Cortical Networks for Visual Reaching: Physiological and Anatomical Organization of Frontal and Parietal Lobe Arm Regions

The functional and structural properties of the dorsolateral frontal lobe and posterior parietal proximal arm representations were studied in macaque monkeys. Physiological mapping of primary motor (MI), dorsal premotor (PMd), and posterior parietal (area 5) cortices was performed in behaving monkeys trained in an instructed-delay reaching task. The parietofrontal corticocortical connectivities of these same areas were subsequently examined anatomically by means of retrograde tracing techniques.

Signal-, set-, movement-, and position-related directional neuronal activities were distributed nonuniformly within the task-related areas in both frontal and parietal cortices. Within the frontal lobe, moving caudally from PMd to the MI, the activity that signals for the visuo-spatial events leading to target localization decreased, while the activity more directly linked to movement generation increased.

Physiological recordings in the superior parietal lobule revealed a gradient-like distribution of functional properties similar to that observed in the frontal lobe. Signal- and set-related activities were encountered more frequently in the intermediate and ventral part of the medial bank of the intraparietal sulcus (IPS), in area MIP. Movement- and position-related activities were distributed more uniformly within the superior parietal lobule (SPL), in both dorsal area 5 and in MIP.

Frontal and parietal regions sharing similar functional properties were preferentially connected through their association pathways. As a result of this study, area MIP, and possibly areas MDP and 7m as well, emerge as the parietal nodes by which visual information may be relayed to the frontal lobe arm region. These parietal and frontal areas, along with their association connections, represent a potential cortical network for visual reaching. The architecture of this network is ideal for coding reaching as the result of a combination between visual and somatic information.

The act of reaching to visual targets requires the combination of information regarding the locations of external objects with information concerning the configuration of our own body segments with respect to those objects. The present studies were undertaken to investigate, within the cortical areas involved in reaching, the relationships between the representations of sensorimotor information and the anatomical substrates by which this information is combined and transformed in selected cortical areas that are directly involved in the control of movement: the primary motor cortex (MI), the dorsal premotor cortex (PMd), and parts of area 5 in the superior parietal lobule (SPL). The relationship between the physiological properties and the extrinsic cortical connectivity of these cortical regions was studied by combining physiological and anatomical approaches, to obtain data on both the representation and the flow of information to, and through, the cortical frontal and parietal areas involved in the control of reaching.

The proximal arm representations of MI and PMd have been well identified by neurophysiological studies (Georgopoulos et al., 1982; Weinrich and Wise, 1982; Kurata and Tanji, 1986; Schwartz et al., 1988; Caminiti et al., 1991) and many neurons in both regions are active with arm-reaching movements. A difference between these areas has been observed during the performance of instructed-delay tasks. Neurons exist in the proximal arm regions that are preferentially active during the delay period between the "cue" signal and the "go" signal in such tasks (for reviews, see Wise, 1984, 1985). While these types of signal- and set-related activities are present in MI (Tanji and Evarts, 1976; Lucass and Gemba, 1986; Georgopoulos et al., 1988; Alexander and Crutcher, 1990), they have been found to be more prevalent in PMd (Weinrich and Wise, 1982; Weinrich et al., 1984; Godschalk et al., 1985; Richel and Requin, 1989; Richel, 1991). Although these activities cannot be regarded as purely sensory related, their existence, along with other data, have led to the hypothesis that PMd is involved in the sensory guidance of movement (see Wise, 1984, 1985). Studies employing experimentally induced lesions or inactivations of PMd have shown that, while this cortical motor area is not essential for the generation of movement, impairment of PMd seems to affect the processing of the sensory information used to elicit movement (Sasaki and Gemba, 1986; Rea et al., 1987; Passingham, 1988; Kurata and Hoffman, 1994).

Early degeneration and autoradiographic tracing studies revealed anatomical connections between PMd and MI (Pandya and Kuypers, 1969; Pandya and Vignolo, 1971; Künzle, 1978a,b). These studies showed reciprocal connections between the two areas, although the projection from PMd to MI has gained more attention in subsequent retrograde tracing experiments (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984; Ghosh et al., 1987). The anatomical experiments of recent years have revealed that both MI and PMd form part of an extensively interconnected network of frontal motor areas that also include the arcuate premotor area, the supplementary motor area (SMA), and the cingulate motor areas (Muakkassa and Strick, 1979; Mattelli et al., 1984; Primrose and Strick, 1985; Barbas and Pandya, 1987; Dum and Strick, 1991; Tokuno and Tanji, 1993). Furthermore, there is evidence of substantial projections from PMd to the spinal cord segments controlling the proximal arm (He et al., 1993), indicating that MI is not the only output region of the frontal lobe areas involved in reaching. As a result, the intrinsic functional organization of the frontal lobe areas controlling reaching is currently in question.

Knowledge of the extrinsic anatomical connectivities of these areas could provide insight into their functional roles. Previous anatomical studies of PMd and MI have been accomplished either without physiological characterization of the investigated region or, at most, with cortical stimulation mapping in anesthetized animals. The first objective of the present study was to characterize physiologically the MI and PMd reaching-related regions using a directional instructed-delay task and then to correlate the distributions of functional properties with the extrinsic corticocortical connectivity of the region.

The motor and premotor areas receive anatomical projections from the SPL (Chavis and Pandya, 1976; Jones et al., 1978; Strick and Kim, 1978; Petrides and Pandya, 1984; Ghosh et al., 1987; Cavada and Goldman-Rakic, 1989b; Kurata, 1991).
as well as motor areas of the medial frontal lobe (Pandya and Kuypers, 1969; Jones et al., 1978; Künzle, 1978a; Matsumura and Kubota, 1979; Mulkassa and Strick, 1979; Leichtnet, 1986; Ghosh et al., 1987; Dum and Strick, 1991; Morecraft and van Hoesen, 1992). The SPL has traditionally been viewed as being primarily somatosensory and somatomotor in function (Sakata et al., 1973; Mountcastle et al., 1975; Kalaska et al., 1983, 1990; Kalaska, 1988), and the projection from this area to the frontal lobe is a likely pathway by which information concerning arm configuration reaches the motor areas.

An issue that remains open, however, concerns the pathway by which visual information about target location is relayed to the frontal lobe motor centers controlling reaching. Recent anatomical studies have shown that the SPL is corticocortically connected with the newly recognized visual area (area PO) in the parieto-occipital sulcus (POs). The regions of the SPL that have been shown to receive from area PO are the medial intraparietal area (MIP) in the medial bank of the intraparietal sulcus (IPS; Blatt et al., 1990) and the medial wall of the SPL (area 7m; Cavada and Goldman-Rakic, 1989a). In addition to receiving from area PO, areas MIP and 7m, as well as an area at the caudal pole of the SPL (the medial dorsal parietal area, MDP), also project back to area PO (Colby et al., 1988; Cavada and Goldman-Rakic, 1989a).

The physiological properties of areas MIP, MDP, and 7m have not been well characterized. There have been no recording studies of area 7m, whereas one study has reported visual and oculomotor activity in portions of area MDP (Galletti et al., 1991). Area MIP, which loosely corresponds to area PE of Pandya and Seltzer (1982), has not been considered as directly connected to the remainder of Brodmann's area 5 by most authors. Therefore, many physiological studies of area 5 may have included neurons that could now be classified as being located in MIP. Some recent physiological studies of the SPL have noted differences in properties between superficial (area PE, Pandya and Seltzer, 1982) and deep (MIP) regions of the SPL (Crammond and Kalaska, 1989; Burbaud et al., 1991; Colby and Duhamel, 1991). The data from these experiments suggest that activity in PE is more related to somatosensory function, while that in MIP may be more related to motor and visual functions.

As a result, another goal of the present study was to relate the distributions of visuomotor activity in the areas of the frontal lobe involved in reaching to the distribution of functional properties in the parietal regions where the parieto-frontal projections originate.

A preliminary report has appeared (Johnson et al., 1993).

Materials and Methods

Behavioral Apparatus and Task

The behavioral apparatus consisted of nine metal rods oriented toward the animal. The end of each rod was fitted with a translucent push button that could be illuminated by a red/green LED mounted behind the button. Eight of the push buttons were positioned at the vertices of an imaginary cube of 10 cm on a side. The ninth push button was positioned at the center of the cube (8.7 cm from the vertices). The center button of the cube was located in the midsagittal plane at shoulder height and 25 cm from the animal. During recording sessions, the animal sat in a primate chair with the head fixed and free arm-reaching movements. A personal computer recorded sessions, the animal sat in a primate chair with the head (IPS; Blatt et al., 1990) and the medial wall of the SPL (area 7m; Cavada and Goldman-Rakic, 1989a). In addition to receiving from area PO, areas MIP and 7m, as well as an area at the caudal pole of the SPL (the medial dorsal parietal area, MDP), also project back to area PO (Colby et al., 1988; Cavada and Goldman-Rakic, 1989a).

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The monkeys were trained to perform an instructed-delay reaching task. At the beginning of each trial the center button was illuminated red, and the animal was required to press and hold it depressed for a variable period of time (1000-1500 msec) until the LED was extinguished and one of the peripheral targets was illuminated green (injunctional stimulus, IS). The animal was required to maintain pressing the center button for a variable instructed-delay time (IDT; 600-1800 msec) until the green light turned to red. The change in color of the LED served as a "go" stimulus (GS) for the animal to reach toward that push button, and to press it for a specified target-holding time (THT; 150 msec) in order to receive a liquid reward. Predefined reaction (120 and 250 msec, lower and upper limits) and movement times (1000 msec upper limit) were used to control the animal's performance. Different target buttons were then presented in a randomized block design. Randomization of trials, sequencing of targets, and monitoring of the animals' task performance were all performed by computer.

Animals

Experiments in the Frontal Lobe

Two juvenile female Macaca nemestrina monkeys (body weights 4.2 kg and 5.7 kg) were trained in the above task and used for the neurophysiological and retrograde tracing experiments to map activity and inputs of task-related regions of frontal cortex. The first animal (animal MO) performed the task with the right arm, the second (animal TY) with the left arm. For consistency in presentation, all data from animal TY have been mirror transformed.

Experiments in the Parietal Lobe

Two additional juvenile female Macaca nemestrina monkeys (body weights 3.2 and 3.5 kg) were used for parietal recording, to provide functional mapping of the SPL in the same task. The animals were trained to use either arm to perform the task. Recordings were always made in the hemisphere contralateral to the performing arm.

Neuropophysiological Recordings

After each animal was trained in the task, a recording chamber and a head holder were surgically implanted under aseptic conditions. Surgical and extracellular recording procedures were similar to those reported in a previous study (Caminiti et al., 1990a) to which the reader is referred for details.

For each isolated neuron, a qualitative examination of the animal was performed in an effort to determine whether the cell's activity was related to arm movements at the shoulder and/or elbow joints and to determine the presence and quality of passive inputs to the cell from skin, deep tissues, muscles, and joints. Only those cells that were related to proximal arm movements were selected for further study since the task involved primarily the proximal musculature (see Caminiti et al., 1990b).

Relative loci of the recording sites were reconstructed based upon the recording chamber coordinates of the microelectrode penetrations. Recording chamber coordinates were related to the histological tissue and to brain surface features by means of a marking dye (Aldan blue) injected into the cortex at known chamber coordinates (see anatomical Methods below).

Quantitative Physiological Analyses

In each trial, four epochs of interest were identified: (1) the first 300 msec of the instructed-delay time (IDT; DT1); (2) the remainder of the IDT (DT2); (3) the 400 msec epoch extending from 200 msec before movement onset until 200 msec after movement onset (reaction/movement-time; RTMT); (4) the target-holding time; THT. For each cell, the mean neuronal spike frequency during each epoch of each trial was calculated by dividing the number of spikes in an epoch by its duration. As a statistical measure of whether a cell was modulated during a particular epoch, a one-factor ANOVA (Zar, 1984) was performed on these frequencies. The ANOVA tested the null hypothesis that there was no effect of movement direction on mean firing frequency during the given epoch (see Schwartz et al., 1988). Probability levels were approximated from the F statistic (Press et al., 1992).

A quantitative measure was used in this study to examine the distribution of the amount of neuronal activity across the tangential dimension of the cortex. For each neuron n and each epoch i, the amount of directional activity, A_{ni}, was computed as

\[ A_{ni} = \max_{j} (F_{nj}) - \min_{j} (F_{nj}) \]

where \( F_{nj} \) is the mean firing frequency of cell n during epoch i for movements in direction j. \( \max \) and \( \min \) are the functions that take the maximum and minimum over all directions j, respectively. Mean levels of this measure for each penetration were computed by aver-
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In the frontal lobe, the rostrocaudal positions of neurons were determined by relating the recording chamber coordinates of the microelectrode penetrations to the histological tissue and to brain surface features by means of a marking dye (Alcian blue) injected into the cortex at known chamber coordinates. In order to pool data across animals, data were combined using the cytoarchitectonically defined area 4/6 border as an alignment guide.

In the parietal lobe, most penetrations were performed within the cortex forming the rostral (dorsomedial) bank of the intraparietal sulcus (IPS). These penetrations entered the cortex on the crown of the sulcus and traversed the cortex tangentially for varying distances (e.g., see Fig. 9). Therefore, the position of each neuron was determined relative to the location where the first sign of neural activity was recorded (top of the neural activity). The latter was determined, for each penetration, both on entering and exiting the cortex.

For the analysis of neuronal latencies with respect to behavioral events, times of onset of changes in firing frequency were determined using the cumulative sum (cusum) of the peri-event time histogram (PETH). Activities of neurons were aligned to the time of behavioral events and 20 msec bin PETHs were calculated separately for each direction class of each neuron. A significance threshold for the cusum of the PETH was set at three times the standard deviation of the PETH during a control period (Ellaway et al., 1983; Davey et al., 1986). For PETHs aligned to instruction stimulus (IS) or go stimulus (GS) delivery, the control period was defined as the last 1 sec preceding stimulus delivery. For PETHs aligned to movement onset, the control period was defined as the last 1 sec preceding the presentation of the GS. The cusum was calculated by subtracting the mean control period bin height from each bin of the PETH and then forming the cumulative sum of bins. The moment in time when the cusum crossed the significance threshold, departure (p < 0.01) from the prestimulus firing frequency is judged to have occurred. If the subsequent two bins showed changes from the control rate in the same direction (increase or decrease), this departure was taken as the onset of neuronal activity. This latter condition was added as a measure of consistency of the observed change in activity. For each neuron studied, the earliest onset in activity across movement directions was used as the latency for that neuron. Comparison of the distributions of onset times of firing of frontal and parietal neurons were performed using the Kolmogorov-Smirnov test.

Anatomical Tracer Injections

In the two frontal lobe animals, after approximately 30 d of recording, a second surgery was performed under anesthetic conditions. The animal was anesthetized (35-40 mg sodium pentobarbital i.p. per kg of body weight), and the dura within the recording chamber was incised and reflected. A 30 gauge hypodermic needle mounted directly to the microdrive was used to inject the cortex with small quantities of tracer. After the dura was sutured closed and sealed with fibrinogen and Menetrey, 1987). The locations and quantities of injected tracers were removed and postfixied in the same fixative. After infiltration with 30% sucrose, the brains were cut on a freezing microtome. Sections were cut at 40 µm in the coronal plane. Colloidal gold conjugated tracers were visualized in a series of sections by silver intensification (IntenseN, Amersham). Intensified and unintensified sections were mounted, dried, cleared briefly in xylene, and coverslipped. From each animal, a series of sections for cytoarchitectonic analysis was counterstained with thionin (0.025%).

Analyses of Anatomical Data

For each animal, a series of coronal sections at 800 µm intervals from each animal was plotted using a computer-based plotting system. X and Y coordinates of labeled neurons, tracer injection sites, dye injection sites, and other landmarks were measured by transducers mounted on the stage of a epifluorescence/dark-field microscope. The outputs of the transducers were fed to an interactive plotting program. Gold-conjugated, silver-intensified tracers were viewed under dark-field illumination, while the microspheres were viewed using appropriate epifluorescence filter sets.

Flattened cortical maps showing the tangential distribution of labeled neurons in the SPL were generated from plots of individual sections. The computer-based flattening procedure that was used has been described in detail previously (Johnson et al., 1989). Briefly, the computer first generated a series of radial line segments extending from the layer VI/white matter boundary to the cortical surface. Second, a “trend line” was generated by connecting the midpoints of the radial line segments. Third, the tangential locations of the items of interest were projected onto the trend line by using the radial line segments as “guides.” Fourth, within each section, the cell distributions along the mediolateral trend line were binned into 0.1 mm bins. Finally, two-dimensional gray scale maps of cell densities were created by aligning successive sections to fixed anatomical landmarks and interpolating the cell densities at 0.1 mm intervals in the rostrocaudal dimension.

Cytoarchitectonic Classification

Traditionally, the distribution of giant pyramidal cells has been used almost exclusively for the determination of the border between areas 4 and 6 (Sessle and Wiesendanger, 1982; Weinrich and Wise, 1982). To allow comparison with other studies, the area 4/6 border was established at the rostral extent of the distribution of giant pyramidal cells (soma widths > 29 µm). In this study, we refer to MI, PMd, and the MI/PMd border region, loosely defined as the cortex surrounding 4/6 border. The size distributions of counterstained pyramidal cell bodies were compiled from thionin-stained coronal sections. The cell diameter was measured along the minor axis (90 degrees relative to the major axis) of all neurons in layer V using a computer-based video microscopy system. The diameters of all neurons with minor axes greater than 15 µm were plotted as a function of their anterior-posterior position.

Results

Frontal Lobe Reach-Related Activity

Neuronal Data Base

The frontal lobe physiology portions of this article are based on quantitative analyses of the activities of 208 neurons recorded in 93 successful microelectrode penetrations in two
hemispheres of two monkeys (92 neurons in 44 penetrations in monkey MO, 116 neurons in 49 penetrations in monkey TY). Most penetrations were made in the flat, exposed surface of cortex lying rostral to the central sulcus (CS), medial to the spur of the arcuate sulcus (spAS), and lateral to the superior precentral sulcus (SPcS). The locations of microelectrode entry points are shown in Figure 1 for the two animals. In both animals, the recording penetrations spanned a caudal to rostral extent of cortex in which there was a marked decrease in the size of the largest pyramidal cells (Fig. 1).

**Types of Neuronal Activity**

Neurons in the recorded regions displayed activity related to various aspects of the instructed-delay task. In accord with numerous previous studies, certain characteristic types of activity were observed during four temporally distinct epochs of the task: phasic signal-related activity immediately following the presentation of the IS; tonic set-related activity during the interval between IS and GS; movement-related activity that usually began before the initiation of movement; and position-related activity that occurred while the monkey held its hand at the different target positions. The defined time epochs (DT1, DT2, RTMT, THT) used in the study were selected to distinguish these four types of activity. Figure 2A–D shows prototypical examples of these activity types. Signal- and set-related activities were broadly tuned to the direction of the upcoming movement as has been previously reported for movement-related activity (Schwartz et al., 1988; Caminiti et al., 1991). The majority of recorded neurons exhibited more than one of these types of activity. Some neurons were found to display all four of the above-defined activity types.

**Effects of Movement Direction**

Neurons were found to vary their activity during these four epochs in relation to the direction of movement. Such directional modulation was not the only type of task-related activ-
The diagram illustrates neuronal activity over time, aligned with different phases of a behavioral task. Each horizontal line represents a behavioral trial, and vertical ticks represent specific events (IS, GS, movement). The time scale is in milliseconds, and the data is shown for two sets of conditions: signal-related and set-related neurons. The activity patterns vary, with some showing bursts following the presentation of the IS, indicating specific neuronal responses to task-related events.
Figure 3. Plots of directional activity (measure 0) ratios as functions of rostrocaudal position. A, Plots of the logarithm of the ratio of signal- to movement-related activity as a function of cell position relative to the area 4/6 border. Positive values indicate a high signal-related activity relative to movement-related activity. Negative values indicate relatively more movement-related activity. Solid line is a linear regression with slope significantly different from zero ($p < 0.0001$, regression $F_{test} = 0.322$). B, Plot of the logarithm of the ratio of set- to movement-related activity. Conventions as in A. Regression slope is significantly different from zero ($p < 0.0001$, regression $F_{test} = 0.235$).

Figure 4. Percentages of neurons with significant directional modulation ($p < 0.01$, ANOVA) as a function of rostrocaudal location. Percentages were calculated for 2 mm wide rostrocaudal bins relative to the area 4/6 border. A, Signal-related directional modulation. B, Set-related directional modulation. C, Movement-related directional modulation. D, Position-related directional modulation.

ity observed in the regions studied, as some neurons exhibited nondirectional increases or decreases in mean firing rate following stimulus presentation or in association with the generation of movement. The directional design of the task, however, provided a simple method to quantify those changes in activity associated with changes in movement direction. An ANOVA was used to determine significance of the effect of direction on neuronal activity during each behavioral epoch. Neurons with statistically significant directional modulation were considered task related. Because of the existence of nondirectional neuronal modulation, the set of neurons that fulfill this criterion is only a subset of all task-related neurons.

Most neurons were found to be modulated in more than one epoch. While 189 of 208 (90.9%) neurons were directional in at least one epoch, only 45 of these (45/189, 23.8%) neurons were directional in only one single epoch. Neurons exhibiting significant directional modulation in more than one epoch tended to do so in temporally adjacent epochs. Of the 144 neurons with directional modulation in more than one epoch, only 18 (12.5%) exhibited temporally nonadjacent directional activities.

Distributions of Functional Properties across the Frontal Lobe

Distributions of Directional Modulation

The region of significant directional modulation (ANOVA, $p < 0.01$, see Materials and Methods) extends from the CS rostrally for approximately 15 mm. In the mediolateral dimension, this region extends at least from the SPCs, medially, to the level of the spAS, laterally. Given that directionally modulated neurons are only a subset of all task-related neurons, the region identified by this method is a conservative estimate of the entire extent of the task-related region of MI and PMd. A few directional neurons were encountered in penetrations medial to the SPCs and lateral to the spAS. The extent of reach-related activity in these latter two areas is not addressed by the present study.

The distributions of significant directional modulation during each of the four epochs covered wide areas within the studied region. A common feature of these distributions was the degree to which they overlapped in the cortex. Often, usually within the central areas of the reach representation, significant directional modulation for all four epochs was encountered within the same penetration (27/93 = 29.0% of
Figure 5. Micrographs showing cross-sections of injection sites. All images are of coronal sections through the MI/PMd arm representation. Broken lines indicate the layer VI/white matter border. Scale bar in panel D is 1.0 mm. A, Dark-field/fluorescence image of a section through PMd showing four injections (arrowheads) of green fluorescent latex microspheres. B, Dark-field/fluorescence image showing three injections (arrowheads) of red fluorescent latex microspheres in MI. C, Dark-field image of a silver-intensified section through the MI/PMd border region showing three injections (arrowhead) of cholera toxin B subunit conjugated to colloidal gold. D, Bright-field image of a silver-intensified, thionin-stained section showing a single MI/PMd border region injection of WGA-apoHRP conjugated to colloidal gold.
Figure 6. Series of coronal sections through the parietal lobes of two monkeys. A, Data from animal MO. Locations of frontal lobe tracer injections are indicated by colors in the inset (red, RLM; yellow, CTB-Au; green, GLM). Locations of neurons labeled by each of these tracers are indicated by the corresponding colors in the sections. Levels of sections are indicated on the brain figurine. Abbreviations: AS, arcuate sulcus; CS, central sulcus; SPcS, superior precentral sulcus; IPS, intraparietal sulcus; MIP, medial intraparietal area; MDP, medial dorsal parietal area; m, medial; r, rostral. B, Data from animal TY. Yellow indicates WGA-apoHRP-Au injections and labeled neurons. All other conventions as in A.
Retrograde Tracer Injections

A total of 23 tracer injections were made at six sites in the frontal lobes of the two monkeys used for MI and PMd recordings (see Table 1). The tracers used in these experiments were chosen for their limited diffusion at the injection site. Upon histological inspection (Fig. 5), the fluorescent microsphere injection sites exhibited a dense core of injected material surrounded by a zone of extracellular label. Surrounding this zone was an area of dense cellular labeling. The minor axis diameters of the cores ranged from 250 to 800 μm. The injections sites of CTB-Au and WGA-apoHRP-Au possessed a central dense core and a “halo.” Surrounding this halo was a larger area of dense labeling of cell bodies. The diameters of the core regions for CTB-Au and WGA-apoHRP-Au ranged from 300 to 650 μm. The core regions of all of the injections were found to be limited to the gray matter of the cortex. In addition, multiple injections were made at six sites in two other monkeys. Results from these two animals were consistent with the results from the animals studied in the instituted delay task.

In both animals MO and TY there was one type of retrograde tracer injected in each of MI, PMd, and the MI/PMd border region (Table 1, Fig. 1). In animal MO the injection sites were located slightly more laterally and rostrally than in animal TY. In each animal the injection sites were located within the physiologically characterized regions.

Tangential Distributions of Labeled Neurons

Following all injections, labeled cortical neurons were found in the areas immediately surrounding the injection sites, in various frontal motor areas, and in the superior parietal lobule. Many labeled cells were found in the posterior wall of the genu of the arcuate sulcus (AS) and the medial wall of its spur. There was a slight tendency for the cells projecting to the more caudal portions of the proximal arm representation to be located more laterally in the AS. Neurons projecting to the rostral injection sites tended to be located in the lateral wall of the spur of the AS. The cortex in the depth of the superior precentral sulcus was also labeled following most injections. Label in this region was notable for the tendency of the distributions of cells labeled with the different tracers to overlap.

Labeled Neurons in the Parietal Lobe

Within the parietal lobe, labeled neurons were located almost exclusively in the SPL. A few were found in area 7b following the MI and MI/PMd injections. Within the SPL, labeled cells were found in the exposed cortex on the surface of the lobe and extending caudoventrally into the medial wall of the IPS. There were additional sites of labeling at the caudalmost tip of the SPL and within the caudal portions of the SPL cortex located on the medial wall of the hemisphere.

Neurons Projecting to MI

Following the injections in the caudal regions of the frontal lobe reaching-related area, labeled cells were found dorsally in the exposed cortex of the SPL and in the medial crown of the IPS. In animal TY the label extended caudolaterally from the level of the postcentral dimple to the crown of the IPS and ventrally into the dorsalmost 5 mm of the medial wall of the IPS (Figs. 6B, red; 7D). Although the border between areas 2 and 5 is difficult to determine with certainty, it is probable that labeled neurons were located within both of these areas. Labeling in animal MO was limited to a small focus in the medial crown of the IPS (Figs. 6A, red; 7A).

Neurons Projecting to the MI/PMd Border Region

Injections in intermediate locations at the MI/PMd border labeled SPL neurons at intermediate locations between the cells labeled by MI and PMd injections. In animal TY, neurons were located caudolaterally on the exposed surface and extended into the dorsal part of the medial wall of the IPS (Figs. 6B, yellow; 7E). In animal MO, labeled cells occupied much of the medial wall of the IPS as well as a restricted region of the ventral wall of the posterior cingulate sulcus (CIs; Figs. 6A, yellow; 7B). In this latter animal, some label also extended onto the exposed surface of the SPL.

Neurons Projecting to PMd

Injections in the PMd proximal arm area labeled neurons in separate regions of the SPL. In animal TY, labeled neurons were found primarily in the medial wall of the IPS, in area MIP (Figs. 6B, green; 7F). Some additional labeled cells were observed in the most caudal and dorsal extent of the SPL, in area MDP. In animal MO, where the injection site was more rostrally located, the labeling was observed in area MDP and on the medial aspect of the SPL (Figs. 6A, green; 7C). The medial SPL label in this animal extended from the ventral wall of the most caudal portion of the CIs onto the medial surface of the hemisphere (area 7m; Cavada and Goldman-Rakic, 1989a). Rostral injections in the frontal lobe arm region of the two additional animals labeled neurons in the medial wall of the IPS. In one of these additional cases, injections were made in a further rostral region, which corresponds approximately to the cortex lying immediately anterior to the proximal arm representation. These
Figure 7. Flattened reconstructions of a portion of the superior parietal lobule showing densities of labeled neurons on a gray scale. A–C, Data from animal MO. A, Map of density of cells labeled by PMd injection of GLM. B, Map of density of cells labeled by MI/PMd injection of CTB-Au. C, Map of density of cells labeled by RLM injection in M1. D–F, Data from animal TY. D, Map of density of cells labeled by PMd injection of GLM. E, Map of density of cells labeled by MI/PMd injection of WGA-apoHRP-Au. F, Map of density of cells labeled by RLM injection in M1. Figureines at left identify landmarks indicated in the maps (fIPS, fundus of intraparietal sulcus; cIPS, crown of intraparietal sulcus; cIF, crown of interhemispheric fissure). Scale at center shows the rostrocaudal locations of the injection sites relative to the area 4/6 border.
Physiological Trends in the Parietal Lobe

Intrinsic Organization of Frontal and Parietal Cortices • Johnson et al.

The frequency of occurrence of significant directional modulation (ANOVA, \( p < 0.01 \)) during each of the behavioral epochs was not uniform across the dorsoventral extent of the studied region (Fig. 11). Cells with significant signal and set-related modulations were more frequent at the more ventral locations. Significant movement- and position-related modulation were distributed more evenly throughout the dorsoventral extent of the medial wall of the IPS.

Comparison of Neuronal Activity Onset Latencies

In the frontal lobe, the mean onset latencies of neuronal activities with respect to the presentation of the IS, GS, and movement onset were 166 msec, 166 msec, and -69 msec, respectively. In the parietal cortex, respective mean onset latencies were 179 msec, 191 msec, and -37 msec. The distributions of onset times were compared across frontal and parietal lobes (Fig. 12). Onset time distributions with respect to the IS were practically identical (\( p = 0.8266 \), Kolmogorov-Smirnov test; Fig. 12A). Onset times with respect to the GS and with respect to movement onset displayed significant differences between frontal and parietal lobes (\( p = 0.001, p < 0.0001 \), Kolmogorov-Smirnov test). For these epochs, while the times of firing onset of the earliest neurons were similar in the frontal and parietal lobes, a population of neurons with late onset times was present in the parietal lobe (Fig. 12B,C). Neurons in the frontal lobe were more tightly locked temporally to the onset of movement (Fig. 12C). Note that both the PETH aligned to GS and the PETH aligned to movement onset are derived from the same neuronal activity during the reaction time. Thus, these two measures provide two complementary views of the same physiological event.

Discussion

The aim of the present study was to combine the techniques of behavioral neurophysiology with those of neuroanatomy to characterize the functional organization of the areas involved in reaching of both frontal and parietal cortices. There are two principal findings of this study. First, while characteristic activity types were observed in both frontal and parietal cortices, these different types were generally recorded in overlapping cortical regions and often from the same individual neuron. Second, the regions of SPL projecting into the frontal lobe functional gradient contain functional trends similar to those observed in the frontal cortex, suggesting that gradients of inputs from the SPL underlies the functional gradients observed in the frontal lobe. Interestingly, similar trends have been observed in other studies (Alexander and Crutcher, 1990; Matsuzaka et al., 1992) of SMA.

These results will be discussed in relation to the functional differentiation of motor cortical areas, to the information flow of the task was quantified for the studied population of neurons by using the same measure of activity used in the frontal cortex. There is a relative lack of signal- and set-related directional activity in the more dorsal regions of the medial wall of the IPS. The distributions of movement- and position-related directional activity show a converse trend: there is a relative lack of these activity types in the deeper, more ventral regions.

As in the frontal cortex, the relative activation of neurons was analyzed by plotting the ratios of those types of directional activity coexisting within the same neuron as a function of the tangential location of each neuron studied (Fig. 10). The results show significant (\( p < 0.0005 \), regression test) trends for the directional activity during the earlier epochs of the task to increase relatively as one moves ventrally through the cortex toward area MIP.

Distribution of Directional Neurons

In the frontal lobe, the mean onset latencies of neuronal activities with respect to the presentation of the IS, GS, and movement onset were 166 msec, 166 msec, and -69 msec, respectively. In the parietal cortex, respective mean onset latencies were 179 msec, 191 msec, and -37 msec. The distributions of onset times were compared across frontal and parietal lobes (Fig. 12). Onset time distributions with respect to the IS were practically identical (\( p = 0.8266 \), Kolmogorov-Smirnov test; Fig. 12A). Onset times with respect to the GS and with respect to movement onset displayed significant differences between frontal and parietal lobes (\( p = 0.001, p < 0.0001 \), Kolmogorov-Smirnov test). For these epochs, while the times of firing onset of the earliest neurons were similar in the frontal and parietal lobes, a population of neurons with late onset times was present in the parietal lobe (Fig. 12B,C). Neurons in the frontal lobe were more tightly locked temporally to the onset of movement (Fig. 12C). Note that both the PETH aligned to GS and the PETH aligned to movement onset are derived from the same neuronal activity during the reaction time. Thus, these two measures provide two complementary views of the same physiological event.

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These results will be discussed in relation to the functional differentiation of motor cortical areas, to the information flow

![Figure 8. Brain figure displaying locations of successful microelectrode penetrations in the superior parietal lobule of four hemispheres of two animals. Insets are enlargements of the region outlined in the brain figure. Dots are entry points of microelectrode penetrations. IPS and CS indicate intraparietal and central sulci, respectively. PCD indicates postcentral sulcus.](https://example.com/brain-figure.jpg)
Figure 9. Example of a typical microelectrode penetration within the rostral bank of the IPS showing the different activity types (A–E) encountered by recording cell activity at different cortical tangential locations within the sulcus. Five replications of neuronal activity were collected for each movement direction (11–18). Rasters in A–D are aligned to movement onset, in E to presentation of the IS. Sections at the lower left display the microelectrode tracks of the same penetration as seen in the histological material.
between them, and to the possible parietofrontal mechanisms involved in the composition of motor commands for reaching. In addition, combined with other results available in the literature, they assign to the superior parietal lobule a novel role as intermediate link in the corticocortical connections for visual reaching.

**Differentiation of Motor Cortical Areas**

The results of the present study are in agreement with previous studies in indicating different amounts of signal-, set-, and movement-related activities in MI and PMd. Our data, however, do not support the existence of a sharp functional boundary between MI and PMd under the behavioral conditions imposed. While some studies have reported set-related activity primarily confined to PMd (Weinrich and Wise, 1982; Weinrich et al., 1984), we have found wide distributions of set-related activity that extend caudally into MI. The existence of set-related activity in MI has been reported previously (Tanji and Evarts, 1976; Lecas et al., 1986; Georgopoulos et al., 1989; Riehle and Requin, 1989; Alexander and Crutcher, 1990). In addition, movement-related activity was found to extend rostrally into PMd, overlapping the distributions of set- and signal-related activity.

There has been a long-running debate over the existence and definitions of the "premotor" cortex (for reviews, see Wise, 1984, 1985). Considerable recent evidence has been accumulated to support the existence of a premotor cortex and, in fact, the existence of multiple premotor cortices (see He et al., 1993). Although our data do not indicate a clear-cut functional border between MI and PMd, they confirm the existence of anatomical and physiological differences between the rostralmost and caudalmost portions of the frontal lobe proximal arm representation investigated.

**Physiological Trends in the Frontal Lobe**

To measure the degree of relationship between neuronal activity and task performance we quantified the incidence of significant directional modulation for each of the task epochs. Our results show the same general trends observed in previous studies (Weinrich and Wise, 1982; Weinrich et al., 1984). The data of the present study, however, indicate more gradual changes in the incidences of the signal- and set-related modulation than was reported in those studies. Our data agrees with studies that have shown a consistent amount of delay time modulation in MI (Tanji and Evarts, 1976; Lecas et al., 1986; Georgopoulos et al., 1989).
The physiological data of the present study confirm the existence of a gradual functional trend within the proximal arm representation of the dorsolateral frontal lobe. These trends were not obvious in terms of the absolute firing frequency of neurons. However, they were evident in relative measures of directional activity and in terms of the incidence of significant modulation corresponding to behavioral parameters of the task (directional ANOVA).

**Anatomofunctional Trends in the SPL**

The gradient of connectivity from sources in the SPL suggests that these anatomical pathways may be anatomical substrates of the observed functional trends in MI and PMd. If this is the case, parallel functional trends could be expected in these other cortical areas. So far, physiological studies had provided only limited data on the distribution of functional properties within the regions of the SPL labeled in this study. The results of the present study show that functional trends in the distribution of activity types exist also in the parietal lobe. In the cortex of the medial bank of the intraparietal sulcus, while neurons displaying significant movement- and position-related activity are distributed throughout the tangential extent of area 5 and MIP, neurons rich in signal and set-related activity predominates in MIP. We should stress that our studies shows that MIP projects preferentially to the more rostral portions of the MI and PMd arm region, those frontal regions that are rich in signal- and set-related neurons. Thus, within the cortical distributed system controlling reaching, regions of different cortical areas displaying the same functional properties tend to be preferentially connected through association corticocortical fibers.

We know of no physiological studies of MDP or 7m attempting to characterize these areas with respect to visuomotor control. Galletti et al. (1991, 1993) recorded visual and oculomotor activity in a region that they considered partially overlapping with area MDP. Within area MIP, a gradient of physiological properties has been reported. Colby and Duhamel (1991) found that, as they moved their recording electrode down through the medial wall of the posterior portion of the IPS, they successively passed through regions with differing activity types. Dorsally, neurons respond to passive somatosensory stimulation. Deep within the sulcus, neurons have purely visual driving. At intermediate depths they found cells that were related to active reaching movements and "bimodal" cells that were driven by combinations of passive somatosensory stimuli, visual stimuli, and active reaching.

**The SPL as a Source of Visually Derived Information**

Anatomical tracing studies have indicated visual area PO (Cowey et al., 1982; Gattass et al., 1985; Colby et al., 1988) to be a
Parietofrontal Network for Reaching to Visual Targets

For the generation of motor commands appropriate for carrying the hand to a visually located target, information concerning both the target location and the current configuration of the arm must be combined. Psychophysical studies have suggested that these types of information are linked within a reference frame that is centered on the shoulder joint (Soechting and Flanders, 1989a,b). Data from neurophysiological experiments have shown that such a combination of inputs can be detected in the activities of populations of neurons within MI (Caminiti et al., 1990a), PMd (Caminiti et al., 1991), and posterior parietal cortex (Ferraina and Bianchi, 1994).

The results of the present study suggest that these different sources of information can be combined within the parietal and frontal network. The frontal lobe motor centers are shown by the data of the present study to receive projections from parietal areas currently thought to be involved in the processing of either somatosensory or visual information, or a combination of both. The existence of SPL neurons with such response properties (Seal and Commenges, 1985; Colby and Duhamel, 1991) indicates that visual and somatosensory inputs are already combined at the parietal level. Projections to MIP from the somatosensory areas in the exposed dorsal portion of area 5 and in area 2 (Pandya and Seltzer, 1982; Pons and Kaas, 1986) and from the more visually related areas MDp and PO (Pandy and Seltzer, 1982; Cavada and Goldman-Rakic, 1989a; Blatt et al., 1990) provide plausible anatomical substrates for this combination of information within the SPL. However, the data of the present study do not support the hypothesis that the parietal lobe is the sole region involved in the combination of these types of information. The distribution of functional properties in the frontal regions and the pattern of corticocortical connectivity suggest that information from throughout the visual to somatosensory continuum is transmitted from the parietal to frontal lobes for the composition of motor commands.

The temporal properties of cell activity relative to the presentation of the instruction-stimulus are very similar in both frontal and parietal populations, displaying virtually identical recruitment curves. This suggests that the recruitment is generated by mechanisms operating in parallel in both cortical regions, mechanisms based on local excitatory connections among assemblies of neurons within each population and by corticocortical connections between the two populations. These last connections, if reciprocal, play a role similar to that of local connections within the parietal and frontal populations, which can therefore be considered as a unitary distrib-

Figure 13. Diagram of connections of the cortical visual areas modified from Colby and Duhamel (1991). Bold lines have been added to indicate the connections revealed in the present study. Note that while areas MIP and 7m receive projections from visual area PO, their involvement in the traditional visual information processing streams is minimal. Areas MDP and 7m are indicated here as a unique area, 7m.
duced assembly. The onset time of cell activity with respect to the go signal has similar shape in both parietal and frontal cortex, but the rise time is significantly faster in the frontal than in the parietal cortex, suggesting that the recruitment time of the parietal cells population depends on an efferent copy of the motor command composed in the frontal cortex.

It is interesting to note that IS and GS are both visual stimuli, with the crucial difference, however, that, within the behavioral context of the task, the first one signals for target location, the second one for movement generation. It is therefore not surprising that the recruitment time of neuronal populations is similar in both cortices with respect to the events leading to target location, while it is faster in the frontal cortex when the events concerning movement generation are considered. This suggests that the use of visually derived information concerning target location for the generation of the appropriate motor command, in other words, the visual to motor transformation, occurs in a parallel fashion in both frontal and parietal cortices, while the decision-making process for movement occurs first in the frontal cortex and then influences the parietal lobe, probably through corollary signals. Finally, it is worth stressing that in the process leading from target location to movement generation, very little time is spent in the relay of the visual information to the precentral motor fields, while most of the time is devoted to the intracortical processing within the frontal and parietal network.

 Portions of this study have focused on the parietal to frontal projection. While the detailed organization of the frontal to superior parietal projection is not known, such a projection is known to exist (Pandya and Kuypers, 1969; Jones et al., 1978; Caminiti et al., 1985; Johnson et al., 1989; Blatt et al., 1990). Communication along this pathway has been proposed as a means to relay and transform movement-related information (Caminiti et al., 1985; Johnson et al., 1989). The functional significance of these fronto-parietal projections, on theoretical grounds, could be expected to be important for shaping the tuning of parietal neurons (Burnod et al., 1992a,b). The temporal lead of frontal over parietal cell activity with respect to those events concerning movement generation is in accord with this view. It has been hypothesized (Mel, 1991) that the projections from posterior parietal cortex back to area PO should result in the activity of PO neurons being modified by arm orientation. The significance of these "motor" to "sensory" projections should not be underestimated.

 The entire MI and PMd proximal arm representation has recently been shown to project to the spinal cord (He et al., 1993). As such, the motor centers of the spinal cord and convergence and divergence within the corticospinal projection could represent additional layers of the network within which visual, somatosensory, and motor information are combined.

Notes
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Appendix

Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>7m</td>
<td>Medial area 7</td>
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<tr>
<td>APA</td>
<td>Arcuate premotor area</td>
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<tr>
<td>AS</td>
<td>Arcuate sulcus</td>
</tr>
<tr>
<td>CTB-Au</td>
<td>Cholera toxin subunit B labeled with colloidal gold</td>
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<tr>
<td>CGL</td>
<td>Cingulate sulcus</td>
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<tr>
<td>CS</td>
<td>Central sulcus</td>
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<tr>
<td>DT1</td>
<td>First 500 msec of instructed-delay time</td>
</tr>
<tr>
<td>DT2</td>
<td>Instructed-delay time, excluding first 300 msec</td>
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<tr>
<td>GLM</td>
<td>Green (fluorescein isothiocyanate)-labeled microspheres</td>
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<tr>
<td>GS</td>
<td>Go stimulus</td>
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<tr>
<td>IDT</td>
<td>Instructed-delay time</td>
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<tr>
<td>IPS</td>
<td>Intraparietal sulcus</td>
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<tr>
<td>IS</td>
<td>Instruction stimulus</td>
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<td>MDP</td>
<td>Medial dorsal parietal area</td>
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<td>MI</td>
<td>Primary motor cortex</td>
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<tr>
<td>MIP</td>
<td>Medial intraparietal area</td>
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<tr>
<td>PETH</td>
<td>Perievent time histogram</td>
</tr>
<tr>
<td>PMd</td>
<td>Dorsal premotor cortex</td>
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<tr>
<td>PO</td>
<td>Parieto-occipital visual area</td>
</tr>
<tr>
<td>POS</td>
<td>Parieto-occipital sulcus</td>
</tr>
<tr>
<td>RLM</td>
<td>Red (rhodamine)-labeled microspheres</td>
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<tr>
<td>RT</td>
<td>Reaction time</td>
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<tr>
<td>RTMT</td>
<td>400 msec time interval centered on movement onset (reaction time/movement time)</td>
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<tr>
<td>SMA</td>
<td>Supplementary motor area</td>
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<tr>
<td>spAS</td>
<td>Spur of the arcuate sulcus</td>
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<tr>
<td>SPL</td>
<td>Superior parietal lobule</td>
</tr>
<tr>
<td>SPCs</td>
<td>Superior precentral sulcus</td>
</tr>
<tr>
<td>THT</td>
<td>Target holding time</td>
</tr>
<tr>
<td>WGA</td>
<td>Inactivated horseradish peroxidase conjugated to wheat germ agglutinin and labeled with colloidal gold</td>
</tr>
</tbody>
</table>

References


Petrides M, Pandya DN (1984) Projections to the frontal cortex from


