Simultaneous Recording of Macaque Premotor and Primary Motor Cortex Neuronal Populations Reveals Different Functional Contributions to Visuomotor Grasp

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1Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom; and 2Dipartimento di Neuroscienze, Sezione di Fisiologia, Università di Parma, Parma, Italy

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Umilta MA, Brochier T, Spinks RL, Lemon RN. Simultaneous recording of macaque premotor and primary motor cortex neuronal populations reveals different functional contributions to visuomotor grasp. J Neurophysiol 98: 488–501, 2007. First published February 28, 2007; doi:10.1152/jn.01094.2006. To understand the relative contributions of primary motor cortex (M1) and area F5 of the ventral premotor cortex (PMv) to visuomotor grasp, we made simultaneous multiple electrode recordings from the hand representations of these two areas in two adult macaque monkeys. The monkeys were trained to fixate, reach out and grasp one of six objects presented in a pseudorandom order. In M1 326 task-related neurons, 104 of which were identified as pyramidal tract neurons, and 138 F5 neurons were analyzed as separate populations. All three populations showed activity that distinguished the six objects grasped by the monkey. These three populations responded in a manner that generalized across different sets of objects. F5 neurons showed object/grasp related tuning earlier than M1 neurons in the visual presentation and pre-movement periods. Also F5 neurons generally showed a greater preference for particular objects/grasps than did M1 neurons. F5 neurons remained tuned to a particular grasp throughout both the premovement and reach-to-grasp phases of the task, whereas M1 neurons showed different selectivity during the different phases. We also found that different types of grasp appear to be represented by different overall levels of activity within the F5-M1 circuit. Altogether these properties are consistent with the notion that F5 grasping-related neurons play a role in translating visual information about the physical properties of an object into the motor commands that are appropriate for grasping, and which are elaborated within M1 for delivery to the appropriate spinal machinery controlling hand and digit muscles.

INTRODUCTION

One of the key features of the human motor system is the highly developed capacity of the hand to grasp and manipulate objects under precise visual control. The skilled use of the hand is fundamental to the technological, social and cultural progress of the human species (Lemon 1993; Tallis 2004; Wood Jones 1920). In recent years, there have been significant advances in our understanding of the circuits involved in transforming visual information about an object in the outside world into motor commands that allow the hand to be shaped for efficient grasp of the object. The huge variation in the shape, size, and texture of the objects with which we must daily interact in a skillful and precise manner demands that this transformation provides a highly specific and selective matching of the object’s properties to the motor commands for grasp and manipulation. Grasp of each object is known to be specified as precise levels of spatiotemporal activity in each of the many muscles involved in moving the hand and digits (Brochier et al. 2004; Santello et al. 2002; Weiss and Flanders 2004).

An important step forward in understanding how the brain controls grasp was the identification of a “visuomotor grasping circuit” by Jeannerod et al. (1995). This model proposed that the representations of visual and other sensory properties of external objects in posterior parietal cortex (Murata et al. 1996, 2000; Taira et al. 1990) were able to influence the ventral premotor area of the frontal lobe (PMv), which has long been known to be important for visual guidance of the hand (Godschalk et al. 1981; Moll and Kuypers 1977; Passingham 1987; Rizzolatti et al. 1988; Weinrich and Wise 1982). The hypothesis was that the type of grasping movement to be performed is selected within a specialized subdivision of the ventral premotor cortex, termed area F5 by Rizzolatti and his colleagues (Matelli et al. 1985; Murata et al. 1997; Raos et al. 2006; Rizzolatti and Lupino 2001). The different roles played by the posterior parietal cortex and by ventral (PMv) and dorsal premotor (PMd) cortices has been recently addressed by Raos et al. (2006) with F5 seen as playing a key role in the visual-to-motor transformation.

How is the resulting neural code transmitted as motor commands to the hand and digit muscles? This question is now the subject of intense scrutiny. Recently much attention has been focused on the final stage of the visuomotor grasping circuit, namely the interactions between area F5 and the hand area of the primary motor cortex (M1). M1 is the major source of descending control of hand and finger muscles, including a major contribution to the cortico-motoneuronal (CM) system, which allows the motor cortex direct access to the motoneurons of these muscles (Dum and Strick 1991, 2005; Maier et al. 2002; Porter and Lemon 1993; Rathelot and Strick 2006). The hand area of M1 receives one of its strongest inputs from the ventral premotor cortex (Dancause et al. 2006a; Godschalk et al. 1984; Matelli et al. 1986; Muakkassa and Strick 1979). A recent quantitative labeling study by Dum and Strick (2005) confirmed the strong reciprocal PMv-M1 interconnections.

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PMv, together with the dorsal division of the premotor cortex (PMd), provides the numerically largest input to the hand representation within M1. These results suggest that PMv, PMd, and M1 form a densely interconnected network for hand control.

Recent electrophysiological studies have suggested that the projections to M1 from area F5 may provide an important pathway for it to influence M1 corticospinal outputs to hand and digit muscles. Thus stimulation of F5 resulted in significant facilitation of M1 evoked corticospinal activity, and of subsequent responses in hand motoneurons (Shimazu et al. 2004) and EMG responses in muscles (Cerri et al. 2003; Prabhu et al. 2005).

Although either permanent or reversible lesions in the M1 hand area result in severe paresis of the hand and loss of fine motor control (Kuypers 1978; Liu and Rouiller 1999; Matsumura et al. 1991), inactivation of the ventral premotor area does not cause paresis but rather an inability to match hand shape to the target object, such that the grasp becomes uncoordinated and clumsy (Fogassi et al. 2001; Moll and Kuypers 1977; Passingham 1987).

To understand the unique functional contribution to grasp of M1 and F5, it is imperative to make a systematic study of the activity of M1 and F5 neurons during the same reach-to-grasp behavior. Here we report a study in which two adult macaque monkeys were trained to reach out and grasp a number of differently shaped objects, selected so as to evoke a wide range of different hand grasps from the monkeys. We then made recordings from neurons located within the hand representations of area F5 and of M1. Many of these recordings were made simultaneously, using separate microdrives to record from each area. One reason for employing this approach was that we wished to look for signs of synaptic interactions between the two areas (Shimazu et al. 2004; Spinks et al. 2005; Tokuno and Nambu 2000). A second reason was that we have previously shown that average muscle activity is consistent across trials and sessions (Brochier et al. 2004), and this prompted us to ask whether such consistency is also seen in both M1 and F5, two of the key cortical areas involved in the control of visuomotor grasp. To identify the specific contributions of each area, we wanted to compare their activity during the same set of trials, thereby ensuring that both the object grasped and the grasp used were identical for both sets of neuronal recordings.

A preliminary report (Umilta et al. 2003) has been published.

**METHODS**

**Behavioral task**

We trained two purpose-bred adult female macaque monkeys (*Macaca mulatta*) to perform grasping movements of differently shaped objects for food rewards. All procedures were carried out in accordance with the UK Home Office regulations. The monkeys (M37, 5.5 kg, and M39, 5.0 kg) were initially trained to perform the task with the right hand. Subsequently, after completion of recording in the left hemisphere, monkeys were trained to perform the task with the left hand, and recordings continued from the right hemisphere (see Table 1). The carousel apparatus used for this study was similar to that used by Murata et al. (1996) and by Raos et al. (2004, 2006) and has been fully described previously (Brochier et al. 2004). It allowed pseudorandom presentation to the monkey of six different objects, each mounted on a spring-loaded shuttle.

The trial sequence is shown in Fig. 1A. The monkey sat in darkness during the intertrial interval (1–2.5 s); it was trained to press simultaneously on two key or homepads (HPs), located near the monkey’s waist, with the left and right hands. After both HPs had been activated by gentle downward pressure and held down for \( \geq 0.2 \) s (period HP), the object was illuminated (Fig. 1A, IL) and a red LED was switched on that was reflected onto the object through a half-mirror. This marked the beginning of the visual presentation (VP) period. After a variable interval (800–1,800 ms), the LED changed from red to green, and the monkey had to release the trained hand (HP release, HPR in Fig. 1A) within 1 s to reach out, grasp, and pull the object under full vision. The immediate premovement period was identified as movement period 1 (Mv1), and the reach, grasp, and early pull of the object as movement periods 2–4 (Mv2–4), respectively. Object displacement (DO, Fig. 1A) required the monkey to move the object into a position window between 4 and 14 mm from the rest position and hold it there for 1 s (period H). To displace the spring-loaded object by this amount required a gentle force of 0.9 (4 mm) to 2.4 N (14 mm), and a tone was given to indicate that the object was correctly positioned. At the end of this hold period, the monkey had to release the object and take a food reward (RW in Fig. 1A) with the other hand. The light was then turned off and the carousel rotated so as to present a new object.

In summary, the task involved four main events: IL, HPR, DO, and RW (Fig. 1A), and 8 intervening periods: HP, VP, Mv1–Mv4, and H1 and H2 (Fig. 1A).

Both monkeys were carefully trained to use a specific grasp for each object, and we used two video cameras to control that these grasp movements were consistent across trials and sessions. We

<table>
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<tr>
<th>TABLE 1. Summary of the database</th>
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<tbody>
<tr>
<td>M37L</td>
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<tr>
<td><strong>List of objects</strong></td>
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<tr>
<td>L-plate 1</td>
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<td>L-ring 2</td>
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<tr>
<td>L-cyl 3</td>
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<td>S-p.grip 4</td>
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<td>S-cone 5</td>
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<td>cube-side 6</td>
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<td><strong>Weeks of recording</strong></td>
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<td>19</td>
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<tr>
<td><strong>Number of sessions</strong></td>
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<td>16</td>
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<tr>
<td><strong>Simultaneous recordings</strong></td>
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<td>2</td>
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<td><strong>Number of units</strong></td>
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<tr>
<td>MI-PTNs  — —         — — — — — —</td>
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<td>MI-UIDs 20 74 68 60 222</td>
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<tr>
<td>F5</td>
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<td><strong>Total</strong></td>
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also used a video camera to monitor the monkey’s eye movements to ensure that it fixated the object correctly. The video monitoring confirmed that in the absence of object fixation during the VP period, the animal failed to initiate the movement within the reaction time limits and the trial had to be restarted. Training took 8 mo in M37 and 10 mo in M39.

**Objects used**

The objects used during the recordings from the four hemispheres investigated are shown in Fig. 1B and listed in Table 1. These objects were described in a previous report (Brochier et al. 2004). We used a different set of six objects during the recordings from each hemisphere. We adopted this approach because one of the main objectives of this study was to determine whether premotor and motor cortex neurons could represent a particular set of six objects and their associated grasps in an unambiguous manner and then to demonstrate that this property was generalized across different sets of objects.

**MRI scan and image analysis**

A structural MRI scan of both monkeys was carried out early on in the study. Monkeys were anesthetized with ketamine and medetomidine (Dormitor, Pfizer). The monkey’s head was placed in a plastic stereotaxic frame with atraumatic eye and ear bars. Small hollow cores, machined into the bars, were filled with vegetable oil for high contrast in MR images. The monkey was then transferred to the scanner and positioned with the head aligned with the scanner coordinates. Scans were performed with a GE Medical Systems Sigma Horizon 1.5 Tesla system, with two 3-in circular receiver coils in a phased array configuration and using spin echo (2D) and gradient echo (3D volume) for data acquisition. Voxel dimensions were ∼0.4 × 0.4 × 0.4 mm. The scan took ∼12 min. Respiration rate, end tidal pCO2, and body temperature were monitored throughout the scan.

Images were first converted to an Analyze-compatible format for work on a PC, and processed through custom-made software (3D Workstation, Medical Graphics, UCL), which allowed perfect re-alignment within the Horsley-Clarke stereotaxic system. The software allowed three-dimensional (3-D) rendering of the calvarium surface, which was then used to prepare a custom-fitted stainless steel headpiece for subsequent implantation. The software also allowed surface rendering of the cortical surface, which was used to guide the accurate placement of recording chambers and plan penetrations in the banks of the arcuate and central sulci (see Fig. 2).

**Surgery**

All surgeries were performed under deep general anesthesia, induced with 10 mg/kg im ketamine and maintained with 2–2.5% isoflurane in 50:50 O2:N2O. Full aseptic procedures were used. At a first surgery, a custom-designed stainless-steel circular headpiece was securely attached to the monkey’s skull (Baker et al. 1999; Lemon 1984). This headpiece was used for head restraint during recording sessions. In a second surgery, we implanted chronic EMG patch electrodes on ≤12 shoulder, arm, hand, and digit muscles (Brockier et al. 2004).

In a final surgery, we implanted a rectangular stainless steel recording chamber (20 × 10 mm) over the inferior limb of the arcuate sulcus (for F5 hand area recordings) and over the middle third of the central sulcus (for M1 hand area recordings) in the same hemisphere. The position of the craniotomy was based on previous MRI estimates, and after the craniotomy had been made, these sulci, visible through the exposed dura, were identified and measured stereotactically. The top of the chamber was ∼5–7 mm above the dura. Between recording sessions, the chamber was sealed with a flat lid that was secured with screws. The lid carried fiducial markers that allowed the exact stereotaxic position of each new penetration to be calculated by triangulation (Baker et al. 1999). In the second monkey (M39), a pair of fine tungsten stimulating electrodes was chronically implanted in the left medullary pyramid for subsequent antidromic identification of pyramidal tract neurons (PTNs) (see Olivier et al. 2001).

After each surgery, the monkeys received a full course of antibiotics (20 mg/kg im oxytetracycline, Terramycin/LA, Pfizer) and analgesic (10 µg/kg im buprenorphine, Vetergesic, Reckitt and Colman).
Recording

CORTICAL NEURONS. After the chamber had been opened and cleaned, two Thomas Recording drives were mounted over it, so that one of them was targeted at area F5 and the other at M1. The stereotaxic position of each drive was calculated by triangulation on the chamber lid (see preceding text), and the tip of the drive was lowered and positioned just above the dura. The tips of the two probes were usually ∼7–8 mm apart. Each drive carried two to six glass-insulated platinum electrodes (diameter, 80 μm) with an interelectrode spacing of 300 μm. After the electrodes had been inserted through the dura into the cortex, the depth of each electrode was independently adjusted to record clearly isolated activity from a single neuron. Both drives were controlled through a single controller, and a networked system allowed several experimenters (usually 2–3) to advance and control the position of particular electrodes (Baker et al. 1999). Before preamplification, the signals from each electrode were filtered to split it into local field potential (LFP, 10–250 Hz) and single-unit activity (1–10 kHz). Sampling rates on the A/D interface were 500 Hz and 25 kHz for LFP and spikes, respectively. Only spike data are analyzed in this paper. Electromyographic (EMG) and spike data were recorded together with key behavioral events, including the timing of HP release, first movement of object and an analog record of DO.

PTNS. Some neurons were identified during the experiment as PTNs by antidromic activation from pyramidal tract electrodes and collision test (Baker et al. 1999); antidromic latencies varied from 0.7 to 3.8 ms (M39L, mean 1.2 ± 0.6 ms; M39R, mean 1.4 ± 0.7 ms) thresholds varied from 50 to 350 μA using a single biphasic current pulse of 0.2 ms duration (M39L, 180 ± 68 μA; M39R, 194 ± 79 μA).

ICMS. At the end of each recording session an isolated stimulator (Neurolog NL800 stimulus isolator, Digitimer, UK) was used to deliver trains of repetitive intracortical microstimulation (ICMS) through each recording electrode (13 pulses at 333 Hz, intensity typically ≤30 μA using electrodes with impedances of >1 MΩ) to characterize the output effects from the site of recording. After the electrodes had been withdrawn, the exposed dura was treated for 5 min with the antimitotic compound 5-flurouracil, to counteract dural scarring (see Spinks et al. 2003), before the chamber was thoroughly washed with sterile saline and then sealed.

Histology

At the end of the experimental period, the monkeys were killed by an overdose of pentobarbitone (50 mg/kg ip, Euthanal; Rhone

FIG. 2. Recording sites. A: surface reconstruction of the brain of M39 from the magnetic resonance imaging (MRI) scan (see METHODS for details). The recording chambers were positioned with respect to identified sulcal landmarks. B: surface location of the electrode penetrations in area F5 (triangles) and M1 (circles) for the right (R) hemisphere in monkeys M37 and M39 and left (L) hemisphere of M39. Filled symbols indicate penetrations in which intracortical microstimulation (ICMS), at intensities ≤30 μA, evoked hand or digit movements; unfilled symbols indicate unresponsive sites. At this intensity many of the F5 sites were unresponsive to ICMS. AS, arcuate sulcus; CS, central sulcus. The dotted lines indicate the extent of the bank of the AS and CS at a depth of ∼3 mm from the surface.
Merieux, Harlow, UK) and perfused through the heart. The cortex and brain stem were photographed and then removed for histological analysis, and the location of the implanted electrode tips within the pyramidal tract was confirmed. Maps of cortical penetrations were constructed by combining the data obtained during each session with postmortem histology.

Analysis

Off-line, single units were discriminated by principle component analysis on spike waveforms and cluster cutting (Eggermont 1990) using custom-written software. Considerable care was taken to ensure that all trigger events were derived from action potentials from one and the same neuron throughout the analysis period. The quality of the discrimination was confirmed by showing that the interspike interval histogram did not contain counts in the first 1–2 ms.

To analyze the task-related modulation of the activity of F5 and MI neurons, each trial was divided into eight time periods (see Fig. 1A). Period 1, termed HP was the period, 200 ms before IL, during which the monkey sat in the dark and depressed the two HPs. Period 2, termed VP was the early visual presentation (VP) period, 400 ms after IL, during which the monkey was still depressing the HPs while looking at the illuminated object. Periods 3–6, termed movement (Mv1–Mv4) were movement-related periods. The duration of these periods was computed by measuring the time between HPR and the onset of DO for each trial (usually between 300 and 500 ms), and by dividing this time into three consecutive periods (Mv2–Mv4). The duration of the Mv1 period, which occurred before movement onset, was arbitrarily set to the same duration as periods Mv2–Mv4 (i.e., 1/3 of the HPR-DO duration). Periods 7 and 8 were the early and late hold periods (H1 and H2). The duration of these periods was set to 1/3 of the time between the onset of the DO and the end of the trial (reward time, RW). H1 and H2 correspond to the first and last third of this time interval, respectively.

Single-neuron analysis

In all three populations of recorded neurons (F5, M1, and MI-PTNs neurons), task-related responses of each single neuron were statistically assessed. An object (6 levels) × period (8 levels) analysis of variance (ANOVA, P < 0.05) on each neuron’s firing rate was performed. All neurons that displayed a significant interaction object × period were further tested with a Newman-Keuls post hoc test to compare the neuron’s activity recorded during HP with the other task-related periods (VP and Mv1–Mv4). All neurons displaying statistically significant differences (P < 0.05) in activity between HP and at least one of the three movement-related periods (Mv2–Mv4) were considered task-related neurons. These strict criteria were used to ensure that the selected neurons were modulated both during the task and for the different objects.

In addition we compared the activity between HP and the VP and premovement periods (Mv1). Each neuron showing a statistically significant difference (P < 0.05) in activity between HP and VP was defined as an “early responsive neuron.”

Population analyses

For each neuron, the activity was averaged within each of the task periods and then across trials for each object. The activity was then normalized for all periods and objects by subtracting the average level of activity in the first HP period for all six objects and by dividing the resulting value by the absolute maximum level of activity observed across all objects and periods. Therefore for a given unit, the normalized activity varied between 0 in the HP period and 1 at the peak period for the grasp evoking the highest discharge rate. After normalization, the net average discharge frequency of each neuron was used for further population analyses, using one entry for each neuron.

A population analysis, in which all task-related recorded neurons were included, was performed taking into account the net average discharge frequency of each neuron averaged across all six tested objects. A population (2: F5, F5 early responsive) × period (8) multivariate analysis of variance was performed (MANOVA, P < 0.01). To compare, at population level, the response of F5 early responsive neurons during VP with the response of the other F5 neurons, a planned comparison (P < 0.01) was performed for task period 2 for these two subpopulations.

The net average discharge frequency of each neuron was further used for the construction of a data set in which, for each neuron, the object that evoked the highest firing rate across all eight periods was identified and was considered the “best” object. The other five objects were then ranked as the “second-best” object, with a lower firing rate with respect to the one of the best object, “worst” object (object evoking the lowest firing rate), and the “third,” “fourth,” and “fifth” objects formed an intermediate set of objects that evoked a firing rate between that of the second-best and worst objects.

To assess whether the responses of the three populations of neurons differed during grasping of the different objects across all periods of the task, the object-based rank order was used for a population (F5—including the F5 early responsive neurons—, M1, M1–PTNs) × object (6 levels) × period (8 levels) MANOVA (P < 0.01). The same analysis was performed on the subpopulations of F5, MI, and MI-PTNs neurons from the sessions in which simultaneous recordings were obtained from F5 and MI (see Table 1). This analysis was also carried out separately for the subpopulations of neurons recorded in the left and right hemispheres of M39.

To assess the differences of response of all recorded neurons of the three populations during the visual period and the premovement period of the task, the minimum net normalized activity for each neuron was subtracted from the maximum net normalized activity in four Periods (HP, VP, Mv1, and Mv2) for all objects. These values gave the degree of differentiation among objects performed by each neuron of the three populations and were used for a further population (F5, M1, M1–PTNs) × period (8 levels) MANOVA (P < 0.01). By means of multiple planned comparisons (P < 0.05), the response of the three populations in periods VP, Mv1, and Mv2 were compared.

The same analysis was separately applied also to the neurons recorded from the two hemispheres of M39. The P values were P < 0.01 for the MANOVA and P ≤ 0.01 for the multiple planned comparisons.

To assess the preference of the recorded neurons for the different grasped objects we calculated the preference index (PI) that computes the difference in response of each neuron to the six different objects

\[
PI = \frac{n - \left( \sum_{i=1}^{n} r_{i} \right)}{n-1}
\]

where \( n \) is the total number of objects, \( r_{i} \) the activity for object \( i \), and \( r_{\text{max}} \) the maximum \( r_{i} \). The index PI, which can range from 0 to 1, was calculated for each neuron of the three populations. A value of 0 indicates an identical response to the six different objects; a value of 1 indicates modulated discharge for only one object. For each neuron, PI was calculated for the period of the task in which the level of activity averaged across all six objects reached its maximum value.

To determine the individual contribution of each population during the different periods of the task, correlation matrices were constructed using the net average discharge frequency of each recorded neuron for all the different objects. For each hemisphere of monkey M39 three correlation matrices were constructed, one for each of the three populations.

To investigate whether the grip used by the monkey to grasp different objects was differently coded by the three populations, the net normalized activity of each of the three populations of neurons recorded from the two hemispheres of monkey M39 were analyzed by relating it to common types of grip used by the monkey. The net
normalized discharge frequency was used for a population (F5, M1, M1-PTNs) × grips (6 levels) × period (8 levels) MANOVA (P < = 0.01) for M39L and M39R population of neurons, respectively.

RESULTS

Database

We recorded a total number of 547 neurons for ≥10 trials per object; 83 did not show a significant interaction object × period or significant differences between the HP period and any of the following task-related periods and were therefore discarded. The results presented here relate to the 464 neurons with significant task-related activity for which a full analysis was possible (see Table 1). The number of trials for which each neuron was recorded ranged from 60 to 500.

These 464 neurons were recorded in 129 recording sessions from four hemispheres of two macaque monkeys (16 and 34 in M37, left and right, respectively; 46 and 33 in M39, left and right, respectively). In total, 326 neurons were recorded from M1, 104 of which were identified by means of antidromic stimulation of the pyramidal tract as PTNs (M39); most of these had short antidromic latencies (71% between 0.7 and 1.5 ms). The remaining 222 were M1 neurons that either did not respond antidromically to PT stimulation (M39) or were untested (M37) and that are referred to as “unidentified” M1 neurons. A total of 138 neurons were recorded from ventral premotor area F5. Many F5 neurons were active during both task performance with the contralateral hand and retrieval of the food reward with the ipsilateral hands.

In 55/129 sessions (43%), successful recordings were made from both M1 and ventral PMv (area F5). In all, 146 M1 neurons and 70 MI-PTNs were recorded in a session in which at least one F5 neuron was also recorded. One hundred and twenty-one F5 neurons were recorded in a session in which at least one MI (or MI-PTN) neuron was also recorded. In 23 sessions, recordings were confined to area F5, and 51 sessions to M1.

Cortical location of recordings

MRI reconstruction of the brain surface was used to position accurately the recording chamber (Fig. 2A). Figure 2B shows the estimated location of the recording sites in three hemispheres (left and right from M39; right hemisphere from M37; only a few neurons were recorded in M37, left). The sulci on these maps matched precisely the MRI-based reconstructions. Penetrations are marked according to whether cells in them were recorded superficially (<3 mm from 1st signs of neural activity) or deeper (>3 mm); most of the latter were encountered in the rostral bank of the central sulcus (M1 hand area) and around the inferior limb of the arcuate sulcus (F5; dotted lines in Fig. 2B). Many of the M1 sites yielded hand or digit movements with ICMS at low or moderate intensities (16.8 ± 6.3, 17.1 ± 6.3, and 16.3 ± 5.8 μA for M37R, M39L, and M39R, respectively). Motor effects were rarely evoked by the stimulation of F5 at the maximal intensity used in the present study (30 μA).

Despite the rather caudal location of some of the premotor cortex penetrations (see M39R reconstruction map), several observations suggest that the recordings were made within the boundaries of the hand representation in F5. In all the tracks made in the premotor cortex, the majority of neurons responded during the grasping movement in a manner selective for different types of grasp (see following text). We were careful not to record from cortical locations in which activity was related to undifferentiated reaching movements toward the target objects. These selection criteria were based on the observation that the transition between the representation of proximal and distal movements broadly coincides with the physical border between area F4 and F5 (Gentilucci et al. 1988; Rizzolatti et al. 1988). One should also stress out that the overall properties of the premotor sample in M39 closely resembled that recorded in M39L (see following text, Figs. 5 and 9), in which penetrations were clustered more rostrally, closer to the inferior limb of the arcuate sulcus (Fig. 2). Overall, the grasp-related activity of our population of F5 neurons is consistent with the functional properties of the F5 canonical neurons described by Rizzolatti and coworkers (Gallese et al. 1996; Rizzolatti et al. 1996). At the end of some sessions, we removed the behavioral task and tested neurons in a more naturalistic setting and occasionally found evidence of mirror neurons properties (Gallese et al. 1996). Finally, a small number of PTNs could be identified among the population of F5 neurons in M39L (1 PTN) and M39R (8 PTNs). This observation fits with the anatomical data showing that the main corticospinal output from the premotor cortex originates from a cortical area located in the inferior limb of the arcuate sulcus just lateral to the spur (Dum and Strick 2005; He et al. 1993).

In summary, although we cannot exclude the possibility that a few penetrations were located at the border between area F4 and F5, the overall properties of our premotor neurons strongly suggests that a large majority of them were recorded from area F5.

Activity during the visuomotor task

It is clear from Fig. 1B that each of the six objects presented to the monkey in a given session was grasped in a different manner, and it is important to note from the outset that most of our analysis did not attempt to dissociate between neuronal activity associated with a particular object as opposed to the grasp that the monkey used to displace it. However, in a second stage of the analysis, we investigated whether the populations of neurons recorded were actually representing particular types of grasp.

Figure 3 shows the activity of three representative neurons recorded from F5, from M1, and from a PTN in M1 during observation and grasp of six differently shaped objects identified by the number on the far left (see Fig. 1B). The histograms of neuronal activity (Fig. 3B) have been aligned at the moment in which the monkey’s hand released the homepad (HPR). These neurons were recorded simultaneously, and activity over the same 10 trials is plotted as rasters in Fig. 3A. The F5 neuron showed a build-up in premovement activity that began after VP (IL) of object 11 (large disk, Fig. 1B) and ~1 s before HPR. This activity increased sharply in the premovement period immediately before HPR for object 11 and continued to discharge vigorously during the reach-to-grasp movement for this same object. Lower levels of premovement and reach-to-grasp activity were seen for both objects 6 and 12 (cube and small plate; Fig. 1B). This variation in premovement activity after presentation of different objects was not seen in either the M1
neuron or the M1-PTN. These neurons showed brisk activity only after HPR and during reach to grasp, which for the M1 neuron was particularly striking for objects 11 (large disk) and 14 (small ring). The M1-PTN neuron also showed clear differences in activity for the different objects grasped; in general its activity was sustained well into the periods in which the monkey displaced and held the object (especially for objects 6, 11, and 14), but it also showed variability in discharge pattern as exemplified by the phasic burst of activity for object 13 (small ring, side grip).

Early responsive neurons in area F5

A large proportion (43%) of F5 neurons was active in the VP and premovement periods (periods 2 and 3). Of particular interest was a subset of F5 neurons that were classified as early responsive. A neuron was considered early responsive when its discharge during the VP period (period 2; Fig. 1A) was significantly different from background activity (HP). An example of an F5 early responsive neuron (M39R) is shown in Fig. 4, A and B, in which activity is aligned with the onset of IL. There was a strong response ∼140 ms after the presentation of objects 3 and 5. To test for this early response, we carried out a post hoc Newman-Keuls, ($P < 0.05$) comparison for each neuron comparing VP period with the background activity in the HP period. This analysis showed that 21 of 138 F5 neurons (15%) had early responsive properties. None of the M1 neurons or M1-PTNs showed such early responsive features.

A population analysis was carried out to look at the relative discharge frequency of these early responsive F5 neurons compared with the remaining F5 task-related neurons (see METHODS). Figure 4C highlights the enhanced activity of the 21 early responsive neurons during VP (period 2). The planned comparison showed that the activity of F5 early responsive neurons during this period was significantly higher ($P < 0.01$, indicated by * in Fig. 4C) than that during the same period for the remaining F5 neurons.

Are populations of F5 and M1 neurons tuned to the VP and grasp of different objects?

A key issue in our study was to ascertain whether the three main populations of neurons (all F5, M1, and PTNs) showed activity that was significantly different for the different objects encountered in the task and whether this was true for each of the different task periods (VP, reach, grasp, displacement, and hold). To address this question, the discharge of each neuron was normalized and rank ordered from best to worst object (see METHODS). For each of the six rank-ordered objects, the mean value ($±$SE) for activity among each population of neurons (F5, M1, M1-PTNs) has been plotted in Fig. 5.

Data presented for all neurons recorded in both monkeys (Fig. 5A) demonstrate that neuronal activity in each of the three
populations clearly distinguished the six different objects presented to and grasped by the monkey. This is indicated by the clear separation between the plots for best, second best, and other objects. The separation is clearly greatest during the reach-to-grasp movement (periods 4–6) but also present during object hold (periods 7 and 8). A characteristic feature of the F5 population is that it showed modulated activity for the different objects/grasps in period 2 (that is, just after object presentation). Modulation during this period was absent for both the M1 or M1-PTN populations. During the premovement phase (period 3) the plots for F5 activity were also more divergent than for M1 or M1-PTNs, indicating a greater range of activity across the different objects and grasps. The results were similar when the comparison was performed on populations of neurons from recording sessions in which simultaneous recordings were obtained from F5 and MI areas (Fig. 5B).

Figure 5, C and D, shows subsets of data recorded from the left (Fig. 5C) and right (Fig. 5D) hemispheres of M39. These have been plotted separately to make the point that the basic pattern is identical despite the fact that the two sets of recordings were made while the monkey grasped a very different set of objects. During the left hemisphere recording from M39, the monkey worked with the objects shown in Fig. 1B: objects 1, 2, 8–10, and 14 (Table 1), whereas during the right hemisphere sessions, objects 6, 7, and 11–14 were used. This makes the important point that in this monkey the distinctive grasp-related activity across the population of neurons in both F5 and M1 generalized across different sets of objects and grasps.

The rank ordered data for the entire population of neurons and for the subpopulation of simultaneously recorded neurons were analyzed using a MANOVA: population (F5, M1, PTNs) × objects (6) × Period (8; P < 0.01). The results of this analysis showed that all main effects and the pair wise and triple interactions among factors were significant. Thus the mean activity in the three populations discriminated between the six objects and their associated grasps: at all times after HPR, activity was rank-ordered according to grasp.

To clarify the role of each population during the early VP and Mv1, the minimum net normalized activity for each neuron was subtracted from the maximum net normalized activity for the entire population of neurons and for the subpopulation of simultaneously recorded neurons. This analysis of the activity across all objects in periods 1–3 for the population of F5 early responsive neurons and F5 nonearly responsive neurons. * denotes a significant difference between the early responsive neurons in period 2 with the other F5 neurons (planned comparison, P < 0.01).

Figure 4. Activity of typical F5 early responsive neuron unit recorded in M37R. Rasters (A) and histograms (B) are aligned with respect to object illumination (IL, black vertical line). The black triangles shown on the rasters represent HPR and DO, respectively. For objects 3 and 5, the neuron showed a clear response shortly after IL. C: population analysis. Comparison of the average activity across all objects in periods 1–3 for the population of F5 early responsive neurons and F5 nonearly responsive neurons. * denotes a significant difference between the early responsive neurons in period 2 with the other F5 neurons (planned comparison, P < 0.01).

Figure 5. Rank-ordered analysis of F5 and M1 neuronal activity. A: average activity across the total population of F5, M1, and M1-PTNs neurons recorded in both monkeys for the 8 predefined periods of the task indicated in Fig. 1. For this analysis, the activity of each neuron for the 6 different objects grasped was rank-ordered by level of activity (see METHODS for details) from “best object” (●), through “2nd best” (○), 3rd (●), 4th (□), 5th (△), and “worst” (□) object. B: similar plots for the population of neurons from sessions in which recordings were obtained simultaneously in F5 and MI (F5, n = 121; M1, n = 146; M1-PTNs, n = 70). C and D: similar plots for neurons recorded in M39 left (L) and right (R) hemispheres, respectively.
Object and grip selectivity in the three populations

To assess the degree of selectivity of the three populations of recorded neurons to the different objects/grasps during all periods of the behavioral task, the PI was calculated (see METHODS). PI is a “tuning” measure indicating how the activity in a given neuron discriminates between the different objects/grasps tested in a given set; a value close to 1 indicates that the neuron is mainly active for only one specific object, and a value close to zero indicates that the neuron is similarly active for all six objects.

Figure 7A shows a wide variation in PI across the neurons making up the different populations. Within the F5 population, 47% of recorded neurons had a high index (0.6–1), compared with just 22.6 and 28.8% for the M1 and M1-PTNs populations, respectively. Figure 7B displays the average value of PI together with the percentage of neurons used to compute this index for each period of the task. Overall the 12% of F5 neurons that were most active before movement onset showed PI values >0.6. The PI remained high for F5 neurons that were active later, during the movement-related periods (periods Mv2–Mv4). In contrast, neurons in the M1 and PTNs populations that were active early in the task showed low selectivity (period Mv1, 8 and 9% of the MI and MI-PTNs populations, respectively), with higher values in the later stages, peaking during the late movement epoch 6 (Mv4). For all three populations, a high value of PI (>0.5) was also observed for neurons that were most active during the holding period of the task (H1 and H2). Because only one F5 neuron and none of the neurons in the MI or MI-PTNs populations were most active during period HP (1) and VP (2), these periods are not represented in Fig. 7B.

Do F5 and M1 neurons show the same object-grasp specific discharge throughout the task?

Close inspection of Fig. 3 shows that the highest discharge of the F5 neuron during any one period of the task was recorded in trials with the same object (11). In contrast, the M1-PTN showed maximal activity in different periods for different objects, with a striking burst of activity just after HPR for object 13 but higher discharge the hold period for objects 6 and 11.

To follow the correlation through the successive periods of the task of the three populations, correlation matrices were constructed with the net normalized activity of each population of neurons recorded from the two hemispheres of M39. The results from the right hemisphere are shown in Fig. 8. The F5 population (Fig. 8A) displayed a stronger and prolonged correlation between premovement (period 3) and the subsequent reach and grasp phases (periods 4 and 5). Later activity in period 5 was less well correlated with activity during the reach-to-grasp movement and hold of the object (period 6 and 7–8). For the M1 population (Fig. 8B), the correlation was low across the whole task; rather, activity within any one task period was correlated only with the periods immediately before and after it. The highest correlation was between periods 5 and 6 (grasp) and between periods 7 and 8 (DO and hold). Similarly, the population of PTNs (Fig. 8C) did not show any clear correlation between premovement activity (period 3) and activity later...
in the task. This population showed prolonged correlation from period 4 onward, and particularly with the later and hold periods (periods 6–8). This analysis reveals that the rank-ordering within F5 was more consistent through the time course of the task compared with M1 and M1-PTNs. Similar correlation matrices were obtained from the F5, MI, and MI-PTNs population of neurons recorded in M39L. The population of neurons from M37 were not used for this analysis because no MI-PTNs were identified in this monkey.

Clustering of neuronal activity by type of grasp used

Although we presented the monkeys with a wide variety of different objects, there were some broad similarities in the type of grip used to grasp them. We carried out an analysis to see if particular types of grasp were better represented within F5 and M1 and whether activity was clustered according to grip type. We analyzed the net normalized activity of each neuronal population recorded from M39 according to six broad categories of grasp used. The grasps investigated in the left hemisphere (M39L) are all illustrated in Fig. 9A: small “side grip” (grasp G1) between the tip of the thumb and the radial side of the index finger; precision grip between index and thumb (G2); large side grip with the hand supinated (G3), with a wider grip aperture than G1; whole hand prehension (of a sphere; G4); insertion of index finger (hook grip) into the small ring (G5); and insertion of all fingers, but not the thumb, into the large ring (G6).

The three populations clearly show clustering of activity by grasp category. Thus both of the finger insertion grips (G5 and G6) were associated with relatively low activity levels throughout the task, whereas the small side grip (G1) and the precision grip (G2) were generally associated with the highest mean discharge rates. Throughout the task, precision grip (G2) was associated with higher rates than the whole hand prehension (G4), and this was particularly striking for M1-PTNs. Generally, the plots for the F5 neurons show greater separation, indicating a greater range of overall discharge rates for different types of grasp.

**FIG. 7.** Preference index. Modulation of the preference index (PI), which measures the degree of selectivity of each neuron across the tested objects in the most active periods of the task. A PI of 0 signifies identical discharge for all six objects, whereas 1 indicates modulated discharge for only 1 object. A: distribution of PI for the F5, MI, and MI-PTN populations. The categories of PI are color coded. Note the larger proportion of F5 neurons with a high PI values (>0.6). B: modulation of PI during the task. The consecutive periods of the task are coded light blue (period 3; Mv1) to dark blue (period 8, H2). For each period, the number at the top of the bin indicates the percentage of neurons used to calculate the PI within each population. Note the high PI of F5 neurons throughout the task and the gradual increase of PI in MI between periods 3 and 6 (Mv1 and Mv4).

**FIG. 8.** Correlation of neuronal activity across the 8 different task periods. The correlation matrices for the 3 populations of F5, MI and MI-PTNs neurons recorded in M39R are shown in A–C, respectively. Each matrix shows the average the level of correlation between each task-related period for M39R computed using the average discharge frequency of each recorded neuron for all the different objects/grasps tested. Levels of correlation are color-coded from negative correlation levels (in green) to low (in yellow) and high correlations (in red).
A similar finding applied to the data recorded for M39R (Fig. 9B) in which a different set of objects was involved, but in which some of the grips were similar to those used for M39L. Thus G1 was again a small side grip of the small ring, and G3 was a large side grip, with the hand semi-supinated. G4 was whole hand grip Va (this time of a large disc); G5 once again insertion of index finger (hook grip); and G6 the insertion of all fingers but not the thumb into a slot cut in the top of a cube. G7 was a small side grip of the small plate. Once again, the two insertion grips (G5, G6) were associated with the lowest overall discharge rates across all three populations, while the small side grips (G1, G7) evoked the highest rates of discharge except for the population of F5 neurons. F5 data again showed the widest spread of overall discharge rates across grips.

A population (F5, M1, PTNs) × grip (6) × period (8) MANOVA showed that the population × grip × period interactions were significant ($P < 0.01$) for both M39L and M39R. The fact that the interaction population × grip × period was significant indicates that the three populations of recorded neurons differ in the way they represent the six different grips across the eight periods of the visually guided grasping task. Figure 9 highlights the early differential activity in F5 neurons for different grips: notice that although the plots for F5 neurons already begin to diverge during the VP period (period 2), those for M1 and M1-PTNs superimpose almost exactly and only begin to diverge after the reach to grasp movement has begun (period 4).

It is important to understand the difference in the rank-ordered plots in Fig. 5 from those shown in Fig. 9. The previous rank-ordered analysis showed that all three populations of neurons could represent different sets of object and grasp in an unambiguous fashion. However, this rank-ordering does not reveal if there was more overall activity for one type of grasp compared with another. If activity was equal for all types of grasp, the datasets should overlap completely, as they do in period 3, compared with the clear separation revealed by the rank-ordering analysis (Fig. 5). The plots in Fig. 9 suggest that some types of grasp (e.g., precision grip) are associated with a higher mean level of activity in all three populations, whereas others (hook grip with the index finger) evoke far lower discharge rates.

**DISCUSSION**

The present study investigated the relative contribution of ventral premotor area F5 and of area M1 in the control and execution of visually guided hand-grasping actions of objects of different shape and size. Our results reveal that F5 neurons show object-grasp-related tuning earlier than M1 neurons and that F5 neurons generally show a greater preference for particular objects and their associated grasp than do M1 neurons and are tuned to that particular grasp throughout both the VP and reach-to-grasp phases of the task.

Several previous studies have documented the specific activation of F5 neurons during visually guided grasp (Godschalk et al. 1981; Murata et al. 1997; Rizzolatti et al. 1988). A recent report described activity of F5 neurons during performance of a task similar to that used here (Raos et al. 2006). All of the neurons tested showed a preference for grasp of an object or a set of objects, and the same preference was maintained when grasping was performed in the dark. In addition to this motor-related discharge, about half of the neurons recorded by Raos et al. (2006) also responded to VP of an object or a set of objects, even when a grasping movement was not required. Generally, the object evoking the strongest activity during VP also evoked optimal activity for grasp of the same object. These authors concluded that the selectivity of both the motor and the visual evoked discharge of the F5 neurons was determined not by the object shape but by the grip posture used to grasp the object.

A number of other studies have emphasized the extensive M1 activity that occurs during performance of grasping tasks (Hepp-Reymond 1998; Lemon 1981; Lemon et al. 1976; Smith et al. 1975), including the demonstration that M1 neurons show remarkably different activity during performance of different types of grip (Lemon et al. 1986; Mason et al. 2002; Morrow and Miller 2003; Muir and Lemon 1983). However, what is so far lacking in the literature on cortical control of grasp is a systematic documentation of neuronal activity in the hand areas of both M1 and F5 during performance of grasp. Our study investigated activity in these two structures while monkeys performed a number of contrasting
grips that were selected so as to exploit the rich repertoire of primate grasp. A significant proportion of the recordings (43%) were obtained simultaneously in M1 and F5, and this allowed us to analyze M1 and F5 activity during the same trials, which is important given the trial-by-trial variability that can occur even in trained subjects (Maier and Hepp-Reymond 1995).

Both F5 and M1 neurons are tuned to grasp, but F5 neurons exhibit object-grasp specificity earlier than M1

Our study confirms that F5 contains neurons the discharge of which is modulated during VP of different objects well before movement onset. The earliest discharge observed was from a subset of F5 neurons classified as early responsive, that is they showed significant differences in firing rate during the VP of objects (period 2) compared with background, and their firing rates during this period varied according to which object the monkey was observing (Fig. 4, A and B). These early responsive neurons made up 15% of the F5 sample. In contrast, the M1 populations studied did not show any differential activation for objects and grasps during the VP period (period 2; see Fig. 5). The activity of F5 early responsive neurons in the grasping task share some of the properties of the visuomotor neurons described by Raos et al. (2006). However, one must be cautious in comparing directly these two types of neurons because our early responsive neurons were not tested in a movement in the dark condition or in a visual fixation task in which no grasping movement is required. Further, the relatively higher percentage of F5 visuomotor neurons (45%) reported by Raos et al. (2006) may reflect the fact that their study focused on recordings in the bank of the arcuate sulcus, where neurons responding to object presentation (so-called canonical neurons) tend to be clustered (Murata et al. 1997; Rizzolatti et al. 2002), compared with the anatomical location of our recordings, which also sampled the convexity region of F5 (Fig. 2).

Most of the remaining, non-early responsive F5 neurons showed build-up of activity in the MV1 (period 3), such as in the example shown for object 11 in Fig. 3. The population of F5 neurons as a whole was able to represent in an unambiguous manner the different set of objects that were presented to the monkey during this period (Fig. 5A). Importantly we have now shown that this modulation in object-related F5 activity occurs earlier than similar changes in either unidentified M1 neurons or in M1-PTNs (see Fig. 5). We demonstrate that this was also true for the large subpopulation of neurons recorded simultaneously (Fig. 5B). Figures 5, C and D, and 6 show that this was also true for different subpopulations of neurons recorded with different sets of objects, suggesting that F5 activity is able to respond in a manner that generalizes across different objects.

F5 neurons show a higher PI for different objects than do M1 neurons

During the VP period, differences in the overall firing rate across the objects (Figs 5 and 6), and the percentage of neurons showing a higher PI for different objects (Fig. 7), were both higher in the F5 population compared with M1 neurons. As shown in Fig. 7A, the percentage of neurons showing the highest PI values (0.6–1) for the different objects was greater in F5 than in M1 during all task periods. The PI for the different periods (Fig. 7B) shows that the object selectivity of M1 and M1-PTN neurons increased gradually between the premovement period 3 (MV1) and the late movement period 6 (MV4). This pattern contrasts with the modulation of PI in the F5 population. The highest values of the PI (0.8–1) in F5 were observed in periods 3 and 4 (MV1 and MV2), which is consistent with the hypothesis that single F5 neurons represent plans for specific types of hand action before they are implemented.

F5 neurons continue to represent the same object-grasp combination in the late VP and early grasp

The marked differentiation across different objects and grasps displayed by F5 neurons during premovement (period 3) carried over into early grasp (periods 4 and 5) for the entire F5 population (Fig. 8). Altogether, these properties are consistent with the notion that F5 grasping-related neurons play a role in translating visual information about an object’s physical properties into the appropriate motor plans to interact with the same object (see Murata et al. 1997; Raos et al. 2006; Rizzolatti et al. 1988).

In contrast it appears that M1 neurons do not show this continued representation of the upcoming grasp but rather show much more complex correlations between activity in premovement/early grasp (periods 3 and 4) and later phases of the task, involving DO and hold (periods 6–8; see Fig. 8). These correlations probably reflect the involvement of these neurons in the execution of the different motor components of the task (Bennett and Lemon 1986; Brochier et al. 2004; Morrow and Miller 2003).

Different types of grasp are represented by different levels of activity within populations of F5 and M1 neurons

The final part of our investigation studied the differential contribution of the three populations to the specification of grasp type. It is known that much of the premovement activity among visuomotor and motor neurons in F5 is related to the upcoming grasp. For example, Raos et al. (2006) demonstrated that the majority of F5 visuomotor neurons (see Figs. 10 and 11 of Raos et al. 2006) showed similar activity when monkeys grasped the object in the dark.

In our experiment, the monkeys always grasped in the light, and we did not attempt to dissociate object- from grasp-related activity. However, Fig. 9 shows that the mean activity across each of three populations varied according to the type of the grasp used by the monkey. The lack of overlap between the different plots actually shows that there were quite different levels of activity in both F5 and M1 for the different types of grip, and this became more and more evident during reach-to-grasp (periods 4–6). Some types of grasp (e.g., precision grip between the tips of the index finger and thumb or grip between the thumb and the side of the index) were accompanied by higher overall activity in these periods, compared with, for example, an index finger insertion or “hook” grip needed to grasp the small ring. During the hold period of the task, there was some convergence of the plots, although sustained maintenance of different grasp postures (period 8) was still reflected in different mean firing rates. In a subsequent paper (unpublished data), we shall argue that these overall differences in activity may reflect encoding of the muscle patterns needed to shape the hand appropriately for grasping a particular object.
either of the M1 populations sampled. Indeed there was a trend in the unidentified M1 neurons for relative suppression of activity during VP (period 2). Note that although the rank-ordered analysis showed that M1 neurons represent objects/grasps differentially in the premovement period 3 (see Fig. 5), there was no overall difference in the net activity across the whole population during this period (Fig. 9).

**F5 and M1 as different components in the visuomotor grasping circuit**

It has been proposed that in area F5 there is a “vocabulary” of elementary motor acts in which each “word” corresponds to a category of motor neurons that represent the goal of the action, and the way in which the action is to be executed, that is the specific type of grasp required to retrieve an object of given size and shape (Raos et al. 2006; Rizzolatti et al. 1988).

There has been considerable recent interest in the different pathways through which representations in F5 might be transformed into motor outputs controlling the spinal machinery that innervates the hand and digit muscles. One obvious possibility is the direct corticospinal projection from PMvs. However, this projection is relatively weak (only 4% of frontal corticospinal projections arise from PMv) (Dum and Strick 1991) and projections to the lower cervical cord are sparse (Dum and Strick 2005; He et al. 1993). In keeping with these findings, electrophysiological experiments show that direct stimulation of the F5 subdivision of PMv with single intracortical stimuli results in little or no detectable corticospinal output and does not evoke any responses in hand or digit muscle motoneurons or muscles (Cerri et al. 2003; Shimazu et al. 2004).

In contrast to its relatively weak corticospinal projection, PMv makes strong cortico-cortical connections with the M1 hand area (Dancase et al. 2006a,b; Dum and Strick 2005; Godschalk et al. 1984; Matelli et al. 1986; Muakkassa and Strick 1979), and indeed PMv provides the largest single corticocortical input to M1 (Dum and Strick 2005). These projections may underlie the marked facilitation of M1 corticospinal output that can be demonstrated by activation of PMv (Cerri et al. 2003; Shimazu et al. 2004). M1 outputs, which constitute almost half the total corticospinal projection from the frontal lobe (Dum and Strick 1991), represent one of the major descending pathways controlling hand and digit movements (Lemon and Griffiths 2005; Porter and Lemon 1993). The strong reciprocal interactions between M1 and F5 may explain the disruption of skilled grasp when PMv is inactivated, by lesion (Rizzolatti et al. 1998), GABAergic blockade (Fogassi et al. 2001), or rTMS in humans (Davare et al. 2006). The latter study showed dramatic changes in the spatial pattern of fingertip placement on the grasped object that was specific to disruption of PMv.

These same F5-M1 corticocortical pathways may therefore also be involved in the transformation between F5 and M1 of information about the performed movement. Previous studies have shown that this information is transformed from an extrinsic reference framework, which defines the position of the object and the hand in space, to an intrinsic framework, based on muscle and joint space which is related to shaping of the hand and digits (Kakei et al. 2001, 2003; Kurata and Hoshi 2002). For example, Kakei et al. (2003) found that although 81% of PMv neurons coded wrist movements in extrinsic coordinates, only 24% of M1 neurons did so compared with 39% of M1 neurons encoding in an intrinsic system.

In keeping with these different lines of evidence, we propose that the F5 representation of object-specific grasp described in the current study is transformed within M1 to recruit motor outputs to the hand that can modify hand shape appropriate for successful grasp and manipulation of the object.

**Conclusions**

These results suggest that the three populations of neurons play different roles at different times. F5 seems to be more involved in the premovement and early movement phases, and this activity is a strong predictor of activity later in the task. In contrast, M1 neurons are involved in all phases of reach, grasp-and-hold task but in a manner that suggests that their contribution varies during different phases of the task. This may reflect the different patterns of activity required from the hand and digit muscles during grasp (Brochier et al. 2004).

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