Early Coding of Reaching in the Parietooccipital Cortex

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[1]*Dipartimento di Fisiologia Umana e Farmacologia, Università di Roma 'la Sapienza,' 00185 Rome;* [2]*Istituto di Ricovero e Cura a Carattere Scientifico Santa Lucia, 00179 Rome; and* [3]*Dipartimento di Neuroscienze, Università di Roma 'Tor Vergata,' 00133 Rome, Italy*

Battaglia-Mayer, Alexandra, Stefano Ferraina, Takashi Mitsuda, Barbara Marconi, Aldo Genovesio, Paolo Onorati, Francesco Lacquaniti, and Roberto Caminiti. Early coding of reaching in the parietooccipital cortex. *J. Neurophysiol.* 83: 2374–2391, 2000. Neural activity was recorded in the parietooccipital cortex while monkeys performed different tasks aimed at investigating visuomotor interactions of retinal, eye, and arm-related signals on neural activity. The tasks were arm reaching *1*) to foveated targets; *2*) to extrafoveal targets, with constant eye position; *3*) within an instructed-delayed paradigm, under both light and darkness; *4*) saccadic eye movements toward, and static eye holding on peripheral targets; and *5*) visual fixation and stimulation. The activity of many cells was modulated during arm reaction (68%) and movement time (58%), and during static holding of the arm in space (64%), when eye position was kept constant. Eye position influenced the activity of many cells during hand reaction (45%) and movement time (51%) and holding of hand static position (69%). Many cells (56%) were also modulated during preparation for hand movement, in the delayed reach task. Modulation was present also in the dark in 59% of cells during this epoch, 51% during reaction and movement time, and 48% during eye/hand holding on the target. Cells (50%) displaying light-dark differences of activity were considered as related to the sight and monitoring of hand motion and/or position in the visual field. Saccadic eye movements modulated a smaller percentage (25%) of cells than eye position (68%). Visual receptive fields were mapped in 44% of the cells studied. They were generally large and extended to the periphery of the tested (30°) visual field. Sixty-six percent of cells were motion sensitive. Therefore the activity of many neurons in this area reflects the combined influence of visual, eye, and arm movement–related signals. For most neurons, the orientation of the preferred directions computed across different epochs and tasks, therefore expression of all different eye- and hand-related activity types, clustered within a limited sector of space, the *field of global tuning*. These spatial fields might be an ideal frame to combine eye and hand signals, thanks to the congruence of their tuning properties. The relationships between cell activity and oculomotor and visuomanual behavior were task dependent. During saccades, most cells were recruited when the eye moved to a spatial location that was also target for hand movement, whereas during hand movement most cells fired depending on whether or not the animal had prior knowledge about the location of the visual targets.

INTRODUCTION

Most neurophysiological studies of reaching have been devoted to the analysis of motor and premotor cortical mechanisms, regarded as a late stage in the information processing flow leading from vision to movement (for reviews see Caminiti et al. 1996, 1998; Georgopoulos 1996; Wise et al. 1997); some have been devoted to the operations of parietal cortex, considered as an intermediate node responsible for holistic representations of movement (for reviews see Caminiti et al. 1996, 1998; Mountcastle 1995; Wise et al. 1997). No study exists in the literature on the early cortical mechanisms of reaching.

Psychophysical studies (e.g., McIntyre et al. 1997, 1998) indicate that coding of reaching could be achieved through the combination of different information, such as those concerning target location, gaze direction, arm position, and movement direction. Nothing is known about how and where, in the cortex, this combination of information first occurs. Knowledge of signal processing at the early nodes of the parietofrontal network could be of critical importance, because it could reveal "motor" influences on the composition of motor commands and, at the same time, could shed some light on the nature of the visual-to-motor transformation underlying reaching.

Potential candidate for such study are those superior parietal areas that receive substantial visual inputs from peristriate cortex and are linked to frontal premotor areas, and/or to intermediate parietal areas that in turn are linked to frontal cortex (for a recent review see Caminiti et al. 1998). Lesions of these areas in humans result in optic, or visuomotor ataxia (Balint 1909; Rondot et al. 1977; for critical reviews see Battaglia-Mayer et al. 1998; Caminiti et al. 1996; Harvey and Milner 1995), i.e., in a severe and persistent deficit in the execution of arm movements under visual guidance, often associated to disturbances of certain hand postures, such as those necessary to match hand to target orientation in space (Perenin and Vighetto 1988).

Our study of the "early" mechanisms of reaching was addressed at the parietooccipital cortex (PO) (Colby et al. 1988; Gattas et al. 1985). Single-cell activity was recorded in the dorsal part of PO of monkeys while these performed different behavioral tasks aimed at dissociating retinal, gaze, and saccadic signals from arm position and movement direction information. This part of PO has recently been relabeled as area V6A (Galletti et al. 1996). Relationships between neural activity and arm movement in this area have been described in preliminary reports (Battaglia-Mayer et al. 1998; Caminiti et al. 1998, 1999; Galletti et al. 1997; Johnson et al. 1997).

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METHODS

Animals, apparatus, and tasks

Two rhesus monkeys (*Macaca mulatta;* body weights 3.7 and 3.3 kg) were used in this study.

The monkeys sat on a primate chair with head fixed, and the eyes 17 cm in front of a 21-in. touch-sensitive (MicroTouch Systems, Wilmington, MA) computer monitor used to display the tasks and control the animals' hand position.

Monkeys performed six different tasks, in separate blocks. Four arm-reaching tasks were performed with the hand contralateral to the hemisphere where recordings were made. Arm movements originated from a central position and were made toward eight peripheral targets (subtending 1.5° in visual angle) located on a circle of 7.5 cm radius (23.8° visual angle).

To dissociate hand from eye signals, reaches were performed both in the presence and absence of eye movements. To evaluate the influence of the visual feedback about hand movement and static holding in the visual field, reaches were performed both in the light and in the dark.

REACH TASK. This task (Fig. 1) was used to assess the relationships between cell activity and coordinated eye/arm movement. A red center light was first presented, and the animal fixated and touched it with the hand (*a*) for a variable control time (CT, 1–1.5 s). Then, one of the eight red peripheral targets was lit (*b*), in a randomized block design. Within given reaction and movement times (RT, 0.5 s, upper limit; MT, 1 s upper limit), the animal moved the eyes (*b*) and then the hand (*d*) to the target and was required to keep them there (Fig. 1, *e*) for a variable target holding time (THT, 1–1.5 s), before receiving a liquid reward. In this and in all reaching tasks, RT and MT are defined relative to the hand behavior.

REACH-FIXATION TASK. This task (Fig. 1) was used to dissociate eye position, which remained constant, from arm position and move-

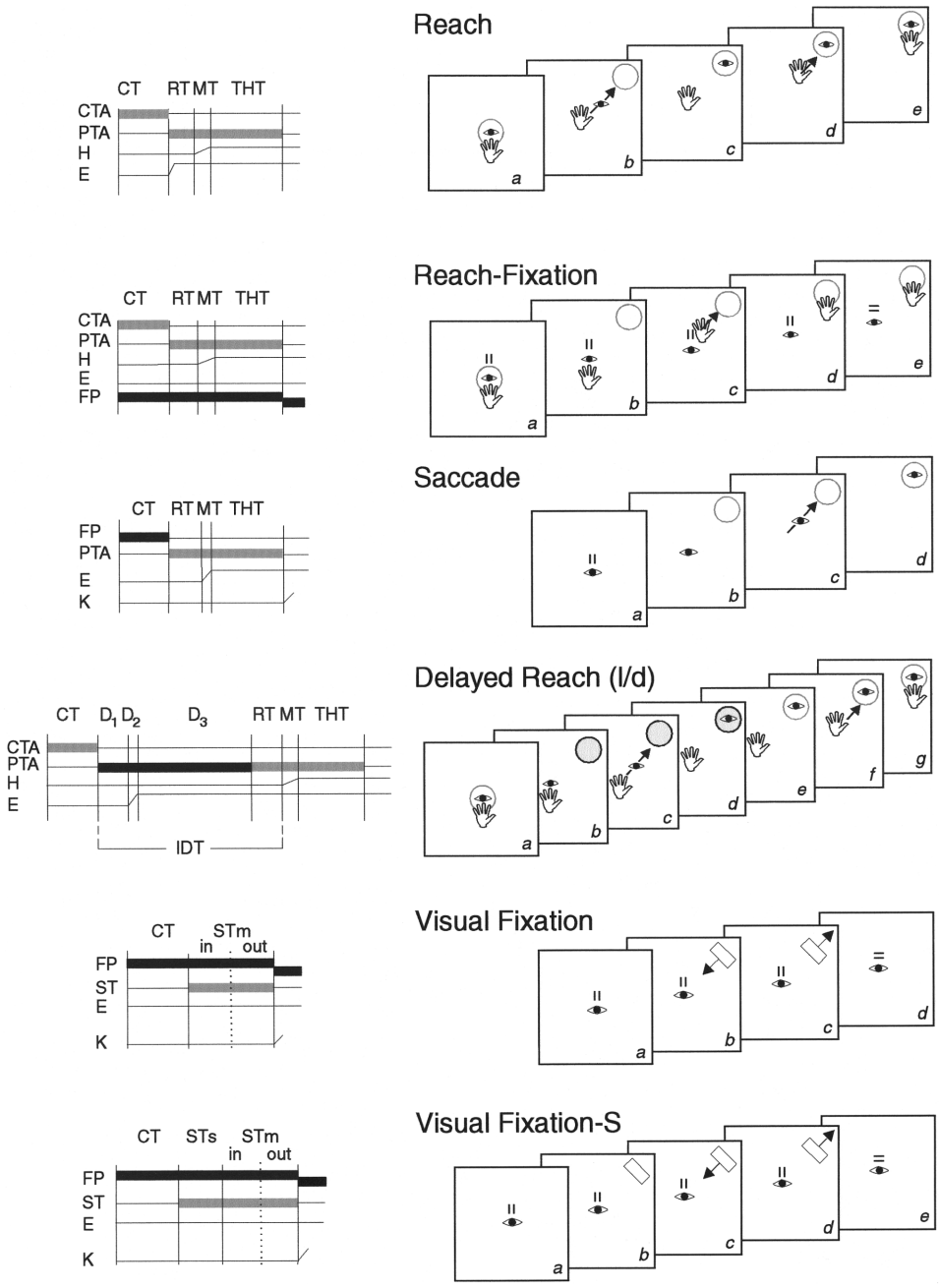


FIG. 1. Temporal and spatial structure of behavioral tasks. Schematic representation of the temporal sequence of the behavioral epochs of the different tasks (*left*). CTA, central target; PTA, peripheral target; H, hand; E, eye; FP, fixation point; K, key; ST, stimulus presentation; CT, control time; STs, stationary presentation of the visual stimulus; STm, stimulus motion inward to the fovea (in) or out (out) from the fovea to the periphery of the visual field. In each *inset* (*right*), white circles represent target position, small arrows indicate the direction of movement of the hand or of the eye in the Reach tasks, of the eye in the Saccade task, and of the visual stimulus, in the Visual Fixation tasks. Small vertical bars in Reach-Fixation, Saccade, and Visual Fixation tasks indicate the fixation point. RT, reaction time; MT, movement time; THT, target holding time. RT and MT are defined relative to the hand behavior in the reaching tasks, relative to the eye behavior, in the Saccade task. In the Reach task, THT refers to combined eye-hand position on the target (*e*), in the Reach-Fixation task, to hand position on the target (*d*), in the Saccade task to eye position on the target (*d*). The Delayed Reach task was performed both under light (*l*) and dark (*d*) conditions*;* white and gray circles indicate red and green targets, respectively. D_1, D_2, indicate eye reaction (*b*) and movement (*c*) times, D_3 is that part of the instructed delay time (IDT) when the eyes are already on the target and the hand prepares to move (*d*); RT (*e*) and MT (*f*) refer to the reaction and movement time of the hand; THT refers to combined eye-hand static position on the target (*g*). In the Visual Fixation tasks, visual stimuli were moved in 16 directions while the animal maintained constant fixation. Small rectangles in each *inset* indicate the visual stimulus, during stationary presentation (Visual Fixation-S, b), moving (arrow) toward the fovea and from the fovea to the periphery of the visual field. The 90° rotation of the fixation point at the end of the trial in both visual tasks is also shown.

ment direction. The monkey fixated the fixation point (consisting of 2 yellow vertical bars of 0.4° side, divided by a narrow black gap) located at the center of the screen and touched a red center light for a variable CT (*a*). Then one of the eight red peripheral targets was lit and the center light extinguished, whereas the fixation point remained on (*b*). The animal had to maintain the central fixation, move the hand (*c*) to the target, and keep it there for a variable THT (*d*), until a 90° rotation of the fixation point occurred (*e*). Behavioral epochs had same duration as in the Reach task.

SACCADE TASK. This task (Fig. 1) was used to assess the relationships of cell activity with saccadic eye movement and with eye position in the orbit. Monkeys made saccades from a common origin to eight targets of the same locations as those used in the arm reaching tasks. A fixation point (see REACH-FIXATION TASK) was presented at the center of the workspace (*a*). During CT (1–1.5 s, *a*), the animal pressed a key (key-down) and kept central fixation. Then one of eight peripheral targets was presented (*b*), in a randomized block design, and the fixation point extinguished. Within given eye RT (0.5 s, upper limit) and MT (0.5–1 s; *c*), the animals made a saccade to the target and were required to keep their eyes immobile there (*d*) for a variable eye THT (1–1.5 s). The target was then extinguished, and the animal had to release the key (key-up), to receive a liquid reward. The key was used to control hand position throughout the task.

DELAYED REACH TASK. In this task (Fig. 1), the target presentation was separated in time from hand movement (MT), and execution of eye movement (D_1, D_2) was separated in time from execution of hand movement (RT, MT). The animals fixated and touched a red center stimulus (*a*) for a variable control time (CT, 1–1.5 s). Then one of eight green targets was lit (*b*), as instruction signal (IS) for the next intended arm movement. After a variable reaction time (D_1; *b*) and movement time (D_2; *c*), the eye achieved the green target (*d*) and stayed there for the remainder (D_3; *d*) of the instructed-delay time (IDT, 1–2.5 s; *b–e*) and during the upcoming hand movement and static holding on the target (*e–g*). During the entire IDT the animal was required to withhold the hand movement until the green IS was turned red (*e*). This was the go-signal (GS) for the hand to reach toward the target. Within given RT (0.5 s, upper limit; *e* and *f*) and MT (1 s, upper limit; *f*), the hand achieved the target and stayed there for a variable THT (1–1.5 s; *g*). The duration of D_1 and D_2 was determined in off-line analyses. The monkeys performed the task under both normal light (*l*) conditions and in darkness (*d*; green target, 21 cd/m^2; red target, 3 cd/m^2).

VISUAL FIXATION TASK. This task (Fig. 1) was used to determine visual responses and presence, position, and extent of the visual receptive field of individual cells. A fixation point (see REACH-FIXATION TASK) was presented at the center of the workspace (*a*). During the control time (CT, 1–1.5 s) the monkeys fixated the fixation point and kept the key-down (*a*). A visual stimulus was then moved in 1 of 16 directions (22.5° angular intervals) from the periphery of the visual field inward (in) toward the fovea (*b*) and outward (out) from the fovea to the periphery (*c*). At the end of the fixation time, the visual stimulus was extinguished, and the animal had to detect a 90° rotation of the fixation point (*d*), by releasing the telegraph key (key-up). In other instances (Visual Fixation-S), the visual stimulus was initially presented in a stationary fashion (*b*) for a variable time (0.5–1 s) and then moved in the visual field as described above. Stimuli consisted of white solid bars (3.27 × 7.60°) or of bars of static or dynamic random dots and were moved at constant speed (25°/s) during attentive fixation. Visual stimuli were presented up to 30° eccentricity.

Behavioral control

Hand position was monitored using the touch screen, with 0.28 × 0.3 mm (1 screen pixel) resolution. Hand accuracy was controlled through 3 cm diam circular windows (10° visual angle). Eye position signals were recorded by using implanted scleral search coils (1° resolution) and sampled at 100 Hz (Remmel Labs, Ashland, MA). Fixation accuracy was controlled through circular windows (7.5° diam) around the targets. Eye velocity was calculated in off-line analysis. The onset time of the saccade was defined as the time when eye velocity exceeded 50 and 180°/s, respectively, in the two adjacent 10-ms intervals beginning at the onset time of change of eye velocity. The end of the saccade was defined as the time when eye velocity fell below 50°/s.

Neural recording

The activity of single neurons was recorded extracellularly. A 7-channel multielectrode recording system (System-Echkorn, Thomas Recording, Marburg, Germany) was used. Electrodes were glass-coated tungsten-platinum fibers (1–2 MΩ impedence at 1 kHz), sometime "labeled" with the fluorescent carbocyanines DiI or DiI-C5 (Molecular Probes, Eugene, OR), to facilitate reconstruction of the microelectrode penetrations on the histological material. The eye-coil, recording chamber and head-holder were implanted aseptically under general anesthesia (pentobarbital sodium, 25 mg/kg iv). The recording chamber was placed on the midline, at stereotaxic coordinates P 14.

Data analysis

ANALYSIS OF CELL MODULATION. The mean firing rates during the different epochs of the task were calculated for each trial. Some epochs were adjusted to avoid that effects in one time interval influenced another one. In all tasks, activity during the first 500 ms of CT and THT was removed from the analysis, to prevent potential effects of previous eye and/or hand movement on cell activity. To avoid carry-over effects of eye movements on neural activity during preparation for arm movement, neural activity during the first 100 ms after the end of eye movements (D2) in the Delayed Reach tasks was excluded from the analysis. The data were analyzed by using the repeated measures model provided by 5V program of the BMDP statistical package (Statistical Software, Los Angeles, CA), to assess *1*) significant modulation (Wald χ^2 test) of cell activity during different epochs (or combinations of them, i.e., RT + MT = RMT) of the same task, relative to the control time; *2*) significant changes of cell activity with movement direction and static position of eye and/or hand; *3*) differences of cell activity during similar or different epochs of different tasks; and *4*) the interaction term (task × direction) of the repeated measure ANOVA was used to assess differences in the directional properties of cells across task conditions. The significance level for all statistical tests was set at $P < 0.05$.

From the information available during the control time, the animal knew in advance which task had to be performed. Some cells showed significant changes of activity during the CT of different conditions (Reach/Reach-Fixation, Delayed Reach light/dark). In such instances, the CT of each task was used as a covariate in the repeated measures analysis.

For each individual cell, a directional modulation index *D* (Johnson et al. 1996) was computed to quantify differences in activity across directions. For each neuron *n* and each epoch *i*, the amount of directional activity D_{ni} was computed as

$$D_{ni} = \max_j (f_{nij}) - \min_j (f_{nij})$$

where f_{nij} is the mean firing frequency of cell *n* during epoch *i* for movement direction *j*. $\max_j$ and $\min_j$ are the functions that take the maximum and the minimum over all directions *j*, respectively. This index is a measure of directional modulation but does not provide information about the cell modulation relative to the control time. Therefore a second modulation index M_{ni} associated to each cell *n* and epoch *i* was computed as

$$M_{ni} = \frac{f_{ni} - f_{nc}}{f_{nc}}$$

where f_{ni} is the mean frequency across repetitions and directions of the cell n during epoch i, and f_{nc} is the mean frequency of the same cell during the CT.

These indices were plotted as cumulative frequency distributions and were used to compare (Kolmogorov-Smirnov test, $P < 0.05$) the proportion of cells that showed significant modulation (index M) or significant directional changes (index D) across epochs and task conditions.

Color-coded maps of the visual receptive field were created off-line from data collected during the Visual Fixation task. For each trial, the arrays of neuronal spikes were divided into 16 bins located along the movement trajectory of the visual stimulus, at even intervals, with each bin representing a specific area of the visual field. Any given spike was allocated to a specific bin based on the trial and the time of spike occurrence. This assumes that any activity of the cell is due to the presence of the visual stimulus. The number of spikes in each bin was then divided by the time the visual stimulus stayed in that bin, to obtain the frequency of cell discharge in that particular part of the visual field. The cell activity in each discrete area of the visual field was normalized by averaging the activity of the three closest bins.

DIRECTIONAL RELATIONSHIPS. A cosine tuning function with adjustable width (Amirikian and Georgopoulos 1998) was used to describe the relationships between cell activity and direction of movement. In our two-dimensional experimental setup, the angular variable of interest is the location of the target, univocally determined by the angle α, varying from 0 to 360°.

The standard cosine function (Georgopoulos et al. 1982) has the general form

$$y_1(\alpha) = A + K \cos (\alpha - C) \quad (1)$$

where $y_1(\alpha)$ is the frequency of neuronal discharge and A, K, and C are the regression coefficients characteristic for each neuron. This standard cosine function (1) implies that the cell has a directional tuning with fixed width. To account for variations in the breadth of the fitting curve, a more general cosine model was used.

The new function that describes neural activity is defined as

$$y_2(\alpha) = \begin{cases} A + K \cos (x*S) & \text{if } |x*S| < \pi \\ A - K & \text{elsewhere} \end{cases} \quad (2)$$

where the transformation $x = \arccos [\cos (\alpha - C)]$ has been performed to guarantee that the function is periodic, with a period of 2π.

In this model A, K, C, and S are regression coefficients determined by a least-squares method (BMDP,3R). The three parameters A, K, and C play the same role as in the standard cosine function (C still representing the *preferred direction*), whereas S is the additional parameter that controls the *tuning width*. This parameter defines the angular interval in which $y_2(\alpha)$ is cosine modulated, therefore for the particular case of $S = 1$, (2) reduces to (1), whereas $S < 1$ corresponds to a broader function and, on the contrary, $S > 1$ to a sharper one, relative to the simple cos (α). For the goodness-of-fit, a coefficient of determination $R^2 \geq 0.7$ was used as threshold to assess whether or not neural activity was directionally tuned.

Because a fitting curve was calculated from average firing frequency during all the epochs of the Reach, Reach-Fixation, Delayed Reach (l-d), and Saccade tasks, several preferred directions were obtained for each neuron, depending on the epochs in which the cell was directionally tuned ($R^2 \geq 0.7$). A global measure of the tuning properties of each neuron was computed for those cells directionally tuned in at least three different epochs. Each preferred direction was considered as a unit vector, and the *mean vector* was computed as the resultant of the new sample of vectors of unit length (Batschelet 1981). The angle of this vector is the *mean direction* of the sample, and its length is the *mean resultant length*, that lies in the range (0, 1). It is a measure of the concentration of the population of preferred directions. To assess whether the distribution of the preferred directions of each neuron was unimodal, i.e., if the mean vector differed significantly from zero, the Rayleigh test of randomness ($P < 0.05$) was performed. For those cells that showed a unimodal distribution, the *angular deviations* were calculated as a measure of dispersion (Batschelet 1981) of their preferred directions and plotted as frequency distribution. Finally, the Rayleigh test of uniformity (Batschelet 1981) was performed on all the mean directions.

RESULTS

Neurophysiological database

Seventy-one microelectrode penetrations were made in two animals in a regions of the superior parietal lobule that has been identified as area V6A, on the basis of two main criteria: *1*) the histological reconstructions of the tracks of the electrodes "labeled" with DiI or DiI-C5 (Fig. 2*B*) on the histological material and *2*) the pattern of association connection of the region where most penetrations (62) were made, in one animal (Fig. 2, *A* and *C*). At the end of the neurophysiological recording session, the region of recording and the ipsilateral rostral (PMdr, F7) and caudal (PMdc, F2) dorsal premotor cortex (Barbas and Pandya 1987; Matelli et al. 1985) were injected for the anatomic study of their association connections (Caminiti et al. 1999). The zone of recording was linked to parietal areas 7m, MIP (medial intraparietal) and PEa, and, to a lesser extent, to frontal area PMdr (F7) and PMdc (F2). Additional, less substantial connections were observed with F5, 7a, ventral (VIP) and lateral (LIP) intraparietal areas. This pattern of association connections conforms to that of other studies of V6A (Matelli et al. 1998; Shipp et al. 1998).

Qualitative observations on the visual responsiveness of cells was made by presenting and moving on the screen search stimuli of different size, orientation, and colors. This was possible thanks to an interactive computer program that required attentive fixation by the monkey while visual stimuli were manipulated by the experimenter through the computer mouse. Cell firing during natural reaching movements to objects of interest was also used as a criterion of selection.

Table 1 offers a summary of the basic results obtained from those cells that were analyzed in a quantitative way in the different tasks. Ninety-five cells were studied in the Reach, 93 in the Reach-Fixation, 92 in the Saccade, 123 during the Delayed Reach-light, 75 during the Delayed Reach-dark, and 99 in the Visual Fixation tasks. Fifty-seven cells were studied in all behavioral tasks and were used for comparison of cell activity across task conditions.

Visual properties of V6A neurons

The visual properties of neurons in the cortex of the rostral bank of the parietooccipital sulcus have been described by previous works (Colby et al. 1988; Galletti et al. 1991; Gattas et al. 1985). In our study, the Visual Fixation tasks were used to assess the basic visual feature of neurons in the dorsalmost part of traditional area PO, recently relabeled as area V6A (Galletti et al. 1996, 1999). This was a necessary step to evaluate the influence of visual signals on the neural activity observed during the different reaching tasks.

We were able to map the visual receptive fields (Fig. 3) of 44/99 (44%) cells. They were generally large and located in the periphery of the visual field. Thirty cells (68%) had a bilateral receptive field (Fig. 3, *C* and *D*), and 11 (25%) had a contralat-

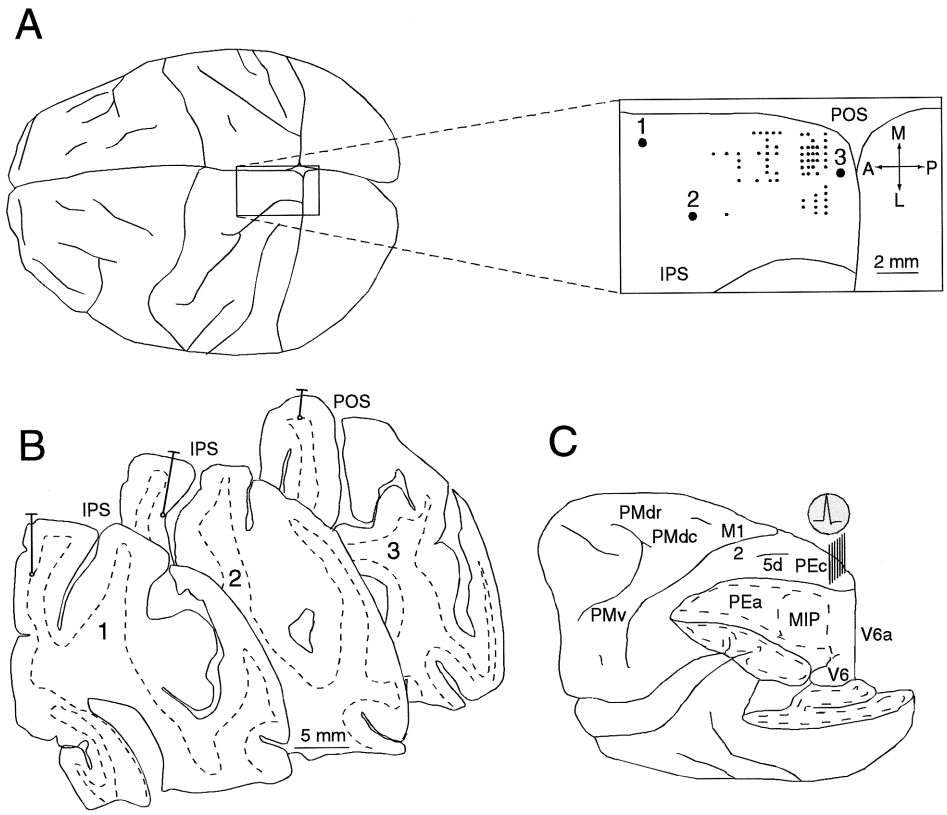


FIG. 2. *A*: brain figurine with reconstruction of the entry sites (*inset*) of microelectrode penetrations in the posterior part of the superior parietal lobule of one animal. Penetrations were rostral to the parietooccipital sulcus (POS) and medial to the intraparietal sulcus (IPS), as determined through the histological identification (*B*) of the microelectrode penetrations of reference (entry point: large black dots 1–3 in the *inset* of *A*), made by "labeling" the electrodes with fluorescent carbocyanines. A, anterior; P, posterior; M, medial; L, lateral. *C*: schematic representation of the recording performed through a 7-channel multielectrode (thin vertical lines) system in the cortex of the rostral bank of the POS, exposed after "removal" of large part of the inferior parietal lobule. M1, primary motor area; PMdc, dorsocaudal premotor area; PMdr, dorsorostral premotor area; PMv, ventral premotor area; MIP, medial intraparietal area.

eral one (Fig. 3*B*), whereas 3 (7%) cells were responsive to stimuli presented in the ispilateral quadrants of the visual field only. In only one instance (Fig. 3*D*) we were able to map a receptive field centered on the fovea, although those of many cells included the fovea.

The quantitative analysis (ANOVA) showed that 4/44 (9%) cells were modulated only by visual stimuli moving inward (IN) toward the fovea, 1/44 (2%) cells responded only to stimuli moving outward (OUT) from the fovea to the periphery of the visual field, whereas 39/44 (89%) were significantly modulated by both inward and outward component of stimulus motion. Among these, a significant difference of activity between the inward and the outward motion was observed in 24/39 (62%) cells. Therefore 29/44 (66%) cells were sensitive to stimulus motion. Finally, 33/44 (75%) cells were sensitive to the stationary presentation of the visual stimulus (Visual Fixation-S task).

The presence of visual properties in many V6A cells must be considered when evaluating neuronal activity observed during reaching, because activity during hand movement and static postures might depend, at least in part, on stimulation of the cell's visual receptive field. Therefore influences of arm movement and/or position on neuronal activity can only be assessed by comparing cell modulation across similar and/or different epochs of the different tasks employed in this study.

Arm- and eye-related influences on V6A neuronal activity

SINGLE-CELL ANALYSIS. Figures 4 and 5 illustrate the activity of a typical cell of V6A in the form of rasters and directional tuning curves across epochs and task conditions. In the Reach task the activity of this cell was directionally modulated and

TABLE 1. *Modulation of cell activity relative to the control time, and across tasks comparison of cell activity (repeated measures ANOVA), during different epochs*

Task	*n*	RT	MT	THT
Reach	95	68 (72)	59 (62)	61 (64)
Reach-Fixation	93	63 (68)	54 (58)	60 (64)
Saccade	92	19 (21)	23 (25)	63 (68)

Task	*n*	$D_1 + D_2$	D_3	RMT	THT
Delayed Reach 1	123	67 (54)	63 (56)	74 (60)	67 (54)
Delayed Reach d	75	33 (44)	44 (59)	38 (51)	36 (48)

Reach-Fixation/ Reach	*n*	RT	MT	THT
Modulation of activity	87	39 (45)	44 (51)	60 (69)
Task × direction interaction	87	25 (29)	45 (52)	61 (70)

Delayed Reach 1/d	*n*	$D_1 + D_2$	D_3	RMT	THT
Modulation of activity	74	26 (35)	42 (57)	40 (54)	36 (49)
Task × direction interaction	74	18 (24)	34 (46)	35 (47)	33 (45)

Numbers in parentheses are percentages; *n* is number of cells. RT, reaction time; MT, movement time; THT, target holding time; RMT, RT + MT; $D_1 + D_2$, eye reaction and movement time; D_3, hand movement delay time.

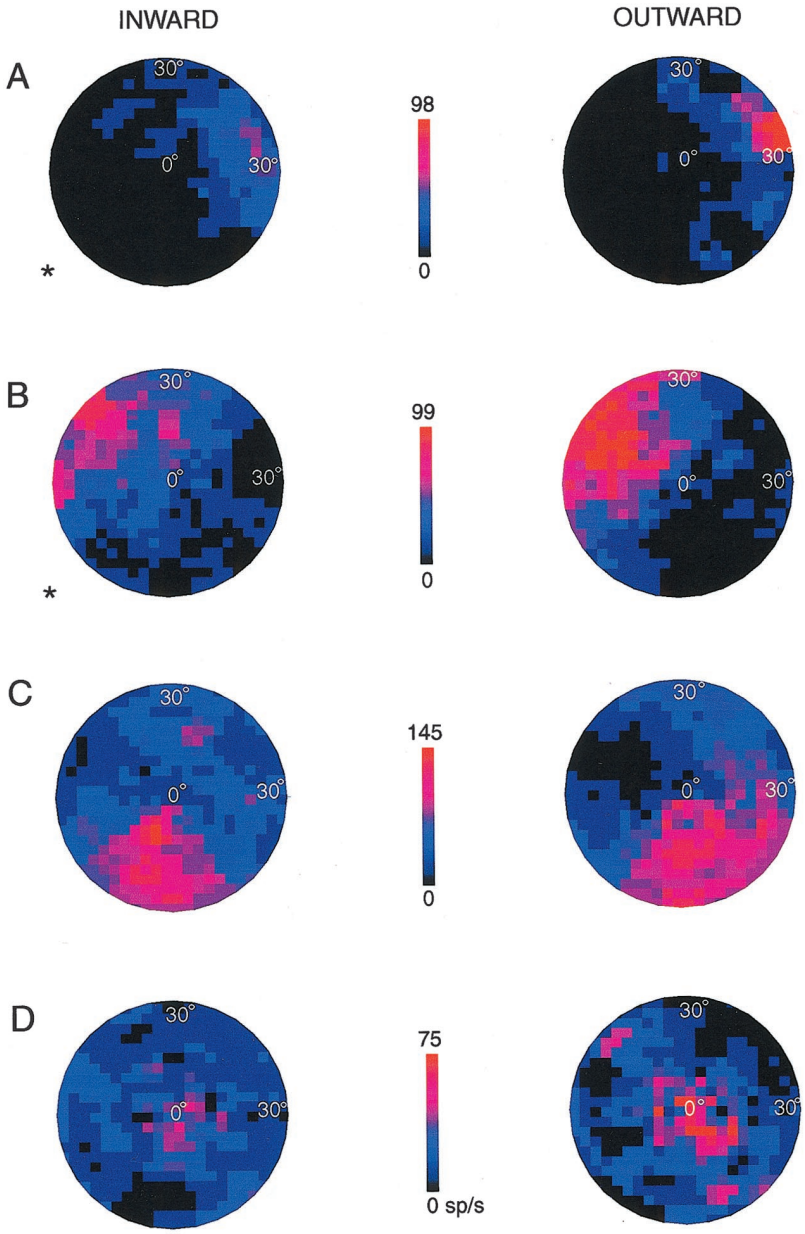


FIG. 3. Visual Fixation task. Color-coded maps of the frequency of neuronal discharge (see color-coded scale of spike frequency) during IN and OUT components of stimulus motion. These maps show the location and extent of the visual receptive field and the motion sensitivity of different cells. Asterisks indicate cell studied simultaneously. These cells, with receptive field located in the contralateral (*A*) and ispilateral (*B*) upper quadrant of the visual field were located 915 μm apart in the tangential cortical domain.

tuned in all epochs, but during combined eye-hand static holding on the targets (THT). In the Reach-Fixation task, the directional tuning remained significant and virtually unchanged during hand RT and MT; cell activity was also broadly tuned to static holding of the hand on the targets (THT), when eye position was constant. In the Saccade task, this cell's activity was not directionally tuned in any epoch. The visual receptive field of this cell (Fig. 4*F*), when mapped through stimuli moving inward to the fovea, extended over both the ipsi- and the contralateral upper quadrants of the visual fields, but occupied part of the ipsilateral upper quadrant only when studied through visual stimuli moving outward from the fovea. The extension of this field overlaps the 90–180° region of the directional continuum of the workspace of the hand. Thus the modulation observed during different epochs of the Reach-Fixation task could not be attributed to the stimulation of the visual receptive field, because cell activity was maximal when the hand prepared to move and moved, or remained immobile, within the contralateral upper quadrant, as also shown by the orientation of the cell's preferred directions (PD) during arm movement (MT; PD = 63°) and static position (THT; PD = 92°) of the Reach-Fixation task (Figs. 4*G* and 5). From the analysis in this first group of behavioral tasks, we can conclude that cell activity relates in an orderly directional fashion to hand reaching and position in space. In the Delayed Reach task (Figs. 4, *D* and *E*, and 5) this cells showed significant directional tuning during eye movement time (tuning curves not shown in Fig. 5; see Fig. 4*D*), during planning (D_3) and execution (RMT) of arm movement, under both light and dark conditions, and, during holding of static hand position (THT) in the dark. Significant light/dark differences of cell activity (ANOVA) were observed only during hand static holding on the targets (THT), suggesting that neural activity was also modulated by the sight of the hand in the visual field.

A remarkable feature of the directional properties of this cell emerged when the preferred directions computed during dif-

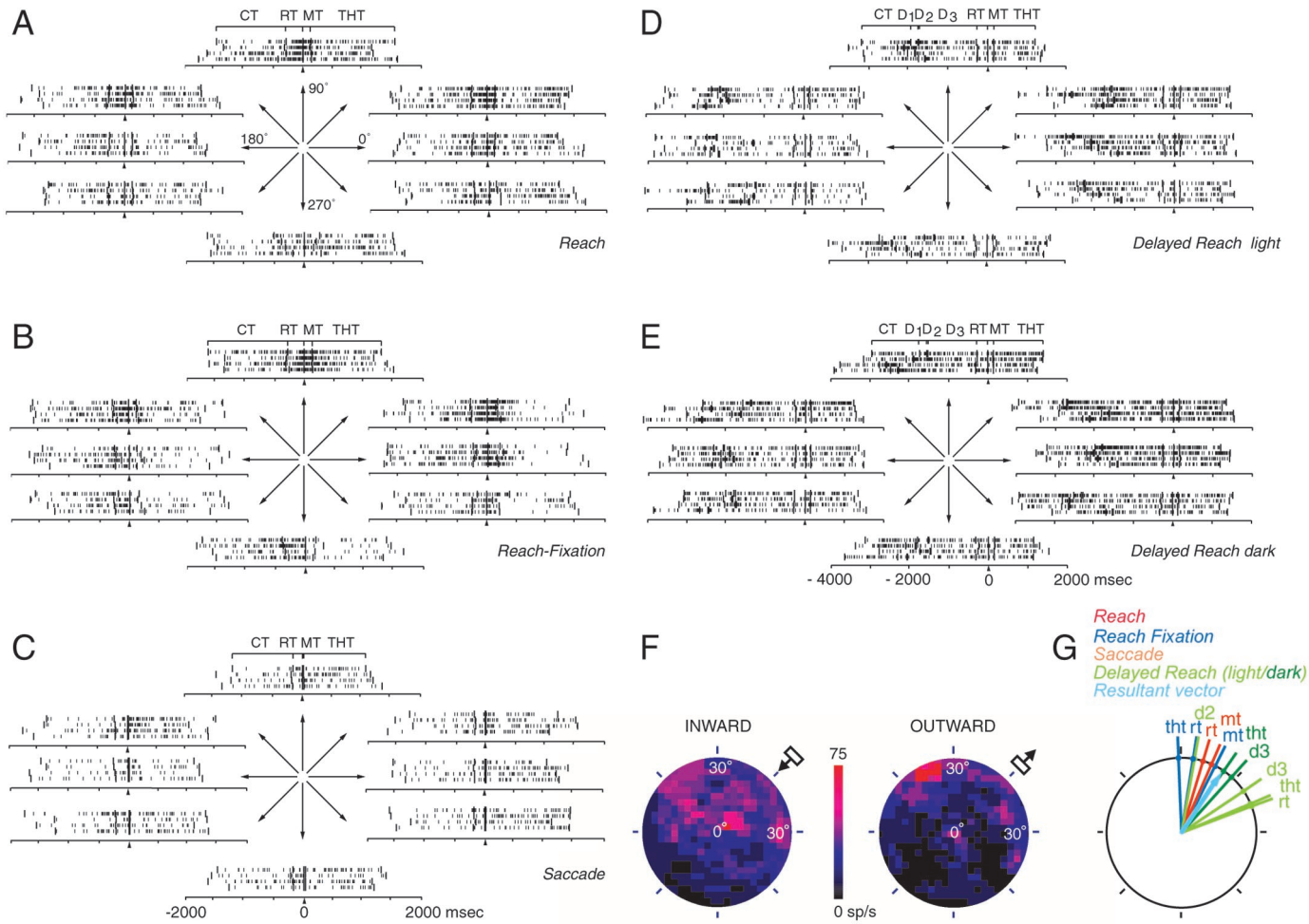


FIG. 4. Impulse activity of a neuron studied during the Reach (*A*), Reach-Fixation (*B*), Saccade (*C*), Delayed Reach, under light (*D*) and dark (*E*) conditions, and in the Visual Fixation (*F*) task. Rasters of 4 replications for every movement direction (arrows) were aligned to the hand movement onset (small arrow under temporal axis) in *A*, *B*, *D*, and *E*, and to eye movement onset in *C*. Thin vertical lines indicate the occurrence of an action potential; thick vertical lines define the behavioral epochs. In the Delayed Reach task, D_1 and D_2 indicate eye RT and MT; D_3 indicates the segment of the instructed delay time referring to preparation for next intended hand movement; RT and MT indicate hand reaction and movement time, respectively; THT refers to holding of combined eye-hand position at the target. *F*: color-coded maps of the frequency of neuronal discharge during inward and outward components of stimulus motion in the Visual Fixation task. These maps define the location and extent of the visual receptive field of the cell. *G*: field of global tuning. Each colored vector, represented on a circle of unit radius, is a significant ($R^2 \geq 0.7$) cell's preferred direction, computed during a given task epoch (color). The thick blue sky vector is the mean resultant vector ($P = 0.00$) of the sample ($n = 11$) of preferred directions. Its mean direction was 58°; its length, the mean resultant length, was 0.92. The angular deviation of the preferred directions was 22.7°.

ferent epochs of all tasks were plotted together (Fig. 4*G*), because their orientations clustered within a restricted spatial field of the eye and hand workspace that occupied 72° of the directional continuum. We will refer to it as field of "global" tuning.

Interesting differences in this cell's activity were noticed during both eye and arm movement across task conditions. In the Saccade task (Fig. 4*C*), neural activity was not directionally tuned during eye reaction and movement time, and it was only weakly modulated (relative to the control time) during eye movement time; on the contrary, this neuron fired significantly during the same epochs of the Delayed Reach task (Fig. 4, *D*, *E*, and *G*). Furthermore, cell activity was strong during arm movement (Figs. 4, *A* and *B*, and 5) in the Reach and Reach-Fixation tasks, but weaker during the same epochs of the Delayed Reach task (Figs. 4, *D* and *E*, and 5).

Of 55 cells active during saccades in the Saccade (RMT) and/or in the Delayed Reach (D_1-D_2), 24 (44%) were active in both tasks. Their activity was therefore context independent. On the contrary, 25 (45%) cells were modulated when saccades were made in the context of the Delayed Reach task, whereas the opposite was true for 6 (11%) cells. In conclusion, the activity of 56% of the cells studied under these conditions displayed a task-dependent relationship to eye movement. The highest proportions of cells were recruited when saccades brought the eye to a spatial location that was also target for hand movement.

Similarly, of 73 cells modulated during the Reach and/or Delayed Reach tasks, 42 (57%) were active during hand movement in both tasks, 16 (22%) were active only in the Delayed Reach, whereas 15 (21%) were active only in the Reach task. Thus cells showing context dependency of their activity during hand movement were 43% of the sample. A plausible explanation for this observation is that in the Delayed Reach, hand

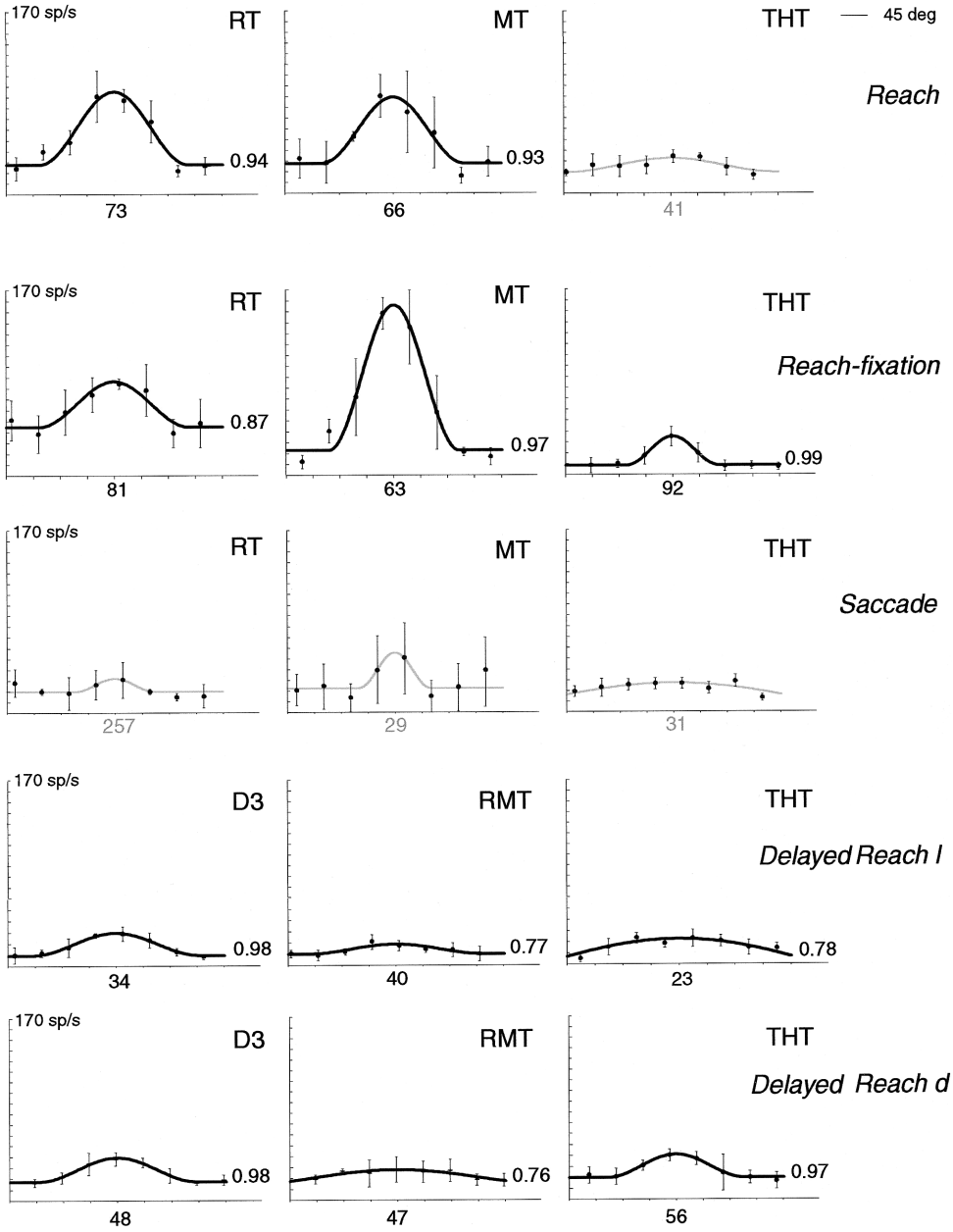


FIG. 5. Directional tuning curves of the cell shown in Fig. 4, during different epochs and task conditions. In each graph, the number under the abscissa indicates the cell's preferred direction, that on the right of the tuning curve the value of the coefficient of determination R^2 for the goodness-of-fit (see METHODS). A significant fit required $R^2 \geq 0.7$ (black curves). Whenever the fit was not significant (gray curves), the value of the R^2 was not shown. Each division on the abscissa corresponds to 45°.

movement direction was precued by the instruction signal, and therefore hand movement was made under conditions of spatial certainty. On the contrary, the Reach task was a typical reaction time task where the animal could not predict where the target would appear. Hand movement was therefore made in conditions of spatial uncertainty. These results point to the existence of temporary and task-dependent relationships of cell activity to eye and arm movement in this area and postulate the need of a multiple-task approach before any assignment of cell functions is made.

Figures 6 and 7 show the activity of another cell of V6A. This cell was modulated in all epochs of Reach, Reach-Fixation and Saccade tasks (Fig. 6, *A–C*) and displayed significant directional tuning during some of them (Fig. 7), such as combined eye-hand holding (Reach, THT), hand holding (Reach-Fixation, THT), and eye holding (Saccade, THT) on the target. Therefore it was influenced by eye and hand position signals, which were probably interacting on cell activity when the hand position was coincident with the fixation point (Reach, THT). In such an instance (Fig. 7), in fact, cell activity was greater than during isolated eye (Saccade, THT) or hand (Reach-Fixation, THT) holding in the periphery of the visual field. This cell was also directionally tuned during arm movement (Reach-Fixation, MT), when eye position was constant (Fig. 7). The cell's visual receptive field was large and bilateral and extended over the ipsilateral upper quadrant and both contralateral quadrants of the visual field (Fig. 6*F*). Therefore the modulation observed during arm movement and static position in the Reach-Fixation task could be attributed to the stimulation of the cell's visual receptive field by hand movement and static posture. This, however, cannot explain the clustering of the cell's preferred directions from these epochs within a limited sector of the hand workspace, the sector that overlaps only one part of the visual receptive field, which is located in

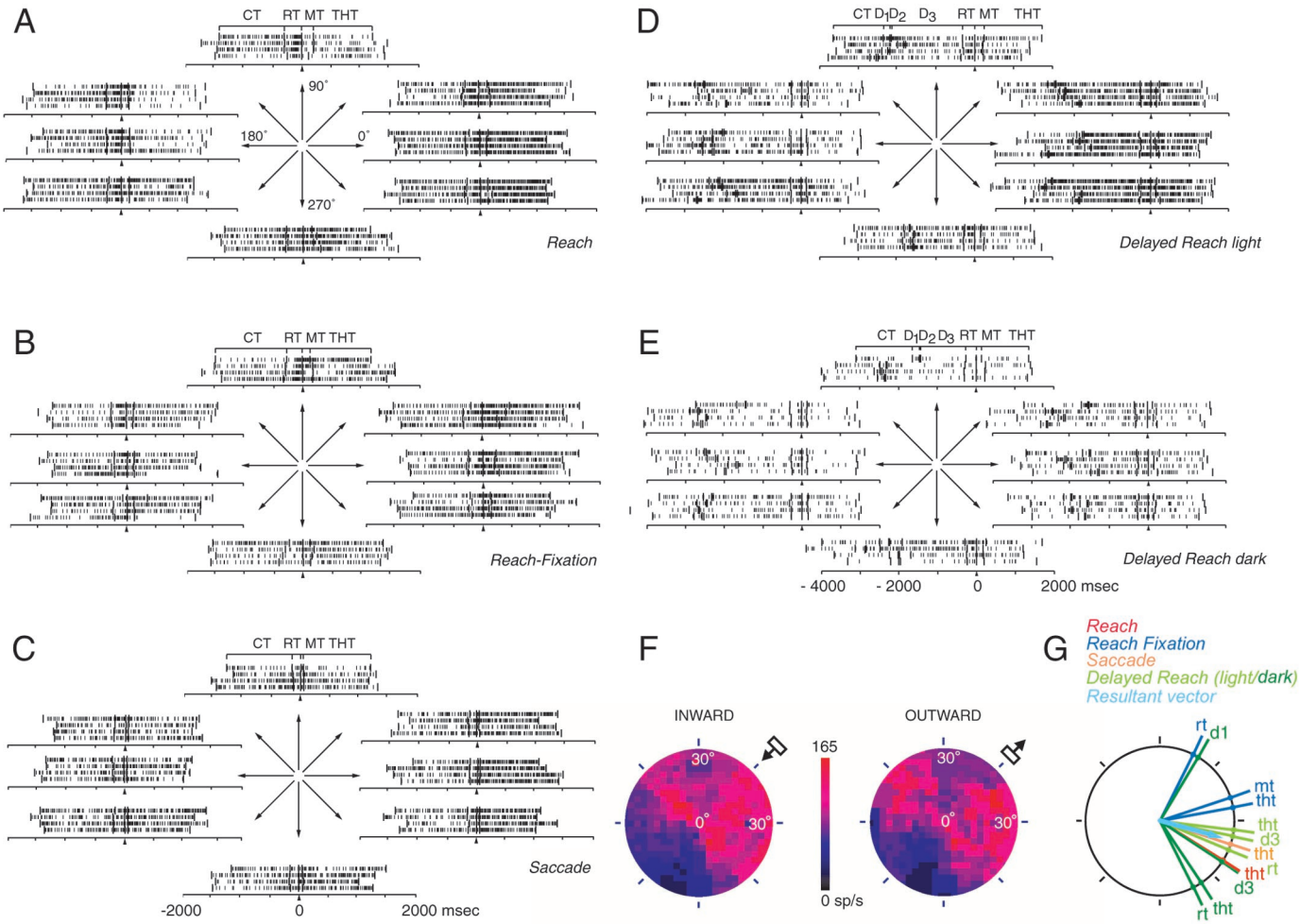


FIG. 6. Impulse activity of a neuron studied during the Reach (*A*), Reach-Fixation (*B*), Saccade (*C*), Delayed Reach, under light (*D*) and dark (*E*) conditions, and in the Visual Fixation (*F*) task, during inward and outward components of stimulus motion. Conventions and symbols as in Fig. 4. *G*: field of global tuning. The mean resultant vector ($P = 0.00$) of the sample ($n = 12$) of preferred direction had mean direction at 350.5°. Its length, the mean resultant length, was 0.80. The angular deviation of the preferred directions was 36.5°. Conventions and symbols as in Fig. 4.

the contralateral quadrants. "Apparent" hand movement- and position-related activity merely dependent on the stimulation of the visual receptive field should have been detected also when the hand moved and stayed in the ispilateral upper quandrant, where cell activity was very high in the Visual Fixation task. This was not the case.

The analysis of cell activity in the Delayed Reach tasks (Figs. 6, *D* and *E*, and 7) showed significant modulation and light/dark differences in all epochs. The directional tuning (Fig. 7) was significant and with light-dark changes in the shape and width of tuning curves during preparation for hand movement (D3), hand movement (RMT), and holding of active hand position (THT). It is remarkable that, in spite of changes in the amount of modulation across epochs and task condition, the preferred directions of the cell during planning of arm movement and arm movement remained identical (Delayed Reach, D_3) or very similar (Delayed Reach, RMT) to that observed during eye holding (Saccade, THT). This suggests that this cell's activity was probably related to the preparation and execution of hand movement toward the fixation point. In conclusion, the activity of this visually responsive neuron was modulated by an eye position signal, by the sight of the hand and by its movement in the visual field, and by the direction of the planned hand movement toward the fixation point. The field of global tuning (Fig. 6*G*) for this cell was broader than that of the previous one and extended over 127° of the directional continuum.

NEURONAL ACTIVITY TYPES IN V6A. The analysis of the two previous cells indicates that, in addition to visual inputs, eye- and arm-related signals influence cell activity in V6A.

Reach-related activity was rather common (Table 1) in this region, during both combined eye-hand movements to foveated targets (Fig. 8*A*; Reach RMT), and during reaches to extrafoveal targets (Fig. 8*A*; Reach-Fixation, RMT), when eye position was kept constant. In this cell, neural activity changed significantly across these conditions, suggesting that reach-related activity was modulated by eye position. At the population level (Table 1), significant main task effects (Reach vs. Reach-Fixation) were observed during both hand reaction and movement time in about half of the cells studied. Significant directional activity during RT and MT of the Reach-Fixation task was observed, respectively, in 20/42 (48%) and 18/42 (43%) cells that were not

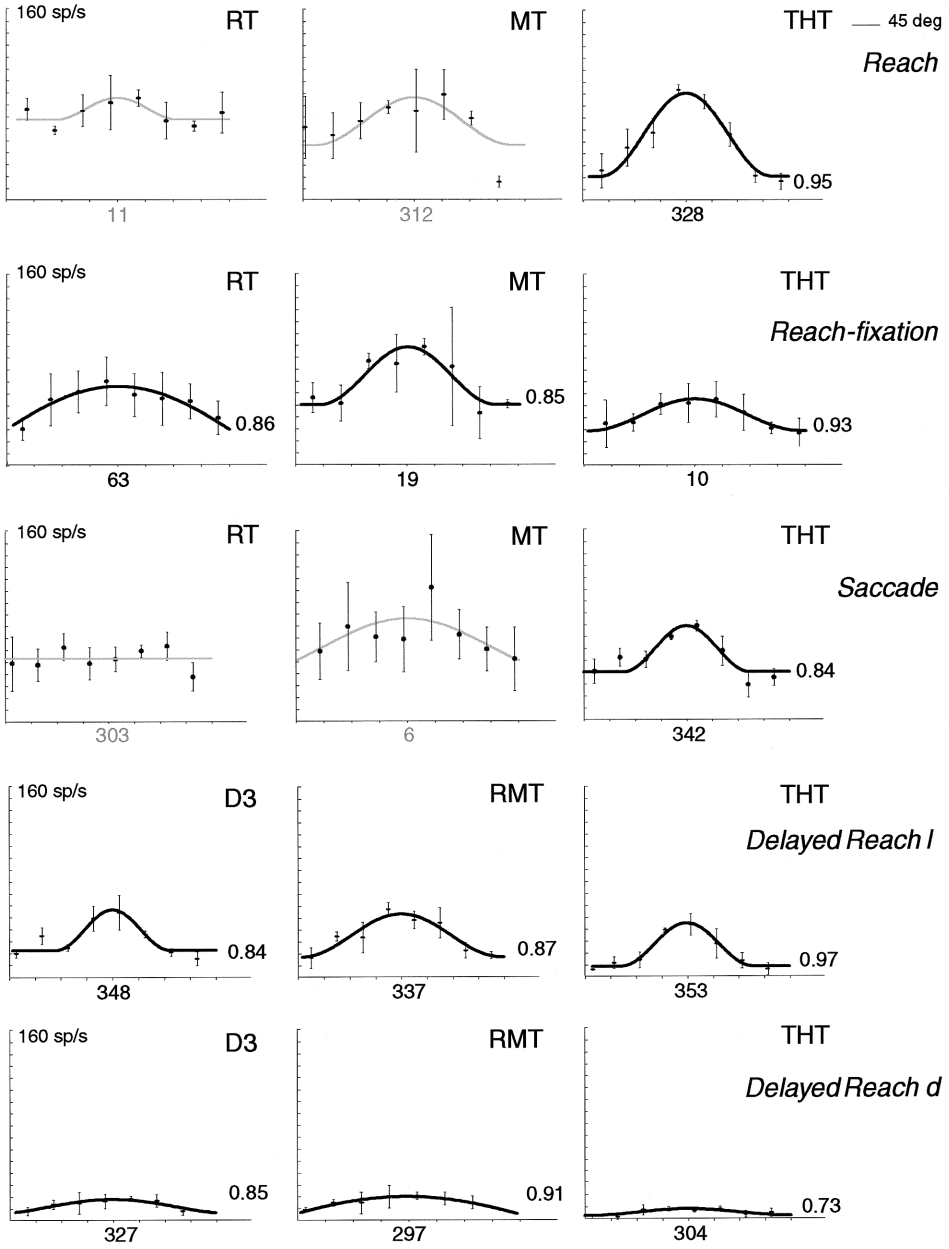


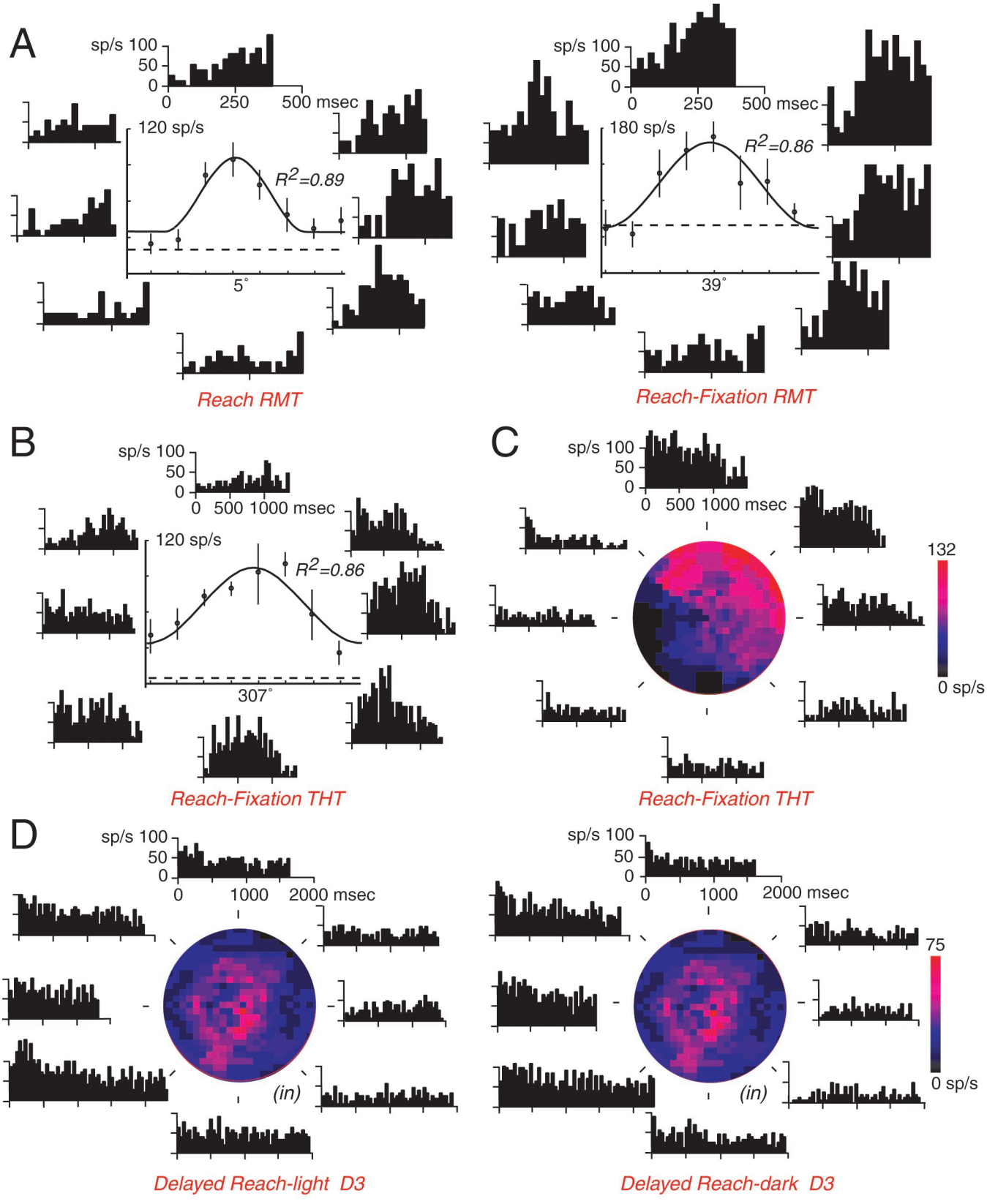
FIG. 7. Directional tuning curves of the cell shown in Fig. 6, during different epochs and task conditions. Conventions and symbols as in Fig. 5.

visually related. These cells were therefore influenced by a genuine hand movement signal.

Static holding of the hand on the target (Reach-Fixation, THT) revealed the existence of hand position signals (Table 1). These signals were often observed in cells that did not have a visual receptive field (16/32; 50%; Fig. 8*B*). However, hand position–related activity could also be sustained by visual activity, i.e., by the sight of the hand in the visual field. In the cell of Fig. 8*C*, neural activity varied significantly when the hand occupied different parts of the cell's visual receptive field and decreased to control level when the hand was immobile on other parts of it, as in the case of the target at 135°. This suggests the coexistence of visual and hand position signals in this cell's activity.

Another interesting aspect concerns the possibility of a combined influence of eye and hand position information on cell activity. The comparison of neural activity when the hand was on the target with or without concomitant presence of the eye (Reach vs. Reach-Fixation, THT) showed significant main task effects in ~60% of the cells studied (Table 1). Therefore these neurons might combine signals concerning eye position in the orbit and hand position in space.

Neural activity related to preparation for hand movement during the delay time (Delayed Reach, D_3, Table 1) was also observed, under both light and dark conditions. Figure 8*D* illustrates the case of a cell endowed with a large bilateral visual receptive field, and displaying significant directional activity during preparation for hand movement, both in the light and in darkness. Thus cell modulation related to the preparation for hand movement does not seem to depend on the sight of the hand in the visual field, as also suggested by its directional nature in an epoch during which the hand position in the visual field remained constant. Nevertheless, the existence of significant light/dark differences of activity indicates



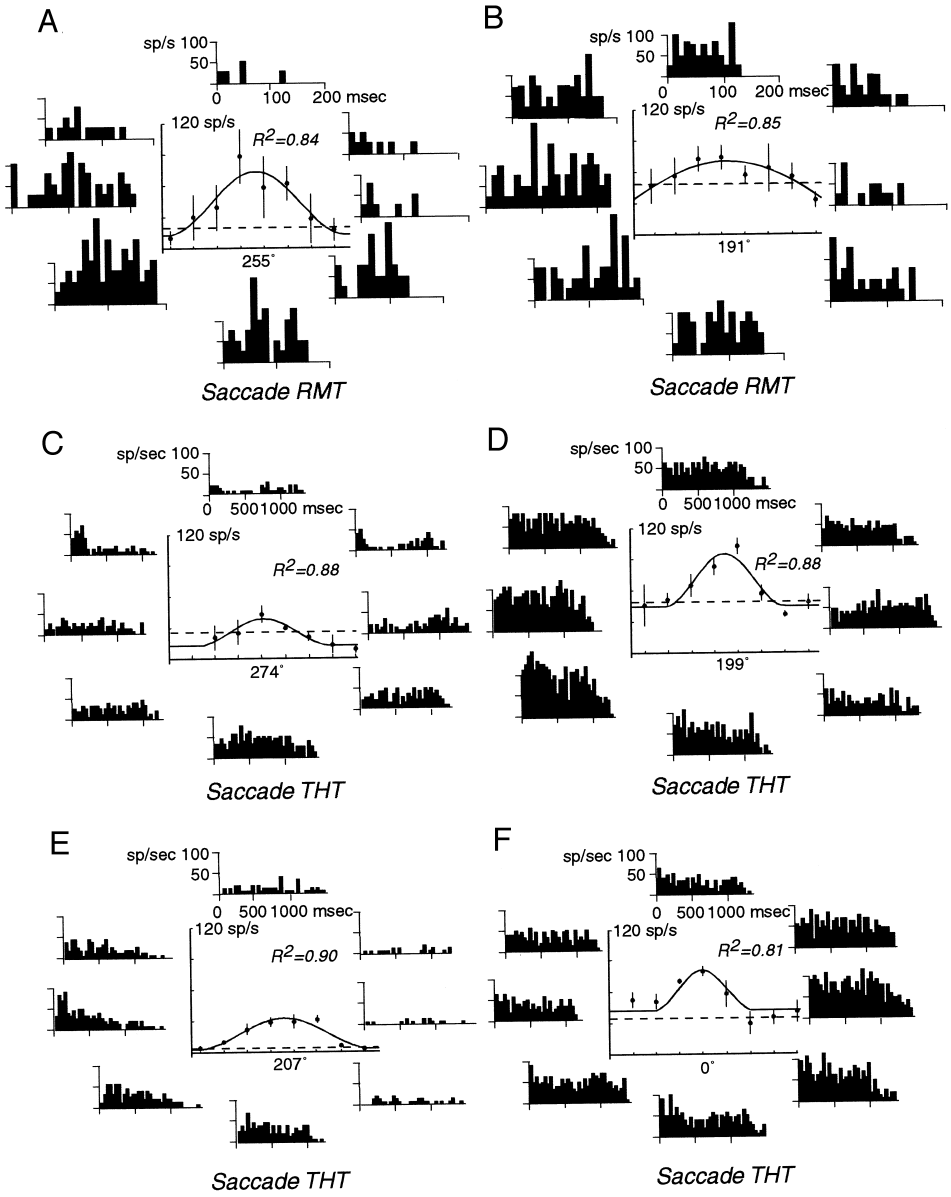


FIG. 9. Perievent time histograms of neuronal activity with relative tuning curve indicating the orientation of the cell preferred direction during specific time epochs. *A* and *B*: histograms during eye RT and MT (Saccade task) for 2 different neurons are aligned to the presentation of the visual target. Tuning curves are centered on the preferred direction. Bin size is 10 ms. *C–F*: histograms and tuning curves of neuronal activity during eye static holding on different targets for 4 different cells. Data are aligned to the beginning of THT (Saccade task). Bin size is 40 ms. Conventions as in Fig. 8.

that vision of the hand during preparation for hand movement played a role. Light/dark changes of activity and directional modulation during preparation for hand movement in the instructed delay time occurred in more than one-third of the cells studied (Table 1; Delayed Reach, l/d, D_3).

Saccadic eye movements (Fig. 9, *A* and *B*) recruited a smaller population of parietooccipital neurons (Saccade task, RT-MT; Table 1), when compared with arm-related signals. On the contrary, eye position signals were a major determinant of cell modulation. Sustained changes of cell activity during active fixation of different targets were observed in ~60% of the cells studied (Table 1). Eye position signals modulated in a cosine-like fashion are shown (Fig. 9, *C–F*) for four different cells.

As an additional example of the degree to which cell activity in V6A was influenced by a combination of different signals, it is worth noticing that, among the activity types shown in Figs. 8 and 9, those related to arm movement preparation (Fig. 8*D*,

FIG. 8. Perievent time histograms of neuronal activity types obtained by selecting cell activity during given epochs. *A*: activities of a same neuron in the Reach and Reach-Fixation tasks during RMT are aligned to the presentation of the peripheral target and are shown both in the form of histograms and directional tuning curves, where the horizontal interrupted line is the average firing frequency during CT. This cell did not display any significant visual activity, and it was not possible to map a visual receptive field. *B* and *C*: activity of 2 different neurons during hand static holding on the peripheral targets in the Reach-Fixation task is aligned to the beginning of THT and shown with the relative tuning curve in *B* and with the map of the visual receptive field in *C*. The cell in *B* did not have any visual activity, whereas the cell in *C* had a large bilateral visual receptive field, here shown as obtained during the Visual Fixation task. In this and the following maps of the visual field, 0° is at 3 o'clock, 90° is at 12 o'clock, etc. *D*: neuronal activity of another V6A neuron during preparation for hand movement (D_3) in the Delayed Reach task under both light and dark conditions. Histograms are aligned to onset of delay time (D_3). The visual receptive field of this neuron, as obtained during inward (in) stimulus motion in the Visual Fixation task is also shown. Bin size for histograms is 20 ms in *A*, 40 ms in *B–D*.

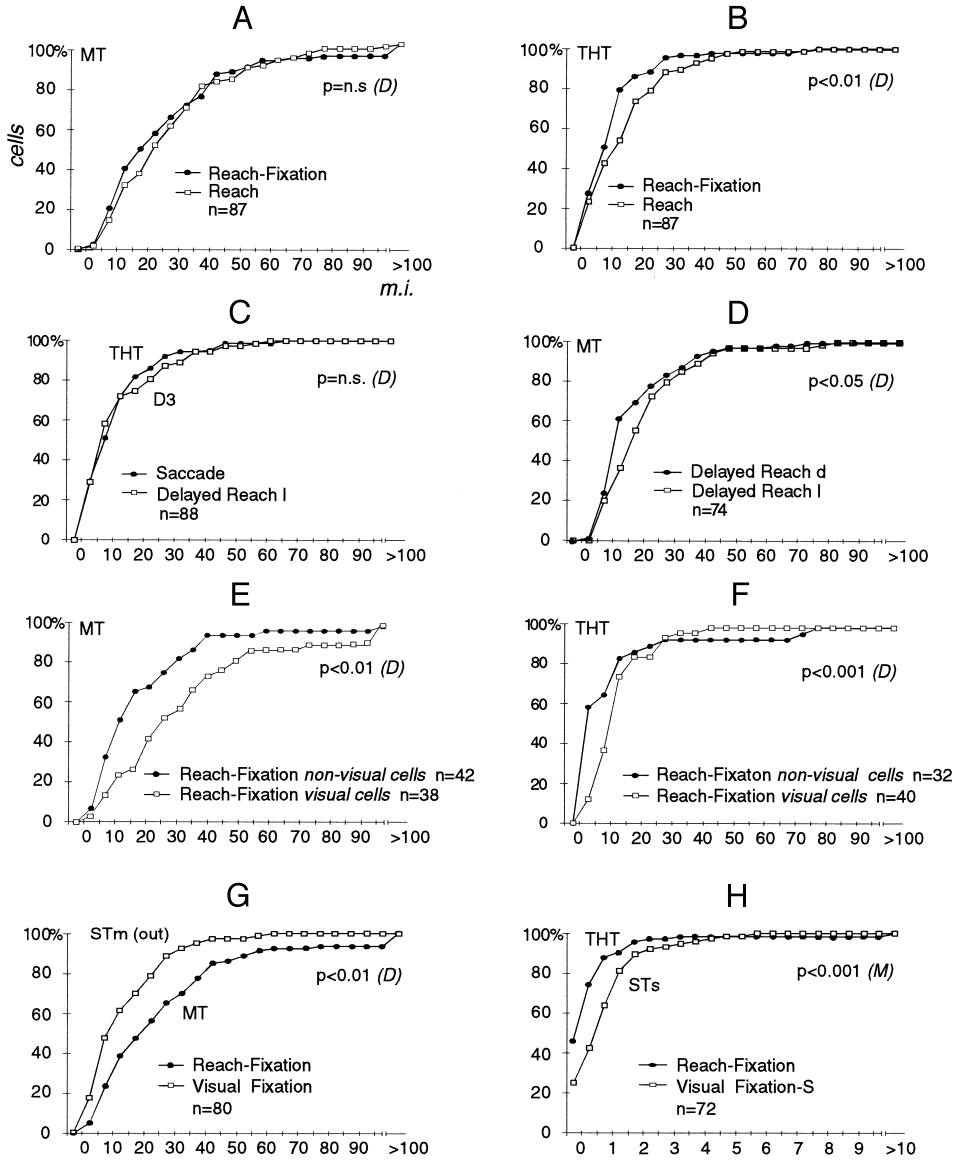


FIG. 10. Comparison of the cumulative frequency distributions of the modulation indexes *D* and *M* during certain epochs of different tasks.

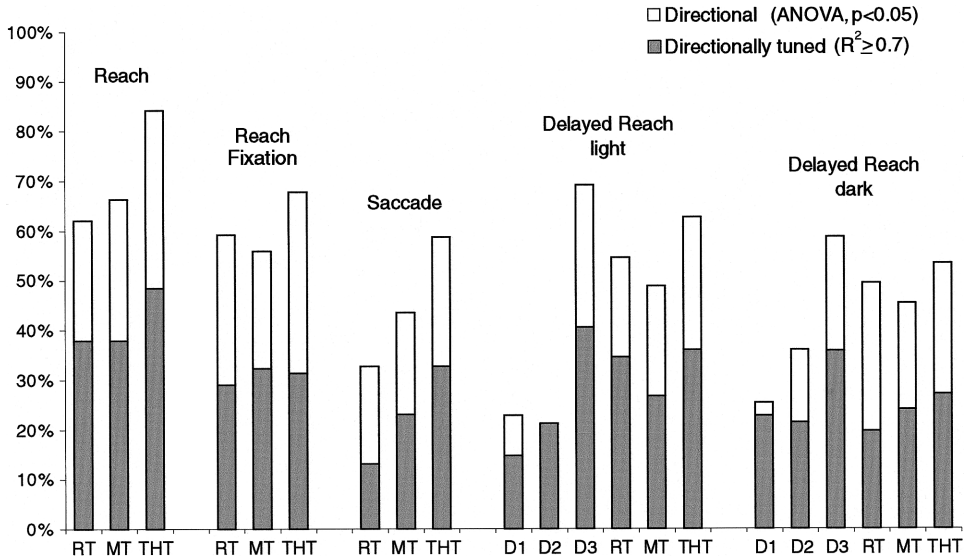


FIG. 11. Percentage of cells directionally modulated (ANOVA, $P < 0.05$) and tuned ($R^2 \geq 0.7$) during different epochs of different tasks. D_1, D_2 indicate eye reaction and movement time in the Delayed Reach tasks; D_3, preparation for hand movement during the instructed delay time.

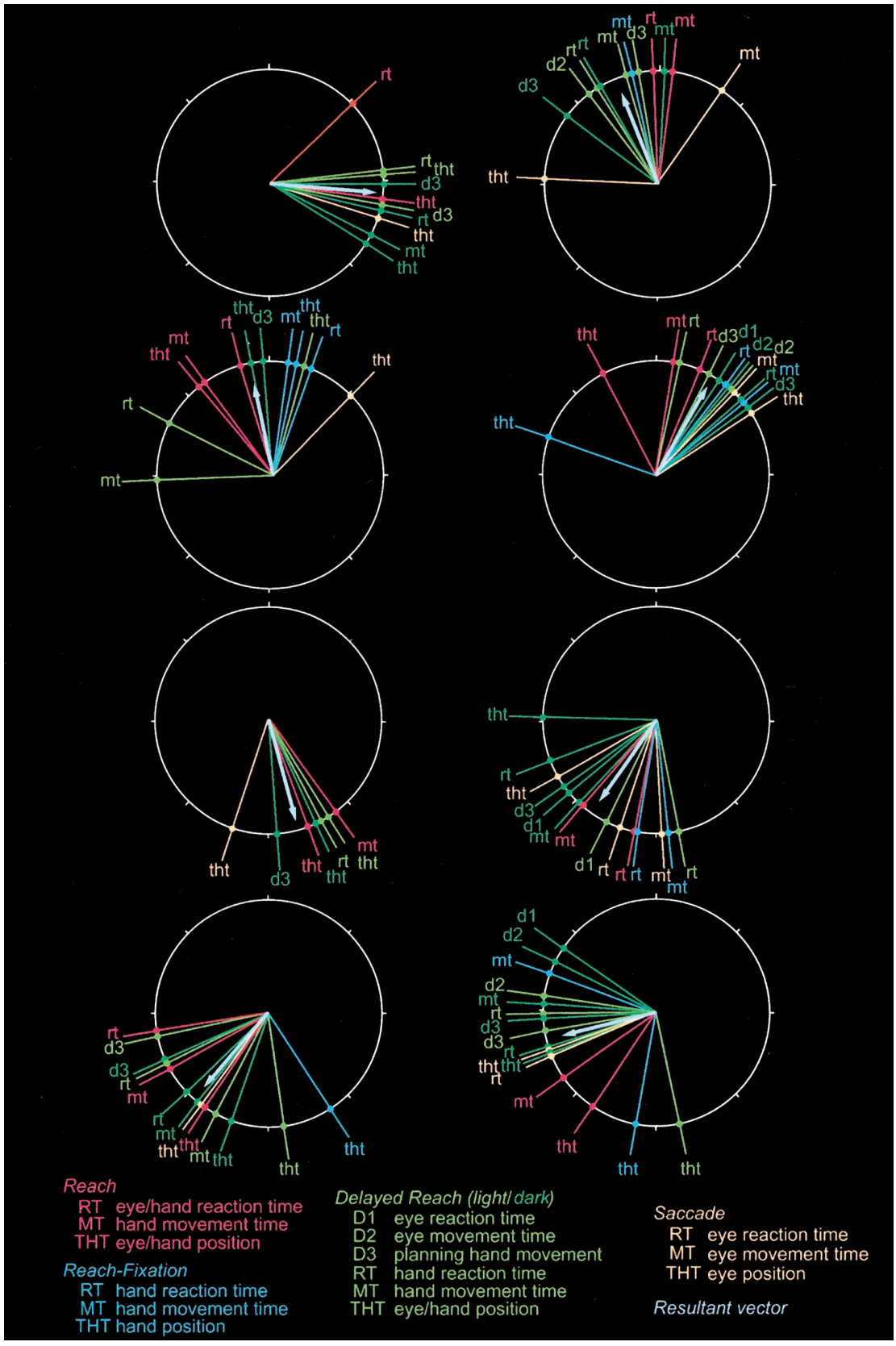


FIG. 12. Fields of global tuning for 8 different cells whose preferred directions had a unimodal distribution (Rayleigh test, $P < 0.05$).

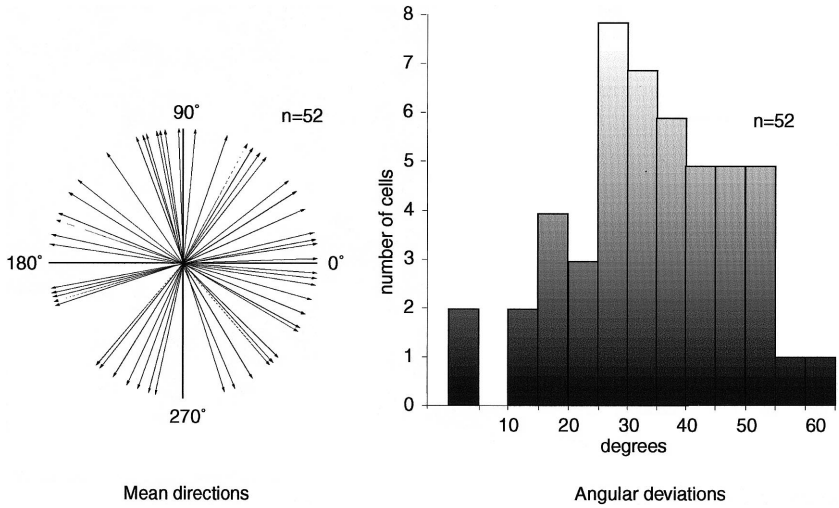


FIG. 13. *Left*: spatial distribution of the mean directions of the population of cells displaying a unimodal distribution (Rayleigh test, $P < 0.05$) of preferred directions. *Right*: frequency distribution of the angular deviations of the preferred directions of the same cells.

Delayed-Reach, D_3, light-dark), eye movement (Fig. 9*B*), and eye position (Fig. 9*D*) were observed in the same cell.

MODULATION OF CELL ACTIVITY BY DIFFERENT SIGNALS: A POPULATION ANALYSIS. A population analysis was attempted to evaluate the influence and efficacy of visual, eye, and arm related signals on neuronal activity. Two different modulation indexes (see METHODS) were computed. One index (*D*) was a measure of directional modulation; the other (*M*) was a measure of the change of modulation relative to the control time. The cumulative frequency distributions of these indexes across epochs and task conditions were compared through the Kolmogorov-Smirnov test ($P < 0.05$).

As a first step, we studied the influence of eye position and movement on reach-related activity. Figure 10*A* shows that hand movements (Reach-Fixation, MT) were as effective as coordinated eye-hand movements (Reach, MT) in modulating cell directional activity (index *D*). The same result was obtained when the amount of change of activity relative to the control time (index *M)* was used. On the contrary (Fig. 10*B*), combined eye/hand position signals (Reach, THT) influenced directional activity (index *D*) significantly more than hand position information alone (Reach-Fixation, THT). This suggests an interaction of eye and hand position information on neural activity. In this respect, it is worth noticing that during the delay interval (D_3) of the Delayed Reach task, the eyes were already on the target, and the animals planned to make a reaching movement to the fixation point. It is therefore reasonable to assume that, in addition to visual signals, eye position signals were used in planning hand movement. The distribution of the modulation indexes computed during planning hand movement was therefore compared (Fig. 10*C*) to that obtained during target fixation (Saccade, THT), and no significant differences were observed between them (index *D*). There was also no significant difference between the distributions of the modulation indexes of the activity related to eye position (Saccade, THT) and arm position (Reach-Fixation, THT).

The contribution of visual inputs to reach-related activity was evaluated in different ways. First, the distribution of the modulation indexes obtained in the light and dark conditions of the Delayed Reach task were compared. Significant light/dark differences were only observed in the distributions of the index *D* during hand movement-time (Fig. 10*D*), with more directional activity observed when the hand was moving in the light than in the dark.

Then, the indexes obtained in the Reach-Fixation task, for both visual and nonvisual cells, were compared during hand movement and active holding (Fig. 10, *E* and *F*). Hand reaches (Fig. 10*E*, MT) and active holding on the target (Fig. 10*F*, THT) recruited more directional activity (index *D*) in visually related than in non visually related cells. However, this difference was not observed when the amount of modulation relative to the control time (index *M*) was taken into account (not shown). This indicates a significant contribution of hand movement and position to cell modulation and suggests that visual signals more than influencing the amount of activity in the population contribute to confer directional features to the population activity during hand reaches and static posture.

Finally, hand movement evoked significantly more directional activity than the movement of the visual stimulus in the visual field (Fig. 10*G*). On the contrary, stationary visual stimuli (Visual-Fixation, STs) were more effective than static hand positioning (Reach-Fixation, THT) in the visual field in modulating cell activity. This difference emerged only when the amount of change of activity relative to the control time (Fig. 10*H*, index *M*) was considered, not when the directional index *D* was used.

DIRECTIONAL TUNING PROPERTIES. Figure 11 shows the percentage of cells displaying directional modulation (ANOVA, <0.05) and directional tuning ($R^2 \geq 0.7$). The highest percentage of cells directionally modulated and tuned were observed in the reaching task, fewer during saccadic eye movement, whereas a large percentage of them showed an eye position signal (Saccade, THT, ANOVA), which was modulated in a cosine-like fashion ($R^2 \geq 0.7$) in about one-half of the cases. The directional tuning was different for different cells, depending on the task epoch considered.

For each cell, many preferred directions were obtained, one for each epoch in which the directional model fitted cell activity. For those cells ($n = 75$) with at least three preferred directions, a quantitative analysis was attempted to evaluate, if the distribution of these preferred directions across epochs and task conditions had any order. Figures 12 and 13 show that this was, indeed, the case. The distribution of preferred directions was unimodal for 52/73 (71%) cells (Rayleigh test, $P < 0.05$).

Thus each cell's preferred directions, when represented on a circle of unit radius, occupied a limited part of space, here referred to as "field of global tuning" (Fig. 12), which is descriptively defined as the sector of the directional *continuum* within which all the cell's preferred directions lie. For each sector of global tuning, the mean resultant vector was calculated from the distribution of the preferred directions. The length of the mean resultant vector, the mean resultant length, is a measure of the concentration of the preferred directions, and varied for different cells. This can be seen (Fig. 13) through the frequency distribution of the angular deviations, which confirms the limited spread of the preferred directions around the mean vector. All the cells shown in Fig. 12 had significant unimodal distribution of their preferred directions. At the population level (Fig. 13), the angles of the mean resultant vectors, the mean directions, were isotropically distributed in space (Rayleigh test, $P < 0.05$).

DISCUSSION

Multiple tasks approach to the study of parietooccipital cortex

This study was addressed at the mechanisms underlying the "early" composition of motor commands for reaching in the cerebral cortex. Neural activity was recorded in the dorsal part of area PO (Colby et al. 1988; Gattas et al. 1985), recently relabeled as V6A (Galletti et al. 1996), while monkeys performed a variety of behavioral tasks. These were aimed at evaluating the influence of reaching related signals, such as hand position, movement direction, and preparation for hand movement, on neuronal activity. The existence of reaching-related activity in area V6A, in fact, need to be substantiated beyond qualitative observations (Galletti et al. 1997). More important, a genuine relationship between neural activity and reach-related information has to be shown independently of visual and ocular influences. Finally, the potential combination of these different signals should be properly evaluated (see Caminiti et al. 1998).

Arm reaching modulates neuronal activity of many cells in area V6A. This was shown both by the increase of the population activity during RT and MT of hand reaches in the Reach and Reach-Fixation tasks, as well as by the observation that in this last task, when eye position was constant, a significant reach-related activity was observed in cells with no visual properties, as well as during hand reaches in the dark. In V6A's cell with visual properties, the level of directional activity during hand movement in the Reach-Fixation task was higher than that observed for nonvisual neurons. These visually related cells also modulated by hand movement could be involved in the monitoring of hand movement trajectory in the visual field.

The overall level of activity in the population did not differ depending on whether or not the eye moved with the hand, but was higher when the hand was held with the eye on the target, i.e., when the positions of the hand and of the fixation point coincided, than when the hand was stationary in the periphery of the visual field. That hand position signals are an important determinant of cell activity in V6A was confirmed by their influence on cells without visual properties, although, for these cells, the activity levels observed during holding of static hand position were lower than those of visually related cells. These last cells could integrate visual and hand position information in the visual field and therefore could play a role in the visual monitoring of hand position in space.

Overall, these results indicate that there exists in V6A an important contribution of hand movement and position-related activity, which is often influenced by eye position signals as well.

In the Delayed Reach task, light/dark differences were observed in the degree of directional modulation during hand movement only. Such differences were not observed in the delay-interval during which the animal planned the next hand movement. Doubts still exist on the information encoded by this "set-related" activity. It probably reflects the process of matching target location and arm position, to represent both into a common coordinate system, thus providing a code of hand position relative to the fixation point. This interpretation is suggested by the observation that both the amount of activity and the level of directional modulation in the population activity did not differ during preparation for hand movement and holding of eye position. Furthermore, the directional tuning of set-related activity in another parietal region, area 5, depends on the position of the hand in the workspace (Ferraina and Bianchi 1994). In some V6A cells, preparatory activity was present, often with unchanged directional tuning, in the light and also in darkness, therefore in the absence of any visual feedback about hand position in the visual field. This suggests that in the process of combining information about target location and hand position, in these particular cells, signals about the latter depend on proprioceptive and/or efferent copy inputs. For other cells, however, the level of preparatory activity changed in the dark, although their directional tuning tended to remain constant. This was also observed when individual cells had no visual receptive fields and suggests that in the transition from light vision to darkness, a change from a control mechanism based on proprioception and vision to one based mainly on proprioceptive signals probably occurred. This fits the results of recent psychophysical studies (McIntyre et al. 1997, 1998) indicating that the target is represented in a viewer-centered frame of reference when reaching to memorized target location is performed in the light, but into an hybrid viewer-arm centered frame in the dark.

The results of this study do not contradict the recent claim (Batista et al. 1999) that reaching in parietal cortex is coded in eye-centered coordinates. In this last study, reaching was performed only in the dark and within a delayed-memory task. As indicated by psychophysical results (McIntyre et al. 1997, 1998), any conclusion about frame of references for reaching must be referred only to the experimental situation tested. The context dependency of the saccade and hand-related activity of parietal neurons illustrated in the present paper support this contention. Our study shows a combination of retinal, eye, and hand-related signals that, at least in V6A, makes unlikely a unique coding scheme in exclusive eye coordinates. Any further comparison of the results of our study with that of Batista et al. (1999), beyond the difference in the behavioral tasks adopted, is prevented by the fact that, in the latter, the exact definition of the area of recording is not yet available.

Signal processing by parietooccipital neurons

This study indicates that neural activity in area V6A encodes not only visual (Colby et al. 1988; Galletti et al. 1991, 1996, 1999; Gattas et al. 1985) and eye-related (Galletti et al. 1995; Nakamura et al. 1999) signals, but also arm-related information, as suggested by previous preliminary reports (Battaglia-Mayer et al. 1998; Caminiti et al. 1998, 1999; Galletti et al. 1997; Johnson et al. 1997). These signals influence different cells to different degrees.

When studied only in one task, the activity of most cells seemed to relate to visual, oculomotor, or to arm motor variables. However, when studied under different task conditions, the activity of most cells was related to a combination of signals. Although different combinations of response properties were observed, the activity of some cells was dominated by eye position information and influenced by hand signals. For other cells, the relationships with hand movement and position were dominant, but these were influenced by the position of the eye in the orbit.

Another interesting feature of this combinatorial mechanism consists in its dynamic nature, because the relationships of cell activity to oculomotor and/or visuomanual behavior resulted to be context dependent in most neurons. Under the experimental conditions of this study, about one-half of the saccade-related neurons were recruited only when the animal moved the eye toward a spatial location that was also target for subsequent hand movement (Delayed Reach task), and not when saccades were made in the context of the classical Saccade task. Similar observations were made for the relationships between cell activity and hand movement. This was variable, depending on whether or not hand movements were made within a reaction time task (Reach), therefore in a condition of uncertainty about the spatial location of the next target, or within the instructed-delay paradigm (Delayed Reach), where target location was precued by a visual signal, and therefore hand movements were made in conditions of spatial certainty.

Visual signals exert a major influence on the activity of V6A neurons. These have large visual receptive fields, rarely including the fovea, always extending to the extrafoveal regions of the visual field, as observed by previous studies on the properties of parietooccipital cortex (Colby et al. 1988; Galletti et al. 1996, 1999; Gattas et al. 1985). In addition, the results of this study show that visual neurons in V6A are tuned to stimulus motion, because they responded differently when the visual stimulus moved either inward toward the fovea, or outward from the fovea to the periphery of the visual field. This property is reminiscent of the "opponent vector organization" of visual responses described by Motter and Mountcastle (1981) in area 7a. Most of these visual cells were also modulated by eye and hand position and movement direction. Therefore they have all the functional properties necessary for the visual monitoring of hand movement trajectory and static posture in the visual field.

Combinatorial properties of parietooccipital neurons

The overall picture emerging from this multiple task approach to the study of the dynamic property of neurons in area V6a is striking, although not surprising. First, the activity of most cells was influenced by reaching related signals. Second, the activity of very few cells in this area was related in an exclusive fashion to individual retinal, eye, or hand information. On the contrary, the activity of most cells was influenced by all these signals or by different association of them. Third, the eye and hand directional and positional tuning properties of most parietooccipital neurons, as represented by the cell-preferred directions computed during different epochs of different tasks, clustered within a limited range of the angular variable, here referred to as field of global tuning. These fields had different sizes in different cells, being broad for some, sharper for others, always extending over a limited part of the workspace. They could be an ideal spatial frame (Colby 1998) where to combine retinal, eye and hand positional and directional signals relevant for the early composition of commands for reaching, because spatial congruence is a necessary prerequisite for any such combination and coordinate transformations. These fields of global tuning can be a general property of all areas of the parietofrontal system underlying reaching, visuomotor primitives necessary for that combination of information from which coordinate systems emerge. Selection of specific frames for reaching such as eye-centered (McIntyre et al. 1997, 1998) ones, arm-centered (Caminiti et al. 1990, 1991; Lacquaniti et al. 1995) etc., will depend on specific tasks and on the functional repertoire of each cortical area. The results of our study, whereas compatible with recent studies on encoding of reaching in the parietal cortex (Batista et al. 1999; Snyder et al. 1997, 1998), only support temporary and task-dependent assignments of reference frames to parietooccipital neurons. The spatial congruence of tuning properties within the global tuning fields could create a "combinatorial explosion" that makes it unlikely that individual neurons encode reaching within a single reference frame. Even more unlikely is that each cortical area of the parietofrontal system encodes information within its own coordinate system and that the coordinate transformation can be regarded as a step-wise addition of new signals from one cortical region to another. The combination of these signals already occurs at the early stage of composition of commands for reaching.

If this is true, results similar to those of this study should be expected in other nodes of the parietofrontal network, if appropriately studied through a multitask approach. Combinatorial properties are certainly not unique to V6A neurons (for a review, see Caminiti et al. 1998). Recent observations (Boussaoud et al. 1998; Jouffrais and Boussaoud 1999; Mushiake et al. 1997) have shown that reach-related activity in dorsal premotor cortex, an area corticocortically connected to V6A (Caminiti et al. 1999; Matelli et al. 1998; Shipp et al. 1998), is influenced by eye position signals, as well as neurons of the so-called "parietal reaching related region" (Batista et al. 1999).

The partial similarity of properties of parietal and frontal neurons identifies in the frontal cortex a likely source of hand "motor" signals for parietooccipial cortex and suggests that the coordinate transformation underlying arm movement to spatial targets is based on a parallel and recursive mechanism, probably dependent on reentrant signals (Edelman 1993), traveling through association connections. Elucidating the degree to which neurons in different areas combine different signals will be prerequisite to shed light on the mechanisms whereby visual information is transformed into motor commands.

This combinatorial mechanism operates at a very early stage

in the information processing flow leading from vision to movement, and emerges as a prominent functional feature of parietooccipital cortex. Its breakdown after superior parietal lesions, and the consequent failure in matching spatially congruent retinal, eye, and hand-related signals, might be responsible for the deficits of the visual guidance of arm and hand movement observed during optic ataxia (for a discussion see Battaglia-Mayer et al. 1998; Caminiti et al. 1996).

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