Mirror Neurons Responding to Observation of Actions Made with Tools in Monkey Ventral Premotor Cortex

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Abstract

■ In the present study, we describe a new type of visuomotor neurons, named *tool-responding mirror neurons*, which are found in the lateral sector of monkey ventral premotor area F5. Tool-responding mirror neurons discharge when the monkey observes actions performed by an experimenter with a tool (a stick or a pair of pliers). This response is stronger than that obtained when the monkey observes a similar action made with a biological effector (the hand or the mouth). These neurons respond also when the monkey executes actions with both the hand and the mouth. The visual and the motor responses of each neuron are congruent in that they share the same general goal, that is, taking possession of an object and modifying its state. It is hypothesized that after a relatively long visual exposure to tool actions, a visual association between the hand and the tool is created, so that the tool becomes as a kind of prolongation of the hand. We propose that tool-responding mirror neurons enable the observing monkey to extend action-understanding capacity to actions that do not strictly correspond to its motor representations. Our findings support the notion that the motor cortex plays a crucial role in understanding action goals. ■

INTRODUCTION

In area F5 of monkey ventral premotor cortex, there are neurons that become active both when the monkey executes hand and mouth goal-directed actions and when it observes similar actions made by another individual (Ferrari, Gallese, Rizzolatti, & Fogassi, 2003; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). These neurons have been called *mirror neurons* (Gallese et al., 1996). Mirror neurons do not respond either to simple object presentation or to vision of an action mimed with the hand or with the mouth. Observation of actions performed using a tool, such as pliers, is not effective in eliciting mirror neuron response. The visual response of mirror neurons is largely independent from the distance at which the observed action is performed and from the properties of the object's target of the observed actions. Most importantly, mirror neurons show a very good congruence between the effective observed and the effective executed action. This visuomotor congruence has prompted the idea that the basic function of mirror neurons consists in understanding actions made by other individuals (Rizzolatti, Fogassi, & Gallese, 2000; Gallese et al., 1996; Rizzolatti, Fadiga, Gallese, et al., 1996; di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992) by a process that matches the visual description of an action with the internal motor representation of the same action in the observer.

Although many mirror neurons are activated by the observation of actions made with a specific effector, a considerable number of F5 mirror neurons are activated by the observation of actions independent of the effector (see Ferrari, Fogassi, Gallese, & Rizzolatti, 2001). For example, a mirror neuron may respond when the monkey observes another individual breaking a peanut with the hand and also when the same action is performed with the mouth. Thus, mirror neurons have the property to generalize the meaning of an observed action independently of its specific visual features.

Brain imaging and magnetic encephalogram studies have demonstrated in humans a system for action recognition similar to that of monkeys. It includes the premotor cortex and the adjacent area 44, Broca's area (Buccino, Binkofski, et al., 2001; Nishitani & Hari, 2000; Iacoboni et al., 1999; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Rizzolatti, Fadiga, Matelli, et al., 1996), the human homologue of area F5 (Petrides & Pandya, 1994; von Bonin & Bailey, 1947). However, differently from monkeys, fMRI studies showed that the human inferior frontal cortex is activated also by observation of mimed actions (Buccino, Binkofski, et al., 2001; Grèzes, Costes, & Decety, 1998). This latter finding is in agreement with the common observation that humans interpret movements as goal-directed also when there is no target (mimed actions) or when the target is present, but the action is made with a tool.

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The experiments reported above are evidence that action understanding in humans is linked to an activation of the mirror system, also when understanding implies a high level of generalization. Apparently, this latter property seems absent in monkeys as far as mimed actions and actions made with tools are concerned. However, few observations made in our laboratory showed that at the end of a relatively long period of experiments, it was possible to find mirror neurons responding also to actions made by the experimenter with tools (see Arbib & Rizzolatti, 1999).

In the present study, we describe the properties of a new class of F5 visuomotor neurons (tool-responding mirror neurons) responding to the observation of actions performed with a tool. In accord with the above-mentioned observations, all neurons reported in the present study were found after a long period of experiments, during which the monkeys had been highly exposed to actions made with tools by the experimenters. Considering the importance of the idea of generalization of action goal at the single neuron level, the aim of this study was that of verifying in a quantitative way the properties of this new class of neurons and their differences with hand mirror neurons.

RESULTS

Properties of Recorded Neurons

We recorded a total of 209 neurons from area F5 of two macaque monkeys (*Macaca nemestrina*). One hundred forty-one neurons were recorded from Monkey 1 (right hemisphere) and 68 from Monkey 2 (left hemisphere). Most recorded neurons were located in the lateral part of area F5, as defined by Matelli, Luppino, and Rizzolatti (1985). In Monkey 1, we investigated also part of medial F5.

All neurons were tested for their responsiveness to monkey active movements and to visual stimuli (see also Methods). Testing motor properties mainly consisted in eliciting hand, arm, and mouth actions by presenting to the monkey pieces of food and objects of different sizes, shapes, and orientations, introduced in every spatial quadrant. Testing of visual properties consisted in the presentation of actions made by the experimenter with the hand, the mouth, and a tool. The tools used in this study were chosen based on the similarity between the types of goal that could be achieved with them and the types of goal normally achieved with the biological effector. Two types of tools were employed: a stick with a metal tip and a pair of pliers. Other visual stimuli consisted of the presentation of static and moving objects at different space locations.

All recorded neurons, but 8 (3.8%), had motor properties. More specifically, 52 (24.9%) discharged in association with active hand actions, 40 (19.1%) with mouth actions, and 109 (52.2%) with both hand and mouth

actions. The large prevalence of mouth-movement-related neurons is most likely because of the lateral location of most penetrations.

Of all recorded neurons, 143 (68.4%) responded to visual stimuli. This percentage is relatively high when compared with previous work from our laboratory on area F5. This is probably because of the fact that during recording the focus of our interest was concentrated on neurons with visual responses and in particular on those responding to biological stimulation. Forty-two neurons (20.1% of all recorded neurons) responded best to the observation of actions performed with a tool by an experimenter. Because of the similarity of their visuo-motor properties with those of mirror neurons, these neurons will be referred to as *tool-responding mirror neurons*. They do not respond to simple presentation of the tool or of other objects or food. All tool-responding mirror neurons had a motor response. Of 42 tool-responding mirror neurons, 8 (19.0%) responded during the execution of actions made with the hand, 3 (7.2%) with the mouth, and 31 (73.8%) with both the hand and the mouth.

Of the other visual neurons, 74 (35.4% of the total number of recorded neurons) were typical mirror neurons responding best to the observation of hand, mouth, or hand and mouth actions. A subset of these mirror neurons (*n* = 12) presented also a weaker response to observation of actions performed with a tool. The remaining visual neurons (*n* = 27, 12.9% of the total number of recorded neurons) responded to other types of visual stimuli, such as object presentation or object motion.

Tool-Responding Mirror Neurons Properties

Thirty-three tool-responding mirror neurons were studied long enough to quantitatively assess their properties. The specificity of the neuron discharge was assessed by comparing its response during the condition in which the monkey observed an action made with a tool, with the response during the other conditions as, namely, observation of actions made with a biological effector, observation of mimed actions performed with a tool, and simple object observation. All tool-responding mirror neurons had higher responses to observation of actions made with a stick (*n* = 26), with pliers (*n* = 4), or with both (*n* = 3) when compared with actions made with a biological effector, either the hand or the mouth (*p* < .05, two-way analysis of variance [ANOVA] for repeated measures followed by a post hoc test). These neurons did not respond to observation of actions mimed with the tool or with a biological effector without the target object. Similarly, they did not respond to simple presentation of an object when this was presented on the tip of the tool. When tested, tool-responding mirror neurons did not respond to the observation of actions made with an

unfamiliar tool (a signal stick, which is a wooden, colored circle attached to the tip of a long stick) aimed to touch the target object, but devoid of the possibility to pick it up. The visual response of tool-responding mirror neurons was always excitatory. Note that in 29 neurons, there was also a weak response to observation of an action made with the biological effector, whereas in 4 neurons, this response was absent.

The responses of tool-responding mirror neurons were independent of the distance and the space sector where the observed action was performed by the experimenter. Similarly, the size and shape of the object target did not seem to affect the intensity of the response, provided that the differences of these physical properties were not such as to modify the meaning of the action. For example, sticking a small or a large piece of apple evoked the same discharge. Although not tested in all neurons, the direction of the action toward the target did not seem to influence the neuron response.

Table 1 summarizes the main categories of "tool-responding mirror neurons" (see Methods section for the definition of the types of actions made with the stick and the pliers). The classification criterion was based on the most effective observed action performed with a tool. The most represented categories, either alone or associated to other actions, were "sticking" and "holding."

Figure 1 shows an example of a neuron (Unit 88) selective for the observation of a sticking action. The experimenter approached a small piece of food placed on one hand with a stick held with the other, took the food, and held it (Condition A). This neuron began to respond during the approaching phase of the stick to the food. The response peak occurred when the food was punctured, and the discharge continued during the holding phase. The neuron response was smaller when the experimenter grasped the same piece of food with his hand (B). Mimicking the sticking action

Table 1. Tool-Responding Mirror Neurons Subdivided According to the Most Effective Observed Actions in Activating Them

Category	Number of Neurons
Sticking	5
Holding	4
Others	4
Sticking or grasping*/holding	13
Sticking/manipulating	2
Approaching/sticking	2
Others	3
Total	33

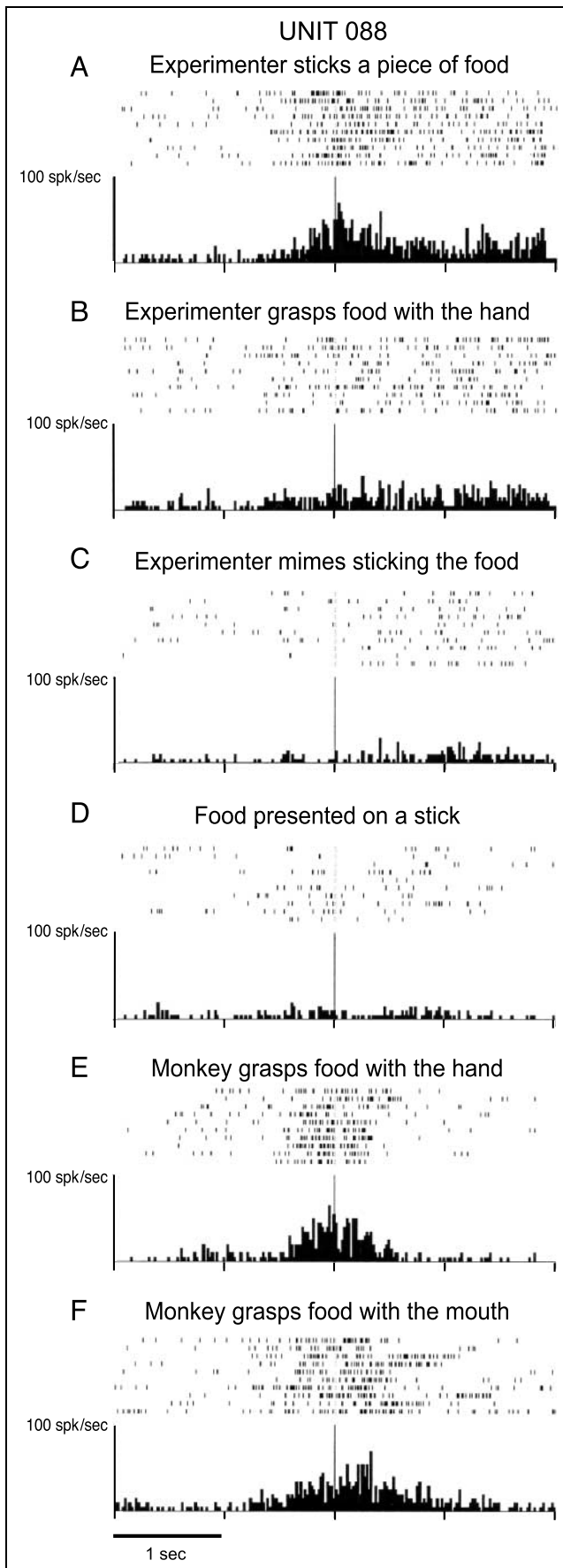*The term *grasping* is referred to action made with pliers.

without food elicited only a very weak response (C). No response was elicited by the simple presentation of a piece of food held on the stick (D). A strong response was evoked when the monkey grasped a small piece of food with its hand (E) or its mouth (F). Note that also the motor response, as the visual response, began during the approaching phase of grasping and peaked when the hand or the mouth closed on the food.

Figure 2 shows an example of a neuron (Unit 102) selective for the observation of an action made with pliers. The neuron discharged when the experimenter grasped and broke a peanut, held on his hand, using a pair of pliers (A). The response occurred during both grasping and breaking phases. The same grasping and breaking actions performed by the experimenter with his hand were much less effective (B). This neuron responded also when the monkey broke a small piece of food with the hand (C) or the mouth (D). Note that the intensity of neuron discharge during monkey breaking action is lower than that during action observation, probably because the breaking action made by the monkey is more prolonged in time.

Figure 3 shows an example of a neuron (Unit 111) selective for the observation of an action made with pliers. The neuron discharged when the experimenter grasped and held a piece of food, placed on a tray, using a pair of pliers moved with his right hand (A). The response occurred during both grasping and holding phases. The same grasping and holding actions performed by the experimenter with the stick (B) was less effective, in particular during the approaching phase until the contact of the tool with the food. During observation of grasping action made with the hand (C), the neuron response was almost absent. This neuron responded also when the monkey grasped and held a piece of food with the hand (D).

Figure 4 shows an example of a neuron (Unit 95) responding to the observation of actions made on a piece of food with both stick (A) and pliers (B). A strong discharge was present during the approaching, grasping, and holding phase with both tools. Statistical analysis revealed that the response to observation of the action performed with the stick was greater than that performed with the pliers. In contrast, the observation of a grasping action performed with the hand was not effective (C). Miming a sticking action was also poorly effective (D). Finally, the strongest response was found when the monkey grasped food with the hand (E).

In general, most "tool-responding mirror neurons" differentiated between observed actions made with tools and those made with biological effectors, as expressed by the quantitative significant difference in the discharge displayed in the two different conditions. In few cases ($n = 2$), this difference was further strengthened by a completely opposite excitatory/inhibitory behavior of

UNIT 088

A Experimenter sticks a piece of food

100 spk/sec

B Experimenter grasps food with the hand

100 spk/sec

C Experimenter mimes sticking the food

100 spk/sec

D Food presented on a stick

100 spk/sec

E Monkey grasps food with the hand

100 spk/sec

F Monkey grasps food with the mouth

100 spk/sec

1 sec

the neuron discharge. A clear example of this type of neurons is presented in Figure 5. This neuron (Unit 92) was selective for the observation of sticking a piece of food. The excitatory response (A) was observed from the moment in which the experimenter approached the food with the stick to the whole holding phase. In contrast, when the experimenter grasped food with the hand (B), during the approaching and grasping phase, there was a complete inhibition of the neuron response. However, the holding phase, similarly to condition A, was excitatory. Thus, the discrimination between the two actions is present during the approaching and grasping/sticking phase only. When the experimenter mimed the sticking action (C) and when the food was simply presented on the stick (D), the neuron did not fire. An excitatory motor response occurred when the monkey grasped a small piece of food (not shown in the figure).

The capacity of these neurons to discriminate between actions made with the tool and actions made with a biological effector is evident also when the two observation conditions are presented in alternation during the same acquisition. The neuron (Unit 100) shown in Figure 6 is selective for the observation of an action made with a stick, the response occurring during the holding phase (A). When the experimenter grasped food with the hand (B), there was only a weak neuron response. The same difference in response between the two conditions is clear also when the two visual stimuli are presented in alternation (C).

Considering the clear difference, at least in pictorial terms, between the effectors involved in the observed and the executed actions (i.e., tool and hand, respectively), we analyzed whether it was possible to find a relationship between the visual and motor response of each neuron in terms of action goal. For example, if a neuron responded to the observation of sticking and holding a piece of food and when the monkey grasped

Figure 1. Example of a tool-responding mirror neuron responding to a sticking action. In each panel, the rasters and the histogram represent the neuron response during a single experimental condition. The histogram represents the average of 10 trials. Rasters and histograms are aligned with the moment in which the stick held by the experimenter touched the food or the tray (observation conditions), when the monkey touched the food with the hand or the mouth (motor conditions), or when the food was abruptly presented (presentation condition). Ordinates, spikes per sec; abscissa, time; bin width, 20 msec. (A) The experimenter approaches with the stick, held in his hand, a piece of food placed on a tray, and then punctures and holds it. (B) The experimenter grasps with his hand a piece of food placed on a tray and then holds it. (C) The experimenter makes the same approaching and sticking movement as in (A), but no food is present. (D) The experimenter introduces abruptly a piece of food held on a stick in the monkey visual field and then keeps it still. In all observation conditions, the stimulus was presented at about 75 cm from the monkey. (E) Monkey grasps a piece of food with the hand. (F) The experimenter moves a piece of food toward the monkey's mouth; the monkey grasps it with its teeth and eats it.
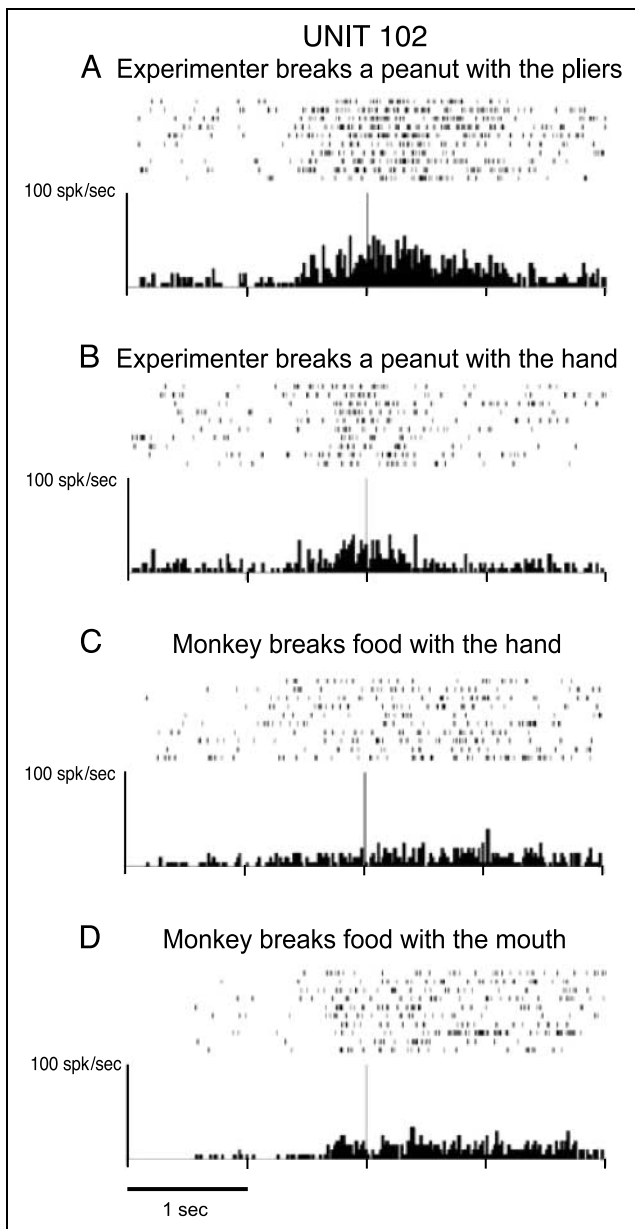
UNIT 102

A Experimenter breaks a peanut with the pliers

100 spk/sec

B Experimenter breaks a peanut with the hand

100 spk/sec

C Monkey breaks food with the hand

100 spk/sec

D Monkey breaks food with the mouth

100 spk/sec

1 sec

Figure 2. Example of a tool-responding mirror neuron responding to an action made with pliers. (A) The experimenter approaches, with a pair of pliers held in his hand, a peanut held on the other hand, then he closes the pliers on the peanut and breaks it. (B) The experimenter grasps with his hand a peanut held on the other hand and then breaks it. (C) Monkey breaks a piece of food with the hand. (D) The experimenter moves a piece of food to the monkey's mouth; the monkey grasps it with its teeth, breaks it, and eats it. Other conventions as in Figure 1.

rons (30/33) show a very good similarity between the goal of the observed and executed effective actions. In several neurons, the similarity was very strict. Thus, the visual and motor responses of tool-responding mirror neurons can be interpreted as sharing the same type of action code.
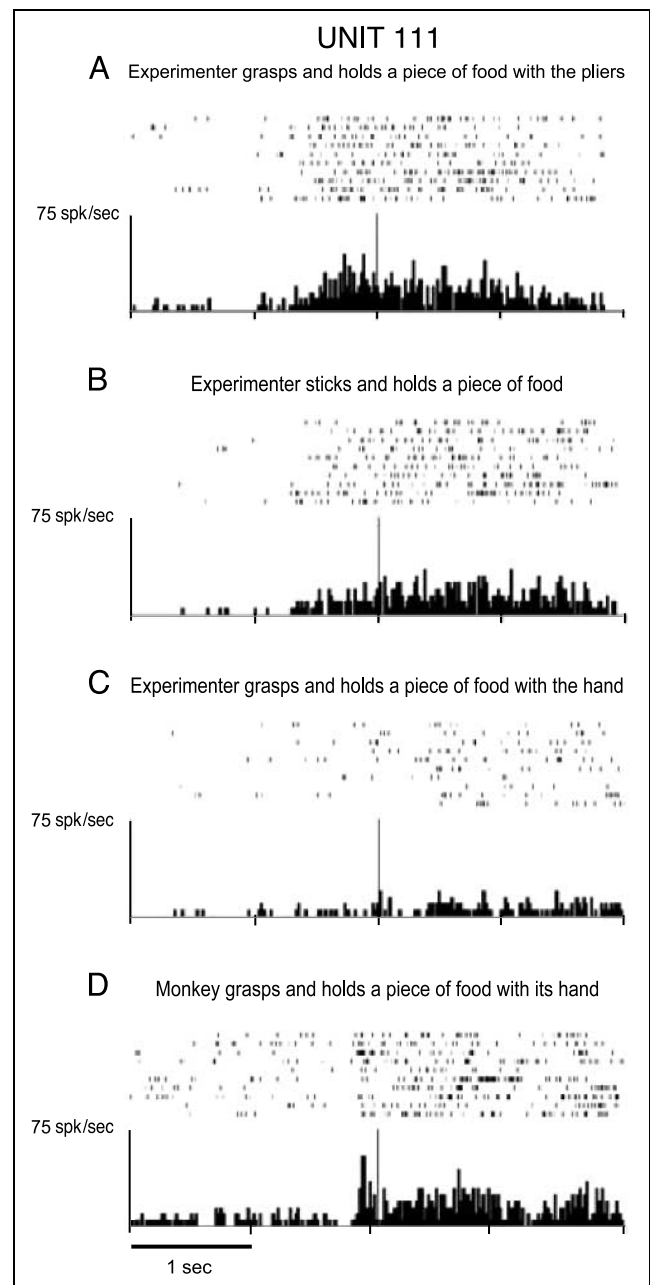
UNIT 111

A Experimenter grasps and holds a piece of food with the pliers

75 spk/sec

B Experimenter sticks and holds a piece of food

75 spk/sec

C Experimenter grasps and holds a piece of food with the hand

75 spk/sec

D Monkey grasps and holds a piece of food with its hand

75 spk/sec

1 sec

Figure 3. Another example of a tool-responding mirror neuron responding to an action made with pliers. (A) The experimenter approaches, with a pair of pliers held in his hand, a piece of food placed on a tray, then he closes the pliers on the piece of food, grasps it, and holds it. (B) The experimenter approaches with the stick, held in his hand, a piece of food placed on a tray, and then punctures and holds it. (C) The experimenter grasps with his hand a piece of food placed on a tray and then holds it. (D) Monkey grasps a piece of food with the hand and holds it. Other conventions as in Figure 1.

and held a similar piece of food, the two responses were considered similar in terms of action goal, as both responses signaled taking and keeping possession of food. Differently, if a neuron responded to the observation of taking away food from a tray with the stick and during grasping execution by the monkey, the two responses were considered not similar. From this analysis, it emerges that most tool-responding mirror neu-

Behavioral Observation

At the end of the recording sessions, we tested in one of the recorded monkeys (Monkey 1) the ability to use the familiar tool (the stick used as a visual stimulus during the experiment) to stick food out of reach. A small
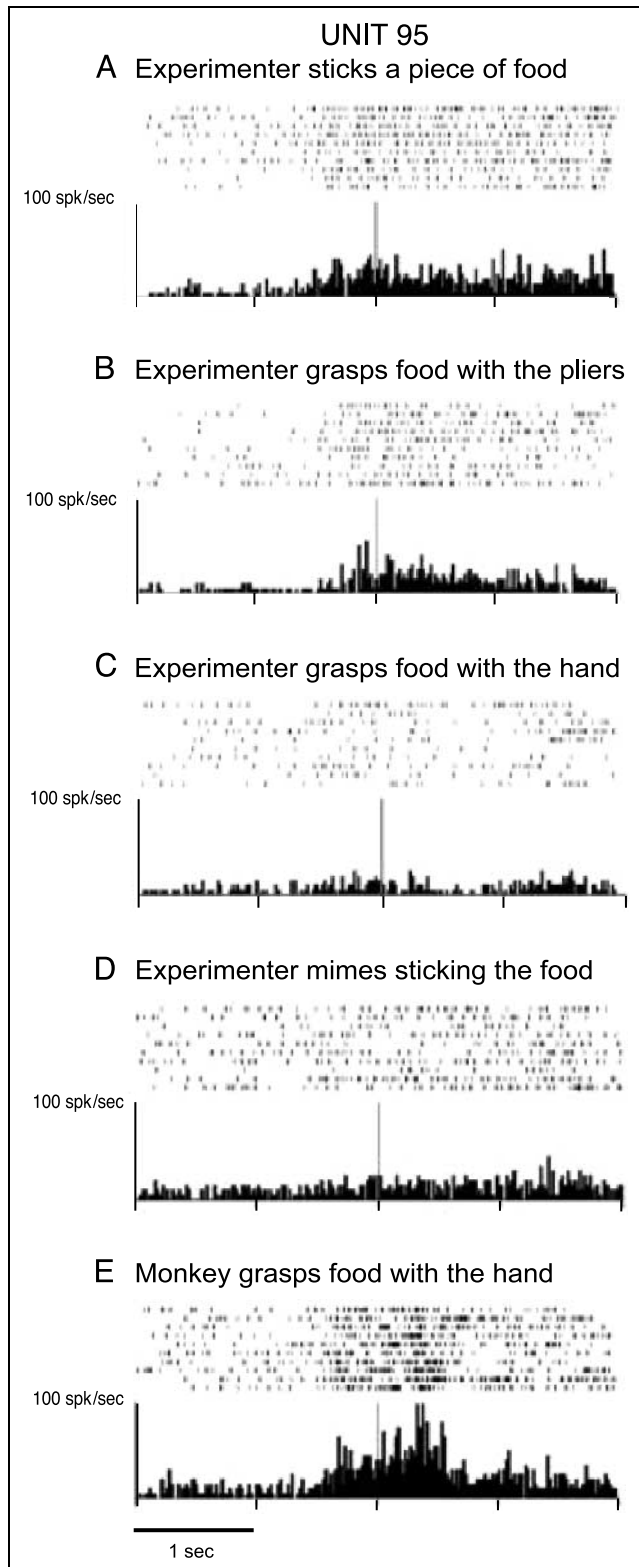
wooden platform (1 × 1 m) was attached to the monkey's home cage at floor level. Small pieces of food (raisins, apple, and peanuts) were placed on the platform at a distance that did not allow the monkey to reach the food with its hand. Ten minutes after food presentation, in which the monkey made some unsuccessful attempts to take the food, we introduced the stick, placing it on the platform at a reaching distance. The experimenter went out of the monkey room and monitored for 1 hr the monkey's behavior watching a screen connected to a video camera placed 2 m away in front of the monkey. The videotape was then analyzed by two experimenters. During this brief test, the monkey never attempted to use the tool for reaching food, although in the first minutes after the stick was available, the monkey grasped it and bit it. After few minutes, the monkey ignored the stick, trying to take the food by moving the platform.

Histology and Anatomical Location of Tool-Responding Mirror Neurons

Figure 7 shows the location of the penetrations where tool-responding mirror neurons were found. Histological analysis of the microelectrode tracks showed that most penetrations were located in the rostrolateral sector of the post-arcuate cortex. This sector is included within the limits of area F5, as defined based on cytochrome oxidase method (Matelli et al., 1985). It should be noted, however, that the cytochrome oxidase histochemical material was not available in this case. In fact, because the experimental monkeys were also used for neuroanatomical experiments in which fluorescent dyes were injected in other cortical areas, a fixation protocol was used (paraformaldehyde 3.5%), which, in our experience, gives very poor results in cytochrome oxidase histochemistry. Thus, our penetrations have been assigned to lateral F5 based on their anatomical location. Note, however, that in Monkey 1, about one third of penetrations were located in the medial part of F5 (see Figure 7A). In this monkey, we made a comparison between the percent of tool-responding mirror neurons recorded in lateral F5 and those recorded in medial F5. In medial F5, 11.8% (4/34) of the recorded neurons were tool-responding mirror neurons, while in lateral F5, the

Figure 4. Example of a tool-responding mirror neuron responding to an action made with both the stick and the pliers. (A) The experimenter approaches with the stick, held in his hand, a piece of food placed on a tray, and then punctures and holds it. (B) The experimenter approaches with the pliers, held in his hand, a piece of food placed on a tray, and then grasps it and holds it. (C) The experimenter grasps with his hand a piece food placed on a tray and then holds it. (D) The experimenter makes the same approaching and sticking movement as in (A), but no food is present. (E) Monkey grasps a piece of food with the hand. Other conventions as in Figure 1.
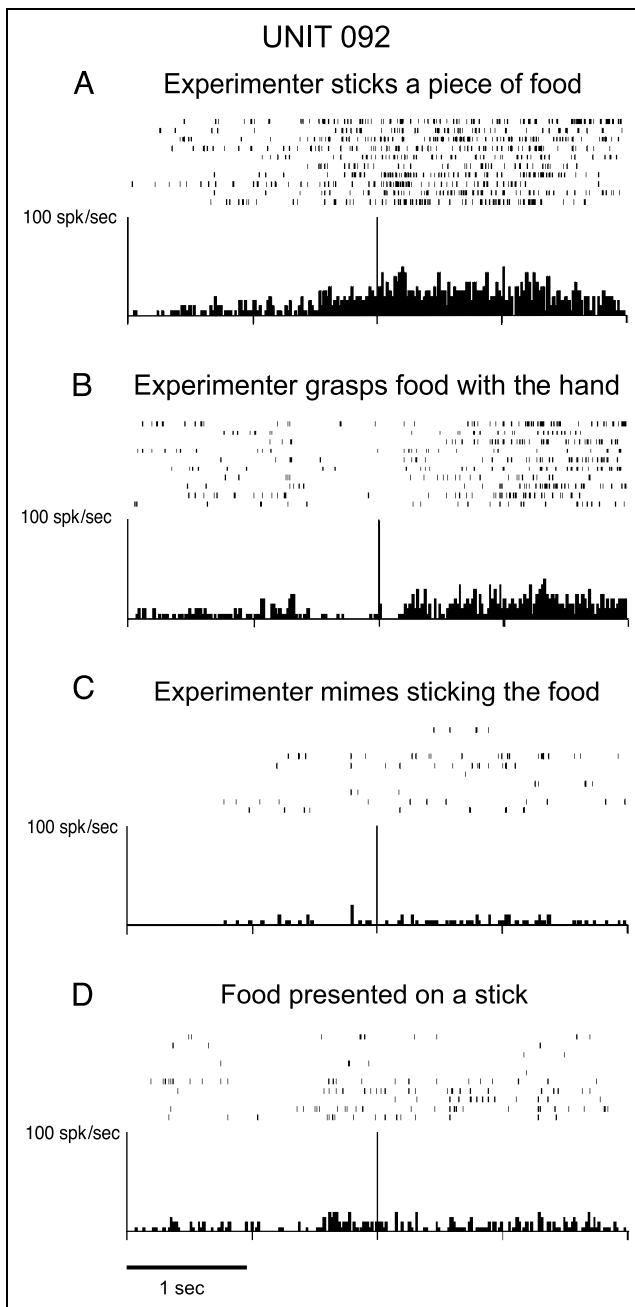
UNIT 092

A Experimenter sticks a piece of food

100 spk/sec

B Experimenter grasps food with the hand

100 spk/sec

C Experimenter mimes sticking the food

100 spk/sec

D Food presented on a stick

100 spk/sec

1 sec

Figure 5. Example of a tool-responding mirror neuron responding to a sticking action. (A) The experimenter approaches with the stick, held in his hand, a piece of food placed on a tray, and then punctures and holds it. (B) The experimenter grasps with his hand a piece of food placed on a tray and then holds it. (C) The experimenter makes the same approaching and sticking movement as in (A), but no food is present. (D) The experimenter introduces abruptly a piece of food held on a stick in the monkey visual field and then keeps it still. Other conventions as in Figure 1.

percent of tool-responding mirror neurons was 31.3% (26/83). As far as the depth location of tool-responding mirror neurons is concerned, almost all of them (more than 90%) were recorded at a depth ranging from 200 to 2200 μm from the cortical surface (Figure 7B).

Time of Exposure to the Acting Tools, Period of Recording, and Frequency of Tool-Responding Mirror Neurons

During the training period preceding recording experiments, both monkeys were exposed, among other visual stimuli, to the tools used in the present experiment (see also Methods). Recordings lasted 9 months in Monkey 1 and 5.5 months in Monkey 2, with a frequency of 3–4 days of recording per week. The data of the recording period before discovery of tool-responding mirror neurons have been used for other purposes. Note, however, that also in this period, both monkeys were exposed to tools. The period during which tool-responding mirror neurons have been collected (that is the last period of recording) was the same in both monkeys (1.5 months). In this period, because recording was focused on the acquisition of tool-responding mirror neurons, both monkeys were certainly more exposed to tools than in the previous recording period, although this cannot be quantified. The number of penetrations performed in the lateral part of F5 in the period in which tool-responding mirror neurons have been found was the same in the two monkeys ($n = 18$). The number of penetrations where tool-responding mirror neurons were found in the lateral part of F5 was significantly higher in Monkey 1 than in Monkey 2 (15/18 in Monkey 1, 6/18 in Monkey 2; $p < .01$, Fisher's Exact Probability test). The frequency of tool-responding mirror neurons in Monkey 1 was significantly higher than in Monkey 2 ($Z = -3.10$, $p < .005$, Mann–Whitney test).

In Monkey 1, a tendency to increase the frequency of occurrence of tool-responding mirror neurons (expressed as total number of tool-responding mirror neurons per penetration) was observed in the last part of the recording sessions. In fact, subdividing the total number of penetrations into three equivalent, temporally subsequent, blocks, there was a significant difference between the frequency of tool-responding mirror neurons (out of all recorded neurons) recorded in the third, last block and that of those recorded in the second block (15/36 vs. 7/34, $p < .05$, Fisher's Exact Probability test), whereas the frequency of the second block was not significantly different from that of the first block. In Monkey 2, we did not observe any change in the frequency of tool-responding mirror neurons over time. This could be partly because of the lower number of tool-responding mirror neurons found in this monkey in respect to the other.

DISCUSSION

The present study describes for the first time neurons of a premotor area (F5) responding to the observation of actions made with tools. These visual responses are not evoked by the simple motion of the tool, but by the observation of the interaction between the tool and an

object. In this respect, these responses resemble the visual responses of typical F5 hand mirror neurons, which have been found in the medial part of area F5.

The presence in F5 of neurons responding to the observation of tool actions, although not previously quantitatively described, is not completely unexpected, because, as mentioned in the Introduction, in some mirror neurons, visual responses to actions made with tools were found after a long period of experiment and of repeated visual exposure to the observation of the experimenter using tools (see Arbib & Rizzolatti, 1999). Consistent with this observation, also in our study, tool-responding mirror neurons were found during the later stage of the experiment.

A comparison between the present and the previous studies shows a difference in the location of different types of mirror neurons. In the present study, tool-responding mirror neurons have been found mainly in the lateral sector of the post-arcuate cortex, whereas the older studies on hand mirror neurons were mainly performed in its medial sector (Gallese et al., 1996; Rizzolatti, Fadiga, Gallese, et al., 1996; di Pellegrino et al., 1992). According to the histochemical parcellation of Matelli et al. (1985), the lateral sector of the post-arcuate cortex up to, and often beyond, the inferior tip of the arcuate sulcus is considered as part of area F5. Based on this parcellation, all our penetrations appear to belong to area F5. Note that area F5 has always been included in the cytoarchitectural area 6 of Brodmann. The cytoarchitectonic studies on ventral premotor cortex define the lateral part of the post-arcuate cortex until the inferior tip of the arcuate sulcus as part of the agranular cortex (Brodmann, 1905) or as a dysgranular cortex (Preuss & Goldman-Rakic, 1991; Barbas & Pandya, 1987; von Bonin & Bailey, 1947; Vogt & Vogt, 1919). According to some of these

authors (Preuss & Goldman-Rakic, 1991; Barbas & Pandya, 1987; Vogt & Vogt, 1919), the lateral part of the post-arcuate cortex is considered as a subsector partially different from the medial-most sector, thus, suggesting that the histochemically defined area F5 could be inhomogeneous. It must also be noted that for Roberts and Akert (1963), the region lying behind the most lateral part of the inferior arcuate sulcus would belong to the opercular cortex (PrCO). Although we are more inclined to think that tool-responding mirror neurons were located inside the border of ventral premotor cortex, we cannot completely exclude that some of the most lateral penetrations were located in another anatomical subdivision.

As far as the homogeneity of area F5 is concerned, functional data suggest that although the medial and the lateral sectors of F5 have similarities, they also have partially different visual and motor properties. The similarities between the medial and the lateral sectors consist, on the motor side, in the presence of neurons coding goal-directed actions and, on the visuomotor side, in the presence of neurons responding to the observation and execution of similar actions (mirror neurons). However, in the medial sector mirror neurons respond mostly to the observation of hand actions (Gallese et al., 1996), whereas in the lateral sector, most mirror neurons respond to observation of mouth actions (Ferrari et al., 2003). In the medial-most sector, the hand motor representation prevails, whereas in the lateral sector there is a predominance of mouth-related motor neurons (Rizzolatti et al., 1988). In addition to these functional distinctions, it is worth noting that in the lateral sector of F5 there are also several motor neurons that activate during actions made with both mouth and hand (see Ferrari et al., 2001, and the present study), suggesting that neurons of this sector could be endowed

Figure 6. Example of a tool-responding mirror neuron responding to a holding action made with a stick. (A) The experimenter approaches with the stick, held in his hand, a piece of food placed on a tray, and then punctures and holds it. (B) The experimenter grasps with his hand a piece food placed on a tray and then holds it. (C) The two conditions (A and B) are presented in alternation with the tool (left) and with the hand (right). Numbers at the side of each panel indicate the number of each trial. Other conventions as in Figure 1.
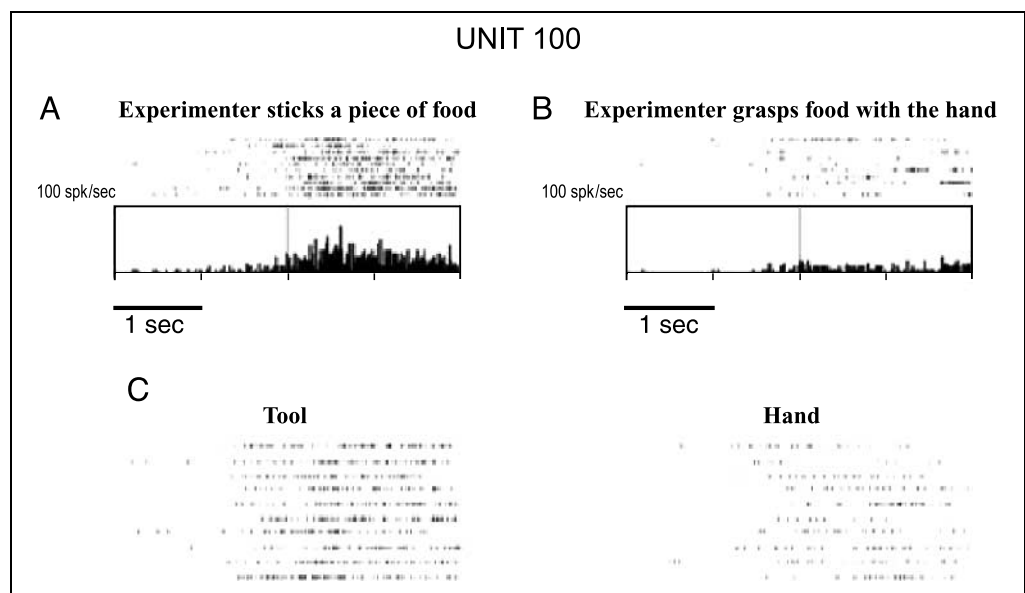
Figure 7. (A) Lateral view of the 3-D reconstruction of the right hemisphere of Monkey 1. The rectangle reported on the brain reconstruction on the left panel, enlarged on the right panel, includes the part of the ventral premotor cortex explored in the present study. Black circles indicate the penetrations in which tool-responding mirror neurons were recorded, white circles the penetrations in which no tool-responding mirror neurons were found. Vertical lines represent the level of three coronal sections, whose outlines are reported in (B). For the classification of the areas of the agranular frontal cortex, see the work of Matelli, Luppino, and Rizzolatti (1985, 1991). (B) Penetration tracks reported on the outlines of three coronal sections passing through the recorded sectors. The dots plotted at different depths indicate sites at which tool-responding mirror neurons were found. c = central sulcus; ia = inferior arcuate sulcus; ip = intraparietal sulcus; l = lateral sulcus; p = principal sulcus; sa = superior arcuate sulcus; sp = spur of the arcuate sulcus; st = superior temporal sulcus.
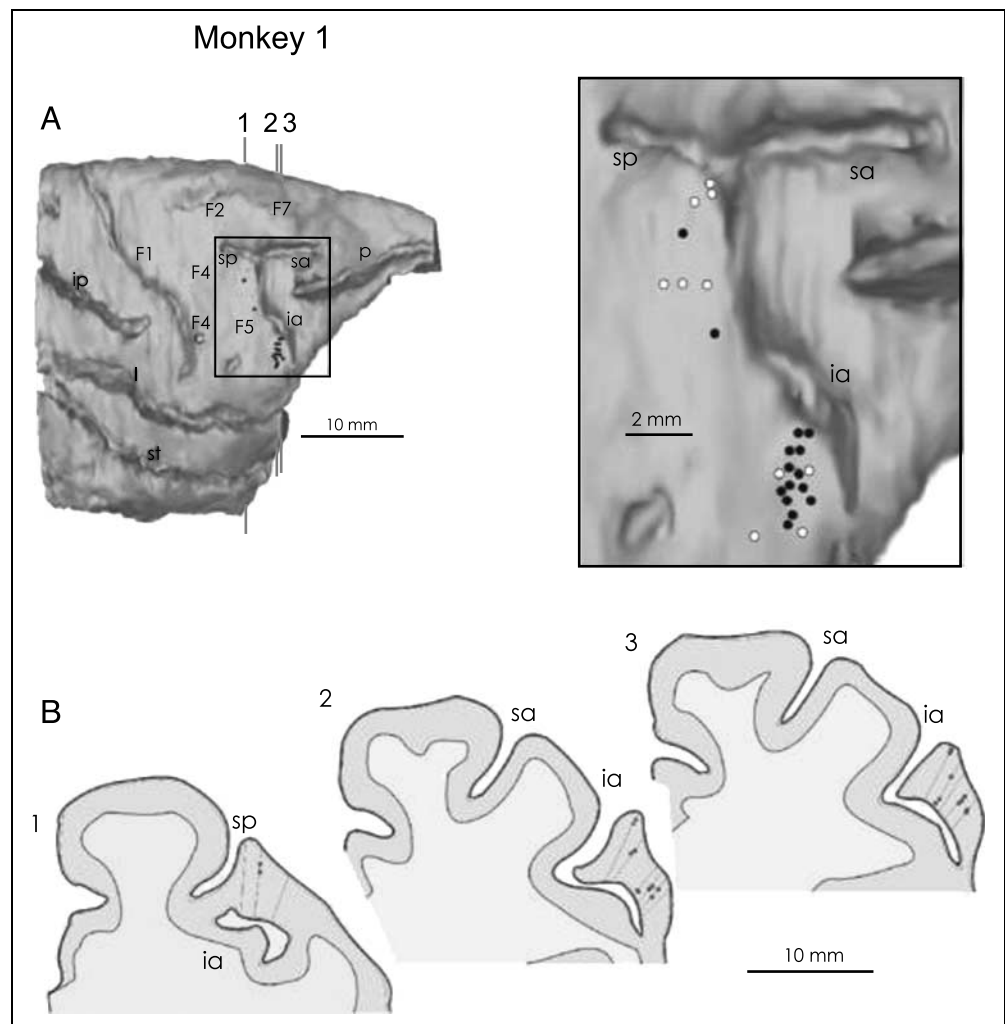
with a higher capacity of generalizing the action goal. Summing up, although F5 was originally thought of as an homogeneous region, the cytoarchitectonic and functional data open the possibility that it can be further subdivided in different subregions.

The visual responses of tool-responding mirror neurons do not relate to different attention paid to tools in respect to the biological effector or to a differential oculomotor behavior. If the neuron response were related to a higher level of attention given to the tool than to the hand of the experimenter, we would expect to find a very high number of neurons activated by the sight of the action made with the tool and a smaller number of neurons responding to the observation of actions made with the hand or the mouth. In contrast, we observed both types of neurons in the same recorded region. As far as oculomotion is concerned, previous works demonstrated that the responses of F5 mirror neurons to action observation are typically not influenced by eye behavior (Ferrari et al., 2003; Kohler et al., 2002). In addition to this, it is known that neurons of area F5 are not related to the control of eye movements.

Another possible variable that could determine a different neuron discharge during observation of actions made with the tool in respect to those performed with the hand is represented by a difference in kinematics. In fact, the kinematics of actions made with the tool, although reflecting that of the hand moving it, is different from that of the biological effector alone (unpublished data). On the other hand, the kinematics of goal-directed and mimed actions made with the tool is very similar. Thus, if kinematics were the crucial factor, the neuron should show a similar discharge in both conditions. This is not what occurs. Tool-responding mirror neurons discharge only when the tool movement is directed to a target. In addition, many tool-responding mirror neurons discharge when the tool, after having reached the object, holds it, whereas they do not discharge when the same holding action is performed with the hand. Because no movement is occurring in the holding phase, kinematics cannot contribute to the neuron response.

A further alternative explanation of the visual response of tool-responding mirror neurons is that during

observation, the monkey prepares to pick up the food with the hand or with the mouth, planning to grasp the tool with different types of grip depending on the type of tool used. This explanation seems unlikely, because if this were true, the neuron response should have been observed when food was simply presented to the monkey with the same tool used in the condition of action observation. This was never observed.

The visuomotor properties of tool-responding mirror neurons resemble those of classical mirror neurons in that they code the goal of an action. It has been hypothesized that mirror neurons allow understanding of action goal through a mechanism that matches action observation with action execution (Gallese et al., 1996). Note that this matching mechanism can reach a considerable degree of abstraction. In fact, it has been recently demonstrated that one category of mirror neurons can recognize the goal of an action when the monkey only hears the action sound (Kohler et al., 2002). Furthermore, it has been shown that several mirror neurons become active during action observation also when the final part of the observed action is occluded to the monkey's sight (Umiltà et al., 2001). Taken together, these studies indicate that the goal of the action can be retrieved through different sensory inputs and suggest that the goal can be inferred also when only part of the visual information is provided.

Keeping with this perspective, tool-responding mirror neurons represent a new population of neurons with the capacity to retrieve the action goal. For example, a neuron responding to the observation of a sticking and holding action made with a stick respond also when the monkey grasps and holds a piece of food. Thus, the visual (sticking) and motor (grasping) effective neuron responses signal the same general goal, that is taking possession of an object. The fact that tool-responding mirror neurons code a general action goal is also reflected by their motor discharge. In fact, more than 70% of them respond equally well during the monkey's execution of actions with the hand and the mouth, the goal of the effective action being the same for both effectors.

How can a movement toward a target performed with a tool be recognized as goal-directed? A possible explanation is that after a relatively long exposure to actions made with tools, a visual association between the tool and the hand is created, so that it becomes as a kind of prolongation of, or even a surrogate for, the hand. The association between the two agents would facilitate the generalization of the action meaning. The possibility of the existence of cortical mechanisms able to represent a tool as a prolongation of the arm was already proposed by Iriki, Tanaka, and Iwamura (1996), who demonstrated in monkeys that after a motor training to use a tool, the properties of forelimb-related neurons in the parietal cortex could be extended to tools held by the forelimb, as if these tools would constitute the natural prolonga-

tion of the biological effector (see also Maravita & Iriki, 2004). The same group, in a recent monkey PET study (Obayashi et al., 2001), showed that in two monkeys trained to retrieve food with a rake, there was an activation of both parietal and ventral premotor cortex when the monkey used a rake to retrieve food, as compared with a condition in which the monkey made a simple manipulation of a stick. These findings suggest that the motor training aimed to use a tool can change not only the body schema (see Maravita & Iriki, 2004; Iriki et al., 1996) but also the motor representation of body parts involved in goal-directed actions. Summing up, the link between the tool and the hand holding it endows the tool with the notion of the goal normally associated to the biological effector.

Whether visual exposure to tool actions without motor training produce similar changes in the body schema and/or in the motor representation of the observer, as those shown by Iriki et al. (1996), has to be determined. Comparing observational and motor learning, the latter can rely on both the visual feedback of the acting tool held by the hand and the kinesthetic feedback, whereas the former relies only on a visual feedback that is not directly correlated with a concurrent kinesthetic input. This difference is very important because it could represent one of the reason why the observed actions made with tools cannot be directly translated into own motor repertoire as also suggested by our behavioral observations.

A process of association between hand and tool should be facilitated by a prolonged time of presentation of the acting hand holding the tool. Our findings support this hypothesis in that tool-responding mirror neurons were discovered after several experimental sessions in both monkeys. In fact, in both monkeys, these neurons have been found only in the last part of experiments, after months of training and recording sessions. It is also interesting to note that in Monkey 1, which was subjected to a longer experimental period than Monkey 2, there was a higher number of penetrations in which tool-responding mirror neurons were found compared with that of Monkey 2. Furthermore, the increase in frequency of tool-responding mirror neurons in the last penetrations of Monkey 1 suggests that the period of exposure to actions made with tools can be an important factor to facilitate the association between hand and tool. Despite these observations, further studies are needed to directly specify the relationship between different times of exposure to tool actions and the emergence of tool-responding mirror neurons.

The process of generalization of the action goal between the hand and the tool can be helped by several factors: (1) The experimenter in both cases is making movements that end on a target; (2) the general kinematic properties are similar. For example, in both actions made with the tool and with the hand, there is an

acceleration and a deceleration phase, followed by a static phase in which the effector is in contact with the target; (3) there is a similarity of the context (same environment, same experimenters) in which the actions take place; (4) experimenter's hand and tools can both be associated, by the monkey, to the possibility to receive food. In fact, both hand and tools were used during the experiments to give food to the monkeys, sometimes, also during action-observation conditions. In particular, the stick was the tool mostly used for feeding the monkey. In agreement with this observation, there were more tool-responding mirror neurons responding best to the observation of actions made with the stick than with the pliers.

Accepting the idea that the tool can acquire the same meaning of the acting hand, the issue is raised on why neurons of premotor cortex can respond, visually, better to actions made with tools than to actions made with the hand. The hypothesis we propose is that different visual inputs related to stimuli with similar biological motion and directed to the same target object can access F5 motor neurons that on the motor side encode mouth and hand actions having the same goal, but on the visual side are probably still uncommitted. The reason why tool-responding mirror neurons prefer tools and mirror neurons prefer biological effectors can be attributed to a competition mechanism between two visual inputs for the same population of uncommitted neurons, which in some cases, after long visual exposure, become dominated by one input that is not a biological effector. This possibility seems not unlikely because the monkeys used in this experiment had not only the opportunity to see actions made with biological effectors (both by conspecifics and human experimenters) but also to observe very frequently actions made with tools. An extreme case of the proposed competition mechanism can be manifested by the neuron shown in Figure 5, in which observation of a sticking action elicits a neuron excitation, whereas observation of a hand-grasping action produces an inhibitory response.

Ethological studies show that monkeys are able to use tools in captivity or in the wild (Tokida, Tanaka, Takefushi, & Hagiwara, 1994; Westergaard, 1988; Beck, 1976; see Tomasello & Call, 1997, for a review). In macaques, tool use is a behavior that can be often observed by group members both in the wild and in captivity (Tomasello & Call, 1997), although it is usually not very widespread within each wild population concerned (i.e., shown by many different individuals, regularly or predictably) (van Schaik, Deaner, & Merrill, 1999). The fact that tool use in monkeys rarely becomes habitual or customary in a given population is in agreement with the finding that a relatively long period is necessary before a new skill with the tool is acquired (see Tomasello & Call, 1997). As some authors have proposed, the acquisition of tool use requires processes involving observational and individual learning (Zuberbühler, Gygax, Harley, &

Kummer, 1996; Tokida et al., 1994; Beck, 1976). These findings could explain why the monkey used in our experiment did not use the stick to retrieve food. The monkey probably would have needed a longer time of learning in which the observation of another individual using tool were combined with its own sensorimotor interaction with the same tool.

In the light of the present findings and of the above considerations, what could be the function of tool-responding mirror neurons? They probably are part of a system enabling the observing individual to extend its action understanding capacity to actions that are not strictly part of its motor representation. Hence, this extension would include also acting objects.

It is common observation also in humans that it is possible to understand the meaning of an action without possessing the immediate capacity to reproduce it. In agreement with this, a recent fMRI experiment in humans (Buccino, Vogt, et al., 2004) demonstrates that the pure observation of a sequence of actions (playing guitar chords) that were not familiar to the observing subjects determines an activation of the inferior frontal gyrus (Broca's area), a region considered homologue to monkey's area F5. This supports the notion that premotor areas in primates can be involved in processes of abstraction of the goal aimed to understand actions also when the individual has never experienced them or when he has not yet acquired the capacity to master them.

Conclusions

The large use of tools in primates and the diversity of their use among the different populations suggest the existence of neural mechanisms not only aimed to understand actions made with tools but also to learn their use and to transmit the new acquired skills to other individuals. Studies made in apes have suggested that this transmission can be achieved through observational learning processes such as imitation (van Schaik et al., 2003; Whiten et al., 1999). In contrast, imitation in monkeys has not been demonstrated to occur, and this can account for the lack of population-wide tool use in the wild. However, it is very likely that the neurophysiological mechanisms that lead to the wide use of tools in apes and humans rely on the action understanding system, described above and in previous studies (see Rizzolatti, Fogassi, & Gallese, 2001), already present in monkey's premotor area F5. The involvement of this area during monkey's tool use (Obayashi et al., 2001) supports this hypothesis. In an evolutionary perspective, it is not the first time that the emerging properties of a brain area can favor the evolution of new functions. This view is congruent with the increasing evidence that a mirror mechanism, which evolved in monkeys for action understanding, emerged subsequently in human evolution as suitable neural substrate for imitation.

METHODS

General Procedures

The experiments were carried out on two awake (Monkey 1 and Monkey 2), partially restrained macaque monkeys (*M. nemestrina*). All experimental protocols were approved by the Veterinarian Animal Care and Use Committee of the University of Parma as well as by the Italian Minister of Health. All experiments complied with the European law on the humane care and use of laboratory animals.

Before starting the single-neuron recording experiments, the monkeys were habituated to the experimenters and to the experimental conditions. Each monkey was seated on a primate chair and habituated to observe different types of visual stimuli and to execute different types of hand and mouth actions. During this training period, both monkeys could see, among other visual stimuli, the tools used in the present experiment. The stick was used both for picking up food and for presenting and giving pieces of food to the monkey. Pliers were mainly used for grasping food or objects and giving them to the monkey. In general, the monkeys were more exposed to stick than to pliers. The monkey training lasted approximately 2 months.

The surgical procedures for single-neuron recordings were the same as previously described (Fogassi et al., 1996). The head implant included a head holder and a chamber for single-unit recordings. Neurons were recorded using tungsten microelectrodes (impedance 0.5–1.5 MΩ, measured at 1 kHz) inserted through the dura that was left intact. Neuronal activity 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 voltage–time discriminator was monitored and fed to a PC for analysis.

The recording microelectrodes were used also for electrical microstimulation (train duration, 50 msec; pulse duration, 0.2 msec; frequency, 330 Hz; current intensity, 3–40 μA). The current strength was controlled on an oscilloscope by measuring the voltage drop across a 10-KΩ resistor in series with the stimulating electrode.

Recording Sites

The chamber for single-unit recordings was implanted stereotactically. The chamber rostro-caudal and medio-lateral axes dimension (20 × 15 mm) was such as to allow to record from the whole ventral premotor cortex. The chamber covered a region from area F1 (primary motor cortex) posteriorly to the caudal part of the frontal eye fields anteriorly. After chamber implantation, the ventral part of the agranular frontal cortex was functionally explored (single-neuron recordings and intracortical microstimulation) to assess the location of areas F1 (primary motor cortex), F4, and F5 (ventral premotor

cortex). For the criteria used to functionally characterize these areas, see the work of Umiltà et al. (2001). Once the location of these areas was characterized, we concentrated our recordings on area F5.

Neuron Testing

Each neuron, once isolated, was tested to ascertain its motor and visual properties. The type of testing is described below.

Motor Properties

Neurons discharging in association with active hand actions were tested using the same stimuli and procedures as in previous studies. Briefly, the monkey was presented with a variety of objects of different size and shape. They consisted of food items and objects at hand in the laboratory. The objects were presented in different parts of space within the monkey reaching distance. The monkey was trained to reach for and grasp them with different types of grip (for details, see Rizzolatti et al., 1988, 1990). Neurons discharging in association with mouth actions were studied by giving the monkey food or juice, thus eliciting a variety of mouth actions (see Ferrari et al., 2003).

Visual Properties

Testing of visual properties consisted in the presentation of actions performed with the hand, the mouth, and a tool by the experimenter in front of the monkey. The tested hand actions were object grasping, holding, manipulating, breaking, and tearing. The tested mouth actions were "grasping," "holding," "breaking," "sucking," "reaching with the tongue," "taking away," and "chewing." Movements of the hand or the mouth miming actions in the absence of the target were also presented (for other details, see Ferrari et al., 2003; Gallese et al., 1996).

The tool actions were performed by the experimenter with a wooden stick (length 37 cm) having a metal tip on one extremity and a pair of pliers. The actions performed with the stick were sticking, holding, manipulating, and taking away. (A) *Sticking*. The food, held on the experimenter's hand or on a tray, was approached by the stick held by the experimenter with his other hand and then punctured with the tip of the stick. (B) *Holding*. Once the food was punctured, it was held on the stick without subsequent movement. (C) *Manipulating*. After reaching the food, the stick was moved around a piece of food. During this action the food was touched but not punctured. (D) *Taking away*. Once the food was punctured, it was held on the stick tip and then taken away from the tray or from the supporting hand. The actions performed with the pliers were grasping, holding, manipulating, breaking, and taking

away. (A) *Grasping*. The experimenter, holding the pliers with one hand, approached a piece of food held by a support or by the other hand and grasped it by opposing the tips of the pliers. (B) *Holding*. Once the food was grasped, it was held with the pliers without subsequent movement. (C) *Manipulating*. After reaching the food, the pliers were moved around a piece of food, touching it but without grasping it. (D) *Breaking*. The experimenter, holding the pliers with one hand, approached a piece of food held by a support or by his other hand and broke it employing force with the tips of the pliers. (E) *Taking away*. Once the food was grasped, it was held between the tips of the pliers and then taken away from the support/hand.

To assess the specificity of the neuron response to the observation of actions performed with the tool, movements of the stick or of the pliers miming actions without the target object were presented. In some neurons, the specificity of the response was further tested using elongated tools similar to the stick (i.e., a signal stick, which is a 15-cm diameter, wooden, colored circle attached to the tip of a 1-m long stick) to approach, to touch, and to go away from the target. Note that these tools could not be used to grasp or take possession of objects.

All of the above-described actions were performed by an experimenter standing in front of the monkey. The actions were presented to the monkeys mostly by two experimenters. Although the two monkeys were particularly familiar with the experimenter who trained the monkey before recording, no obvious difference in neuron response related to which experimenter performed the action was observed.

Other visual stimuli such as static or moving objects were presented on a tray or on a stick held by an experimenter, in all parts of the visual field, inside and outside the monkey's reaching distance.

Data Analysis

After neuron visual and motor characterization, histograms of visual and motor responses were constructed. By using a contact-detecting circuit (a switch), a signal was sent to a PC whenever the monkey (motor conditions) or the experimenter (visual conditions) touched a metal surface, connected to the target, with their hand, their mouth, or with the tool. This signal was used to align the trials and, subsequently, to construct the response histograms. Switch closing produced a signal that was used for the response alignment. Response histograms were constructed by summing 10 individual trials. Unless some technical problems did not interfere with trial acquisition (e.g., delays in closing the contact-detecting circuit), no trials were discarded.

To statistically assess the neuron discharge, the neuronal activity, expressed as mean firing rate (spikes per second), was measured in two different time epochs.

Epoch 1 corresponds to the time interval (1 sec) centered at the alignment signal (500 msec before and 500 msec after it) and Epoch 2 corresponds to a period of 2000 msec to 1000 msec before alignment (background activity). To compare, for each neuron, the discharge in different epochs and conditions two-way ANOVA (2 × 2 ANOVA, factors condition and epoch, two levels each) was performed. ANOVA was followed by Newman–Keuls post hoc tests comparisons to compare the neuron activity recorded during observation of actions performed with the tool with the activity recorded during observation of actions made with the hand, the mouth, or during simple presentation. All analyses were performed using a significance criterion of $p < .05$.

Histological Control

Histology was performed in both monkeys. For detailed description of the histological processing, see Fogassi, Gallese, Buccino, Craighero, and Rizzolatti (2001). Briefly, each animal was anaesthetized with ketamine hydrochloride (15 mg/kg im) followed by an intravenous lethal injection of pentobarbital sodium and perfused through the left cardiac ventricle with buffered saline, followed by fixative (paraformaldehyde 3.5%). After the monkey was sacrificed, the brain was removed from the skull, photographed, and then frozen and cut coronally. The sections (60 μm thick) were stained using the Nissl method. For each section, outer and inner cortical contours were drawn. The locations in the cortex of the electrode tracks were assessed under optic microscope and then plotted and digitalized using an Inside PC program. The tracks location was subsequently related to the areas of the ventral premotor cortex. For each electrode track, the depth at which tool-responding mirror neurons were found was reported. A second PC program (CRS4, Cagliari, Italy, see Bettio, Demelio, Gobbetti, Luppino, & Matelli, 2001) was then used for 3-D reconstruction of the brain, which allowed also brain reslicing in a different plane of cutting.

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