Neural Correlates of a Spatial Sensory-To-Motor Transformation in Primary Motor Cortex

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Shen, Liming and Garrett E. Alexander. Neural correlates of a spatial sensory-to-motor transformation in primary motor cortex. *J. Neurophysiol.*, 77: 1171–1194, 1997. Primary motor cortex (MC) has been strongly implicated in motor processing, but there have been relatively few attempts to determine whether MC may also play a role in either sensory or context-dependent processing. In the present study, neuronal activity in MC was characterized in relation to the planning and execution of visually instructed limb movements whose trajectories were dissociated from their spatial targets. This design permitted the dissociation of neuronal activity related to motor processing from activity related to sensory or context-dependent processing. Two macaque monkeys were trained to perform a visually instructed, delayed reaching paradigm with indirect visual feedback. Subjects used the right forelimb to capture targets presented on a video display by moving a two-dimensional joystick whose position was reflected by a cursor. The target to be captured on each trial was indicated by a visual instruction stimulus (IS), which was separated from a movement-triggering stimulus (TS) by a variable delay. The direction of forelimb movement was dissociated from the location of the target by varying the spatial mappings between joystick and cursor across two conditions, unrotated (0° offset between cursor and limb direction) and rotated (90° offset). Task-related activity was recorded from a total of 180 MC neurons. The focus of this study was on directionally tuned neuronal activity that included phasic, stimulus-related activity following the IS; tonic, set-related activity between IS and TS; and phasic, movement-related activity following the TS. Of the entire sample of MC neurons with directionally tuned activity, 119 cells were tested under both rotation conditions, permitting dissociation of directional responses that depended on target location from those that depended on limb trajectory. Task-related neuronal activity was classified as target dependent if it covaried exclusively with target location across both conditions, and as limb dependent if it covaried exclusively with limb trajectory. Directional activity that did not fulfill the criteria for either target or limb dependence, because of changes across rotation conditions, was classified as complex. Approximately one quarter of MC neurons showed weak, but consistent, stimulus-related activity that was directionally tuned (24%, 29 of 119). Nearly all of the directionally classifiable stimulus-related activity was target dependent (94%, 15 of 16 responses), with the exception of a single limb-dependent response (6%, 1 of 16). A majority of MC neurons showed set-related activity that was directionally tuned (61%, 72 of 119). Of the directionally classifiable set-related activity, there were comparable numbers of target-dependent (37%, 16 of 43) and limb-dependent responses (35%, 15 of 43), with the remainder being complex (27%, 12 of 43). Movement-related activity following the TS was considered to be early or late, depending on whether it preceded or followed the onset of movement. The large majority of MC neurons showed early movement-related activity that was directionally tuned (86%, 102 of 119): among those whose early activity was directionally classifiable, there were only one third as many target-dependent responses (14%, 11 of 79) as limb-dependent responses (43%, 34 of 79), with the remainder being complex (43%, 34 of 79). There was also a large majority of MC neurons that showed late movement-related activity that was directionally tuned (84%, 100 of 119): among those whose late activity was directionally classifiable, there were only one ninth as many target-dependent responses (5%, 4 of 88) as there were limb-dependent responses (41%, 36 of 88), with the remainder being complex (55%, 48 of 88). The instructed delay task employed in this study required a sensory-to-motor transformation through which the instructed target location was associated with a limb movement of the appropriate direction. Over the extended interval between IS and motor response, we observed a gradual decline in the frequency of target-dependent activity and gradual increases in the respective frequencies of both limb-dependent and complex activity. This suggests that MC neurons may play a role in mediating the spatial sensory-to-motor transformation required by the task. The substantial proportions of target-dependent activity observed in this study reinforce the growing evidence that at least some MC neurons do play a role in either sensory or context-dependent processing of spatial information relevant to specific motor tasks.

**Introduction**

Among the multiple cortical motor areas identified thus far (Dum and Strick 1991; He et al. 1993, 1995; Luppino et al. 1991, 1993; Matsuzaka et al. 1992), primary motor cortex (MC) has long been regarded as the motor field with the most direct and robust linkages to the segmental motor apparatus (Biber et al. 1978; He et al. 1993, 1995; Murray and Coulter 1981). Although MC is not the only cortical motor area to send direct projections to spinal levels, it is the only one that shares reciprocal connections with each of the premotor areas that project directly to spinal levels, and with none of those that do not (He et al. 1993, 1995; Luppino et al. 1993). Functional comparisons of MC with other motor fields have consistently shown it to contain higher proportions of neurons whose activity covaries with the purely motor aspects of various behavioral tasks (Alexander and Crutcher 1990b; Johnson et al. 1996; Mushiake et al. 1991; Weinrich and Wise 1982). Thus, although the distributed network of cortical motor fields has a decidedly parallel organization, the weight of evidence suggests that MC may be appropriately regarded as playing a preferential role in purely motor processing, as opposed to information processing related to sensory and/or associative (i.e., context-dependent) functions. On the other hand, some have argued that MC may have a role in various cognitive processes.
purely motor processing, there have been graphic (EMG) signals, while maintaining a net zero static load.

Motor processing, including those of limb kinematics (Alexander and Crutcher 1990b; Georgopoulos et al. 1989;
Hoehman and Wise 1991; Lurito et al. 1991). Visually guided reaching to instructed target locations is a
behavioral paradigm that has been used extensively to evaluate the response properties of MC neurons (Caminiti
Scott and Kalaska 1995, 1997). In the simplest version, that of direct reaching to the site of a visual instruction stimulus (IS),
the physical properties of the IS (specifically, its spatial location), the instructed location of the target (i.e., the goal
of the movement), and the trajectory of the subject’s reach all covary with one another in a stereotypic manner (Caminiti
et al. 1991; Georgopoulos et al. 1982, 1985; Schwartz et al. 1988). However, it is also possible for these three factors
to be dissociated from one another with the use of appropriate variations on the targeted reaching paradigm.

Viewed as a sensory-to-motor transformation, the simplest model might be that of a chain (or cascade) of information
processing leading from purely sensory processing to associative processing to purely motor processing. Neural correlates
of these different levels of information processing may be defined operationally in the following way: correlates of
sensory processing should covary unconditionally with some physical property of the sensory input, correlates of motor
processing should covary unconditionally with some physical property of the motor output, and correlates of associative
or context-dependent processing should covary with some aspect of the behavioral context, being neither purely motor
nor purely sensory.

There have been numerous studies of the response properties of MC neurons that have dissociated some of the purely
motor variables involved in voluntary limb movements, such as hand trajectory, force, direction, amplitude, velocity,
and joint configuration (Alexander and Crutcher 1990a; Bauswein et al. 1991; Crutcher and Alexander 1990;
Fu et al. 1993; Georgopoulos et al. 1992; Kalaska et al. 1989; Riehle and Requin 1989, 1995; Riehle et al. 1994b;
Scott and Kalaska 1995, 1997; Thach 1978; Werner et al. 1991). These studies have provided evidence that MC neurons may participate at several discrete sublevels within the domain of purely motor processing, including those of limb kinematics (Alexander and Crutcher 1990a; Crutcher and Alexander 1990;
Fu et al. 1993, 1995; Kalaska and Hyde 1985; Kalaska et al. 1989; Riehle and Requin 1989, 1995) and limb dynamics
(Alexander and Crutcher 1990a; Bauswein et al. 1991; Crutcher and Alexander 1990; Georgopoulos et al. 1992;
Kalaska and Hyde 1985; Kalaska et al. 1989; Riehle and Requin 1995; Riehle et al. 1994b; Scott and Kalaska 1995,

Despite a wealth of data concerning the participation of MC neurons in purely motor processing, there have been relatively few attempts to study the functional properties of MC neurons with the use of paradigms that dissociated purely motor variables from context-dependent or purely sensory variables. In a study that dissociated limb trajectory from the spatial endpoint of a targeted reaching movement, Hoehman and Wise (1991) found that some MC neurons did discharge exclusively in relation to the spatial endpoint rather than the trajectory of the reach. Lurito et al. (1991) dissociated the location of a visual IS from the trajectory of an instructed reach. They reported that most of the directional, movement-related activity in MC could not be classified as depending exclusively on either the direction of limb movement or the location of the visual IS. Riehle et al. (1994a) dissociated the location of a visual IS from the direction of a targeted wrist movement, and found that some MC neurons did show directional movement-related activity that covaried exclusively with IS location, independent of the direction of wrist movement.

A previous study in our laboratory dissociated the trajectory of a one-dimensional elbow movement from the location of a visual IS, while the latter also served as the target (i.e., goal) of the movement. In that study, the set- and movement-related discharge of some MC neurons was found to covary with IS (i.e., target) location, independent of the limb’s trajectory (Alexander and Crutcher 1990b). In the present study we implemented a similar dissociation with the use of a two-dimensional delayed reaching paradigm. The purpose of this study was to provide a further test, extended to two-dimensional arm movements, of the concept that MC neurons participate not only in purely motor processing, but also in associative or purely sensory processing of visuospatial information. Some of these results have been presented elsewhere in abstract form (Shen and Alexander 1994).

**METHODS**

**Subjects and experimental apparatus**

Two female macaque monkeys [one Macaca mulatta (JA); the other Macaca nemestrina (KO)], each weighing 4–5 kg, were used in these experiments. In all aspects of their care, the monkeys were treated in accordance with the Guiding Principles in the Care and Use of Animals of the American Physiological Society. Each monkey was trained to perform a set of motor behavioral paradigms in which reaching movements were made with the right forelimb to guide a two-dimensional joystick that controlled the position of a cursor on a video display. The display (20-in. diagonal color monitor) was centered at eye level, 30 cm in front of the subject. The subject was seated in a primate chair with the right hand resting on the handle of a vertically oriented joystick and the left arm lightly restrained with foam padding. An opaque neck plate prevented the subject from viewing the working forelimb.

The pivot point of the joystick was located ~15 cm forward and 15 cm lateral to the subject’s right hip. With the handle of the joystick centered directly above the pivot point (center position), the upper arm was able to hang vertically (shoulder neither flexed nor extended), with the forearm held in a roughly horizontal orientation (elbow flexed 90°). The joystick was of symmetrical design, with one shaft extending upward for the monkey to grasp, the other extending downward from the pivot point. The two 30-cm shafts were fitted with balanced weights (~300 g each) to increase the dynamic load, and thereby enhance the task-related electromyographic (EMG) signals, while maintaining a net zero static load throughout the workspace (because the center of gravity was located at the pivot point).
The displacement of the joystick handle was measured with two precision potentiometers attached to gimbals (that supported the joystick shafts) whose axes passed through the pivot point. The displacement signal was reflected by the position of a cursor (consisting of a 3 x 3-mm white square) presented on the video display. The joystick and cursor mappings were calibrated so that a 10-cm tangential displacement of the joystick handle (~20° angular displacement of the joystick shaft) from its center position would result in a corresponding 12-cm displacement of the cursor on the video display.

**Behavioral paradigms**

There were two behavioral paradigms, illustrated in Fig. 1, which differed from each other only with respect to the mappings between joystick and cursor. In one paradigm, designated the nonrotated (or 0° mapping) condition, forward movement of the joystick (with respect to the monkey) moved the cursor upward on the display and rightward movement of the joystick moved the cursor rightward (from the monkey's perspective). In the other paradigm, designated the rotated (or 90° mapping) condition, the mapping between joystick and cursor was rotated by 90°. In the rotated condition, rightward movement of the joystick moved the cursor upward on the display, and backward movement of the joystick moved the cursor rightward.

The basic task was a delayed reaching paradigm with indirect visual feedback. Because the subjects were not allowed to view the working limb or joystick, they had to rely on the cursor for visual feedback about their reaching movements. Each trial began with the presentation of a center fixation target (CF), which consisted of a 2 x 2-cm white square, in the center of the display. The subject was required to "capture" the CF by positioning the cursor within its boundaries, at which time the shading of the CF switched from white to gray. Once the CF had been captured, four peripheral targets were displayed simultaneously above, below, and to the right and left of the CF. Each was located 12 cm from the CF (visual angle ≈ 22°), and each consisted of a 2 x 2-cm white square. These peripheral targets remained illuminated for the rest of the trial. After capture of the CF and illumination of the peripheral targets, the subject was required to hold in the center position during a variable (0.6-1.6 s) preinstruction period, during the 400-ms presentation of the visual IS, and during a variable (0.6-1.6 s) postinstruction period (which was timed from IS offset). The IS consisted of the transient dimming of one of the four peripheral targets, selected in a pseudorandom sequence (balanced, but unpredictable). At the end of the postinstruction period, the CF dimmed briefly (200 ms), which served as a nondirectional trigger stimulus (TS). The monkey was then permitted to move the cursor away from the CF and into alignment with the peripheral target whose dimming had served as the IS on that trial. As CF capture, the shading of the peripheral target switched from white to gray once it was captured. After holding briefly (0.5-1.0 s) at the peripheral target location, the monkey received a liquid reward (0.2 ml of dilute apple juice) delivered through a stainless steel mouthpiece. If the cursor left the CF before presentation of the TS, the trial was immediately terminated without reward. Minimal constraints were placed on response times following the TS (capture times of up to 5.0 s were permitted), because of the inevitable directional errors and associated corrective movements that occurred early in the adaptation process that accompanied every switch between nonrotated and rotated conditions. Subjects were taught to perform the basic task under both the nonrotated and rotated conditions with an accuracy of >90%. This required ~3-4 mo of training for each subject. Performance was considered correct or accurate on trials in which the initial direction of cursor movement—as the cursor exited the center window—was appropriate, i.e., within 15° of the correct target direction.
It is important to note that from the standpoint of the visual display, the task was identical in both conditions. However, the limb trajectories associated with capturing any one of the peripheral targets differed by 90° in the two conditions. Thus, for example, in the nonrotated condition, successful capture of the top target required a forward movement of the hand, whereas in the rotated condition the subject moved the hand to the right to capture the top target. The cursor trajectory on the visual display was similar in both conditions. Across the two conditions, limb (i.e., hand) trajectory and target location were dissociated from one another. The subject made similar reaching movements to capture targets that were 90° apart, and captured identical targets with reaching movements whose trajectories differed by 90°.

Surgical procedures

Once training had been completed, each monkey was surgically prepared for chronic single-cell recording experiments. All surgical procedures were carried out with general anesthesia (induction with ketamine 10 mg/kg im followed by 1.5–3.0% isoflurane gas anesthesia) and standard aseptic technique. A scleral search coil for monitoring eye position was implanted in the left eye of each monkey (Judge et al. 1980). With stereotaxic guidance, a stainless steel recording chamber (29 mm ID) was positioned over a circular opening in the skull that permitted access to the lateral convexity of the left frontal lobe, including motor and premotor cortex. The recording chamber was then cemented to the calvarium with dental acrylic. Stainless steel bolts for immobilization of the head during behavioral performance were also cemented in place with dental acrylic, and the entire assembly was anchored to the calvarium with small stainless steel screws.

Chronic EMG electrodes were also implanted at the time of surgery. These consisted of 11 (monkey JA) or 12 pairs (monkey KO) of bipolar patch electrodes that were sutured to the connective tissue on the surface of each muscle. The leads from these electrodes were tunneled subcutaneously to a connector embedded in the acrylic skull assembly. Electrodes were implanted in task-related muscles of the working (right) forelimb, including brachialis, biceps, deltoid, infraspinatus, lateral triceps, medial triceps, pectoralis major (2 pairs of electrodes in monkey KO), rhomboid, subscapularis, supraspinatus, and teres major.

Recording procedures

Action potentials from cortical neurons were recorded extracellu larly with glass-coated platinum-iridium microelectrodes (impedance 0.5–1.5 MΩ measured at 1,000 Hz). After appropriate amplification and filtering (0.3–5.0 kHz), the action potentials of individual neurons were discriminated from one another by a computerized spike sorter (Alpha Omega Engineering) that operates on the principle of adaptive template matching. Discriminated, digitized neuronal activity (the spike sorter generated one 0.1-ms standard pulse per action potential) was sampled by the laboratory computer at 1-ms intervals.

Eye position was monitored with the scleral coil–magnetic field technique (Indiran Instruments) (Robinson 1963). EMG activity was recorded differentially from each pair of chronic electrodes. These signals were amplified, filtered (100–500 Hz), and rectified. All analog data, including eye position, joystick position, and EMG activity, were sampled by the laboratory computer at 1,000 Hz and then averaged across five adjacent time bins for an effective sampling rate of 200 Hz.

Data acquisition

During experimental sessions, the monkey’s head fixation bolts were attached to a restraining device. Under the control of a hydraul ic microdrive (Narishige MO-95), a microelectrode was advanced through the dura and into the precentral cortex. The monkey performed one of the two behavioral paradigms (nonrotated or rotated condition) as task-related neurons were identified and discrimi nated from one another. Administration of the behavioral par adigms and collection of electrophysiological data were controlled by the laboratory computer (586/66 IBM-compatible PC). On line rasters of neuronal activity were displayed and continuously updated to permit the rapid identification of neurons with obvious task-related activity, that is, neurons whose activity showed consistent changes—either tonic or phasic, of either polarity—preceding or following either the IS or the TS. When neurons were identified that appeared to show task-related activity, directional or otherwise, an attempt was made to collect complete data files under both rotation conditions. For each rotation condition, a complete data file consisted of 10–15 repetitions of each of the four trial types (corresponding to the 4 peripheral target locations). After the shift from the first to the second rotation condition, we attempted to wait until the monkey had adapted completely to the new rotation condition before collecting the data file for the second condition. Nevertheless, because of the pressures of time associated with experimental recording sessions, the data files occasionally included some trials in which the monkey had not yet managed to adapt completely to the new rotation condition. On trials such as these, the initial direction of limb movement (as the cursor exited the center window) was often incorrect, being more appropriate for the previous rotation condition, even though a midtrajectory correction usually enabled the monkey to reach the correct target and thereby receive a reward. Because of this, our data analysis procedures took into account the actual trajectory of limb movement on each trial, rather than simply assuming that a rewarded response had involved a trajectory that was directed straight toward the appropriate target (see below). In some cases we were able to test a given neuron through two or even three rotation shifts (repeating either the 1st or both the 1st and 2nd rotation conditions), but most cells were tested with only a single rotation shift.

Because of the adaptation process that was required whenever the rotation condition was switched, we generally did not attempt to switch the rotation condition back to the original state after data collection had been completed for a given cell. Thus, for successive neurons along a particular microelectrode track, the order in which the two rotation conditions were presented was generally reversed.

Microstimulation through the recording microelectrode was used to help identify the proximal arm representation in motor cortex, and to characterize the stimulation-evoked motor responses at the cortical recording sites. Currents were limited to 35 μA, delivered in 100-ms trains of balanced bipolar pulse pairs (0.2-ms cathodal pulse, 0.1-ms gap, 0.2-ms anodal pulse) at a frequency of 300 Hz. Microstimulation was carried out at most recording sites, usually as the microelectrode was being withdrawn from each track at the end of the recording session.

After termination of the recording sessions, each monkey was deeply anesthetized with pentobarbital sodium and perfused transcardially with aldehyde fixatives. Immediately before the perfusion, three stainless steel pins were inserted into the brain of each monkey at known coordinates within the recording chamber, with the use of the same microdrive that was used for the single-cell recordings. The pins remained in place during the perfusion, after which the calvarium, recording chamber, and dura were removed and the frontal lobe over which the chamber had been placed was photographed with pins still in place. The brain was then removed from the skull and placed briefly (1–2 days) in additional fixative, following which the pins were removed. The brain was then blocked in the coronal plane, frozen, and sectioned at 40-μm intervals on a freezing microtome. Every fifth section was stained with cresyl violet. With the use of the records of chamber coordinates.
for each microelectrode track, the site of surface penetration for each microelectrode track was reconstructed with reference to the chamber coordinates of the pin tracks, which were referenced in turn to sulcal landmarks on the basis of the surface photographs and the histological material. We did not attempt to identify each microelectrode track within the histological material, or to reconstruct the precise depth of each of the neuronal recording sites.

**Data analysis**

All data files containing task-related activity were subjected to statistical analysis. Movement-aligned and stimulus-aligned (CF, IS, TS) rasters and peri-event histograms of each cell’s activity were inspected and evaluated, but the final classification of task-related responses was based on a formal statistical analysis. The categorical analysis of task-related activity was based on two orthogonal classification schemes. One scheme involved a temporal classification according to the task-related events with which the response was associated, such as presentation of the IS, onset of movement, etc. This was based on the temporal dissociation of events that was built into the experimental paradigms. The other scheme was based on the level of information processing with which the response was associated, as determined operationally by the effects of the spatial dissociation between target location and limb trajectory that was built into the paradigms.

We defined four temporal epochs within each trial. Each epoch was a 200-ms window whose boundaries were defined with respect to a specific intratask event. In addition, an epoch for characterizing baseline discharge rates was defined within the intertrial interval (ITI). The four intratrial epochs and the single intertrial epoch are described in Table 1.

Neuronal activity (spike discharge rate) was classified in terms of its dependence on both the temporal and spatial features of the two behavioral tasks. To be considered task related, neuronal activity occurring during one of the four intratrial epochs was required to show either 1) significant dependence on the spatial features of the tasks, as measured by the target and limb analyses of variance (ANOVAs) described below or 2) significant deviation from the baseline discharge rate as measured during the ITI. The latter determination was made across all trials by the use of a paired Student’s t-test (2-tailed, \( P < 0.001 \)), which was applied if and only if both the target and limb ANOVAs failed to demonstrate a significant directional effect.

On the basis of the epoch in which it occurred, task-related activity was categorized (Table 1) as stimulus related, set related, reaction time; and TS, trigger stimulus.

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### TABLE 1. Classification of task-related responses based on temporal epochs

<table>
<thead>
<tr>
<th>Epoch</th>
<th>Event</th>
<th>Interval</th>
<th>Description</th>
<th>Response Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITI</td>
<td>CF on</td>
<td>–200, 0</td>
<td>ITI (before CF)</td>
<td>Baseline</td>
</tr>
<tr>
<td>IS</td>
<td>IS on</td>
<td>50, 250</td>
<td>after IS onset</td>
<td>Stimulus</td>
</tr>
<tr>
<td>Delay</td>
<td>TS on</td>
<td>–200, 0</td>
<td>preparing to move</td>
<td>Set</td>
</tr>
<tr>
<td>RT</td>
<td>TS on</td>
<td>50, 250</td>
<td>after TS</td>
<td>Early mvt</td>
</tr>
<tr>
<td>MT</td>
<td>MO on</td>
<td>0, 200</td>
<td>after MO</td>
<td>Late mvt</td>
</tr>
</tbody>
</table>

CF, center fixation stimulus; IS, instructional stimulus; ITI, intertrial interval; MO, movement onset; RT, reaction time; TS, trigger stimulus.

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(CF window. This measured direction was then coded in terms of the nearest cardinal direction of joystick movement (i.e., 0°, 90°, 180°, or 270°). The initial direction of limb (joystick) movement was measured directly, for each trial, at the instant the cursor exited the CF window. This measured direction was then coded in terms of the nearest judgment of joystick movement (i.e., 0°, 90°, 180°, or 270°). Thus it was the actual initial direction of limb movement, rather than an assumed ideal direction, that was used in the assessment of spatial dependencies. Each epoch-specific neural response was subjected to two separate ANOVAs, one in which the effect of target location was assessed across rotation conditions (target ANOVA) and another in which the effect of limb trajectory was assessed across rotation conditions (limb ANOVA). For the two-way target ANOVA, the factors were target location and rotation condition. For the two-way limb ANOVA, the factors were initial direction of limb movement and rotation condition.

After a preliminary, exploratory analysis of the neural data, the significance level for both the target and the limb ANOVAs was set at \( \alpha = 0.001 \). With this significance level, we found close agreement between the ANOVA assessments and the apparent task relatedness of cells as judged by visual inspections of the rasters and peri-event histograms.

Table 2 shows how epoch-specific neuronal activity was categorized according to its spatial dependencies. Target-dependent activity covaried exclusively with target location across both conditions. Activity was classified as target dependent if the target ANOVA showed a main effect for target location and no location × condition interaction. Limb-dependent activity was defined as limb dependent if the limb ANOVA showed no main effect for limb direction or showed a direction × condition interaction. Limb-dependent activity showed a significant deviation from the definition of both target and limb interactions. For the two-way limb ANOVA, the factors were target location and orientation interaction. It is important to emphasize that, for a cell’s activity to be categorized as either target dependent or limb dependent, there must have been an adequate dissociation between target and limb directions across rotation conditions. Had there not been an adequate dissociation between these two variables, directional activity that showed dependence on one variable (say, target dependence) would necessarily have shown dependence on the other variable as well, and that was prohibited in the definitions of both categories. And conversely, neither target-dependent nor limb-dependent activity could be attributable to a simple failure to dissociate target and limb directions across rotation conditions (i.e., a failure of the monkey to adapt sufficiently to the second rotation condition). For the limb ANOVA was based on the actual, measured directions of initial limb movement; any substantial failure of the monkey to adapt to the second rotation condition, so that target and limb directions were not dissociated across rotation conditions, would lead to results for the limb ANOVA that were similar to those of the target ANOVA, and that would be incompatible with the definitions of both target dependence and limb dependence.

Complex activity, although directional, did not show consistent covariance with either target location or limb direction across both rotation conditions. If a directional response did not meet the strict criteria for either target dependence or limb dependence (i.e., a main effect for either target or limb direction without a corresponding direction × condition interaction) because of significant directional × condition interactions, it was classified as complex. Complex activity was subclassified according to whether it showed a main effect only for target direction (complex-T), only for limb direction (complex-L), or for both target and limb direction (complex-TL, “intermediate”).

Neuronal activity that met the specific criteria for being either target dependent, limb dependent, or complex was considered to...
be directionally classifiable. However, if activity within a given epoch met the criteria for both target and limb dependence, it was considered to be directionally unclassifiable. This is because, in principle, if target and limb directions had been adequately dissociated across rotation conditions, it would have been logically impossible for a neuron’s activity to simultaneously fulfill the criteria for both target and limb dependence. In fact, instances of directionally unclassifiable activity were generally explained by a monkey’s failure to adapt sufficiently to the second rotation condition before the recordings from a given neuron had been suspended.

If there were no main effect either for target location or for limb direction, yet the epoch-specific activity differed significantly from baseline levels (paired, 2-tailed t-test, $\alpha < 0.001$), the activity was categorized as nondirectional.

This classification scheme, based on spatial dependencies, was inherently conservative in the designation of directional responses as either target or limb dependent, because of the stipulation that neural activity assigned to either of these categories was required to show no corresponding direction $\times$ condition interaction. Another important feature of this classification scheme is that it effectively precluded the misclassification of truly limb-dependent activity as target dependent, and vice versa. This was due to two factors: 1) the use of actual limb trajectories in computing the limb ANOVAs and 2) the fact that the definitions of target and limb dependence were mutually exclusive. In combination, these two factors guaranteed that even if the monkey failed to adapt to the second rotation condition, in which case the initial limb trajectories would maintain the same target mappings as in the previous rotation condition, truly limb-dependent activity (or truly target-dependent activity) would have met the criteria for both limb and target dependence, in which case it would have been categorized as ‘‘unclassifiable.’’ This is demonstrated in the APPENDIX, which describes the results of a computer simulation of how trajectory errors, including those due to incomplete adaptation to the second rotation condition, may have influenced our spatial classification scheme.

Categorical comparisons of the frequencies of neuronal response types across epochs were made with the use of Pearson’s $\chi^2$ test.

RESULTS

Task performance

Even after each subject had been fully trained and was performing both paradigms at >90% correct, both monkeys required a brief period, consisting of ~80–120 trials, to adapt to the new joystick/cursor mapping each time the condition was changed. The same adaptation period was required whether the task condition changed from nonrotated to rotated or from rotated to nonrotated. Immediately after the condition was changed, the monkey would continue to generate initial limb trajectories that were appropriate for the previous mapping condition, so the initial cursor trajectory would be directed ~90° away from the correct target location. Corrective movements would be required to bring the cursor into alignment with the target, and the result would be a curvilinear hand trajectory early in the course of adaptation. As adaptation progressed, the trajectories to each of the peripheral targets would gradually straighten. When the mapping was changed again, the process would be repeated. Even after each monkey had been performing both tasks for >1 yr, an adaptation process of approximately the same length was required every time the joystick/cursor mapping was changed.

For both subjects, the reaction times (RTs) were comparable across trials of differing target locations and mapping conditions. For monkey JA, the mean RT across all target locations was 349 ± 65 (SD) ms during the 0° mapping condition and 351 ± 72 ms during the 90° mapping condition for monkey KO, the mean RT values were 385 ± 84 ms and 369 ± 75 ms, respectively.

During the adaptation process, the average movement time (MT) increased temporarily because of the curvilinear trajectory errors, including those due to incomplete adaptation to the second rotation condition, may have influenced our spatial classification scheme.

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Even after each subject had been fully trained and was performing both paradigms at >90% correct, both monkeys required a brief period, consisting of ~80–120 trials, to adapt to the new joystick/cursor mapping each time the condition was changed. The same adaptation period was required whether the task condition changed from nonrotated to rotated or from rotated to nonrotated. Immediately after the condition was changed, the monkey would continue to generate initial limb trajectories that were appropriate for the previous mapping condition, so the initial cursor trajectory would be directed ~90° away from the correct target location. Corrective movements would be required to bring the cursor into alignment with the target, and the result would be a curvilinear hand trajectory early in the course of adaptation. As adaptation progressed, the trajectories to each of the peripheral targets would gradually straighten. When the mapping was changed again, the process would be repeated. Even after each monkey had been performing both tasks for >1 yr, an adaptation process of approximately the same length was required every time the joystick/cursor mapping was changed.

For both subjects, the reaction times (RTs) were comparable across trials of differing target locations and mapping conditions. For monkey JA, the mean RT across all target locations was 349 ± 65 (SD) ms during the 0° mapping condition and 351 ± 72 ms during the 90° mapping condition. For monkey KO, the mean RT values were 385 ± 84 ms and 369 ± 75 ms, respectively.

During the adaptation process, the average movement time (MT) increased temporarily because of the curvilinear trajectories that were associated with the error correction process. Once the subject had adapted to the new rotation condition, however, the MTs in the new adapted state were comparable with those recorded before the change in rotation condition. The average MT for monkey JA was 285 ± 38 ms when the monkey was fully adapted to the 0° mapping condition and 278 ± 45 ms when adapted to the 90° mapping condition. For monkey KO, the comparable MT values were 296 ± 75 ms and 290 ± 87 ms.

All of the sampled muscles in both monkeys showed directional, movement-related activity patterns during task performance. All of these movement-related responses were limb (direction) dependent. This is illustrated in Fig. 2, which shows the task-related EMG patterns for two muscles, deltoid and brachialis, sampled from monkey JA. In each case, the movement-related activity pattern can be seen to covary with the direction of limb movement rather than with target location. It should also be noted that both muscles were silent during the postinstruction period. None of the muscles sampled from either monkey showed significant directional activation during the postinstruction period.
FIG. 2. Task-related electromyographic (EMG) activity recorded from 2 of the forelimb muscles, deltoid and brachialis, that were monitored throughout the experiments in monkey JA. The data sample presented in this figure was obtained in the course of testing a single primary motor cortex (MC) neuron for its task relatedness. A: data recorded during the 0° mapping condition. B: data from the 90° mapping condition. Each of the 4 rows of illustrations represents the EMG and kinematic data obtained from trials in which the same peripheral target served as the locus for the visual IS: in clockwise order of targets, the 1st (top) row contains data from top target trials, the 2nd row for right target trials, the 3rd row for bottom target trials, and the 4th row for left target trials. Within each rotation condition, the 2 leftmost columns show the EMG data from the deltoid and brachialis muscles, and the column to their immediate right shows the corresponding kinematic data. The EMG records for trials of a given type (based on target location and rotation condition) are organized in raster form. EMG records are aligned with TS (trigger) onset. In the columns of kinematic data, the target-capturing hand trajectories from all trials of a given type are superimposed and presented on a facsimile of the monkey’s behavioral display, with the designated target for each trial type indicated by shading. Trajectories shown as upward in the illustration represent forward limb movements, whereas those shown as downward represent backward limb movements. The units for the horizontal scale under each kinematic display represent hand displacement (cm); this same scale is applicable to the vertical axis as well. The time scale for the EMG records is in ms. Both muscles showed directional, movement-related responses that covaried with the trajectory of limb movement rather than with target location. Under both rotation conditions, the deltoid was maximally activated by rightward movements of the joystick, and the brachialis by backward movements. Neither muscle showed significant directional activity during the postinstruction (delay) interval.

Subjects were not required to maintain fixation during performance of the behavioral paradigms. However, once the IS had been delivered, both subjects did maintain fixation on the CF throughout the postinstruction period until the TS appeared, at which point a saccade was made to the appropriate peripheral target in rough synchrony with the onset of limb movement. A sample of task-related eye movement recordings from monkey JA is presented in Fig. 3.
FIG. 3. Task-related eye movements. Samples of eye position recordings from monkey JA, illustrating the pattern of eye movements that was associated with task performance. The layout is similar to that of Fig. 2. Each row contains data from trials with the same target location. For clarity, only data from a single example of each of the 8 types of behavioral trials are shown. The examples chosen for this illustration were selected randomly, as the first instances of each trial type to occur within a block of 0° mapping trials and a block of 90° mapping trials collected during a single recording session. Solid lines: horizontal eye position signals (right is up, left is down). Broken lines: vertical signals. The times of occurrence of capture of CF (f), IS or cue onset (c), TS or trigger onset (t), onset of limb movement (m), and end of trial (e) are indicated on each record. These records demonstrate a pattern of task-related eye movements that was common to both monkeys. During the preinstruction period, after the CF had been captured, there was a tendency for the subject to maintain central fixation of the CF, but this was frequently interrupted by random saccades. Once the IS had been presented, however, fixation of the CF was rarely broken again until the postinstruction period was terminated by delivery of the TS. At this point, a saccade would be made to the correct target, followed shortly thereafter by the onset of the target-capturing limb movement. Gaze was then maintained at the correct peripheral target until the end of the trial, when all targets were extinguished. The vertical scale to the left of each record represents gaze angle (°); the horizontal scale beneath each record represents time (ms).

Data base

A total of 180 MC neurons (108 from monkey JA, 72 from monkey KO) showed task-related activity, that is, activity that showed significant directional effects or that differed significantly from baseline levels during at least one of the task-defined epochs. The final data base included only those task-related neurons that had been shown by local microstimulation to lie within a zone where proximal arm movements were represented (as evidenced by shoulder and/or elbow movements evoked with currents of ≈35 μA), and whose activity had been tested with both rotation conditions. The final data base comprised 119 MC neurons.

Overview of task-related activity

For the sample as a whole, the most prominent task-related responses that we observed among MC neurons were move-
A delay period on trials in which the IS had indicated that the target was independent of the target that had been signified by the IS. The large majority of MC neurons (86%, 102 of 119) showed early movement-related activity that was directionally classifiable or followed the onset of limb movement (Table 1). Many MC neurons also showed phasic, stimulus-related activity during the delay period, after delivery of the directional IS. The late, limb-dependent activity was associated with forward or leftward limb movements, irrespective of the rotation condition. We also encountered several examples in which two distinct limb-dependent responses could be discerned (1 early, 1 late) because of differences in their respective preferred directions (PDs). However, there were no examples of limb-dependent components preceding target-dependent components.

**TABLE 3. Categorization of task-related neuronal activity in MC**

<table>
<thead>
<tr>
<th></th>
<th>Stimulus (IS)</th>
<th>Set (Delay)</th>
<th>Early MVT (RT)</th>
<th>Late MVT (MT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classifiable†</td>
<td>16 (100)</td>
<td>43 (100)</td>
<td>79 (100)</td>
<td>88 (100)</td>
</tr>
<tr>
<td>Target†</td>
<td>15 (94)</td>
<td>16 (37)</td>
<td>11 (14)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Limb†</td>
<td>1 (6)</td>
<td>15 (35)</td>
<td>34 (43)</td>
<td>36 (41)</td>
</tr>
<tr>
<td>Complex†</td>
<td>0 (0)</td>
<td>12 (28)</td>
<td>34 (43)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>(T/L/I)</td>
<td>(0/0/0)</td>
<td>(0/0/12)</td>
<td>(1/2/31)</td>
<td>(2/4/42)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>13</td>
<td>29</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>119 [100]</td>
<td>119 [100]</td>
<td>119 [100]</td>
<td>119 [100]</td>
</tr>
</tbody>
</table>

* Number of cells (% of total sample, N = 119 cells). † Number of cells (% of total number of cells with directionally classifiable activity in each epoch). ‡ Respective numbers of complex-T, complex-L and complex-I responses contributing to total number of complex responses in each epoch.

The late, limb-dependent activity was associated with forward or leftward limb movements, irrespective of the rotation condition. All MC neurons showed movement-related responses contributing to total number of complex responses in each epoch.

**Phasic, movement-related activity following the TS**

Movement-related responses following the TS were considered to be early or late, depending on whether they preceded or followed the onset of limb movement (Table 1). The large majority of MC neurons (86%, 102 of 119) showed early movement-related activity that was directionally tuned (Table 3). Of the early movement-related responses that were directionally classifiable, there were only one third as many target-dependent responses (14%, 11 of 79) as limb-dependent responses (43%, 34 of 79), with the remainder being complex (34%, 34 of 79). There was also a large majority of MC neurons that showed late movement-related activity that was directionally tuned (84%, 100 of 119). And of the late movement-related responses that were directionally classifiable, there were only one ninth as many target-dependent responses (4%, 4 of 88) as there were limb-dependent responses (41%, 36 of 88), with the remainder being complex (55%, 48 of 88).

**Phasic, stimulus-related activity following the IS**

Three quarters of the sample of MC neurons (76%, 91 of 119) showed brief, phasic responses to the IS (Table 3), but the majority of these were nondirectional. Approximately one quarter of the entire sample showed phasic responses to the IS that were directionally selective (24%, 29 of 119). Nearly all of the stimulus-related responses that were directionally classifiable were target-dependent (94%, 15 of 16), whereas only one was found to be limb-dependent (6%, 1 of 16). None were judged to be complex. An example of a stimulus-related response that was classified as target-dependent is illustrated in Fig. 4. In both the nonrotated and the rotated conditions, this cell showed a weak, phasic burst of activity that began shortly after IS onset at the right target. There was no response when the IS was presented at any of the other three targets. The response was independent of the direction of the instructed limb movement.

**Tonic, set-related activity preceding the TS**

Approximately three fifths of the sample of MC neurons (61%, 72 of 119) showed tonic, directionally selective set-related activity during the delay (i.e., postinstruction) epoch between IS and TS (Table 3). Of the set-related responses that were directionally classifiable, 37% (16 of 43) were target-dependent, 35% (15 of 43) were limb-dependent, and 28% (12 of 43) were complex. All MC neurons with directional set-related activity showed movement-related responses as well.

An example of target-dependent, set-related activity is illustrated in Fig. 5. In both rotation conditions, this cell showed a sustained increase in discharge rate throughout the delay period on trials in which the IS had indicated that the left target was to be captured following the TS. The cell also showed a target-dependent, movement-related response with the same directionality.

An example of limb-dependent, set-related activity is illustrated in Fig. 6. In both rotation conditions, this cell showed a sustained increase in activity during the delay period on trials in which the instructed motor response involved a rightward limb movement. This set-related activity was independent of the target that had been signified by the IS. The cell also showed strong movement-related activity that was limb-dependent (maximal with forward or rightward limb movements), and weak (but statistically significant) stimulus-related activity that was target-dependent (right target).
Combinations of set- and movement-related activity

The cell whose activity is illustrated in Fig. 9 showed set-related activity that was target dependent (maximal for the bottom target and minimal for the left target), and late movement-related activity that was limb dependent (maximal after the onset of movements to the left). The late movement-related activity was preceded by early movement-related activity that was target dependent (present for all targets but the left). Of the four possible combinations of target- and limb dependencies, only one was not represented in our sample of MC neurons with combined set- and movement-related activity: we encountered no neurons that combined limb-dependent set-related activity with target-dependent movement-related activity.

In some of the cells that combined both set- and movement-related activity that was target dependent, such as the example illustrated in Fig. 10, the movement-related activity was so early and so brief as to suggest that it might have been appropriate to classify it as stimulus-related activity (related to the visual TS). It is important to emphasize, however, that the TS itself contained no spatial information; it served only to trigger the delayed motor response whose spatial target had been instructed by the preceding IS.

Complex activity

Some of the directional set- and movement-related activity observed in this study did not meet the criteria for classification as either target or limb dependent, because of complex interactions between direction and rotation condition. An example of complex set-related activity is illustrated in Fig. 11. In the 0° mapping condition, this cell showed maximal set-related activity before backward movements of the joystick that were associated with capturing the bottom target. In the 90° mapping condition, the directionality of the set-related activity shifted so that the activity was now comparable for trials in which the movement was either leftward, to capture the bottom target, or backward, to capture the right target. (The cell also showed late movement-related activity that was clearly limb dependent, associated with backward movements of the joystick.) This set-related activity might
have been characterized, equivalently, as being either target dependent or limb dependent with its PD shifting across rotation conditions. Because of this ambiguity, it was classified as complex-I (intermediate), because both the target ANOVA and the limb ANOVA showed significant direction effects as well as significant direction × condition interactions (Table 2).

Most of the complex activity observed in MC was of this complex-I variety (90%, 85 of 94; Table 4). However, there were also small numbers of neurons whose movement-related activity was classified as complex-T (3 cells) or complex-L (6 cells) because of main direction effects plus direction × condition interactions that were seen exclusively with either the target ANOVA or the limb ANOVA, respectively (Table 2).

Temporal distribution of directionally classifiable activity

Figure 12 shows the temporal distribution of target-dependent versus limb-dependent versus complex activity across the task-defined epochs that followed the IS onset. It is evident that over the extended interval between IS and motor response, there was an initial predominance followed by a gradual decline in the proportion of MC neurons showing target-dependent activity, and a gradual increase in the proportion of neurons showing limb-dependent activity. There was also a gradual increase in the proportion of neurons showing complex activity. An overall \( \chi^2 \) analysis of the relative frequencies of these three categories of directionally classifiable activity across the four task epochs showed that the ap-
FIG. 6. Limb-dependent set-related activity in combination with limb-dependent movement-related activity. Conventions are the same as in Fig. 5. Under both rotation conditions, this MC neuron showed tonic, set-related activity during the postinstruction interval before TS onset on trials that required rightward limb movements, regardless of target location. The cell also showed early movement-related activity that was limb dependent: under both rotation conditions, activity was maximal with forward or rightward movements of the limb, intermediate with backward movements, and minimal with leftward movements. Note that even the temporal pattern of the movement-related response covaried with limb direction across both rotation conditions, independent of target location: for example, with forward movements the activity was relatively tonic and sustained, whereas with rightward movements the activity was much more phasic. There was also a weak stimulus-related response that was target dependent, being selective for right target trials. 

Parent temporal changes were highly significant ($\chi^2 = 78.01$, df = 6, $P = 9.21 \times 10^{-15}$).

To clarify the relationships between directional categories and task epoch, we used additional $\chi^2$ tests to partition the variance associated with the overall $\chi^2$ analysis (Snedecor and Cochran 1989). Those results are presented in Table 4. Because of the apparent similarity in proportions of limb-dependent activity and complex activity across epochs (Table 3), we compared the frequencies of these two categories across epochs and found that they did not differ significantly (Table 4, row b: $\chi^2 = 2.70$, df = 3, $P = 0.44$). Consequently, these two categories were combined, and their combined frequency was then compared with the frequency of target-dependent activity across epochs. The result (Table 4, row c: $\chi^2 = 76.28$, df = 3, $P = 2.22 \times 10^{-16}$) showed that nearly all of the variance in the overall $\chi^2$ analysis could be accounted for by the difference across epochs in the frequencies of target-dependent versus limb-dependent plus complex activity.

To determine whether the trend toward declining proportions of target-dependent activity was significant for each successive epoch, we made those comparisons as well and found that the trend was significant across each pair of adjacent epochs (Table 4, rows d-f). However, the sum of $\chi^2$ values for these last three comparisons ($\chi^2 = 28.19$, df = 3) was substantially less than the $\chi^2$ for the
FIG. 7. Limb-dependent movement-related activity in MC. Conventions are the same as in Fig. 4, except that the neural data are aligned with movement onset. Heavy dots: TS onsets. Under both rotation conditions, this neuron showed early movement-related activity that was directionally tuned. Beginning before movement onset, the phasic discharge was maximal with rightward limb movements and only slightly less prominent with backward movements. The response was independent of target location.

comparable comparison across all epochs (Table 4, row c), because of the fact that the latter comparison also accounted for variance across nonadjacent epochs. This last point was demonstrated by combining the corresponding frequencies of the first two epochs (IS and delay), and those of the last two epochs (RT and MT), and comparing the resulting frequencies across the two composite epochs. When the $\chi^2$ resulting from this comparison (Table 4, row g; $\chi^2 = 51.03$, df = 1, $P = 9.10 \times 10^{-13}$) was added to those obtained from the independent comparisons made across the first and last two epochs (Table 4, rows d and f, respectively), the sum of $\chi^2$ values ($\chi^2 = 73.16$, df = 3) approximated that of the $\chi^2$ for the comparable comparison across all epochs (Table 4, row c: $\chi^2 = 76.28$, df = 3). The small residual difference is attributable to slight, but unavoidable, algebraic differences between the overall and partitioned analyses (Snedecor and Cochran 1989).

Locations of neurons with task-related activity

The surface penetration sites of microelectrode tracks that contributed to the final data base are indicated in Fig. 13. All of these tracks were located within zones of proximal arm representation in MC, as evidenced by contralateral shoulder and/or elbow movements evoked by local microstimulation at currents of $\pm 35 \mu$A.

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

DISCUSSION

The primary purpose of this study was to determine whether neurons in MC participate in sensory and/or associative (context-dependent) processing of spatial information relevant to visually guided reaching movements. We found that substantial proportions of MC neurons did show behavior-correlated discharge, termed target dependent, that
depended on the visuospatial target of the monkey’s instructed reach, irrespective of the limb trajectory that was used to acquire the target. There were also substantial proportions of neurons with limb-dependent activity, discharging selectively in relation to the direction of limb movement, irrespective of target location. The relative frequencies of target-dependent versus limb-dependent activity varied considerably across the various task epochs. There was more target-dependent activity in the early stages of the task, before the TS, whereas limb-dependent activity was predominant during later stages, during the generation of targeted reaching movements.

**Target-dependent activity**

Although the directional tuning of target-dependent activity was constant with respect to target location and independent of limb trajectory, thereby indicating that it could not be related to purely motor processing, we cannot be certain whether activity of this type was preferentially related to the sensory properties or the associative features of the visual IS. Because the IS and the instructed target of movement were one and the same, target-dependent activity could have represented either sensory processing that reflected the physical location of the visual IS or associative processing that reflected the instructed target of limb movement.

There have been two prior studies of MC neuronal activity in monkeys, and one in cats, in which the spatial target of movement was dissociated from the trajectory of the limb movement itself. Hocherman and Wise (1991) sampled task-related activity from MC neurons in monkeys that had been taught to reach to the same target locations (endpoints) along three different trajectories and to reach to three different targets along trajectories that had the same curvature (although the trajectories themselves were not identical). In that study, the visuospatial IS covaried with limb trajectory. A minority of MC neurons (8–13%) did show either stimulus-, set-, or movement-related activity whose directionality depended strictly on the target/goal of the movement, independent of limb trajectory. In an earlier study from our laboratory, task-related activity was recorded from MC neurons in monkeys that were trained to perform a one-dimensional
FIG. 9. Target-dependent set-related activity in combination with 2 early movement-related responses, the latter of which was limb dependent. Conventions are the same as in Fig. 6. Under both rotation conditions, this MC neuron showed tonic set-related activity (during the postinstruction interval, before trigger onset) that covaried with the location of the target independent of the direction of limb movement, being maximal for bottom target trials and absent on left target trials. Accompanying the set-related activity was an early and very brief movement-related response that was also target dependent, with the same directionality as the set-related activity. A 2nd movement-related response was also seen: it began after the 1st component but before the onset of limb-movement. This 2nd movement-related response was limb dependent in that it was characterized by a large, phasic discharge that was selective for trials that required a leftward limb movement, independent of target location.

step-tracking task in which limb trajectory was dissociated from target location while target and visual IS covaried (Alexander and Crutcher 1990b). Substantial proportions (22–40%) of the directional movement- and set-related activity were found to be target dependent. Similar results were obtained by Martin and Ghez (1985), who recorded task-related activity from the MC of cats.

There have also been two studies in monkeys in which MC neurons were tested in tasks that dissociated the spatial sensory properties of a visual IS from its associative significance, that is, the location of the instructed target of movement. Lurito et al. (1991) dissociated the location of a visual IS from the spatial target (i.e., goal) of an instructed reach while the target and the reaching trajectory were allowed to covary. They concluded that, in general, task-related neuronal activity in MC could not be consistently classified as depending either on IS location or on the trajectory of the instructed reach. They did not indicate how much of the observed neuronal activity may have covaried exclusively either with IS location or with the target (and trajectory) of the instructed limb movement (Lurito et al. 1991). However, a population analysis showed that both IS location and the instructed target (and trajectory) of limb movement were reflected in the net activity of the entire sample of task-related neurons (Lurito et al. 1991).

Riehle et al. (1994a) dissociated the location of a visual IS
from the spatial target of a one-dimensional wrist movement while the target and the direction of limb movement were allowed to covary. They found that a small proportion of MC neurons (7%, 20 of 277) showed RT activity that covaried exclusively with the location of the visual IS, independent of the direction of wrist movement. Those results would suggest that at least some of the target-dependent activity we observed could have represented true sensory processing, being dependent on the physical location of the visual IS independent of the instructed target of movement. The remainder would presumably have been dependent on the location of the instructed target, irrespective of the physical location of the visual IS.

There are several alternative interpretations for the target-dependent activity that should also be considered. Nondirectional factors such as arousal and motivation can be excluded because of the strongly directional properties of the target-dependent activity. A possibility that must be considered, however, is that some of these responses might have been related to covert motor activity that was not controlled or detected in the course of our experiments. Chronic EMG recordings from task-related muscles revealed directional activations that were confined to the movement period. There were no directional activations during the pre- or postinstruction periods, during which most of the muscles were silent. The movement-related EMG activations covaried with the direction of limb movement, irrespective of target location. These observations suggest that target-dependent responses of MC neurons cannot be accounted for by any simple relations to proximal forelimb muscle activity. However, we cannot exclude the possibility

**FIG. 10.** Target-dependent set- and movement-related activity. Conventions are the same as in Fig. 6. Under both rotation conditions, this MC neuron showed tonic set-related activity and phasic early movement-related activity only on trials in which either the top or left target was specified by the visual IS. There was sustained suppression of neural activity throughout the postinstruction and movement intervals on trials in which either the right or bottom target was specified. Although the movement-related activity was so early and so brief that it might have been construed as a sensory response to the visual TS, it is important to note that the TS itself contained no directional information.
that other muscles that were not included in our samples might have shown task-related activations that, like the target-dependent neural responses, may have covaried with target location rather than limb trajectory.

Another possibility is that some of the target-dependent responses might have been related to spatial attention or spatial memory, or to the preparation or execution of eye movements. Eye position recordings showed that during the postinstruction (delay) epoch the eyes would tend to remain fixated on the central target; occasional breaks in fixation during this period were associated with small saccades made in random directions. Immediately after the TS, the subject would make a saccade to the appropriate peripheral target. Because the direction of the post-TS saccade covaried with target location, it is possible that some of the target-dependent set- and/or movement-related activity may have been related to these target-directed eye movements, or to associated processes such as spatial attention. To our knowledge, there is no independent evidence that would implicate MC in oculomotor or attentional processes. On the other hand, there is evidence that neuronal activity in certain premotor areas with direct or indirect connections to MC may reflect attentional processes (Boussaoud and Wise 1993; diPellegrino and Wise 1993a,b) or high-level oculomotor functions (Boussaoud 1995; Boussaoud et al. 1993).

*Stimulus-related activity*

The overall frequency of directional stimulus-related activity observed in this study (24%) was somewhat surprising, be-
cause MC is traditionally considered to be relatively isolated from visuospatial processing areas. However, neuronal activity triggered by visual stimuli has been reported previously in MC in several studies (Kwan et al. 1981, 1985; Lamarrre et al. 1983; Riehle 1991; Wannier et al. 1989), and in the study by Hocherman and Wise (1991), the majority of such responses showed directional dependence on the visual target of the instructed motor response. In the present study, nearly all of the stimulus-related activity that was directionally classifiable reflected the spatial location of the visual IS and not the direction of the instructed limb movement.

MC does have indirect sources of visual inputs that might account for the target-dependent activity observed in this study, stimulus related or otherwise. For example, MC shares reciprocal connections with the dorsal premotor area (Barbas and Pandya 1987; He et al. 1993; Kurata 1991; Matsumura and Kubota 1979; Tokuno and Tanji 1993), which receives inputs from two posterior parietal areas that have been implicated in visuospatial processing, namely the medial intraparietal area and area 7m (Cavada and Goldman-Rakic 1989; Chavis and Pandya 1976; Johnson et al. 1996; Kurata 1991; Petrides and Pandya 1984; Tokuno and Tanji 1993). MC also shares reciprocal connections with the supplementary motor area, which in turn is interconnected with the presupplementary motor area (He et al. 1995; Luppino et al. 1993; Matsumaka et al. 1992; Tokuno and Tanji 1993). The presupplementary motor area receives substantial projections from posterior parietal area 7a (Andersen et al. 1990; Cavada and Goldman-Rakic 1989; Colby and Duhamel 1991; Luppino et al. 1993; Petrides and Pandya 1984; Vogt and Pandya 1987), which has been strongly associated with various visuospatial processes, including spatial attention (Mountcastle et al. 1981; Steinmetz and Constantinidis 1995; Steinmetz et al. 1994).

**Limb-dependent activity**

Because limb-dependent activity covaried with the direction of limb movement, and did not covary with target location, we consider such activity to be strictly motor, rather than context-dependent or sensory, according to the operational definitions discussed earlier. However, motor processing may itself be functionally subdivided in different ways, and even for the simplest of goal-directed limb movements it is possible to differentiate several levels of motor processing by dissociating the behavioral variables associated with each level (Saltzman 1979). A number of studies have included behavioral dissociations that demonstrated selective activation of some MC neurons in relation to discrete subsets of these motor variables, such as hand trajectory, joint kinematics, and limb kinetics (Crutcher and Alexander 1990; Georgopoulos et al. 1992; Kalaska et al. 1989; Riehle and Requin 1995; Scott and Kalaska 1995, 1997; Thach 1978; Werner et al. 1991). Because we did not include such dissociations in the present study, we can only assert that the limb-dependent responses covaried with limb trajectory, and may have been related to any of the multiple motor variables that covaried with limb trajectory.

**Complex activity**

Neuronal responses that we classified as complex were directional, but did not fulfill the criteria for either target dependence or limb dependence, because of complex interactions between directionality and rotation condition. The large majority (90%) of complex responses were classified as complex-I or intermediate (Fig. 11, Tables 2 and 3), because they showed significant main effects of both target and limb directions. This type of directional activity could have represented either target- or limb-dependent activity in which there was a difference in the PD across the two rotation conditions. Alternatively, this same disparity in tuning across rotation conditions might be viewed as representing directional information in a form that was simply intermediate between the categorical extremes of target- versus limb-dependent activity, or as representing context-specific information.

### TABLE 4. Task-related activity in MC: frequency analysis of directionally classifiable activity across epochs

<table>
<thead>
<tr>
<th>Activity</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Overall: T/L/C across all epochs</td>
<td>78.01</td>
<td>6</td>
<td>$9.21 \times 10^{-15}$</td>
</tr>
<tr>
<td>b. L/C across all epochs</td>
<td>2.70</td>
<td>3</td>
<td>0.44 (NS)</td>
</tr>
<tr>
<td>c. T(L+C) across all epochs</td>
<td>76.28</td>
<td>3</td>
<td>$2.22 \times 10^{-16}$</td>
</tr>
<tr>
<td>Totals: (compare with a)</td>
<td>[78.98]</td>
<td>[6]</td>
<td></td>
</tr>
<tr>
<td>d. $T(L+C)<em>{IS} &gt; T(L+C)</em>{IS_d}$</td>
<td>14.95</td>
<td>1</td>
<td>$1.10 \times 10^{-4}$</td>
</tr>
<tr>
<td>e. $T(L+C)<em>{IS_d} &gt; T(L+C)</em>{MT}$</td>
<td>8.76</td>
<td>1</td>
<td>$3.08 \times 10^{-3}$</td>
</tr>
<tr>
<td>f. $T(L+C)<em>{IS} &gt; T(L+C)</em>{MT}$</td>
<td>4.48</td>
<td>1</td>
<td>$3.43 \times 10^{-2}$</td>
</tr>
<tr>
<td>Totals: (compare with c)</td>
<td>[28.19]</td>
<td>[3]</td>
<td></td>
</tr>
<tr>
<td>(d.) $T(L+C)<em>{IS} &gt; T(L+C)</em>{IS_d}$</td>
<td>14.95</td>
<td>1</td>
<td>$1.10 \times 10^{-4}$</td>
</tr>
<tr>
<td>(f.) $T(L+C)<em>{MT} &gt; T(L+C)</em>{IS}$</td>
<td>4.48</td>
<td>1</td>
<td>$3.43 \times 10^{-2}$</td>
</tr>
<tr>
<td>g. $T(L+C)<em>{IS_d} &gt; T(L+C)</em>{MT}$</td>
<td>51.03</td>
<td>1</td>
<td>$9.10 \times 10^{-13}$</td>
</tr>
<tr>
<td>Totals: (compare with c)</td>
<td>[73.16]</td>
<td>[3]</td>
<td></td>
</tr>
</tbody>
</table>

C. instances of complex activity; del. activity during delay epoch; df, degrees of freedom; IS, activity occurring during IS epoch; L, instances of limb-dependent activity; MT, activity during MT epoch; NS, not statistically significant; RT, activity during RT epoch; T, instances of target-dependent activity; NS, not significant.
FIG. 13. Surface diagrams of the MC region explored in each monkey. Center of each circle marks the penetration site for each microelectrode track that contributed task-related responses to the final data base. Area of each circle is proportional to the number of neurons that contributed to the final data base along that track. The smallest circles represent 1 neuron per track. In monkey JA, the largest circle represents 7 neurons for that track. In monkey KO, the largest circles represent 8 neurons per track. The X- and Y-axes of each map (with scales in mm) correspond to the axes of the microdrive stage. AS, arcuate sulcus; CS, central sulcus; SPS, superior precentral sulcus.

... the rotation condition itself. Similar activity has been observed in MC in two studies in which the spatial target of an instructed limb movement was dissociated from the spatial location of a visual IS (Lurito et al. 1991; Riehle et al. 1994a).

**Evidence for a spatial sensory-to-motor transformation**

The substantial amount of target-dependent activity observed in this study, especially during the early phases of the instructed delay tasks, indicates that MC is not limited to purely motor processing. Instead, it would seem that at least some MC neurons do participate in the processing of sensory and/or context-dependent spatial information that is relevant to the control of visually instructed reaching movements. The behavioral paradigm employed in this study required a sensory-to-motor transformation through which the instructed target location was associated with a limb movement of the appropriate direction. Considering our sample of MC neurons as a whole, over the extended interval between IS delivery and delayed motor response, we observed an initial predominance followed by a gradual decline in the proportion of MC neurons with target-dependent activity and a gradual increase in the proportion of cells with limb-dependent activity. This is consistent with the possibility that MC may participate in mediating the sensory-to-motor transformation required by the visually instructed reaching paradigm.

The suggested temporal flow of information from target-dependent representations to limb-dependent representations was seen not only at the population level, but also in the response profiles of individual MC neurons. Thus, among neurons with combined set- and movement-related responses, our sample contained no examples of cells in which set-related activity that was limb dependent preceded movement-related activity that was target dependent, even though we did encounter all other possible combinations of target- and limb-dependent responses. Similarly, among MC neurons with movement-related responses that contained more than one component, when the first component was found to be limb dependent it was never followed by one that was target dependent. Taken together, these results suggest that MC neurons may play a direct role in transforming spatial sensory information into appropriate motor commands.

Our results are consistent with the hypothesis that target-dependent visuospatial information may be gradually transformed into specific motor commands by the progressive recruitment of MC neurons with appropriate limb-dependent activity. Such a recruitment process would require that both the current target location and the current behavioral context be specified. Complex activity showed task-dependent directionality that varied according to rotation condition; such activity could be construed as reflecting the current behavioral context. We speculate that the aggregate target-specifying features of the cells with target-dependent activity, in
combination with the context-specifying features of the cells with complex activity, would provide sufficient information to permit the selective recruitment of limb-dependent activity appropriate for the current target location and rotation condition.

The progressive sensory-to-motor transformation envisioned here is different from that proposed by Lurito et al. (1991) to explain the apparent rotation of an MC neuronal population vector during a redirected movement task. In that study, there was a 90° offset between visual IS and the spatial target of an instructed reaching movement. The neuronal population vector, representing the sum of activity-weighted directional contributions from all task-related MC neurons (Georgopoulos et al. 1986), was found to rotate during the RT from an initial direction close to that of the visual IS to a final direction approximating that of the hand trajectory (Georgopoulos et al. 1989; Lurito et al. 1991). It was suggested that the observed rotation of the population vector might be accounted for by an orderly recruitment of hand-trajectory-encoding neurons whose PDs spanned the angular distance between IS direction and the instructed direction of hand movement (Lurito et al. 1991). That interpretation was consistent with the original population vector hypothesis (Georgopoulos et al. 1984), according to which MC participates in the sensory-to-motor transformations required for visually guided reaching through the differential recruitment of trajectory-specifying neurons according to their respective PDs.

The population vector hypothesis, and the method for calculating a neuronal population vector, are based on the underlying assumption that most if not all MC neurons are effectively coding for the same motor variable, namely, hand trajectory (Caminiti et al. 1991; Georgopoulos 1995; Georgopoulos et al. 1988, 1989; Lurito et al. 1991). However, that assumption is inconsistent with a growing body of evidence indicating that relatively few MC neurons are likely to encode hand trajectory per se. When appropriate paradigms have been used to dissociate hand trajectory either from extrinsic visuospatial variables (such as IS location or target location), or from variables associated with lower levels of purely motor processing (such as joint kinematics or limb kinetics), substantial proportions of MC neurons have been found to encode one or more of these other variables, rather than hand trajectory (Alexander and Crutcher 1990a,b; Crutcher and Alexander 1990; Lurito et al. 1991; Riehle et al. 1994a,b; Scott and Kalaska 1995, 1997; Thach 1978). The model proposed here takes these other data into account. According to our hypothesis, the functional transformation from extrinsic visuospatial cues into appropriate motor commands involves the successive recruitment of separate populations of MC neurons, with neuronal activity that reflects IS and target location being recruited first, and activity that reflects purely motor variables, such as hand trajectory, being recruited last. Both of these are testable hypotheses, so future experiments should be able to determine whether either of these models provides a reasonable account of how MC may participate in spatial sensory-to-motor transformations.

**Appendix: Computer Simulations of the Effects of Directional Errors on the Classification of Task-Related Neuronal Activity**

**Simulation of error effects on neuronal classification system**

To assess the potential impact of initial trajectory errors on our system of classifying directional neuronal activity, we carried out a computer simulation of how the system would classify two predefined populations of task-related responses, target-dependent and limb-dependent, assuming a constant rate of error trials and variable proportions of unadapted trials. We constructed sample sets of target- and limb-dependent activity profiles (data files), each sample containing 1,000 data files that were coded in precisely the same manner as the real data files. There were four cardinal target directions (designated 1–4), and four cardinal hand/lirm directions (also designated 1–4). For the 0° mapping condition, adapted trials would have target-limb pairings of 1-1, 2-2, 3-3, and 4-4, whereas unadapted trials would have target-limb pairings of 1-2, 2-3, 3-4, and 4-1. For the 90° mapping condition, these two sets of pairings would have been reversed. Error trials, under both rotation conditions, included any of the following pairings: 1-3, 1-4, 2-1, 2-4, 3-1, 3-2, 4-2, and 4-3.

Each simulated data file contained 120 trials, 60 from each rotation condition, with 15 "repetitions" of each of the eight trial types. Each "cell," i.e., data file, was assigned a random PD between 0° and 360°, measured with respect to the extrinsic coordinate system of the targets, and then for each trial a simulated discharge rate was calculated assuming a noisy tuning curve (injected noise ranged randomly between 0% and 25% of the maximum discharge rate) with a cosine function centered on the assigned PD. If the cell was considered truly target-dependent, its PD was the same for both rotated and nonrotated trials. If the cell was considered truly limb-dependent, its PD "rotated" clockwise by 90° on rotated trials. Thus the discharge rate for each trial (d) was calculated according to the following equation

\[ d = 1 + \cos (TD - PD) + \text{noise} \]

where TD was target direction and the noise term was simulated by a uniform random number generator from the range [0, 0.5].

Separate simulations were run for pure samples of truly target-dependent cells and pure samples of truly limb-dependent cells. All data files included 10% random error trials (randomly selected from the 8 possible target-limb pairings indicated above). Variable proportions of unadapted trials were also included in the data file for one of the two rotation conditions (randomly assigned), to simulate the experimental observation that unadapted trials tended to occur only during the second of the two rotation conditions with which each cell was tested. In repeated simulations, the proportion of adapted trials was varied from 10% to 90% in increments of 10%. Each simulation consisted of two parts. First, the sample data files were constructed. Second, each data file in the sample was analyzed with both the target ANOVA and the limb ANOVA as described above, and the results were then categorized according to the criteria summarized in Table 2.

The results of the simulation of directional error effects are presented in Fig. 14. The simulations included a fixed proportion of random error trials (10%). In addition, the trials for one of the two rotation conditions included a variable proportion of unadapted trials (10–90%). Shown on the left are the effects of unadapted trials on the classification of truly target-dependent activity. Target-dependent activity was classified correctly in 100% of cases provided there were ≥40% adapted trials in each data file (for the 2nd rotation condition), and in >80% of cases provided each data
FIG. 14. Performance of the directional classification system on simulated data sets comprising either cells with purely target-dependent activity (left) or purely limb-dependent activity (right). In each case, 9 simulations were carried out, with increasing proportions of adapted trials (from 10% to 90%). Top row: graphs showing the percentage of simulated target-dependent (left) or limb-dependent responses that were correctly classified, as a function of the percentage of adapted trials. Broken vertical lines highlight the boundary of 40% adapted trials, for comparison with Fig. 15. Bottom row: bar graphs showing the detailed composition of the resulting classifications that were associated with different percentages of adapted trials.

file contained as few as ≥30% adapted trials. Nearly all of the misclassifications consisted in categorizing a truly target-dependent response as directionally unclassifiable. Less than 0.1% of the misclassifications involved the designation of a truly target-dependent response as limb-dependent. Similarly, <0.1% of the misclassifications involved the designation of a truly target-dependent response as complex.

Comparable results were obtained for the simulated samples of truly limb-dependent activity. Limb-dependent activity was classified correctly in 100% of cases provided there were ≥50% adapted trials in each data file, in >98% of cases if there were ≥40% adapted trials, and in >80% of cases if there were ≥30% adapted trials. And, as with the simulations of target-dependent activity, nearly all of the misclassifications of truly limb-dependent activity consisted in falsely assigning it to the category of directionally unclassifiable. Less than 0.2% of the misclassifications involved the false designation of a limb-dependent response as target-dependent, and <0.1% of the misclassifications involved the designation of a truly target-dependent response as complex.

Behavioral data: random error trials and unadapted trials

Each monkey made two types of directional errors. One type of error was essentially random, and was unrelated to the rotation condition: in this case, the monkey simply attempted to capture the wrong peripheral target after the TS. The other type of error occurred exclusively during the period of adaptation following a shift in rotation condition: in this case, the initial hand trajectories associated with a given target location showed a systematic bias in the direction appropriate for the previous rotation condition. During the period of adaptation, the rotational bias gradually disappeared so that the monkey was eventually generating hand trajectories that were appropriate for the current rotation condition, with the cursor moving directly toward the correct target location.

We analyzed the frequencies of both types of directional errors for all of the data files that were used in constructing the final data bases of task-related neuronal activity. This included the data files from MC recordings and from dorsal premotor area recordings from both monkeys. The neuronal activity data from the dorsal premotor area are presented in the accompanying paper (Shen and Alexander 1997). The combined behavioral data with respect to directional errors are presented in Fig. 15.

For this analysis, a directional error was considered to occur whenever the initial hand trajectory deviated from the “ideal” hand trajectory by ≥45° or more, the ideal hand trajectory being that which would move the cursor in a straight line from the CF to the correct peripheral target. Trials were considered to be adapted when the initial hand trajectory was within ±45° of the
direction that would have been ideal for the current rotation condition. Trials were considered to be unadapted when the initial hand trajectory was within ±45° of the direction that would have been ideal for the previous rotation condition. Trials in which the initial hand trajectory was not consistent with either the adapted or unadapted classification were considered to be random error trials. (By directional criteria alone, random error trials in the "unadapted" direction were obviously indistinguishable from trials in which the monkey had not yet managed to adapt to the new rotation condition. From the standpoint of the limb ANOVAs that were used to classify directional neuronal activity, errors in the unadapted direction had the same consequences whether they were random or systematic, so we have included both types in the category of unadapted trials.) Figure 15A shows the distribution of data files with various proportions of error trials. For both rotation conditions, a little less than one half of the data files contained no error trials at all, with nearly all of the remaining data files containing from >0% to 10% error trials. Less than 2% of the data files contained from >10% to 20% error trials, and none contained >20% error trials.

Figure 15B shows the distribution of data files with various proportions of adapted trials. For both rotation conditions, most of the data files contained 80–100% adapted trials. As emphasized by the dashed vertical lines in each histogram, only a small proportion of data files contained <40% adapted trials, which has important implications for the reliability of our classification of task-related neuronal activity.

Comparison of behavioral data with simulation results

Comparison of the behavioral data presented in Fig. 15 with the simulation results in Fig. 14 indicates that for all but 4% of the data files (viz., those with <40% adapted trials) directional activity that was either truly target-dependent or truly limb-dependent would have been classified appropriately >98% of the time by the methods we employed. Moreover, nearly all (>99.5%) of the potential miscategorizations predicted by the simulation study would have involved the erroneous designation of truly target-dependent or truly limb-dependent activity as directionally unclassifiable. Thus for all practical purposes it would seem reasonable to conclude that task-related activity that was designated as either target-dependent or limb-dependent in the present study was classified correctly >99.5% of the time. On the other hand, it is quite possible that at least some of the activity that was designated as directionally unclassifiable may have included truly target-dependent or truly limb-dependent responses that were simply miscategorized because of the confounding effects of the monkey’s directional errors.

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