Preferential Representation of Instructed Target Location Versus Limb Trajectory in Dorsal Premotor Area

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Shen, Liming and Garrett E. Alexander. Preferential representation of instructed target location versus limb trajectory in dorsal premotor area. J. Neurophysiol. 77: 1195–1212, 1997. The dorsal premotor area (PMd) of monkeys has been implicated in processes relating to movement preparation and movement selection. In the present study, we sought to determine whether PMd neurons that are activated during a delayed reaching task have directional responses that reflect either the target (i.e., the goal) of an intended movement or the physical properties of the movement itself. Two macaque monkeys were trained to perform a visually instructed, delayed reaching task with indirect visual feedback. The subjects and methods were identical to those described in the preceding paper. In the behavioral task, each subject moved a two-dimensional joystick with the right forelimb to align a cursor with targets presented on a video display. The paradigm dissociated the direction of forelimb movement from the spatial location of the target. This was accomplished by varying the spatial mappings between joystick and cursor. A variable delay separated the visual stimulus that instructed the target location (IS) from the visual stimulus that triggered the instructed movement (TS). Task-related activity was recorded from a total of 181 PMd neurons. The focus of this study was on directionally tuned neuronal responses that included 1) stimulus-related activity (phasic, following IS); 2) set-related activity (tonic, between IS and TS); and 3) movement-related activity (phasic, following TS). Of the entire sample of PMd neurons with directionally tuned activity, 114 were tested with two joystick/cursor mappings, permitting dissociation of directional responses that depended on limb trajectory from those that depended on target location. Task-related neuronal activity was classified as target-dependent if it covaried exclusively with target location across both conditions, and as limb-dependent if it covaried exclusively with limb trajectory. Directional activity that changed significantly across rotation conditions was classified as complex. Approximately one half of the sample of PMd neurons showed stimulus-related activity that was directionally tuned (56%, 64 of 114). Nearly all of the directionally classifiable stimulus-related activity was target dependent (94%, 44 of 47 responses), and none was limb dependent. A small proportion was classified as complex (6%, 3 of 47 responses). More than two thirds of the PMd neurons showed set-related activity that was directionally tuned (68%, 78 of 114). Among those cells whose late movement-related activity was directionally classifiable, there were comparable numbers of target-dependent (25%, 15 of 61) and limb-dependent responses (28%, 17 of 61), with the remainder being complex (47%, 29 of 61). These results indicate a preferential representation of target location rather than limb trajectory among PMd neurons.

INTRODUCTION

The dorsal premotor area (PMd) of monkeys has been implicated in processes relating to movement preparation and movement selection, particularly with respect to movements whose selection depends on the behavioral context (Boussaoud and Wise 1993a,b; Crammond and Kalaska 1994; diPellegrino and Wise 1993b; Kurata and Hoffman 1994; Kurata and Tanji 1986; Kurata and Wise 1988; Mauritz and Wise 1986; Mushiake et al. 1991; Passingham 1988; Riehle and Requin 1989; Weinrich and Wise 1982; Weinrich et al. 1984; Wise and Mauritz 1985). Injections of muscimol into the PMd of monkeys resulted in increased numbers of directional errors during performance of a visually instructed, conditional forelimb movement task (Kurata and Hoffman 1994). Injections of bicuculline into PMd led to irrepressible reaching movements that were comparable with those that subjects had been trained to make in a delayed, visually instructed reaching task (Sawaguchi et al. 1996). Many PMd neurons show selective activation during an enforced delay when a movement-instructing stimulus (IS) has been delivered just before the delay begins. When directional, such delay- or set-related neuronal activity in PMd has generally been found to covary mainly with the trajectory of the instructed limb movement, rather than with any sensory features (i.e., physical properties) of the IS (Boussaoud and Wise 1993b; Crammond and Kalaska 1994; diPellegrino and Wise 1993b; Kurata and Wise 1988; Weinrich and Wise 1982; Weinrich et al. 1984). Similarly, movement-related activity in PMd has generally been found to covary with the trajectory of limb movement rather than with any sensory features of the IS.
features of the IS (Boussaoud and Wise 1993b; Weinrich and Wise 1982; Weinrich et al. 1984). On the other hand, many PMd neurons also show transient responses to the IS itself, and much of this activity has been found to covary with specific properties of the sensory stimulus (such as its spatial location) rather than with the trajectory or other features of the resulting limb movement (Boussaoud and Wise 1993b; Crammond and Kalaska 1994; diPellegrino and Wise 1993b).

It is important to note that in most of the previous studies of stimulus-, set-, and movement-related activity in PMd the primary purpose was to dissociate the sensory features of the IS from the purely motor aspects of an instructed limb movement, and there was no attempt to dissociate the physical properties of the movement from its spatial target or goal (Boussaoud and Wise 1993b; Crammond and Kalaska 1994; diPellegrino and Wise 1993b; Kurata 1993; Weinrich and Wise 1982; Weinrich et al. 1984; Wise and Mauritz 1983, 1985). However, in one recent study monkeys were trained to reach along three different trajectories to capture the same target, and there it was found that some PMd neurons did show either stimulus-, set-, or movement-related activity that covaried with target location irrespective of the trajectory of limb movement (Hocherman and Wise 1991). In the present study we used a two-dimensional delayed reaching task that dissociated target location from the trajectory of limb movement to determine whether PMd neurons have directional responses that reflect either the target (i.e., the goal) of an intended movement or the physical properties of the movement itself. These data were collected from the same subjects with the use of the same techniques as were described in the accompanying report of task-related neuronal activity in primary motor cortex (MC) (Shen and Alexander 1997). Some of these results have been presented elsewhere in abstract form (Alexander and Shen 1995; Shen and Alexander 1995).

**METHODS**

The subjects, behavioral paradigms, and experimental design, including data acquisition and data analysis procedures, were those described in the accompanying paper (Shen and Alexander 1997), which focused exclusively on data obtained from MC. The data described in this report were obtained from single-cell recordings in PMd. The following is a brief summary of the methods.

Two macaque monkeys were trained to perform a visually instructed, delayed reaching task with indirect visual feedback. Each subject moved a two-dimensional joystick with the right forearm to align a cursor with targets presented on a video display. The paradigm dissociated the direction of forelimb movement from the spatial location of the target. This was accomplished by varying the spatial mappings between joystick and cursor across two rotation conditions: nonrotated (0° mapping), in which forward and rightward movements of the joystick moved the cursor upward and rightward, respectively; and rotated (90° mapping), in which rightward and backward movements of the joystick moved the cursor upward and rightward, respectively. A variable delay separated the directionally visual stimulus that instructed the target location (IS) from the nondirectional visual stimulus that triggered the instructed movement (TS).

After training had been completed, the monkeys were surgically prepared for chronic recording of task-related neuronal activity from PMd. A scleral search coil was implanted in each monkey for recording of eye position. Chronic electromyographic electrodes were also implanted in 11 (monkey JA) or 12 (monkey KO) muscles of the working forelimb.

Task-related neuronal activity was classified according to its temporal relations to the various task-defined events, and according to its dependence on the spatial features of the task. The temporal categories of neuronal responses included: stimulus-related (IS epoch immediately following IS onset), set-related (delay or postinstruction epoch, before the TS), early movement-related [reaction time (RT) epoch, before movement onset], and late movement-related [movement time (MT) epoch, following movement onset]. We also included a category of task-related activity that was not observed in MC, namely, anticipatory or precue activity. This type of activity occurred during the interval between the monkey's capture of the center fixation point and delivery of the visual IS (please see the accompanying paper for a detailed description of the behavioral paradigm). The epoch was designated pre-IS, and comprised the 200 ms before IS onset. Analyses of variance (α = 0.001) were used to determine whether epoch-specific responses showed directional dependencies on the location of the target or on the trajectory of the instructed limb movement. The categories of spatial dependencies for neurons with directional responses included target-dependent (covarying selectively with the location of the target across both rotation conditions); limb-dependent (covarying selectively with the initial direction of limb movement across both rotation conditions); complex (directional, but not fulfilling the criteria for either target or limb dependence because of significant differences in spatial tuning across rotation conditions); and unclassifiable (fulfilling the criteria for both target and limb dependence).

**RESULTS**

**Data base**

A total of 181 PMd neurons (95 from monkey JA, 86 from monkey KO) showed some form of task-related activity, that is, activity that showed significant directional effects or that differed significantly from baseline levels during at least one of the task-defined epochs (including the pre-IS epoch). Only neurons whose task-related responses had been tested with both rotation conditions were included in the final data base, which comprised 114 cells.

**Overview of task-related activity**

For the sample as a whole, the most prominent task-related activity that we observed among PMd neurons was set-related. The distribution and functional categorization of task-related activity across the various epochs that followed the IS are summarized in Table 1. Approximately four fifths of the neurons in the sample showed tonic, set-related activity during the postinstruction (delay) period. The majority of the stimulus-, set-, and movement-related responses were directional, that is, they showed significant dependence on the spatial features of the task. Approximately two thirds of the stimulus- and set-related responses that were directional were found to depend strictly on either the direction of limb movement or the location of the target. Nearly one half of the sample of PMd neurons showed tonic, nondirectional anticipatory activity preceding delivery of the visual IS, and a small proportion of neurons showed only this type of task-related activity.
TABLE 1.  Categorization of task-related neuronal activity in PMd

<table>
<thead>
<tr>
<th></th>
<th>Stimulus (IS)</th>
<th>Set (Delay)</th>
<th>Early MVT (RT)</th>
<th>Late MVT (MT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directional*</td>
<td>64 [56]</td>
<td>79 [69]</td>
<td>89 [78]</td>
<td>78 [68]</td>
</tr>
<tr>
<td>Classifiable†</td>
<td>47 (100)</td>
<td>63 (100)</td>
<td>66 (100)</td>
<td>61 (100)</td>
</tr>
<tr>
<td>Target‡</td>
<td>44 (94)</td>
<td>48 (76)</td>
<td>34 (51)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Limb§</td>
<td>0 (0)</td>
<td>5 (8)</td>
<td>9 (14)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Complex†</td>
<td>3 (6)</td>
<td>10 (16)</td>
<td>23 (35)</td>
<td>29 (47)</td>
</tr>
<tr>
<td>(T/L/I)</td>
<td>(0/0/3)</td>
<td>(0/0/10)</td>
<td>(3/2/18)</td>
<td>(6/4/19)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>17</td>
<td>16</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>114 [100]</td>
<td>114 [100]</td>
<td>114 [100]</td>
<td>114 [100]</td>
</tr>
</tbody>
</table>

* Number of cells [% of total sample, N = 114 cells]. † Number of cells (% of total number of cells with directionally classifiable activity in each epoch). ‡ Respective numbers of Complex-T, Complex-L and Complex-I responses contributing to total number of Complex responses in each epoch.

Phasic, stimulus-related activity following the IS

Approximately three quarters of the sample of PMd neurons showed brief, phasic activity changes immediately following the IS (Table 1), and the majority of these responses were directionally tuned. Slightly more than one half of the entire sample showed stimulus-related activity that was directionally selective (56%, 64 of 114 responses). Of the stimulus-related activity that was directionally classifiable, nearly all was target-dependent (94%, 44 of 47 responses), and none was limb-dependent. A small proportion was classified as complex (6%, 3 of 47 responses). An example of stimulus-related activity that was classified as target-dependent is illustrated in Fig. 1. In both the nonrotated and the rotated conditions, this cell showed a phasic burst of activity that began shortly after presentation of the IS at either the right target or the bottom target, irrespective of the eventual direction of limb movement. There was no response when the IS was presented at either of the other two targets.

Tonic, set-related activity preceding the TS

Approximately four fifths of the entire sample of PMd neurons showed tonic, set-related activity during the postinstruction (delay) epoch between IS and TS (Table 1), and the majority of this activity was directionally selective. Approximately two thirds of the entire sample showed set-related activity that was directionally tuned (69%, 79 of 114 responses). Among cells with set-related activity that was directionally classifiable, there were ~9 times as many target-dependent responses (76%, 48 of 63) as there were limb-dependent responses (8%, 5 of 63), with the remainder being complex (16%, 10 of 63).

An example of set-related activity that was target dependent is illustrated in Fig. 2. In both rotation conditions, this cell showed a sustained increase in discharge rate throughout the delay period on trials in which the IS had indicated that the bottom target was to be captured after the TS. The response was clearly independent of the intended direction of limb movement.

Figure 3 shows an example of target-dependent set-related activity combined with stimulus-related activity that was also target dependent. Both responses were maximal on trials in which the monkey was instructed to capture the right target, regardless of rotation condition or the direction of limb movement.

Set-related activity that was limb-dependent was encountered infrequently in PMd. An example of this type of activity is illustrated in Fig. 4. Under both rotation conditions, this neuron showed maximal set-related discharge on trials in which the instructed motor response involved a leftward limb movement, and the next-highest set-related discharge was on trials in which the instructed response involved a forward limb movement. The set-related discharge was clearly independent of the target that had been signified by the IS. This neuron also showed early movement-related activity that was limb-dependent, being characterized by a phasic burst of activity following the TS, before the onset of leftward limb movements.

Anticipatory or pre-cue activity preceding the IS

Although this was not an intended focus of our study, in nearly one half of our sample of PMd neurons (48%, 55 of 114) we observed tonic increases in discharge rate during the interval between the monkey’s capture of the center fixation point and onset of the IS (pre-IS epoch). Such activity, described previously by Wise and colleagues, was designated “anticipatory activity” by Mauritz and Wise (1986) and as “precue activity” by Vaadia et al. (1988) because it appears to anticipate predictable environmental events. All of the anticipatory or precue activity observed in the present study was nondirectional, and it was generally comparable in magnitude with the tonic, set-related activity that preceded the TS. This is illustrated by the PMd neuron whose task-related activity is shown in Fig. 5. In this example, nondirectional anticipatory activity was followed by target-dependent set-related activity. The set-related activity was maximal on trials in which the monkey was preparing to capture the top target for both rotation conditions. Most (48 of 55 responses) of the anticipatory activity observed in the present study was combined with set-related activity, as in this example.

In some instances, however, anticipatory activity might occur in complete isolation from any other form of task-related activity. This was the case for 7 of the 55 PMd neurons in which anticipatory activity was observed. An example of this type of isolated anticipatory activity is shown in Fig. 6.

Phasic, movement-related activity following the TS

Movement-related activity following the TS was considered to be early or late, depending on whether it preceded or followed the onset of limb movement. Movement-related activity in PMd was generally monophasic, consisting of only a single component (either early or late, but not both). Approximately three quarters of the sample of PMd neurons showed early movement-related activity that was directionally tuned (Table 1). Of the early movement-related activity that was directionally classifiable, there were >3 times as many target-dependent responses (51%, 34 of 66) as limb-dependent responses (14%, 9 of 66), with the remainder...
FIG. 1. Target-dependent, stimulus-related activity recorded from a dorsal premotor area (PMd) neuron. Each of the 4 rows of illustrations represents the neural and kinematic data obtained from trials in which the same peripheral target served as the locus for the visual movement-instructing stimulus (IS, cue). Data from both 0° and 90° mapping conditions are presented. In this and subsequent figures that illustrate neuronal responses, data from the 2 rotation conditions are ordered from left (A) to right (B) in the sequence in which they were administered. The neural data are shown as corresponding raster displays (top) and peri-event histograms (bottom). Each dot in the raster displays represents a single action potential, and each line of dots contains the data from a single trial. The time base (ms) is the same for raster and histograms, both of which are aligned on the same behavioral event. The alignment point for the rasters is indicated by a single caret mark at the bottom of each raster display. Binwidth for histograms: 25 ms. Units for vertical scale: spikes/s. Trials are aligned with cue onset. The kinematic data are shown to the right of each corresponding set of neural data. The target-capturing hand trajectories from trials of a given type are superimposed and presented on a facsimile of the monkey’s behavioral display, with the designated target for each trial type indicated by shading. Trajectories indicated as upward in the illustration represent forward limb movements, whereas those indicated as downward represent backward limb movements. The units for the horizontal scale under each kinematic display represent hand displacement (cm). This neuron responded to the presentation of the instructional cue with a brisk, phasic discharge whenever the visual IS was located at either the right or the bottom target, irrespective of rotation condition or movement trajectory. Although movements to the right target in the 0° mapping condition were not fully adapted (i.e., the initial direction of movement was more appropriate for the 90° mapping condition), the lack of stimulus-related activity preceding the fully adapted leftward movements to the left target in the 0° mapping condition confirms that this cell’s stimulus-related activity depended on target location rather than the direction of limb movement.

being complex (35%, 23 of 66). Approximately two thirds of the sample of PMd neurons showed late movement-related activity that was directionally tuned (Table 1). Of the late movement-related activity that was directionally classifiable, there were comparable numbers of target-dependent (25%, 15 of 61) and limb-dependent responses (28%, 17 of 61), with the remainder being complex (47%, 29 of 61).

Figure 7 shows an example of early movement-related activity that was classified as target dependent. Under both rotation conditions, this cell discharged maximally before
FIG. 2. Target-dependent set-related activity in PMd. Conventions are similar to those in Fig. 1, except that for each rotation condition there are 2 columns of rasters and histograms aligned, respectively, with the onsets of IS (cue) and movement-triggering stimulus (TS, trigger). Heavy dots in the trigger-aligned rasters: times of movement onset after delivery of the TS. Under both rotation conditions, this cell showed a tonic, set-related discharge throughout the postinstruction (delay) epoch between IS and TS on trials in which the bottom target had been designated as the correct target by the IS.

the onset of movements to capture the left or bottom targets, irrespective of the direction of limb movement.

Late movement-related activity that was classified as limb dependent is illustrated in Fig. 8. Under both rotation conditions, this cell showed maximal discharge after the onset of rightward or backward limb movements, irrespective of the target that was being captured.

Another late movement-related response that was classified as limb dependent is illustrated in Fig. 9. In this example, the movement-related activity, present under both rotation conditions during either leftward or forward limb movements, was combined with a set-related response that was target dependent. The set-related discharge that followed delivery of the IS was maximal on trials in which the left target was designated for capture, with reciprocal suppression of postinstruction period activity on trials in which the designated target was on the right.

Among our sample of PMd neurons with combined set- and movement-related responses that were specific for either target or limb direction, only three of the four possible combinations of target and limb dependencies were encountered. There were no examples of neurons that combined limb-dependent set-related activity with target-dependent movement-related activity.

Complex activity

Some of the directional activity observed in this study (including stimulus-, set-, and movement-related responses) did not meet the criteria for classification as either target or limb dependent, because of complex interactions between direction and rotation condition. An example of complex set-related activity is illustrated in Fig. 10. In the 90° mapping condition, this cell showed a directional set-related response,
FIG. 3. Combined stimulus-related and set-related responses, both of which were target dependent. Conventions as in Fig. 2. This PMd neuron showed phasic, stimulus-related discharge followed by tonic, set-related discharge on trials in which the right target had been designated as the correct target by the IS. This directional selectivity was the same under both rotation conditions.

with maximal discharge during the delay epoch that preceded leftward movements of the joystick to capture the bottom target. In the 0° mapping condition, however, the set-related response became nondirectional, consisting of sustained suppression of activity throughout the postinstruction period regardless of the designated target (or the instructed direction of limb movement). When this cell was again tested in the 90° mapping condition, the same directional set-related response was observed once more. This type of response might have been characterized, equivalently, as either a target- or a limb-dependent response whose directionality changed across rotation conditions. Because of this ambiguity, we have chosen to designate this type of response as complex.

**Temporal distribution of directionally classifiable activity**

Figure 11 shows the temporal distribution of target-dependent versus limb-dependent versus complex activity across the task-defined epochs that followed the IS onset. It is evident that, over the extended interval between IS and motor response, there was an initial predominance followed by a gradual decline in the proportion of PMd neurons showing target-dependent activity, and a gradual increase in the proportion of neurons showing limb-dependent activity. There was also a gradual increase in the proportion of neurons showing complex activity. An overall χ² analysis of the relative frequencies of these three categories of directionally classifiable activity across the four task epochs showed that the apparent temporal changes were highly significant (χ² = 63.96, df = 6, P = 7.02 × 10⁻¹²).

To clarify the relationships between directional categories and task epoch, we used additional χ² tests to partition the variance associated with the overall χ² analysis (Snedecor and Cochran 1989). Those results are presented in Table 2. Because of the apparent similarity in proportions of limb-dependent activity and complex activity across epochs (Ta-
FIG. 4. Limb-dependent set-related and movement-related responses. Conventions are the same as in Fig. 2. Under both rotation conditions, this PMd neuron showed tonic, set-related activity and phasic, early movement-related activity, both of which were maximal on trials that required leftward limb movements. Both responses were also characterized by reciprocal depression of discharge on trials that required rightward or backward limb movements, regardless of rotation condition. These responses were independent of target location.

Table 1, we compared the frequencies of these two categories across epochs and found that they did not differ significantly (Table 2, row b: $\chi^2 = 2.15$, df = 3, $P = 0.46$). Consequently, these two categories were combined, and their combined frequency was then compared with the frequency of target-dependent activity across epochs. The result (Table 2, row c: $\chi^2 = 62.58$, df = 3, $P = 1.65 \times 10^{-11}$) showed that nearly all of the variance in the overall $\chi^2$ analysis could be accounted for by the difference across epochs in the frequencies of target-dependent versus limb-dependent plus complex activity.

To determine whether the trend toward declining proportions of target-dependent activity was significant for each successive epoch, we made those comparisons as well and found that the trend was significant across each pair of adjacent epochs (Table 2, rows d–f). However, the sum of $\chi^2$ values for these last three comparisons ($\chi^2 = 24.14$, df = 3) was substantially less than the $\chi^2$ for the comparable comparison across all epochs (Table 2, row c), because of the fact that the latter comparison also accounted for variance across nonadjacent epochs. This last point was illustrated by combining the corresponding frequencies of the first two epochs (IS and delay), and those of the last two epochs (RT and MT), and comparing the resulting frequencies across the two composite epochs. When the $\chi^2$ resulting from that nearly all of the variance in the overall $\chi^2$ analysis was added to those obtained from the independent comparisons made across the first two epochs (IS vs. delay; Table 2, row g: $\chi^2 = 49.65$, df = 1, $P = 2.22 \times 10^{-16}$) was added to those obtained from the independent comparisons made across the first two epochs (IS vs. delay; Table 2, row d) and across the last two epochs (RT vs. MT; Table 2, row f), the sum of $\chi^2$ values ($\chi^2 = 65.32$, df = 3) approximated that of the $\chi^2$ for the comparable comparison across all epochs (Table 2, row c: $\chi^2 = 62.58$, df = 3). The small residual difference is attributable to slight, but unavoidable, algebraic differences between the
FIG. 5. Combined anticipatory activity and target-dependent set-related activity. Conventions as in Fig. 2. This PMd neuron showed a pattern of tonic, nondirectional anticipatory discharge that began after center fixation point (CF) capture (not shown) and continued until shortly after the IS had been delivered (cue onset), followed by tonic, set-related activity that depended on the location of the designated target. The set-related discharge was maximal on trials in which the top target had been designated as the correct target, with reciprocal depression of discharge during the postinstruction period on trials in which either the right or bottom targets had been so designated. Both the directional, set-related activity and the nondirectional anticipatory activity were similar under both rotation conditions.

overall and partitioned analyses (Snedecor and Cochran 1989).

Locations of neurons with task-related activity

Figure 12 shows the surface penetration sites for all microelectrode tracks that produced neuronal recordings that contributed to the final data base. The entire sample of PMd neurons with task-related responses was drawn from the immediate vicinity of the superior precentral sulcus. In each monkey, most of the task-related neurons were located in a region just ventral to the rostral half of the sulcus.

We made and examined plots of stimulus-related, set-related, and early and late movement-related activity, and of target-dependent, limb-dependent, and complex activity, and found no apparent differences in the spatial distributions of these different types of task-related activity within the PMd recording area of either monkey; nor were any such differences apparent when the data from both monkeys were pooled and projected onto composite maps.

Comparison of neuronal responses in PMd with those in MC

We compared, epoch by epoch, the relative frequencies of target- and limb-dependent responses observed in PMd with those observed in MC in the same experimental animals. The data from MC recordings were described in the preceding paper (Shen and Alexander 1997). Figure 13 shows the comparative data in a normalized format.
Although both PMd and MC showed similar patterns of declining proportions of target-dependent responses and increasing proportions of both limb-dependent and complex responses across the sequence of epochs leading from IS onset to execution of the delayed motor response, on an epoch-by-epoch basis the observed frequency of target-dependent activity was significantly higher in PMd than in MC for all but the earliest of these epochs. This was determined by means of a $\chi^2$ analysis. Because there were no significant differences in the relative frequencies of limb-dependent versus complex activity across any of the epochs, either for PMd (Tables 1 and 2) or for MC (Tables 3 and 4 of the accompanying paper [Shen and Alexander 1997]), these two categories were combined and their combined frequency was compared with the frequency of target-dependent activity across the two cortical regions, epoch by epoch. The results are presented in Table 3. They indicate that there were significantly higher frequencies of target-dependent activity in PMd than in MC during the delay, RT, and MT epochs. During the IS epoch, the directionally classifiable (stimulus-related) activity was overwhelmingly target-dependent in both cortical regions (94% in each).

**DISCUSSION**

One of the principal findings of this study was that the large majorities of directional stimulus-, set-, and early movement-related responses among PMd neurons proved to be target-dependent, showing selective dependence on the location of the target that guided the delayed reaching movement and not on the trajectory of the limb movement itself. The other main finding was that the relative frequencies of target-dependent, limb-dependent, and complex activity showed a systematic pattern of variation across the different task epochs between IS presentation and motor response.
Evidence for a sensory-to-motor transformation in PMd

To perform the instructed delay task that was used in this study, each monkey was required to transform the spatial information contained in the visual IS into a limb movement of appropriate trajectory. Over the sequence of epochs leading from IS onset to delayed motor response, we observed a gradual decline in the frequency of target-dependent activity and a gradual increase in the frequency of limb-dependent activity. This is consistent with the possibility that PMd may participate in mediating the sensory-to-motor transformation required by the task.

The suggested temporal flow of information from target-dependent to limb-dependent representations was seen not only at the population level, but in the response profiles of individual neurons as well. Thus, among PMd neurons with combined set- and movement-related activity, our sample contained no examples of cells in which set-related activity that was limb dependent preceded movement-related activity that was target dependent, even though we did encounter all other possible combinations of target- and limb-dependent responses.

Comparison of recruitment patterns in PMd and MC

The fact that the PMd data described here and the MC data described in the accompanying paper (Shen and Alexander 1997) were collected from the same experimental animals invites direct comparisons of the task-related responses observed in these two regions. The parallels between the recruitment patterns observed in the two regions were striking. Both PMd and MC showed a predominance of target-dependent activity at the time of stimulus presentation, followed by increasing proportions of limb-dependent activity over the extended interval that concluded with the delayed motor response. In addition, both regions showed a corresponding increase in complex activity over this same interval. Within PMd, as within MC, the pattern of recruitment of limb-dependent activity was statistically indistinguishable from the pattern of recruitment of complex activity. These similarities in recruitment patterns suggest that both regions may participate in the spatial sensory-to-motor transformation required by the delayed reaching task.

The chief difference we observed between PMd and MC was in the consistently larger proportion of target-dependent
TARGET REPRESENTATION IN PREMOTOR CORTEX

**FIG. 8.** Limb-dependent movement-related activity. Conventions as in Fig. 7. This PMd neuron showed late movement-related activity that was maximal on trials that required rightward or backward movements, regardless of rotation condition. Neural response onset coincided with movement onset for backward hand trajectories, and was slightly earlier for rightward trajectories.

representations in PMd for all but the earliest epoch following IS onset (Table 3). This suggests that PMd and MC may play somewhat different roles in the processing of spatial information relevant to the behavioral paradigms used in this study. For example, if both regions participate in the sensory-to-motor transformation required by the delayed reaching task, PMd might play a preferential role in the processing of spatial sensory and/or associative (context-dependent) information relevant to the intended target of movement, whereas MC might be more involved in transforming spatial information about the target of movement into specific motor commands appropriate for generating the proper limb trajectory. The predominance of target-dependent activity in PMd would suggest a possible net flow of sensory and/or associative spatial information from PMd to MC, even though the reciprocity of their interconnections (Barbas and Pandya 1987; Dum and Strick 1991a; Kurata 1991; Muakkassa and Strick 1979; Tokuno and Tanji 1993) implies that much of the communication between these two cortical fields may be bidirectional. This is consistent with other recent evidence that tends to implicate PMd in earlier and more high-level processing—such as target representation and trajectory selection—than MC, with the latter seeming to play a more direct role in specifying the moment-to-moment details of movement execution (Crammond and Kalaska 1996; Johnson et al. 1996).

*Sensory versus associative versus motor activity in PMd*

In the preceding paper (Shen and Alexander 1997) we suggested a simple framework for viewing the spatial sensorimotor transformation required by most tasks that involve visually instructed reaching: namely, as a chain or cascade of information processing leading from purely sensory processing to context-dependent or associative processing to purely motor processing. Neural correlates of purely sensory processing should reflect unconditionally some physical property of the sensory input, correlates of purely motor processing should reflect some physical property of the motor output, and correlates of associative processing should reflect some aspect of the behavioral context, being neither purely motor nor purely sensory.

Several studies of neuronal activity in PMd have dissociated some of the purely motor variables involved in visually
FIG. 9. Target-dependent set-related activity combined with limb-dependent movement-related activity. Conventions as in Fig. 2, except that for both rotation conditions the 2nd set of rasters and histograms is aligned with movement onset rather than trigger onset. In the movement-aligned rasters, TS onsets are indicated by the heavy dots. This PMd neuron showed maximal set-related discharge on trials in which the left target was designated for capture, and reciprocal suppression of set-related activity on trials in which the right target was so designated. There was also a phasic, early movement-related discharge on trials that required either leftward or forward limb movements. The movement-related response was more difficult to discern because it was continuous with, and of the same magnitude as, the set-related discharge that preceded movements to capture the left target (bottom row). This cell also showed nondirectional anticipatory activity that began after CF capture (not shown) and ended with presentation of the visual IS (cue onset). All 3 types of activity were independent of rotation condition.

instructed limb movements, including direction versus extent of movement (Fu et al. 1993, 1995; Kurata 1993; Riehle and Requin 1989), direction (or position) versus force (Bauswein et al. 1991; Riehle and Requin 1995; Riehle et al. 1994b; Werner et al. 1991), and direction versus endpoint (Caminiti et al. 1991). However, these studies were not designed to dissociate either spatial sensory variables (such as IS location) or spatial associative variables (such as instructed target location) from any of the purely motor variables that were being examined.

In the present study, IS location and the instructed target (i.e., goal) of movement were one and the same, whereas both of these variables were dissociated from the trajectory of the instructed reach. As a result, we can be relatively confident that the activity that was designated target dependent did not depend on purely motor variables, such as the trajectory of limb movement, although we cannot be certain whether such activity may have reflected either the associative significance of the visual IS (i.e., the target or goal of the limb movement which the IS instructed) or a purely sensory feature of the IS itself (i.e., the physical location of the IS itself).

Only a few previous studies of neuronal activity in PMd have attempted to dissociate the trajectory of a visually in-
FIG. 10. Complex set-related activity. This cell was tested initially in the rotated condition (A), then in the nonrotated condition (B), and finally in the rotated condition once again (C). For each rotation condition, rasters and histograms are aligned with IS (cue) onset. Heavy dots in the rasters: TS onsets, some of which occurred beyond the time window displayed here. This PMd neuron showed tonic, set-related discharge on trials in which leftward limb movements were required to capture the bottom target, but only during the rotated condition (3rd rows of A and C). In the nonrotated condition, there was no set-related response.

Structurally reach from either the location of the instructed target of movement (Hocherman and Wise 1991) or the location of the IS itself (Crammond and Kalaska 1994; diPellegrino and Wise 1993b). Hocherman and Wise (1991) sampled the task-related activity of PMd neurons in monkeys that had been trained to make reaching movements along three different trajectories to acquire the same spatial targets. They found that only a small proportion of the stimulus-, set-, and movement-related responses (7–9% of each) fulfilled their strict criteria for target selectivity by showing the same preferential response to a particular target location across all three trajectories of movement. However, in that study the spatial IS included not only a terminal target, which designated the endpoint for the reach, but also intermediate targets that specified the via points through which the trajectory was required to pass. By design, those intermediate targets or via points were not fully dissociated from the corresponding trajectories. It is possible, therefore, that the study may have underestimated the proportion of task-related responses that were actually target-dependent.

Crammond and Kalaska (1994) sampled neuronal activity from PMd in monkeys performing two delayed reaching tasks that dissociated the location of a visual IS from the spatial target of limb movement while target and limb trajectory were allowed to covary. The experimental design was complementary to that of the present study, in which the trajectory of limb movement was dissociated from the instructed target location while target and IS location were allowed to covary. Crammond and Kalaska found that only 8% of the directional set-related activity was IS-dependent, whereas 62% was either target- or limb-dependent. We found that only 8% of the directional set-related activity was limb dependent, whereas 76% was either IS- or target-dependent. The common variable that was left undissociated
in both studies was target location. Because of the complementary designs of the two studies, their combined results suggest that the majority (54–68%) of the directional set-related activity observed in PMd may have been exclusively target dependent. The indicated range was obtained by subtracting the percentage of strictly limb-dependent activity identified in our present study from the percentage of either target- or limb-dependent activity identified in the study by Crammond and Kalaska (62% – 8%) and by subtracting the percentage of strictly IS-dependent activity observed in the latter study from the percentage of either IS- or target-dependent activity observed in ours (76% – 8%).

DiPellegrino and Wise (1993b) sampled the task-related activity of rostral PMd neurons in a monkey that was trained to respond differentially to the same visuospatial stimuli (IS). In that study, the subject was required to maintain spatial attention directed toward one of eight radially arranged cue lights until the reillumination of the attended cue light triggered a reaching movement; the reach was directed either toward the previously instructed cue location (compatible condition) or in a fixed direction, regardless of cue location (incompatible condition). Thus across the two conditions the location of the IS was dissociated from the target or goal of the instructed limb movement. In the incompatible condition, DiPellegrino and Wise found that the majority of stimulus-related, set-related, and movement-related activity showed significant directional tuning in relation to IS location, and in some cases this tuning remained invariant across task conditions. Thus some of this activity may have been IS dependent or sensory in nature, according to the definitions employed in the present study.

Recently the data from this last study were subjected to a population analysis by Wise et al. (1997), who used the population vector approach that was pioneered by Georgopoulos et al. (1984, 1988, 1989; Lurito et al. 1995). With the use of the preferred direction of each neuron computed from its RT activity during the compatible task, a population vector was calculated from the summed, activity-weighted contributions of all task-related neurons, assuming that each cell contributed to the population vector along the axis of its own preferred direction (Georgopoulos et al. 1986). In the incompatible task, the population vector pointed mainly toward the attended IS location throughout the postinstruction delay period, although it was deviated slightly toward the constant target of movement (i.e., toward the direction of the eventual motor response) by ~30% of the angular distance between IS and target. After the TS, the population vector shifted rapidly into alignment with the motor response. The authors concluded that the tonic deviation and eventual rotation of the population vector in the incompatible task was most likely to be accounted for by the graded recruitment of two separate categories of neuronal activity, one category being sensory/attentional and the other motor (i.e., limb-dependent) (Wise et al. 1997).

**Interpretational limitations**

We have already considered the main interpretational limitations of our experimental design in the accompanying paper (Shen and Alexander 1997). Extensive sampling of task-related electromyographic activity throughout these experiments indicated that muscles of the proximal forelimb were essentially silent throughout the IS and delay epochs, and showed directional activations that covaried with limb trajectory during the early and late movement epochs. Although this argues against any simple relation between target-dependent neuronal responses and forelimb muscle activity, we cannot exclude the possibility that other muscles, which were not included among our sample, might have shown task-related activations that covaried with target location rather than limb trajectory.

Another possibility is that some of the target-dependent responses might have been related to spatial attention or spatial memory, or to the preparation or execution of eye movements. Boussaoud (1995) has shown that ~80% of

**TABLE 2. Task-related activity in PMd: frequency analysis of directionally classifiable activity across epochs**

<table>
<thead>
<tr>
<th></th>
<th>( \chi^2 )</th>
<th>df</th>
<th>( P \text{ Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Overall: T/L/C over all epochs</td>
<td>63.96</td>
<td>6</td>
<td>( 7.02 \times 10^{-12} )</td>
</tr>
<tr>
<td>b. L/C over all epochs</td>
<td>2.15</td>
<td>3</td>
<td>0.46 (NS)</td>
</tr>
<tr>
<td>c. T/[L+C] over all epochs</td>
<td>62.58</td>
<td>3</td>
<td>( 1.65 \times 10^{-13} )</td>
</tr>
<tr>
<td>Totals: (compare with a)</td>
<td>[64.73]</td>
<td>[6]</td>
<td></td>
</tr>
<tr>
<td>d. ( T/[L+C]<em>{\text{hs}} &gt; T/[L+C]</em>{\text{lat}} )</td>
<td>5.97</td>
<td>1</td>
<td>( 1.46 \times 10^{-2} )</td>
</tr>
<tr>
<td>e. ( T/[L+C]<em>{\text{lat}} &gt; T/[L+C]</em>{\text{her}} )</td>
<td>8.47</td>
<td>1</td>
<td>( 3.61 \times 10^{-3} )</td>
</tr>
<tr>
<td>f. ( T/[L+C]<em>{\text{her}} &gt; T/[L+C]</em>{\text{het}} )</td>
<td>9.70</td>
<td>1</td>
<td>( 1.84 \times 10^{-3} )</td>
</tr>
<tr>
<td>Totals: (compare with c)</td>
<td>[24.14]</td>
<td>[3]</td>
<td></td>
</tr>
<tr>
<td>g. ( T/[L+C]<em>{\text{hs-lat}} &gt; T/[L+C]</em>{\text{het-serr}} )</td>
<td>5.97</td>
<td>1</td>
<td>( 1.46 \times 10^{-2} )</td>
</tr>
<tr>
<td>h. ( T/[L+C]<em>{\text{het-serr}} &gt; T/[L+C]</em>{\text{her}} )</td>
<td>9.70</td>
<td>1</td>
<td>( 1.84 \times 10^{-3} )</td>
</tr>
<tr>
<td>g. ( T/[L+C]<em>{\text{hs-lat}} &gt; T/[L+C]</em>{\text{het-serr}} )</td>
<td>49.65</td>
<td>1</td>
<td>( 2.22 \times 10^{-16} )</td>
</tr>
<tr>
<td>Totals: (compare with c)</td>
<td>[65.32]</td>
<td>[3]</td>
<td></td>
</tr>
</tbody>
</table>

C, instances of complex activity; del, activity during delay epoch; df, degrees of freedom; IS, activity occurring during IS epoch; L, instances of limb-dependent activity; MT, activity during MT epoch; NS, not statistically significant; RT, activity during RT epoch; T, instances of target-dependent activity.

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FIG. 11. Bar plot showing numbers of PMd neurons with target-dependent, limb-dependent, or complex activity in each of the 4 task-defined epochs that followed IS onset. Stimulus-related activity occurred during the IS epoch, set-related activity during the delay epoch, early movement-related activity during the reaction time (RT) epoch, and late movement-related activity during the movement time (MT) epoch [see Table 1 of accompanying paper (Shen and Alexander 1997)].
directional set-related responses in PMd may be modulated by the direction of gaze. Gaze effects could not explain the directional set-related activity recorded in the present study, however, because both monkeys maintained a relatively constant angle of gaze (fixating the center fixation point to detect its dimming) throughout the delay epoch. On the other hand, our eye position recordings did show that a saccade was made to the appropriate peripheral target immediately after the TS was presented. Because the direction of the saccade covaried with target location, it is possible that some of the target-dependent set- and/or movement-related activity may have been related to these target-directed eye movements, or to associated processes such as spatial attention. It is also possible that some of the target-dependent set-related activity may have been related to spatial memory for the location of the visual stimulus.

There is evidence that some directional activity in PMd may be related to spatial attention or spatial memory processes (diPellegrino and Wise 1993a,b). This is consistent with the fact that rostral PMd receives direct input from dorsolateral prefrontal cortex (Lu et al. 1994), which has itself been strongly implicated in spatial memory processes.
TABLE 3. Comparison of directionally classifiable activity in PMd and MC: frequency analysis within task epochs

<table>
<thead>
<tr>
<th>Epoch</th>
<th>Comparison</th>
<th>$\chi^2$</th>
<th>df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS</td>
<td>$\text{IS} &gt; \text{IS}_{\text{IS}}$</td>
<td>$&lt;10^{-3}$</td>
<td>1</td>
<td>$&gt;0.9$ (NS)</td>
</tr>
<tr>
<td>Delay</td>
<td>$\text{IS} &gt; \text{IS}<em>{\text{IS}}$, $\text{IS} &gt; \text{IS}</em>{\text{IS}}$</td>
<td>16.23</td>
<td>1</td>
<td>$5.61 \times 10^{-3}$</td>
</tr>
<tr>
<td>RT</td>
<td>$\text{IS} &gt; \text{IS}_{\text{IS}}$</td>
<td>23.74</td>
<td>1</td>
<td>$1.10 \times 10^{-4}$</td>
</tr>
<tr>
<td>MT</td>
<td>$\text{IS} &gt; \text{IS}_{\text{IS}}$</td>
<td>16.46</td>
<td>1</td>
<td>$4.97 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

C. instances of complex activity; df, degrees of freedom; IS, activity occurring during IS epoch; L, instances of limb-dependent activity; MT, activity during MT epoch; NS, not statistically significant; RT, activity during RT epoch; T, instances of target-dependent activity.

(Barbas and Pandya 1987; Cavada and Goldman-Rakic 1989; Chavis and Pandya 1976; Dum and Strick 1991a; Godschalk et al. 1984; Kurata 1991; Johnson et al. 1996; Matelli et al. 1986; Petrides and Pandya 1984; Tokuno and Tanji 1993; Vogt and Pandya 1987), varying contributions to direct, descending corticospinal pathways (He et al. 1993, 1995; Hummelsheim et al. 1986), and varying patterns of interconnections among themselves (Kurata 1991; Luppino et al. 1990, 1993; Morecraft and VanHoesen 1992; Tokuno and Tanji 1993). We hypothesize that within this distributed motor network, extrinsic, visually derived spatial information is gradually transformed into specific motor commands by a cascading sequence of sensory, associative, and motor processing that takes place both across and within the various cortical motor fields. Despite the reciprocity of many of the connections, the flow of spatial information through the network of cortical motor fields is hypothesized to depend largely on how direct or indirect are the connections that link each of the motor fields (1) with frontal and parietal visuospatial processing areas, (2) other motor fields, and (3) with the segmental motor apparatus.

According to this model, cortical motor fields that are most strongly and directly linked with frontal and parietal visuospatial processing areas (such as PMd, presupplementary motor area, and the rostral cingulate motor area) would be expected to show a relative abundance of spatial sensory and/or associative representations in comparison with motor fields that are relatively isolated from visuospatial inputs (such as supplementary motor area and MC). And conversely, cortical motor fields that are most strongly and directly linked with the segmental motor apparatus (such as supplementary motor area and MC) would be expected to show a relative abundance of strictly motor representations in comparison with motor fields that are relatively isolated from the final common pathway (such as presupplementary motor area and rostral PMd). The studies to date that have addressed these issues have yielded results that are consistent with this general schema (Alexander and Crutcher 1990; Crammond and Kalaska 1994; diPellegrino and Wise 1991b; Hocherman and Wise 1991; Lurito et al. 1991; Niki and Watanabe 1976; Riehl et al. 1994a). However, much more extensive and detailed assessments of the time-dependent distributions of sensory, associative, and motor representations across the various cortical motor fields will be needed to determine whether spatial sensory-to-motor transformations are indeed implemented in the manner proposed here.

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