INTRODUCTION

The brain receives visual inputs cast in retinal coordinates, and the retinotopic maps are propagated throughout the visual system, up to high order visual areas of the parietal and temporal cortices. Ultimately, visual information reaches the premotor cortical regions, where visually guided reaching movements are planned (for reviews, see Boussaoud et al. 1996; Caminiti et al. 1996). On the other hand, the motor system seems to code movements to locations specified relative to shoulder or body axis not in a retinocentric frame of reference. The question then is how the brain transforms the coordinates of a visual target from retinocentric coordinates to body-centered coordinates. This question has motivated several studies in the past 20 yr in both psychophysics (for reviews see Abrams 1992; Flanders et al. 1992; Soechting and Flanders 1992), neurophysiology (see Andersen et al. 1993, 1997; Jeannerod 1991), and modeling (Pouget and Sejnowski 1997; Pouget et al. 1993; Zipser and Anderson 1988). From a conceptual point of view, the prevailing idea has been that this “coordinate transformation” is performed in a serial or hierarchical manner with progressive shifts of target location from retinocentric to head-centered to body-centered coordinates (Flanders et al. 1992; Jeannerod 1991). In most models of coordinate transformations between reference frames, retinal and eye position signals are conceived to converge at low levels of the visual pathways, where a head-centered representation of visual space is computed. Then, at later stages, head position signals are used to create a body-centered representation, which is used by the motor output stage, in conjunction with limb position signals, to produce movements in space. One of the brain regions thought to play a major role in coordinate transformation and space coding is the posterior parietal cortex. Within the inferior parietal lobule, neurons have been shown to receive retinal signals, orbital eye position signals, and head-position signals (Andersen and Mountcastle 1983; Andersen et al. 1985, 1990b; Bremmer et al. 1997a,b; Brotchie et al. 1995). Neurons with activity that reflects a convergence of retinal and eye position signals also have been reported in the parieto-occipital region (Galletti et al. 1991, 1995). Neuroanatomic studies have shown that the parietal and parieto-occipital areas are the major source of visual inputs to the premotor cortex (Cavada and Goldman-Rakic 1989; Johnson et al. 1996; Tanné et al. 1995; Wise et al. 1997), known for its role in the planning of visually guided limb movements. This anatomic organization of the parieto-premotor cortex suggests that premotor cortex neurons receive information about target location in body-centered coordinates, the appropriate reference frame for the planning of limb movements. This view has received support from the fact that...
some cells in the ventral premotor cortex (PMv) of monkey have visual responses independent of eye position (Fogassi et al. 1992; Graziano et al. 1994). However, there is evidence that the same premotor area contains many cells with retinocentric receptive fields and visual responses modulated by gaze angle (Boussaoud et al. 1993), in a manner similar to that described for parietal cortex neurons (Andersen et al. 1985, 1990b). These findings raise the possibility that single neurons in the premotor cortex may use orbital eye position signals to represent target information, and to plan limb movement direction in space. The present study was undertaken to further examine this issue by investigating the effects of orbital eye position on the neuronal properties in the dorsal premotor area (PMd).

The rationale in choosing PMd is that several studies have established that it plays a crucial role in visually guided reaching limb movements. Single-unit recordings in awake monkeys performing limb movement tasks have shown that PMd neu-
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FIG. 2. Surface plots of the recording sites. Lateral views of the anterior half of the right hemispheres of the 2 monkey brains, showing the locations of the recording sites (●). Front of the brain is to the right. Ce, central sulcus; IP, intraparietal sulcus; iAr and sAr, inferior arcuate sulcus, respectively; P, sulcus principalis; PMd, dorsal premotor cortex; M1, the primary motor cortex.

rons discharge in relation with the direction and amplitude of limb movements (Boussaoud and Wise 1993a,b; Caminiti et al. 1991; Crammond and Kalaska 1994; di Pellegrino and Wise 1993; Fu et al. 1993, 1995; Kalaska and Crammond 1995, 1996; Kurata and Wise 1988; Riehle and Requin 1989; Tanji et al. 1988; Weinrich and Wise 1982; Wise 1984). In contrast to the ventral premotor area (PMv) and the dorsolateral prefrontal cortex, PMd is much more related to movement preparation per se, than to attention or sensory processing (Boussaoud and Wise 1993a,b; di Pellegrino and Wise 1993; Kurata 1988), and its temporary inactivation in monkeys results in directional errors (Kurata and Hoffman 1994). Thus PMd stands as one of the premotor areas most related to the initiation and execution of reaching limb movements, as opposed to sensory processing, and for that reason it is suited for examining whether the neuronal activity associated with limb movements varies with changes in gaze angle. We examined PMd neurons while monkeys fixated at various angles and made identical limb movements and found that their activity is modulated highly by orbital eye position. The observed modulation of activity often takes the form of linear changes with deviations of gaze angle along the horizontal and vertical axes. These data suggest that a population of PMd single neurons code limb movements in a head-centered reference frame. A brief report of the present data has appeared before (Boussaoud 1995).

METHODS

Animal training and the behavioral paradigm

Two rhesus monkeys (Macaca mulatta), 5–6 kg, were trained to perform a conditional visuomotor task. They both were subjects for other neurophysiological and anatomic studies (Kermadi and Boussaoud 1995; Tanne et al. 1995). Each monkey was seated in a primate chair, with the head firmly fixed, 32 cm in front of a computer screen, and used the left hand to perform the task (Fig. 1). Located at the bottom of the screen was a panel of three metal touch pads, a central one aligned on the monkey’s body axis, one 12 cm to the right of that axis, and one 12 cm to the left. Eye position was monitored using a scleral search coil. The trials begin when the monkey puts its hand on the central pad, and fixated a 0.2 × 0.2" fixation point. After a delay (250 ms) of steady fixation, a 2 × 2" white square appeared at one of nine locations forming a grid. This stimulus served as a precue (PC), which directs the monkey’s attention to a given location. Next, after a variable delay (0.5–1 ms), a colored square of the same size was presented at the previously cued location. This stimulus (the motor instructional conditional cue, MIC) guided the monkey’s motor response according to a conditional rule: a red MIC instructed a movement to the left touch pad, a green MIC instructed a movement to the right, independently of their spatial location. The MIC cue was presented for a variable delay (1–3 s, 0.5-s steps), and the monkey had to await for its offset, the go signal, to perform the appropriate response. After the go signal, the monkey had 650 ms to contact the appropriate touch pad to receive a liquid reward (Fig. 1B). If the monkey broke fixation or releases the central pad at any time during the pertinent part of the trial, that trial was aborted, and another trial was initiated after an intertrial interval of 1.0 s.

The fixation point was presented at five screen locations defined by their screen coordinates: a central fixation (0,0), fixation to the upper left (−10,10), upper right (10,10), lower left (−10,−10), and lower right (10,−10) quadrants of the screen. For each of these fixation points, the visual cue was presented at the following retinal coordinates: (0,0), (0,10), (−10,10), (−10,0), (−10,−10), (0,−10), (10,−10), (10,0), and (10,10). When the fixation point moves to a new location, visual stimuli moved ac-
EYE POSITION EFFECTS IN DORSAL PREMOTOR CORTEX

Recording and data analysis

Glass-coated, tungsten electrodes (0.5 MΩ impedance) were employed to record extracellular neuronal activity using conventional techniques. Electrodes were inserted into the recording chamber directly through the dura, i.e., without the use of a guide tube. Near the end of the experiments, electromyographic (EMG) activity of hand, shoulder, neck, and trunk muscles was recorded with intramuscular stainless steel electrodes in monkey 1 while he performed the task. EMG signals were amplified, filtered with a band-pass of 10 Hz to 10 kHz, and discriminated with a window discriminator and recorded as pulse replica. A total of 16 muscles were recorded. Among them, the trapezius, gluteus maximus, infra- spinatus, lumbar paravertebral, and latissimus dorsi were monitored bilaterally, whereas the deltoid, flexor carpi radialis and carpi ulnaris, biceps, triceps, and supraspinatus muscles were monitored on the performing side only (left). The isolated action potentials and EMG were collected together with the behavioral events using a PC-based software (Cortex, courtesy Robert Desimone, National Institute of Mental Health). The data were collected for correctly performed trials in interleaved blocks of three trials per target location and per eye position.

Peri-event histograms were constructed for all recorded cells with neuronal activity aligned on various task events, including the onset and offset of visual cues and the end of movement. Analysis of neuronal activity focused on the discharge rate measured during four major epochs (see Fig. 1B): precue activity, measured 100 ms after the presentation of the precue (epoch 1 = 200 ms); a post-MIC, or signal-related activity, taken 100 ms after the MIC onset (epoch 2 = 200 ms); an instructed delay, or set-related activity (epoch 3 = 500 ms) measured just before the go signal; and a response time, or movement-related activity (epoch 4 = 500 ms) measured after the go signal. A one- or two-factor analysis of variance (ANOVA, Wilkinson, SYSTAT, Evanston, IL) was performed on the mean discharge rate of each task-related cell to determine the effects of the different parameters examined (see further). The statistical analysis was aimed at testing the effects of the retinal location of the MIC cue, and those of gaze angle on the neuronal activity. The same analysis was applied to behavioral parameters, namely the response times (time between MIC offset and target acquisition) and EMG activity.

In addition, a two-dimensional linear regression analysis [statistical model: \( z = c + a \cdot x + b \cdot y \), where \( z \) represents the discharge rate, \( c \) the intercept, \( a \) and \( b \) the slopes along the horizontal (\( x \)) and vertical (\( y \)) axes, respectively] was applied to the mean activity of individual cells, as well as to the activity averaged across the population, measured during the three post-MIC cue epochs (signal, set, and movement epochs). \( R^2 \) values and \( F \) ratio were computed for validating the planar model as fit to the observed data.
FIG. 4. Samples of eye movement recordings. Five displays represent 5 different gaze angles, indicated in degrees in parentheses. In each display, the 2 groups of lines represent the recordings of eye position along the horizontal (x) and vertical (y) axes during several trials, aligned on the go signal (vertical line). Thick horizontal bars indicate the average time of presentation of the MIC cue (1.5 s). Two arrow heads in each display indicate the shortest and longest RTs, respectively. In each trial, the upward deflection of the line corresponds to a saccade to the right (for the x axis) or up (for the y axis). MIC cue was red (instructing a leftward arm movement) and was presented at various screen locations.

Histology

Near the end of recording neuronal data, electrolytic lesions (10 \mu A for 15 s, cathodal current) were made in six electrode penetrations in monkey 1. The recording sites were later reconstructed using the electrolytic lesions. In monkey 2, the chamber and head fixation device had to be removed, due to an infection, before the recordings were completed. In this animal, histological reconstruction was based on the remaining lesions caused by electrode penetrations. However, the bone flap removed at the time of chamber implantation was used to obtain a map of the sulci underneath (Wolpaw 1979). Electrode penetrations were made relative to the estimated location of the superior arcuate sulcus with good accuracy (Fig. 2). At the end of all the experiments, each monkey was anesthetized deeply with pentobarbital sodium (75 mg/kg) and perfused intracardially with 3% paraformaldehyde, followed by sucrose solutions of increasing concentrations for anatomic purposes. The brain was removed from the skull, photographed, sectioned on a freezing microtome at 40-\mu m thickness, mounted on glass slides, and stained for Nissl substance with thionin. Surface projections of the recording sites and the estimated track of each penetration were plotted with reference to the recovered electrolytic lesions (monkey 1), or the estimated location of the superior arcuate sulcus (monkey 2; see Fig. 2). No attempt was made to identify individual tracks, but the depth of the recording sites was reconstructed with the tracks. Previously described cytoarchitectonic criteria (Seseler and Wiesendanger 1982; Weinrich and Wise 1982; Wise 1984) were used to distinguish PMd from M1.

RESULTS

Behavioral data

RESPONSE TIMES. The monkeys performed the task at >90% success rate. We measured the means and standard deviations of the response time (RT), as defined in METHODS, for each MIC cue location and each gaze angle. Figure 3 illustrates the RTs for both monkeys. The statistical analysis (ANOVA) of the RT data shows that there was no significant effect of gaze angle. However, RTs were affected by both the location of MIC cues and the direction of limb movement. As Fig. 3 shows, RTs were shorter (monkey 1) or longer (monkey 2) for movements to the left than those for movements to the right, despite the fact that both monkeys used the left limb to perform the task.

EYE MOVEMENTS. As described in METHODS, monkey 2 was trained to fixate throughout the trial period up to the end of movement, whereas monkey 1 was allowed to move its eyes after the go signal. Analysis of eye movement recordings shows that, even in monkey 1, the eyes begin to move relatively late, with response times comparable with those of limb movements (Fig. 4). Thus during the first period of the RTs (as measured above), orbital eye position is the same as it was during the trial period before the go signal. We thus examined the effects of gaze angle on the neuronal activity measured during the response time period (movement-related activity) in both monkeys.

EMG ACTIVITY. Among the 16 muscles recorded in monkey 1, we made two major observations. First, there was typically no EMG activity during the precue period or during the instructed delay period, but all muscles displayed activity in relation to movement execution (see examples in Fig. 5). This movement-related EMG activity varied with movement direction in most cases (11/16 muscles). Second, very few muscles (2/16) showed significant variations of EMG activity in relation to gaze angle (ANOVA, P < 0.05) during the instructed delay period, although the activity of nearly half of the sample varied with gaze during the movement period (7/16). Figure 5 illustrates examples of gaze effects.
FIG. 5. Examples of electromyographic (EMG) activity patterns. Poststimulus histograms were obtained from 20 to 40 trials aligned on the go signal (arrow), while monkey 1 made a limb movement to the left (L) or to the right (R). Binwidth, 20.4 ms; vertical scale, impulses/s, same for all histograms. Top: gaze-independent EMG activity. Note the absence of EMG activity during the task period before the go signal. Also, note the relative constancy of the burst of activity after the go signal across the 3 gaze angles. Bottom: examples of gaze effects on EMG activity (see text for details).
on EMG activity of two muscles. As the figure shows, when the monkey looks straight ahead, the left trapezius displayed tonic activity during the PC and the instructed delay period for both left and right trials. The activity during these two task periods increased significantly (ANOVA, \( P < 0.05 \)) when gaze was deviated to the right and decreased dramatically when gaze was deviated to the left. The phasic, movement-related activity is significantly stronger for movement to the left versus to the right and also varied with gaze angle. Likewise, the lumbar paravertebral muscle was differentially active with gaze angle. These observations will be discussed later in relation to the possible sources of gaze effects.

**Neuronal data**

**GENERAL PROPERTIES.** A total of 241 task-related neurons were recorded from PMd in the two monkeys (Fig. 2). Among them, 205 have been studied sufficiently as to determine their properties, by visual inspection, and classify them into the categories summarized in Table 1. It appears that, in agreement with previous studies (Boussaoud and Kermadi 1997; Boussaoud and Wise 1993a,b; di Pellegrino and Wise 1993; Kermadi and Boussaoud 1995), a minority of PMd cells discharge in relation to visual cues when they simply direct spatial attention with no instructional meaning. As Table 1 shows, only 14 cells showed activity outside the instructional period, among which 12 were active in relation to the PC onset or offset and 2 were active in anticipation of the instructional cue. Figure 6A illustrates an example of cells with precue activity. It begins with a latency of ~150 ms and lasts for 200–300 ms thereafter. For this cell, PC activity is spatially selective in that it appears only if the PC is presented at the fixation point. However, despite its apparent visual nature, the cell’s discharge differs depending on the instructional significance of MIC cues presented later in the trial. If MIC is red, no activity is observed (Fig. 6A, top), but if the cue is green (Fig. 6A, bottom), a phasic, signal-related activity follows the cue’s onset and lasts for ~400 ms. Thus although the neuron appears to be related to spatial attention, it has clear motor preparatory properties as it responds selectively to instructional cues based on the direction of the upcoming movement.

Unlike the example described above, the vast majority of
PMd cells discharge preferentially following motor instructional cues than after the precue. A typical example is shown in Fig. 6B. In this cell, there is no activity after the PC, whereas a strong discharge follows the onset of the MIC cue. Moreover, the neuronal discharge reflects the direction of the upcoming arm movement. In the example of Fig. 6B, the cell has a vigorous discharge after MIC onset when it instructs a movement to the left (top) but no activity for a MIC instructing a movement to the right (bottom). In the DISCUSSION, we will argue that such selectivity is unlikely to reflect color processing per se.

Among the cells with activity variations related to the MIC cue, 141 cells were classified as signal-related, 157 as set-related, and 104 as movement-related. This classification does not preclude that a given cell display two or all three activity patterns. Thus a given cell can be classified into more than one category. Representative examples of these different patterns of activity are shown in Fig. 7.

To determine the effects of gaze angle on the neuronal discharge rate, we selected only cells that were studied under at least three different eye positions. Table 2 summarizes the effects of gaze angle as well as MIC cue location by task period. It appears that gaze angle affects significantly ($P < 0.05$) the discharge rate of a large proportion of cells irrespective of the task period analyzed.

**TABLE 2. Retinal, gaze, and movement effects by task period**

<table>
<thead>
<tr>
<th>Task Period</th>
<th>Retinal Effect</th>
<th>Gaze Effect</th>
<th>Movement Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal</td>
<td>57/133 (43)</td>
<td>99/133 (74)</td>
<td>96/133 (72)</td>
</tr>
<tr>
<td>Set</td>
<td>53/157 (34)</td>
<td>124/157 (79)</td>
<td>150/157 (96)</td>
</tr>
<tr>
<td>Movement</td>
<td>15/52 (29)</td>
<td>41/52 (79)</td>
<td>43/52 (83)</td>
</tr>
</tbody>
</table>

Numbers and proportions (in percent in parentheses) of cells with activity that varied significantly (analysis of variance, $P < 0.05$) with retinal stimulus location, orbital eye position or limb movement direction are summarized for three selected task periods.

Figure 7 shows examples of post-MIC activity patterns. $A$--$D$: activity for 4 different PMd neurons. In $A$--$C$, same conventions as in Fig. 6B. In $D$, same conventions except that the trials are aligned on the Go signal. $A$: cell with phasic activity shortly after MIC onset (signal-related activity) and during the response time period (movement-related activity). $B$: cell with signal-related activity and set-related activity. $C$: cell with set- and movement-related activity. $D$: cell with only movement-related activity. All other conventions are as in Fig. 6.
EFFECT OF GAZE ANGLE. Gaze angle affected the activity of a vast majority of PMd cells in all the task periods examined. Table 2 summarizes the proportions of cells with activity that varied significantly with gaze angle for signal, set, and movement periods, and Figs. 9B and 10–13 illustrate representative examples. Gaze effect was typically large and highly significant (2-factor ANOVA; \(P < 0.05\)). On average, when the monkey fixated in the preferred gaze direction signal-related activity was nearly twice higher (48 ± 23 spikes/s) than the rate observed when the monkey gazed in the nonpreferred direction (25 ± 18). For set-related activity, the average discharge rate varied between 18 ± 14 spikes/s for the nonpreferred gaze direction and 32 ± 18 spikes/s for the preferred direction. Finally, movement-related activity varied between 34 ± 21 and 58 ± 27 spikes/s with gaze direction.

**Gaze effect on signal-related activity.** Of the 133 PMd signal-related cells analyzed quantitatively, 99 showed significant activity variations with gaze angle. Figure 10 shows an example. The graph in Fig. 10 illustrates signal-related activity of a PMd cell, measured for a MIC cue presented at a constant retinal location when gaze angle changed. Signal-related activity in this neuron is selective for leftward movement and shows, in addition, significant variations with gaze angle. Less important variations are observed for the cue presented at the same location but instructing a movement to the right. The rasters of Fig. 10 illustrate the neuronal discharge for two selected gaze angles. It appears that the neuron’s signal-related activity is much more vigorous when gaze is at (10, −10) than when it is at (10, 10).

**Gaze effect on set-related activity.** Of the 157 PMd set-related cells examined, 124 showed significant activity variations with gaze angle. Figures 11 and 12 show representative examples. In Fig. 11, the graph shows that set-related activity is direction-sensitive in that it is vigorous when the upcoming movement is to the right and nearly absent when movement is to the left. In addition, set activity varies dramatically with gaze angle. The cell’s discharge rate is much higher for gaze at center and to the left than for gaze directed to the right. The weakest neuronal discharge is observed for gaze to the lower right quadrant, which coincides with the direction of the forthcoming limb movement. A different pattern of set-related activity modulation by gaze angle is illustrated in Fig. 12. In this case, set activity was observed for both leftward and rightward limb movements, but the degree of selectivity for movement direction varied with gaze. When gaze is straight ahead or deviated to the left, there is no significant difference in the discharge rate for movement to the left versus to the right. However, when gaze is deviated to the right, the discharge rate is significantly higher during the preparation of a leftward movement than during that of a movement to the right. These two examples illustrate one of the most salient aspect of gaze effects in PMd consisting of a modulation of the degree of neuronal selectivity for limb movement direction.

**Gaze effect on movement-related activity.** Of the 52 PMd movement-related cells analyzed, 41 showed significant activity variations with gaze angle. Figure 13 shows an example, which, like the majority of PMd cells, has differential activity during the response time period depending on movement direction. In addition to the clear effect of limb movement-direction on the cell’s discharge rate, the graph in Fig. 13 illustrates the variations of activity with orbital eye position. A clear illustration can be seen in the rasters and histograms (Fig. 13, right). A much stronger discharge rate is observed for eye position in the lower left quadrant.
of the screen, \((-10,-10)\), compared with fixation at the upper right quadrant, \((10,10)\).

**Gaze effect on other types of activity.** Gaze angle affected the neuronal activity during additional task periods including activity associated with the precue as well as that related to anticipation of visual stimuli. Figure 14 shows an example of cells the activity of which during the task period that precedes the MIC onset varies dramatically with eye position. When recorded during central fixation, this neuron displays moderate and inconsistent activity in anticipation of the MIC cue (center of Fig. 14). Analysis of the cell’s activity shows that it is not correlated with the onset or offset of the precue nor with the onset of the MIC cue or the direction of the upcoming limb movement. Most importantly, it appears that the neuron’s activity depends on the fixation angle, with a much stronger and more consistent activity when the monkey fixates to the lower left than when it fixates to other screen locations.

**Regression analysis.** We applied a regression analysis to the mean discharge rate of cells and found that many of them changed their activity in a linear manner with variations of eye position (Table 3). In the majority of neurons, the modulation of the activity may be approximated by a two-dimensional linear regression function with a significant fit \((P < 0.05)\). In addition, the discharge rate as a function of horizontal and vertical eye position may be fitted by a linear regression plane in one or all of the task periods analyzed. On average, 56–67% of cells showed a significant fit at least in one task period, and 58–61% of cells showed a significant fit at least along one axis. Representative examples of the regression planes are shown in Fig. 15. In Fig. 15A, the mean signal-related activity was strongest when the monkey fixates to the right half of the screen, weakest when the monkey fixates to the left half, and intermediate for central fixation. The cell in Fig. 15B (same as in Fig. 11) showed a significant fit for set-related activity associated with rightward limb movement. In this example, the activity decreased linearly as gaze direction shifted from left to right. Finally, Fig. 15C shows an example of cells with movement-related activity that fits significantly within a linear regression plane. These examples illustrate different gradients of activity, represented by the direction of the slope of the regression plane, in relation to gaze angle for individual neurons.

In addition to the regression analysis at the single cell level, we also performed a population analysis of the distribution of the slopes and intercepts of the regression planes and fitted a two-dimensional (2-D) regression plane to the mean discharge rate computed for the total sample of cells. Figure 16 shows the distribution of the intercepts of the 2-D regression planes for leftward and rightward limb movements, and Fig. 17 illustrates the distribution of the slopes obtained for each movement direction. Statistical analysis revealed that, on average, intercept values were not significantly different for the two movement direction (Mann-Whitney rank test: \(P > 0.5\)). In addition, the distribution of the directions of the gradients did not deviate significantly from a uniform distribution \((P > 0.6)\). Finally, Fig. 18 shows the 2-D regression planes fitted to set-related activity averaged across a sample of 114 PMd cells. It appears that,
for both movement directions, the regression planes are virtually flat for all task epochs analyzed. These observations are an indication that, at the population level, there is no directional bias due to the modulatory effect of neuronal activity by gaze angle.

**DISCUSSION**

We found that signal-, set-, and movement-related activity of a vast majority of dorsal premotor cortex cells varies with at least two parameters: limb movement direction and gaze angle. By contrast, the location of the instructional cue affected the neuronal activity of a relatively lower proportion of PMd cells, in agreement with previous studies (Boussaoud and Wise 1993b; Crammond and Kalaska 1994; di Pellegrino and Wise 1993). Indeed, one salient aspect of PMd neuronal activity is its close correlation with movement rather than the visuospatial attributes of the sensory cues that trigger the movement (Boussaoud and Kermadi 1997; Boussaoud...
FIG. 12. Effect of gaze angle on set-related activity of a PMd cell. Same format as Figs. 10 and 11. For conventions and abbreviations, see Figs. 6 and 9. Vertical scale, impulses/s.

and Wise 1993b; Crammond and Kalaska 1994; Kermadi and Boussaoud 1995; Pellegrino and Wise 1993a; di Pellegrino and Wise 1993). Although the present design did not control for attention nor distinguish between stimulus and movement effects by having the same stimulus

FIG. 13. Effect of gaze angle on movement-related activity of a PMd cell. Same format as Figs. 10–12, except that the trials are aligned on the end of movement (target acquisition, TA). For conventions and abbreviations, see Figs. 6 and 9. Vertical scale, impulses/s.
FIG. 14. Effect of gaze on anticipatory activity of a PMd cell. Raster plots and histograms for 5 fixations. Fixation straight ahead is at the center, the other fixations are indicated by the position of each plot relative to the center. Same conventions as Figs. 6 and 9. Note the increase of anticipatory activity with fixation to the lower left corner of the screen.

instruct a movement in opposite directions, it is unlikely that what we refer to as directional preference reflects color processing per se. Indeed, our previous experiments that controlled for such parameters (Boussaoud and Kermadi 1997; Boussaoud and Wise 1993a,b; Kermadi and Boussaoud 1995) have shown that none of the sampled PMd cells did differentiate between stimuli based on their color. Thus despite this control limitation, it is reasonable to assume, based on earlier studies that when the discharge rate of a PMd cell following a green MIC differs from that following a red MIC, that difference reflects the direction of the forthcoming movement rather than the difference in stimulus color. Having said that, the present results bear on important issues of visuomotor transformations such as the so-called coordinate transformation and the coordination of gaze and reaching limb movements in space. We will discuss these issues in the following sections.

Coordinate transformation

The brain mechanisms for the transformation of retinocentric coordinates into head- or body-centered coordinates have been extensively investigated in recent years (for review, see Andersen et al. 1993, 1997; Flanders et al. 1992). It generally is agreed that the neural mechanisms for localizing a visual target relative to the body involve a variety of signals

TABLE 3. Regression planes

<table>
<thead>
<tr>
<th>Task Period</th>
<th>Signal, %</th>
<th>Set, %</th>
<th>Movement, %</th>
<th>Total*, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>52</td>
<td>46</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td>Partial (X)</td>
<td>50</td>
<td>47</td>
<td>47</td>
<td>67</td>
</tr>
<tr>
<td>Partial (Y)</td>
<td>40</td>
<td>40</td>
<td>37</td>
<td>57</td>
</tr>
<tr>
<td>Total†</td>
<td>59</td>
<td>58</td>
<td>61</td>
<td>76</td>
</tr>
</tbody>
</table>

Percentage of cells with significant fit ($P < 0.05$) of a linear regression plane to the cell discharge along both horizontal and vertical axes (Global: F2, 2), only the horizontal (Rx) or the vertical (Ry) axis. * Percentage of cells with a significant fit at least in one task period. † Percentage of cells with a significant fit at least along one axis.
FIG. 15. Regression planes fitted to the activity of 3 PMd cells. Mean activity for 5 fixation angles (black circles) is plotted against eye position along the horizontal and vertical axes. Shaded area represents the regression plane, the regression equation of which is above each graph. Size of the bar between the circles and the plane represents the deviation of activity from the plane. \( P \) value indicates the significance level of the fit. 

A: regression plane for signal-related activity after a red cue (leftward limb movement) presented at 9 different retinal locations.

B: regression plane for set-related activity for a green MIC cue (rightward limb movement) presented at retinal coordinates (0, 0)

C: regression plane for movement-related activity when a green MIC cue was presented at retinal coordinates (10, 0).

including the retinal image of the target, orbital eye position, and head position relative to the body. Neurophysiological studies have shown that the posterior parietal cortex, including areas 7a and LIP, contains neurons with visual response properties that vary with eye position in the orbit (Andersen and Mountcastle 1983; Andersen et al. 1985, 1990b; Bremmer et al. 1997a,b). The linear variations of the responses of these neurons with horizontal and vertical changes in eye position, were termed planar gain fields by Andersen and his colleagues. They are thought of as the mechanism that allows the computation of target location in head-centered coordinates using retinal and eye position signals at the neuronal level (for reviews, see Andersen et al. 1993, 1997).

The conjecture is that when taken together, a population of parietal cells, each with its planar gain field, is capable of creating a distributed neural coding of target location in head-centered coordinates. Such a hypothesis seems likely as Zipser and Andersen (1988) have shown that similar planar gain fields emerge in the hidden units of neural network models that have been trained to produce head-centered coordinates from retinal and eye position information. Further work in this area has shown that approximately half of parietal neurons with activity that varies with orbital eye position also are modulated by changes in head position, thereby producing a gaze signal that may be used in the elaboration of a body-centered spatial coding (Brochwie et al. 1995). The authors suggested that it is a gaze signal (eye position + head position) that combines with the retinal location of targets to code their location relative to body axis.

The modulation of neuronal visual responses by eye position has been reported in other areas of the brain, including striate cortex (V1) (Guo and Li 1997; Trotter et al. 1992, 1996), the parieto-occipital area (PO, also termed V6) (Galletti et al. 1991, 1995), visual area V3A (Galletti and Battaglini 1989), ventral premotor cortex and prefrontal cortex (Boussaoud et al. 1993), internal laminar nuclei of the thalamus (Schlag et al. 1980), and the pulvinar (Robinson et al. 1990). In addition, orbital eye position appears to modulate nonvisual properties of extrastriate cortex cells. For example, auditory responses and saccadic activity have been shown to change with eye position in LIP (Andersen et al. 1990b; Mazzoni et al. 1996). Recently, Bremmer et al. (1997b) have shown that eye position affects not only visual properties of cells in the middle temporal area (MT) and medial superior temporal area (MST) but pursuit-related activity as well. They also reported eye position effects on pursuit-related and fixation-related activity in parietal areas LIP and 7A (Bremmer et al. 1997a). Thus eye position signals are pervasive throughout much of the visual system, as well as beyond, and modulate visual and nonvisual activity. Furthermore, modulation of neuronal activity in most of the reviewed studies takes the form of gain fields, perhaps suggesting a common, distributed mechanism for coordinate transformation.

From a conceptual point of view, coordinate transformation has been thought of as a serial process that gradually...
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FIG. 17. Distributions of the horizontal and vertical gradients of the regression planes of PMd cells for leftward and rightward limb movements (set-related activity). In the 2-dimensional plots (middle), each data point represents the gradient of an individual regression plane. Statistical analysis for both populations revealed that the distribution of the directions of the gradients did not deviate significantly from a uniform distribution (leftward, \( P \geq 0.7 \), rightward, \( P \geq 0.6 \)). Histograms above and beside the central illustrations represent the distribution of along a single dimension (horizontal and vertical, respectively). Normal distribution (represented by the dotted line) appears to be the best fit for the slope values along both horizontal and vertical axes.

transforms retinocentric into body-centered frame of reference (Andersen et al. 1993; Jeannerod 1991). However, the distributed nature of eye position signals suggests that these processing stages do not correspond to serially connected levels of the pathways linking visual and motor cortical areas. Indeed, the findings that in frontal areas, including the premotor cortex (Boussaoud 1995; Boussaoud et al. 1993; Jouffrais and Boussaoud 1996), a substantial proportion of neurons have properties strongly resembling those of posterior parietal cortex argue in favor of a distributed system. For example, cells in the PMv and in the dorsolateral prefrontal cortex have retinocentric receptive fields, and the magnitude of discharge is modulated by orbital eye position (Boussaoud et al. 1993). These frontal areas are hierarchically above the posterior parietal cortex, from which they receive anatomic projections (Andersen et al. 1990a; Cavada and Goldman-Rakic 1989; Johnson et al. 1996; Tanne et al. 1996). Other groups (di Pellegrino et al. 1992; Fogassi et al. 1996; Gentilucci et al. 1983; Graziano et al. 1994) found that neurons in PMv code the location of visual stimuli rela-

FIG. 18. Regression planes for a population of PMd cells (\( n = 114 \)). Same conventions as in Fig. 15. Graphs represent the regression planes for set-related activity for movements to the left (A) or to the right (B). Note that both planes are virtually flat.
tive to body parts; yet another study has shown that move-
ment-related activity of many PMv cells is modulated by eye
position (Mushiake et al. 1997). One possible explanation of
these discrepancies is that PMv contains populations of cells
representing visuomotor information in different reference
frames. The present findings, as well as those published
previously (Boussaoud et al. 1993), indicate that a large
proportion of PMv cells and a substantial number of PMd
neurons have retinocentric receptive fields modulated by
gaze angle. The similarity between these neuronal properties
and those described in the parietal cortex (Andersen et al.
1985, 1990b; Bremer et al. 1997a,b) suggests that the trans-
formation of retinocentric into head-centered coordi-
nates can be computed at the level of both parietal and
premotor cortex.

LOW VERSUS HIGH LEVEL TRANSFORMATIONS. Where does
the dorsal premotor cortex stand in the chain of visuomotor
processes and coordinate transformation? The main objec-
tive of the present study was to examine whether PMd neu-
ronal activity, at the single cell level, is modulated by orbital
eye position. It appears that, just as in the posterior parietal
cortex and ventral premotor cortex, PMd’s neuronal activity
is highly dependent on eye position signals. However, it
contrasts substantially with these cortical regions regarding
retinal signals. Most parietal and ventral premotor neurons
(Andersen et al. 1990b; Boussaoud et al. 1993) have retinal
receptive fields, whereas the proportion of cells with retinal
effects is lower in PMd (see Table 2). This proportion
decreases from 43% shortly after onset of the instructional cue
(signal-related activity) to 29% during the movement period.
Consistent with this observation, Cromand and Kalaska
(1994) have shown that information processing in PMd moves
from stimulus representation (signal-related activity)
to the coding of movement parameters as time progresses
from stimulus onset to movement onset (set and movement-
related activity). However, this does not mean that signal-
related activity represents sensory processing in a strict
sense, as other studies have demonstrated its correlation with
movement direction as well (Boussaoud and Wise 1993b; di
Pellegrino and Wise 1993). Considering the sensory aspect,
modulation of PMd neuronal activity by both retinal and eye
position signals may reflect coordinate transformation, as
has been suggested for the parietal cortex. On the other
hand, eye position modulation of set- and movement-related
activity, which represent further levels in visuomotor pro-
cessing (Boussaoud and Wise 1993b; Cromand and Ka-
laska 1994; di Pellegrino and Wise 1993), may have a differ-
ent functional implication. In particular, these effects may
indicate that movement coding is represented in a reference
frame that uses eye position signals. Thus PMd may be
viewed to contain different hierarchical levels of coordinate
transformation (Flanders et al. 1992). One, low-level trans-
formation, combines retinal and gaze signals to produce tar-
get location in body-centered reference frame. The other,
high-level transformation, combines gaze signals with other
propriocceptive and intentional signals to produce move-
ments.

MOVEMENT CODING BY THE CEREBRAL CORTEX: A NEURONAL
SUBSTRATE FOR EYE-HAND COORDINATION. Much emphasis
has been devoted to the role of orbital eye position in target
localization in both neurophysiological (Andersen et al.
1990b, 1993; Galletti et al. 1991, 1995) and neuropsychologi-
cal studies (Abrams 1992; Gauthier et al. 1992). However,
the presence of eye position signals in the premotor cortex
suggests that these signals may play a role in processes
beyond the level of coordinate transformation and target
localization, as suggested above. We propose that a set of
PMd neurons, and possibly in other cortical areas such as
the medial parietal cortex (Ferraina et al. 1997), use the
direction of gaze to determine the desired direction of arm
movement. Such a conjecture is supported by preliminary
data of one of our recent studies (Jouffrais and Boussaoud
1996) showing that the directional tuning of PMd cells often
changes with gaze direction. Additional evidence that gaze
signals interact with arm related activity comes from a recent
study by Sanes et al. (1996). They have used functional
magnetic resonance imaging to examine the pattern of brain
activation under different gaze angles in a task where normal
human subjects alternated between sequential finger move-
ments and no finger movements. Among their findings, the
authors reported that gaze angle modulates activation in the
primary motor and premotor areas contralateral to the hand
used by the subjects. This gaze modulation of movement
representation supports the idea that eye position information
is used by the motor system not just in the spatial coding of
target location but in the process of movement planning
as well.

These data may be viewed as a potential neurophysiologi-
cal substrate for the well-known concept of eye-hand coordi-
nation in psychophysics (Abrams 1992; Biguer et al. 1982;
Prablanc et al. 1978). These and other studies have shown
that gaze angle affects the performance of arm movements,
but the brain mechanisms by which the oculomotor and skel-
etomotor systems interact are still unclear. Anatomically,
Fries (1985) described direct projections from the premotor
regions and M1 to the superior colliculus, a major oculo-
motor structure. However, it is only recently that some physi-
ological studies reported that the superior colliculus contains
neurons the discharge of which is related to arm movements
(Werner et al. 1991, 1997) and that the discharge of these
superior colliculus neurons is modulated by gaze angle (Stu-
phorn et al. 1995). These findings suggest that the oculo-
motor system might use limb-related signals. On the other
hand, the neuronal properties of premotor cortical areas and M1
are modulated by eye position information (Boussaoud 1995;
Boussaoud et al. 1993; Jouffrais and Boussaoud 1996; Sanes
et al. 1996), suggesting that the skeletomotor system, in turn,
may use gaze signals for arm movement control. Altogether,
these data suggest a reevaluation of the degree of segregation
between the skeletomotor and the oculomotor systems. The
dorsal and ventral premotor areas, as well as M1 (Sanes
et al. 1996) appear to receive gaze signals that may interact
with other proprioceptive signals (Bauswein et al. 1991;
Werner et al. 1991) in the planning of limb movements, thus
forming a possible substrate for the coordination of gaze
shifts and limb movements.

HEAD- VERSUS SHOULDER-CENTERED CODING OF LIMB MOVE-
MENT DIRECTION. In previous studies, Caminiti et al. (Cam-
initi and Johnson 1992; Caminiti et al. 1991) examined the
directional selectivity of motor and premotor cortex cells in
monkeys performing limb movements in similar directions but in three different parts of the work space. They found that the preferred direction of single cells shifted with the angular shift of the work space, although the population as a whole remained a consistent predictor of movement direction. The authors suggested that motor and premotor cortical neurons represent movement direction in an arm-centered frame of reference. However, in the Caminiti et al. (1991) study, gaze direction was not dissociated from the shift of arm relative to shoulder. Indeed, when the work space shifted from the central position to the right or to the left, in the Caminiti et al. (1991) experiment, it is highly likely that gaze shifted accordingly. Under these experimental conditions, it is difficult to assess the relative contribution of gaze and arm shifts to the change in the directional preferences of cells. In view of our findings (Jouffrais and Boussaoud 1996; present study) that the directional selectivity of many PMd neurons changes with gaze angle, it is possible that the shift in the directional preference reported by Caminiti et al. (Caminiti and Johnson 1992; Caminiti et al. 1991) is due to the shift in gaze direction. Such a modulation of the directional properties of PMd suggests that a significant proportion of PMd cells code movement direction in a head-rather than shoulder-centered frame of reference.

Possible Sources of Gaze Effects. Although we suggest an interpretation of the gaze effects in relation to orbital eye position, there are other alternatives that need to be considered, especially proprioceptive signals from the neck or other body muscles. It is possible that even if the monkey’s head was restrained during the performance of the task, such a physical constraint does not prevent brain centers from issuing conjugate commands to both eye and head muscles (Lestienne et al. 1984; Vidal et al. 1982). However, a decoupling of oculomotor from neck EMG is possible under circumstances of fixation (Lestienne et al. 1984). Such a decoupling might explain why we did not find consistent gaze-dependent EMG activity in our sample of 16 muscles. Among these, it appears that EMG activity varies very rarely (2/16) with orbital eye position, at least during the instructed delay period while the monkey fixates. Interestingly, one of the two muscles with gaze-dependent EMG activity is a neck muscle (the trapezius), suggesting that modulations of neuronal activity may reflect neck proprioceptive signals, at least in part. However, although we do not rule out the contribution of head position signals, as has been shown to be the case in the posterior parietal cortex (Andersen et al. 1997; Brotchie et al. 1995), the present EMG data are not sufficient to draw definitive conclusions.

Finally, the modulation of neuronal activity reported here may result from either extraocular proprioception, efference copy, or both. The present study does not address the relative contribution of these extraretinal signals.

Limitations

One of the limitations in the present study is the use of a conditional visuomotor task to investigate gaze and arm movement interactions because often gaze and limb are directed to the same location in space. Thus the findings of this study remain to be confirmed for that common sensorimotor behavior. But the choice of a conditional task was based on the well-known involvement of PMd in conditional visuomotor behavior (see Passingham 1993).

Another interpretational limitation comes from the use of a limited set of movement directions. This limitation may have caused an underestimation of the proportion of cells with movement effect. Therefore, it is likely that some cells (those the preferred direction of which is orthogonal to the left-right axis) failed to show movement effect because they were not tested in their preferred directions.

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