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Common Inhibitory Mechanism for Saccades and Smooth-Pursuit Eye Movements

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Missal, M., and E. L. Keller. Common inhibitory mechanism for saccades and smooth-pursuit eye movements. *J Neurophysiol* 88: 1880–1892, 2002; 10.1152/jn.00060.2002. The premotor pathways subserving saccades and smooth-pursuit eye movements are usually thought to be different. Indeed, saccade and smooth-pursuit eye movements have different dynamics and functions. In particular, a group of midline cells in the pons called omnipause neurons (OPNs) are considered to be part of the saccadic system only. It has been established that OPNs keep premotor neurons for saccades under constant inhibition during fixation periods. Saccades occur only when the activity of OPNs has completely stopped or paused. Accordingly, electrical stimulation in the region of OPNs inhibits premotor neurons and interrupts saccades. The premotor relay for smooth pursuit is thought to be organized differently and omnipause neurons are not supposed to be involved in smooth-pursuit eye movements. To investigate this supposition, OPNs were recorded during saccades and during smooth pursuit in the monkey (*Macaca mulatta*). Unexpectedly, we found that neuronal activity of OPNs decreased during smooth pursuit. The resulting activity reduction reached statistical significance in ~50% of OPNs recorded during pursuit of a target moving at 40°/s. On average, activity was reduced by 34% but never completely stopped or paused. The onset of activity reduction coincided with the onset of smooth pursuit. The duration of activity reduction was correlated with pursuit duration and its intensity was correlated with eye velocity. Activity reduction was observed even in the absence of catch-up saccades that frequently occur during pursuit. Electrical microstimulation in the OPNs' area induced a strong deceleration of the eye during smooth pursuit. These results suggest that OPNs form an inhibitory mechanism that could control the time course of smooth pursuit. This inhibitory mechanism is part of the fixation system and is probably needed to avoid reflexive eye movements toward targets that are not purposefully selected. This study shows that saccades and smooth pursuit, although they are different kinds of eye movements, are controlled by the same inhibitory system.

INTRODUCTION

To direct the fovea toward objects of interest in the visual world, the oculomotor repertoire contains two different kinds of visually induced, conjugate eye movements, saccades and smooth pursuit. Saccades induce a rapid shift of the visual axis between different positions. Their velocity is high (≤1,000°/s), and visual feedback is not used to guide the orientation of the eyes during the movement. If an object of interest starts to move, the pursuit system initiates a movement that smoothly matches eye velocity to that of the target to reduce the "slip" of the image of the moving object on the retina and stabilize it onto the foveal region. Smooth-pursuit eye movements use visual feedback and are slower than saccades (<100°/s) (see reviews: Keller and Heinen 1991; Krauzlis and Stone 1999; Lisberger et al. 1987). Therefore saccades and smooth pursuit are controlled differently by the nervous system. A wealth of data suggests that the neuronal pathways for these eye movements are different (see review in Leigh and Zee 1991). Early theoretical studies of the oculomotor system suggested that different eye movements like saccades and smooth pursuit were controlled by independent subsystems (Robinson 1972). This hypothesis of separate neural pathways for pursuit and saccades has for the most part been supported by subsequent experimental and clinical studies.

Neuronal pathways for smooth pursuit and saccades are complex and involve a network of cortical and subcortical structures (for pursuit: see review in Keller and Heinen 1991; for saccades: see review in Leigh and Zee 1991). In this study, we will discuss only the final premotor pathways for these eye movements. The final premotor pathway for smooth pursuit eye movements involves the medial vestibular nuclei (MVN) and the nucleus prepositus hypoglossi (NPH) where neurons encoding eye and head velocity during pursuit have been recorded (McFarland and Fuchs 1992). The MVN and NPH project to oculomotor neurons (see review in Evinger 1988). These nuclei receive inputs from the flocculus/ventral paraflocculus regions of the cerebellum (Langer et al. 1985), a region known to contain Purkinje cells that discharge according to gaze velocity during pursuit (Lisberger and Fuchs 1978; Miles et al.1980; Stone and Lisberger 1990a,b). Some additional evidence suggests that there is probably a second parallel pursuit pathway involving neurons in the paramedian pontine reticular formation (PPRF) that encode smooth-pursuit signals (Eckmiller and Mackeben 1980). The smooth-pursuit-related signals in the PPRF probably originate from the cerebellar vermis the projections of which via the caudal fastigial nucleus are compatible with this hypothesis (Batton et al. 1977; Noda et al. 1990; Yamada and Noda 1987). The vermis contains Purkinje neurons encoding gaze velocity during pursuit (Suzuki and Keller 1988a) as well as target velocity in space (Kase et al. 1979; Suzuki and Keller 1988b; Suzuki et al. 1981).

The final premotor pathway for horizontal saccades is also located in the PPRF (Keller 1991). A group of neurons in that

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area emit a high-frequency burst of action potentials before the beginning of saccades and are generically referred to as burst neurons (see review in Moschovakis et al. 1996). Burst neurons are usually grouped into two different categories based on the latency of the high-frequency burst of activity preceding saccades. Long-lead burst neurons (LLBNs) are active >15 ms before the beginning of the saccade. Medium-lead burst neurons (MLBNs) are active ~5–15 ms before the beginning of the saccade. A group of excitatory MLBNs monosynaptically contact ipsilateral ocular motoneurons (Büttner-Ennever and Büttner 1988; Strassman et al. 1986). These neurons, referred to as excitatory burst neurons (EBNs), emit a high-frequency discharge of action potentials that determines the dynamics of saccadic eye movements (Van Gisbergen et al. 1981). During periods of fixation when the eyes are immobile, EBNs are kept under the constant inhibition of another group of brain stem neurons called omnipause neurons or OPNs (Keller 1974). Omnipause neurons fire at a constant rate during fixation periods and stop firing (or pause) before and during all saccades, irrespective of their amplitude or direction. The inhibitory action of the OPNs has to be released to allow saccade occurrence (Keller 1977; King and Fuchs 1977). Therefore OPNs can be considered as a "gate" for saccades. Saccades can occur only when OPNs are inactive.

This brief description of the final pathways for smooth pursuit and saccades suggests that they are largely independent. However, recent studies suggest that the hypothesis of completely independent smooth pursuit and saccadic pathways is probably not valid in premotor structures like the superior colliculus (in the cat: Missal et al. 1996; Olivier et al. 1993; in the monkey: Krauzlis et al. 2000), cerebellar vermis (Krauzlis and Miles 1998; Suzuki and Keller 1988b) and mesencephalic reticular formation (in the cat: Missal et al. 2000). In the present study, we tested whether the hypothesis of independent premotor pathways is valid at the level of OPNs. If OPNs were modulated during smooth pursuit, it would suggest that the final pathways for saccades and smooth pursuit partially overlap or share an important group of neurons.

A preliminary account of part of this work has previously been published in abstract form (Missal and Keller 2000).

METHODS

Three monkeys (*FO*, *MA*, and *BU*) weighing between 4 and 7 kg were used in this study. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the California Pacific Medical Center and complied with the guidelines of the Public Health Service policy on Humane Care and Use of Laboratory Animals.

Preparation

The monkeys were initially trained to come out of their cages and sit comfortably in a primate chair. To allow head-fixed eye-movement recordings, a scleral eye coil and a head-restraint system (Crist Instruments) were implanted in each animal using dental cement and titanium orthopedic bone screws under isofluorane anesthesia and aseptic surgical conditions. Anesthesia was induced with an intramuscular injection of ketamine. Heart rate, blood pressure, respiratory rate, and body temperature were monitored for the duration of the surgery. A coil made of four turns of Teflon-coated stainless-steel wire was implanted under the conjunctiva of one eye using the procedure described by Fuchs and Robinson (1966) as modified by Judge et al. (1980). A stainless steel chamber was mounted stereotaxically on the skull, slanted laterally in the frontal plane at an angle of 25°, and aligned on the OPN region (stereotaxic position: 3 mm anterior). At the completion of the surgery, animals were returned to their home cages. Antibiotics cephalosporin (Cefazolin) and analgesics buprenorphine hydrochloride (Buprenex) were administered as needed during the recovery period under the direction of a veterinarian.

Animal training

The monkeys were seated in a primate chair with their heads restrained for the duration of the testing sessions. They were trained to execute behavioral tasks for liquid reward, and were allowed to work to satiation. Records of each animal's weight and health status were kept, and supplemental water was given as necessary. The animals typically worked for 5 days and were allowed free access to water on weekends.

Experimental set-up

Behavioral paradigms, visual displays, and data storage were under the control of a real-time program running on a laboratory PC system. The targets were presented via a computer-controlled analog oscilloscope, which back-projected light spots on a 90 × 90° translucent screen placed 40 cm in front of the monkey (Crandall and Keller 1985). The targets were 1 min arc in diameter and 2 cd/m^2 in intensity against a diffusely illuminated dim homogeneous background (0.05 cd/m^2). The eye-movement signals were obtained by placing the head-restrained animal with an implanted scleral coil in a pair of orthogonally aligned 20-kHz magnetic fields maintained electronically in temporal quadrature. The voltage induced in the coil was passed through a phase detector, which separated the eye position signal into horizontal and vertical components with a sensitivity of 0.25°, zero drift, and a bandwidth of 1 kHz (Robinson 1963). Horizontal and vertical eye-position measurements were sampled by a 12-bit data acquisition card (Data Translation, DT-2831) at 1 kHz and stored on a computer disk. Radial eye position and velocity were computed off-line by the Pythagorean theorem.

Neuronal recordings and microstimulation

Before each experiment, the recording chamber was opened and thoroughly cleaned under aseptic conditions. A double-eccentric micropositioning device with a single drilled hole, which allowed access for a microelectrode track at virtually any location within its 12 mm diam, was positioned in the chamber. A sharpened guide tube was placed in the hole and gently pushed through the dura. By means of a hydraulic drive system, a tungsten microelectrode (Frederick Haer; 0.5–1.5 M impedance, tested at 1 kHz) was lowered through the guide tube into the brain stem (identified by neural activity related to saccades as the monkey scanned the visual field). The microelectrode then was lowered to place its tip in the region where the characteristic activity of OPNs was found and the behavioral paradigm described in the following text was run during recording of a single unit.

Stimulation trains consisted of bipolar pulses (cathodal-anodal) with a duration of 0.2 ms for each phase. Stimulation frequency was 400 Hz, and train duration was 200 ms. Current intensity was usually varied between 5 and 40 μA. Stimulation was delivered by a constant current generator through tungsten microelectrodes (impedance, ~1 M; Frederic Haer). Stimulation trains could be triggered at different times with respect to behaviorally relevant events like fixation point onset and offset or target motion onset. Control and stimulation trials were randomly interleaved in one block containing 10 stimulation and 10 control trials for each pursuit direction tested.

Behavioral paradigms

Animals were trained to pursue a moving target spot back-projected on the tangent screen. Each trial was initiated by the appearance of a

target for 400 ms during which the monkeys had to saccade to that initial position. After the animal foveated the target, the fixation period lasted for 500 ms. During that period, animals had to maintain gaze within a square electronic window of 4 × 4° centered on the target. At the end of the fixation period, the fixation point was turned off and simultaneously a target appeared at an eccentric position. This eccentric target moved at constant velocity. To obtain pursuit trajectories without catch-up saccades, the amplitude of the initial step was varied (Rashbass 1961). The amplitude of the target step was usually 10% of the value of target velocity (e.g., a 4° target step in the direction opposite to that of future target motion before a 40°/s trial).

Animals were also trained to make saccades to stationary targets. At the end of the fixation period, the target stepped to an eccentric position and remained lit for 500 ms. During that period, animals had to orient their gaze to that new position. Saccade trials and smooth pursuit trials were collected in different blocks.

Eye-movement parameters

Eye velocity was obtained by digital differentiation of the eye-position signal. Eye velocity was low-pass filtered with a second-order digital filter (Butterworth, cutoff frequency: 25 Hz). Eye acceleration was obtained by digital differentiation of the eye velocity trace. The onset of the pursuit movement was determined by using an acceleration threshold (50°/s^2 in *monkeys FO* and *MA*, 20°/s^2 in *monkey BU* whose ocular acceleration was lower). The offset of pursuit was the time when eye velocity returned to the value observed at the time of pursuit initiation. Saccade onset was determined using an acceleration threshold fixed at 250°/s^2.

To compare saccade and pursuit dynamics, eye velocity was filtered with the same Butterworth filter but with a higher cutoff frequency (50 Hz). With the cutoff frequency of our digital filter set to 50 Hz, we could reliably detect the presence of saccades >0.2° within ongoing pursuit.

Measures of neuronal activity and statistical analyses

To transform a discrete spike train into a continuous function of time, each spike was convolved with a Gaussian function. The spike density function was then defined as the sum of the Gausssian functions (Richmond et al. 1987). The SD of each Gaussian was set to 10 ms for measures on single trial records and to 5 ms when several trials were averaged.

The significance of response modulation during smooth pursuit was determined by comparing the firing rate during a 100-ms fixation period with the firing rate during a smooth-pursuit period of the same duration. The firing rate during fixation was estimated in each trial by computing the average activity from the spike density record during a 100-ms fixation epoch starting 150 ms before pursuit onset. The firing rate during pursuit was estimated in each trial by computing the average activity from the spike density record during a 100-ms smooth pursuit epoch starting 50 ms after pursuit onset. Statistical comparisons were achieved with a paired Student's *t*-test. The test compared, on a trial-by-trial basis, the firing rate during the fixation epoch with the firing rate during the pursuit epoch. The significance level (α) for all comparisons reported in this paper was set to 0.05 unless stated otherwise. The mean and 95% confidence interval of the firing rate during fixation was also computed using the *t*-statistics.

To characterize neuronal activity during pursuit initiation, the average spike density function was computed from the spike density record of individual trials using a 1-ms time window. The average onset time of the smooth-pursuit-related activity in OPNs was defined as the time when the average spike density function exits the confidence interval of the fixation firing rate. Only trials that did not include a saccade during the first 150 ms of pursuit were included in this average. The idea behind this procedure was to avoid any possible confusion between pursuit- and saccade-related activity by eliminating trials with early saccades.

To establish the relationship between the duration of activity modulation and pursuit duration, a trial-by-trial approach had to be used because of the variability of movement durations. The total duration of the modulation of OPNs' activity during pursuit was determined using the confidence interval of the fixation firing rate. The duration of the pursuit-related activity was defined as the time elapsed during which the spike density function was out of the confidence interval of the fixation firing rate on a trial-by-trial basis. On a trial-by-trial basis, the determination of the onset of activity reduction was more variable than with the averaging procedure described in the preceding text because of the presence of early saccades (latency <150 ms). However, this variability in onset determination was negligible when compared with the total duration of the movement and did not interfere with the correlative approach.

Because it has been shown that there is a linear addition of saccades and smooth pursuit (de Brouwer et al. 2002), i.e., smooth pursuit does not stop during saccades, measuring the total duration of the eye displacement is justified. The duration of saccade-related pauses was included into the total duration, but their contribution to the total was comparatively small.

To quantify the correlation between OPNs firing rate and eye velocity, the spike density and eye velocity were measured and averaged over a 20-ms interval centered 100 ms after pursuit onset. This procedure allowed us to avoid taking an accidental measure of eye velocity during an early catch-up saccade.

The change in activity during smooth pursuit with respect to the activity during fixation will be expressed as a percentage using the formula: [(fixation activity – pursuit activity)/fixation activity]*100.

RESULTS

Forty-eight omnipause neurons were recorded in three alert monkeys trained to perform standard saccade and smooth-pursuit tasks. Neurons recorded were identified as OPNs if they fired at a steady rate during fixation periods and completely stopped or paused before and during saccades in all directions. Figure 1 shows the activity of a typical OPN during saccades in the four cardinal directions (*unit fo45*). Neuronal activity was aligned on saccade onset. This neuron showed the characteristic properties of OPNs: a steady firing rate when the eye was immobile and a complete cessation of activity or pause before and during saccades irrespective of their direction. This pattern of activity during saccades has been well documented before and will not be described in detail here. All units showing this activity pattern were further tested during smooth pursuit. As previously reported, OPNs were clustered together in a narrow region of the brain stem close to the midline. Inspection of histological sections of the brain stem of two monkeys revealed that electrodes tracks were confined to the region of the nucleus raphe interpositus (rip) that contains OPNs as described by Büttner-Ennever et al. (1988).

Activity during smooth pursuit

Figure 2 shows the activity of the same neuron before and during pursuit of a target moving at 40°/s to the left. During the fixation period preceding pursuit onset, the neuron fired at a sustained rate represented by the solid horizontal line superimposed on the spike density function. The horizontal line also represents the firing rate expected if OPNs were not modulated during pursuit. It can be seen that, after a transient increase in activity shortly following the appearance of the target in the

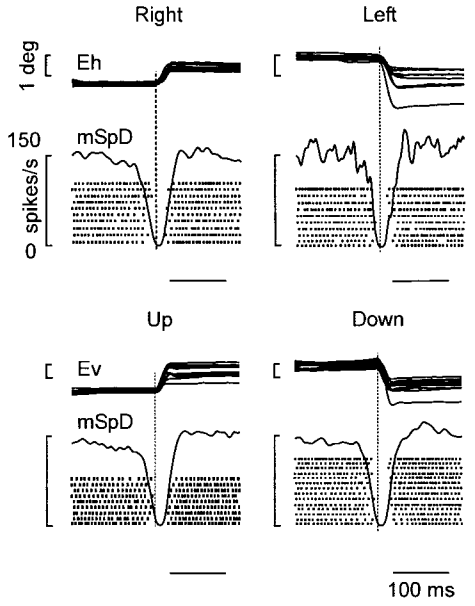

FIG. 1. Activity of a typical omnipause neuron (OPN) during saccades in the horizontal (*top*) and vertical (*bottom*) directions. The traces in each row show the position of the eye (Eh, horizontal eye position; Ev, vertical eye position), the mean spike density function (mSpD, using a Gaussian with σ = 5 ms), and the time of occurrence of each spike (rasters). All traces were aligned on the onset of the saccades (indicated by a vertical interrupted line). Note the typical firing pattern of this unit: a steady firing rate of ~150 spikes/s during fixation periods and a complete cessation of activity starting ~15 ms before saccades onset and ending ~5 ms before saccade end. After the saccade, the firing rate returns to its value during fixation. The small amplitudes of these saccades were selected to be similar to the amplitude of catch-up saccades occurring during pursuit (usually <5°). Calibration bars: 1° for eye position and 150 spikes/s for the spike density function. *Unit fo45.*

periphery (labeled vis in Fig. 2), the neuron showed a significant decrease in its firing rate. This decrease of neuronal activity coincided with the increase of eye velocity that characterizes smooth pursuit initiation. During "catch-up" saccades (labeled s_1, s_2, s_3 on Fig. 2), the typical complete cessation or pause of activity was observed. At the end of the pursuit movement, the spike density returned to its value observed during fixation. Figure 3*A* shows eye velocity, spike density, and the time of individual action potentials during pursuit initiation to the left for a set of 17 smooth movements aligned on pursuit onset (same unit, *fo45*). During these movements the earliest catch-up saccade occurred >150 ms after pursuit onset. A downward deflection of the eye-velocity traces represents an increase of eye velocity to the left. On average, the mean spike density function was reduced by 51% during pursuit initiation, from a firing rate during fixation of 135.2 ± 3.1 (SE) spikes/s (n = 17) to a firing rate of 66.5 ± 3.5 spikes/s (n = 17) after pursuit initiation. Among the 48 OPNs recorded, 23 units (48%) showed a significant reduction of activity during smooth pursuit when the activity during fixation (labeled fix on Fig. 3*A*) was compared with the activity during pursuit (labeled pur on Fig. 3*A*; paired *t*-test, $P < 0.05$). To allow comparisons between neurons, the target velocity most often used during recordings was 40°/s. Eighteen OPNs the discharge of which was modulated during pursuit were recorded in these conditions, and the other units were tested with different speeds (60 or 80°/s). The average firing rate of the 18 neurons during fixation was 154.3 ± 17 and 99 ± 10 spikes/s during pursuit. The reduction of activity was on average was 33.9 ± 4.0%. Activity never completely stopped or paused for the duration of the pursuit movement for any neuron on any trial. As shown on Fig. 3*B*, when neuronal activity was aligned on the appearance of the moving target, the peak discharge rate during the transient response increased to 207.7 spikes/s in comparison to the rate of 184.2 spikes/s shown in Fig. 3*A* where the activity was aligned on pursuit onset. This strongly suggests a visual origin of the transient response. An OPN was classified as visually responsive if the average spike density function exited the upper bound of the confidence interval of the fixation firing rate for ≥20 ms after the target step. Most of the units significantly modulated during pursuit responded transiently to the appearance of the visual target (16/23; 70%). The latency of the visual response in this group was 44.9 ± 0.9 ms. Units that were not significantly modulated during pursuit were less often visually responsive (7/25; 28%) and the latency of the visual response

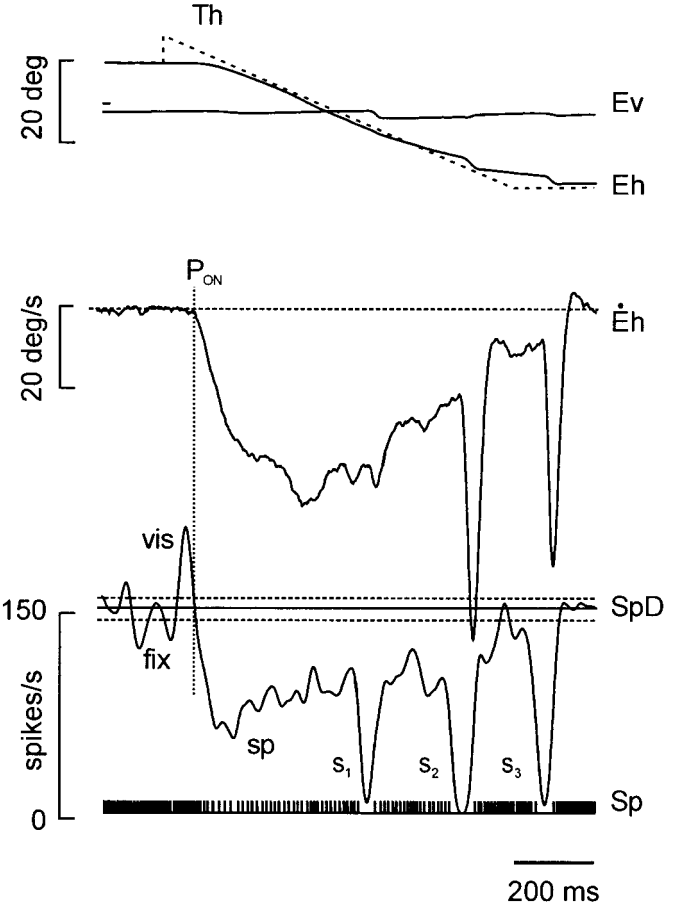

FIG. 2. Response of the same OPN as presented on Fig. 1 during smooth pursuit of a target moving at 40°/s to the left. From *top* to *bottom*: Th, horizontal target position; Ev and Eh; Ėh, horizontal eye velocity; SpD, spike density function (using a Gaussian with σ = 10 ms), and individual spikes, Sp. The vertical interrupted line marks the time of pursuit onset, labeled P_{ON}. As can be seen on the eye-velocity trace, after a latency period of ~80 ms, eye velocity smoothly increased in the direction of target motion. Catch-up saccades occurred toward the end of the trial. The spike density function shows the activity during a short fixation period preceding pursuit onset (labeled fix), during the transient activation related to the appearance of the target in the periphery (labeled vis), during smooth pursuit (labeled sp) and saccades (labeled s_1, s_2, s_3). The horizontal continuous line on top of the spike density function shows the average firing rate (spike density) during fixation and the two dashed lines show the limits of the 95% confidence interval of this estimate. Note that the onset of the eye movement coincides with the decrease in activity below the level observed during fixation. *Unit fo45.*

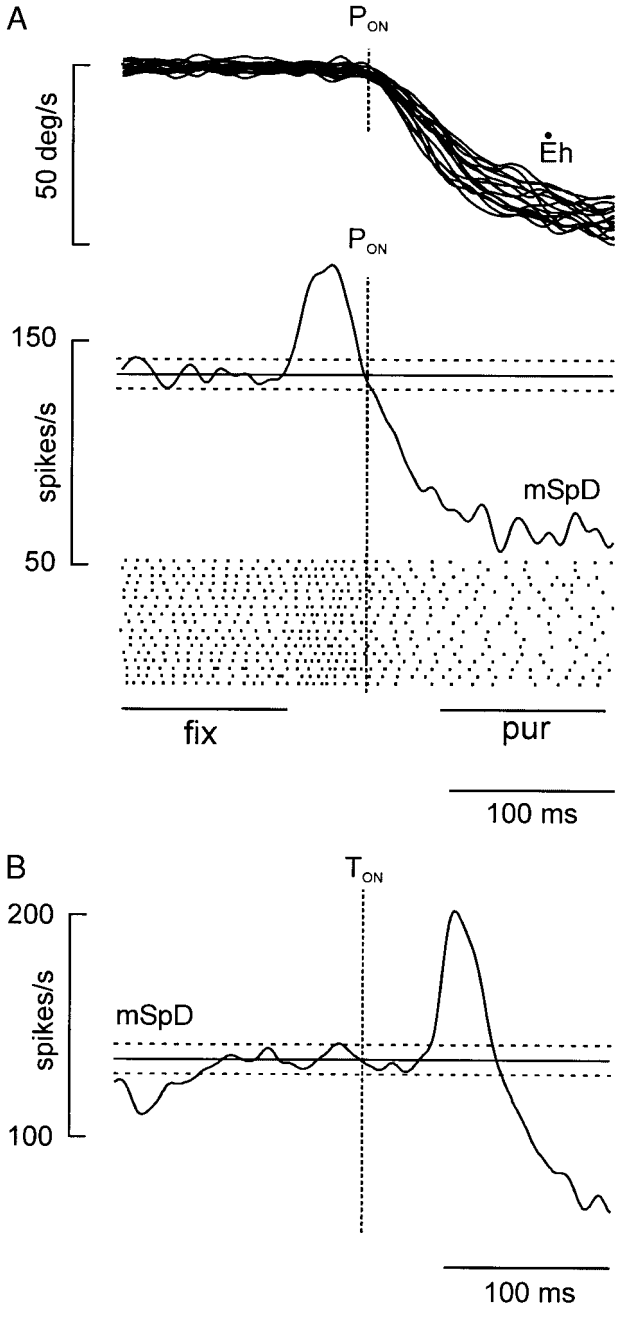

FIG. 3. *A*: eye velocity and mSpD during 17 pursuit trials aligned on pursuit onset (P_{ON}, vertical dashed line). Same neuron as on Figs. 1 and 2 (*unit fo45*). Each trial includes eye velocity and neuronal response from 150 ms before pursuit onset to 150 ms after pursuit onset. The 2 horizontal lines below the rasters indicate the 2 periods that were used to compute statistics and determine whether modulation during pursuit was significant. The 1st period starts 150 ms before pursuit onset and ends 50 ms before pursuit onset (labeled fix). The 2nd period starts 50 ms after pursuit onset and ends 150 ms after pursuit onset (labeled pur). Activity during fixation was estimated by averaging the spike density function during the fix period for each trial. Activity during pursuit initiation was estimated by averaging the spike density function during the pur period for each trial. Activity during fixation was compared with activity during pursuit on a trial-by-trial basis, using a paired *t*-test to establish the significance of the difference in activity. *B*: mSpD during the same 17 pursuit trials as presented in Fig. 3*A*, but this time aligned on the step of the target in the periphery when constant velocity target motion (T_{ON}, vertical dashed line) began.

was 44.1 ± 1.9 ms. Visual responsiveness was therefore more often associated with a significant activity reduction during smooth pursuit.

Statistically, OPNs could be grouped into two different categories: those that were modulated during pursuit and those that were not. To test whether there was a clear dichotomy in the population of neurons recorded, the percentage of activity reduction during smooth pursuit with respect to fixation was computed for all neurons recorded (see METHODS). A total of 36 neurons were recorded with a target velocity of 40°/s, the velocity most often used in this study. Figure 4 shows a distribution of the percentage of activity reduction in this group of neurons (▨) and when reduction reached statistical significance (■). The average activity reduction was 21.9 ± 2.9% ($n = 36$). The minimum activity reduction observed was 2.5%. This result suggests that all OPNs could potentially be modulated during smooth pursuit, but the intensity of the activity reduction varies over a continuum between units.

Onset of activity reduction

The example presented on Fig. 3*A* shows that the onset of the activity reduction in OPNs apparently occurred at the same time as the onset of the pursuit movement. In the saccadic domain, determining the time of the onset of the pause in activity is straightforward: it is the time of the last spike before saccade beginning. During pursuit, the situation is more complex because there is no abrupt pause of activity and eye velocity increases slowly. We made the assumption that the onset of the pursuit-related activity is the time when the spike density function deviates from its value during fixation. However, in half of the neurons recorded, the visual response occurred just before the hypothetical onset time. Therefore the onset of the pursuit-related activity decrease occurred during a transition period the boundaries of which have to be defined. To estimate the average time of the beginning of activity reduction with respect to pursuit onset, a method based on the confidence interval was used. To begin, all signals were aligned on pursuit onset. Then the firing rate during fixation (indicated by the solid horizontal line on Fig. 3*A*) and its confidence interval (indicated by the interrupted horizontal lines on Fig. 3*A*) were computed and compared with the mean spike density near the time of pursuit onset. Two epochs associated with the mean spike density function were measured: the time when the spike density function reenters the

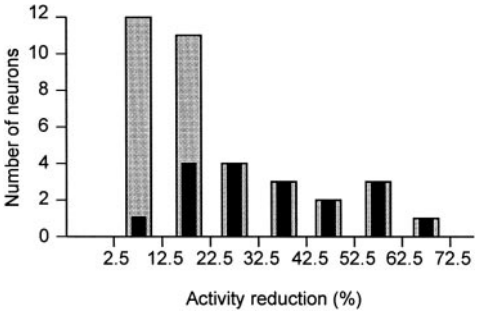

FIG. 4. Distribution of the percentage of activity reduction observed during smooth pursuit initiation with respect to the activity during fixation. ▨, the values of activity reduction for all neurons tested with a target moving at 40 deg/s ($n = 36$). ■, the number of neurons with a significant effect in each bin ($n = 18$).

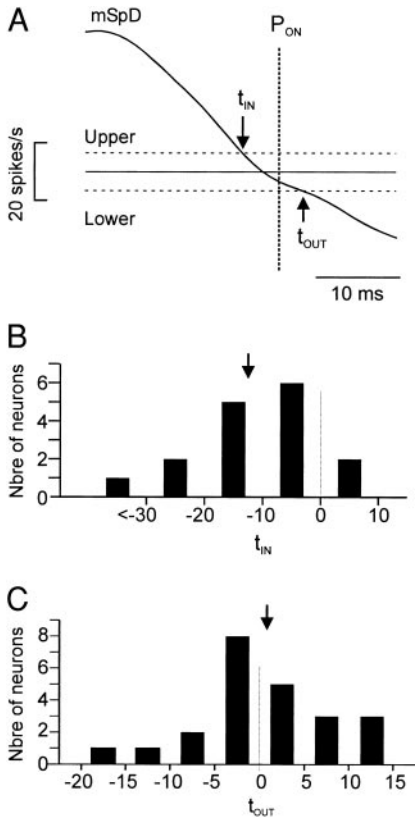

FIG. 5. Onset of activity reduction. *A*: mean spike density function around P_{ON}. Same data as in Fig. 3 but with different scales. The continuous line shows the average value of the spike density during fixation together with the upper and lower limits of the confidence interval (dashed lines, labeled upper and lower). Arrows indicate when the spike density function enters the confidence interval through the upper bound (t_{IN}) and when it exits the interval through the lower bound (t_{OUT}). *B*: distribution of t_{IN} for all neurons with a visual response ($n = 16$). The vertical arrow indicates the mean value of that variable. Negative values show that the spike density function entered the confidence interval before P_{ON}. *C*: distribution of t_{OUT} for all neurons ($n = 23$; significantly modulated units only). The vertical arrow indicates the mean value of that variable. Negative values show that the spike density function exited the confidence interval before pursuit onset.

confidence interval of the fixation activity after the visual response (referred to as t_{IN}) and the time when the spike density function exits the lower bound of the confidence interval near pursuit onset (referred to as t_{OUT}). In neurons that were not visually responsive, there was no event corresponding to t_{IN}. Figure 5*A* shows an example of these measurements on the same data as presented in Fig. 3*A* but with a magnified scale. At the end of the visual response, the spike density function reenters the confidence interval through its upper bound 4.3 ms before pursuit onset (t_{IN}). The spike density function exits the confidence interval through its lower bound 2.6 ms after pursuit onset (t_{OUT}). Therefore there is a transition period of 6.9 ms (4.3 + 2.6 ms) during which the firing rate changed from the firing rate at the end of the visual response to pursuit-related activity. The duration of this transition period depends on the size of the SD of the Gaussian function used to convolve the spike trains (in this case, 5 ms). Therefore the overall temporal accuracy of the methods used is estimated to be ~5 ms. Nevertheless, the time of the transition period between different firing modes of *unit fo45* always coincided with the time of the transition from fixation to pursuit initiation. Figure 5*B* shows the distribution of the time when the spike density function reenters the confidence interval after the visual response (t_{IN}) and Fig. 5*C* shows the distribution of the time when the spike density function exits the confidence interval near pursuit onset (t_{OUT}) for all neurons recorded. Negative values mean that these events preceded pursuit onset (*time 0*). The average value of t_{IN} was -12.1 ± 3.0 ms ($n = 16$) and that of t_{OUT} was 1.3 ± 1.6 ms ($n = 23$). The average value of t_{OUT} was not significantly different from zero or pursuit onset (*t*-test; $P = 0.43$; NS). It is concluded that activity reduction in OPNs most likely coincided with the onset of the smooth pursuit initiation.

Directional sensitivity

The firing rate of the neuron presented in Fig. 2 was significantly reduced during pursuit in all four cardinal directions. Figure 6 shows the average firing rate during fixation and during smooth pursuit for movements in the four directions tested. To allow a direct comparison, only pursuit movements at an approximately similar velocity during initiation were selected (between 29 and 37°/s, sample size varying between 7 and 19 observations). Activity reduction was significant during pursuit in all four directions (1-tailed paired *t*-test; $P < 0.001$ except for upward pursuit where $P = 0.011$) but was the largest during leftward pursuit (51% response reduction) and the smallest during upward pursuit (only 16%). This raises the possibility of a directional sensitivity of activity reduction during smooth pursuit. We tested this possibility in the horizontal and vertical directions only. Twenty-two units were tested during pursuit in both horizontal directions with the same target velocity. The firing rate of 12 of these units was significantly reduced during pursuit both to the left and to the right (12/22; 55%). The firing rate of the other ten OPNs

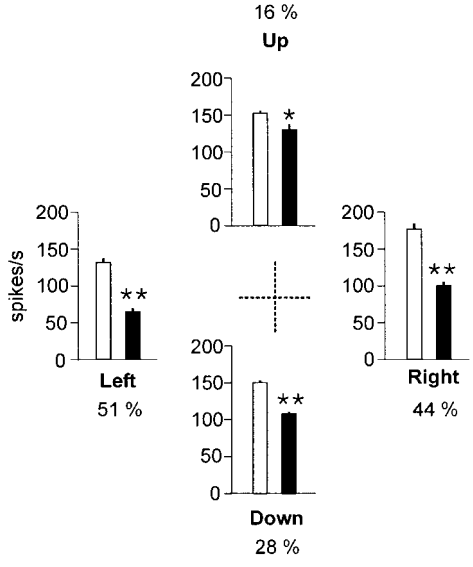

FIG. 6. Directional sensitivity. Schematic representation of the activity during fixation (□) and during smooth pursuit initiation (■) for movements in the 4 cardinal directions. The cross with interrupted lines represents the center of the screen, straight ahead of the monkey. Numbers show the percentage of activity reduction in the different directions. Sample sizes: up, $n = 7$; left, $n = 7$; down, $n = 19$; right, $n = 9$. These samples were selected so that eye velocity was always between 28 and 37°/s 100 ms after pursuit onset. One star symbol: $P < 0.05$; two stars: $P < 0.01$.

showed a directional preference for the decrease in activity during horizontal pursuit (10/22; 45%). Six of the 12 units that showed a significant response reduction during pursuit in both horizontal directions were also tested during vertical pursuit in both directions. Three units showed activity reduction during vertical pursuit among which one unit showed a significant activity reduction in both vertical directions. We conclude that OPNs probably show directional sensitivity for the activity reduction during pursuit. However, the saccade-related pause in activity was always omnidirectional. During pursuit, activity never increased in the direction opposite to the preferred direction of activity reduction. We were unable to determine with certainty the side of the brain stem on which individual OPNs were recorded due to their very close location to the midline (Büttner-Ennever et al. 1999).

Relationship with movement parameters

In the saccadic domain, a correlation between pause duration and movement duration has been found in OPNs (Luschei and Fuchs 1972). As shown in the example presented on Fig. 2, the activity of OPNs was also apparently reduced for the duration of the whole pursuit movement. Therefore we tried to quantify the relationship between pursuit duration and decreased activity duration. Because pursuit trials most of the time included a few catch-up saccades, the duration between pursuit onset and offset, including saccades, was measured on a trial-by-trial basis. The onset of activity reduction was the moment when the spike density function exited the confidence interval of the mean firing rate during fixation. The offset was the moment when the spike density function reentered the confidence interval. We found a linear relationship between pursuit duration and the duration of OPNs' reduced activity. This relationship is illustrated on Fig. 7*A* for movements of different durations obtained with different target velocities. The longest durations correspond to pursuit of a target moving at a velocity of 20°/s, intermediate durations to a target velocity of 40°/s and the shortest durations to a target velocity of 60°/s (*unit fo45;* total $n = 100$). The correlation coefficient was computed with the set of movements during pursuit of a target moving at 40°/s. For the unit shown on Fig. 7*A*, this coefficient was equal to 0.86 and was highly significant ($P < 0.01$, $n = 47$). Similar results were obtained in all OPNs that showed a significant activity reduction during pursuit and in which this relationship could be investigated ($n = 21$). The distribution of the correlation coefficient between pursuit duration and duration of activity reduction is shown on Fig. 7*C*, *left.* The correlation coefficient was high (usually >0.6) and significant in all but one unit.

Another important parameter that could influence the modulation of activity of OPNs during pursuit is eye velocity. Indeed, the purpose of the smooth-pursuit system is to move the eye at a velocity that approximately matches that of the stimulus to stabilize images on the retina. The examples presented strongly suggest that the firing rate of OPNs indeed covaried with eye velocity (see Fig. 2). Therefore neurons were tested during pursuit with several different target velocities (range: 5–100°/s). We also found a linear relationship between eye velocity and the spike density function. However, as shown on Fig. 7*B* (●), the correlation coefficient between eye velocity and spike density was usually lower (e.g., $r = -0.60$ for *unit fo45;* $n = 42$) compared with the relationship between durations and was sometimes not significant (in 4/11 neurons tested, see Fig. 7*C*, *right*). In *unit fo45*, the equation of the relationship between eye velocity during smooth pursuit (independent variable, *X*) and spike density (dependent variable, *Y*) was $Y = 140.4 - 1.9*X$. By extrapolation, it is possible to

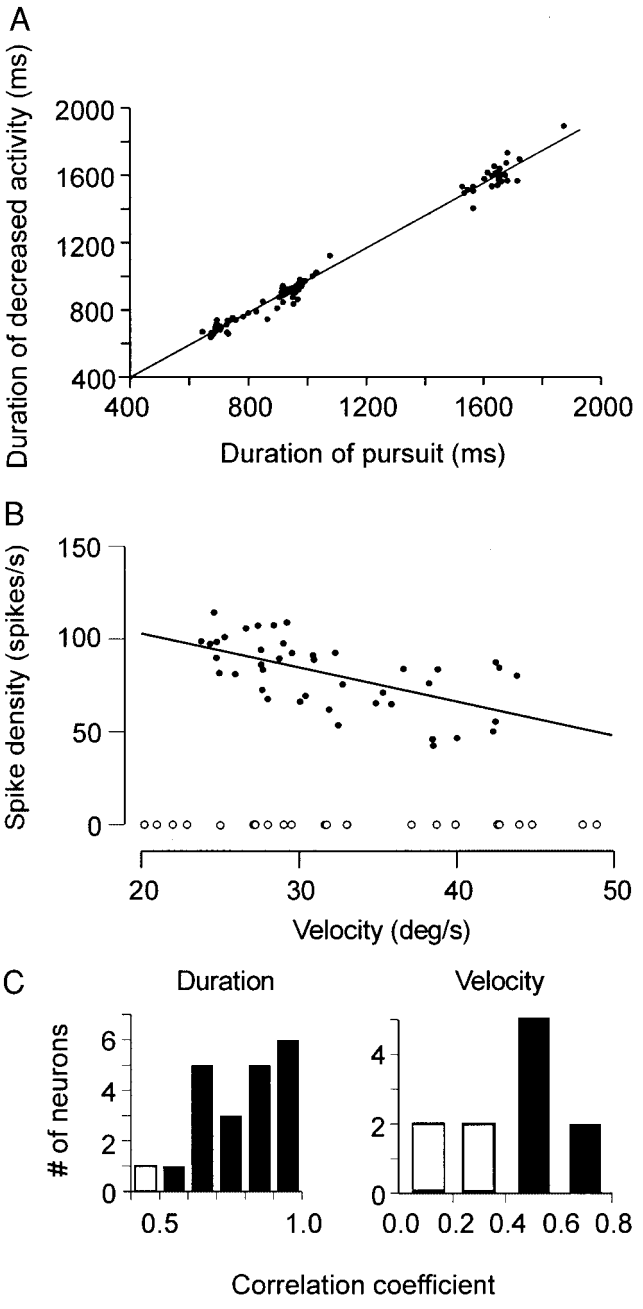

FIG. 7. *A*: relationship between duration of pursuit and duration of decreased activity of OPNs. Different pursuit durations were obtained by having the subject pursue a target moving from 20° left to 20° right of the fixation point at different velocities (20, 40, and 60°/s; $n = 100$). *Unit fo45. B*: relationship between eye velocity 100 ms after pursuit onset and spike density function (●). The subject was pursuing a target moving at 20 or 40°/s ($n = 42$). The maximum velocity of small saccades in the same range of eye velocity is indicated on the same *x* axis for comparison (○). *Unit fo45. C*: summary of the correlation between pursuit duration and spike density decrease (*left*) and eye velocity and spike density (*right*) for all neurons where these correlations could be computed. ■, correlations significant at $P < 0.01$. □, correlations that were not significant.

determine theoretically the firing rate if eye velocity were zero; that is, the intercept of the regression line with the *y* axis. In this example, the value of the *Y* intercept was 140.4 spikes/s, a value close to the firing rate during fixation obtained by averaging the spike density function, 135.2 ± 3.1 spikes/s ($n = 17$). The *Y* intercept was similarly computed for all units where a significant correlation between eye velocity and spike density was found ($n = 7$) and the average value was 181.6 ± 25.4 spikes/s. The average value of the fixation firing rate estimated from the spike density function directly (see METHODS) was 173.9 ± 11.9 spikes/s. These two values did not differ significantly (paired *t*-test; $P = 0.68$; $n = 7$). This result suggests that there was a smooth transition in firing rate between fixation and smooth pursuit.

We conclude that OPNs' firing rate during smooth pursuit is correlated with movement parameters. The correlation between pursuit duration and duration of reduced activity is reminiscent of the known correlation between saccade duration and pause duration.

Difference between the saccade-related pause and pursuit activity

Is there a qualitative difference between the saccade- and pursuit-related activities of OPNs? Indeed, it could be suggested that the saccadic pause results from the high velocity often achieved during saccades. A higher saccadic velocity could lead to a stronger response reduction until a complete pause of activity eventually occurs. There could be a continuous transition between pursuit modulation and saccadic pause. To answer to this question, we first determined the *X* intercept of the velocity-spike density function (Fig. 7*B*). The *X* intercept is the theoretical eye velocity that could induce a complete suppression of activity during smooth pursuit (null ordinate). For the example presented on Fig. 7*B*, the *X* intercept is 73.9°/s. The average value of the *X* intercept in neurons with a significant correlation in the velocity/spike density relationship is 101.2 ± 14.4°/s ($n = 7$). This suggests that a complete activity reduction or pause should be observed during pursuit at ~74°/s in *unit fo45* and ~100°/s on average. Such a high pursuit velocity was very infrequently observed in the animals used for this study. Figure 8 shows an example where smooth pursuit exceptionally peaked at 77°/s. During the high-speed smooth-pursuit period, a pause in firing rate was not observed. A pause in firing rate occurred only during the catch-up saccades. Another way to test the hypothesis that the smooth pursuit activity reduction is qualitatively different from the saccadic pause would be to compare very small saccades with very fast pursuit. It is well known that primates sometimes make very small saccades during fixation, whose amplitude is typically <1°. Therefore very small saccades were selected (amplitude >0.2 but <1.2°). Such small saccades were observed in two monkeys during recording of 12 OPNs (12/23). The occurrence of small saccades was infrequent, sometimes only a few occurrences ($n \sim 5$) being observed during recording of a neuron. However, in two units (*fo44* and *fo45*), >20 small saccades were observed, allowing a direct saccade/pursuit comparison. The example presented on Fig. 8 shows a very small saccade (labeled s_4, amplitude 0.7°) whose maximum velocity (42°/s) was smaller than the maximum velocity of the pursuit movement (77°/s). That saccade was accompanied by a

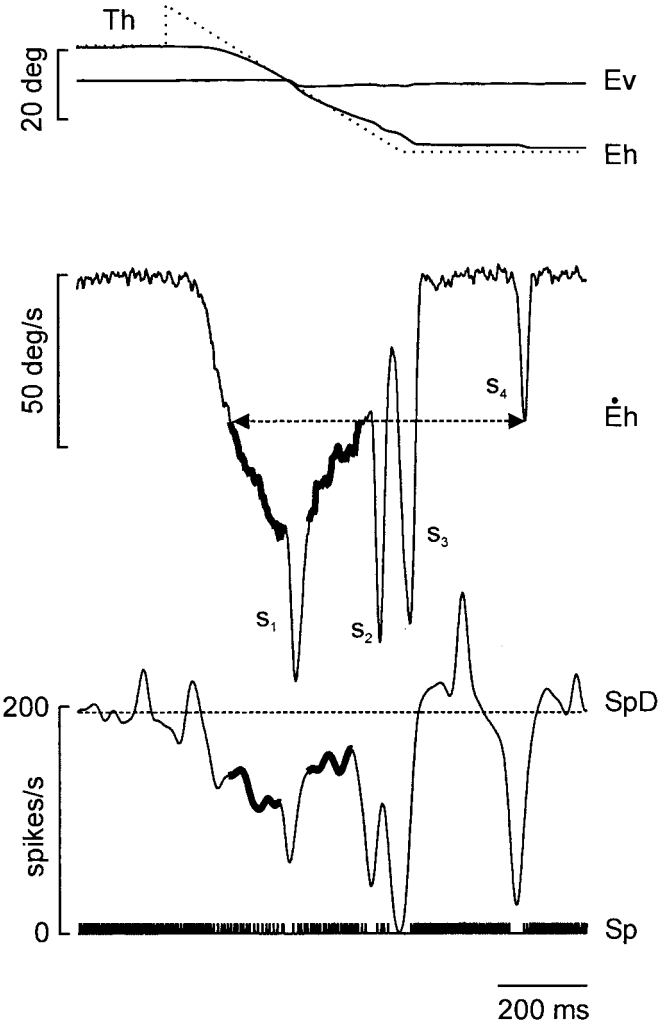

FIG. 8. Response of the same OPN as presented on Fig. 2 during smooth pursuit of a target moving at 80°/s to the left. From *top* to *bottom*: Th, Ev and Eh, Ė, SpD (using a Gaussian with $\sigma = 10$ ms), and Sp. Eye velocity reached 77°/s during smooth pursuit. The eye velocity and spike density traces are thicker during the high-speed pursuit epochs. Catch-up saccades (labeled s_1, s_2, s_3) occur toward the end of the trial and a small fixation saccade occurred after pursuit offset (labeled s_4). The horizontal double headed arrow shows the level of the saccadic maximum velocity for s_4 on the smooth pursuit trace. The horizontal dashed line on top of the spike density function shows the average firing rate (spike density) during fixation in this particular trial. *Unit fo45*.

complete pause in activity. This small saccade was aimed at the visual target and had only a horizontal component (the vertical component was <0.2°, below detection with the system we used). During smooth pursuit at a velocity larger than the maximum velocity of saccade s_4, indicated by thicker eye velocity and spike density traces on Fig. 8, this OPN did not stop firing or pause. Figure 7*B* shows a representation of the qualitative difference between smooth-pursuit modulation and saccadic pause. In Fig. 7*B*, the maximum velocity of all small fixation saccades that occurred during the recording of *unit fo45* was plotted with the same *x* axis as smooth pursuit velocities (○, saccades vs. ●, pursuit). The plot shows that even very small saccades, with maximum velocities clearly in range of smooth-pursuit eye movements, were always accompanied by a complete pause of activity (null ordinate) although a pause was not observed during pursuit at a similar velocity.

For comparison between pursuit and saccades, eye velocity

was always filtered with a cutoff frequency set at 50 Hz (see METHODS). Increasing the cutoff frequency to 75 Hz did not change the maximum velocity by >10%. For the small saccades measured, there was a linear relationship between horizontal amplitude and maximum horizontal velocity, similar to the well known main sequence ($Y = 3.6 + 47.7*X$; $r = 0.96$; $P < 0.0001$; $n = 25$). Because these saccades were not accompanied by any detectable vertical eye deviation, it is suggested that they were not caused by eye blinks.

These results suggest that the mechanism leading to a pause in activity during saccades is not the same as the mechanism inducing response reduction during pursuit. The complete cessation of activity during saccades can probably not be simply attributed to higher eye velocities during these movements compared with lower velocities during smooth pursuit. Furthermore they show that activity reduction during smooth pursuit is not caused by small saccades that could hypothetically occur during pursuit but would remain undetected. Indeed these saccades would always be accompanied by a clear pause in activity.

Activity reduction in the absence of saccade

During saccades and pursuit, OPNs showed a decreased activity the intensity of which was qualitatively different. However, to establish that OPNs are part of the smooth pursuit pathway, it was necessary to show that their activity was reduced even in the complete absence of saccades. Indeed, the decreased activity of OPNs during pursuit might be an early signal related to the preparation of catch-up saccades. Therefore activity reduction might have no direct relationship with pursuit per se. We tried to eliminate the need for a catch-up saccade by reducing the retinal position error during the pursuit movement. This experiment was based on the assumption that if a saccade is not needed to reach the target, it will not be prepared. Saccade-free trajectories were obtained by altering the eccentricity of the target step before the initiation of the smooth movement. In these conditions, the trajectory of the target crosses the trajectory of the eye at the time of smooth pursuit initiation and a saccade is not triggered. In eight neurons, it was possible to reduce the frequency of catch-up saccades to <50% of the trials and even to <20% in four of these neurons. In these four neurons, we succeeded in eliminating catch-up saccades in sequences of ≤12 consecutive trials. We found that the activity reduction during saccade-free pursuit trials was also significant in all eight neurons (paired *t*-test; $P < 0.01$). Moreover, a direct comparison of the level of activity during saccade-free pursuit trials with the level of activity during trials with saccades yielded no significant difference. An example of activity reduction in the absence of saccades is presented on Fig. 9. The activity of this neuron was strongly reduced, in spite of the complete absence of saccades in the sample presented. We conclude that the reduced activity of OPNs during pursuit was probably not due to the preparation of a catch-up saccade as it was still present in conditions when this movement was not occurring during sequences of several trials.

Electrical stimulation

At seven recording sites, electrical stimulation was delivered during pursuit to assess whether OPNs could contribute to an inhibitory control of pursuit eye movements. At five sites (5/7), no eye-movement drifts were detected when stimulation was applied during a fixation period (Keller 1974). This preliminary test was extremely important. Indeed, a modulation of smooth pursuit velocity could be caused by the combination of an electrically evoked smooth movement with the ongoing visually guided pursuit. Therefore any sites where stimulation caused an eye movement were not further tested. This situation occurred two times because of current spread to the neighboring reticular formation. Only five stimulation sites were selected for further study. An example of the effect of stimulation is presented on Fig. 10. Figure 10 shows the mean eye velocity and the confidence interval of the mean during pursuit of a target moving at 40°/s in the control condition (fine continuous trace) and when stimulation was applied (thick continuous trace). Direction of pursuit was leftward (*top*) or rightward (*bottom*). Electrical stimulation caused a strong deceleration of the pursuit movement in both directions, although the effect of stimulation was the strongest to the left. In that direction, eye velocity was 43.4 ± 1.5°/s ($n = 10$) in the control condition and 22.5 ± 1.7°/s ($n = 9$) during stimulation (measured at the time indicated by a star in Fig. 10). Reduction in eye velocity amounted to 48%. This difference was significant (*t*-test; $P < 0.0001$). To the right, eye velocity in controls was 37.2 ± 1.0°/s ($n = 8$) and 26.9 ± 2.3°/s ($n = 9$) during stimulation. Eye velocity decreased by 28% due to stimulation (*t*-test; $P < 0.0001$). To the left, the direction with the strongest stimulation effect, the eye velocity in stimulation trials started to deviate from the average eye velocity in controls 24 ms after stimulation onset and exited the confidence interval of controls 33 ms after stimulation onset. The latency of the stimulation effect probably lies between these two values. Because inhibition occurred during pursuit in both horizontal directions, it cannot

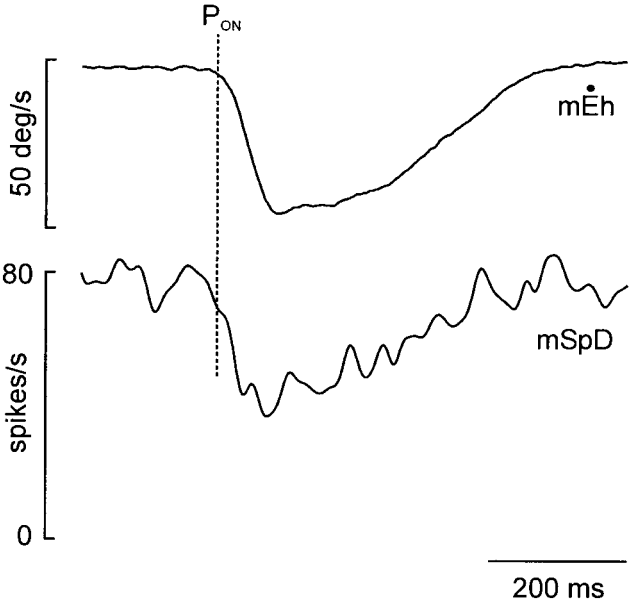

FIG. 9. Example of mean eye velocity (mĖh) and mean spike density (mSpD) during pursuit in the absence of catch-up saccades. Responses were collected from 14 saccade-free pursuit trials preceded and followed by ≥100 ms of fixation. Alignment on pursuit onset (vertical interrupted line). Note the similarity between the shape of the velocity profile and the shape of the spike density function. This neuron (*unit fo10*) did not show a visual response before pursuit onset.

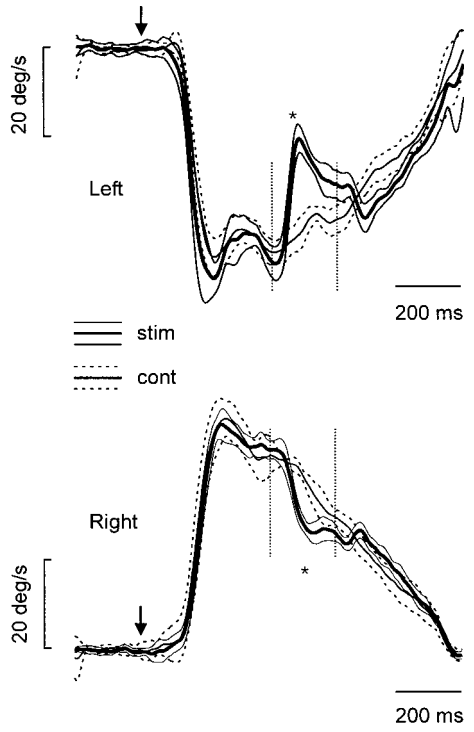

FIG. 10. Influence of electrical microstimulation in the region of OPNs on smooth pursuit velocity. *Top*: pursuit to the left ($n = 9$ for controls and stimulation trials); *bottom*: pursuit to the right ($n = 8$ for controls and $n = 9$ for stimulation trials). Thick continuous lines: mean eye velocity during stimulation trials; thin lines: limits of the 95% confidence interval of the mean. Thin continuous lines: mean of stimulation trials; thin interrupted lines: limits of the confidence interval. Vertical dotted lines indicate the onset and offset of the stimulation train (200 ms, 400 Hz, 15 μA). The vertical arrow indicates the onset of target motion (40°/s).

be explained by the addition of an electrically evoked smooth eye movement that would increase eye velocity in one direction and decrease it during pursuit in the opposite direction. At all sites tested ($n = 5$), electrical stimulation in the OPNs area induced a strong, statistically significant deceleration of eye motion during smooth pursuit (Student's *t*-test; $P < 0.01$, except in 1 case where $P = 0.0139$). Average eye velocity reduction amounted to 29.7%. The latter results support the hypothesis that OPNs exert an inhibitory influence on premotor neurons for pursuit as well as saccades but again emphasize the qualitative difference in this influence. Pulsatile electrical stimulation in the region of OPNs during saccades completely stops these movements in mid-flight (Keller et al. 1996), whereas such stimulation, as shown here, delivered during pursuit merely slows the movement. At one stimulation site where pursuit velocity was reduced during electrical stimulation, we performed the control and showed that saccades to stationary targets were interrupted in mid-flight with the same current intensity that reduced pursuit velocity.

DISCUSSION

The present experiments show clearly that the activity of OPNs decrease during smooth pursuit. This activity reduction reached statistical significance in ~50% of OPNs recorded. The onset of activity reduction coincided with pursuit onset. Activity reduction was proportional to eye velocity and its duration was correlated with pursuit duration. Activity reduction occurred also in the absence of catch-up saccades. Electrical stimulation in the region of OPNs induced a reduction of smooth pursuit velocity. To our knowledge, this study is the first report of activity modulation of OPNs during smooth pursuit eye movements.

Functional hypotheses

There are several possible functional interpretations of the role played by the modulation of OPN activity during pursuit movements. Three separate hypotheses are discussed in the following text.

SACCADE PROBABILITY. The saccade probability hypothesis suggests that the modulation of OPNs' activity during pursuit is not directly related to the control of smooth eye movements but instead to the preparation of catch-up saccades during pursuit. Although this hypothesis is not compatible with the presence of a strong modulation of activity in the absence of catch-up saccades, it can be argued that activity modulation reflects the probability to make a saccade, even if never executed. We cannot completely rule out this interpretation as we did not manipulate the probability of saccade occurrence directly. However, such hypothetical activity modulation related to the probability to make a saccade was not found before saccades toward stationary targets when the same OPNs that were modulated during pursuit were recorded in both conditions. Before a saccade to a stationary target, the probability to make a saccade was the highest. Therefore if the modulation of activity of OPNs during pursuit was related to the probability to make a saccade, we have to postulate that this mechanism is not active before saccades to stationary targets. This makes the saccade probability hypothesis not very parsimonious. The saccade probability interpretation also implies that the slowing of smooth pursuit by stimulation in the OPNs' area does not result from a direct effect on premotor pursuit neurons but instead is a result of current spread to other regions that are involved in pursuit control. Current spread to pontine reticular formation area near the OPN region would cause slow, laterally directed eye movements (Keller 1974) that we did not observe in the present experiments.

GATE HYPOTHESIS. The gate hypothesis suggests that in the presence of strong OPNs discharge, pursuit eye movements are totally inhibited. This hypothesis relies on the idea that the final pathway for pursuit could be organized like the final pathway for saccades, although details of that organization are different. It is well accepted that during attentive fixation, saccades are directly suppressed by the inhibitory activity of OPNs (Keller 1991). This tonic inhibition is necessary to keep burst neurons from firing and producing unwanted movements. A saccade can occur only when the inhibition of OPNs is released, hence the idea that OPNs form a gate for saccades. Similarly, it could be suggested that smooth eye movements occur only when the activity of OPNs decreases below a certain fixed threshold. In this hypothesis, the function of OPNs would be related to the process of suppressing all eye movements, saccades, and smooth pursuit during attentive fixation periods, but then releasing them totally at some fixed lower level of OPN activity. In disagreement with the gate hypothesis, it should be noted that we found a graduated level of decrease in OPN activity that was correlated with pursuit metrics (duration and velo-

city). In addition, electrical stimulation of the OPNs did not totally interrupt smooth pursuit, even when electrical stimulation lasted 200 ms (see Fig. 10). Instead stimulation resulted in a transient decrease of smooth eye velocity. Moreover, the fact that activity reduction in OPNs is gradual and related to eye velocity is not compatible with a simple gate or "ON-OFF" mechanism.

GAIN CONTROL HYPOTHESIS. It has been suggested that the gain of visuomotor pathway for pursuit varies from low during fixation to high during pursuit (Goldreich et al. 1992; Krauzlis and Lisberger 1994; Krauzlis and Miles 1996; Schwartz and Lisberger 1994). This hypothesis is based on the observation that a brief perturbation of target motion introduced during fixation has a weak effect on eye velocity, whereas its effect is larger during pursuit. Therefore the response of the pursuit system to a given motion stimulus varies from low during fixation to high during pursuit. This transition can be modeled by a variable gain mechanism. Such a hypothetical gain control mechanism could be implemented by a modulation of the activity of OPNs if these neurons project to the neurons driving the eye during smooth pursuit. During fixation periods, OPNs would almost completely inhibit premotor pursuit neurons, whereas this inhibition would be released during pursuit. This hypothesis suggests that the gain element is not only affecting visual signals (Schwartz and Lisberger 1994), but also the eye velocity command for pursuit as well (Krauzlis and Miles 1996; Tanaka and Lisberger 2001, 2002). In agreement with the gain control hypothesis, the decrease in OPNs' firing rate was correlated with eye velocity and electrical stimulation of the OPNs resulted in a decrease of smooth pursuit velocity.

An inhibitory gain control mechanism might be necessary because in a complex visual scene many different objects are moving at the same time. Therefore a selection process must first determine which target is going to be pursued. To avoid an inappropriate reflex-like smooth movement induced by multiple motion signals, premotor neurons for pursuit could be under the inhibitory control of OPNs. The appropriate movement would be allowed to occur only after the release of their inhibition by the fixation system. This hypothesis is supported by the temporal synchronization of the onset of activity reduction and the onset of pursuit and the correlation between decreased activity duration and pursuit. In experimental conditions that mimic this situation, when a monkey encounters a situation in which two targets start to move simultaneously in different directions, the animal initiates low-velocity pursuit in a direction that is the vector average of the two movements, but high-speed pursuit does not occur until a saccade to one of the targets is made indicating that a target selection process has occurred (Gardner and Lisberger 2001). It would be interesting to determine if the discharge of OPNs were not modulated downward until the onset of the higher-velocity pursuit in this paradigm.

Mechanism explaining different activities during saccades and smooth pursuit

We favor the gain control hypothesis as an explanation for our results, but it remains to be explained how OPNs could have a different activity pattern during saccades and smooth pursuit. In a critical experiment, Yoshida and coworkers (1999) recorded intracellularly from OPNs in the cat during saccades. These authors showed that the pause of OPNs during saccades is due to a hyperpolarization of their membrane potential for the duration of the movement. This hyperpolarization was caused by inhibitory postsynaptic potentials (IPSPs). The time course of the hyperpolarization of OPNs is similar and correlated with eye velocity except for an initial steep hyperpolarization peaking ~20 ms after saccade onset. This initial intense hyperpolarization leads saccade onset by ~16 ms. Therefore the total inhibition of OPNs during saccades could be initiated by an intense and transient hyperpolarization followed by a lower level sustained hyperpolarization maintained for the duration of saccade. The initial inhibition could originate from local inhibitory neurons that receive inputs from central structures like the SC, and the eye velocity-related sustained inhibition could originate from the burst generator in the brain stem (Kamogawa et al. 1996). These intracellular results strongly support the so-called "trigger" and "latch" hypothesis, first proposed by Van Gisbergen et al. (1981) to explain the firing behavior of OPNs. We hypothesize that the initial steep hyperpolarization of the membrane potential of OPNs that leads saccade onset does not occur during pursuit (no trigger signal), resulting in the absence of a complete pause in firing rate. However, the more sustained inhibition of their activity lasting for the duration of the movement and related to eye velocity would still be present (latch), resulting in a closer approximation in time for the activity reduction with respect to movement onset. The latch mechanism alone does not drive the activity of OPNs to complete silence, but is strong enough to modulate their firing rate downward. Unfortunately, the use of the term, latch, implies, as does "gate," an all-or-nothing action. Clearly during pursuit responses, this mechanism instead is eye-velocity sensitive. Because OPNs are directionally sensitive during pursuit, it is suggested that the inhibitory inputs from the putative latch mechanism is also directional. What determines the inhibitory influence of OPNs during pursuit is the result of the activity of the whole population of neurons.

Possible role of the SC

It is likely that the SC, an important subcortical structure involved in saccade preparation, is involved in producing the pause in firing rate observed during saccades. Indeed, the SC is the origin of a major input to OPNs. Collicular inputs to OPNs come more heavily from the rostral part of that structure (Büttner-Ennever et al. 1999; Gandhi and Keller 1997; Munoz and Guitton 1991; Munoz and Wurtz 1993; Paré and Guitton 1994). Recently, it has been shown that the activity of neurons in the rostral SC is also modulated by small mismatches between the position of the visual axis and the position of the target, a signal called motor error. This activity modulation is present before and during both small saccades and smooth pursuit (Krauzlis et al. 1997, 2000), and might play a role in controlling the firing rate of OPNs during both kinds of eye movements. However, because the direct input of the SC onto OPNs is excitatory (Raybourn and Keller 1977; Yoshida et al. 2001) and the modulation observed in rostral SC was either an increase (for contralaterally directed pursuit) or a decrease (for ipsilaterally directed pursuit), it is difficult to predict what net effect the population of rostral SC neurons would have on OPNs during pursuit. However, electrical stimulation of the rostral SC can induce a decrease of smooth-pursuit velocity

(Basso et al. 2000) similar in its time course to what is described on Fig. 10 of this study. We found that motor error is a poor predictor of the reduced firing rate of OPNs during pursuit. Indeed, motor error should be the largest just after the target step in the periphery and then progressively decreases as the eye reaches the target. In OPNs, the target step increased the firing rate of most units recorded. The decrease in firing rate coincided with the increase in eye velocity. Moreover, large motor errors coincide with lower pursuit gain, i.e., lower eye velocity. Activity modulation was less when eye velocity was lower. Finally, the hypothesis of motor error coding was directly investigated by stabilizing the target on the retina during pursuit during recording of one OPN (result not shown). This introduces a constant motor error that cannot be reduced by an eye movement. The firing rate of the neuron tested decreased for the duration of the pursuit movement, and was apparently not affected by the step in positional error introduced. We conclude that activity modulation in OPNs does not simply reflect the activity of rostral build-up neurons in the SC during pursuit. This suggests that OPNs receive additional inputs from other smooth pursuit related areas that override the collicular influence.

Conclusions

Another input on OPNs comes from the vergence subsystem. Indeed the activity of OPNs is also modulated during vergence eye movements (Busettini and Mays 1999). Vergence eye movements occur when the fixation point changes between targets at different depths. In fact, gaze orientation most often requires a combination of both conjugate (saccades and smooth pursuit) and disconjugate (vergence) eye movements. The activity of OPNs is modulated during all these eye movements. Therefore OPNs could have an inhibitory function across several oculomotor subsystems, although the details and the result of their activity modulations vary between subsystems.

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