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Neural Activity in Primary Motor and Dorsal Premotor Cortex In Reaching Tasks With the Contralateral Versus Ipsilateral Arm

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Cisek, Paul, Donald J. Crammond, and John F. Kalaska. Neural activity in primary motor and dorsal premotor cortex in reaching tasks with the contralateral versus ipsilateral arm. *J Neurophysiol* 89: 922–942, 2003; 10.1152/jn.00607.2002. To investigate the effector dependence of task-related neural activity in dorsal premotor (PMd) and primary motor cortex (M1), directional tuning functions were compared between instructed-delay reaching tasks performed separately with either the contralateral or the ipsilateral limb. During presentation of the instructional cue, the majority (55/90, 61%) of cells in PMd were tuned with both arms, and their dynamic range showed a trend for stronger discharge with the contralateral arm. Most strikingly, however, the preferred direction of most of these latter cells (41/55, 75%) was not significantly different between arms. During movement, many PMd cells continued to be tuned with both arms (53/90, 59%), with a trend for increasing directional differences between the arms over the course of the trial. In contrast, during presentation of the instructional cue only 5/74 (7%) cells in M1 were tuned with both arms. During movement, about half of M1 cells (41/74, 55%) were tuned with both arms but the preferred directions of their tuning functions were often very different and there was a strong bias toward greater discharge rates when the contralateral arm was used. Similar trends were observed for EMG activity. In conclusion, M1 is strongly activated during movements of the contralateral arm, but activity during ipsilateral arm movements is also common and usually different from that seen with the contralateral arm. In contrast, a major component of task-related activity in PMd represents movement in a more abstract or task-dependent and effector-independent manner, especially during the instructed-delay period.

INTRODUCTION

Performance of reaching movements appears to require control at multiple levels of abstraction. For example, the neural mechanisms involved in deciding on the target for a reach need not necessarily take into account all the details of muscular contraction which must ultimately be controlled to accomplish the selected movement. Conversely, mechanisms involved in overt muscular control need not be sensitive to the criteria by which a particular action was selected. One therefore expects that different neural populations represent a given movement in different ways, emphasizing some cognitive, temporal, or spatial aspects while ignoring others.

Indeed, many lines of evidence support a diversity of functions in reach-related areas of the cerebral cortex (for review, see Caminiti et al. 1998; Kalaska et al. 1997; Wise et al. 1997). For example, cells in primary motor cortex (M1) are strongly tuned to the direction, speed, and extent of movement (Caminiti et al. 1991; Crammond and Kalaska 1996; Crutcher and Alexander 1990; Fu et al. 1993; Georgopoulos 1991, 1995; Georgopoulos et al. 1982; Moran and Schwartz 1999) as well as to joint posture and muscle force (Cabel et al. 2001; Caminiti et al. 1991; Evarts 1968; Evarts et al. 1983; Kakei et al. 1999; Kalaska et al. 1989; Scott et al. 2001; Scott and Kalaska 1997; Sergio and Kalaska 1997, 1998, 2003).

In contrast, while cell activity in premotor cortex (PM) also covaries with direction and extent of movement (Caminiti et al. 1991; Crammond and Kalaska 1996, 2000; Fu et al. 1993; Messier and Kalaska 2000), it is less sensitive than M1 to limb-related motor output details such as joint posture and force (Crammond and Kalaska 1996; Kakei et al. 1999; Riehle et al. 1994; Scott et al. 1997) and preferentially reflects more abstract aspects of the task (Caminiti et al. 1998; Crammond and Kalaska 2000; Johnson et al. 1996; Mitz et al. 1991; Shen and Alexander 1997b; Wise et al. 1996, 1997, 1998; Wise and Murray 2000). For instance, in a visuomotor rotation task that dissociated the direction of hand movement on a joystick from the direction of motion of an on-screen cursor, Shen and Alexander (1997b) found that during the "instructed delay period" (IDP) between the target instruction and the signal to start the movement, most of the activity in dorsal premotor cortex (PMd) was related to the direction of motion of the cursor and not to the direction in which the hand would move. Even during movement itself, many PMd cells continued to signal cursor movement direction but hand direction related activity became more prominent than during the delay period. A similar trend was also seen in M1, but hand direction related activity was more common than in PMd at all times during the trial (Shen and Alexander 1997a). These results prompted Shen and Alexander (1997a,b) to suggest that PMd and M1 neurons participate in the transformation of information describing the global goal of the task (movement of the cursor toward the instructed target) into information describing how the goal will be accomplished (movement of the hand on the joystick).

Wise and colleagues have likewise suggested that a major role of PMd is to map arbitrary associations between sensory inputs and motor actions (Wise et al. 1996, 1997; Wise and Murray

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2000). Task-related activity in this region increases as an animal learns a novel and arbitrary nonspatial stimulus-response association (Mitz et al. 1991), and the directional preferences of single cells may even change with each new learned stimulus-response mapping (Wise et al. 1996, 1998). Thus the activity of cells in PMd is neither simply related to the stimuli which instruct a particular action nor to the means by which the action is executed (Boussaoud and Wise 1993a; Crammond and Kalaska 1994; di Pellegrino and Wise 1993; Shen and Alexander 1997a,b; Wise et al. 1992), but is more involved in the selection of an action under particular task conditions.

Another difference between PMd and M1 relates to the degree of ipsilateral activation during motor tasks. For example, many functional imaging studies have shown activation of premotor regions in both hemispheres, but activity in M1 primarily on the contralateral side during a variety of motor tasks, including isolated movements of the distal arm (Cramer et al. 1999; Kim et al. 1993; Kollias et al. 2001; Li et al. 1996; Nirkko et al. 2001). Proximal arm movements additionally activate ipsilateral M1 regions, but to a lesser extent than the contralateral M1 (Nirkko et al. 2001), consistent with callosotomy results showing that the ipsilateral hemisphere has some control over arm transport, but not over hand and finger preshaping (Brinkman and Kuypers 1973).

Similar trends have been seen in single-unit studies. During a key-press task, the activity of the majority of M1 cells was related only to movements performed by the contralateral fingers (Tanji et al. 1987, 1988). Nevertheless, about 13% of M1 cells discharged during isolated ipsilateral finger movements. Thus even in a task involving the distal limb, a small amount of ipsilaterally related activity was observed in M1. During the instructed delay period, Tanji et al. (1987, 1988) found that the majority of M1 cells active during the IDP (13%) were active only before contralateral movements, but 3% were active before ipsilateral movements.

Single-unit activity in ipsilateral M1 has been reported more frequently during movements of the *proximal* limb. Kazennikov et al. (1999) recorded activity in M1 during bimanual coordination to open a drawer with the left hand and to retrieve a food pellet with the right, and during unimanual tasks in which each of these two motions were performed separately. They found that 65% of M1 neurons exhibited task-related activity changes only during bimanual and unimanual contralateral movements, but 14% were also active during the unimanual ipsilateral task. In contrast, using a variation of the unimanual task in which monkeys both opened the drawer and retrieved the food with the same hand, Kermadi et al. (1998) found that 22% of M1 neurons were active only when the contralateral arm was used and 2% were active only with the ipsilateral arm. However, 75% of M1 cells showed some task-related activity during *either* contralateral or ipsilateral movements. Donchin et al. (1998) examined the activity of cells in M1 while monkeys held two independent planar manipulanda and performed either contralateral, ipsilateral, or simultaneous bimanual center-out reaching tasks. Although half of the M1 cells were most strongly modulated during movements involving only the contralateral limb, 21% were most strongly modulated during isolated ipsilateral arm movements and 29% were more or exclusively active during the bimanual task. Of these latter cells, 89% were more strongly related to the direction of movement performed by the contralateral limb. Finally, Steinberg et al. (2002) reported that 34% of M1 cells tested discharged during reaching movements of the ipsilateral arm. In summary, a number of studies have reported that activity in M1 is modulated to differing degrees during movements of the ipsilateral arm.

Recent studies have also examined effector dependence in PMd. In their unimanual task involving opening a drawer and retrieving food with the same hand, Kermadi et al. (2000) found that 85% of PMd cells were active during both contralateral and ipsilateral trials. Hoshi and Tanji (2000, 2002) reported that during an instructed-delay period after both target and arm-choice information was given, a majority of PMd cells reflected both the information indicating the target of a reaching movement and the information instructing which arm to use. Of the PMd cells that were sensitive to the choice of effector, a majority were more active with the contralateral arm (Hoshi and Tanji 2002). These results suggest that effector-independent task information and information on effector choice converge in dorsal premotor cortex, while more effector-specific activities are found in primary motor cortex. A particularly interesting finding supporting this interpretation is that when one signs one's name with either the index finger or the toe, primary motor cortex is activated in the region related to the effector which is performing the movement, but activity in anterior PMd is found in the same nominally arm-related region regardless of which effector is used (Rijntjes et al. 1999).

Here, we report additional evidence supporting the abstract nature of movement representations in PMd. We compared the directional tuning properties of cells in M1 and PMd during instructed-delay center-out reaching tasks performed separately with either the limb contralateral or ipsilateral to the recording site. Unlike many of the single-unit studies discussed above, in our tasks the monkeys performed contralateral and ipsilateral movements in separate blocks of trials while the unused arm was restrained at the monkey's side. Therefore the choice of effector arm was not a decision variable for the animals. We found that the level, pattern, and directionality of activity in the caudal part of M1 were usually very different during unimanual movements of the contralateral and ipsilateral arms. In contrast, directionally tuned PMd activity prior to movement onset was largely effector-independent. In particular, the directional preference was similar regardless of which arm performed the movement, especially during the instructed-delay and reaction-time epochs. The dynamic range of task-related PMd activity also tended to be more similar with either arm than was observed for M1. Very consistent results were found in PMd in two separate studies, and the results of both are presented. In the second study, gaze direction was monitored with an oculometer allowing us to assess the relation between PMd activity and oculomotor behavior (Cisek and Kalaska 2002a) and to confirm that contralateral and ipsilateral tuning is not an artifact of gaze-related modulation. Some of these results have appeared previously in abstract form (Crammond and Kalaska 1991; Kalaska et al. 2000).

METHODS

Behavioral tasks

Monkeys performed two variations of an instructed-delay center-out reaching task (Fig. 1). Detailed descriptions of these tasks have been published previously (*experiment 1*: Crammond and Kalaska

1996, 2000) (*experiment 2*: Cisek and Kalaska 2002b). A brief synopsis follows.

EXPERIMENT 1. Two monkeys (male *Macaca mulatta*, 5 kg, 5.5 kg) were trained to move a 2-df vertical pendulum suspended over a horizontal target panel. The target panel contained nine triplets of miniature red, green, and yellow light-emitting diodes (LEDs), with one triplet at the center and eight triplets distributed evenly around it in a circle of 8-cm radius. The monkeys were trained to grasp the handle of the pendulum and move it to whichever red LED was illuminated. As a result, visual target information, focus of gaze and attention, and limb movements were all located in the same horizontal workspace. Handle position was measured ultrasonically at 100 Hz (Graf/Pen 3, Science Accessories).

Each "direct-delay" (DD) trial began when the central red LED was illuminated and the monkey placed the handle over it. The monkey held the handle within a window of 4- to 5-mm radius around the central LED for a 1- to 3-s *center-hold-time* (CHT). Next, one of the peripheral green LEDs was illuminated for a 1- to 3-s *cue period* (CUE), during which the monkey had to maintain the handle over the central red LED which remained illuminated. Finally, both the central red LED and the peripheral green LED were extinguished simultaneously, and a red LED appeared at the cued peripheral location. This spatial GO signal instructed the monkey to move the handle over the peripheral red LED. The *reaction-time* (RT) epoch was defined between the GO signal and movement onset, and *movement-time* (MT) epoch was defined between movement onset and offset. To receive a liquid reward, the monkey then had to hold the handle over the peripheral red LED for a further *target-hold-time* (THT) of 2 s. Trials were presented in a randomized-block sequence until 5–10 successful movements were performed to each of the eight target locations. If the monkey made an error, either by moving the handle away from the central LED before the GO signal was given, by moving to the wrong location, or by not meeting the time constraints, the trial was not rewarded and was immediately repeated after a brief inter-trial interval. A block of trials was performed sequentially by the monkey using either the arm contralateral or the arm ipsilateral to the recording chamber, while the other arm was comfortably restrained in an arm rest at the animal's side using Velcro straps. Simultaneous bimanual actions using both arms were not studied (Donchin et al. 1998; Kazennikov et al. 1999; Kermadi et al. 1998, 2000; Steinberg et al. 2002; Tanji et al. 1988).

This report describes results from DD trials only. The DD trials were randomly interleaved with standard reaction-time trials in which no green cue appeared (results from the noncued trials are not included here). The monkeys were also trained to perform other kinds of instructed-delay tasks described elsewhere (Crammond and Kalaska 1996, 2000; Kalaska and Crammond 1995), which were presented in separate blocks.

EXPERIMENT 2. Two monkeys (male *M. mulatta*, 6 kg, 6 kg) performed an instructed-delay task using the same manipulandum described above, but instead of placing the handle over LEDs presented on a horizontal plane, the monkeys used the manipulandum to control a cursor on a computer screen positioned vertically at eye-level 48 cm away. The position of the cursor on the vertical screen was determined by the horizontal position of the manipulandum sampled at 50 Hz (Graf/Pen 9, Science Accessories), with 1:1 scaling between handle and cursor movement. This effectively dissociated the spatial location of limb movements from the visual inputs guiding action. The monkeys' unconstrained gaze direction was sampled at 100 Hz using an infrared oculometer (Dr. Bouis, Karlsruhe, Germany).

Each trial began when a central circle (1.5 cm radius) appeared and the monkey placed the cursor within it for a 500-ms CHT. Next, a cue circle (2 cm radius) appeared in one of eight possible target locations on the circumference of an 8-cm-radius circle, for a CUE period lasting 1000 ms. The cue then disappeared for a *memory period* (MEM) lasting from 1500 to 4000 ms. Finally, the central circle disappeared and eight identical circles (2-cm radius) appeared at the eight peripheral locations. This nonspatial GO signal instructed the monkey to move to the location of the cued target. The RT was defined between the GO signal and the movement onset, and MT was defined between movement onset and offset. To receive a liquid reward, the monkey had to hold the cursor within the correct cued target for a THT of 1000 ms. Trials were presented in a randomized-block sequence until 6–10 correct reaching movements were made to each of the eight targets. If the monkey made an error, the trial was *not*

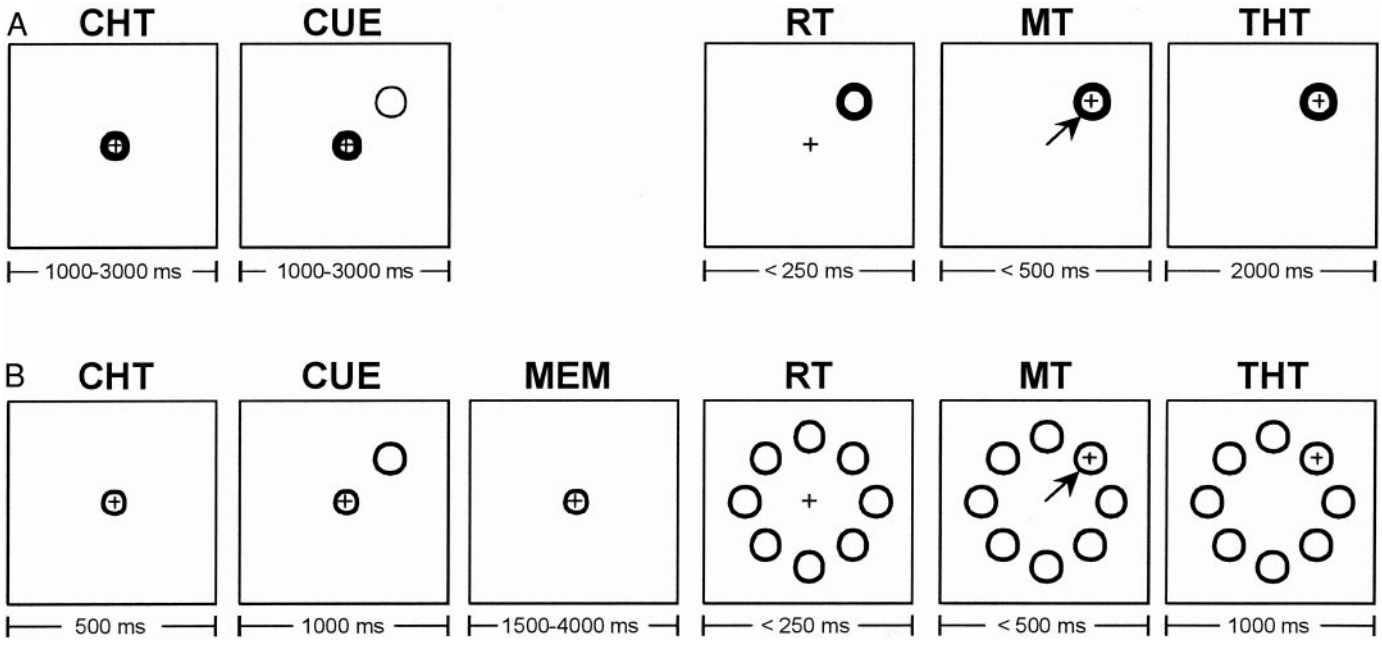

FIG. 1. Behavioral tasks. *A*: task used in *experiment 1*. The "+" symbol indicates the position of the handle over the target panel; the thin circle indicates an illuminated green light-emitting diode (LED), and thick circles indicate red LEDs. *B*: task used in *experiment 2*. The "+" symbol indicates the location of the cursor on the screen, and circles represent the cues and target regions into which the monkey was trained to move the cursor.

immediately repeated but was shuffled back into the remaining trial sequence. As in *experiment 1*, data files were collected sequentially while the monkey used one or the other arm, but never while using both arms to move the manipulandum.

EMG recordings

EMG activity of all the major muscles of the shoulder joint and shoulder girdle as well as several axial, paraspinal, and neck muscles was recorded, for both the performing arm and the restrained arm. This was undertaken at various times prior to, during, and after the several months of electrophysiological data collection. Pairs of fine, 40-μm Teflon-insulated stainless steel wires were inserted percutaneously into the bellies of selected muscles using 30-gauge hypodermic needles. All electromyographic (EMG) activity was amplified ($\times$1,000 to $\times$5,000), band-pass filtered (100 Hz–3 kHz), rectified, and integrated (10-ms bin duration) before storage. The identity of the implanted muscles was verified by observation of EMG activity outside of the task and by microstimulation of the implanted muscles via the recording electrodes. If microstimulation failed to evoke a palpable local contraction of the desired muscle belly or the expected joint motions, the electrodes were removed and re-inserted. EMG records were made when the arm on the same side of the body as the implanted muscle was used to perform the reaching movement (we refer to these as EMG records for the "Performing arm") and also when it was restrained at the monkey's side and the other arm was used (we refer to these as records for the "Restrained arm").

Neuronal recording

After training to a success rate of 70–90% (the large majority of errors resulted from a failure to enter the central target to start a trial within 3 s, or a failure to hold the arm in the central window for the prescribed CHT), the monkeys were surgically prepared for data collection. Using standard aseptic techniques and barbiturate anesthesia (35 mg/kg iv) (*experiment 1*) or gas inhalation anesthesia (*experiment 2*), a trephine hole was opened in the skull over the precentral gyrus. A Plexiglas recording chamber was fixed over the craniotomy using vitallium screws and neurosurgical acrylic cement, along with a stainless steel head-fixation post. For *experiment 1*, the recording chambers were positioned to span the precentral cortex between the central and arcuate sulci. For *experiment 2*, the chamber was positioned more rostrally, centered between the precentral dimple and the arcuate sulcus.

Daily recording sessions began after a postoperative recovery period of 10 days during which prophylactic antibiotics and analgesic drugs were administered. Standard chronic extracellular recordings were made using glass-insulated platinum-iridium electrodes. The discriminated, extracellular spike activity of single neurons was recorded during performance of the task and also tested for response properties outside of the task. Cells were examined if they exhibited task-related changes of activity and showed directional preferences in at least one task epoch. At the end of certain penetrations, microlesions (10 μA, 10–20 s) were made in the cortex at specific locations along the electrode track. At the end of each daily recording session, the cylinder was cleaned, flushed with sterile saline, and closed.

Data collection lasted 8–12 wk in each chamber. When the experiments were completed, the monkeys were deeply anesthetized and perfused with saline and then 10% Formalin solutions. The dura was removed, and dissecting pins were inserted in the brain at known coordinates to delimit the cortical region studied. Using the pins as cutting guides, the cortex was blocked and 30-μm frozen sections were cut, stained with cresyl violet, and examined by light microscopy to locate the microelectrode penetrations.

Data analysis: EMG activity

The rectified and integrated (bin duration: 10 ms) EMG signals were collected over 5–10 trials in each direction. Activity during CUE, RT, MT, and THT epochs was tested for a significant main effect of direction using analysis of variance (ANOVA; $P < 0.01$), and a preferred direction (PD) was computed using trigonometric moments. This was done for EMG records from both the performing arm and the restrained arm. In cases where a significant directional effect existed for both arms, the difference in PD was computed by subtracting the restrained-arm PD from the performing-arm PD. In these same cases, the dynamic range of activity for each arm was calculated as the difference in the area of the EMG envelope between the movement directions with the largest and smallest EMG activities during a given epoch. The normalized difference between the dynamic range with the performing and the restrained arm was calculated using the following contrast ratio formula: $CR = (P - R)/(P + R)$, where P is the dynamic range of activity recorded from the performing arm, and R is the dynamic range recorded from the restrained arm. The resulting CR ranges from -1 to $+1$, with positive numbers indicating stronger activity with the performing arm, negative numbers indicating stronger activity with the restrained arm, and zero indicating no difference.

Data analysis: neural activity

For each cortical cell recorded in the task, the mean discharge rate (including partial spike intervals) was calculated for each epoch of each trial. A directional tuning function was calculated for each epoch by averaging the activity for all trials at each of the eight directions separately. The PD of each cell in each epoch was calculated using trigonometric moments. Tuning functions were tested for unimodal directional tuning by a nonparametric bootstrap test (Georgopoulos et al. 1988) with 1,000 repetitions and a criterion of $P < 0.01$.

For many cells, significantly directional tuning functions were obtained when either the arm contralateral or the arm ipsilateral to the recording chamber was used to perform movement. In these cases, the contralateral and ipsilateral tuning functions were compared using two measures: the difference between preferred directions, and the difference in depth of modulation (or dynamic range). Directional differences were quantified by subtracting the ipsilateral PD from the contralateral PD, and the significance of this difference was determined using a nonparametric bootstrap procedure (Sergio and Kalaska 2003). Briefly, a tuning function was generated from the contralateral data by random re-sampling, with replacement, of the single-trial firing rates in a given epoch *within* each of the movement directions. A second tuning function was generated using the ipsilateral data, and a PD difference calculated between these two. This procedure was repeated 1,000 times to generate a distribution of PD differences, reflecting the inherent variability in the contralateral and ipsilateral tuning functions on the basis of the number of samples collected in each direction. The PD differences were rank-ordered to determine the upper and lower limits of the 99% confidence interval for their distribution. If the value of 0° PD difference fell outside of the confidence interval, it was concluded that the directional tuning was significantly different ($P < 0.01$) between the contralateral and ipsilateral blocks (Sergio and Kalaska 2003).

The dynamic range of the directional tuning curve for each arm was computed as the difference between the largest and the smallest mean activities for different directions in the tuning function recorded for each arm in a given epoch. Differences were quantified using a contrast ratio similar to the one used for analyzing muscles: $CR = (C - I)/(C + I)$, where C is the dynamic range with the contralateral arm and I is the dynamic range with the ipsilateral arm. For each cell, the significance of the difference $C - I$ was determined using a bootstrap procedure similar to that described above, in which a distribution of bootstrapped dynamic range differences was generated using re-sampled tuning functions.

In *experiment 2*, the monkeys' unconstrained gaze direction was continuously monitored using an infrared oculometer to determine to what degree cell tuning functions were related to eye movements (Boussaoud et al. 1998; Cisek and Kalaska 2002a). This permitted a second analysis of the cell data recorded from these monkeys. Instantaneous eye movement speed throughout each trial was calculated at 10-ms intervals by differentiation of the oculometer signals. Fixation episodes were identified as time periods of ≥100 ms during which eye speed did not exceed 2.4 times the SD of the speed distribution computed over the entire trial. The average gaze direction was determined for each fixation episode and the average spike rate computed from the portion of each episode which fell within the MEM, after the first 50 ms were excluded to avoid potential confounds of perisaccadic activity. Next, fixation episodes were identified during which the direction of gaze fell within 6° of the center of the target display, corresponding to a circular region on the monitor whose radius was about 5 cm. The spike rates from these episodes were used to construct tuning functions for both contralateral and ipsilateral reaching tasks, and for cells for which significant tuning was obtained in both cases, the directionality and dynamic range of these were compared using the procedures described above. Because they were constructed solely from neural discharge while the monkey looked toward the center of the monitor display, these tuning functions reflected reach-related activity which was not modulated by changes in gaze.

RESULTS

EMG recordings

EMG activity was recorded during separate blocks of unimanual movements with each of the two arms, from 16 muscles of the upper arm and shoulder, as well as several axial and neck muscles. These were as follows: triceps longus, cleidodeltoid, acromiodeltoid, spinodeltoid, subscapularis, infraspinatus, supraspinatus, latissimus dorsi, rostral trapezius, caudal trapezius, teres major, pectoralis major, atlantoscapularis anterior, splenius capitis, cervical paraspinal, and thoracic paraspinal. Two or three separate records were obtained for most of these on different days, for a total of 42 EMG pairs of records for the performing and restrained arms.

Most arm muscles behaved in a simple and expected manner, showing strong and directionally tuned activity when recorded from the performing arm and little or no activity when recorded from the restrained arm (Fig. 2, *A* and *B*). No muscle records showed unique activation during restrained-arm recordings. However, some of the more proximal muscles were active when either arm was used. For example, pectoralis major was strongly active when the arm onto which it inserts was performing the task and making movements across the body midline (Fig. 2*C*). When that arm was restrained and movements were made with the other arm, pectoralis major still showed directionally tuned activity, but was less active and with an opposite preferred direction. This activity may be related to postural adjustments made by the monkey in response to the interaction forces transmitted from the moving arm through the trunk, or to a behavioral strategy in which the monkey used the restrained arm as a brace or lever to assist performance of the task with the other arm. Another example of a muscle that is directionally tuned during task performance with either arm is splenius capitis, a neck muscle (Fig. 2*D*). This muscle exhibited a consistent tuning which was oriented in the same direction regardless of the arm used to perform the movement. This activity may also reflect spurious postural adjustments, or alternatively, an "eye-head synergy" which is observed even in trained head-fixed monkeys performing eye movements (Lestienne et al. 1984). It has been shown that the EMG activity of the splenius capitis increases during ipsilateral horizontal eye movements (Andre-Deshays et al. 1988; Lestienne et al. 1984), and the anatomical placement of the muscle also suggests that it should contract during upward gaze shifts (Andre-Deshays et al. 1988). Since the monkeys always looked at a target before reaching to it, regardless of which arm was being used, one expects that the left splenius capitis would be most active during reaches toward the left and distal targets, as observed. However, it is interesting to note that the activity of splenius capitis was much larger when recorded from the same side as the performing arm than when it was recorded from the side of the restrained arm, regardless of the presumably identical eye movement pattern and eye-head synergy in these two cases.

Figure 2*E* shows, for the different task epochs, the differences in directional tuning observed when a muscle showed directionally tuned activity when recorded on the same side of the body as the performing versus the restrained arm. During the CUE epoch, tuning during performance with both arms was seen in only three EMG records: twice in splenius capitis (in 2 different animals), and once in cervical paraspinal. In all these cases, directional tuning was similar for these axial muscles on both the performing and the restrained side. During RT, MT, and THT epochs, directional tuning during performance with both arms was found in many EMG records (18/42 in RT, 26/42 in MT, and 19/42 in THT), but the differences were uniformly distributed throughout 360° (Rao spacing test, $P > 0.05$).

Although directional tuning was fairly common during post-GO epochs in EMG records collected from the restrained arm, the activity was almost always stronger when collected from the performing arm. As shown in Fig. 2*F*, the dynamic range contrast ratios were strongly skewed toward positive values, and in many cases almost no EMG activity was found in the restrained arm (indicated by a dynamic range contrast ratio near +1). In summary, muscle activity was not confined to the side of the body of the performing arm. Furthermore, although several muscles exhibited directionally tuned activity during performance with either arm, the differences in the directionality of this tuning for the two arms were typically widespread and the level of muscle activity was usually much greater when that muscle was on the same side of the body as the performing arm than when it was on the side of the restrained arm (Fig. 2, *E–F*).

Neuronal data set

In *experiment 1*, 74 cells were recorded in caudal M1 and 61 cells were recorded in PMd while the monkeys performed separate blocks of trials using either the arm contralateral or the arm ipsilateral to the recording chambers (Fig. 3). A further 10 cells were tested in rostral M1. All of these cells formed part of the data sets in studies using a variety of different tasks (Crammond and Kalaska 1994, 1996, 2000; Kalaska and Crammond 1995). In *experiment 2*, 29 cells were recorded only in PMd during blocks with each arm, 20 in monkey 1, and 9 in monkey 2, and oculometer records were obtained for 25 of these. The 20 cells from monkey 1 were part of a data set described elsewhere (Cisek

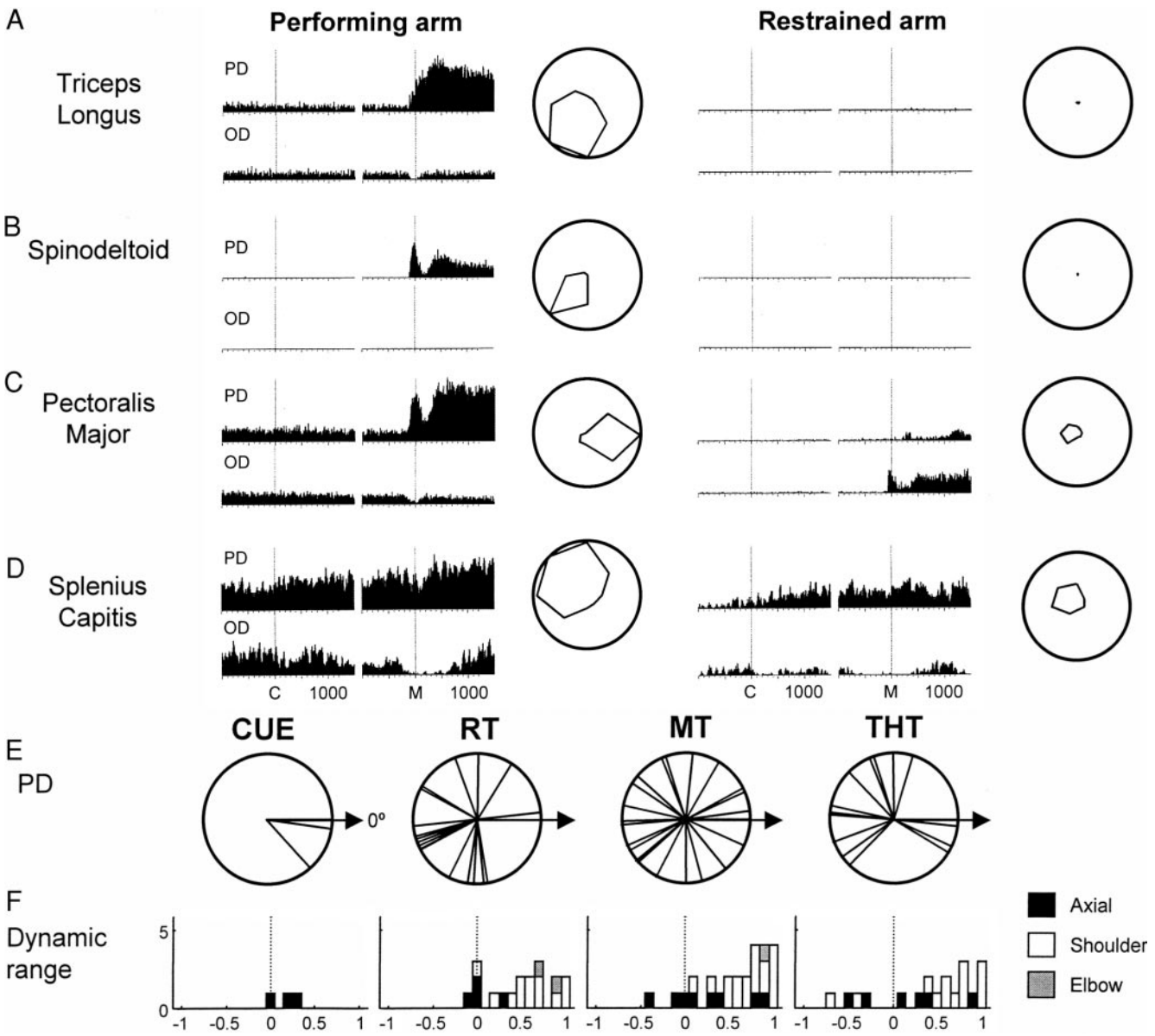

FIG. 2. Electromyographic (EMG) data. *A–D*: EMG records for 4 muscles on the left side of the body. On the left are data collected while the monkey performed movements with the arm on the same side as the recorded muscle, and on the right are data while that arm was restrained and the monkey performed movements with the other arm. Histograms show the EMG activity profiles for movements in the direction which elicited the largest EMG with the performing arm (*top histograms*) and movements in the opposite direction (*bottom histograms*). Tuning functions collected over the period from GO signal onset to the end of target-hold-time (THT) are shown as polar plots. *E*: differences between the preferred directions collected from the performing arm minus the preferred directions collected from the restrained arm, during the 4 task epochs, for muscles showing directional activation while performing the task with each arm [analysis of variance (ANOVA), $P < 0.05$]. *F*: distribution of dynamic-range contrast ratios between the performing arm and the restrained arm dynamic ranges, for the same muscles as in *E*.

and Kalaska 2002a,b). Because no significant differences were observed in data collected from the right versus the left hemisphere, in either M1 or PMd, all the analyses below pool data from both hemispheres.

Response patterns in primary motor cortex

In general, response patterns in caudal primary motor cortex were quite different when the two arms were used to perform the reaching movements. A particularly striking example is shown in Fig. 4. This cell was recorded in the left hemisphere. When the movements were performed using the right arm, contralateral to the recording site, the cell had a high tonic discharge rate during CHT, and strong directional tuning during RT, MT, and THT. The PDs during these three epochs were 272°, 285°, and 287°, respectively, i.e., the cell discharged most strongly during movements toward the body. In contrast, when the task was performed using the left arm, ipsilateral to the recording site, the cell was almost completely inactive including a near total absence of tonic discharge. After the block of left-arm movements was completed, the cell was recorded again during movements with the right arm to verify

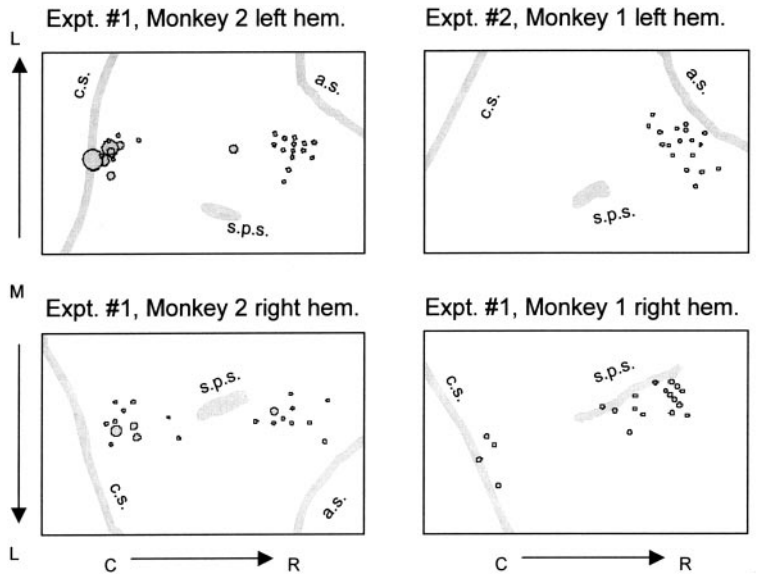

FIG. 3. Recording sites of cells included in this study (except for 9 cells from the second monkey in *experiment 2*, which is still involved in experiments). The top row shows the 2 left hemispheres used and the bottom row shows 2 right hemispheres used. Ten cells were also recorded in a rostral part of primary motor cortex (M1; not shown). Calibration bar applies to all 4 panels. Abbreviations: c.s., central sulcus; a.s., arcuate sulcus; s.p.s., superior precentral sulcus; M, medial; L, lateral; C, caudal; R, rostral.

that the strong activity shown in Fig. 4 was still present (data not shown). Intracortical microstimulation (ICMS) at this site induced contractions of the right shoulder girdle muscles above the scapula (supraspinatus, rostral trapezius).

Figure 5 shows the activity of a second M1 cell (left hemisphere) which also showed a strong preference for movements performed with the contralateral arm. During the three post-GO epochs, the cell was strongly directionally tuned (PD: RT = 24°, MT = 81°, THT = 35°). The cell was also modestly directionally tuned during the CUE epoch with a PD at 139°. Among the M1 cells tuned in CUE, such large differences in directional tuning between the CUE and post-GO epochs were commonly observed (Crammond and Kalaska 2000). This cell also exhibited task-related changes of activity while the monkey performed the task using the ipsilateral arm. In particular, it exhibited a pronounced suppression of discharge just before and during the movement. The cell was only significantly directionally tuned during MT, with a PD at 184°. The dynamic range of this tuning (10 spikes/s) was significantly lower than the cell's MT dynamic range of 41 spikes/s during performance with the contralateral arm.

Figure 6 shows the activity of a third M1 cell (right hemisphere) which exhibited somewhat more consistent directional tuning during both contralateral and ipsilateral movements. When the contralateral arm was used, the cell discharged briskly just before and during movements away from the body

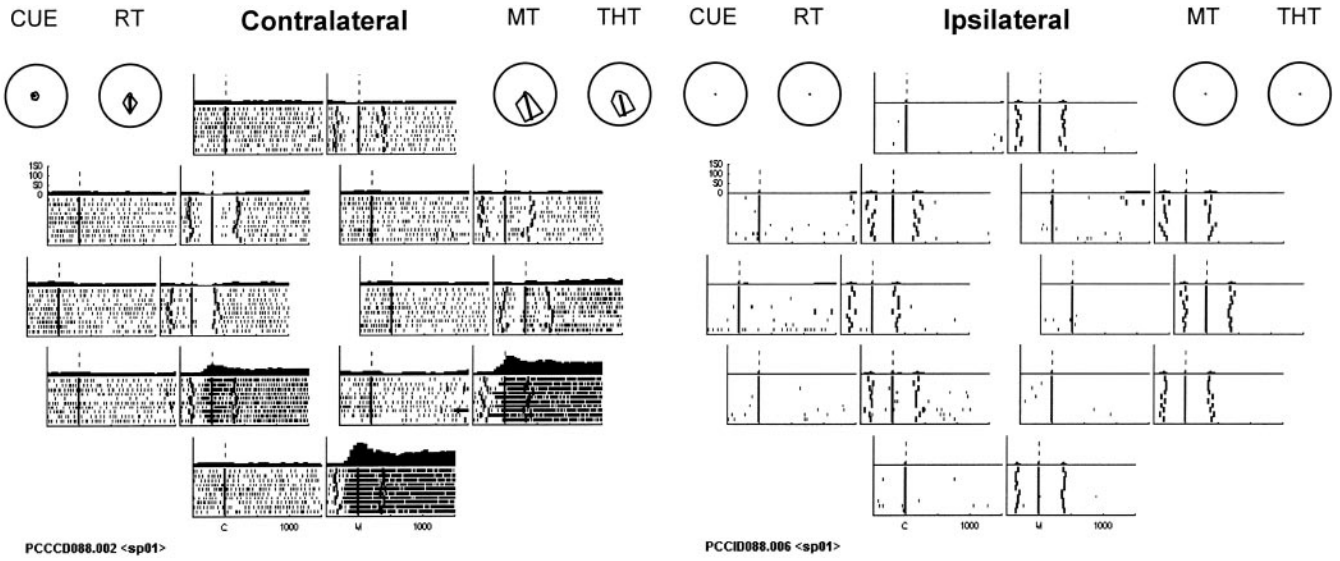

FIG. 4. Neural activity of an M1 cell, recorded in the left hemisphere in *experiment 1*, showing a very strong preference for movements performed with the contralateral arm. For both the contralateral and the ipsilateral blocks, cell activity during direct-delay (DD) trials in each of the 8 directions is indicated using raster and peri-event histogram displays whose placement corresponds to the movement direction. The first raster and histogram of each pair is aligned on the presentation of the green cue LED (*C*), and the second of each pair is aligned on the onset of movement (*M*). In the raster displays, thin marks indicate action potentials and thick marks indicate cue onset, GO signal, movement onset, and movement offset times during individual trials. Polar plots show the tuning functions computed during the cue period (CUE), reaction time (RT), movement time (MT), and THT epochs, and thick lines indicate the preferred direction of significant ($P < 0.01$) tuning. All the polar plots are scaled equally using a radius corresponding to 100 spikes per second.

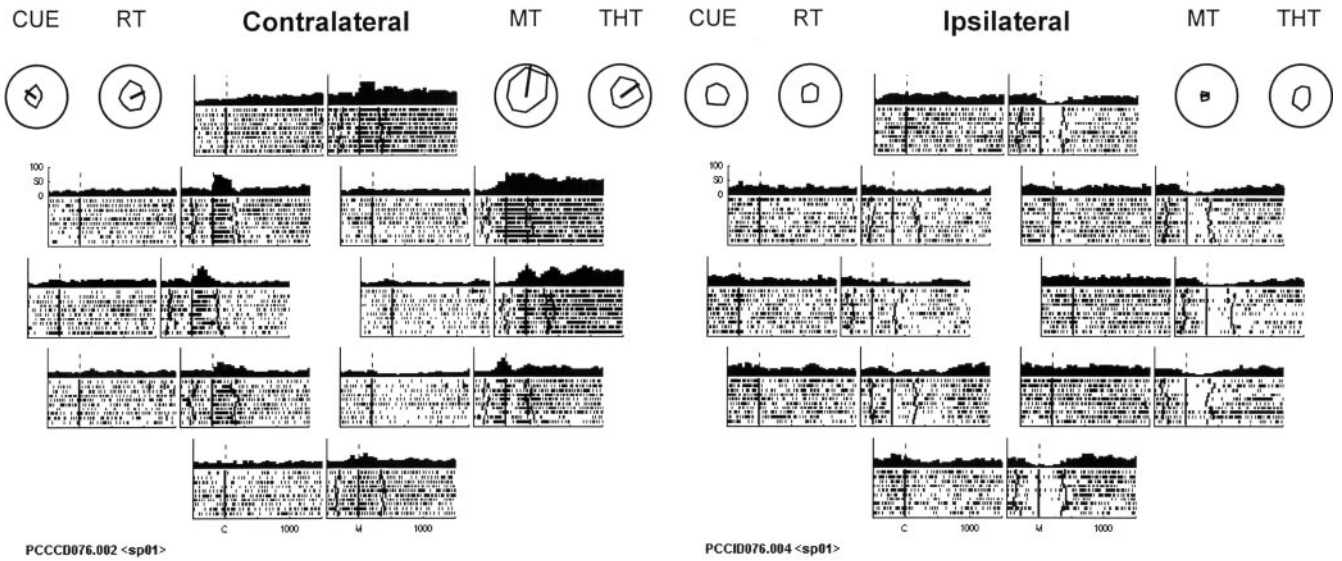

FIG. 5. Neural activity of an M1 cell, recorded in the left hemisphere in *experiment 1*, tuned with the contralateral arm and exhibits task-related changes of activity during movements with the ipsilateral arm. Same format as Fig. 4. In the polar plots, a radius of 70 spikes/s was used.

(PD: RT = 102°, MT = 95°, THT = 96°). When the ipsilateral arm was used to perform the movement, this cell showed a much weaker but significant tuning toward the left and far targets during MT and THT (PD: MT = 147°, THT = 157°). The dynamic range of this tuning, 15 spikes/s during MT, was significantly weaker than that with the contralateral arm (44 spikes/s).

Table 1 and Fig. 7 summarize the trends observed in M1 in *experiment 1*. The most pronounced trend was a systematic increase in the number of cells that were significantly directionally tuned during trials using either arm as time progressed in the trial. During the CUE epoch, 36/74 M1 cells (49%) did not exhibit significant directional tuning, 16/74 (22%) were tuned exclusively during trials with the contralateral arm, 17/74 (23%) were tuned exclusively with the ipsilateral arm, and only 5/74 (7%) were tuned during both contra- and ipsilateral trials (Fig. 7*A*). For those five cells, the directional tuning during CUE tended to be similar, with the mean absolute PD difference being 45° (Fig. 7*B*). For 3/5 cells (60%), there was no significant difference in directional tuning (bootstrap test, $P < 0.01$).

During the RT epoch, a much larger number of cells were directionally tuned (65/74, 88%). Thirty-five cells (47%) were directionally tuned exclusively with the contralateral arm, 2 were exclusively tuned with the ipsilateral arm, and 28 cells (38%) were significantly tuned when either arm was used to perform the movement (Fig. 7*A*). For these 28 cells, the differences in PDs of the tuning functions recorded for each arm ranged throughout 360° (Fig. 7*B*) and the directionality of the tuning functions were significantly different between the two arms for the large majority (23/28, 82%). However, the distribution of PD differences shown in Fig. 7*B* was not uniform

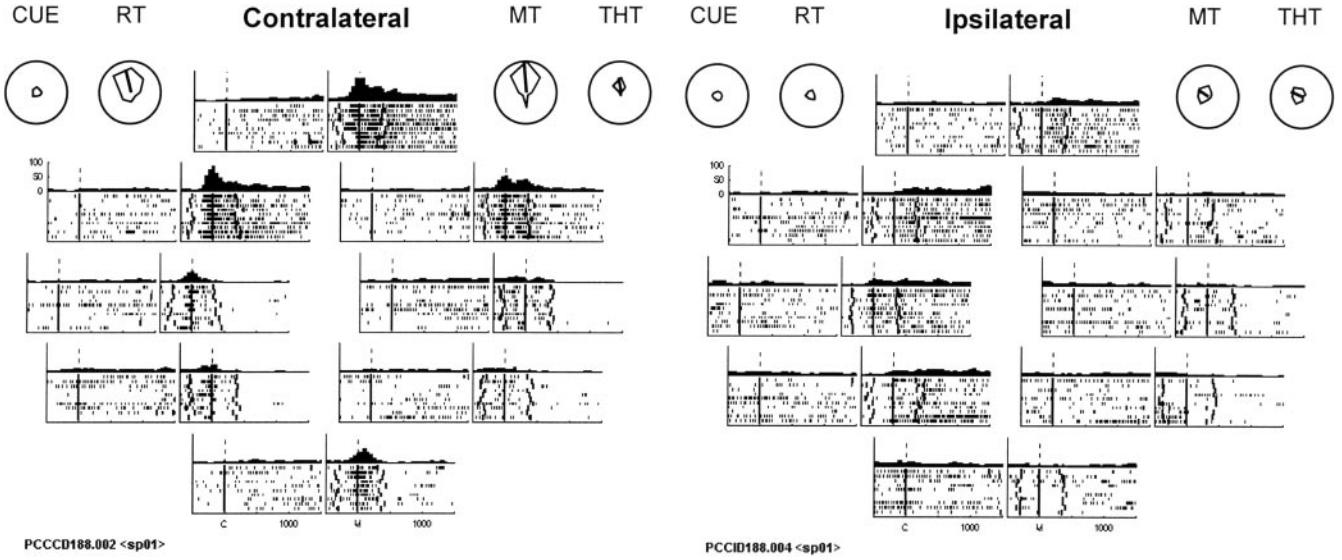

FIG. 6. Neural activity of an M1 cell, recorded in the right hemisphere in *experiment 1*, which is directionally tuned during RT with the contralateral arm, and during MT and THT with both arms. As is the case for most such cells, the activity with the ipsilateral arm is much lower than the activity with the contralateral arm. In the polar plots, a radius of 50 spikes/s was used.

TABLE 1. *Summary of data from experiment 1*

	Untuned	Contra	Ipsi	Both	Sign. ΔPD	ΔPD < 30°	Sign. ΔDR	ΔDR > 0
				M1 cells ($N = 74$)				
CUE	36	16	17	5	2	3	2	1
RT	9	35	2	28	23	6	12	9
MT	1	27	5	41	30	9	24	23
THT	3	26	1	44	41	4	27	26
				PMd cells ($N = 61$)				
CUE	8	15	2	36	13	28	16	14
RT	8	12	3	38	19	23	15	12
MT	10	13	9	29	12	16	15	10
THT	7	15	9	30	19	13	11	7

Values are number of cells not tuned with either arm, tuned with the contralateral arm only, the ipsilateral arm only, or tuned with both arms. Also, the number of cells with significant preferred direction (PD) differences (ΔPD) is shown along with the number of PD differences smaller than 30°, the number of significant dynamic range differences (ΔDR), and the number of significant dynamic range differences greater than zero (i.e., number of cells for which the dynamic range with the contralateral arm was significantly greater than with the ipsilateral arm). *N* is total number of cells. CUE, cue period; RT, reaction time; MT, movement time; THT, target hold time; M1, primary motor cortex; PMd, dorsal premotor cortex.

(Rao spacing test, $P < 0.05$) during the RT epoch, with a bias for PD differences between 90 and 180°. The dynamic range of tuning functions was significantly different for 12/28 cells (43%) with a modest trend toward larger dynamic ranges when the contralateral arm was used (Fig. 7*C*).

These trends were sustained or enhanced during MT and THT epochs. Again, exclusive tuning with the contralateral arm strongly outnumbered exclusive tuning with the ipsilateral arm, but the incidence of tuning with both arms also increased sharply (Fig. 7*A*). Among cells tuned with both arms, there was a trend for stronger activity with the contralateral arm (Fig. 7*C*, Table 1). Of the 41 cells tuned with both arms during MT, 30

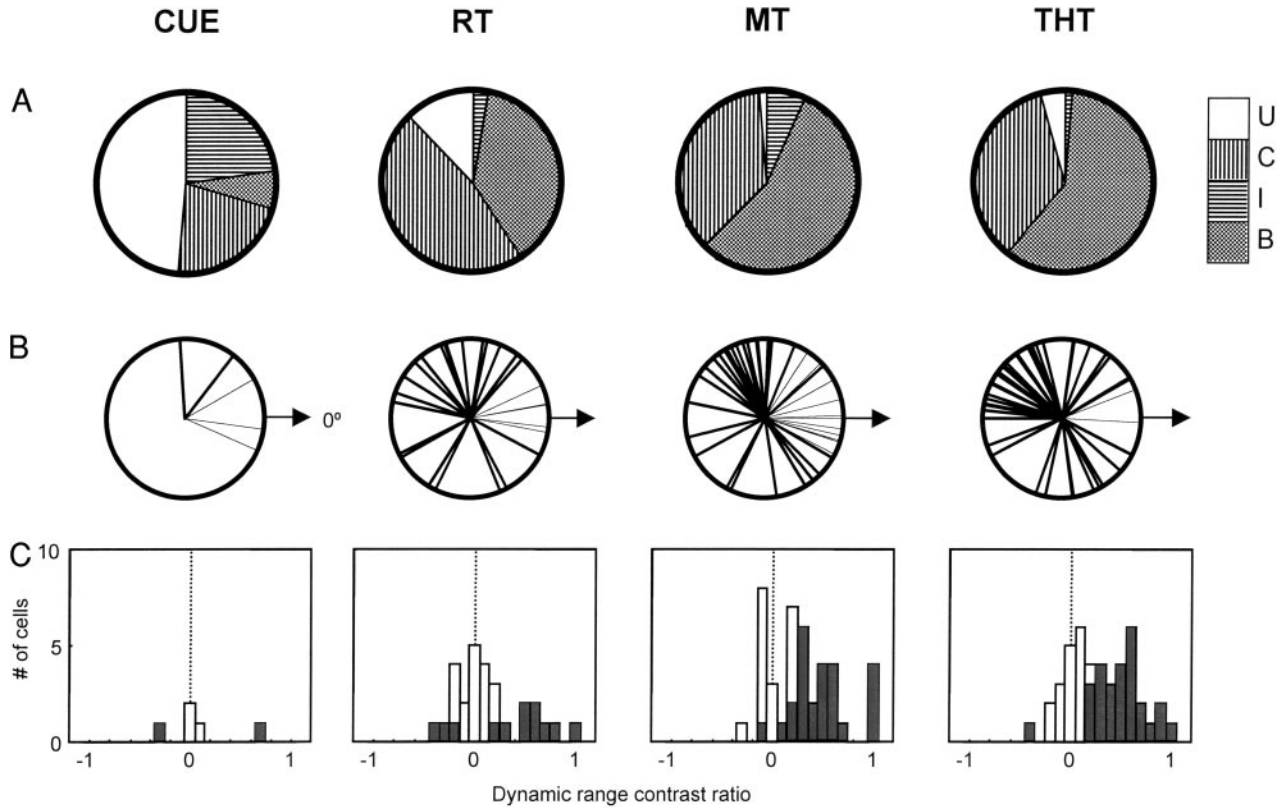

FIG. 7. Summary of the trends in the caudal M1 population during CUE, RT, MT, and THT epochs in *experiment 1*. *A*: pie charts illustrate the proportions of cells which are untuned (*U*), tuned only with the contralateral arm (*C*), tuned only with the ipsilateral arm (*I*), or tuned with both arms (*B*). *B*: angular differences between the preferred direction (PD) of contralateral minus the PD of ipsilateral tuning. Thick lines indicate PD differences that are statistically significant (bootstrap test, $P < 0.01$) and thin lines indicate nonsignificant differences. The arrow shows the orientation of 0° PD difference. *C*: distributions of dynamic range contrast ratios between the contralateral and the ipsilateral tuning functions for the cells in *B*. Positive values indicate greater activity with the contralateral arm. Filled bars denote significant dynamic range differences (bootstrap, $P < 0.01$) and open bars denote nonsignificant differences.

(73%) had significant PD differences, and these were distributed throughout 360°. Again, the PD difference distributions were not uniform (Rao spacing test, $P < 0.05$) with a bias for differences between 90 and 180°. Twenty-four cells (59%) had significant differences in dynamic range, and nearly all of them (23/24, 96%) had higher dynamic range with the contralateral arm (Fig. 7*C*). During THT, 44 cells were tuned with both arms, and 41 (93%) had significant PD differences, again distributed throughout 360° (nonuniform distribution, Rao spacing test, $P < 0.05$) with a bias between 90 and 180°. Twenty-seven cells (61%) showed significant dynamic range differences and once again, nearly all (26/27, 96%) had higher dynamic range with the contralateral arm. The means of the dynamic range contrast ratio distributions shown in Fig. 7*C* were significantly different from zero for the RT, MT, and THT epochs (paired *t*-test, $P < 0.05$), confirming the systematically stronger activity during task performance with the contralateral arm. That trend was not as strong as that seen for muscles, however (cf. Fig. 2*F*).

Many of the cells in caudal primary motor cortex were classified as related to axial, shoulder, or elbow movements according to passive clinical and ICMS examinations. Unlike the muscles, for which these three groups showed different distributions of dynamic range contrast ratios (Fig. 2*F*), M1 cells classified in all three groups showed similar trends (data not shown) that resembled the overall trend for M1. In particular, of 20 M1 neurons found to be related to axial movements, only one was tuned with both arms during the CUE epoch and this cell showed a PD difference of about 90° between the tuning functions for the contralateral and ipsilateral trials.

Response patterns in dorsal premotor cortex

EXPERIMENT 1. In striking contrast to caudal M1, cell activity in PMd was much less sensitive to the effector with which the task was performed in terms of both level of activity and especially with regard to the directional tuning. This trend was observed during both the instructed-delay period and the movement epochs. Examples of neural activities from cells studied in *experiment 1* are shown in Figs. 8 and 9.

When the monkey used the arm contralateral to the recording site, the cell in Fig. 8 was strongly directionally tuned to the right during the CUE (PD = 13°) and RT epochs (PD = 7°), with an apparent reversal in directionality during the MT (PD = 223°) and THT epochs (PD = 195°). When the monkey used the ipsilateral arm, the overall level of activity of the cell was slightly but not significantly lower, and the directionality of tuning was very similar, especially for the pre-GO epochs (PD: CUE = 5°, RT = 6°, MT = 256°, THT = 156°).

The cell in Fig. 9 was recorded from a different monkey but showed very similar properties. It was strongly directionally tuned when the monkey used the arm contralateral to the recording site, especially during the CUE (PD = 215°) and RT epochs (PD = 191°). When the task was performed with the ipsilateral arm, overall activity was significantly lower (bootstrap test, $P < 0.01$) but directionality was quite similar (PD: CUE = 195°, RT = 193°).

These cells exemplify the trends in the entire population of PMd cells recorded in *experiment 1*. In contrast to caudal M1, the discharge of about half of the PMd cells was tuned when either arm was used at all times during the trial, with a small decrease in the incidence of bilateral tuning during MT and THT (Table 1, Fig. 10*A*). This was unlike the progressive increase in bilateral tuning found in M1. Among the remaining PMd cells, the majority was tuned only with the contralateral arm during CUE and RT, whereas contralateral-only and ipsilateral-only cells were about equally common during MT and THT.

The most striking result, however, is the similarity in the contralateral and ipsilateral directional tuning functions of cells tuned with either arm, especially prior to the onset of movement (Fig. 10*B*). During CUE, 36/61 cells (60%) were tuned with both arms. Most (28/36, 78%) had PD differences of <30° between blocks when different arms were used, and the majority of the PD differences (23/36, 64%) were not statistically significant. Significant dynamic range differences were

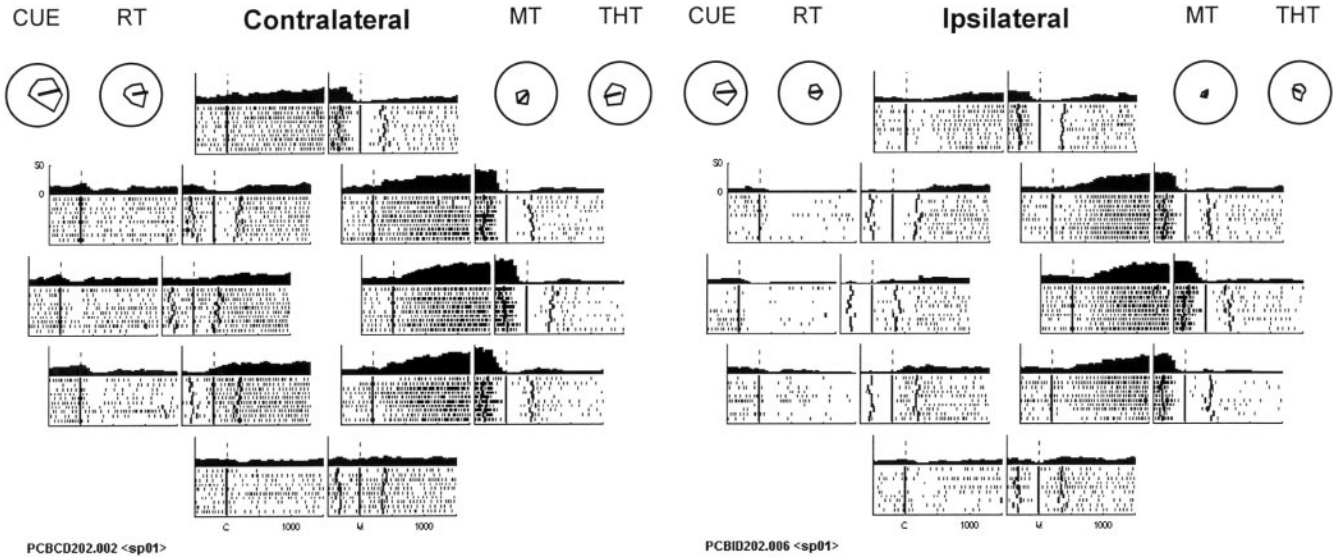

FIG. 8. A dorsal premotor (PMd) cell recorded from the right hemisphere in *experiment 1*. This cell shows sustained activity during the CUE epoch both in blocks performed with the contralateral arm and in blocks performed with the ipsilateral arm. In the polar plots, a radius of 40 spikes/s was used.

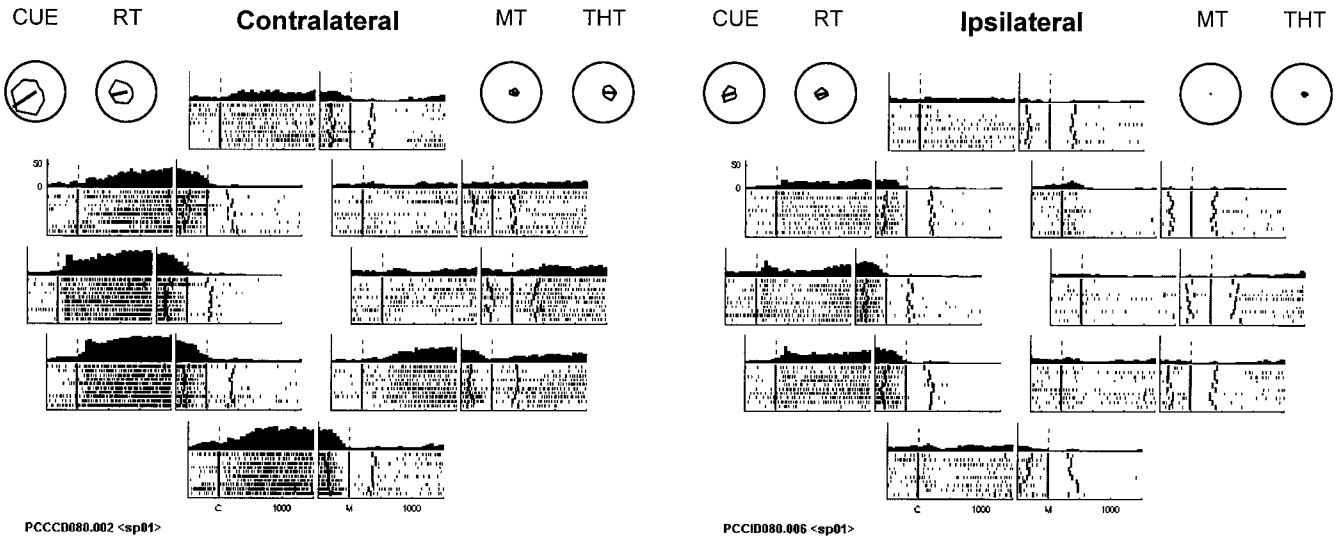

FIG. 9. A PMd cell recorded from the left hemisphere in *experiment 1*. In the polar plots, a radius of 50 spikes/s was used.

found in 16/36 cells (44%) and 14 of these (88%) were larger for the contralateral arm (Fig. 10*C*). During RT, 38 cells (62%) were tuned with both arms and 23 (61%) of these had PD differences <30°. During MT, 29 cells (48%) were tuned with both arms and 16 (55%) of these had PD differences <30°. During THT, 30 cells (49%) were tuned with both arms, but now the PD differences were distributed more widely. The distributions of PD differences were nonuniform for all epochs (Rao spacing test, $P < 0.05$) with a clear bias toward differences of zero.

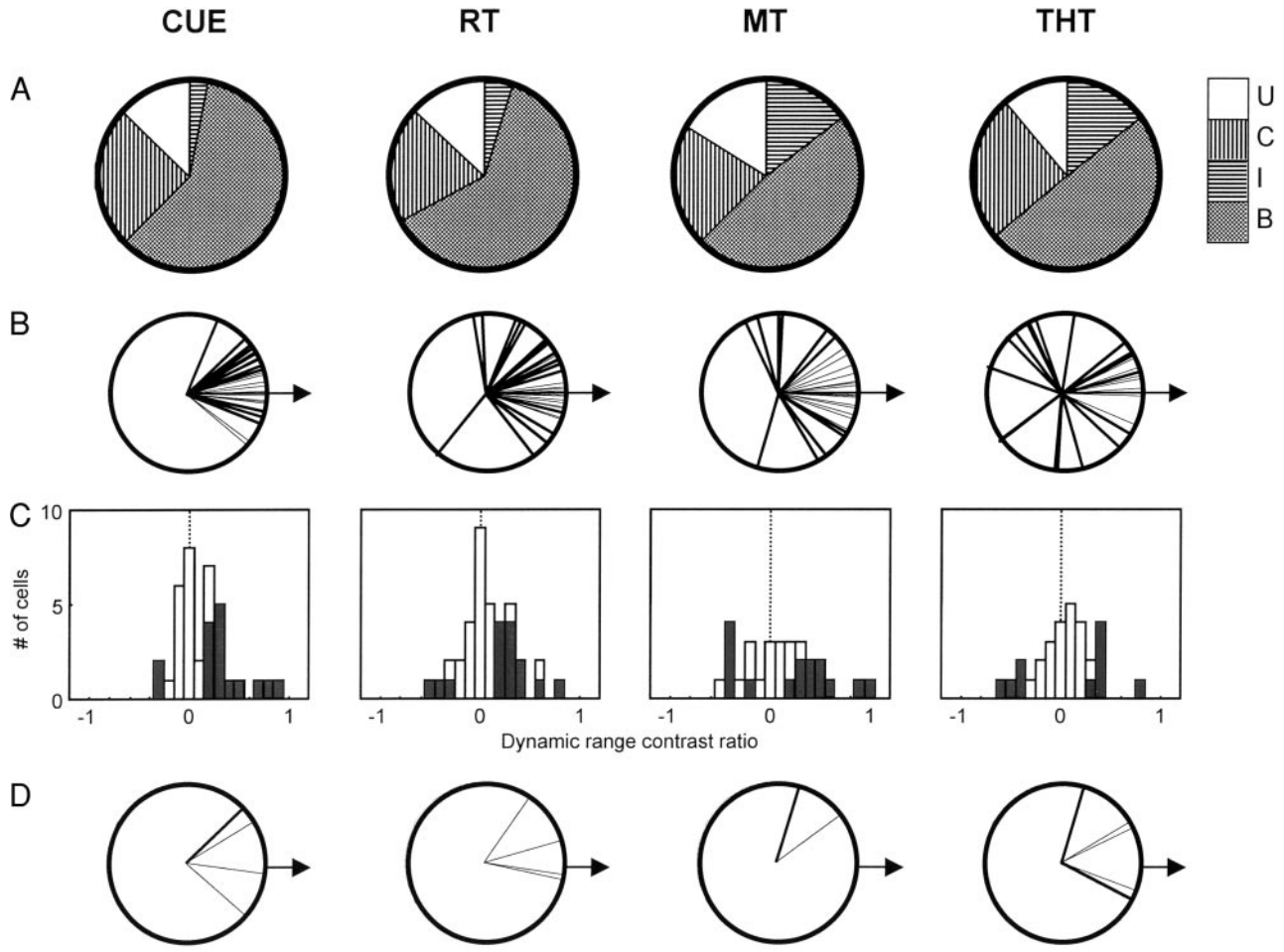

FIG. 10. Summary of the trends in the PMd population recorded in *experiment 1* during CUE, RT, MT, and THT epochs. Same format as Fig. 7. *D*: PD differences from 10 cells recorded from a region intermediate between PMd and M1.

Overall, there was a modest tendency for the number of cells tuned with both arms to decrease over the course of the trial. At the same time, there was a strong tendency for the differences in PDs to increase over time (Fig. 10*B*). In fact, the distribution of PD differences during THT became almost as widespread as that observed in M1, but with a bias toward similar directions, not opposing directions (Fig. 7*B*). Furthermore, while the means of the distributions of dynamic range contrast ratios for the CUE and RT epochs were significantly different from zero (paired *t*-test, $P < 0.05$) with a modest bias toward contralateral preferences, the means of the distributions for MT and THT were not. Thus among the cells tuned with both arms, there was a trend for decreasing similarity of directional preferences over time but a trend for increasing similarity of tuning depth.

A small sample of 10 cells in rostral M1 was tested with both arms, and they showed combinations of properties that were intermediate between more caudal M1 and PMd. For instance, more of the rostral M1 cells (4/10, 40%) were active with both arms during the CUE epoch than in caudal M1, and the directional tuning was fairly similar with either arm (Fig. 10*D*) as was seen in CUE in both caudal M1 and caudal PMd. In contrast, during later trial epochs some cells were again active with either arm, but the directional tuning tended to be more similar in these epochs (Fig. 10*D*) than was seen in more caudal M1 (Fig. 7*B*) and more similar to that in PMd (Fig. 10*B*). However, the small sample size precludes any more definitive quantitative comparisons.

EXPERIMENT 2. The cells recorded in PMd in *experiment 2* showed an even more striking tendency for similar activity with both arms in terms of both directionality and level of discharge. The neural activities of two example PMd cells from *experiment 2* are shown in Figs. 11 and 12. Both illustrated the general trend observed for PMd cells in *experiment 1*: sustained directionally tuned discharge during the CUE and MEM epochs which was similar regardless of whether the task was performed with the contralateral or ipsilateral arm.

Table 2 and Fig. 13 summarize the trends observed in the PMd population studied in *experiment 2*. During all task epochs, the majority of cells were tuned during trials with either arm and exhibited similar tuning for both arms. In particular, 18/19 cells (95%) tuned with both arms during the CUE epoch had PD differences during that epoch which were smaller than 30°, and only 1 of these was statistically significant. During MEM, after the target cue had disappeared (Fig. 1*B*), 24 cells (83%) were tuned with both arms, 22 (92%) of these had PD differences smaller than 30°, and the PD difference was significant for only 2 cells. Thus the directional tuning and the similarity of this tuning with the two arms was not solely related to the presence of a visual stimulus in a particular location. PD differences of <30° were observed in 25 of 26 cells (96%) which were tuned with both arms during RT, 24 of 24 (100%) during MT, and 18 of 20 (90%) during THT. Unlike the findings in PMd in *experiment 1*, there was no pronounced trend for PD differences to increase over time during the course of the trial. Dynamic range differences were significant only 12–35% of the time in different epochs. The means of the distributions of dynamic range contrast ratios shown in Fig. 13*C* were not different from zero (paired *t*-test, $P > 0.05$) in any trial epoch.

We also monitored the unconstrained oculomotor behavior of both monkeys in *experiment 2*. During each trial, both monkeys made numerous spontaneous eye fixations in different locations with a median duration of 420 ms. The pattern of fixations was similar when either arm was used, and the effect of gaze direction on the neural activity in PMd of the first monkey in this task has been described in a separate report (Cisek and Kalaska 2002a). Here, we focus on fixation episodes during MEM. The target cues disappeared at the beginning of this trial epoch, so task-related activity cannot be due to the presence of visual stimuli. More specifically, we defined the directional tuning functions using the cell activity only during those fixation episodes in which the monkey directed gaze within 6° of the center of the target display, i.e., within a circular region whose radius was approximately two-thirds of the distance from the center to the outer targets. Separate tuning functions were calculated during these central fixations in both contralateral and ipsilateral blocks of trials. Figure 14*A* illustrates these tuning functions for the cell shown in Fig. 11. The preferred direction of the tuning function recorded during central fixations during the MEM epoch was 37° while the

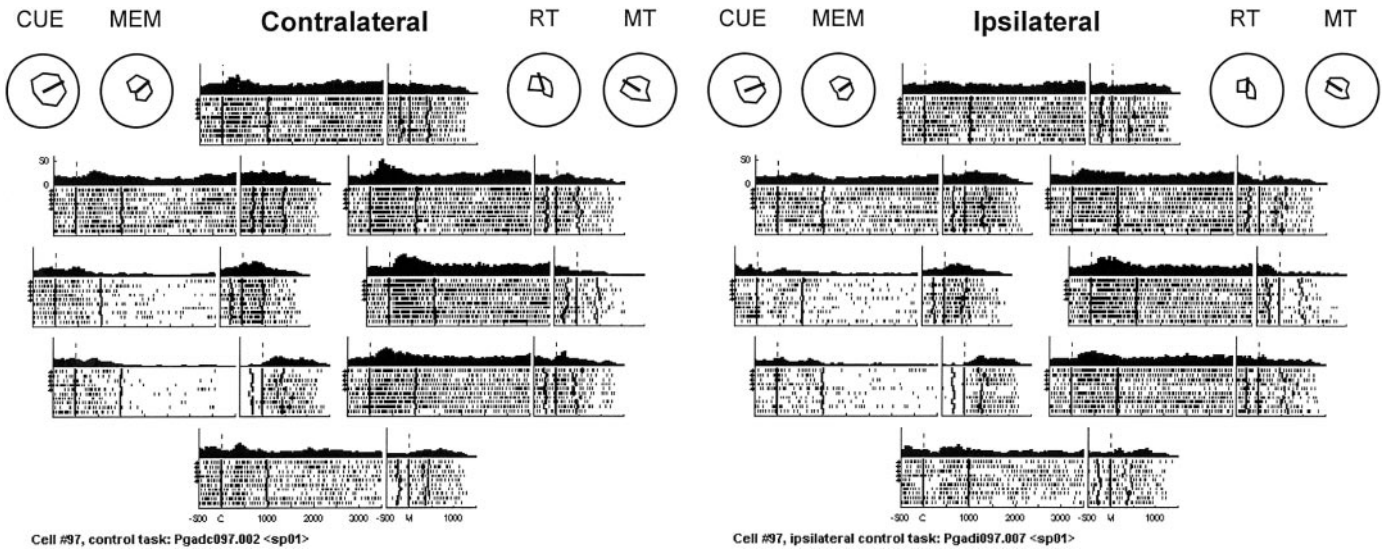

FIG. 11. PMd cell recorded from the left hemisphere in *experiment 2*. In the polar plots, a radius of 50 spikes/s was used.

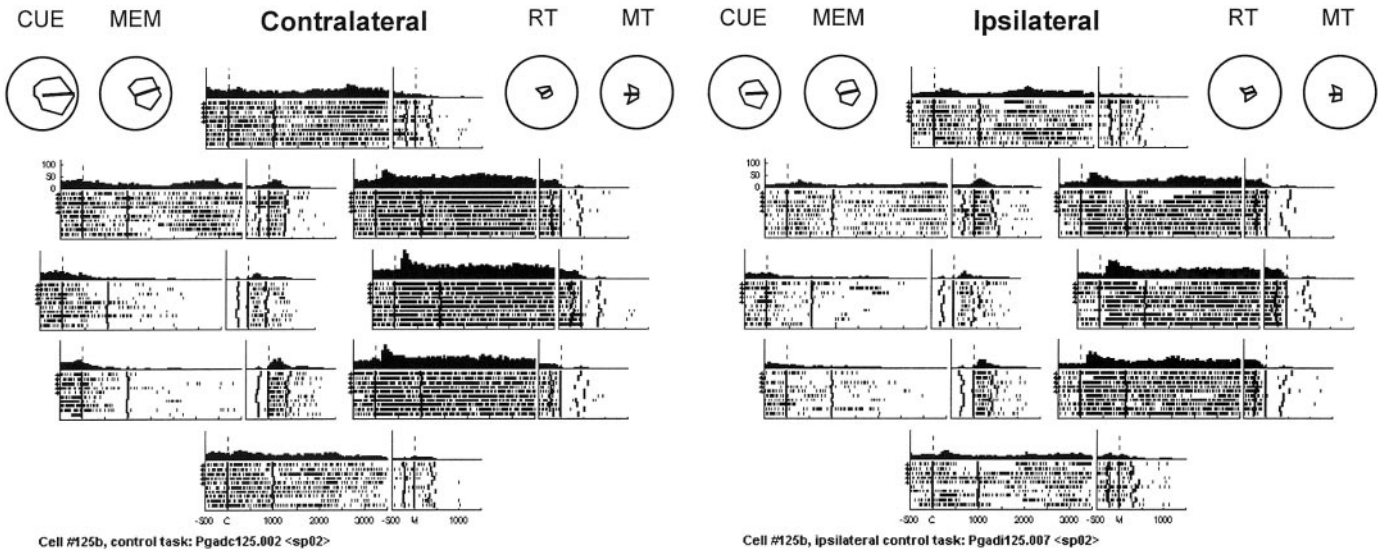

FIG. 12. PMd cell recorded from the left hemisphere in *experiment 2*. In the polar plots, a radius of 70 spikes/s was used.

monkey worked with the contralateral arm and 31° during central fixations while using the ipsilateral arm, and this difference was not significant (bootstrap test for directional differences). These values were very similar to the PDs of the tuning functions derived from the activity during the entire MEM epoch, independent of where the monkey was looking (contralateral PD = 37°, ipsilateral PD = 34°, Fig. 11). The difference between the dynamic range of the two tuning functions was likewise not significant. Because the monkey was looking at the central target during these fixation episodes, neither the tuning functions recorded during that time nor the similarity of directionality while the monkey performed the task with either arm could be explained by gaze direction-related modulation of cell activity (Boussaoud et al. 1998; Cisek and Kalaska 2002a).

Figure 14*B* shows the differences in PDs during contralateral and ipsilateral blocks for the 19 cells in which the data collected during central fixations was significantly tuned with both arms. Eighteen of these PD differences (95%) were smaller than 30° and only two were significant according to the bootstrap test ($P < 0.01$). Figure 14*C* shows the distribution of dynamic range contrast ratios, of which four were significant. Overall, the results of the analysis of reach-related activity limited to the time periods while the monkey fixated toward the center (Fig. 14) were very similar to the analysis using the full data set (Fig. 13, Table 2).

Population activity

The results of single-unit recordings imply that the PMd population is strongly active during the instructed-delay period and exhibits a similar pattern of neural activity regardless of the arm ultimately used to perform the movement. In contrast, cells in caudal M1 are mostly active just before the onset of the movement and throughout its execution, and their tuning functions are strongly dependent on the effector used. These differences between M1 and PMd are illustrated by histograms of average population activity in opposite movement directions (Fig. 15, *A–C*).

As shown, the PMd population activity clearly discriminated the direction of movement throughout the instructed-delay period as well as during movement and did so regardless of whether the contralateral (Fig. 15*A*) or ipsilateral (Fig. 15*B*) arm was used to perform the reach. Furthermore, during ipsilateral trials the mean activity profile was similar regardless of whether neural activity was aligned to the PD calculated using data from the ipsilateral block (Fig. 15*B*) or the contralateral block (Fig. 15*C*). In contrast, the caudal M1 population activity only weakly discriminated the direction of movement during the instructed-delay period and only during its later part, in contralateral-arm trials, and only became strongly active and directionally tuned after the GO signal (Fig. 15*D*). Population activity also discriminated movement direction during ipsilateral trials when each cell's PD was calculated from ipsilateral-

TABLE 2. *Summary of data from experiment 2*

	Untuned	Contra	Ipsi	Both	Sign. ΔPD	ΔPD < 30°	Sign. ΔDR	ΔDR > 0
				PMd cells ($N = 29$)				
CUE	5	4	1	19	1	18	4	2
MEM	1	4	0	24	2	22	5	4
RT	0	2	1	26	4	25	3	1
MT	2	1	2	24	2	24	5	3
THT	6	2	1	20	2	18	7	3
MEM*	0	3	3	19	2	18	4	3

Values same as in Table 1. * This analysis only used data during fixations within 6° of the center of the target display ($N = 25$).

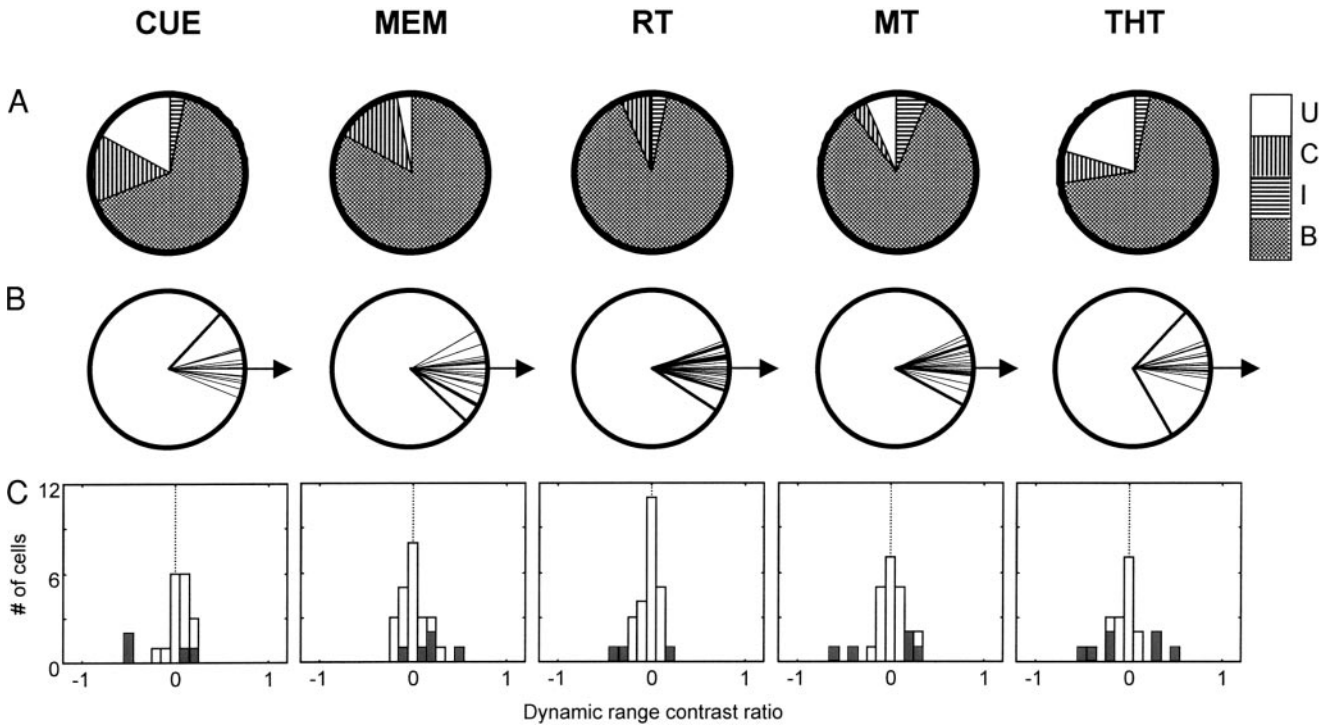

FIG. 13. Summary of the trends in the PMd population recorded in *experiment 2* during CUE, memory period (MEM), RT, MT, and THT epochs. Same format as Fig. 7.

arm data, but the overall activity level was lower during movement (Fig. 15*E*) than during contralateral arm movements (Fig. 15*D*). Note that all of these M1 histograms (Fig. 15, *D–F*) only include data from cells which had significant directional tuning during the RT of both contralateral and ipsilateral blocks (28/74 cells). By definition, these cells will discriminate the direction during reaction time. However, as shown in Fig. 15*F*, when data from ipsilateral-arm trials were aligned on each cell's PD defined during contralateral-arm movements, the summed population response was almost completely flat, and no differential directional signal was observed. This difference in population histograms between caudal M1 (Fig. 15*F*) and PMd (Fig. 15*C*) reinforces the similarity of the PMd directional tuning functions for contralateral and ipsilateral trials versus their nearly complete dissociation in caudal M1.

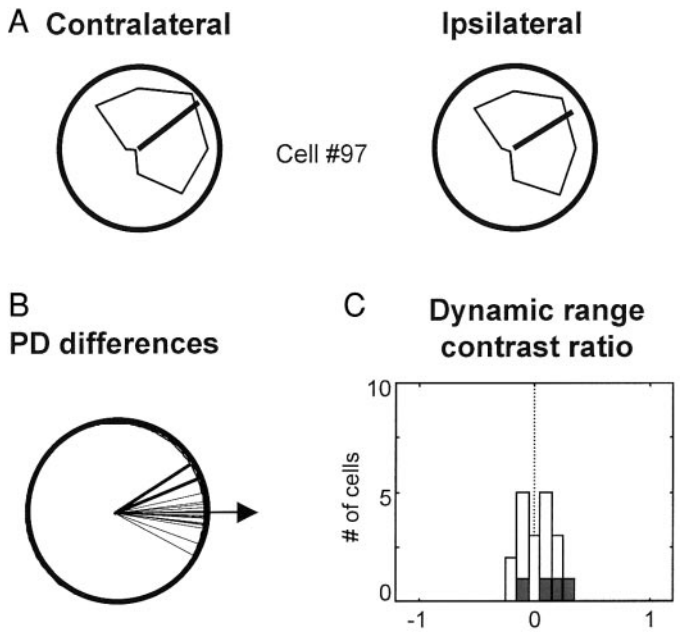

FIG. 14. Comparisons of tuning functions calculated during the MEM epoch of blocks of trials performed with the contralateral and ipsilateral arm, using neural activity recorded only during fixation episodes in which the monkey was looking toward the center of the target display. *A*: tuning functions calculated for the cell shown in Fig. 11. *B*: distribution of PD differences of 19 cells for which the tuning functions calculated during central fixations were directionally tuned (bootstrap test, $P < 0.01$). *C*: distribution of dynamic range contrast ratios for the same 19 cells.

Figure 16 illustrates the distribution of the occurrence of significant contralateral, ipsilateral, or bilateral directional tuning along a rostrocaudal gradient in precentral cortex. While the percentages of cells that are contralateral, ipsilateral, or bilateral are relatively similar along the cortex during the RT, MT, and THT epochs, there is a clear trend from caudal M1 to PMd during the CUE epoch. First, while many caudal cells are untuned during the CUE, there is progressively more directional tuning observed as one moves rostrally into PMd. Second, there is an increase in the number of cells that are tuned with both arms as one moves into PMd. Although these trends are suggestive, they must be viewed with caution due to the small number of cells recorded in the intermediate locations along the rostrocaudal dimension.

DISCUSSION

The main finding of the experiments described here was that a major component of task-related activity in PMd was strongly coupled to the spatial directionality of motor output independent of the effector (contralateral or ipsilateral arm) used to perform the task. This trend was especially prominent

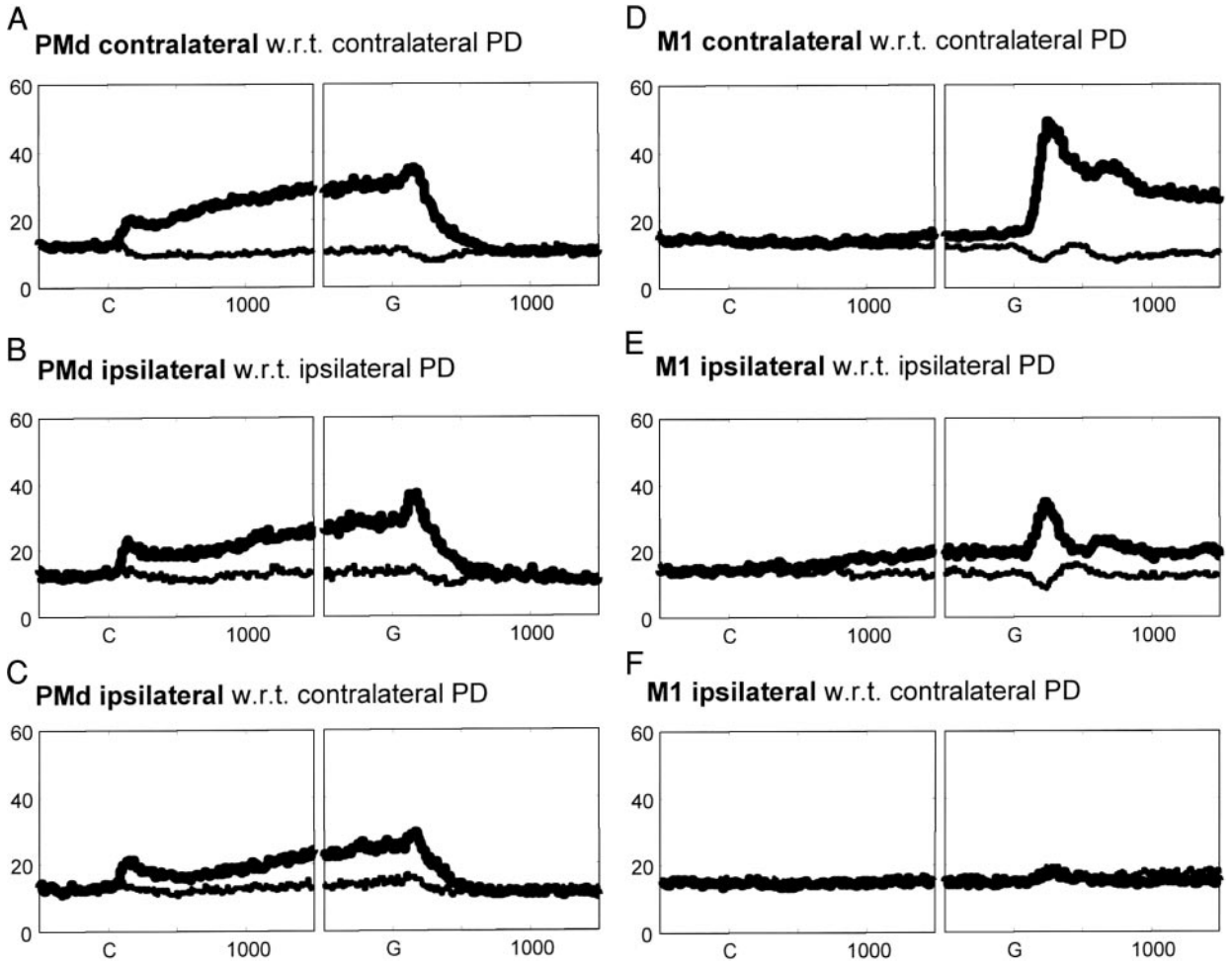

FIG. 15. Population peri-event histograms for cells collected from caudal M1 and PMd during *experiment 1*. *A–C*: summed activity of 38 cells recorded in PMd which had significant tuning with both arms during RT. The activity of these cells was aligned on CUE onset (*C*) and GO signal onset (*G*). *A*: activity during trials performed with the contralateral arm, in the direction of the PD calculated during the RT epoch of the block performed with the contralateral arm (thick line), and in the direction of the opposite target (thin line). *B*: activity during trials performed with the ipsilateral arm, in the direction of the PD calculated during the RT of the ipsilateral block (thick line) and opposite target (thin line). *C*: activity during *ipsilateral* arm trials, in the direction of the PD calculated during the RT of the *contralateral* arm block (thick line) and opposite target (thin line). *D–F*: summed activity of 28 M1 cells tuned with both arms during RT, same format.

during the instructed-delay period. During and after arm movement, many PMd cells continued to be tuned with both arms, but over the course of time in a trial the directional tuning became progressively more dissimilar for the two arms in *experiment 1*, but not in *experiment 2*. In contrast, caudal M1 became active mainly just before and during the course of movement and was directionally tuned more often when the task was performed using the contralateral arm than when the ipsilateral arm was used. Moreover, for the majority of M1 cells with tuned activity during movements of either arm, the contralateral and ipsilateral tuning functions usually had very different directional preferences.

Effector-independent activity in PMd

The well-documented IDP activity in PMd has implicated this region in processes related to movement planning and/or preparation (Boussaoud and Wise 1993a; Crammond and Kalaska 1994, 2000; Hoshi and Tanji 2000; Johnson et al. 1996; Kalaska and Crammond 1995; Riehle et al. 1994; Wise et al. 1992, 1997). In that context, the finding that the IDP directional tuning functions of most PMd cells were not strongly dependent on the effector used to perform the movement raises a number of intriguing theoretical possibilities.

One hypothesis is that a major component of the neural activity in PMd specifies reaching movements at an abstract level of movement planning, independent of the effector which will be used to perform the reach. Several studies have shown that PMd activity related to reaching movements is not as strongly dependent on the details of movement production as is activity in M1 (Caminiti et al. 1998; Crammond and Kalaska 2000; Johnson et al. 1996; Kakei et al. 1999; Scott et al. 1997; Shen and Alexander 1997a; Wise and Murray 2000; Wise et al. 1996, 1997, 1998). In particular, Shen and Alexander (1997b) demonstrated that when the mapping between physical limb movements and the motion of an on-screen cursor changed, the instructed-delay activity in PMd correlated more with the direction of cursor motion than with the direction of the actual limb movements. Over the course of a trial, cursor direction-

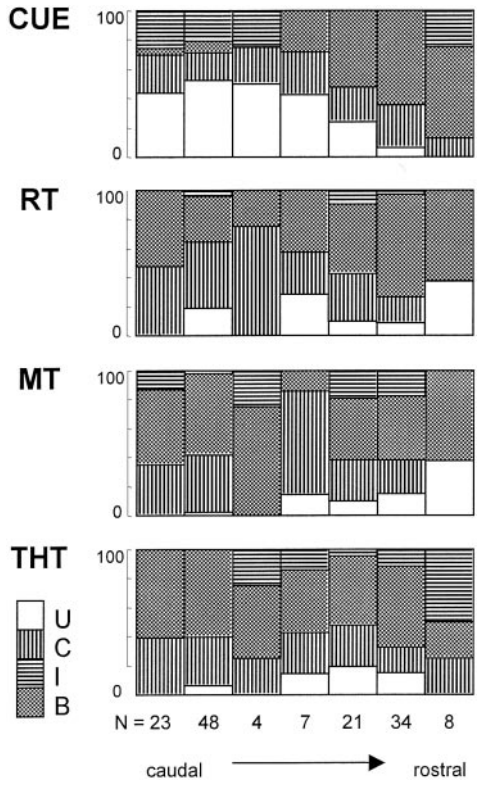

FIG. 16. Proportion of cells tuned with the contralateral arm only (*C*), with the ipsilateral arm only (*I*), with both arms (*B*), or untuned (*U*), measured in 7 bins along a rostro-caudal line in cortex during the different task epochs. The leftmost bin contains cells 6–8 mm from the junction where the central sulcus meets the midline and each succeeding bin contains cells from the next 2 mm more rostral. Numbers below the bins indicate the number of cells recorded in that part of the cortex. Data from *experiment 1* are used and include the 10 "intermediate zone" cells not classified as either caudal M1 or PMd.

related activity became slightly less prominent while activity correlating with limb movement emerged in the PMd population. These trends are very similar to our results in *experiment 1*. In that experiment, PMd tuning functions during the CUE period may carry information primarily about the intended motion of the hand toward the target, which is the same with both arms. Later in the trial (RT, MT, THT), as activity related to the movement of a particular limb begins to emerge in PMd, the tuning functions begin to reflect the details of movement production, which are dissimilar for the two arms for movements toward the same target. However, whereas effector independence during the delay period in Shen and Alexander (1997a,b) pertains mainly to the mechanical details of motions of the contralateral limb, our results show that for many PMd cells it even extends to the identity of the arm used. It is noteworthy, however, that a temporal trend toward a more limb-specific representation was not evident in PMd in *experiment 2*.

A corollary of this hypothesis is the conjecture that much of the early delay-period activity in PMd is not related to the intention to make a limb movement per se, but to a more global intention to accomplish some overall task goal. After months of training, the monkeys learned that moving its arm to displace the handle (*experiment 1*) or the cursor (*experiment 2*) into the correct target results in a reward. How that task is ultimately accomplished depends on many important factors, such as effector choice, starting arm posture, task dynamics, etc., but these factors are not necessarily germane to processes implicated in defining task goals such as selecting which target is the correct one. To perform this selection, the nervous system requires neural activity which discriminates among the possible movement choices, however many they might be, and which reflects the accumulation of evidence for choosing one option over the others. Neurons in PMd with effector-independent spatial tuning properties could serve such a role. There are a number of lines of evidence suggesting that a major role of premotor cortex is the selection of actions from among alternatives (Boussaoud and Wise 1993a,b; Cisek and Kalaska 2002b; Crammond and Kalaska 1994, 2000; Hoshi and Tanji 2000; Kalaska and Crammond 1995; Kettner et al. 1996a,b; Mitz et al. 1991; Mushiake et al. 1991; Wise et al. 1992, 1997), a role shared with prefrontal regions (Bechara et al. 1998; Funahashi et al. 1997; Fuster 2000; Hoshi et al. 2000; Kim and Shadlen 1999; Miller 2000; Tanji and Hoshi 2001).

This same interpretation is relevant for comparing the results presented here with those of Hoshi and Tanji (2000, 2002). Those authors studied premotor activity during tasks in which monkeys had to select, on the basis of two stimulus cues, both the correct target for a reach and the correct arm with which to reach, on a trial-by-trial basis. They found that the IDP activity of the majority of PMd cells was dependent on both the target and the effector, with a tendency for stronger discharge with the contralateral arm (Hoshi and Tanji 2002). For the majority of PMd cells (69%), the preferred target did not change with the effector (E. Hoshi, personal communication). This finding is consistent with the trend for similar directional tuning across arms found in our study.

An alternative explanation for the effector independence of PMd activity during the delay period is the possibility that the activity in each hemisphere is in fact related primarily to contralateral arm use and that the monkey is covertly planning these movements even when the contralateral arm is restrained and a movement using the ipsilateral arm is planned simultaneously (cf. Snyder et al. 1997). We do not believe this to be a likely explanation. Although neural correlates of simultaneous planning of multiple potential reaching actions have been reported in PMd (Cisek and Kalaska 2002b), such activity was present only while multiple options were available: signals related to an unwanted movement were suppressed as soon as information for rejecting that option was given (cf. Kalaska and Crammond 1995). In both of the experiments described here, the monkey performed movements with each arm in blocks of 64–80 trials, while the other arm was restrained at the side. It was very clear throughout each recording session which arm was to be used to perform the movement, and covert planning of movements of the restrained arm would have served no obvious purpose. Even if despite this, a reaching movement with the restrained contralateral arm was being covertly planned in PMd during ipsilateral trials, one would expect a greater difference to be apparent in the post-GO movement-related activity between those trials and those in which that arm was actually used to perform the movement. However, no such difference was observed (compare Fig. 15, *A–C*).

In addition to the effector-independent activity on which we have focused, there were also effector-dependent and effector-specific signals in PMd. For instance, a sizable minority of cells (25–39%: *experiment 1*, 11–17%: *experiment 2*) were

uniquely directionally tuned for only the contralateral or ipsilateral arm at different times in the trial. For cells that were directionally tuned with both arms, effector dependence took the form of significant differences in the PD or dynamic range during movements with either arm. Finally, the overall directional signal generated by the PMd population was somewhat stronger during task performance with the contralateral arm than the ipsilateral arm (Fig. 15, *A–C*).

In caudal M1, there was a strong bias toward contralateral arm preference, including many cells that were uniquely directionally tuned for contralateral trials. Among cells activated during both contralateral and ipsilateral trials, almost all of the cells with significant dynamic range differences showed a preference for the contralateral arm, in all three post-GO epochs of *experiment 1*. Interestingly, however, nearly half of the M1 cells showed directional tuning for only one or the other arm during the CUE epoch (Fig. 7*A*), unlike the results in PMd (Fig. 10*A*). This shows that even during the instructed-delay period, activity in caudal M1 is much more strongly effector-dependent than the activity in PMd.

Limits of interpretation: PMd activity as axial control

In the two experiments described here, 61% of PMd cells showed significant directional tuning with both arms during the CUE period, and the majority of these had similar tuning functions with either arm (Figs. 10 and 13). A similar observation was made for two of six axial muscles (33%). This raises the possibility that the activity of many PMd neurons was involved in control of these axial muscles. This is consistent with long-standing hypotheses that the premotor cortex is primarily concerned with control of axial muscles, postural adjustments, and gross orienting behavior of the head and trunk (cf. Humphrey 1979). However, we reject this explanation of our results.

First, only splenius capitis and cervical paraspinal muscles behaved in the aforementioned manner, which may reflect eye-head coupling despite head fixation (Andre-Deshays et al. 1988; Lestienne et al. 1984). Many other axial muscles such as thoracic paraspinal and the rostral and caudal portions of trapezius did not behave in this way, exhibiting no activity changes at all during CUE with either arm. Therefore an explanation of PMd activity as predominantly associated with axial control would require that the majority of cells recorded over a wide region of PMd in the two experiments were all involved in control of neck musculature or head orientation. The PMd cells in *experiment 1* were recorded equally from those parts of PMd which send corticospinal axons either to the cervical enlargement, which innervates the muscles of the arm and hand, or to the spinal segments C2–C4, which innervate muscles of the proximal arm, shoulder girdle, and neck (Dum and Strick 1990; He et al. 1993), with no obvious difference in response properties in the two unimanual tasks. Furthermore, most of the cells described here from *experiment 2* were recorded in that part of area 6 superior to the medial branch of the arcuate sulcus and rostral to its genu. This region does not project to either the spinal cord or M1 (He et al. 1993; Picard and Strick 2001).

Second, if the PMd cells described here were all involved in control of neck and axial muscles, then similar behavior should be found among the M1 cells whose discharge also appeared to be related to axial control. However, of 20 M1 neurons related to axial structures on the basis of intracortical micro-stimulation or passive examinations, only 1 was tuned with both arms during the CUE epoch, and this cell showed a PD difference of 90° between the two arms.

Finally, the behavior of the cells in the present studies during movements with the contralateral arm is similar to that seen in many studies of PMd in a wide variety of tasks (Boussaoud and Wise 1993a; di Pellegrino and Wise 1993; Shen and Alexander 1997a,b; Wise and Murray 2000; Wise et al. 1992, 1996, 1997, 1998). We do not believe it likely that a putative role of PMd in axial control could account for the complex and often highly context-dependent nature of single-neuron activity in PMd during a wide range of instructed-delay tasks. Bilateral activation of premotor cortex is also seen in many imaging studies, in an equally wide variety of tasks (Cramer et al. 1999; Kawashima et al. 1993, 1998; Kollias et al. 2001; Li et al. 1996; Nirkko et al. 2001; Remy et al. 1994). It is equally difficult to account for this systematic bilateral activation by an association with axial control, when many of the tasks used in the imaging studies required no activation of axial musculature, postural adjustments, or either overt or covert orienting behavior.

Limits of interpretation: PMd activity reflecting direction of gaze or attention

Several studies have shown that the arm movement-related activity of many cells in PMd is modulated by the direction of the monkey's gaze (Boussaoud et al. 1993, 1998; Jouffrais and Boussaoud 1999), even during free fixation conditions (Cisek and Kalaska 2002a). This raises the possibility that the directional tuning observed in PMd was partially generated by the monkey's unconstrained oculomotor behavior. Since gaze behavior was similar during both contralateral and ipsilateral movement blocks, this could explain why the PMd tuning functions were so similar during these conditions. However, the strength of the gaze-related modulation of PMd activity during free gaze is typically much weaker than the discharge related to arm movements, and arm movement signals in PMd do not appear to be coded in gaze-centered coordinates (Cisek and Kalaska 2002a). Moreover, our analysis of tuning functions calculated solely from neural activity recorded during central fixations (Fig. 14 and Table 2) allows us to reject the possibility that PMd tuning functions were solely due to gaze behavior. For the large majority of cells for which oculometer data were obtained, directional tuning calculated on the basis of data recorded only during central fixations was very similar to the tuning calculated on the basis of data collected from the entire trials in each arm block, independent of the direction of gaze. Furthermore, the tuning functions for contralateral and ipsilateral blocks during central fixation were also very similar. Thus one can infer that the trends observed for PMd cells which were not studied with the oculometer (*experiment 1*) were likewise not due to gaze-related modulation.

A similar logic may be used to consider the alternative explanations that the spatially constant tuning functions observed in PMd with both arms were related to the direction of attention, rather than to some effector-independent aspect of movement planning. When oculomotor behavior is unconstrained, primates tend to direct gaze toward the locus of

attention (Kowler et al. 1995; Kustov and Robinson 1996; Lebedev and Wise 2001). Thus one can infer that while the monkeys looked toward the center they were also attending there (Cisek and Kalaska 2002a,b), and so the spatially constant tuning functions collected during central fixations while performing the one-target tasks described here with either arm were probably not caused by covert or overt shifts of attention. Furthermore, many of the same cells from *experiment 2* also contributed to a bi-lobed population signal oriented toward the spatial locations of two potential movement targets during the initial delay period of a two-target task before the monkeys could choose between them (Cisek and Kalaska 2002a,b). The attention hypothesis would require that this bi-directional activity pattern reflected a process of divided covert attention to two different peripheral spatial locations while overtly gazing at a third cenral location and attending the appearance there of a nonspatial instructional cue, an explanation that lacks the appeal of simplicity. Nevertheless, it must be acknowledged that none of our tasks fully dissociated the direction of potential movement targets from the potential direction of overt or covert spatial attention, so that attentional processes may be responsible, at least in part, for the gaze- and effector-independent directional signals described here.

Activity in caudal M1 during ipsilateral movements

Although many caudal M1 cells in the present study showed tuning only with the contralateral arm, as many or more cells were tuned with both arms during RT, MT, and THT. Of these, the majority showed much stronger activation during contralateral than ipsilateral movements (Fig. 7*C*). Nevertheless, directionally tuned activity during movements with the ipsilateral arm was observed, in agreement with previous studies (Donchin et al. 1998; Kermadi et al. 1998, 2000; Steinberg et al. 2002).

This activation of caudal M1 during unimanual movements of the ipsilateral arm may reflect a role for M1 in the bilateral control of muscles on either side of the body and in coordination of actions involving both arms (Donchin et al. 1998; Kazennikov et al. 1999; Kermadi et al. 1998, 2000; Steinberg et al. 2002). This is consistent with anatomical evidence. There are axonal pathways by which M1 neurons, especially from parts of M1 related to proximal muscles, can influence ipsilateral muscular activity, either directly via descending projections that are uncrossed (Brinkman and Kuypers 1973; Glees and Cole 1952), or indirectly via the corpus callosum to the contralateral M1 (Rouiller et al. 1994).

Ipsilateral and bimanually related activity in M1 is not limited to proximal motor output, however. It has also been described in a small percentage of M1 cells in tasks which involved carefully isolated movements of the hand and fingers (Aizawa et al. 1990; Tanji et al. 1987, 1988). This confirms the presence of M1 activity related to ipsilateral motor output in tasks that require no postural adjustments, no overt orienting behavior, and no muscle activity in more proximal or axial parts of the body.

Nevertheless, activation of M1 neurons during ipsilateral motor output is more prominent in tasks that involve movements of the whole arm (this study, Donchin et al. 1998; Kazennikov et al. 1999; Kermadi et al. 1998, 2000; Steinberg et al. 2002). While this may reflect a greater role for M1 in bilateral and bimanual control of actions that involve more proximal and axial structures, it is also important to consider the degree to which this may actually be causally related to spurious contralateral muscular activity. In any whole-arm task such as reaching, the movement of the arm has nontrivial effects on the rest of the body (e.g., interaction forces, shifts in the center of gravity) that must be compensated by postural and other adjustments. Some of these compensatory adjustments may engage muscles contralateral to the recording site even when it is the ipsilateral arm which performs the movement. Different directions of reaching will generate different perturbations and will require different patterns of compensation. Moreover, during blocks of trials performed with the ipsilateral arm in this study, the contralateral arm was restrained at the side and may have been used by the monkeys to brace themselves against the perturbations produced by the movements of the ipsilateral arm, or even as a lever to assist the performance of the task with the other arm. EMG recordings showed that some of the muscles on the same side of the body as the restrained arm were nevertheless active and directionally tuned during performance of the task with the other arm (Fig. 2). Consequently, it is possible that at least some of what appears as tuning with respect to ipsilateral movement trials in this study may be related to the documented mechanically coupled activation of muscles on the nominally "nonperforming" side of the body. This same explanation may also account for some of the ipsilateral, bilateral, and bimanual M1 activity observed in other whole-arm tasks (Donchin et al. 1998; Kazennikov et al. 1999; Kermadi et al. 1998, 2000; Steinberg et al. 2002). Nevertheless, it must be acknowledged that the design of the tasks used in the present study does not permit a definitive conclusion for or against either interpretation of the causal origin of ipsilateral activation in caudal M1.

Another relevant factor may be the location of recording sites in the precentral gyrus. Kazennikov et al. (1999) reported a strong contralateral bias for their M1 cell sample and argued that most ipsilateral activations were spurious consequences of uncontrolled postural adjustments of the contralateral body. This contralateral bias is reminiscent of the properties of caudal M1 cells recorded in the present study. In contrast, Kermadi et al. (1998, 2000) reported much more prominent bilateral and bimanual activation in M1. Comparison of recording sites suggests that Kazennikov et al. (1999) recorded their cells in the most caudal part of M1 within the central sulcus, as in the present study, whereas Kermadi et al. (1998, 2000) collected data from the entire expanse of M1 up to the border with PMd. The properties of cells in more rostral parts of M1 appear to be transitional between those in caudal M1 and PMd (this study, Crammond and Kalaska 1996, 2000). Therefore the degree to which ipsilateral activation may be a spurious consequence of mechanically coupled activations of muscles contralateral to the recording site, a reflection of bilateral control of muscles on both sides of the body, or a task-dependent but effector-independent representation of motor outputs may depend on where the neurons are located along a rostrocaudal functional gradient across precentral motor areas (Fig. 16).

This may also account for one apparent difference in results of the present study and those of Steinberg et al. (2002). In the latter study, the preferred movement directions of most M1 cells that were directionally tuned during movements of each arm differed by $<60°$. This is a much greater degree of

similarity of directional tuning that was shown by the cells that we collected in caudal M1 (Fig. 7*B*), but is consistent with the behavior of the very small sample of cells in more rostral M1 (Fig. 7*D*). Unfortunately, the exact recording sites were not specified in Steinberg et al. (2002).

Differences between experiments 1 and 2

Although the two experiments described here were conceptually very similar, there were a number of important differences between them. Most significantly, in *experiment 1* the instructional stimuli were presented in the same planar workspace in which the monkey moved its arm and the manipulandum handle, and the head fixation was arranged so that the monkeys gazed at their arm as they moved it between targets. In contrast, in *experiment 2* the instructional stimuli and cursor feedback were presented in a vertical plane at eye level in front of the monkey, orthogonal to the actual movements. The arm movements that determined cursor motion were made in a horizontal plane at the level of the abdomen and the monkey did not see its arm. Consequently, the monkey in *experiment 2* had to learn a nontrivial arbitrary sensorimotor association, as well as a sensorimotor transformation between cursor and arm movement to apply this association during task performance. Furthermore, visual feedback about progress in the task was very direct and natural and feedback from the two arms was different in *experiment 1*, while it was more symbolic and abstract and identical with both arms in *experiment 2*. A second important difference was that the CUE remained visible for the entire duration of the delay period in *experiment 1* but was removed for an extended MEM period in *experiment 2*. A third difference between the tasks was that in the blocks of trials described for *experiment 1*, the GO signal was a unique stimulus which appeared at the cued target location, and so the monkeys were not strictly required to use the CUE information to perform the task correctly. In contrast, the GO signal in *experiment 2* always consisted of all eight possible target locations, and so the monkey had to remember the prior CUE signal to select the appropriate target when the nonspecific GO signal appeared. Finally, there were a number of important differences in the training history of the two groups of monkeys which learned different sets of tasks (Cisek and Kalaska 2002b; Crammond and Kalaska 1994, 1996, 2000; Kalaska and Crammond 1995). These differences in training regimes and task demands may have led to differences in the strategies the monkeys used to solve the tasks.

Nevertheless, despite various differences in task requirements, the basic results from both experiments were in close agreement (Compare Figs. 10 and 13, and Tables 1 and 2). The only significant difference is that in *experiment 2*, the differences in directional tuning functions with the two arms tended to be even smaller than in *experiment 1*, and there was no trend for these tuning differences to increase over the course of the trial as seen in *experiment 1*. This may be partly due to the task differences discussed above. They may also be due in part to differences in the cortical locations from which cells were recorded. The recordings in *experiment 1* were taken mainly from the part of PMd between the genu of the arcuate sulcus and the precentral dimple [area F2 of Matelli et al. (1985)], while recordings in *experiment 2* were taken from a more rostral portion of PMd (possibly extending into area F7). This trend is consistent with the well-documented rostro-caudal gradients of cell properties observed in precentral cortex (Battaglia-Mayer et al. 2001; Johnson et al. 1996; Marconi et al. 2001).

Given the significant differences in the two tasks, it is interesting to speculate whether the PMd cell populations in the two studies were functionally equivalent. If monkeys were trained to perform both tasks, it is not possible to predict at this point whether the same set of PMd cells would be active in both or whether different sets of PMd cells would be preferentially activated in one or the other of the tasks. Nevertheless, the results of the present study predict that they would all share in common a strong degree of effector independence, especially during the instructed-delay period prior to movement initiation.

NOTE ADDED IN PROOF

Ochiai et al. 2002 have recently reported results that complement the present findings. Monkeys used a video image of their unseen arm to guide reaches to targets. The directional tuning of many PMd cells during a delay period varied with the intended direction of motion of the video image of their arm whether it was seen in the normal or in a mirror-reversed orientation, rather than with the actual physical direction of motion of the arm itself (cf. Shen and Alexander 1997a,b). The results of *experiment 1* here show that this effector-independent representation of the directionality of motor output applies not just to different movements of the same arm, but even to different arms. Furthermore, this property is seen whether the actions are guided by visual feedback of an arm viewed directly (*experiment 1*) or indirectly on a monitor (Ochiai et al. 2002), or even by arbitrary visual symbols (Shen and Alexander 1997a,b; *experiment 2*). Taken together, these findings demonstrate that a major component of the delay-period activity in PMd in these task conditions is a visually based representation of the sensory information used to guide action and of the associated motor responses, that is not closely coupled to the physical details of the actual motor output.

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