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Eye Position Effects in Monkey Cortex. II. Pursuit- and Fixation-Related Activity in Posterior Parietal Areas LIP and 7A

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Bremmer, F., C. Distler, and K.-P. Hoffmann. Eye position effects in monkey cortex. II. Pursuit- and fixation-related activity in posterior parietal areas LIP and 7A. *J. Neurophysiol.* 77: 962–977, 1997. We studied the effect of eye position on pursuit-related discharges and activity during fixation in darkness for neurons of monkey visual cortical areas (lateral intraparietal area) LIP and 7A. In a first step, neurons were tested for direction-specific activity related to pursuit eye movements while the monkey tracked a moving target. In consecutive trials the pursuit target moved in random order in one of four directions on a translucent screen. For 39% of the neurons, located mostly in a dorsoposterior region of area LIP, as well as 42% of the neurons tested in area 7A, a direction-specific pursuit-related activity could be found. To test whether responsiveness of these neurons was modulated by eye position, we employed a pursuit paradigm. In this paradigm, the monkey had to track a target that started to move in the preferred direction with constant speed from five different locations on the screen in random order. For the majority of cells in both areas, pursuit-related activity was modulated by eye position. Most of the neurons tested also revealed an influence of eye position on their spontaneous activity during fixation in darkness (fixation paradigm). For the majority of cells (>50%) recorded in both areas, two-dimensional regression planes could be approximated significantly ($P < 0.05$) or nearly significantly ($P < 0.1$) to the neuronal discharges observed on the fixation paradigm and pursuit paradigm. For 79% of the LIP neurons and 83% of the 7A neurons tested in both experimental paradigms, the directions of the gradients of the regression planes pointed into the same hemifield, suggesting a common neuronal mechanism mediating the eye position effect regardless of the behavioral task the monkey was performing. The observed effects very much resemble the effects of eye position on light-sensitive and saccade-related responses already described for areas LIP and 7A. Regarding also our results observed for the middle temporal and medial superior temporal areas, it is suggested that the observed modulatory effect of eye position on neuronal activity is a common phenomenon in the macaque visual cortical system subserving an internal representation of the external space in a nonretinocentric frame of reference.

INTRODUCTION

Pursuit-related activity is a well known and described phenomenon for the monkey middle temporal area (area MT) and medial superior temporal area (area MST) in the superior temporal sulcus (Komatsu and Wurtz 1988a,b). A direction-specific increase of neuronal discharge related to smooth tracking eye movements also has been described by Sakata et al. (1983) for area 7A and by Colby et al. (1993) for the ventral intraparietal area (area VIP), which is located in the fundus of the intraparietal sulcus. Areas MT, MST, LIP (lateral intraparietal area), VIP, and 7A are considered as constituents of the dorsal visual processing stream of the macaque brain. According to Felleman and van Essen (1991), area LIP receives a feed-forward input from hierarchically lower area MT. Areas LIP, VIP, and MST are considered as being hierarchically at the same level. All three areas themselves send a feed-forward input to the hierarchically highest area within the dorsal stream of the visual cortical system: area 7A. Area LIP is located in the lateral bank of the intraparietal sulcus and without exception surrounded by visual cortical areas that are shown to contain neurons whose discharge can be related to pursuit eye movements (Andersen et al. 1990a; Boussaoud et al. 1990; Neal et al. 1988a,b; Pandya and Seltzer 1982; Ungerleider and Desimone 1986b; van Essen et al. 1981). Area LIP is reciprocally connected with these areas. Furthermore, it is interconnected with the frontal eye field (Felleman and van Essen 1991; Leichnetz 1980; Neal et al. 1990), for which pursuit-related activity has also been shown in recent studies (Gottlieb et al. 1994; Keating 1993; MacAvoy et al. 1991). Finally, area LIP projects directly to pontine nuclei involved in the control of smooth pursuit eye movements (Blatt et al. 1990; May and Andersen 1986). Area LIP thus is closely involved in a cortical and subcortical network subserving the representation and control of smooth tracking eye movements. Nevertheless, pursuit-related activity has not yet been shown for area LIP.

Modulation of activity of neurons in areas 7A and LIP by different eye positions during active fixation in darkness has been described qualitatively by several studies (Andersen and Mountcastle 1983; Andersen et al. 1990b; Sakata et al. 1980). However, in none of these studies was this pure influence of eye position related quantitatively to other observed influences of eye position during visual stimulation or during oculomotor tasks, such as visually guided or memory guided saccades.

The present experiments were thus designed to study two major questions. In a first step, we investigated whether LIP neurons show direction-specific pursuit-related activity and whether, if present, it is modulated by eye position. Indeed, ~39% of the neurons tested in a mostly dorsoposterior part of area LIP exhibited a direction-specific pursuit-related activity. In area 7A, 42% of the investigated neurons revealed an increase of their discharge frequency during tracking eye movements. For most of the neurons investigated in both areas, pursuit-related activity was modulated by eye position. Discharges as a function of horizontal and vertical eye position could be approximated by two-dimensional regression planes.

In a second step, neurons in both areas were tested for an influence of eye position during fixation of a small spot of

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light in darkness. The majority of neurons tested in areas LIP (62%) and 7A (70%) revealed such a modulation. This finding is in accordance with qualitative results from previous studies. Two-dimensional regression planes could be fit to most of the recorded data. As in areas MT and MST, for the majority of the LIP and 7A neurons tested in the pursuit and the fixation paradigm the gradients of the computed regression planes for both paradigms were directed into the same hemifield. This finding again suggests that the modulatory effect operates in the same spatial direction during both fixation and smooth tracking eye movements.

At the population level the influence of the position of the eyes in the orbit on neuronal discharges proved to be balanced out. This finding holds true for neurons from area LIP and area 7A, and for neurons tested in the fixation paradigm as well as in the pursuit paradigm. Preliminary results have already been published (Bremmer and Hoffmann 1993, 1995).

METHODS

Single-cell recordings were made from a total of two hemispheres of two awake male monkeys (*Macaca mulatta,* 7.5 and 11.8 kg) performing fixation and pursuit tasks. All procedures were in accordance with published guidelines on the use of animals in research (European Communities Council Directive 86/609/EEC).

Surgery

Monkeys were surgically prepared for experiments by use of the same procedures described in detail in the preceding paper. Briefly, under general anesthesia and sterile surgical conditions each animal was implanted with a device for holding the head. A recording chamber for microelectrode penetrations through the intact dura was placed flat to the skull centered on AP−5, ML12. This nonstereotaxic approach allowed long electrode penetrations parallel to the intraparietal sulcus. Finally, scleral search coils for monitoring eye position were implanted.

Behavioral paradigm

As for the experiments in areas MT and MST, the monkeys were trained to perform pursuit or fixation tasks for liquid reward. Testing cells for pursuit-related discharge was accomplished as described in detail in the preceding paper (Bremmer et al. 1997). Briefly, for determining an eventually existing preferred pursuit direction a conventional step ramp paradigm was utilized, i.e., after an initial fixation period (1.000 ms) the central fixation light ($[X,Y] = [0°,0°]$) was extinguished, the pursuit target was switched on in the periphery and moved centripetally. Testing for an influence of eye position on pursuit-related activity was accomplished by use of the pursuit paradigm. In this task the monkey had to track a target that, after an initial fixation period ($[X,Y] = [0°,0°]$), started moving in random order from one of five different locations on the screen ($[X,Y] = [\pm 10.6°,\pm 10.6°]$, $[0°,0°]$), always with the same speed into the neuron's preferred pursuit direction.

To test for the eye position effect during active fixation, targets were presented in random order at nine different locations on the screen without any further visual stimulation (fixation paradigm). Locations were the center of the screen plus eight concentrically located points 15° away from the center ($[X,Y] = [0°,\pm 15°]$, $[\pm 15°,0°]$, $[\pm 10.6°,\pm 10.6°]$, $[0°,0°]$). Presentation of fixation targets always lasted for 1,000 ms after the animal's eye position had been located continuously within an electronically defined window for ≥300 ms.

Histology

At the end of the experimental sessions, small electrolytic lesions were made in the recorded hemisphere by passing small direct current (10 μA for 20 s) through the recording electrode at different depths along the electrode track. The monkey then was given an overdose of pentobarbital sodium and, after respiratory block and cessation of all reflexes, transcardially perfused. Sections were cut at a thickness of 50 μm and stained alternately with cresyl violet for cytoarchitecture and with the Gallyas method for myeloarchitecture. Two-dimensional maps of the recorded hemispheres were constructed as a standard procedure (Ungerleider and Desimone 1986a; van Essen and Maunsell 1980). Recording locations were reconstructed by relating the penetration scheme to the electrolytic lesions.

Data analysis

For assessing data observed in the pursuit paradigm, we employed the same methods as described in the preceding paper. Briefly, individual trials were aligned to the onset of the initial saccade preceding the smooth pursuit phase. Pursuit-related discharge (raw activity) was computed for the steady-state phase excluding the initial catch-up saccade, i.e., from an epoch beginning 100 ms after the onset of this initial saccade and lasting until the end of the pursuit target movement (typically ~1,000 ms). Background activity was subtracted from raw activity and the difference was defined as relative activity. As a convention, background activity was defined as mean activity during the initial central fixation period lasting until 100 ms before saccade onset. This value was chosen because the only fixation location that was always presented within the pursuit paradigm and that therefore could act as reference value was the straight-ahead position.

For analyzing data observed in the fixation paradigm, the mean neuronal activity was computed for each fixation location.

Statistics

Differences in neural activity resulting from different eye positions in the pursuit paradigm or the fixation paradigm were tested for statistical significance with a distribution free analysis of variance (ANOVA). A multiple comparison procedure (Dunn's test) was sometimes used to determine which individual groups differed significantly from others. Multiple linear regression with the independent variables x (horizontal eye position) and y (vertical eye position) was used to quantify the influence of eye position on the neuronal discharge z as dependent variable, i.e., we employed the regression equation $z = a*x + b*y + c$. For validating the planar model as fit to the observed data, the r^2 values and the F ratio were computed. A significant F ratio per se does not ultimately exclude the possibility of a nonoptimal regression model. To test for this possibility, we employed a step-down regression model $z = a*x + b*y + c*xy + d*x^2 + e*y^2 + f$ including interaction (xy) or higher-order quadratic (x^2, y^2) terms. The outcome of this analysis proved whether or not nonlinear terms could contribute significantly to the ability of the regression equation to predict the observed neuronal discharges.

RESULTS

Recordings were made from two hemispheres of two monkeys. A total of 320 cells was recorded quantitatively, 212 cells from area LIP and 108 cells from area 7A. During recording sessions, neurons were identified as being located in area LIP or 7A by their recording depth and by their known response characteristics. Brisk responses to an onset of a light stimulus could be found above all for neurons in area LIP. Spatially tuned saccade-related activity as one of the most prominent features in both areas was observed for many of the neurons investigated. However, this functional behavior was not tested systematically. Two hundred seventy-five of the investigated neurons were tested for a pursuit-related activity, 119 from the right hemisphere of the first animal and 156 from the left hemisphere of the second animal. In the second monkey 89 neurons were additionally tested in the fixation paradigm. Figure 1 shows two-dimensional map reconstructions (Ungerleider and Desimone 1986a; van Essen and Maunsell 1980) of the recording sites in both monkeys. Recording sites were located mostly in the dorsoposterior part of area LIP and at a posteromedial aspect of area 7A.

Pursuit paradigm

NEURON LEVEL. A total of 275 neurons from areas LIP and 7A was tested for pursuit-related activity with the step ramp paradigm: 177 neurons from area LIP and 98 neurons from area 7A. Neurons were classified as having pursuit-related activity if their discharge was significantly stronger ($P < 0.05$) during tracking of a moving visual target than during fixation of a stationary target. Furthermore, pursuit-related activity was required to be directionally selective. Of 275 neurons, 110 revealed such an activity: 69 from area LIP (39%) and 41 from area 7A (42%).

Figure 2 shows the activity of an LIP neuron tested in the step ramp paradigm. The histograms are arranged with respect to the movement direction of the target, e.g., the *left histogram* represents the neuronal activity for the trials where the target moved to the left. Histograms are aligned to the onset of target movement. Examination of the discharges of this individual neuron revealed a preferred tracking direction upward and to the left.

Preferred pursuit directions proved to be uniformly distributed in area LIP (χ^2 test: $P > 0.6$) and area 7a (χ^2 test: $P > 0.7$). Clearly circumscribed receptive fields could be mapped for almost one third (22 of 69) of the LIP neurons and about half (21 of 41) of the area 7A neurons. On average, receptive fields of area 7A neurons proved to be larger than those of neurons in area LIP, sometimes extending into the ipsilateral visual field. Only two (5%) neurons from area 7A, and four neurons (6%) from area LIP, responded to motion of a visual stimulus while the monkey fixated a stationary target.

For 81% (56 of 69) of the area LIP neurons as well as 80% (33 of 41) of the area 7A neurons an influence of eye position on the pursuit-related activity could be observed. Quantitative results from testing another LIP neuron in the pursuit paradigm are shown in Fig. 3. This individual neuron preferred target movement to the left (see also Fig. 4). Thus the pursuit target in this paradigm started moving to the left in random order from one of the five locations labeled I–V. The eye position traces during this recording are shown in Fig. 3*A*. Figure 3*B* shows the resulting pursuit-related responses and sample horizontal eye velocity traces. Each response histogram is located with respect to the starting location of the pursuit target, i.e., the *top left histogram* represents the discharges for the trials where the target started moving in the upper left, etc. Neuronal discharges in each histogram as well as eye velocity traces are aligned to the onset of the saccade that precedes the smooth pursuit phase. For this individual neuron, pursuit response was best when the target started to the left of the vertical meridian. Pursuit response was reduced when the target started from the center of the screen and was lowest when the pursuit started to the right from the vertical meridian. Onset of the pursuit-related discharge was earlier (perisaccadic) for tracking of targets starting to the left of the vertical meridian. Because the neuron did not reveal any saccade-related discharge or direction selective visual response, this early onset activity must be interpreted as ''prepursuit'' activity.

Figure 4 summarizes the results from testing this neuron for pursuit in all directions (conventional step ramp paradigm) and pursuit only in the preferred direction, starting from different locations (pursuit paradigm). Figure 4*A* depicts the mean discharge plus SDs for the four directions tested in the step ramp paradigm. Pursuit to the left led to strongest discharge ($P < 0.0002$), whereas pursuit in the other directions was accompanied by a discharge just at the level of activity during fixation of a central target (ANOVA and Dunn's multiple comparison method). Figure 4*B* illustrates the directional tuning in a polar plot. Figure 4*C* shows mean values plus SDs for the discharges (raw activity) observed for pursuit in the preferred direction from different starting locations. As already shown in the response histograms, discharges were better for starting points to the left of the vertical meridian (ANOVA plus multiple comparison method: $P < 0.0001$).

To quantify the modulatory influence of the position of the eyes in the orbit on the neuronal discharges, we applied linear regression analysis. Figure 4*D* shows the result for fitting a two-dimensional regression plane to the obtained data. Step-down regression had proven interaction terms ($P > 0.5$) or higher-order quadratic terms ($P > 0.4$) not to significantly add to the ability of the regression equation to predict the observed neuronal discharge. The X-Y-base of this three-dimensional cube represents the central ±20° × ±20° of the tangent screen where the pursuit targets were presented. The mean pursuit-related discharge (raw activity) is represented in the third (Z) dimension, symbolized by a vertical drop line. As a convention, the base point of each drop line depicts the starting point of target movement. We also could have chosen, e.g., the average eye position during a single pursuit trial as base point for the regression function. Because we approximated linear functions to the observed discharges, plotting firing rate as a function of average eye position only would have caused a shift of the regression function along the Z-axis. Thus both conventions lead basically to the same results. The two-dimensional linear regression function that could be approximated significantly ($P < 0.01$) to the responses is symbolized by the shaded plane. Statistics for the regression parameters are given in Table 1.

SYSTEM LEVEL. A total of 110 neurons tested did show a pursuit-related response: 69 from area LIP and 41 from area 7A. Eighty-nine neurons, 56 from area LIP (81%) and 33 from area

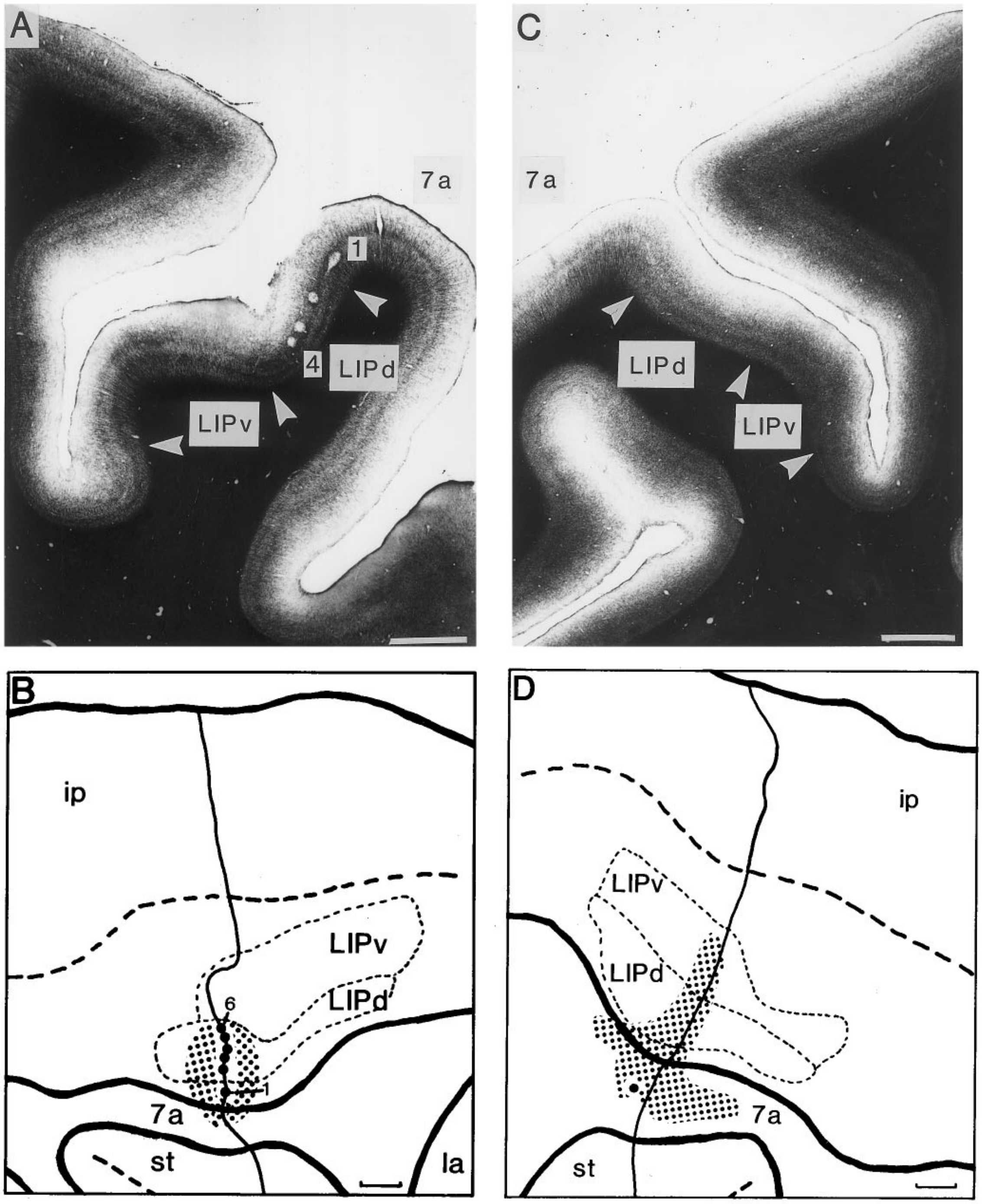

FIG. 1. Cortical regions recorded from in the 2 *Macaca mulatta* monkeys in this study. *A* and *C*: representative sections through the recorded area in the right (*A*) and left (*C*) parietal cortex stained for myelin. Arrows: areal borders. Numbers in *A*: row of microlesions marking recording sites in the intraparietal sulcus. *B* and *D*: 2-dimensional maps of the parietal regions investigated. Thick solid lines: lips of sulci. Thick dashed lines: fundi of sulci. Thin lines: layer IV lines of the sections shown in *A* and *C*. Thin dashed lines: borders of the dorsal and ventral parts of the lateral intraparietal area (LIPd and LIPv) as determined on the basis of myeloarchitecture. Because of the extended recording period a very high density of performed penetrations resulted. Individual recording locations would cover the whole area and are therefore not shown. Instead, dotted areas mark the cortical region where the electrophysiological recordings were performed. In *B*, the row of microlesions is indicated by solid dots and numbers. In *D*, the dot indicates an horseradish peroxidase injection site. Scale bars: 2 mm. la, lateral sulcus; ip, intraparietal sulcus; st, superior temporal sulcus.

7A (80%), were affected by the position of the eyes in the orbit. Two-dimensional regression planes were approximated to the mean of neuronal discharge during pursuit starting from different locations. The planes fit significantly ($P < 0.05$) for 52.2% (36 of 69) of the LIP neurons and 39% (16 of 41) of the 7A neurons. The fit was nearly significant ($P < 0.1$) for another

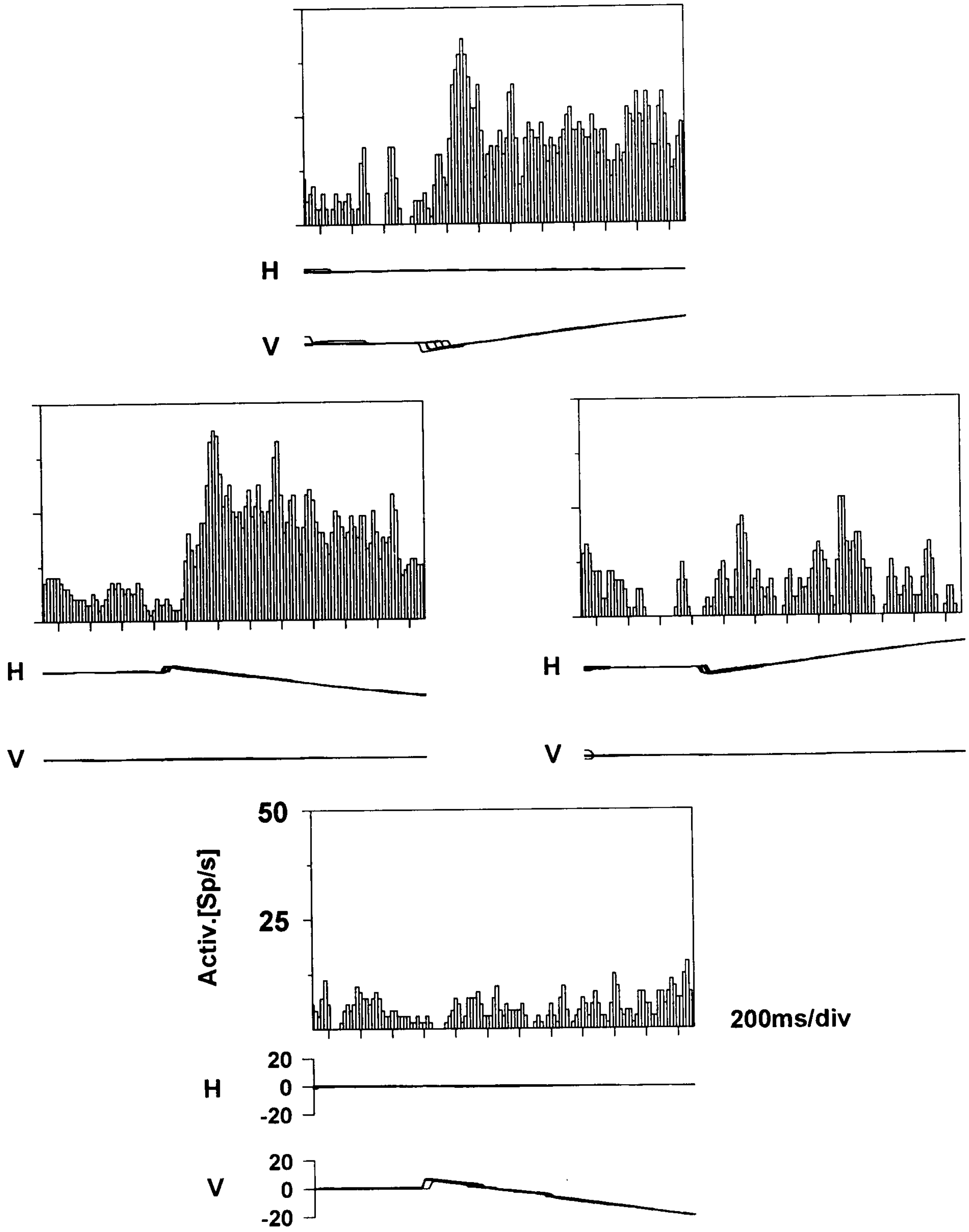

FIG. 2. Pursuit-related responses of an LIP neuron tested in the step ramp paradigm. All histograms are aligned to the onset of target movement. In each average response histogram neuronal discharge is shown from 500 ms after the beginning of each trial until the end of the smooth pursuit phase. Each histogram is located in the direction of target movement. Recorded horizontal and vertical eye positions are shown below each individual histogram. This individual neuron revealed a preferred pursuit direction upward and to the left.

2.8% (2 of 69) of the LIP neurons and 14.6% (6 of 41) of the 7A neurons. This two-dimensional linear regression model was validated by step-down regression analysis for 84% (32 of 38) of the LIP cells and 86% (19 of 22) of the 7A cells, i.e., for the vast majority of cells with a fit of $P < 0.1$ the regression plane proved to be the optimal statistical model to describe the observed neuronal discharges.

In the example given above, the direction of the gradient of the regression plane was directed to the left and coincided with the preferred pursuit direction. We thus wanted to investigate whether this directional colinearity was a general phenomenon for neurons located in areas 7A and LIP. In a first step, we computed for each individual neuron the direction of the gradient of the regression plane (D_{GradPurs}) fit to the

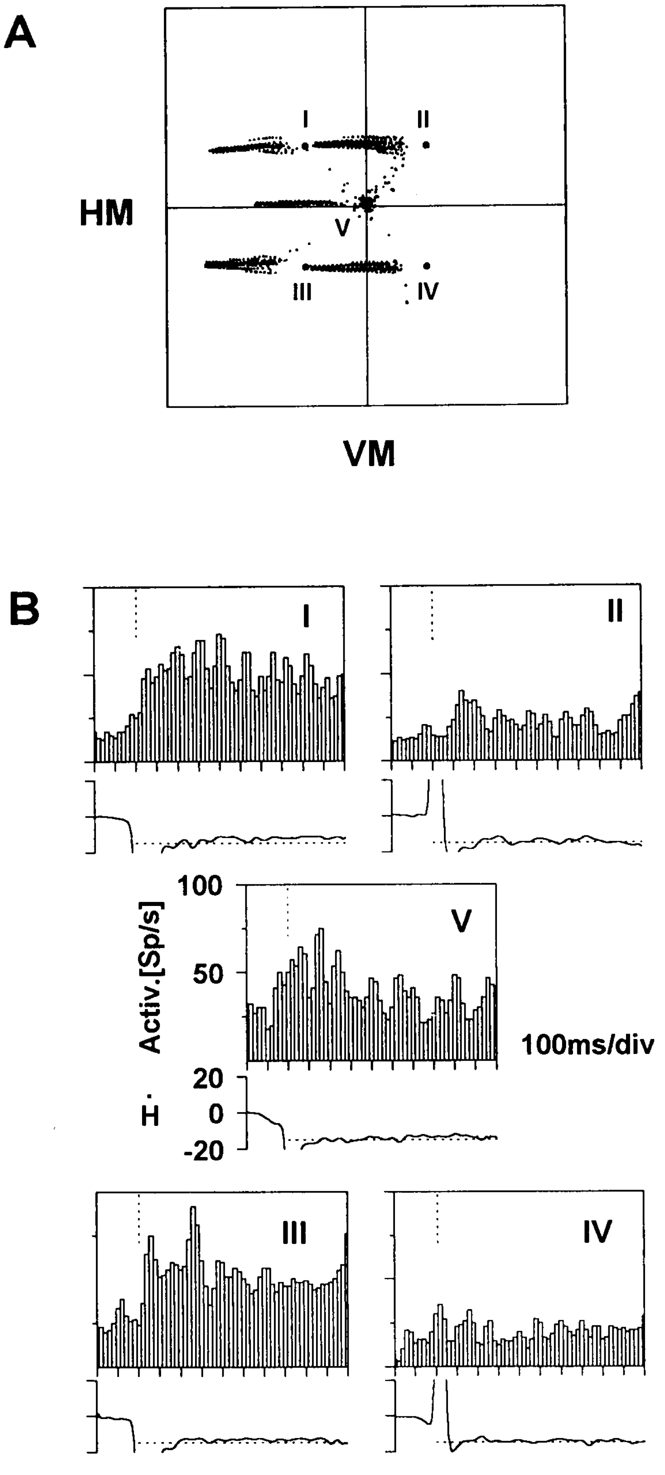

FIG. 3. Neuronal discharges during the pursuit paradigm. For this individual neuron the target started in random order from 5 different locations (labeled I–V) and then always moved to the left in the preferred direction of pursuit. Recorded eye positions are shown in *A*. Histograms in *B*: averaged neuronal activity during pursuit. Histograms are aligned to the onset of the saccade that precedes each smooth pursuit phase. Saccade onset is given by the vertical line within each response histogram. Sample horizontal eye velocity traces are shown below each individual histogram; dotted lines indicate target speed. The histograms are arranged like the starting location of the target, i.e., the response histogram in the *top left* represents the discharges for the trials where the target started in the upper left ($[X,Y] = [-10.6°,10.6°]$), etc. For this individual neuron, pursuit-related responses were best [analysis of variance (ANOVA) plus multiple comparison method: $P < 0.0001$] for starting locations I and III, which were to the left of the vertical meridian ($[X,Y] = [-10.6°,\pm10.6°]$). HM, horizontal zero meridian; VM, vertical zero meridian; Ḣ, horizontal eye velocity.

TABLE 1. *Statistics of regression parameters*

Parameter	Regression Value	SE	*P* Value
a	−1.314	0.096	0.005
b	0.064	0.096	>0.5
c	40.48	0.907	0.0005

The regression plane was approximated to the observed values according to an equation $z = ax + by + c$, where x and y are horizontal and vertical eye position, respectively.

discharges obtained in the pursuit paradigm. The direction of the gradient of the regression plane was computed as

$$D_{\mathrm{GradPurs}} = \arctan\,(b/a)$$

where *a* and *b* are the horizontal and vertical slopes of the regression plane, respectively (see preceding paper). A value of, e.g., $D_{\mathrm{GradPurs}} = 180°$ would have resulted from a regression plane with purely negative slope in horizontal direction and no slope in vertical direction (as in the example shown above). In a second step, we computed the difference between the direction of the gradient of the regression plane D_{GradPurs} and the preferred pursuit direction D_{PursPD} of each individual neuron. As commonly used, a preferred pursuit direction, e.g., to the left, was classified as $D_{\mathrm{PursPD}} = 180°$, preferred upward direction as $D_{\mathrm{PursPD}} = 90°$, etc. Depending on this kind of measure, angular differences

$$F(i) = D_{\mathrm{PursPD}}(i) - D_{\mathrm{GradPurs}}(i)$$

could range from −180° to 180°. For the neuron whose responses were shown in Fig. 4 we obtained an angular difference of

$$F(i) = D_{\mathrm{PursPD}}(i) - D_{\mathrm{GradPurs}}(i) = 180.0° - 177.2° = 2.8°$$

The outcome of computing the angular differences for the entire population of neurons from both parietal areas is shown in Fig. 5. In the circular scatter plots, the angle of each line depicts the angular difference for an individual neuron from area 7A (Fig. 5*B*) and area LIP (Fig. 5*D*). To quantify this relationship, we grouped the absolute difference values in 30° bins. From this we obtained the frequency distributions shown in Fig. 5, *A* (for area 7A) and *C* (area LIP). For both areas statistical analysis revealed a significant deviation of the obtained distribution from the null hypothesis of a uniform distribution (χ^2 test). This was true for the entire population of neurons from both areas [$P < 0.05$ for area 7A ($n = 41$) and $P < 0.001$ for area LIP ($n = 69$)] as well as the subpopulation of neurons with a significant fit of the regression plane without interaction or higher-order terms [$P < 0.05$ for area 7A ($n = 19$) and $P < 0.02$ for area LIP 9 ($n = 32$)]. Thus for the population of neurons there exists a positive correlation between preferred pursuit direction D_{PursPD} and the direction of the gradient of the regression plane D_{GradPurs}. For 41% of the LIP neurons as well as 32% of the 7A neurons, the difference between D_{PursPD} and D_{GradPurs} was less than ±30°. Eighty-four percent of the direction pairs in area LIP and 80% in area 7A did deviate less than ±90°.

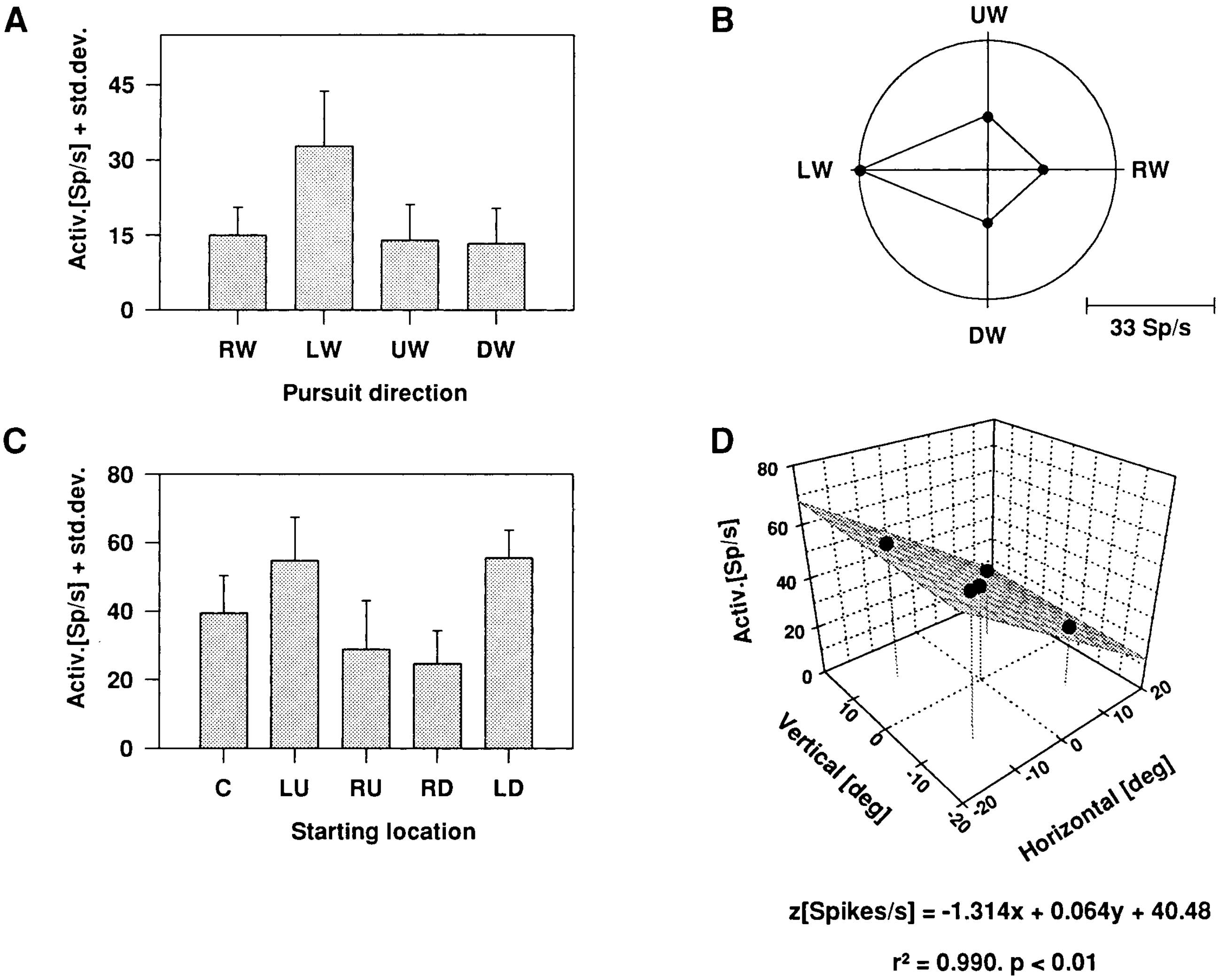

FIG. 4. Summary of neuronal discharges obtained in the step ramp and the pursuit paradigm. *A*: mean discharges plus SDs observed in the step ramp paradigm. Pursuit directions are indicated as follows: RW, rightward; LW, leftward; UW, upward; DW, downward. *B*: directional tuning derived from the mean discharges during pursuit. *C*: mean discharges plus SDs observed in the pursuit paradigm. Starting locations for the pursuit target moving always in the same directions (see Fig. 3*A*) are indicated as follows: C, center LU, left up; RU, right up; RD, right down; LD, left down. *D*: 2-dimensional linear regression plane approximated to the pursuit-related responses shown in *C*. *X-Y* base represents the central ±20° × ±20° of the screen where the monkey had to pursue the target. The base point of each drop line depicts the starting location of pursuit and the height of each line depicts the mean raw activity as defined in the methods section. A linear regression plane could be approximated with significant confidence ($P < 0.01$).

A regression plane was approximated to the relative response (pursuit-related discharge minus background activity) of each individual neuron. The distribution of the regression plane intercepts is shown in Fig. 6. On average, discharge rates proved not to be significantly different in the two areas (Mann-Whitney rank test: $P > 0.1$). The distribution of the slopes of the regression planes for the entire population of each area is shown in Fig. 7. Each data point in the central two-dimensional graphs depicts the gradient of one individual plane. For example, a modulatory effect that results in a linear regression function with a positive slope in horizontal direction and negative slope in vertical direction is located in the lower right quadrant within this diagram. For both areas the directions of the gradients proved to be uniformly distributed, i.e., statistical analysis (χ^2 test) revealed no difference between the observed distribution and the null hypothesis of a uniform distribution ($P > 0.5$ for areas 7A and LIP considering the entire population, $P > 0.4$ considering those subgroups for which the 2 dimensional linear regression was the optimal statistical method). The histograms above and to the side of the central illustrations represent the distributions of the one-dimensional horizontal (*top histograms*) and vertical (*left* and *right histograms*) slopes of the regression planes. Gaussian distributions, represented by the dotted curve within each histogram, gave the best approximation for the slope distributions along the horizontal and vertical axis when tested against other statistical distributions. These approximations were statistically significant for areas LIP (horizontal and vertical: $P < 0.01$) and 7A (horizontal and vertical: $P < 0.05$).

The fact of a uniform distribution of gradients of regression planes does not automatically exclude the possibility

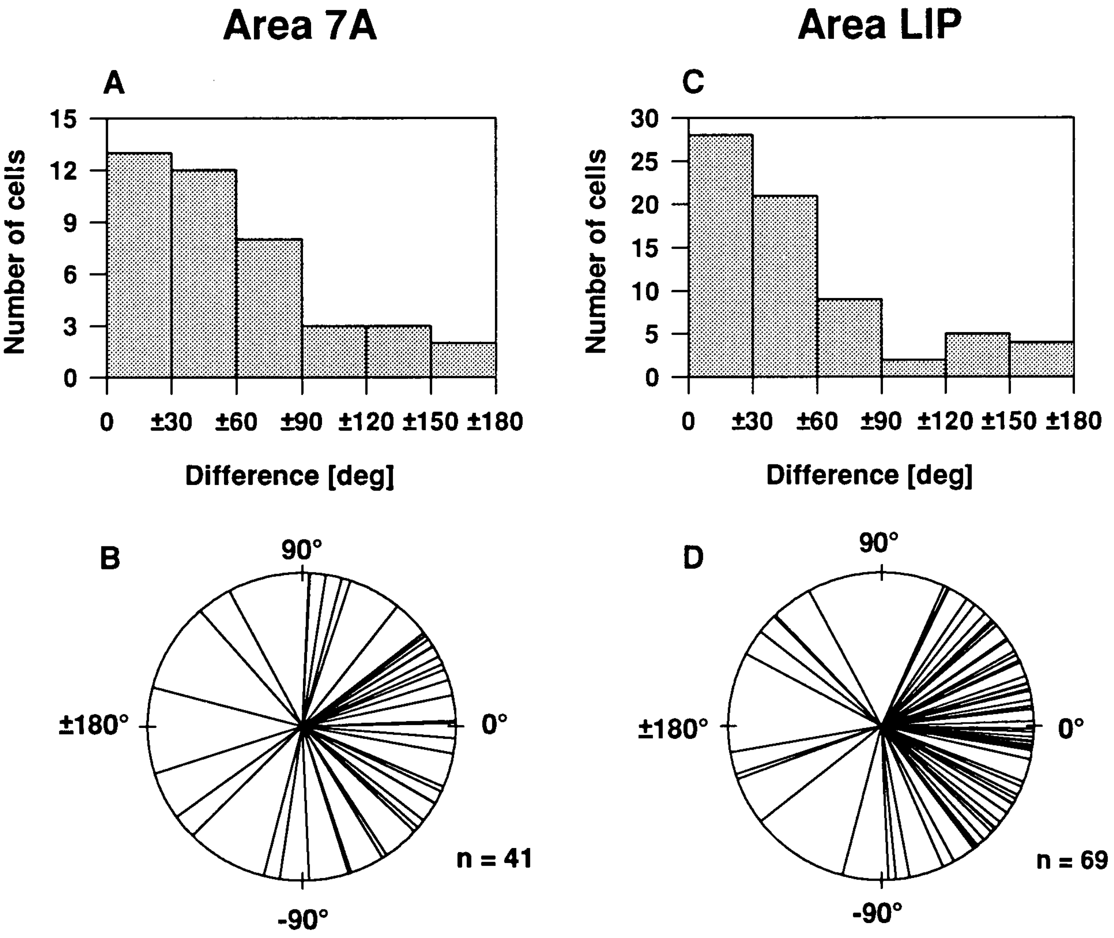

FIG. 5. Correlation of the preferred direction of pursuit and the direction of the gradient of the regression plane in areas 7A and LIP. *A* and *C*: histograms of the absolute values of the angular differences between both directions. Statistical analysis did reveal a significant deviation ($P < 0.05$ for area 7A and $P < 0.001$ for area LIP) of the obtained distribution from a uniform distribution (null hypothesis), i.e., a coupling between both directions. *B* and *D*: difference values represented in a circular scatter plot.

of an asymmetric or biased response strength with respect to eye position at the population level of the recorded neurons. To test for any bias of discharge frequency within one part of the oculomotor space, we computed the mean pursuit-related activity (relative activity) for the ensemble of neurons tested in both areas. This was done by two means. First, we computed the average of all linear regression planes fit to the single-cell data. The outcome of this computation is shown in Fig. 8. Graphically, the resulting ensemble response planes for area LIP (Fig. 8*D*) and area 7A (Fig. 8*B*) appeared to be more or less flat, indicating that the modulatory effect of eye position that could be observed at the single-cell level was balanced out at the population level. This qualitative estimation could be confirmed statistically: when testing each individual distribution of slopes (horizontal and vertical, area LIP and 7A) against a group of gaussian distributed random numbers of equal size, equal SD and mean 0, a Mann-Whitney rank test did not reveal any significant difference between both groups of experimental and randomly generated data. [Area LIP: $P > 0.8$ (horizontal) and $P > 0.2$ (vertical); area 7A: $P > 0.8$ (horizontal) and $P > 0.1$ (vertical), considering the entire population. Area LIP: $P > 0.7$ (horizontal and vertical); area 7A: $P > 0.6$ (horizontal) and $P > 0.4$ (vertical), considering the subgroup of neurons with the regression plane as optimal statistical model.] In a second approach, we computed from

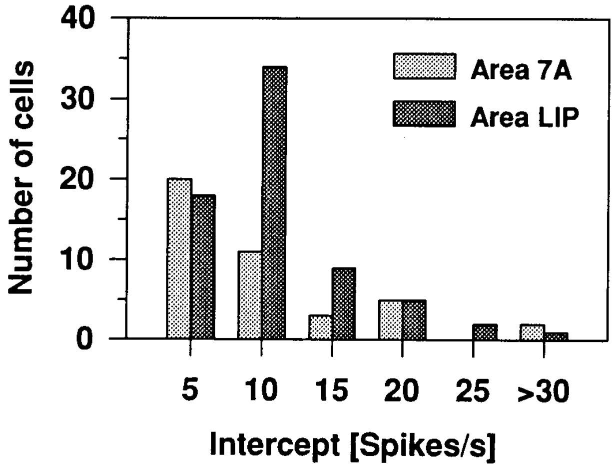

FIG. 6. Distribution of the intercepts of the regression planes for area 7A and area LIP neurons. The mean discharge rates for both areas proved not to be significantly different.

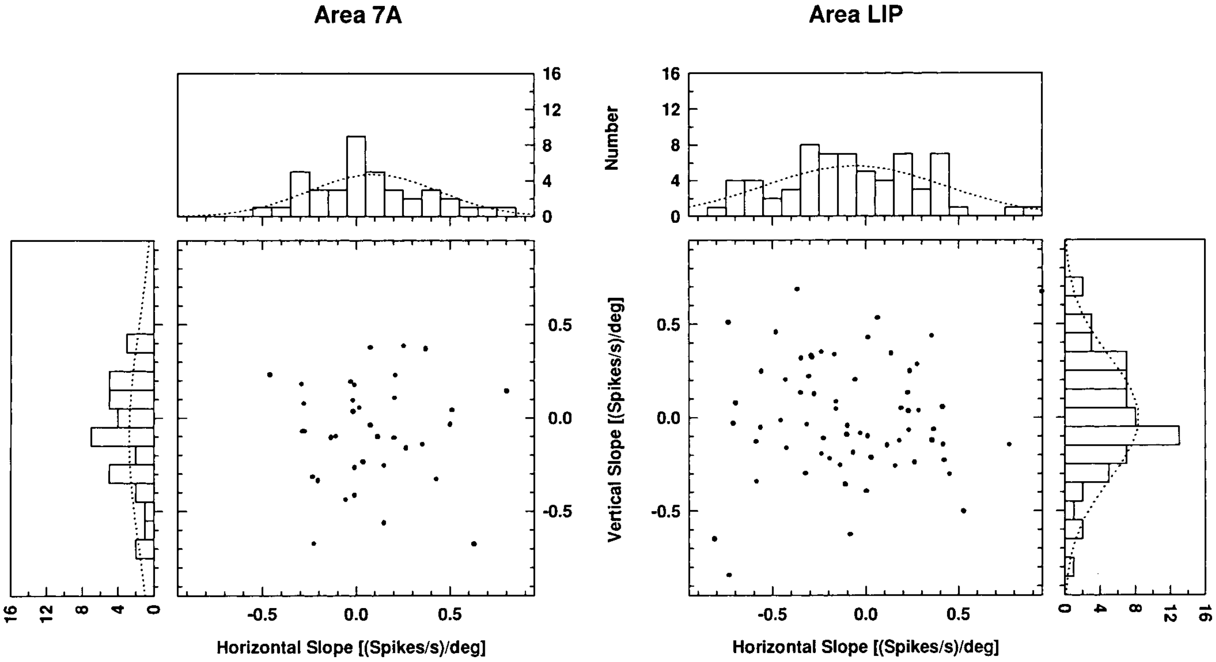

FIG. 7. Distribution of the horizontal and vertical gradients of the regression planes of area 7A and LIP neurons tested in the pursuit paradigm. *Middle*: gradients of an individual linear regression plane are represented by a single data point. Statistical analysis proved the directions of the gradients to be uniformly distributed. A normal distribution turned out to be the best fit for both the values of the horizontal as well as vertical slopes of the 7A and LIP neurons tested.

the original spike data (relative activity) the mean discharges for the different starting positions of target movement (Fig. 8, *A* and *C*). Statistical analysis confirmed the result from the first approach for the entire population as well as the subgroups without interaction or higher-order quadratic terms: discharges proved to be not significantly different from each other. (Entire population: ANOVA, $P > 0.5$ for area LIP and $P > 0.25$ for area 7A.) Subgroup: ANOVA, $P > 0.95$ for area LIP and $P > 0.5$ for area 7A.) Approximation of a regression plane to these mean discharges resulted in exactly the same average plane as the one from the first approach.

Fixation paradigm

NEURON LEVEL. An influence of the position of the eyes in the orbit on the neuronal activity during fixation in darkness has already been shown in previous studies (e.g., Andersen et al. 1990b). To test whether an obtained modulatory effect on the neuronal discharges during pursuit does spatially coincide with a modulatory effect during active fixation, in the second monkey 89 neurons (26 from area LIP and 63 from area 7A) were also tested in the fixation paradigm. In this experimental task, the monkey had to fixate a dim spot of light on an otherwise dark screen. A typical result of such an experimental condition is shown in Fig. 9. For this individual LIP neuron, ''spontaneous'' activity during fixation without any other visual stimulation was modulated by the position of the eyes in the orbit. Discharge was strongest when the monkey fixated in the lower left of the visual field ($[X,Y] = [-10.6°,-10.6°]$, $P < 0.002$). The activity gradually decreased for fixation sites located more to the right and up. Consequently, neuronal discharge was lowest for fixation in the upper right ($[X,Y] = [10.6°,10.6°]$). A regression plane could be approximated highly significantly ($P < 0.0005$) to the activity of this neuron. Regression parameter statistics are shown in Table 2. Step-down regression analysis proved the regression plane to be the optimal statistical mode, i.e., interaction terms ($P > 0.8$) or higher-order quadratic terms ($P > 0.8$) did not significantly add to the ability of the regression equation to predict the observed neuronal discharge.

SYSTEM LEVEL. A total of 89 neurons was investigated in the fixation paradigm, 26 neurons from area LIP and 63 neurons from area 7A. A regression plane was approximated to the discharge of each individual neuron. For 39.7% (25 of 63) of the 7A neurons and 34.6% (9 of 26) of the LIP neurons this fit was significant at $P < 0.05$. For another 12.7% (8 of 63) of the neurons from area 7A and 19.2% (5 of 26) of the neurons from area LIP the approximation was nearly significant at $P < 0.1$. Step-down regression proved a two-dimensional linear regression to be the optimal statistical model to describe the neuronal activities for 86% (12 of 14) of the LIP cells and 82% (27 of 33) of the 7A cells with a significant or nearly significant approximation of the regression plane.

A total of 38 neurons from both areas (14 LIP neurons and 24 7A neurons) was tested in both the pursuit and the fixation paradigms, respectively. This allowed us to quantify an eventually existing correlation between the eye position effect on the neuronal discharges observed in the pursuit and the fixation paradigms. To achieve this we computed for each cell tested in both paradigms the direction of the gradient of the regression plane obtained for the fixation paradigm (D_{GradFix}) and the pursuit paradigm (D_{GradPurs}). As before, gradient directions were computed as $D_{\mathrm{GradFix}} = \arctan\,(b/$

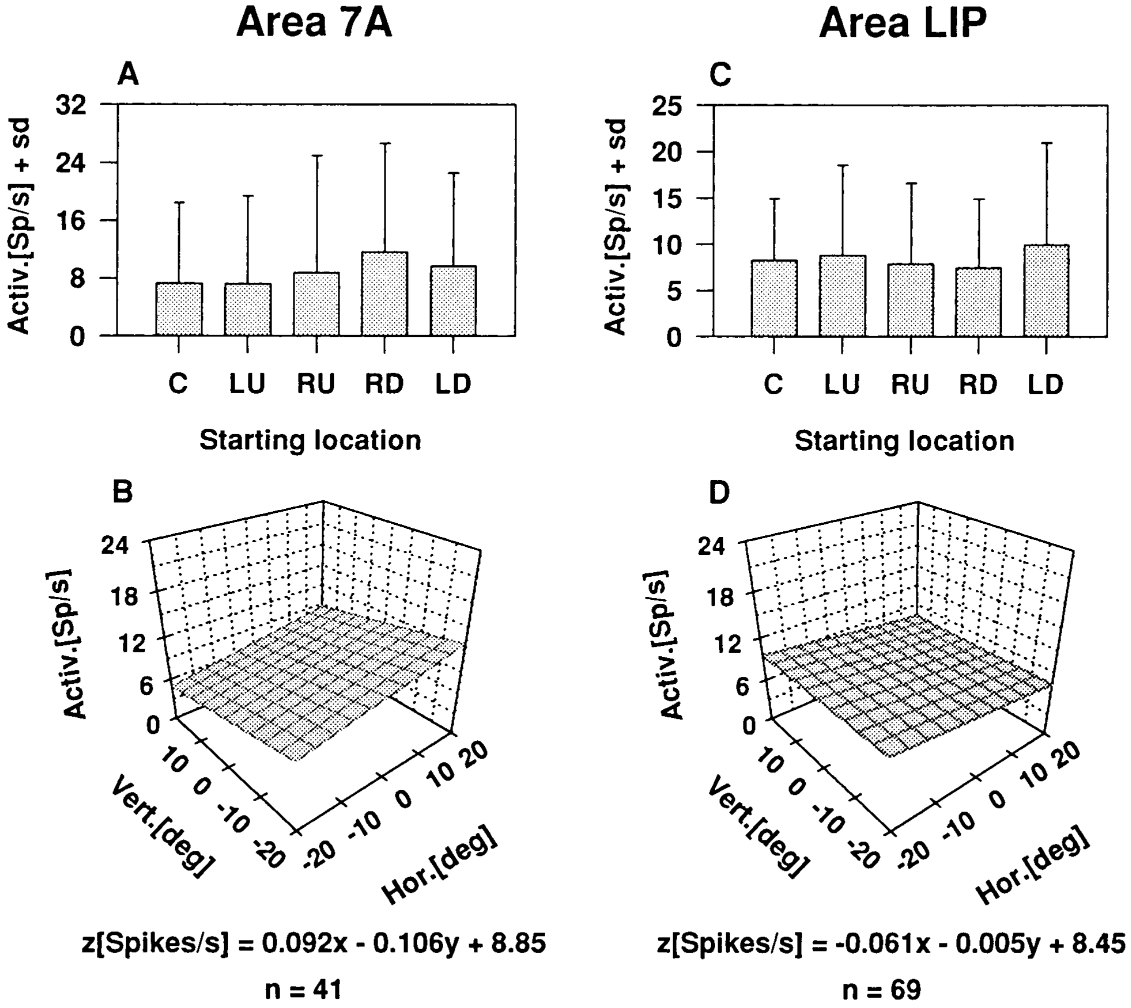

FIG. 8. Population response for neurons from areas 7A and LIP tested in the pursuit paradigm. *A* and *C*: mean relative activity (raw activity minus background activity) plus SDs for different target starting locations. The values for the different starting locations were not significantly different, indicating that the modulatory effect of eye position is balanced out at the population level for both area 7A and area LIP, respectively. *B* and *D*: mean population response planes were obtained by summing up all linear regression planes and dividing this value by the respective number of investigated neurons.

a) for the regression plane obtained in the fixation paradigm and $D_{\mathrm{GradPurs}} = \arctan(b/a)$ for regression plane obtained in the pursuit paradigm. In this computation a and b depicted the slopes of the regression planes in horizontal and vertical directions, respectively. For each individual neuron (i) we then computed the angular difference $Y(i)$ between both directions as

$$Y(i) = D_{\mathrm{GradFix}}(i) - D_{\mathrm{GradPurs}}(i)$$

The outcome of this computation revealed a strong relation of both gradient directions, i.e., statistical analysis (χ^2 test) revealed a significant deviation of the observed distribution from the null hypothesis of a uniform distribution [$P < 0.005$ for the entire group ($n = 38$), $P < 0.02$ for only those cells from both areas for which the 2-dimensional linear regression was the optimal statistical model in both paradigms ($n = 15$)]. For 29% of the LIP neurons and 42% of the 7A neurons the angular difference between the directions of the gradients D_{GradFix} and D_{GradPurs} was less than ±30° (considering the entire population). For 79% of the LIP neurons and 83% of the 7A neurons this difference was less than ±90°. A histogram and a circular scatter plot of the distribution of the angular differences are shown in Fig. 10.

It thus can be concluded that for most of the cells in areas LIP and 7A the eye position signal produces the same effect on the response strength during pursuit and fixation.

A histogram of the distribution of the intercepts of the regression planes is shown in Fig. 11. Overall discharges observed in area LIP were higher (Mann-Whitney rank test: $P < 0.02$) compared with those obtained in area 7A. The distribution of the slopes of the regression planes for both areas is shown in Fig. 12. Each data point in the central two-dimensional graphs depicts the gradient of an individual plane for the entire population of neurons. Statistical analysis (χ^2 test) proved the directions of the gradients to be uniformly distributed. (Entire population: $P > 0.25$ for area LIP and $P > 0.4$ for area 7A. Considering only those neurons with the regression plane as the optimal statistical model: $P > 0.2$ for area LIP and $P > 0.95$ for area 7A.) When tested against other statistical distributions, gaussian distributions, which are represented by the dotted curves within each histogram, gave the best approximation

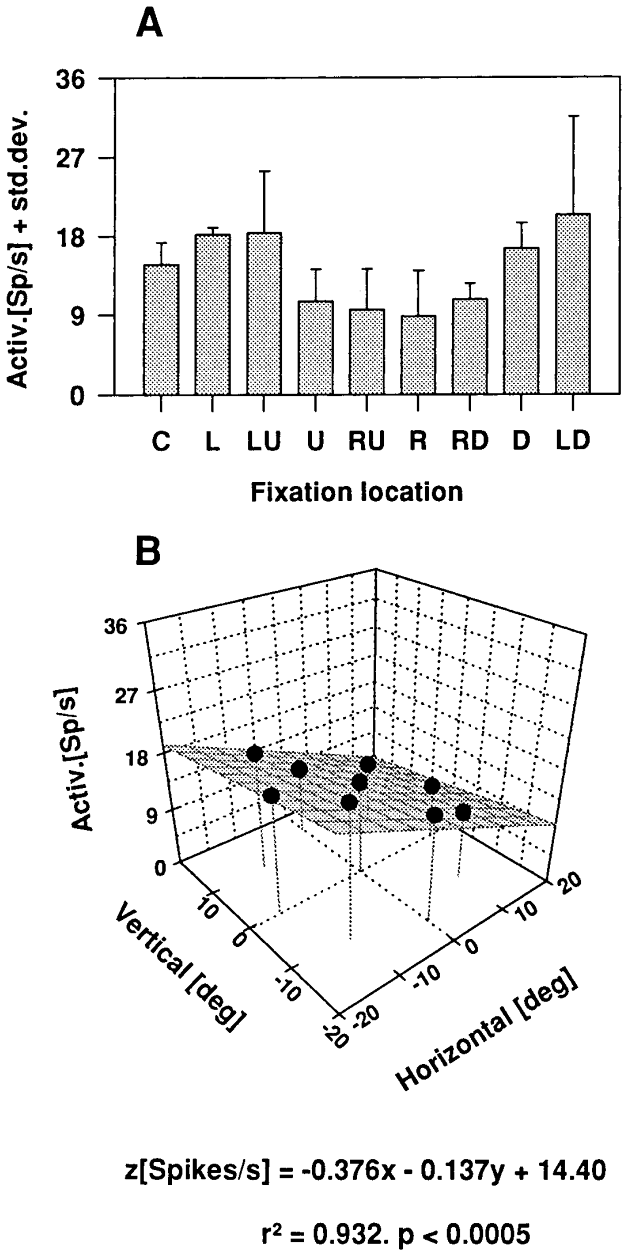

FIG. 9. Activity of an LIP neuron tested in the fixation paradigm. *A*: mean responses plus SDs for the different fixation locations. Neuronal discharges were best ($P < 0.002$) for fixation in the lower left quadrant ($[X,Y] = [-10.6°,10.6°]$). *B*: 2-dimensional linear regression plane approximated to the obtained neuronal discharges. The *X-Y* base of the cube depicts the central ±20° × ±20° of the screen where the monkey had to fixate. The base point of each drop line represents the fixation location. The height of each line gives the mean neuronal discharge during fixation at this location. The regression plane could be fit highly significantly ($P < 0.0005$) to the observed data.

for the slopes along the horizontal and vertical axis. These approximations were statistically significant for area 7A (horizontal: $P < 0.05$, vertical: $P < 0.02$), but not for area LIP.

TABLE 2. *Statistics of regression parameters*

Parameter	Regression Value	Standard Error	*P* Value
a	−0.376	0.044	0.0001
b	−0.137	0.044	0.02
c	14.40	0.439	0.0001

Computing the mean response of the whole ensemble of neurons recorded within each area led to a similar result as for the pursuit paradigm (see Fig. 13). Again, we used two different approaches to estimate the ensemble activity. First, we computed the mean response plane by averaging the approximated regression planes. Qualitatively, the resulting planes turned out to be essentially flat, indicating that the effect of the position of the eyes in the orbit on the population response vanishes in these areas also in the fixation paradigm (see Fig. 13, *B* and *D*, for areas 7A and LIP, respectively). Quantitatively, when testing each individual distribution of slopes (horizontal and vertical, area 7A and LIP) against an equally sized group of gaussian distributed random numbers with equal SD but mean 0, no statistically significant difference could be observed. [Considering the entire population:

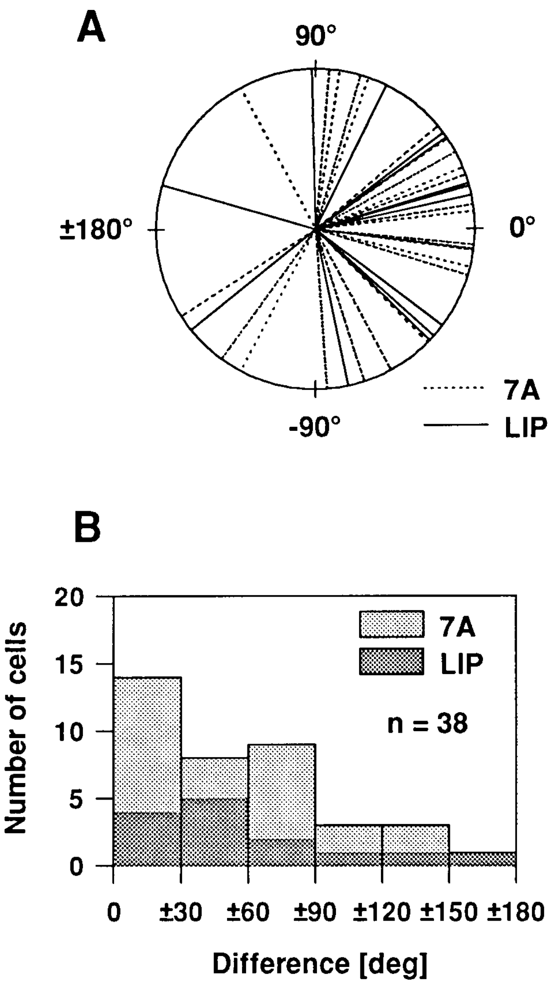

FIG. 10. Correlation of the directions of the gradient of the regression planes approximated to the responses of area 7A and area LIP neurons tested in the fixation (D_{GradFix}) and the pursuit paradigm (D_{GradPurs}). In the circular scatter plot (*A*) each individual line represents the difference between the gradient directions D_{GradFix} and D_{GradPurs} obtained for a single neuron tested in both paradigms (for computational details see text). For 83% of the 7A neurons (- - -) and 79% of the LIP neurons (——) the differences between both gradient directions were less than ±90°. Histogram in *B*: distribution of the absolute angular differences between both gradient directions.

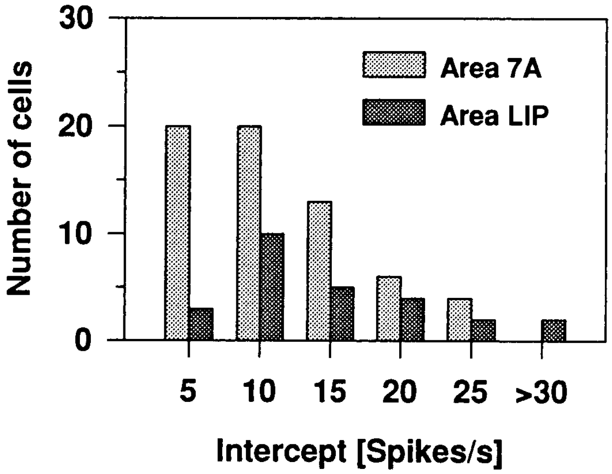

FIG. 11. Distribution of the intercepts of the regression planes for area 7A and area LIP neurons tested in the fixation paradigm. Overall, area LIP neurons have higher discharge rates than area 7A neurons.

area 7A: $P > 0.3$ (horizontal), $P > 0.2$ (vertical). Area LIP: $P > 0.1$ (horizontal), $P > 0.4$ (vertical). Considering only the subgroup with the regression plane as optimal statistical model: area 7A: $P > 0.2$ (horizontal), $P > 0.3$ (vertical). Area LIP: $P > 0.2$ (horizontal and vertical).] In a second approach, we computed from the original spike data the mean discharges for the different fixation locations. Statistical analysis proved the discharges to be not significantly different from each other. (Entire population: ANOVA, $P > 0.9$ for areas LIP and 7A. Subgroup only: ANOVA, $P > 0.7$ for area LIP and $P > 0.9$ for area 7A). Approximation of a regression plane to these mean discharges led to exactly the same average plane as the one resulting from the first approach.

DISCUSSION

Neurons in area LIP discharge in relation to pursuit

Pursuit-related activity so far has been shown for visual cortical areas MT and MST (Komatsu and Wurtz 1988a,b) as well as the LIP adjacent areas 7A (Lynch et al. 1977; Sakata et al. 1983) and VIP (Colby et al. 1993). Anatomic studies (Andersen et al. 1990a; Neal et al. 1988a,b; Pandya and Seltzer 1982; Ungerleider and Desimone 1986b; van Essen et al. 1981) revealed reciprocal connections between cortical areas MT, MST, VIP, and 7A with area LIP. The first goal of this study therefore was to investigate whether pursuit-related activity can also be found in area LIP. With the use of the step ramp paradigm, direction-specific pursuit-related activity could be shown for ~39% of the neurons tested in area LIP, in comparison with 42% in area 7A. The same neurons did not respond to retinal slip of a stimulus while the monkey was fixating. The percentage of neurons firing during smooth tracking eye movements in areas 7A and LIP resembles the values we observed for areas MT (35%) and area MST [48%, see preceding paper (Bremmer et al. 1997)]. However, the proportion is a little less than the number given for neurons in area VIP firing in accordance with smooth pursuit (10 of 17) (Colby et al. 1993).

Recent studies revealed that even neurons in the monkey frontal eye field that were thought to be exclusively involved in the control of saccadic eye movements showed a pursuit-related discharge (Gottlieb et al. 1994; MacAvoy et al. 1991). Keating (1993) could show an impairment of smooth pursuit eye movements after lesions of the frontal eye field, which is reciprocally connected with area LIP, too. Furthermore, as for areas MT and MST, projections of area LIP (Blatt et al. 1990; May and Andersen 1986) as well as the frontal eye field (Leichnetz 1989; Stanton et al. 1988) to

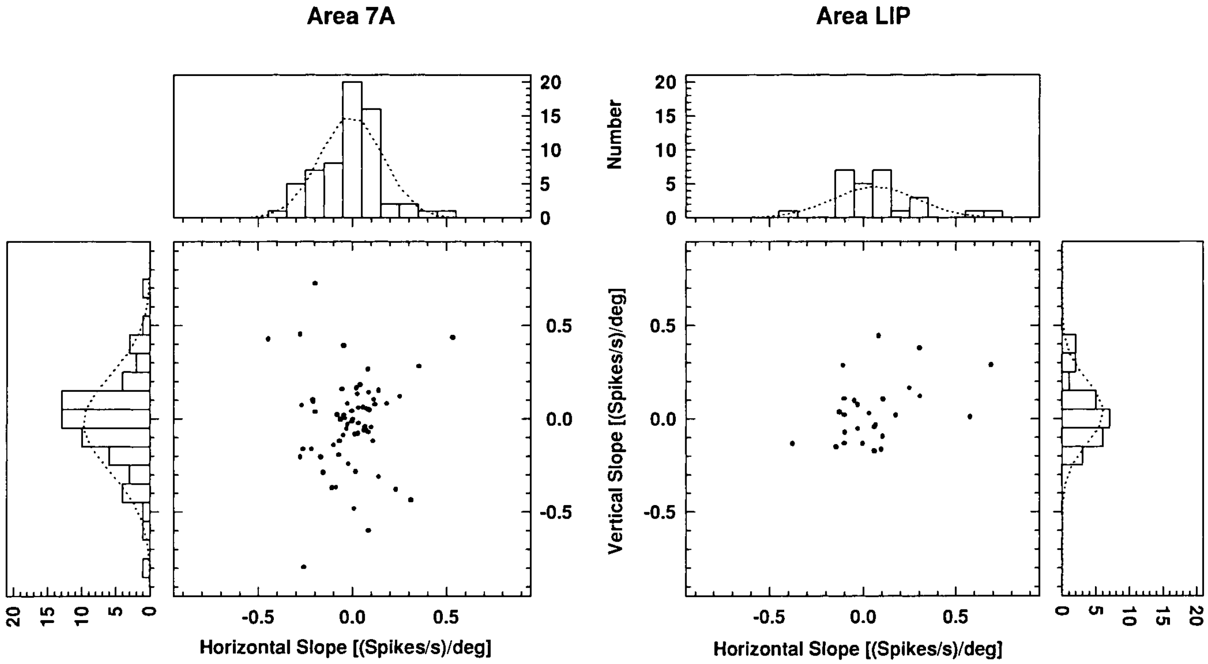

FIG. 12. Distribution of the gradients of the regression planes. *Middle*: gradient of an individual linear regression plane, treated as a 2-dimensional vector, is represented by a single data point. Statistical analysis proved the directions of the gradients to be uniformly distributed for both area 7A and area LIP.

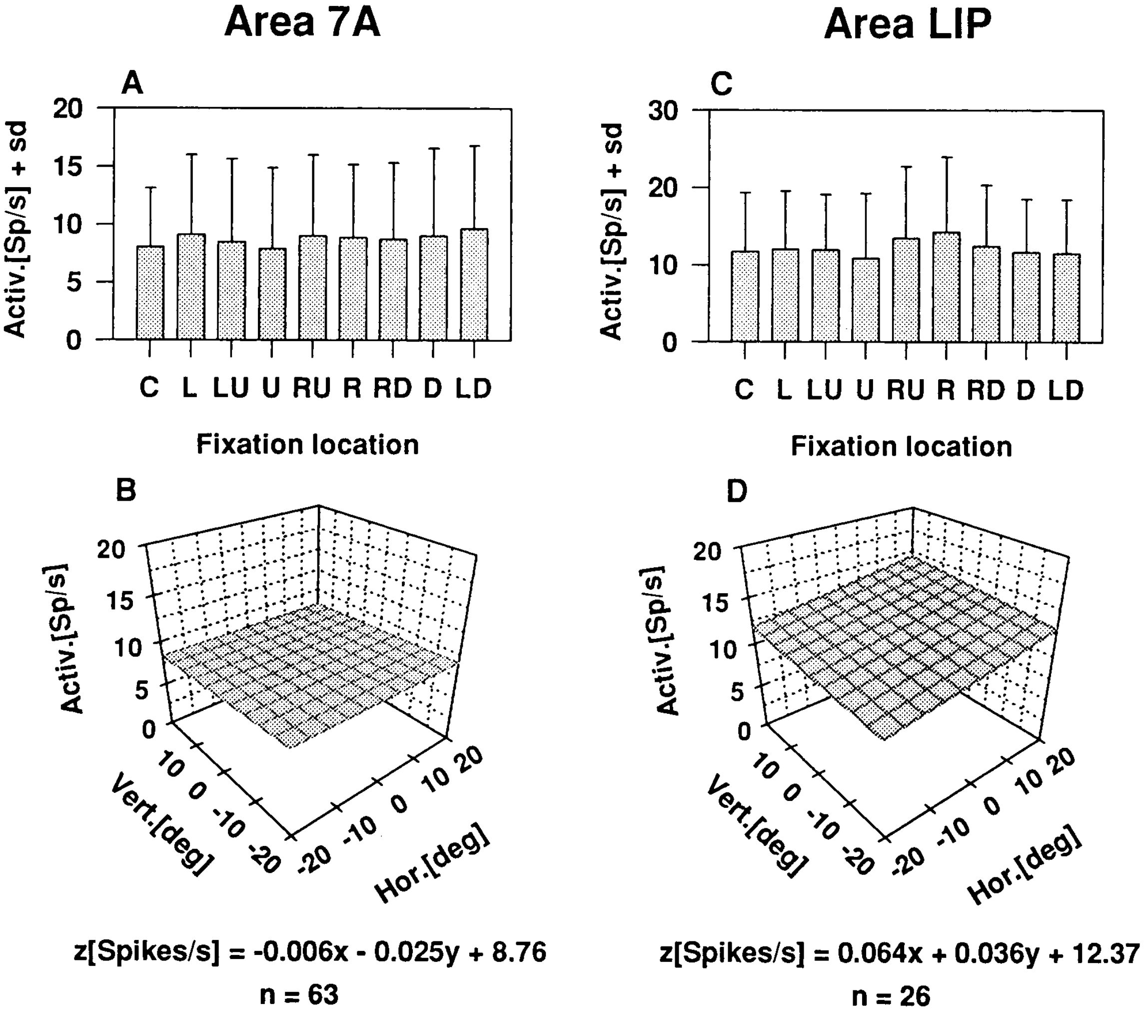

FIG. 13. Population response for area 7A and LIP neurons tested in the fixation paradigm. Histograms in *A* and *C*: mean discharges plus SDs observed during fixation at the 9 different locations. Mean discharges within a single area were not significantly different, implying that the modulatory effect of eye position was balanced out at the population level. Population response planes in *B* and *D* were obtained by averaging all approximated regression planes. The resulting response planes for both areas proved to be essentially flat.

pontine structures are clearly demonstrated. Neurons in area LIP thereby are involved in a cortical and subcortical network of neurons proven to discharge in relation to smooth pursuit eye movements. The finding of pursuit-related discharges for neurons in area LIP therefore is very well in line with the described connectivity scheme.

The question of specific pursuit functions in LIP was not addressed by our experiments. Studies employing permanent or reversible inactivation would allow direct testing of LIP's involvement in pursuit. Furthermore, experiments in which microstimulation is used could give more detailed information about the role of area LIP in the cortical circuitry of pursuit.

Eye position influences pursuit-related activity in neurons of areas LIP and 7A

A modulatory effect of eye position on the mean neuronal discharge during pursuit could be shown. Of the 110 neurons tested in the pursuit paradigm in both cortical areas, ~81% (56 of 69) in area LIP and 80% (33 of 41) in area 7A were modulated in their response by the position of the eyes in the orbit. The proportion of affected 7A and LIP neurons thus very much resembles the values observed for areas MT (78%) and MST (80%) when tested in the pursuit paradigm. However, one aspect of the results of the present study was different from what we observed in areas MT and MST [see preceding paper (Bremmer et al. 1997)]. In areas MT and MST, the preferred pursuit direction of a single neuron was not correlated with the ''ON direction'' of the eye position effect, i.e., the direction of the gradient of the approximated regression plane. This was different in areas LIP and 7A, where both directions tended significantly to be colinear. This colinearity suggests a functional coupling between the two parameters within both parietal areas.

As for the saccade tasks investigated by Andersen et al. (1990b), effects observed in the pursuit paradigm turned out to be planar. Neuronal discharges as a function of horizontal and vertical eye position could mostly be fit significantly by a two-dimensional linear regression plane. It therefore seems as if the same neuronal processes and inputs, working on saccade and memory-related responses as well as light-driven activity in areas LIP and 7A, do also work on pursuit-related activity. The amounts of changes of discharge with change in eye position are fairly equal for all four kinds of responses (saccade, memory, and light-sensitive as well as pursuit).

Influence of eye position is independent of the behavioral paradigm

The same neurons tested in the pursuit paradigm often also showed a modulation of ongoing activity during fixation of a dim spot without any further visual stimulation. Thirty-eight neurons (14 from area LIP and 24 from area 7A) were tested in the pursuit paradigm as well as in the fixation paradigm. For 79% of the LIP neurons as well as 83% of the 7A neurons the directions of best responses did coincide in the sense that the directions of the gradients approximated to the responses in both paradigms differed less than ±90°. This confirms the finding of a colinearity of gradient directions found for areas MT and MST (see preceding paper) as well as those described by Andersen et al. (1990b) for neurons tested for saccade and light-sensitive responses. Our findings furthermore underline the hypothesis that the same neural mechanisms influence the activity of the neurons in the investigated areas regardless of experimental conditions.

Origins of the modulatory eye position signal

The influence of the position of the eyes in the orbit on the activity of neurons in the macaque has been described mostly for cortical areas within the dorsal stream of the visual system (areas V3A, V6, MT, MST, LIP, and 7A). Furthermore, a modulatory effect of eye position has been described for apparent visual responses in monkey ventral premotor cortex (Boussaoud et al. 1993), activity during fixation in the supplementary eye fields (Schlag et al. 1992), and saccade-related activity in monkey superior colliculus (Hepp et al. 1993; van Opstal et al. 1995). However, the origin of the modulatory input is still unclear. If the input signal is acting directly, the question arises whether it is a proprioceptive signal [as suggested for the explanation of results of psychophysical experiments by Holt (1903) or Sherrington (1918)] or whether the input signal is an efference copy (corollary discharge), as already suggested for the explanation of psychophysical experiments by von Helmholtz (1867), Sperry (1950), and von Holst and Mittelstaedt (1950).

Eye position effects also have been described for the cat visual system. Schlag et al. (1980) could demonstrate the existence of an influence of the direction of gaze on visual responses of neurons in the cat thalamic internal medullary lamina. Toyama et al. (1984) could show saccade-related neuronal facilitation as well as inhibition for cat striate cortex. Lal and Friedlander (1990a,b) could demonstrate eye-position- as well as eye-movement-related activity in the lateral geniculate nucleus of the anesthetized and paralyzed cat. Finally, Weyand and Malpeli (1993) could demonstrate an influence of the position of the eyes in the orbit on visual responses in cat area 17 (in a few sample recordings we also found an influence of eye position on the visual-driven activity of neurons in monkey striate cortex). To determine the origin of the eye-position- or eye-movement-related signal, Lal and Friedlander applied a retrobulbar block. Application of lidocaine to the extraocular muscles abolished the effects of eye position and eye movement on the investigated lateral geniculate nucleus neurons. The authors thus proposed extraocular muscle proprioception as the source of the afferent input signal. Toyama et al. (1984), on the other hand, could show the survival of eye-movement-related signals after retrobulbar paralysis. They therefore suggested an efference copy of oculomotor signals as the origin of influence. These two mechanisms do not exclude each other, which also could mean that both could work simultaneously to produce the eye position signals on neurons in monkey visual cortex.

Eye position effects at the system level

The effects of different horizontal and vertical eye position quantified by the two-dimensional linear regression planes were fairly uniformly distributed. This was true for both experimental tasks, the fixation paradigm and the pursuit paradigm. Statistical analysis revealed no significant preference for any direction of the modulatory influence of the position of the eyes in the orbit on neuronal discharge. The values of the slopes of the regression planes along each single axis (horizontal or vertical) were normally distributed. This observation is in accordance with our findings for areas MT and MST (see preceding paper) as well as for LIP and 7A neurons when tested in the saccade task or for their light sensitivity (Andersen et al. 1990b).

Eye position effects and sensory-motor integration

The influence of eye position in the orbit on the discharge of neurons in monkey visual cortex was claimed in all studies so far as evidence for the generation of a visual environment representation in a nonretinocentric frame of reference within a cortical area. Theoretical studies have shown the potential of ensembles of neurons affected by eye position to encode sensory signals in a nonretinocentric frame of reference (e.g., Pouget et al. 1993; Zipser and Andersen 1988). Concerning response characteristics, model neurons were very similar to real cortical neurons. It thus might be concluded that neurons affected by eye position are involved in accomplishing or at least preparing a coordinate transformation from sensory signals at the input stage to motor commands at the output stage.

Different concept of spatial encoding

A different concept for the representation of spatial information was introduced by Duhamel et al. (1992). The authors proposed an oculocentric representation of space within monkey cortical area LIP. The authors could show the shifting of the RFs of single neurons in advance of a saccade and proposed this shifting as a mechanism for updating the representation of visual space by intended eye movements. With this concept a coordinate transformation of the incoming sensory signals no longer seems to be necessary.

However, from our point of view the one hypothesis (nonretinocentric encoding by means of a coordinate transformation) does not rule out the other (oculocentric encoding by means of a perisaccadic updating mechanism). One could imagine both mechanisms working in parallel. The updating mechanism, e.g., could be used for generating visual stability across saccadic eye movements.

Conclusions

In our two experimental series we could show an influence of eye position on neuronal activity in four visual cortical areas of the monkey (areas MT, MST, LIP, and 7A). The observed effects were very similar in all four areas investigated. Similar eye position effects have furthermore been shown in monkey visual cortical areas V3A and PO (parietooccipital area) as well as premotor areas PMd and PMv (dorsal and ventral premotor areas, respectively) and the supplementary eye fields. Thus the influence of the position of the eyes in the orbit on the neuronal discharges appears to be a general concept in monkey cortex. Finally, all observed experimental data taken together with results from theoretical studies suggest the eye position effect to be the basis for the representation of spatial information in a nonretinocentric frame of reference by a common scheme of distributed coding throughout all monkey cortical areas.

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