIC-BNs project to eye motoneurons, which has yet to be demonstrated but is a reasonable assumption.

Another possible premotor role for NIC-BNs is the integration process. After a saccade, elastic forces tend to bring the eye back to the primary position. To keep the eye at an eccentric position after the saccade, extraocular muscles need a tonic position signal. This signal has been referred to as the “step” of motor innervation. This tonic signal is supposed to result from the integration of the phasic saccadic signal that allows the eye to counter viscous forces opposing its movement, the “pulse.” It has been shown that the neural integrator for vertical eye movements probably lies in the NIC (Fukushima et al. 1992). A similar integration has to occur during smooth pursuit as well. Therefore NIC-BNs could be interneurons at the input of a common neural integrator, and thus exhibit a large sensitivity to eye velocity and a low sensitivity to eye position. Probable sources of the pursuit signal could be pursuit cells like those described in the monkey by Eckmiller and Mackeben (1980) or the vestibular nuclei (see review in Keller and Heinen 1991). There would be a convergence of the saccadic and smooth pursuit velocity signals at the input of the velocity-to-position neural integrator. In agreement with this, it has been shown in the squirrel monkey (Moschovakis et al. 1991) that some MLBNs with downward ON-directions and a discharge tightly correlated with saccades metrics do not project to the oculomotor nucleus. These neurons were found in the NIC and project back to the NIC, the riMLF, and the mesencephalic reticular formation. riMLF and NIC-BNs may subserve different functions, the former being the premotor relay for saccades and the latter interneurons at the input of the neuronal integrator for eye movements. A similar hypothesis has been suggested to explain the role of VSNs by Kaneko and Fukushima (1998) and could be justified if NIC-BNs and VSNs are members of a same group of neurons. However, would the integration hypothesis be true, we would expect to find a large number of cells with eye position sensitivity among the neurons recorded or in the same region, as found by Dalezios et al. (1998) in the NIC of the squirrel monkey. This was obviously not the case in this study.

Conclusions

What the premotor role of NIC-BNs is remains to be determined, possibly by an anatomic study. However, our results show that there is a convergence of signals from the saccadic and smooth pursuit systems at the premotoneuronal level because activity correlated with both saccadic and smooth pursuit velocity were found in the same cells. A similar convergence of oculomotor signals has been suggested to occur in the cerebellum as well (Krauzlis and Miles 1998). Therefore NIC-BNs might be part of a network of interconnected structures involved in the control of the conjoint saccadic and smooth movements needed to pursue a moving object.

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