

Functional Properties of Grasping-Related Neurons in the Ventral Premotor Area F5 of the Macaque Monkey

Vassilis Raos,^{1,3} Maria-Alessandra Umiltá,¹ Akira Murata,^{1,4} Leonardo Fogassi,^{1,2} and Vittorio Gallese¹

¹Dipartimento di Neuroscienze, Sezione di Fisiologia and ²Dipartimento di Psicologia, Università di Parma, Parma, Italy; ³Department of Basic Sciences, Faculty of Medicine, School of Health Sciences, University of Crete, and Institute of Applied and Computational Mathematics, Foundation for Research and Technology Hellas, Heraklion, Crete, Greece; and ⁴Department of Physiology, School of Medicine, Kinki University, Osaka-sayoma, Japan

Submitted 6 May 2005; accepted in final form 23 October 2005

Raos, Vassilis, Maria-Alessandra Umiltá, Akira Murata, Leonardo Fogassi, and Vittorio Gallese. Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. *J Neurophysiol* 95: 709–729, 2006. First published October 26, 2005; doi:10.1152/jn.00463.2005. We investigated the motor and visual properties of F5 grasping neurons, using a controlled paradigm that allows the study of the neuronal discharge during both observation and grasping of many different three-dimensional objects with and without visual guidance. All neurons displayed a preference for grasping of an object or a set of objects. The same preference was maintained when grasping was performed in the dark without visual feedback. In addition to the motor-related discharge, about half of the neurons also responded to the presentation of an object or a set of objects, even when a grasping movement was not required. Often the object evoking the strongest activity during grasping also evoked optimal activity during its visual presentation. Hierarchical cluster analysis indicated that the selectivity of both the motor and the visual discharge of the F5 neurons is determined not by the object shape but by the grip posture used to grasp the object. Because the same paradigm has been used to study the properties of hand-grasping neurons in the dorsal premotor area F2, and in the anterior intraparietal area (AIP), a comparison of the functional properties of grasping-related neurons in the three cortical areas (F5, F2, AIP) is addressed for the first time.

INTRODUCTION

The hand has a very complex anatomical structure. Functionally, movements of the hand require a coordinated interplay of the 39 intrinsic and extrinsic muscles acting on 18 joints. Among all the joints of the hand, of particular importance is the carpometacarpal joint of the thumb. This joint is of a saddle type and its immense significance for the hand function emanates from the extra mobility this joint is endowed with, resulting in the opposition of the thumb to the other fingers (Napier 1955).

The plethora of bones, joints, and muscles of which the hand is constituted gives to this structure amazing biomechanical complexity. From the kinematic perspective, the hand has over 20 degrees of freedom (Soechting and Flanders 1997). Thus the question arises: how does the brain control the hand? Converging data from a variety of experimental approaches, ranging from the study of finger movement kinematics to recording of electromyographic and neural activity and to

modeling, underline the need of simplifying strategies that reduce the number of degrees of freedom and thereby reduce the complexity of the control problem (Arbib et al. 1985; for a review see Schieber and Santello 2004).

A proposal emphasizing the importance of the goal of hand movements was introduced many years ago by Napier (1956) in a study of the anatomy and function of the hand. In one of his more cited articles he states that “this diversity (of the prehensile activities of the hand) is in fact not so much an expression of a multiplicity of movements but of the vast range of purposive actions involving objects of all shapes and sizes that are handled during everyday activity.” According to Napier (1993), there are only two main and two subsidiary prehensile patterns. The main ones are precision grip, in which the object is pinched between the pulpar surface of the finger(s) and that of the thumb, and power grip, in which the object is held in a clamp formed by the partly flexed fingers and the palm. The subsidiary patterns consist in the hook grip, which is achieved by flexing all the fingers, and the scissor grip, in which the object is grasped between the sides of the terminal phalanges of the adjacent index and middle fingers.

Single-neuron recordings carried out using the naturalistic approach showed that the firing of the majority of neurons of area F5, which is located in the posterior bank of the inferior limb of the arcuate sulcus and the cortical convexity immediately adjacent to it (Matelli et al. 1996; Rizzolatti et al. 1998), is correlated with specific goal-related distal motor acts and not with single movements (Rizzolatti et al. 1988). Execution of distal motor acts such as grasping, holding, manipulating, and tearing are very effective in triggering F5 neurons' responses. Interestingly, many hand-grasping neurons also show specificity for the type of prehension (precision, finger, whole hand prehensions) that is performed to grasp an object. 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 either the goal of the action, or the way in which an action is executed, or the temporal segmentation of the action (Rizzolatti and Gentilucci 1988). Besides motor neurons, there are also F5 neurons responding to the visual presentation of three-dimensional (3D) objects. Very often there is a strict relationship between the type of prehension coded by a neuron and the physical characteristics of the

Address for reprint requests and other correspondence: V. Raos, Department of Basic Sciences, Faculty of Medicine, School of Health Sciences, University of Crete, P.O. Box 2208, 71003 Heraklion, Crete, Greece (E-mail: vraos@med.uoc.gr).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

stimulus effective in triggering its visual response (Rizzolatti et al. 1988).

Given the central role of area F5 in the control of grasping (Jeannerod et al. 1995), our study was aimed at a thorough investigation of the motor and visual properties of F5 grasping neurons, using a controlled paradigm that allows the study of the neuronal discharge during both observation and grasping of many different 3D objects with and without visual guidance. Because the same paradigm has also been used to study the properties of hand-grasping neurons in the dorsal premotor area F2 (Raos et al. 2004) and in the anterior intraparietal area (AIP; Murata et al. 1996, 2000), a comparison of the properties of the grasping neurons in the three cortical areas (F5, F2, AIP) can be addressed for the first time.

The present study demonstrates that all F5 grasping neurons displayed a preference for grasping of an object or a set of objects. This preference was also maintained when grasping was performed in the dark in the absence of any visual feedback. In addition to the motor-related discharge, about half of neurons also responded to the presentation of an object or a set of objects, even when a grasping movement was not required. Often the object that evoked the strongest activity during grasping also evoked optimal activity during its observation.

A preliminary account of these data was previously presented (Murata et al. 1997).

METHODS

Basic procedures

Single-unit activity was recorded from area F5 in the posterior bank of the inferior limb of the arcuate sulcus in three hemispheres (contralateral to the moving forelimb) of two awake monkeys (*Macaca nemestrina*). The monkeys (one male and one female, weighing 4 and 5 kg, respectively) were seated on a primate chair with the head fixed and familiarized with the experimental setup. They were trained to perform a behavioral paradigm (see following text). After completion of the training a recording chamber was implanted. Surgical and recording procedures were previously described (Fogassi et al. 1996). All experimental protocols were approved by the Veterinarian Animal Care and Use Committee of the University of Parma and complied with the European law on the humane care and use of laboratory animals.

Single-neuron recording was carried out using tungsten microelectrodes inserted into the dura perpendicularly to the cortical surface (impedance 0.5–1.5 M Ω , measured at 1-kHz frequency). The recorded signal was amplified and monitored on an oscilloscope. Individual action potentials were isolated with a dual-voltage time-window discriminator (Bak Electronics, Germantown, MD). The output signal from the discriminator was monitored and fed to a PC for acquisition.

Recording sites

The size of the stereotactically implanted recording chamber provided access to a large cortical area that included the entire ventral premotor cortex and extended from area F1 (primary motor cortex) posteriorly, to the caudal part of the frontal eye fields anteriorly. The stereotactic parameters were chosen on the basis of our previous single-neuron recording experience in the ventral premotor cortex (see Fogassi et al. 1996; Gallese et al. 1996; Gentilucci et al. 1988; Rizzolatti et al. 1988). After chamber implantation the accessible cortical area was functionally explored (single-neuron recordings and intracortical microstimulation) to assess the location of areas F1, F4,

and F5 and to identify the sector of F5 where hand-grasping neurons responding to object presentation are most often encountered. The criteria used to characterize functionally the different areas were the following. Area F1: excitable with low-threshold currents, vigorous discharge during active movements, and responses during somatosensory stimulation. Area F4: rostral to the F1 hand field, proximal, and axial movements evoked by microstimulation at thresholds higher than those in F1, large tactile receptive fields on the face and body, visual receptive fields mostly driven by moving stimuli very often in register with the tactile receptive fields. Area F5: further rostrally, distal movements evoked by microstimulation at thresholds higher than those in F1, neurons discharging in association with goal-directed actions, neurons discharging to the observation of actions. The identification of area F5 on the basis of its functional properties was subsequently confirmed histologically (see *Histology* below).

Naturalistic testing

Naturalistic testing preceded the selection of neurons tested with the behavioral paradigm. The activity of each recorded neuron was correlated with the execution of active movements and with somatosensory and visual stimulation. Active movements consisted of *forelimb movements*, such as reaching for and grasping objects of different size, shape, and orientation, presented in all space sectors, and *trunk movements*, such as orienting toward interesting stimuli or avoiding threatening stimuli. Neurons were classified as distal only when they fired consistently during a particular distal movement regardless of whether the arm was flexed, extended, adducted, or abducted. The objects used for testing distal movements were selected to elicit different grip types. For example, a raisin placed inside a slit required a precision grip consisting in the opposition of the first phalanx of the thumb to the first phalanx of the index finger, whereas a syringe filled with juice required a whole hand prehension consisting of a flexion of all fingers around the object. The characterization obtained with the naturalistic testing was congruent with the characterization resulting from testing with the behavioral paradigm.

Behavioral apparatus and paradigm

The grasping neurons preselected with the naturalistic test were further thoroughly studied by means of the behavioral paradigm originally devised by Sakata and coworkers (see Murata et al. 1996, 1997, 2000). The monkey was seated in front of a box containing a PC-controlled rotating turntable subdivided into six sectors, each containing a different object presented one at a time. A spot of light from a red/green light-emitting diode (LED) was projected onto the object through a half mirror. Neurons were tested in four experimental conditions run separately one after the other. Each trial in all conditions started in complete darkness. The temporal sequence of the events during the four conditions is illustrated in Fig. 1.

1) *Movement in light condition (ML)*: When the LED was turned on (red color), the monkey had to fixate it and press a key for a variable period of 1.0 to 1.2 s. When the key was pressed, the box was illuminated and the object became visible. Subsequently, the LED changed color (from red to green) and the monkey was required to release the key, reach for and grasp the object, pull, and hold it. The moment the key was released, the LED color changed from green back to red. After the object was grasped, the monkey was required to keep the object pulled, until the LED changed color again from red to green, and then release it. The different objects were presented in random order.

2) *Movement in dark condition (MD)*: In this condition after a first discarded trial in which the object was grasped in light, the light inside the box was turned off and all the following trials were executed in complete darkness. In this condition the objects were presented in blocks.

In *conditions 1* and *2*, the monkey was rewarded at object release.

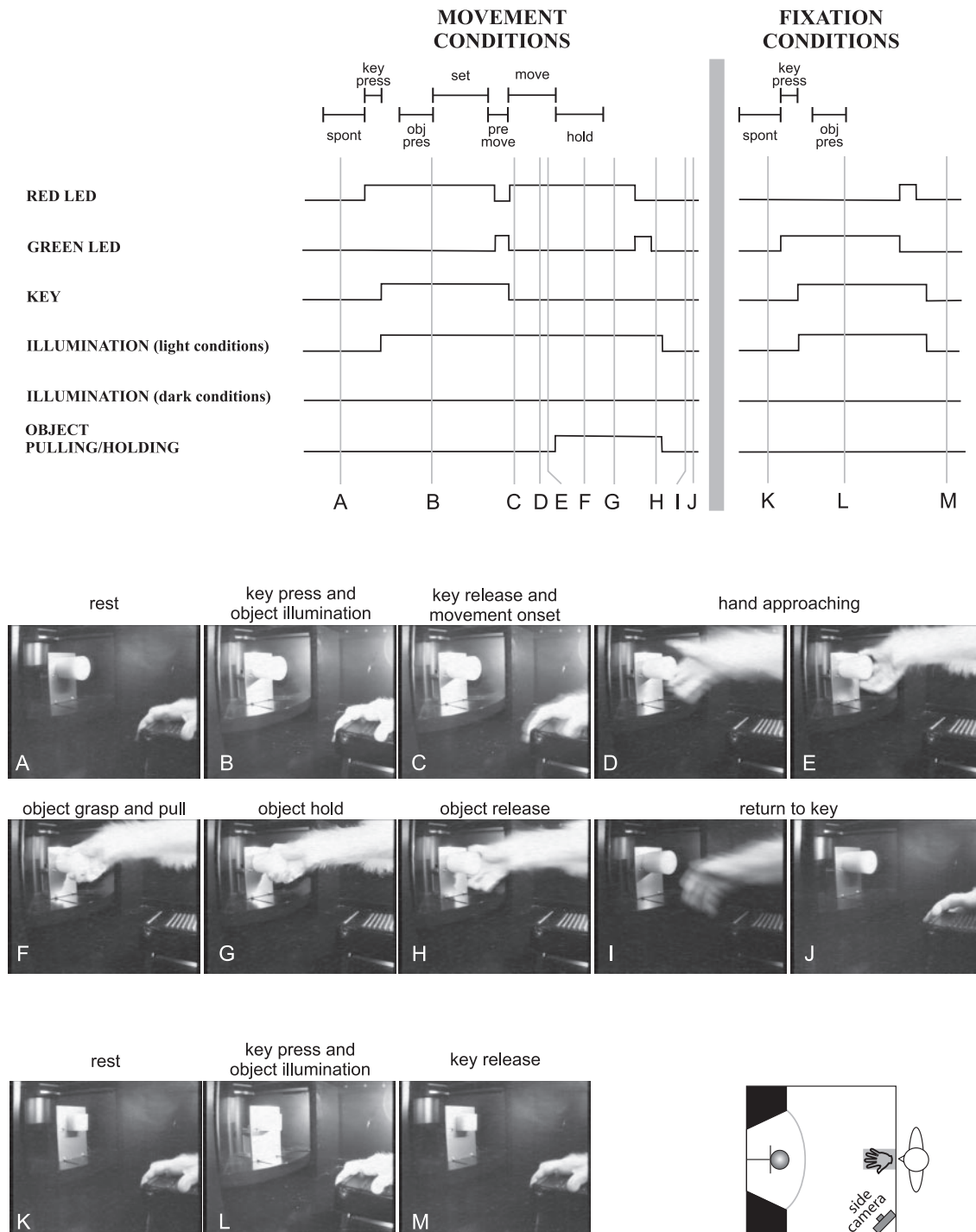


FIG. 1. *Top half:* diagrammatic representation of the time sequence of the task events in movement and fixation conditions. Upward deflection: on; downward deflection: off. Epochs of each condition are marked on the top of the diagram. *Bottom half:* video frames illustrating the monkey behavior during movement in light (A–J) and fixation in light (K–M) conditions. Time at which the video frames are taken is indicated by the gray vertical lines on the diagram in the top half of the figure. *Bottom right corner:* diagram of position of camera in the behavioral apparatus.

3) *Object fixation (OF):* A green LED was turned on. The monkey had to fixate the LED and press the key. Key press determined the illumination of the box. The monkey had to maintain fixation for 1–1.2 s, and then release the key when the LED changed color to red. The different objects were presented in a random order.

4) *LED fixation:* The task was the same as that in condition 3 but in this case key press did not lead to the illumination of the box and no object was visible. The monkey was simply required to fixate the

spot of light. This condition was run to rule out a possible effect of LED fixation per se on the neural response.

In conditions 3 and 4, the monkey was rewarded at the release of the key. All the events of the four conditions were acquired by a PC, together with neuronal activity.

The objects were presented one at a time, always in the same central position and at the same distance from the animal's hand (16 cm). In all conditions, monkeys' hand movements were continuously video-

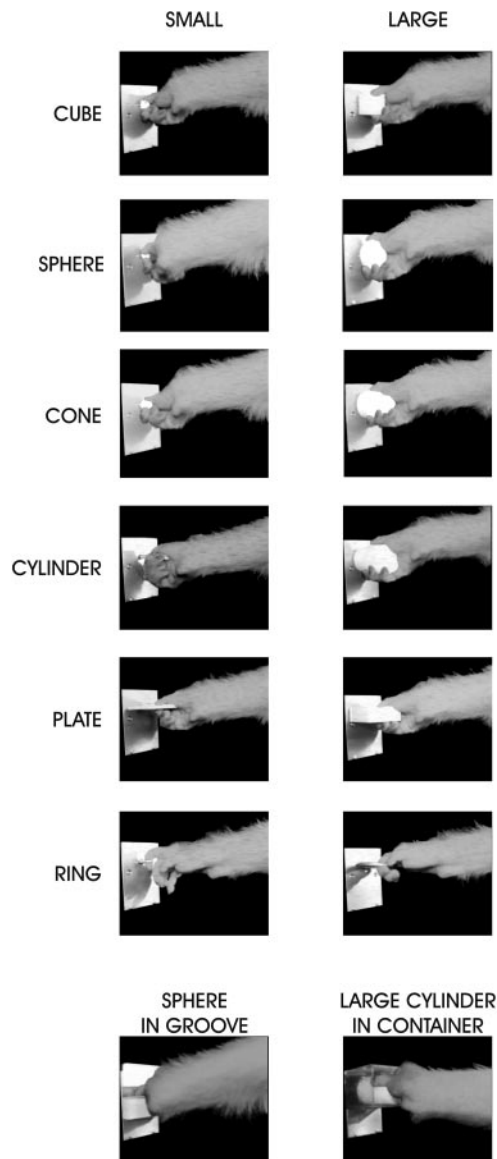


FIG. 2. Video frames taken from a side camera, presenting the grip types used for grasping the objects.

monitored by means of miniature, infrared-illumination-sensitive videocameras. One of them provided the top view, the other one the side view of the performing hand. Before the go signal in all conditions the monkey was engaged in a motor behavior (key press) that prevented any possible unwanted movement of the performing arm/hand. The initial LED color (red or green) used in the movement and fixation conditions, respectively, allowed the monkey to discriminate immediately between the movement and the fixation conditions. Trials in which the motor behavior was not correct were discarded. Eye movements were always monitored using a third infrared camera mounted inside the box. All trials in which the monkey broke fixation were discarded.

A variety of objects of different size, shape, and axis orientation was used. The types of grip evoked by the various objects varied according to their physical characteristics. The grip types used for grasping the objects are illustrated in Fig. 2. The two monkeys were trained to use identical hand postures for grasping the same objects and the overall similarity of the grips performed by the two monkeys was confirmed by comparing the video images of their hand postures during grasp. The load force resisting object pulling and the frictional properties of the object surface were the same for all objects.

In the initial part of the study, we used six geometric solids (horizontal plate, horizontal ring, cube, cone, sphere, and cylinder) originally used by Sakata and coworkers (Murata et al. 1996, 1997, 2000). Each object had three sizes: small, medium, large. Three turntables each containing the six objects of the same size were used. The selection of the turntable to be used was based on the preference exhibited by the neuron during the naturalistic test. The grips with which the objects were grasped are as follows: *Horizontal plate*: width, 45 mm; length, 40 mm; small thickness, 3 mm; medium thickness, 7.5 mm; large thickness, 15 mm; primitive precision grip performed using the thumb and the radial surface of the second and third phalanges of the index finger with the hand half-pronated. *Horizontal ring*: diameter: small, 15 mm; medium, 30 mm; large, 50 mm; hook grip with the fingers inserted into the ring (small: index; medium: index and middle; large: four fingers); hand pronated. *Sphere*: diameter: small, 10 mm; medium, 20 mm; large 30 mm. *Cone*: small: base diameter, 10 mm; length, 15 mm; medium: base diameter, 20 mm; length, 30 mm; large: base diameter, 30 mm; length, 45 mm. *Cube*: face diagonal: small, 10 mm; medium, 20 mm; large, 30 mm; side grip performed using the thumb and the radial surface of the last phalanx of the index finger with the hand half-pronated. *Cylinder*: length: 45 mm; small base diameter, 5 mm; medium base diameter, 15 mm; large base diameter, 30 mm; finger prehension using the first three fingers (hand half-pronated).

To test a broader variety of grips, in the second part of the study, we introduced a new turntable (special), which contained the following objects: small sphere, small horizontal ring, large horizontal ring, small sphere in horizontal groove (short dimension, 12 mm; depth, 12 mm; long dimension, 50 mm), large cylinder in horizontal container (depth, 45 mm; short dimension, 55 mm; long dimension, 100 mm), and very large sphere (diameter, 60 mm). The small sphere in horizontal groove was grasped with advanced precision grip performed with the pulpar surface of the last phalanx of the index finger opposed to the pulpar surface of last phalanx of the thumb (hand half-pronated). For grasping of the large cylinder in horizontal container, all the fingers were inserted in the container, with the four fingers in opposition to the thumb (hand half-pronated). For grasping of the very large sphere, all the fingers wrapped around the object and the palm was in contact with the object (hand half-pronated).

To study the influence of the wrist rotation on the neuronal discharge, a group of neurons was tested with a set of the following objects: horizontal and vertical plates, small sphere in horizontal and vertical groove, large cylinder in horizontal and vertical container (horizontally oriented: hand half-pronated; vertically oriented: hand pronated), horizontal and vertical rings (horizontally oriented: hand pronated; vertically oriented: hand half-pronated). The set of the objects to be used was based on the preference exhibited by the neuron.

Data analyses for the behavioral paradigm

Analysis of the neuronal activity during the movement conditions was made by subdividing the discharge recorded during each trial in the following epochs: 1) *spontaneous activity*: time before the onset of the trial, duration 500 ms; 2) *key-press*: time from red LED on to key-press; 3) *object presentation*: from 100 to 400 ms after key-press; 4) *set*: from 400 ms before the go signal to 100 ms before key release; 5) *premovement*: end of set period to key release; 6) *movement*: from key release/movement onset to the beginning of object pulling; 7) *holding*: a period of 500 ms calculated from the moment in which the monkey began to pull the object. In the fixation conditions, each trial was subdivided into three epochs that corresponded to the three first epochs of the movement conditions. The relation of the task epochs with the task events is illustrated in Fig. 1.

The subdivision between an object presentation epoch and a set epoch, although arbitrary, was done to keep as separate as possible the peak of the visual response from the subsequent sustained activity

preceding movement onset. The same epoch definition was used in other studies in which the same behavioral paradigm was used (Murata et al. 1997; Raos et al. 2004). For the definition of the set-related activity we used the classical criterion introduced in the early 1980s by Wise and coworkers (Weinrich and Wise 1982; Weinrich et al. 1984) and subsequently used in many other studies (di Pellegrino and Wise 1993; Johnson et al. 1996; Kurata 1993; Kurata and Wise 1988).

Response histograms were constructed by summing seven to eight individual trials. In each trial, the mean discharge frequency was calculated for each epoch. The mean discharge frequency of epochs 2–7 for the movement conditions and of epochs 2–3 for the fixation conditions was compared with the mean background discharge frequency of epoch 1 using one-way ANOVA ($P < 0.01$) followed by a Newman–Keuls procedure (two-tail, $P < 0.01$). All neurons displayed statistically significant differences in activity between epoch 1 and at least one of the movement or observation epochs and were therefore considered task-related neurons. A two-way ANOVA ($P < 0.01$) was performed (factors: condition, object) followed by a Newman–Keuls procedure (two-tail, $P < 0.01$).

To quantify the preference of the recorded neurons we computed two indices: the preference index (PI) and the depth-of-preference index (dPI). The PI, which takes into account the magnitude of the neuron response to each of the six objects contained in each turntable, was computed as defined by Moody and Zipser (1998)

$$PI = \frac{n - \left(\frac{\sum r_i}{r_{pref}} \right)}{n - 1}$$

where n is the number of objects, r_i is the activity for object i , and r_{pref} is the activity for the preferred object in the movement epoch of the ML condition. The PI can range between 0 and +1.0. A value of 0 indicates the same magnitude of response for all six objects, whereas a value of 1 indicates a preference for only one object. In the dPI, the magnitude of the neuron response for the preferred object in the movement epoch of the ML condition was scaled by the magnitude of the neuron response for the nonpreferred object. The dPI was computed as defined by Luck et al. (1997): $dPI = (\text{preferred} - \text{non_preferred}) \div (\text{preferred} + \text{non_preferred})$. The dPI can range between -1.0 and +1.0, with a value of 0 indicating no preference. Positive values indicate maintenance of the preference, whereas negative values indicate reversal of the preference. The objects that were defined as preferred and nonpreferred based on the magnitude of the neuron response in the movement epoch of the ML condition were used also for the calculation of the dPI in the object presentation, set, and premovement epochs of ML and MD conditions as well as in the object presentation epoch of the OF condition. A two-way ANOVA ($P < 0.01$) was performed (factors: condition, epoch) followed by a Newman–Keuls procedure (two-tail, $P < 0.01$).

To assess how the neurons in area F5 encode the similarity among the six objects of the original turntable and among the six objects of the special turntable we performed hierarchical cluster analysis using SPSS software. For this analysis, the average firing rate for each object was taken into account. At the first step of the hierarchical cluster analysis, each object represents its own cluster and the similarities between the objects are defined by a measure of their distance. In the present study we used the squared Euclidean distance, which places progressively greater weight on objects that are further apart. On the basis of the calculated distance, the two closest clusters are merged to form a new cluster replacing the two old clusters. The distances between these new clusters are determined by a linkage rule. In the present study, the average linkage rule has been used. This rule uses the average similarity of observations between two groups as the measure of the distance between the two groups. Merging of the two closest clusters is repeated until only one cluster remains. The steps in a hierarchical clustering solution that shows the clusters being com-

bined and the values of the distance coefficients at each step are shown by dendrograms. Connected vertical lines designate joined cases. The dendrogram rescales the actual distances to numbers between 0 and 25, preserving the ratio of the distances between steps. Hierarchical cluster analysis was performed in the following cases: (a) movement epoch of all the neurons tested with the original turntable in ML condition, (b) movement epoch of all the neurons tested with the special turntable in ML condition, (c) object presentation and movement epochs in the ML condition as well as object presentation epoch in the OF condition of the visuomotor neurons (see RESULTS) tested with the original turntable, (d) the same epochs as in (c) for the visuomotor neurons tested with the special turntable.

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 for each grip, in each orientation, epoch, and condition. Each neuron contributed one entry in each data set constructed.

The first data set contained the population response to the “best” grip (associated with the maximum discharge), the “second best” grip, and the “worst” grip according to the net average discharge frequency in the ML condition. The resulting grip rank order was also used for the MD condition. The second data set contained the population response to the preferred grip in the preferred orientation (the one that evoked the maximum discharge) and the preferred grip in the non-preferred orientation in the ML condition. In analogy with the first data set, the preference found in ML was also used in the MD condition. Depending on where the peak of the activity was, the net discharge frequency in premovement or movement epoch of the best grip/orientation in the ML condition was considered as 100. The discharge frequency of all the other epochs, conditions, and grips/orientations was expressed as a percentage of the peak discharge frequency. To assess the variation of the normalized discharge frequency in relation to the condition, the grip/orientation, and the epoch, a three-way ANOVA ($P < 0.01$) was performed followed by a Student–Newman–Keuls procedure (two-tail, $P < 0.01$).

Histology

Histological analysis was carried out in both monkeys. The reconstruction of the electrode tracks was based on the penetration traces, recording coordinates, recording data, and surface landmarks. For each animal, the cytoarchitectonic borders delimiting the areas of the ventral premotor cortex were matched with the electrophysiological maps (see Luppino et al. 1991; Raos et al. 2004).

RESULTS

Single-unit activity was recorded from the posterior bank of the inferior arcuate sulcus (area F5) in three hemispheres of two monkeys (Monkey 1 and Monkey 2). The same monkeys had been used in the study of the F2 grasping neurons (Raos et al. 2004). The anatomical location of the studied region in the right hemispheres of Monkey 1 and Monkey 2 is shown by the gray area in Fig. 3. The studied area was histologically identified.

A total of 108 grasping neurons were recorded with the behavioral paradigm: 71 neurons were tested with the objects of the original turntable and 37 with the objects of the special turntable. Thirty-eight neurons were also tested with objects of different orientation axis. All neurons displayed a preference for the grasping of an object or a set of objects. No anatomical segregation of neurons preferring a particular type of grip has been observed.

The recorded neurons were subdivided into two main classes: motor neurons ($n = 55$) and visuomotor neurons ($n = 53$).

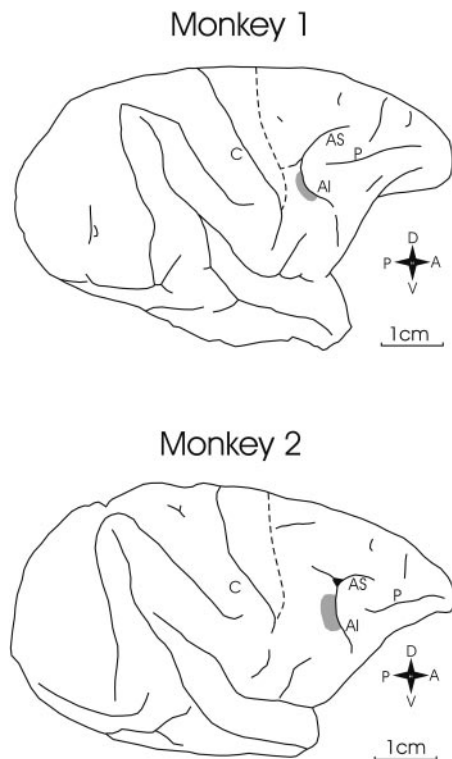


FIG. 3. Side views of the right hemisphere of Monkey 1 and Monkey 2, respectively. Dashed lines delimit the primary motor area (F1). Shaded regions indicate the sector of F5 from which neurons were recorded. AI, inferior limb of the arcuate sulcus; AS, superior limb of the arcuate sulcus; C, central sulcus; P, principal sulcus.

Neurons of both classes discharged during grasping movements. Visuomotor neurons, in addition, also responded during object presentation. The response to the presentation of the object was considered valid only if 1) it existed in the object presentation epoch of the OF condition when no grasping movement was required, was selective for an object or a set of objects, and was higher than the response in the same epoch during the LED fixation; and 2) it was present in the presentation epoch of ML condition, was selective for an object or a set of objects, and higher than in the corresponding epoch of MD condition. Motor neurons, besides the lack of response to object presentation, were also not active during the motor planning period (set and premovement epochs). In contrast, visuomotor neurons displayed a sustained tonic activity several hundreds of milliseconds before movement onset. Furthermore, motor neurons usually displayed higher levels of activity than those of the visuomotor neurons during the hold epoch.

The neurons belonging to the two classes were intermingled within the recorded region.

F5 motor neurons

Figure 4 illustrates two F5 selective *motor* neurons tested with the objects of the original turntable. Panels show neural activity recorded during the ML condition. The neuron shown in the *left column* displayed the strongest discharge [$F(5,42) = 61.784$, $P < 0.0001$] during the execution of side grip. Indeed, the motor response for the three objects (cube, sphere, cone) grasped with the same type of grip, which requires the flexion of the index finger and the thumb, was of similar magnitude.

Although similar movements were also performed during grasping of the plate or the cylinder, the neuron discharge in these cases was substantially less. The neuron shown in the *right column* was a highly selective neuron that discharged maximally for the “hook grip” used for grasping the small ring [$F(5,42) = 543.299$, $P < 0.0001$]. This grip requires the flexion of the index finger only. Although the flexion of the index finger was also performed during grasping of all the other tested objects, the neuron in these cases was silent.

Two other examples of F5 *motor* neurons are presented in Fig. 5. These neurons were tested with the objects of the special turntable. Panels show neural activity recorded during the ML condition. The neuron shown in the *left column* showed a preference for the execution of the “hook grip” performed for grasping the small ring as well as for the “finger” prehension performed for grasping the large ring [$F(5,42) = 137.100$, $P < 0.0001$]. It is noteworthy that the performance of both grips does not require thumb opposition. The neuron shown in the *right column* preferred the execution of the side grip performed for grasping the small sphere [$F(5,42) = 167.654$, $P < 0.0001$]. The same neuron exhibits lower motor response during the “advanced precision grip” performed for grasping small sphere in groove, as well as during the “finger with thumb opposition” prehension performed when the large cylinder in container was grasped.

F5 visuomotor neurons

Figure 6 illustrates an F5 *visuomotor* neuron, tested with the objects of the original turntable. Panels show neural activity recorded during the ML, MD, and OF conditions. Based on the motor response in the ML condition, this neuron shows a preference for the execution of the “hook grip” performed for grasping the small ring [$F(5,84) = 170.761$, $P < 0.0001$]. The same preference is also exhibited in the MD condition, although the motor discharge is lower than that in the ML condition [$F(1,84) = 23.830$, $P < 0.0001$]. The neuron also displays high activity during the presentation epoch of the small ring, in both ML [$F(5,84) = 21.333$, $P < 0.0001$] and OF conditions [$F(6,49) = 9.826$, $P < 0.0001$] (this latter in the absence of any grasping movement), thus exhibiting highly congruent visual and motor preferences. Note that the discharge during the presentation epoch of the small ring in ML is greater than that during the corresponding epoch in MD [$F(1,84) = 141.806$, $P < 0.0001$]. Both the motor and visual responses of this neuron for the cylinder and the plate are lower than the corresponding ones for the preferred object. Furthermore, the neuron has minimal or no response during presentation and grasping of cube, sphere, and cone, which are grasped with side grip.

Figure 7 illustrates an F5 *visuomotor* neuron tested with the objects of the special turntable. Based on the motor response in the ML condition, this neuron shows a preference for the execution of the “advanced precision grip” performed for grasping the small sphere in groove [$F(5,72) = 487.688$, $P < 0.0001$]. The same preference is also exhibited in the MD condition. Congruently with the motor-related activity, this neuron also displays high activity during the presentation of the preferred object, in both ML [$F(5,72) = 25.410$, $P < 0.0001$] and OF [$F(6,42) = 29.235$, $P < 0.0001$] conditions. Discharge during the presentation epoch for the preferred object is greater

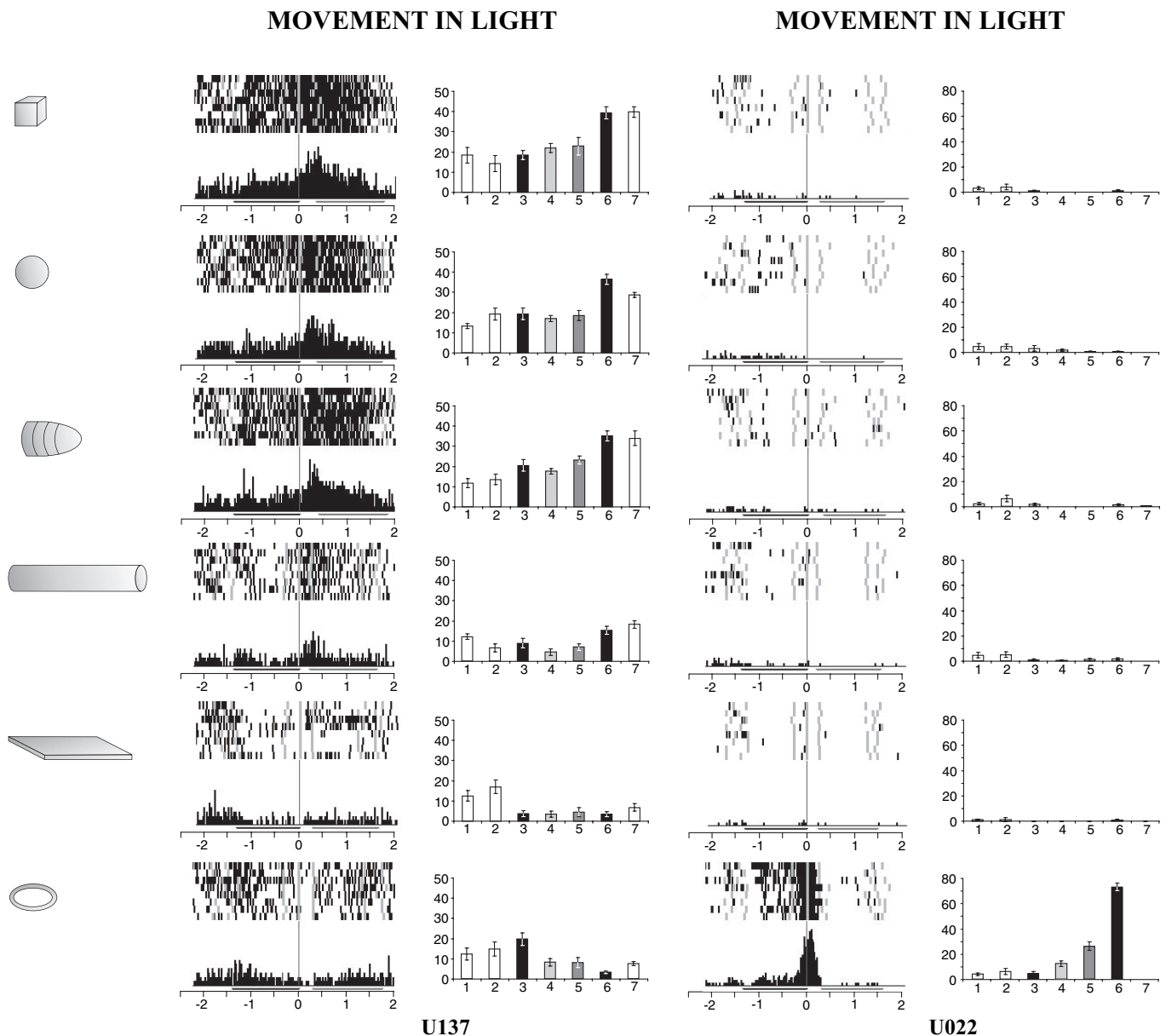


FIG. 4. Two examples of F5 *motor* neurons tested with the original turntable. For each object, rasters of 8 trials, the resulting histogram and a bar graph with the mean firing rate and SE during each epoch of the ML condition are presented. Small gray bars in each trial correspond to the different events of the task. First and second horizontal lines below each histogram indicate the object presentation and object holding periods, respectively, averaged across trials. Rasters and histograms are aligned (vertical bar) with the beginning of the movement. A timescale (s) is placed on the abscissa of each histogram. Bar graph abscissa: task epoch (1: spontaneous activity; 2: key-press; 3: object presentation; 4: set; 5: premovement; 6: movement; 7: holding). Bar graph ordinate: mean firing rate (spikes/s).

in ML than that during the corresponding epoch in MD [$F(1,72) = 78.889$, $P < 0.0001$]. Moreover, the neuron also exhibits motor and visual activity, but of smaller magnitude, for the small sphere and the large cylinder in the container. It is noteworthy that the thumb opposition is essential for the performance of all these grips. The neuron's motor and visual responses for the small and the large ring as well as for the very large sphere—objects for which the thumb opposition is either not required or not crucial for the grip execution—are either minimal or absent.

The neuron presented in Fig. 8 is another F5 *visuomotor* neuron tested with the objects of the special turntable. The neuron codes the “hook grip” performed for grasping the small

ring [$F(5,72) = 62.346$, $P < 0.0001$] and also displays a congruent response during the presentation epoch of the same object in both ML [$F(5,72) = 60.966$, $P < 0.0001$] and OF [$F(6,42) = 65.748$, $P < 0.0001$] conditions. When the index finger is used either opposed to the thumb for grasping the small sphere in groove with the “advanced precision grip” or in collaboration with the other fingers for grasping the large ring with the “finger with thumb opposition” prehension, then the average firing rate is reduced by half.

Population response of motor and visuomotor neurons

To quantify the motor preference of the neurons the PI was calculated. For both turntables the PI ranged from 0.1 to 1.

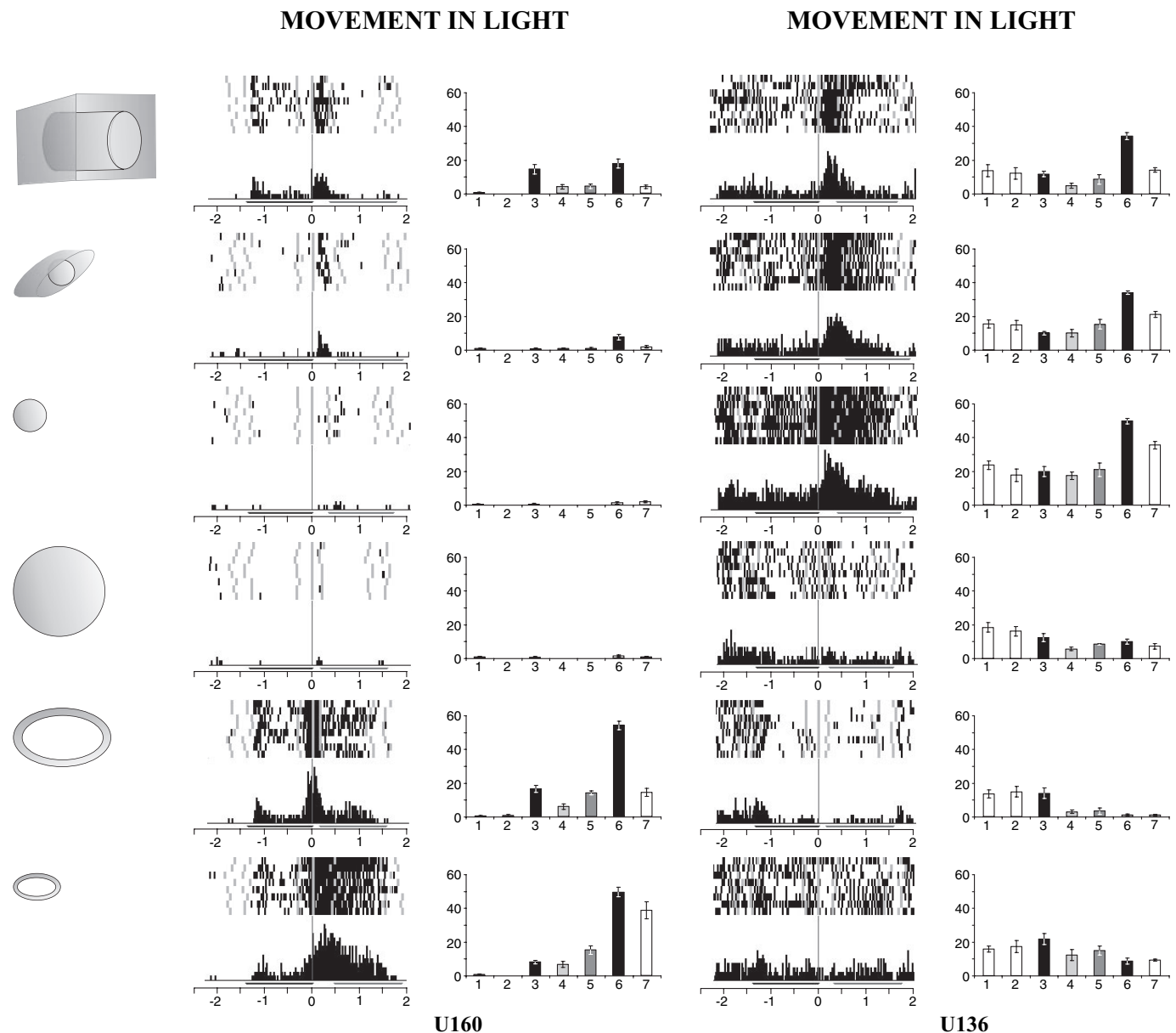


FIG. 5. Two examples of F5 *motor* neurons tested with the special turntable. Conventions as in Fig. 4.

When the PI was plotted as a function of the percentage discharge difference between the best and the worst object (Fig. 9, A, C, E, and G), it was evident that for almost all neurons this difference was $>20\%$. However, when the PI was plotted as a function of the percentage discharge difference between the best and the second best object, 58% of the neurons tested with the original and 50% of the neurons tested with the special turntable displayed a difference of $<20\%$ (Fig. 9, B, D, F, and H). These results suggest that some objects, although different in shape, evoke similar motor responses.

Figure 10 illustrates the net normalized mean activity of the entire neuronal population as well as of each one of the two classes of neurons (motor and visuomotor), separately, during the execution of the best, second best, and worst grips in ML and MD. The first fact to be noticed is that the activity during grasping execution in both ML and MD conditions depends on the type of grip for all neurons [$F(2,583) = 38.370$, $P <$

0.0001]. The lack of visual information in the MD condition does not affect the selectivity between the grips [$F(1,583) = 3.036$, $P = 0.082$]. The second fact concerns the activity during the object presentation, set, and premovement epochs. It is evident that the activity present in the entire population during these epochs derives from the class of visuomotor neurons. The visuomotor neurons display selectivity for the type of grip during the epochs preceding the grasping execution. Moreover, the activity during the object presentation epoch for the best and second-best grip is higher in the ML than that in the MD condition. Motor neurons do not respond during all epochs preceding grasping execution in either the ML or the MD condition.

Correlation of object preferences with task epoch

To assess the motor specificity of the motor and visuomotor neurons in the various epochs and conditions, the dPI was

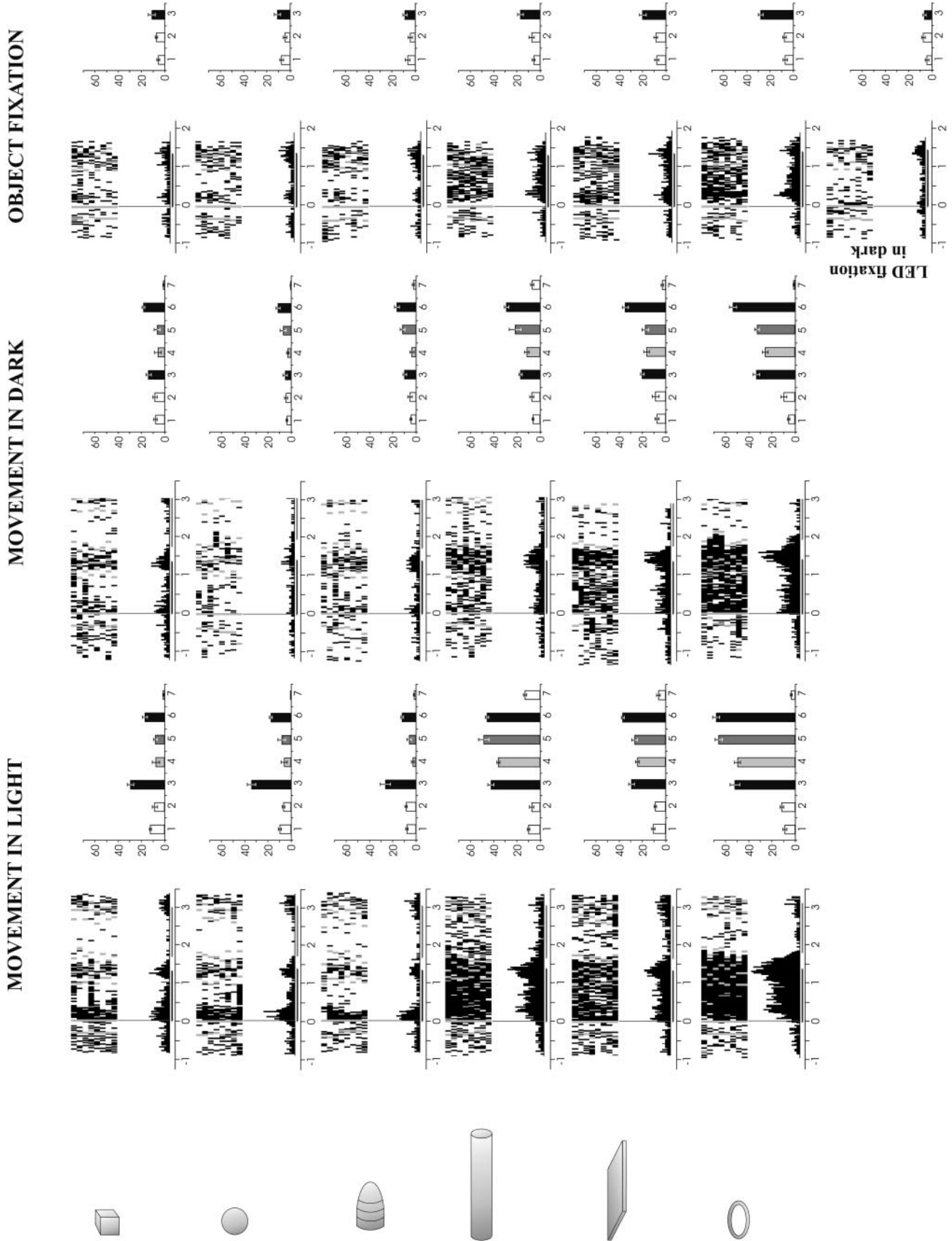


FIG. 6. Example of an F5 visuomotor neuron tested with the original turntable. Panels show neural activity recorded during movement in light (ML) condition (left column), movement in dark (MD) condition (central column), and object fixation (OF) condition (right column). Rasters and histograms are aligned (vertical bar with key press (object illumination). Bottom right corner: neuron activity during LED fixation condition. Other conventions as in Fig. 4.

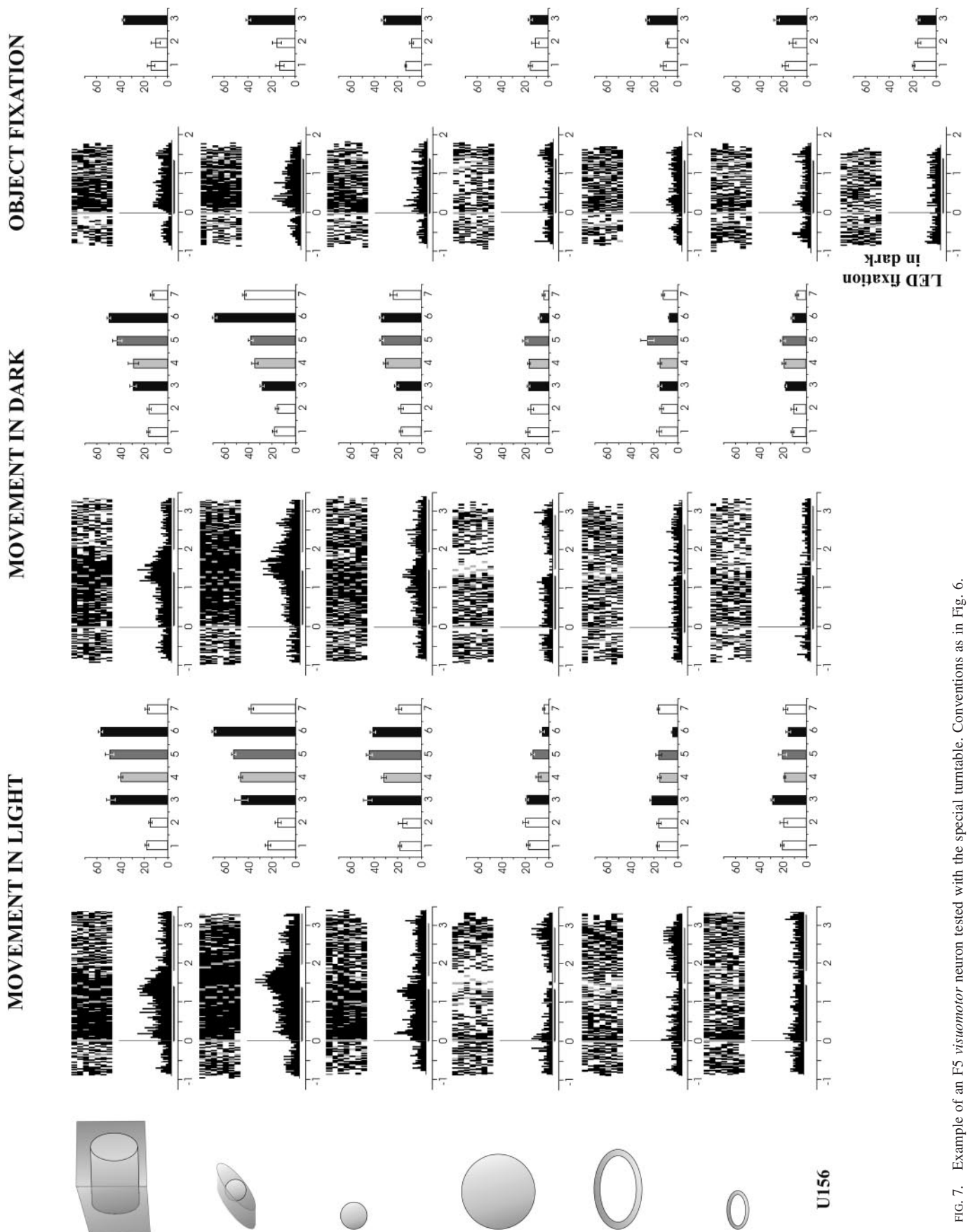


FIG. 7. Example of an F5 visuomotor neuron tested with the special turntable. Conventions as in Fig. 6.

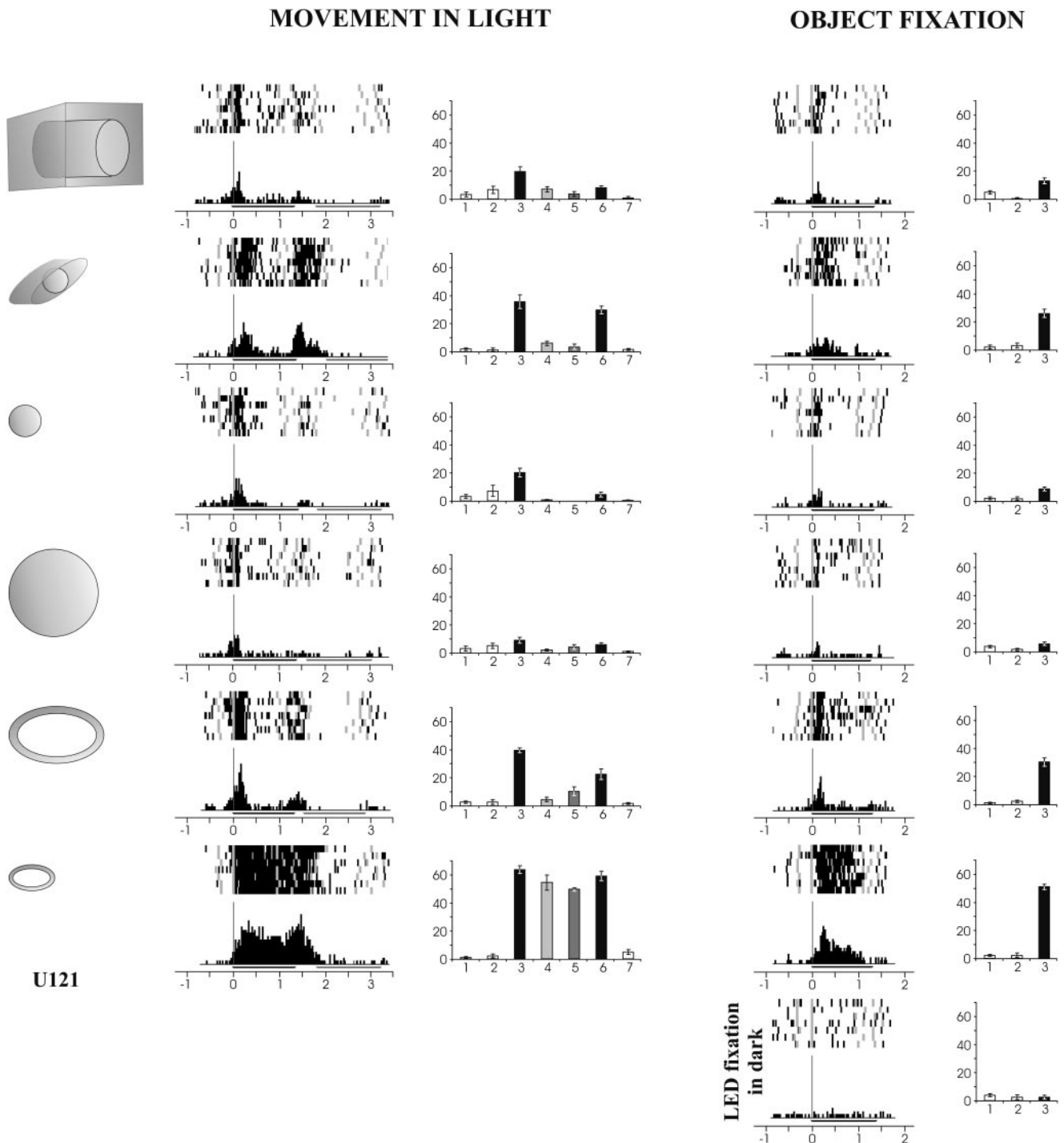
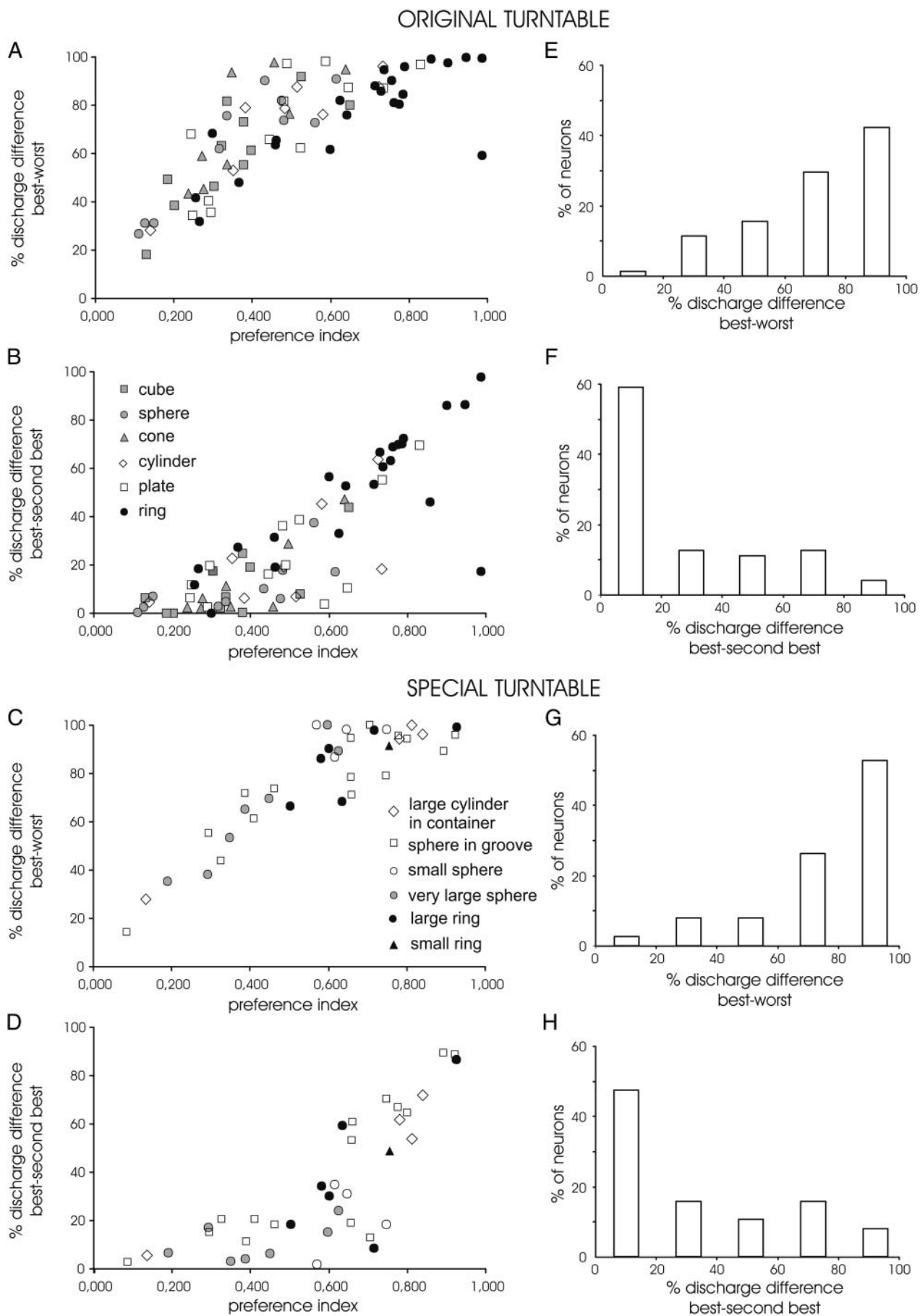


FIG. 8. Example of another F5 visuomotor neuron tested with the special turntable. Conventions as in Fig. 6.

calculated. The dPIs of the motor neurons in premovement and movement epochs of the ML and MD conditions are significantly different from the dPIs in the corresponding spontaneous activity epochs [$F(4,388) = 23.82$, $P < 0.0001$] (Fig. 11A). The distribution of the dPIs in the movement epoch of ML and MD conditions presented in Fig. 11I demonstrates that the motor selectivity of the neurons remains essentially the same in the two conditions.

With respect to the visuomotor neurons, the dPIs in all epochs in all conditions are significantly different from the

dPIs in the corresponding spontaneous activity epochs [$F(4,388) = 68.597$, $P < 0.0001$] (Fig. 11B). Moreover, the distribution of the dPIs shows that the selectivity is progressively improved as the grasping execution approaches. The dPIs of the object presentation epochs are lower than the dPIs of the movement epochs. There is no difference in the selectivity between the conditions [$F(1,97) = 0.133$, $P = 0.716$]. In sum, visuomotor neurons display selectivity across all the task stages from object presentation to movement, whereas motor



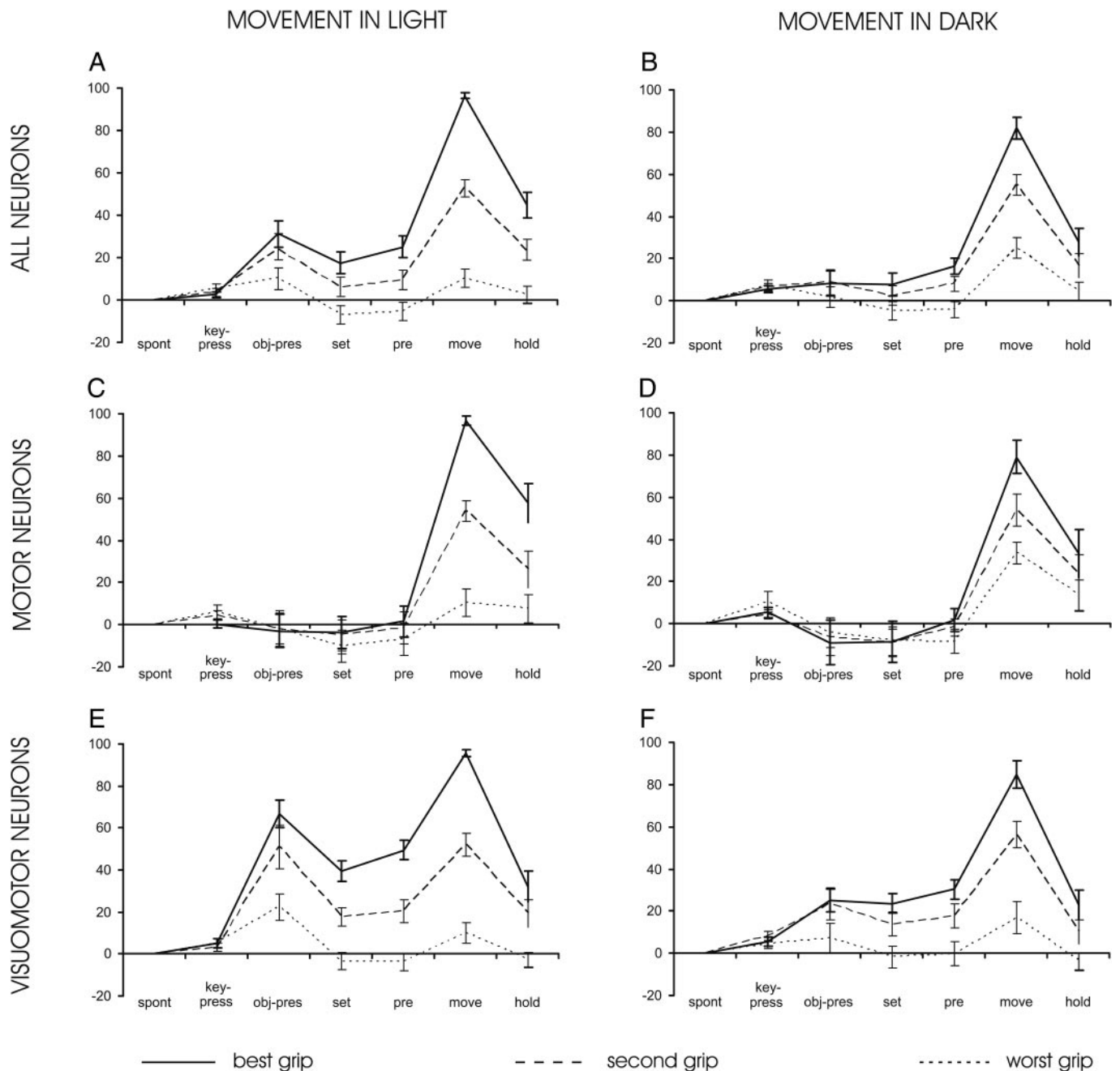


FIG. 10. Charts displaying the results of the population analysis. Activity of the entire neuronal population ($n = 108$; A, B), the class of motor ($n = 55$; C, D), and the class of visuomotor ($n = 53$; E, F) neurons in all epochs during the execution of the best, second best, and worst grip in ML (left column) and MD (right column) conditions. Grip rank order was based on the net average discharge frequency in the ML condition. Resulting rank was used also for the MD condition. Depending on where the peak of the activity was, the net discharge frequency in premovement or movement epoch of the best grip in the ML condition was considered as 100. Discharge frequency of all other epochs, conditions, and grips was expressed as percentage of the peak discharge frequency. Abscissa: task epochs. In movement in the dark condition the “object presentation” epoch corresponds to the moment in which the object was introduced, but was not visible. Ordinate: net average discharge expressed as a percentage.

neurons display a selectivity only during premovement and movement epochs (Fig. 11, C, E, and G).

The visual selectivity displayed by visuomotor neurons in the object presentation epoch of OF coincided with that found

in the object presentation epoch of ML. The motor selectivity was sharper than the visual selectivity. Coincidence for the object evoking the highest visual and motor responses was observed in 60% of the cases.

FIG. 9. Motor selectivity of neurons for grasping of various objects. *Top half*: data from the neurons recorded with the original turntable ($n = 71$). *Bottom half*: data from the neurons recorded with the special turntable ($n = 37$). *Left column*: scatter-plots of neurons' preference indices (PIs) plotted as a function of the percentage discharge difference between best and worst object (A, C), and between best and second best object (B, D), during the movement epoch of ML condition. *Right column*: bar graphs show the normalized distributions of the percentage discharge differences between best and worst object (E, G), and between best and second best object (F, H), during the movement epoch of ML condition.

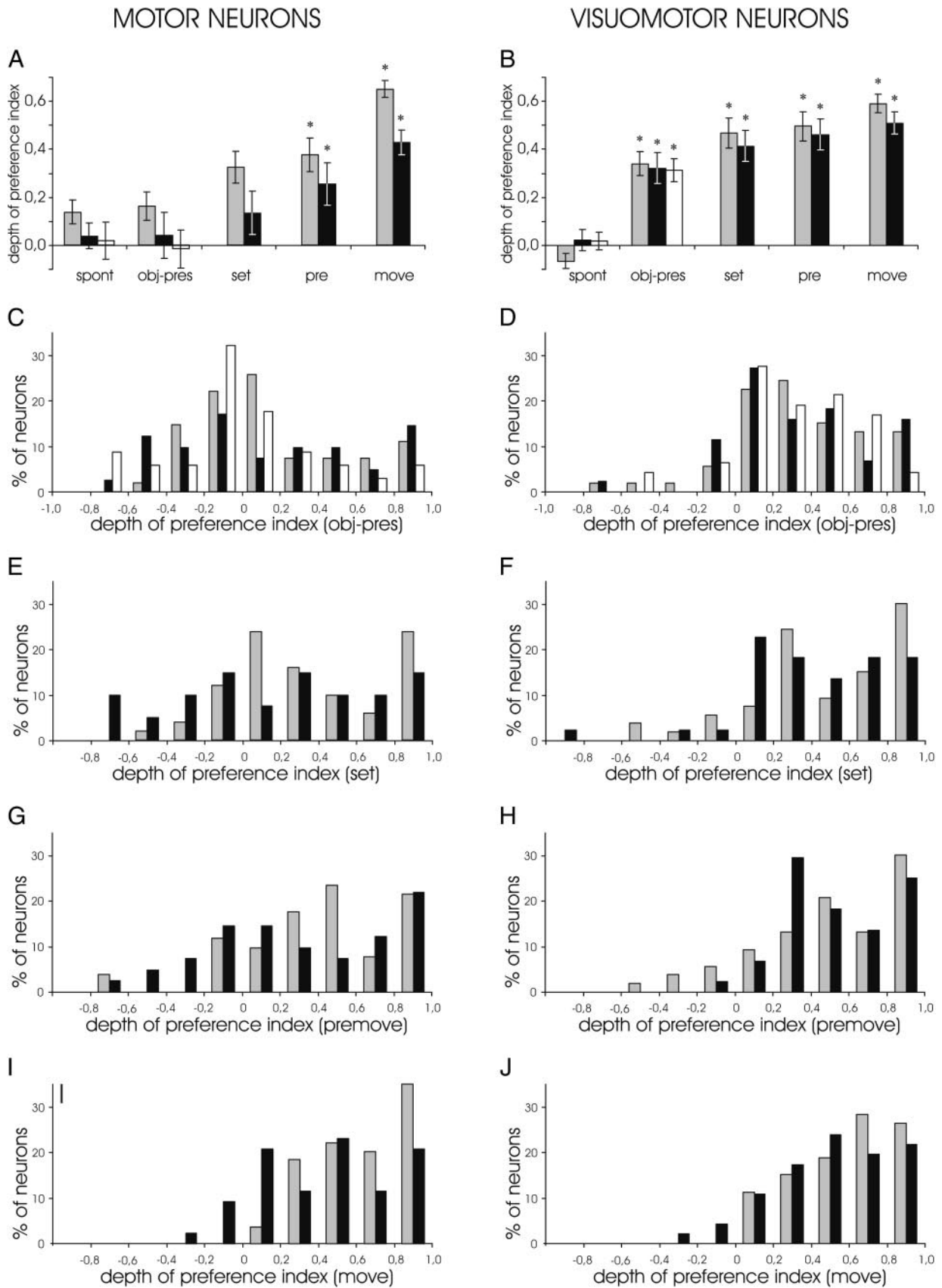


FIG. 11. Object preferences of the 2 neuronal classes in the different task epochs. *Left column*: motor neurons ($n = 55$). *Right column*: visuomotor neurons ($n = 53$). *A, B*: depth-of-preference indices (dPIs; means \pm SE) in each epoch of ML (gray bars), MD (black bars), and OF (empty bars) conditions. Normalized distributions of the dPIs in the object presentation (*C, D*), set (*E, F*), premovement (*G, H*), and movement (*I, J*) epochs of ML (gray bars), MD (black bars), and OF (empty bars) conditions. Asterisks above the bars indicate statistically significant differences from the dPI of the spontaneous activity epoch.

TABLE 1. Number of neurons whose selectivity for different objects was determined using the maximum of neuronal discharge during the movement epoch of the ML condition

| Object | Number of Neurons |
|---------------------------|-------------------|
| <i>Original turntable</i> | |
| Cube | 11 |
| Sphere | 10 |
| Cone | 8 |
| Cylinder | 8 |
| Plate | 12 |
| Ring | 22 |
| Total | 71 |
| <i>Special turntable</i> | |
| Cylinder in container | 4 |
| Sphere in groove | 15 |
| Small sphere | 4 |
| Very large sphere | 7 |
| Large ring | 6 |
| Small ring | 1 |
| Total | 37 |

Distribution of object preferences in the population

Table 1 presents the recorded neurons classified according to the object for which the maximum neuronal discharge during the movement epoch of ML condition was recorded. To unravel the factor that determines the selectivity of the motor discharge, we performed hierarchical cluster analysis. The analysis showed that the motor specificity of F5 neurons does not depend on the object shape but on the grip used to grasp the object. The results for both classes of neurons tested with the original and the special turntables are presented in Fig. 12. Regarding the objects of the original turntable (Fig. 12, A and C), it is evident that the ring—the only object that does not require the opposition of the thumb to be grasped—detaches immediately from all the other objects. Out of the remaining five objects, for which the use of the thumb is necessary, the long objects (plate and cylinder) detach, whereas the cube, the sphere, and the cone remain together forming a single cluster. The way the latter three objects are grasped is identical (side grip); the former two are also grasped with a similar type of grip.

For the objects of the special turntable (Fig. 12, B and D), the two rings form a cluster that detaches immediately from the other objects. Out of the remaining four objects, the very large

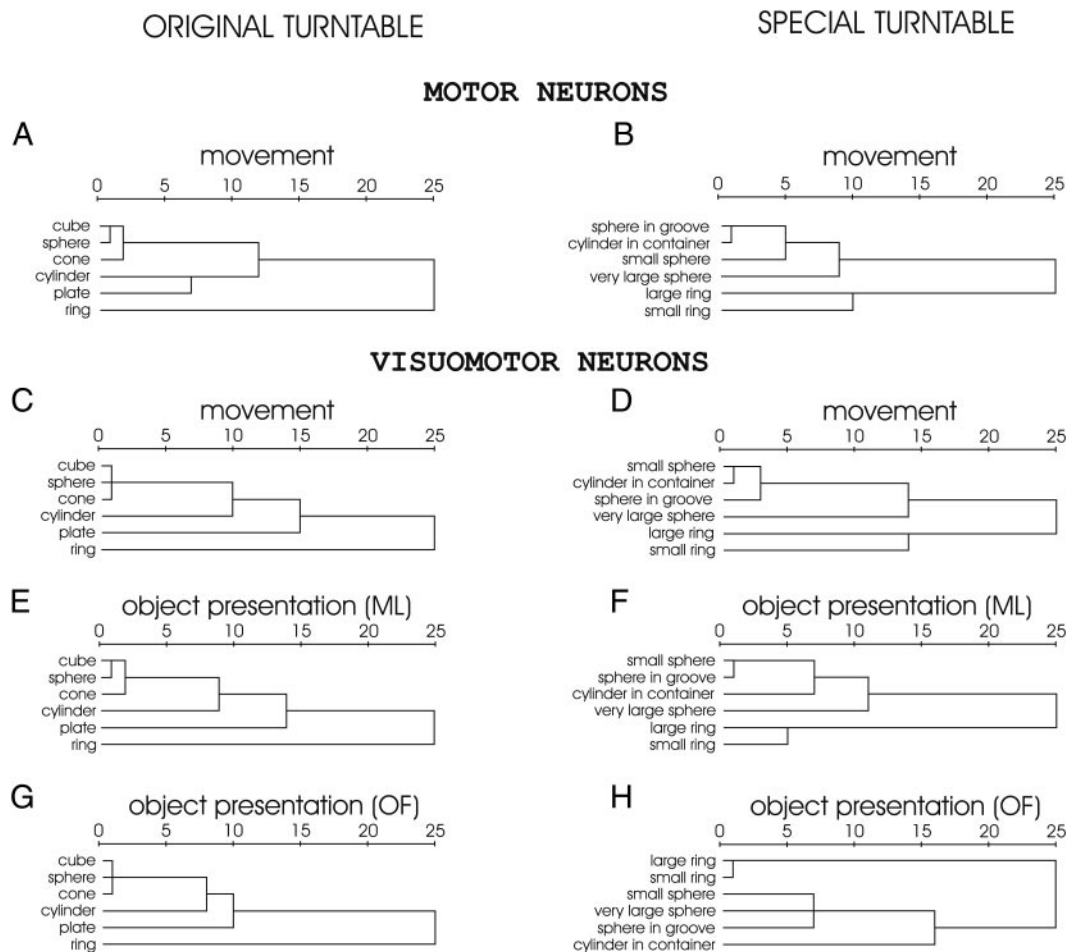


FIG. 12. Dendrograms showing the clustering of objects in the original (left column) and special (right column) turntables based on the discharge of motor (A, $n = 41$; B, $n = 14$) and visuomotor (C, $n = 30$; D, $n = 23$) neurons during the movement epoch of ML condition, as well as on the discharge of the visuomotor neurons during the object presentation epochs of ML (E, F) and OF (G, H) conditions. Horizontal axis in the dendrograms indicates the distance coefficients at each step of the hierarchical clustering solution. Actual distances have been rescaled in the 0–25 range.

sphere detaches, whereas the small sphere, the sphere in groove, and the cylinder in container are clustered together. It appears that the most crucial factor for the grouping among grips is the role played by the thumb in grasping. Irrespective of which part of the index finger is used (radial or pulpar surface of the last phalanx), or the number of fingers (index or all four) that oppose to the thumb, the opposition determines the grouping together of physically different objects such as the small sphere, the sphere in groove, and the cylinder in container. The same-direction factor also points to the grouping shown by the rings. Irrespective of the finger that is inserted into the ring (only index finger for the small, four fingers for the large), the lack of thumb opposition determines the isolation of the rings' cluster. The separation of the very large sphere from the group of other objects may be explained by the role played by the thumb in this type of grip. In contrast to the necessity of thumb use for the performance of the opposition grips, its role for grasping the very large sphere is to act as a buttressing and reinforcing agent.

To investigate at which stage the motor specificity of the visuomotor neurons emerges, cluster analysis was performed in both the object presentation of the ML condition and the object presentation epoch of the OF condition. With respect to the original turntable, which contains only simple objects, the cluster analysis showed the same grouping in the object presentation epochs of both ML (Fig. 12E) and OF (Fig. 12G) conditions, which is identical to the grouping displayed in the movement epoch of the ML condition (Fig. 12C).

For the objects of the special turntable, a slight discrepancy was observed for some objects. In the object presentation epoch of the OF condition (Fig. 12H), the small and the very large sphere, as well as the small sphere in groove, are clustered together and the cylinder in container detaches. In the object presentation epoch of the ML condition (Fig. 12F), the small sphere, the small sphere in groove, and the cylinder in container are clustered together and the very large sphere detaches as in the movement epoch of the ML condition (Fig. 12D). However, the two rings are clustered together in all the epochs.

Table 1 shows that opposition and nonopposition grips are similarly represented by the neurons tested with the two sets of objects. The opposition grips evoked maximum responses in the 69% of the neurons tested with the objects of the original turntable, and in the 81% of the neurons tested with the objects of the special turntable, whereas the corresponding percentages for the nonopposition grips were 31 and 19%, respectively.

Synergies between hand and wrist postures

Figure 13 illustrates a visuomotor neuron tested with objects of different orientation axis. The neuron discharges maximally during grasping [$F(5,84) = 61.773, P < 0.0001$] and presentation (in both ML [$F(5,84) = 42.356, P < 0.0001$] and OF [$F(6,49) = 38.796, P < 0.0001$] conditions) of the horizontally oriented ring with the hand pronated. Presentation and grasping of the same object oriented vertically evoke minimal (if any) response. The fact that the neuronal response during the presentation and grasping of the plate with both orientations is minor demonstrates that the neuron codes a combination of grip and wrist orientation rather than a simple rotation of the wrist.

Thirty-eight neurons were tested with objects having different orientation axes. Among them, 55% ($n = 21$) were highly selective for a specific wrist orientation, displaying a difference between preferred and nonpreferred orientation of $\geq 20\%$. In addition, the number of neurons preferring grips performed with hand pronated was almost equal to that of neurons preferring grips performed with hand half-pronated ($n = 18, 47\%$; $n = 20, 53\%$, respectively).

In Fig. 14, the population response during the execution of the best grip in the preferred and the nonpreferred orientation in ML and MD is presented. The neuronal population shows a preference for a specific wrist orientation during grasping execution in ML that remains unaltered when the visual feedback is absent (MD condition) [Condition $F(1,116) = 0.494, P = 0.484$; Orientation $F(1,116) = 16.332, P < 0.0001$].

DISCUSSION

The present study demonstrates that in area F5 there are neurons that display preference for grasping an object or a set of objects with a specific type of grip. About half of the neurons also respond to the presentation of an object or a set of objects, even when a subsequent grasping movement is not required. Congruence is noted such that the type of prehension associated with the neuron's strongest motor activity involves the object eliciting the strongest discharge when visually presented to the monkey.

The present results confirm and extend the previous findings on F5 grasping-related neurons (Rizzolatti et al. 1988). In this work, greater varieties of objects and grips were tested. Furthermore, it was possible to study in detail the role of wrist orientation on neuronal discharge during grasping execution, and the influence of visual feedback on the neuron grip/wrist orientation selectivity. The selectivity of neurons and the congruence between visual and motor responses were assessed using quantitative indices and cluster analysis across the various epochs and conditions of the task.

Motor responses

The activity of F5 grasping neurons is not related to individual finger movements, but to the grasping action as a whole. The brain uses motor schemata/grasp categories to simplify the control of the many degrees of freedom of the hand. Which motor schema/grasp category will be selected in F5 depends on the physical characteristics of the object (i.e., shape, size, orientation) and on the goal of the grasping action.

Cluster analysis, based on the movement epoch discharge, revealed that the six objects of the original turntable form three distinct sets. Considering the resulting grouping, it is reasonable to assume that the binding feature of the objects constituting a cluster is the way they are grasped. A similar clustering was also revealed for the motor-dominant neurons of area AIP recorded using the same set of objects (Murata et al. 2000). The grip type also seems to be the binding feature for the grouping of the objects of the special turntable used in the present study. Moreover, it appears that the most crucial factor for the grouping among grips is the role played by the thumb in grasping.

In a recent study, electromyographic (EMG) recordings from several muscles in macaques were used to analyze the

OBJECT FIXATION

MOVEMENT IN DARK

MOVEMENT IN LIGHT

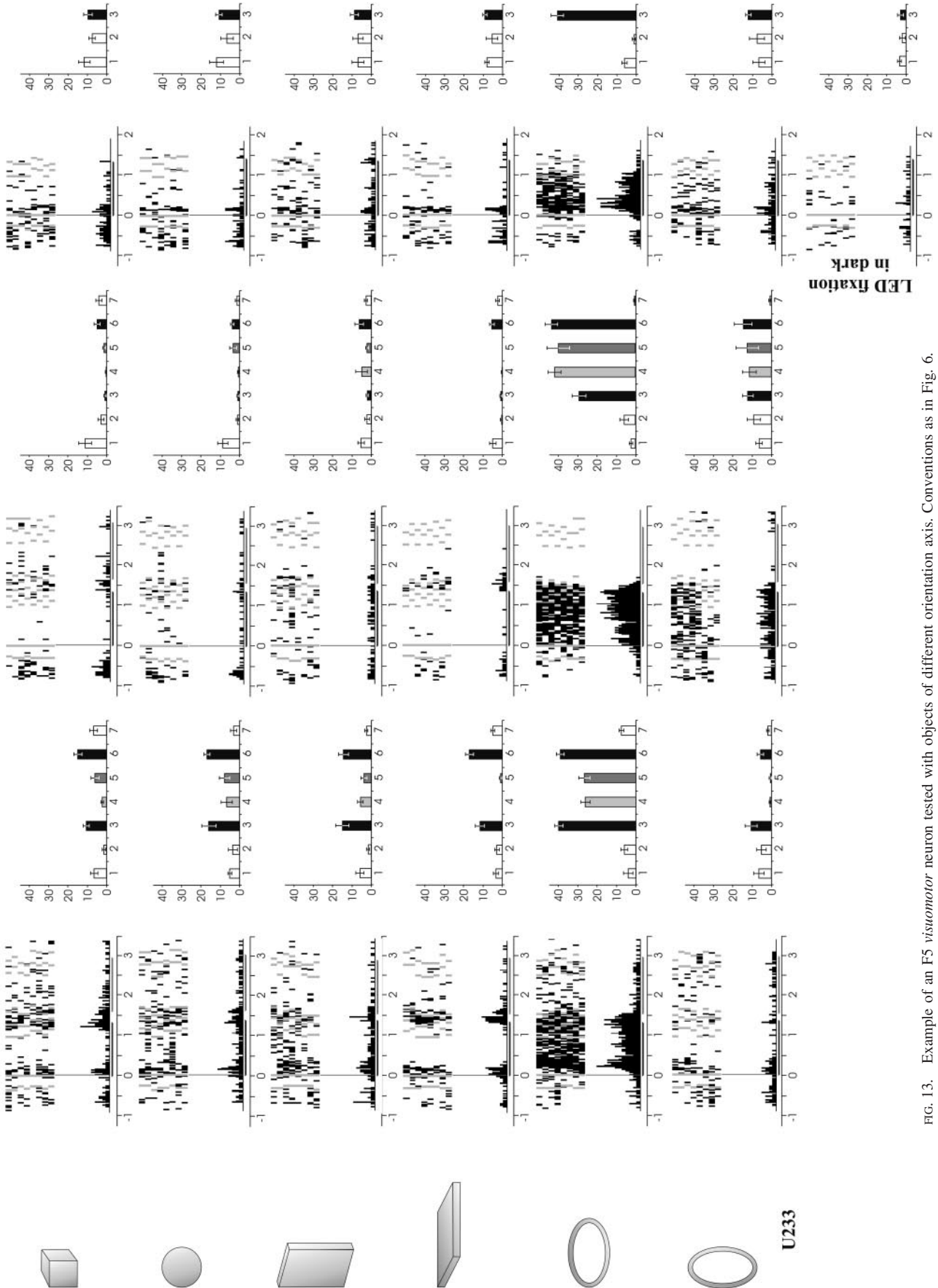


FIG. 13. Example of an F5 visuomotor neuron tested with objects of different orientation axis. Conventions as in Fig. 6.

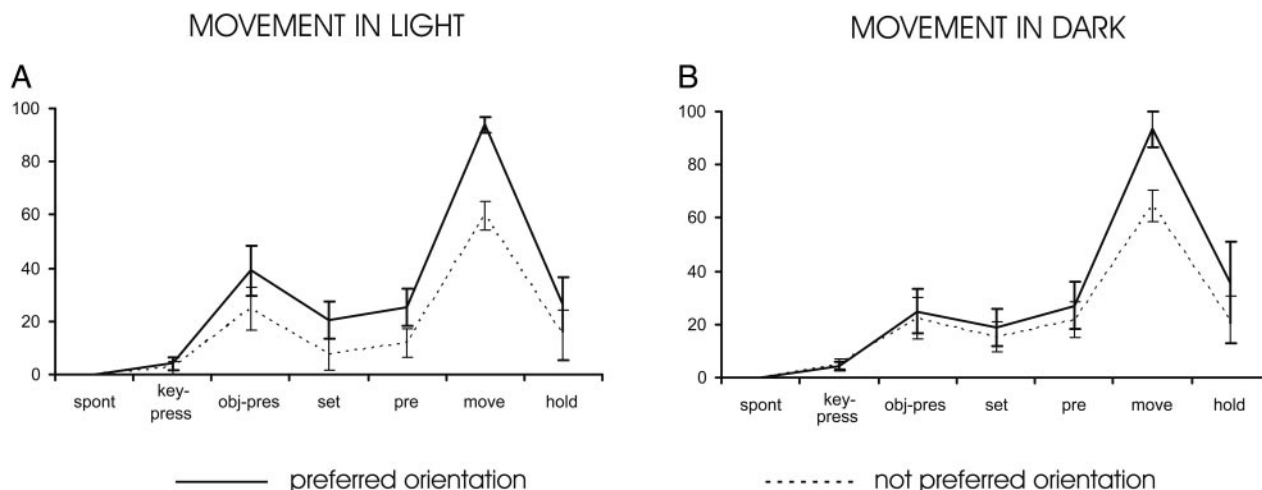


FIG. 14. Activity of the neuronal population ($n = 38$) in all the epochs during grasping execution with the preferred and nonpreferred wrist orientation in ML (A) and in MD (B) conditions.

muscle synergies used in a task similar to that used in the present study (Brochier et al. 2004). Cluster analysis of the EMG patterns revealed that grouping of different objects/grips varied during the different phases of grasping execution. Although our cluster analysis was not performed on different movement epochs, it shows that grouping of different objects/grips remains constant from the object presentation epoch to actual movement epoch. Taken together, the results of the two studies suggest that the grip selectivity coded by F5 neurons does not directly reflect the pattern of EMG activation during the time course of grasping execution.

Frequently, the large distance as revealed by cluster analysis between the opposition and the nonopposition grips was reflected by extremely different motor responses. Although the preferred grip and the other grip members of the group to which it belonged evoked excitatory responses of different amplitude, the nonpreferred grips constituting the opposite group evoked either no response or inhibition. The same tendency was found in a previous naturalistic study of the grasping neurons in area F5 (Rizzolatti et al. 1988). By comparing the results of the present study with those of Rizzolatti et al. (1988), it appears that the prehension of the plate or the cube, cone, and sphere resembles that of the (primitive) precision grip, and the prehension of the very large sphere could be compared with the whole hand prehension.

Besides the grip motor schemata, another motor schema that appears to be coded by F5 grasping neurons is the rotation of the wrist required to match the axis orientation of the object. Note that the grip and wrist rotation motor schemata are not coded separately but appear to be combined at the single-neuron level.

The present results provide a neurophysiological substrate to the concept of virtual fingers, which has been used for the construction of a model for the control of a robotic manipulator performing grasping actions (Arbib et al. 1985; Fagg and Arbib 1998). Virtual fingers are one or more real fingers working together aiming to achieve a stable grip. Thus in the side opposition grip performed by monkeys in our behavioral task, the VF1 and VF2 are the thumb and the index finger, respectively, whereas in the palm opposition grip, the VF1 is the palm and VF2 constitutes any number of real fingers. The present

results also provide neurophysiological grounding to recent psychophysical findings showing that the CNS adopts simplifying strategies to reduce the complexity of hand control (Mason et al. 2001; Schieber and Santello 2004).

Once the grip type/motor schema has been coded by area F5, this area influences the execution of the chosen grip either through its direct connections with the primary motor cortex, area F1 (Dum and Strick 2005; Geyer et al. 2000), or through those with the spinal cord (He et al. 1993), or both. Concerning the former connections, a recent experiment investigated whether M1 outputs to intrinsic hand muscles could be influenced through activation of the bank region of F5 (Cerri et al. 2003). The results of this study show that F5 stimulation could produce substantial, long-lasting facilitation of EMG responses evoked by microstimulation of M1. The authors suggested that the mechanism most likely responsible for these effects would be the facilitation exerted by cortico-cortical input from F5 to M1. This suggestion is further supported by the study of Shimazu et al. (2004), which demonstrated that local microinjection of muscimol in the hand area of M1 abolished the F5-induced facilitation on the corticospinal volleys evoked from M1 stimulation.

Responses to object presentation

About half of the neurons not only responded during grasping execution but also responded to the presentation of an object or a set of objects, even when grasping movement was not required. We proposed that the responses to object presentation represent the description of the presented objects in motor terms ("motor representation" interpretation; see Murata et al. 1997; Rizzolatti et al. 2000). Every time an object is presented, its visual features are automatically "translated" into a potential motor action, regardless of any intention to move aiming at the object. This potential motor action describes the pragmatic physical properties of the objects.

The "motor representation" interpretation is corroborated by the fact that visuomotor neurons show a sustained discharge during the epochs preceding the onset of grasping, even during MD condition. This discharge could be interpreted in terms of unspecific motor preparation. However, two facts make this

hypothesis highly unlikely. First, the sustained activity in premovement epochs differs between the best and worst grip, both at the single and population levels. Second, this sustained discharge is absent in the corresponding epochs in motor neurons. Thus the most likely interpretation of this sustained discharge in visuomotor neurons is the persistence of the motor representation of the object to be grasped.

The results of cluster analysis further support the motor representation interpretation. This analysis for the F5 visuomotor neurons, based on the neural discharge during the object presentation epoch of OF and ML conditions, revealed that the six objects of the original turntable are grouped in the same way as in the cluster analysis based on the movement epoch discharge. It is also evident that clustering during the presentation epochs reflects the type of grip used to grasp these objects and not their shape. This becomes clearer if one compares the present results with the multidimensional scaling performed in AIP (Murata et al. 2000). This analysis, based on the responses of AIP object-type visually selective neurons to the sight of objects during fixation and hand manipulation tasks, resulted in a different object grouping, which was proposed to reflect the common geometric features among the objects of each cluster (Murata et al. 2000). The first cluster contained the cylinder, the cone, and the sphere, which are round objects, whereas the second cluster contained the ring and the plate, which are flat objects.

A slight discrepancy emerged in the cluster analysis of the objects of the special turntable: the clustering of the cylinder in container in the presentation epoch of the OF differs from its clustering in the presentation and movement epochs of ML. The structural complexity of this object may be a factor accounting for its peculiar clustering. However, there are two considerations to be made: First, the separation between the objects grasped with a prehension involving the thumb from the objects whose grasping does not require the participation of the thumb is evident in all three cases (presentation epoch of OF, presentation epoch of ML, movement epoch of ML). Second, the clustering obtained for the presentation epoch of ML highly resembles the one obtained for the movement epoch of ML. Both facts also indicate that in the case of the special turntable, the clustering at the presentation epochs mainly reflects the chosen grip and not the object shape.

The congruence between the visual and motor responses of visuomotor neurons strongly suggests the crucial role played by area F5 in the visuomotor transformation for grasping. This involvement is supported by a recent inactivation study (Fogassi et al. 2001). Inactivation of the bank sector of area F5 (where the visuomotor neurons are located) led to loss of the monkey's capacity to preshape the hand using visual information about the shape and the size of the object to be grasped. The deficit was not purely motor because the monkey was still able to grasp and manipulate the object using haptic information. Note that a similar deficit has been observed after the reversible inactivation of area AIP (Gallese et al. 1994). It has been proposed that both deficits were visuomotor, presumably attributable to the interruption of the F5–AIP circuit (see Fogassi et al. 2001). Indeed, the region of area F5 where visuomotor neurons are located is reciprocally connected with area AIP (Luppino et al. 1999), which occupies the rostral part of the lateral bank of the IPS.

Comparison with two other grasping-related areas (AIP, F2vr)

The behavioral paradigm used in the present study was also used to investigate the functional role of two other cortical areas—AIP, F2vr—both involved in the control of the execution of visually guided hand-grasping actions. This enables us to compare the properties of F5, AIP, and F2vr.

The grasping-related neurons of area AIP fall into three main classes (Murata et al. 2000; Sakata et al. 1995, 1998; Taira et al. 1990). Motor-dominant neurons discharge during grasping both in light and dark conditions and are silent during object fixation; visual-and-motor neurons discharge more strongly during grasping in light than in dark and respond to object presentation; visual-dominant neurons discharge during grasping in light and object presentation conditions, but not during grasping in dark.

The region of area F5 where visuomotor neurons are is also reciprocally connected with the ventro-rostral sector of dorsal premotor area F2, area F2vr (Marconi et al. 2001; Matelli et al. 1999), where grasping neurons are located (Raos et al. 2003, 2004).

Area F2vr contains motor, visuomotor, and visually modulated neurons. The F2vr motor and visuomotor neurons are similar to the corresponding types of F5 neurons. The characteristic of the F2vr visually modulated neurons is that they lose their grip and wrist orientation specificity in the MD condition (Raos et al. 2004).

When the properties of area F5 and AIP are compared, the following differences emerge: 1) in area F5 there are no neurons homologous to the AIP visual-dominant neurons; 2) the motor neurons are more numerous in F5 than in AIP (55 and 26%, respectively); and 3) fewer visually responsive neurons are in F5 than in AIP (45 and 74%, respectively). Moreover, although the object-related visual responses of AIP neurons reflect objects' common geometrical features, the object-related visual responses of F5 neurons reflect the chosen grip (see above). Furthermore, different from AIP, F5 visuomotor neurons also show activity during premovement epochs in the MD condition, when no visual information about the target object is available.

When the properties of area F5 and F2vr are compared, the main difference consists in the presence in area F2vr—both at single-neuron and population levels—of visually modulated neurons that lose their grip and wrist specificity in the MD condition. In contrast, the F5 population also maintains grip and wrist orientation specificity in the dark.

Possible role of F5, AIP, and F2vr in the control of grasping

Objects can be grasped in several ways according to their physical properties, the context, and the goal of the grasping agent. The same object can be grasped differently according to different goals (e.g., grasping a mug to drink from it, or grasping a mug to wash it), whereas different objects can afford similar grasps (e.g., see the clustering effect of cube, sphere, and cone and described in the present study of area F5).

The circuit formed by the three grasping-related areas (AIP, F5, F2vr) seems to play a crucial role in some of the above-mentioned grasping-related functions. Area AIP receives vi-

sual information about objects' 3D features, by means of its connections with inferotemporal cortex (Luppino et al. 2004). In this extrastriate visual region neurons responding to 3D object features (concavity, convexity) have been reported (Janssen et al. 1999). Another possible source of object-related visual information is CIP, where surface-orientation- and axis-orientation-selective neurons have been described (Sakata et al. 2005; Tsutsui et al. 2001). AIP visual-dominant neurons might play a role not simply in coding objects physical properties but, more important, in making available visual affordances to the motor system by means of the reciprocal connections linking AIP and F5. Area F5, with its higher percentage of motor neurons with respect to AIP, could play a major role in providing AIP with different types of motor schemata.

The AIP-F5 network can thus use the physical object properties to select the corresponding suitable motor schema according to the meaning of the object, the context, and the current goal of the action. Visuomotor neurons of both F5 and AIP most likely underpin this process. Considering that the reversible inactivation of area AIP (Gallese et al. 1994) and F5 (Fogassi et al. 2001) produces an impairment that is not just either sensory or motor, but involves the visuomotor transformation process, it is very difficult to disentangle the contribution of each of these two areas to this function. It is probably safer to say that the visuomotor transformation for grasping occurs in the AIP-F5 circuit as a whole. However, given the overall more prevalent motor role of F5 with respect to AIP, and the fact that only visuomotor neurons of the former area show selectivity during premovement epochs in the dark, it can be hypothesized that area F5 might play a leading role in the selection of the more suitable motor schema to be activated.

F2vr codes the grip-wrist orientation combination required to grasp the object under visual guidance, given the loss of specificity of its neurons in the MD condition (Raos et al. 2004). F2vr also appears to associate the motor representation of the object (very likely provided by its connection with F5) with visual information provided by cortical areas of the superior parietal lobe and by area MST (Luppino et al. 2001; Matelli et al. 1998), to continuously update and control on-line the configuration and orientation of the hand as it approaches the object to be grasped. To date no data are available on the inactivation of area F2vr. Only by means of simultaneous multiple neural recordings from all three areas will it be possible to assign more specific roles to the different classes of neurons they contain.

In conclusion, the results of the present study clarify the role of area F5 in "representing" objects in motor terms, and provide neurophysiological grounding to many recent brain imaging results showing that in humans the ventral premotor cortex is also activated during the mere observation, silent naming, and imagery of use of tools and manipulables (see Chao and Martin 2000; Grafton et al. 1996; Martin et al. 1996; Perani et al. 1995).

GRANTS

This work was supported by Ministero Italiano dell'Università e della Ricerca and a European Neuroscience Program fellowship to V. Raos.

REFERENCES

- Arbib MA, Iberall T, and Lyons D. Coordinated control programs for control of the hands. In: *Hand Function and the Neocortex*, edited by Goodwin AW and Darian-Smith I. Berlin: Springer-Verlag. *Exp Brain Res Suppl* 10: 111-129, 1985.
- Brochier T, Spinks RL, Umiltá MA, and Lemon RN. Patterns of muscle activity underlying object-specific grasp by the macaque monkey. *J Neurophysiol* 92: 1770-1782, 2004.
- Cerri G, Shimazu H, Maier MA, and Lemon RN. Facilitation from ventral premotor cortex of primary motor cortex outputs to macaque hand muscles. *J Neurophysiol* 90: 832-842, 2003.
- Chao LL and Martin A. Representation of manipulable man-made objects in the dorsal stream. *Neuroimage* 12: 478-484, 2000.
- Di Pellegrino G and Wise SP. Visuospatial versus visuomotor activity in the premotor and prefrontal cortex of a primate. *J Neurosci* 13: 1227-1243, 1993.
- Dum PR and Strick PL. Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *J Neurosci* 25: 1375-1386, 2005.
- Fagg AH and Arbib MA. Modeling parietal-premotor interactions in primate control of grasping. *Neural Netw* 11: 1277-1303, 1998.
- Fogassi L, Gallese V, Buccino G, Craighero L, Fadiga L, and Rizzolatti G. Cortical mechanism for the visual guidance of hand grasping movements in the monkey: a reversible inactivation study. *Brain* 124: 571-586, 2001.
- Fogassi L, Gallese V, Fadiga L, Luppino G, Matelli M, and Rizzolatti G. Coding of peripersonal space in inferior premotor cortex (area F4). *J Neurophysiol* 76: 141-157, 1996.
- Gallese V, Fadiga L, Fogassi L, and Rizzolatti G. Action recognition in the premotor cortex. *Brain* 119: 593-609, 1996.
- Gallese V, Murata A, Kaseda M, Niki N, and Sakata H. Deficit of hand reshaping after muscimol injection in monkey parietal cortex. *Neuroreport* 5: 1525-1529, 1994.
- Gentilucci M, Fogassi L, Luppino G, Matelli M, Camarda R, and Rizzolatti G. Functional organization of inferior area 6 in the macaque monkey. I. Somatotopy and the control of proximal movements. *Exp Brain Res* 71: 475-490, 1988.
- Geyer S, Matelli M, Luppino G, and Zilles K. Functional neuroanatomy of the primate isocortical motor system. *Anat Embryol (Berl)* 202: 443-474, 2000.
- Grafton ST, Arbib MA, Fadiga L, and Rizzolatti G. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. *Exp Brain Res* 112: 103-111, 1996.
- He SQ, Dum RP, and Strick PL. Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. *J Neurosci* 13: 952-980, 1993.
- Janssen P, Vogels R, and Orban GA. Macaque inferior temporal neurons are selective for disparity-defined three-dimensional shapes. *Proc Natl Acad Sci USA* 96: 8217-8222, 1999.
- Jeannerod M, Arbib MA, Rizzolatti G, and Sakata H. Grasping objects: the cortical mechanisms of visuomotor transformation. *Trends Neurosci* 18: 314-320, 1995.
- Johnson PB, Ferraina S, Bianchi L, and Caminiti R. Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb Cortex* 6: 102-119, 1996.
- Kurata K. Premotor cortex of monkeys: set- and movement-related activity reflecting amplitude and direction of wrist movements. *J Neurophysiol* 69: 187-200, 1993.
- Kurata K and Wise SP. Premotor cortex of rhesus monkeys: set-related activity during two conditional motor tasks. *Exp Brain Res* 69: 327-343, 1988.
- Luck SJ, Chelazzi L, Hillyard SA, and Desimone R. Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *J Neurophysiol* 77: 24-42, 1997.
- Luppino G, Calzavara R, Rozzi S, and Matelli M. Projections from the superior temporal sulcus to the agranular frontal cortex in the macaque. *Eur J Neurosci* 14: 1035-1040, 2001.
- Luppino G, Matelli M, Camarda RM, Gallese V, and Rizzolatti G. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J Comp Neurol* 311: 463-482, 1991.
- Luppino G, Murata A, Belmalih A, Calzavara R, and Rozzi S. Ventral visual stream information to the AIP-F5 circuit for grasping: a tracing study in the macaque monkey. Program No. 655.5. *2004 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, Online, 2004.
- Luppino G, Murata A, Govoni P, and Matelli M. Largely segregated parietofrontal connections linking rostral intraparietal cortex (areas AIP and

- VIP) and the ventral premotor cortex (areas F5 and F4). *Exp Brain Res* 128: 181–187, 1999.
- Marconi B, Genovesio A, Battaglia-Mayer A, Ferraina S, Squatrito S, Molinari M, Lacquaniti F, and Caminiti R.** Eye-hand coordination during reaching. I. Anatomical relationships between parietal and frontal cortex. *Cereb Cortex* 11: 513–527, 2001.
- Martelli M, Wiggs CL, Ungerleider LG, and Haxby JV.** Neural correlates of category-specific knowledge. *Nature* 379: 649–652, 1996.
- Mason CR, Gomez JE, and Ebner TJ.** Hand synergies during reach-to-grasp. *J Neurophysiol* 86: 2896–2910, 2001.
- Matelli M, Govoni P, Galletti C, Kutz DF, and Luppino G.** Superior area 6 afferents from the superior parietal lobule in the macaque monkey. *J Comp Neurol* 402: 327–352, 1998.
- Matelli M, Luppino G, Govoni P, and Geyer S.** Anatomical and functional subdivisions of inferior area 6 in macaque monkey. *Soc Neurosci Abstr* 22: 796.792, 1996.
- Matelli M, Marconi B, Caminiti R, and Luppino G.** Arm representations of dorsal and ventral premotor cortices are reciprocally connected. *Soc Neurosci Abstr* 25: 382, 1999.
- Moody SL and Zipser D.** A model of reaching dynamics in primary motor cortex. *J Cogn Neurosci* 10: 35–45, 1998.
- Murata A, Fadiga L, Fogassi L, Gallese V, Raos V, and Rizzolatti G.** Object representation in the ventral premotor cortex (area F5) of the monkey. *J Neurophysiol* 78: 2226–2230, 1997.
- Murata A, Gallese V, Kaseda M, and Sakata H.** Parietal neurons related to memory-guided hand manipulation. *J Neurophysiol* 75: 2180–2186, 1996.
- Murata A, Gallese V, Luppino G, Kaseda M, and Sakata H.** Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *J Neurophysiol* 83: 2580–2601, 2000.
- Napier J.** *Hands*. Princeton, NJ: Princeton Univ. Press, 1993.
- Napier JR.** The form and function of the carpo-metacarpal joint of the thumb. *J Anat* 89: 362–369, 1955.
- Napier JR.** The prehensile movements of the human hand. *J Bone Joint Surg Br* 38-B: 902–913, 1956.
- Perani D, Cappa SF, Bettinardi V, Bressi S, Gorno-Tempini M, Matarrese M, and Fazio F.** Different neural systems for the recognition of animals and man-made tools. *Neuroreport* 6: 1637–1641, 1995.
- Raos V, Franchi G, Gallese V, and Fogassi L.** Somatotopic organization of the lateral part of area F2 (dorsal premotor cortex) of the macaque monkey. *J Neurophysiol* 89: 1503–1518, 2003.
- Raos V, Umiltà MA, Gallese V, and Fogassi L.** Functional properties of grasping-related neurons in the dorsal premotor area F2 of the macaque monkey. *J Neurophysiol* 92: 1990–2002, 2004.
- Rizzolatti G, Camarda R, Fogassi L, Gentilucci M, Luppino G, and Matelli M.** Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movements. *Exp Brain Res* 71: 491–507, 1988.
- Rizzolatti G, Fogassi L, and Gallese V.** Cortical mechanisms subserving object grasping and action recognition: a new view on the cortical motor functions. In: *The New Cognitive Neurosciences*, edited by Gazzaniga MS. Cambridge, MA: MIT Press/Bradford, 2000, p. 539–552.
- Rizzolatti G and Gentilucci M.** Motor and visuomotor functions of the premotor cortex. In: *Neurobiology of Neocortex, Dahlem Konferenzen der Freien Universität Berlin*, edited by Rakić P and Singer WS. Chichester, UK: John Wiley Ltd, 1988, p. 269–284.
- Rizzolatti G, Luppino G, and Matelli M.** The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 106: 283–296, 1998.
- Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y, and Tsutsui K.** Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. *Philos Trans R Soc Lond B Biol Sci* 353: 1363–1373, 1998.
- Sakata H, Taira M, Murata A, and Mine S.** Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cereb Cortex* 5: 429–438, 1995.
- Sakata H, Tsutsui K, and Taira M.** Toward an understanding of the neural processing for 3D shape perception. *Neuropsychologia* 43: 151–161, 2005.
- Schieber MH and Santello M.** Hand function: peripheral and central constraints on performance. *J Appl Physiol* 96: 2293–2300, 2004.
- Shimazu H, Maier MA, Cerri G, Kirkwood PA, and Lemon RN.** Macaque ventral premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb motoneurons. *J Neurosci* 24: 1200–1211, 2004.
- Soechting JF and Flanders M.** Flexibility and repeatability of finger movements during typing: analysis of multiple degrees of freedom. *J Comput Neurosci* 4: 29–46, 1997.
- Taira M, Mine S, Georgopoulos AP, Murata A, and Sakata H.** Parietal cortex neurons of the monkey related to the visual guidance of hand movement. *Exp Brain Res* 83: 29–36, 1990.
- Tsutsui K, Jiang M, Yara K, Sakata H, and Taira M.** Integration of perspective and disparity cues in surface-orientation-selective neurons of area CIP. *J Neurophysiol* 86: 2856–2867, 2001.
- Weinrich M and Wise SP.** The premotor cortex of the monkey. *J Neurosci* 2: 1329–1345, 1982.
- Weinrich M, Wise SP, and Mauritz KH.** A neurophysiological study of the premotor cortex in the rhesus monkey. *Brain* 107: 385–414, 1984.