

ORIGINAL ARTICLE

# Multimodal Encoding of Goal-Directed Actions in Monkey Ventral Premotor Grasping Neurons

Stefania Bruni<sup>1</sup>, Valentina Giorgetti<sup>1</sup>, Leonardo Fogassi<sup>1</sup> and Luca Bonini<sup>2</sup>

<sup>1</sup>Department of Neuroscience, University of Parma, Parma 43125, Italy and <sup>2</sup>Istituto Italiano di Tecnologia (IIT), Brain Center for Social and Motor Cognition (BCSMC), Parma 43125, Italy

Address correspondence to Leonardo Fogassi, Department of Neuroscience, University of Parma, via Volturno 39, 43125 Parma, Italy. Email: leonardo.fogassi@unipr.it and Luca Bonini, Istituto Italiano di Tecnologia (IIT), Brain Center for Social and Motor Cognition (BCSMC), via Volturno 39, 43125 Parma, Italy. Email: luca.bonini@unipr.it

## Abstract

Visuo-motor neurons of the ventral premotor area F5 encode “pragmatic” representations of object in terms of the potential motor acts (e.g., precision grip) afforded by it. Likewise, objects with identical pragmatic features (e.g., small spheres) but different behavioral value (e.g., edible or inedible) convey different “semantic” information and thus afford different goal-directed behaviors (e.g., grasp-to-eat or grasp-to-place). However, whether F5 neurons can extract distinct behavioral affordances from objects with similar pragmatic features is unknown. We recorded 134 F5 visuo-motor neurons in 2 macaques during a contextually cued go/no-go task in which the monkey grasped, or refrained from grasping, a previously presented edible or inedible target to eat it or placing it, respectively. Sixty-nine visuo-motor neurons showed motor selectivity for the target (35 food and 34 object), and about half of them ( $N = 35$ ) exhibited congruent visual preference. Interestingly, when the monkey grasped in complete darkness and could identify the target only based on haptic feedback, visuo-motor neurons lost their precontact selectivity, but most of them (80%) showed it again 60 ms after hand-target contact. These findings suggest that F5 neurons possess a multimodal access to semantic information on objects, which are transformed into motor representations of the potential goal-directed actions afforded by them.

**Key words:** action goal, haptic information, macaque, reaching-grasping, visuo-motor neurons

## Introduction

One of the most clearly established functions of the ventral premotor cortex (PMv) consists in the transformation of different types of visual (Rizzolatti et al. 1988; Murata et al. 1997; Hoshi and Tanji 2006; Pardo-Vazquez et al. 2008; Fluet et al. 2010; Bonini et al. 2014b) and somatosensory (Rizzolatti et al. 1981a; Rizzolatti et al. 1988; Maranesi et al. 2012; Romo and de Lafuente 2013) information into motor representations.

Pioneering studies (Rizzolatti et al. 1988) described neurons in the ventral premotor area F5 that, besides discharging during hand-related motor acts, also responded to the visual presentation of graspable objects (visuo-motor neurons). Subsequent experiments employed more controlled behavioral paradigms in which monkeys were required to simply observe, or observe

and then grasp with the appropriate type of grip, objects of different size and shape (Murata et al. 1997; Raos et al. 2006; Bonini et al. 2014b). These studies revealed that the responses of F5 grasping neurons encode potential motor acts (e.g., precision grip, whole-hand prehension, etc.) afforded by visually presented objects and suggest that sensorimotor integration is necessary for the emergence of “pragmatic representations” of object (Maranesi et al. 2014).

It is interesting to note that pragmatically similar objects can nonetheless provide an observer with different “semantic” information critical for selecting the most appropriate goal-directed action (Hodges et al. 2000; van Elk et al. 2014; Yamaguchi et al. 2014). For example, a cherry and a marble can be grasped with the same type of grip (precision grip) because they share the

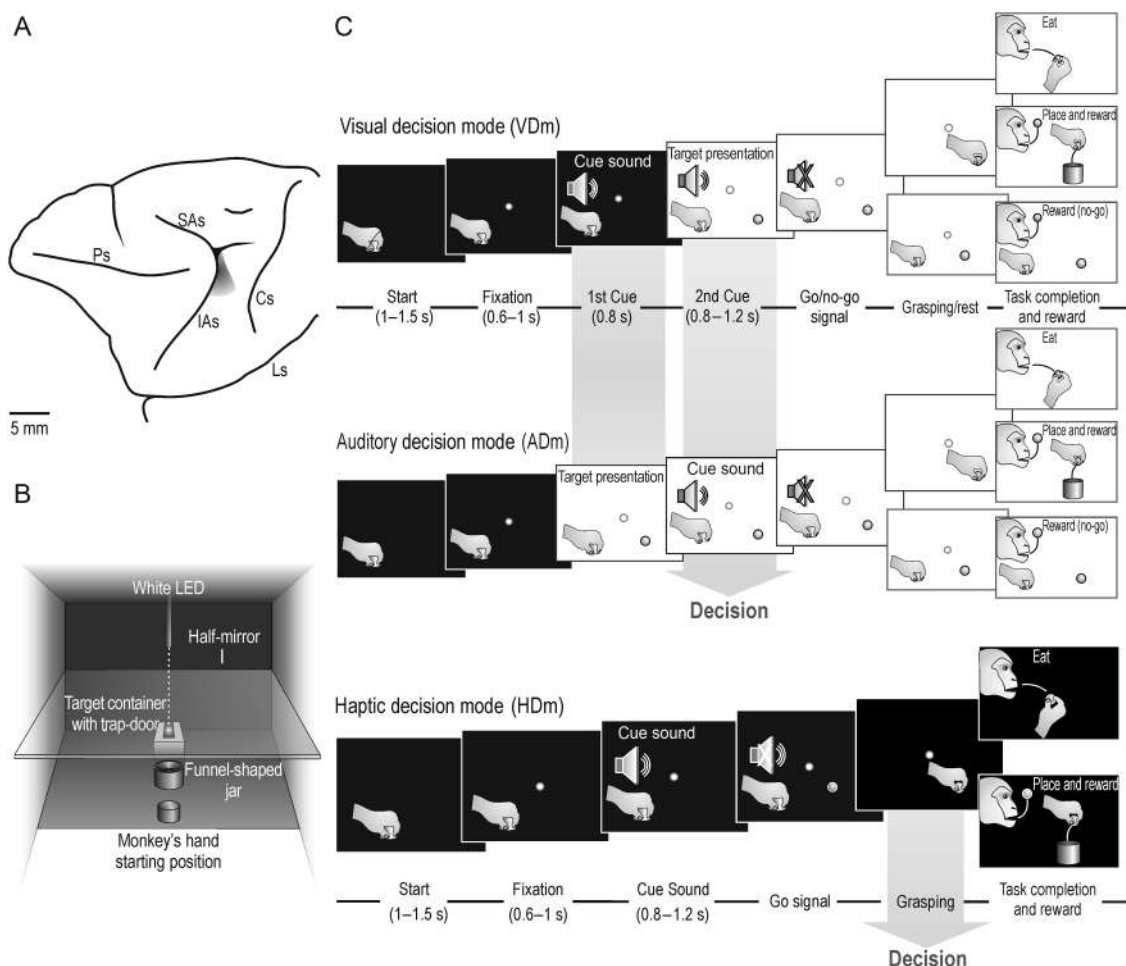
same pragmatic features but obviously afford completely different goal-directed actions (e.g., eating and throwing). Single-unit recordings revealed that the motor activity of area F5 grasping neurons can reflect the goal (i.e., eating or placing) of the action in which grasping is embedded (Bonini et al. 2010, 2011, 2012), suggesting that, besides pragmatic features, information on objects' behavioral relevance plays a role in action selection and affects F5 neurons motor response. However, whether F5 neurons can also extract distinct behavioral affordances from visually presented objects with similar pragmatic descriptions is still unknown.

To address this issue, here we recorded the activity of single neurons from area F5 of 2 monkeys trained to perform the grasp-to-eat/grasp-to-place actions used in previous studies (Bonini et al. 2010, 2012). Relative to these latter studies, here the monkey was required to maintain fixation during all trials and 2 different auditory cues instructed it whether (or not) to grasp the subsequently presented target, thus allowing us to formally investigate neurons visual responses to target presentation and their possible contextual modulations. Importantly, by requiring monkeys to

perform the task in full-light and in the dark, we could segment and independently evaluate the processing and integration of visual and haptic information on target objects identity by area F5 grasping neurons.

## Materials and Methods

The experiments were carried out on 2 female macaque monkeys (*Macaca mulatta*), which will be referred to as M1 and M2. Before recordings, the monkeys were habituated to sit in a primate chair and to interact with the experimenters. Then, they were trained to perform the tasks described below using the hand (right) contralateral to the hemisphere to be recorded (left, see Fig. 1A). When the training was completed, a head fixation system and a plastic recording chamber were implanted under general anesthesia (ketamine hydrochloride, 5 mg/kg intramuscular [i.m.] and medetomidine hydrochloride, 0.1 mg/kg i.m., repeatedly administered during the surgery). Dexamethasone and prophylactic broad-spectrum antibiotics were administered pre- and postoperatively. Furthermore, analgesics were administered intra- and postoperatively. During



**Figure 1.** Recorded region, apparatus, and temporal sequence of task events. (A) The shaded region indicates the cortical sector investigated in the present study, corresponding to the dorsal part of F5p/c cytoarchitectonic subdivisions of area F5 (see Belmalih et al. 2008). Recordings were carried out in the first 3.5 mm of the bank and crown of the most medial part of the inferior arcuate sulcus (hand-field of area F5, see Maranesi et al. 2012). Cs, central sulcus; IAs, inferior arcuate sulcus; Ls, lateral sulcus; Ps, principal sulcus; SAs, superior arcuate sulcus. (B) Task box and apparatus seen from the monkey point of view. (C) The task was constituted by a fixed sequence of events run in 2 main modes, depending on the order of presentation of the 2 cues (sound and target) whose integration allowed the monkey to decide what to do next, namely, 1) grasp-to-eat, 2) grasp-to-place, 3) refrain from grasping an object, or 4) refrain from grasping a food pellet. The monkey could select what to do next (decision) either following the visual presentation of the target (in the VDM), or following the presentation of the cue sound (in the ADM). In a third mode, the target was not presented at all, and monkey could select the action to perform based on haptic information gathered during grasping execution (HDm).

all surgeries, hydration was maintained with continuous infusion of saline solution. A heating pad was used to maintain the temperature constant. The heart rate, blood pressure, respiratory depth, and body temperature were continuously monitored. Upon recovery from anesthesia, the animals were returned to their home cages and closely monitored. All experimental protocols complied with the European law on the humane care and use of laboratory animals (directives 86/609/EEC, 2003/65/CE, and 2010/63/EU), they were authorized by the Italian Ministry of Health (D.M. 294/2012-C, 11/12/2012) and approved by the Veterinarian Animal Care and Use Committee of the University of Parma (Prot. 78/12 17/07/2012).

### Apparatus and Behavioral Paradigm

Both monkeys were trained to perform a sensory-cued go/no-go action sequence task, requiring them to grasp a target in order to eat it or to place it into a container. The task included different experimental conditions, carried out by means of the apparatus illustrated in Figure 1B.

The monkey faced a box divided horizontally into 2 sectors by a half-mirror. The lower sector hosted 2 plastic containers: one was an empty plastic jar (inner diameter 4 cm), whereas the other was used to present the monkey with one of 2 possible targets: a piece of food (ochre spherical pellet of 6 mm of diameter, weight 0.19 g), or an object (a white plastic sphere, of the same size and shape as the food, weight 0.20 g). Note that the surface of the sphere was perfectly smooth, whereas that of the food pellet was rougher, rendering the 2 targets easy to discriminate even in the dark (based on haptic feedback). The target was located into a groove, at the center of the container: The bottom of the groove was closed with a computer-controlled trap-door, with a small cavity in the middle that enabled precise positioning of the target, so that its center of mass was at exactly 11 cm under the lower surface of the half-mirror. The computer automatically opened the trap-door if the monkey moved during no-go trials, preventing it from being self-rewarded when food was used as a potential target. The target was positioned at the center of the groove in complete darkness and in the presence of a constant white noise, in order to prevent the monkey from obtaining any visual or auditory cue during set preparation. The container for the target was positioned along the monkey body midline, at 16 cm from its hand starting position. The monkey's hand starting position was constituted by a metal cylinder (diameter 3 cm, height 2.5 cm), fixed to the plane close to the monkey's body. The empty plastic jar, used as a container for placing the object, was located at the halfway point between the hand starting position and the target. The jar was endowed with a funnel-shaped pierced bottom: In this way, when the object was placed into the jar, it immediately fell down in a box unreachable and not visible to the monkey. The upper sector of the task box hosted a small black tube fixed to the roof, containing a white light-emitting diode (LED) located 11 cm above the surface of the half-mirror. When the LED was turned on (in complete darkness), the half-mirror reflected the spot of light, so that it appeared to the monkey as located in the lower sector, in the exact position of the center of mass of the not-yet-visible target (fixation point). A stripe of white LEDs located on the lower sector of the box (and not directly visible to the monkey) allowed us to illuminate it during specific phases of the task. Note that, because of the half-mirror, the fixation point remained visible even when the lower sector of the box was illuminated.

The task was run in 3 modes, depending on the availability and sequence of presentation of the contextual cues enabling the

monkey to decide "whether" to act and "what" action to perform (Fig. 1C). In the visual decision mode (VDm), the cue sound was presented first, and then the target became visible; in the auditory decision mode (ADm), the target was presented first, and the cue sound subsequently; in the haptic decision mode (HDm) no visual cue was provided, and the monkey could decide to eat or place the target only based on the sensory feedback obtained following hand-target contact. In the VDm and ADm, the task included a go and a no-go condition, each of which run with the food or the object as target, whereas the HDm included only go-trials with the 2 targets. Thus, the experimental design included a total of 10 different conditions, randomly interleaved, each of which repeated for 12 independent trials (120 trials in total).

Each trial, regardless of the decision mode, started when the monkey held its hand on the starting position for a variable period of time, ranging from 1 to 1.5 s (inter-trial period). The temporal sequence of task events was as follows (see Fig. 1C).

#### Go Condition in the VDm

Following presentation of the fixation point, the monkey was required to start fixating it (tolerance window 3.5°) within 1.5 s. After a variable time lag from fixation onset (0.6–1 s), the first cue—a high tone constituted by a 1200-Hz sine wave, associated with Go trials—was presented. After 0.8 s, the second cue was provided: The lower sector of the box was illuminated, and one of the 2 possible targets (food or object) became visible (target presentation). Then, after a variable time lag (0.8–1.2 s), the cue sound ceased (go signal), and the monkey was required to reach and grasp the target: In case of the food pellet (food trials), the monkey brought it to the mouth and ate it (grasp-to-eat), whereas in case of the plastic sphere (object trials), the monkey had to place it into the jar (grasp-to-place). Food trials were self-rewarded, whereas object trials were automatically rewarded with a food pellet (identical to the one used during food trials) delivered into the monkey's mouth by a customized, computer-controlled pellet dispenser (Sandown Scientific), activated by the contact of the monkey's hand with the metallic border of the jar.

#### No-Go Condition in the VDm

The temporal sequence of events in this condition was the same as in the go condition. Following the presentation of the fixation point, the monkey was required to start fixating it within 1.5 s. After a variable time lag from fixation onset (0.6–1 s), the first cue—a low tone constituted by a 300-Hz sine wave, associated with no-go trials—was presented. After 0.8 s, the second cue was provided: The lower sector of the box was illuminated, and one of the 2 possible targets (food or object) became visible (target presentation). Then, after a variable time lag (0.8–1.2 s), the cue sound ceased (no-go signal), and the monkey had to remain still, maintaining fixation for 1.2 s, during both food and object trials. This condition allowed us to assess visual responses to target presentation when the monkey did not perform any movement. After correct task accomplishment, the monkey was automatically rewarded with a food pellet as described earlier.

#### Go and No-Go Condition in the ADm

In the ADm, the temporal sequence of events in the 2 conditions was the same as in the VDm, but the order of presentation of the 2 cue stimuli was inverted: In this way, target presentation occurred before any go/no-go instruction was provided, whereas the go/no-go cue subsequently presented enabled the monkey to decide whether to grasp the target or not. Importantly, in both the ADm and VDm, only the second cue allowed the monkey

to make the final decision on what to do next by integrating the information conveyed by it with that provided by the first cue.

### HDm

In the HDm, all the task stages occurred in the dark, as no visual information was provided to the monkey. Thus, in this condition, the monkey can make a decision on what action to perform only during action unfolding. Following the presentation of the fixation point, the monkey was required to start fixating it within 1.5 s. After a variable time lag from fixation onset (0.6–1 s), the high tone (go cue) was presented. Then, after a variable time lag (0.8–1.2 s), the cue sound ceased (go signal), and the monkey was required to reach and grasp the target in complete darkness (note that the fixation point remained always visible through the half-mirror and served as a guide for reaching in the dark). When the monkey touched the target, it could recognize whether it was the food or the object, and in case of the food it brought it to the mouth and ate it (grasp-to-eat), whereas in case of the object it placed it into the jar (grasp-to-place). The reward contingency was the same as described earlier.

### Recording Techniques

Neuronal recordings were performed by means of 16 channels silicon probes developed in the EU project NeuroProbes (Ruther et al. 2010; Herwik et al. 2011) and distributed by ATLAS Neuroengineering (Belgium). The recording sites had a diameter of 35  $\mu\text{m}$  and were spaced 250  $\mu\text{m}$  from each other (see also Supplementary Fig. 4). Probes were inserted through the intact dura by means of a manually driven stereotaxic micromanipulator mounted on the recording chamber. All penetrations were performed perpendicularly to the cortical surface, with a penetration angle of  $\sim 40^\circ$  relative to the sagittal plane. Previous studies provide more details on the devices and techniques employed to handle the probes (Bonini et al. 2014a).

The recordings were carried out by means of an 8-channel AlphaLab system (AlphaOmega, Nazareth, Israel), and of a 16-channel Omniplex system (Plexon, Dallas, Texas). The wide band (300–7000 Hz) neuronal signal was amplified and digitized at 14-bit or 16-bit resolution at 25 kHz or 40 kHz, depending on the recording system (AlphaLab or Omniplex, respectively), and stored in parallel with the main behavioral events and the digital signals related to the task stages. All quantitative analyses of neuronal data were performed offline, as described in the subsequent sections.

### Recording of Behavioral Events and Definition of Epochs of Interest

Distinct contact sensitive devices (Crist Instruments, Hagerstown, MD) were used to detect when the monkey touched with the hand the metal surface of the starting position, the metallic floor of the groove hosting the target (food or object) during grasping, or the metallic border of the plastic jar during placing of the object. Each of these devices provided a TTL signal, which was used by LabView-based software to monitor the monkey performance.

Eye position was controlled by an eye-tracking system composed by a 50-Hz infrared sensitive CCD video camera (Ganz, F11CH4) and 2 spots of infrared light. The analog signal related to horizontal and vertical eye position was fed to a computer equipped with dedicated software (Pupil), enabling calibration and basic processing of eye position signals.

The eye position signals, together with the TTL events generated during task execution, were sent to the LabView-based software in order to monitor task unfolding and to control the

presentation of auditory and visual cues of the behavioral paradigm. Based on TTL and eye position signals, the software enabled the automatic interruption of the trial if the monkey broke fixation, made an incorrect movement, or did not respect the temporal constraints of the behavioral paradigm. In all these cases, no reward was delivered: All cues were switched off and, at the same time, the trap-door bearing the target opened so that the monkey could not grab it. Note that the monkey always received the same food pellet as a reward after correct accomplishment of each type of trial.

Based on the digital signals related to the main behavioral events, we defined different epochs of interest for statistical analysis of neuronal responses: (1) baseline epoch, including the 500 ms prior to the onset of the first cue, when the monkey was at rest, fixating in the dark; (2) target/sound presentation epoch, from 50 to 450 ms after stimulus onset; (3) hand-shaping epoch, ranging from 100 ms before the detachment of monkey's hand from the starting position to the hand-target contact; and (4) grasping/holding, from the contact of monkey's hand with the object to 300 ms after this event.

### Data Analyses and Classification of the Recorded Neurons

Single units were isolated using standard principal component and template matching techniques, provided by dedicated offline sorting software (Plexon), as previously described elsewhere (see Bonini et al. 2014b). After identification of single units that remained stable over the entire duration of the experiment, neurons discharge has been firstly analyzed in order to identify motor neurons responding during grasping execution. To this purpose, we applied  $2 \times 3$  repeated-measures ANOVAs (factors: Target, Epoch) with a significance criterion of  $P < 0.01$ , followed by Bonferroni post hoc tests ( $P < 0.05$ ). Then, grasping neurons were analyzed in order to identify possible significant responses to the presentation of the sensory cues, as follows.

1. Sensory response to the first cue. Single-neuron responses to the presentation of sounds (low and high tone) and targets (food and sphere) as first cues were assessed with a  $2 \times 2$  repeated-measures ANOVA (factors: Sound/Target, and Epoch) with a significance criterion of  $P < 0.01$ , followed by Bonferroni post hoc tests ( $P < 0.05$ ) in case of significant interaction effects. Neuronal activity during the cue presentation epoch was compared with that of the 500-ms prestimulus epoch.
2. Sensory response to the second cue. Since each stimulus (target or sound) presented as second cue occurred within the context established by the previously presented one, we employed  $2 \times 2 \times 2$  repeated-measures ANOVA (factors: Sound, Target, and Epoch), followed by Bonferroni post hoc tests in case of significant interaction effects to explore not only possible activity changes induced by the second cue, but also possible differences in stimulus processing caused by the context in which it occurred. The same analysis was applied to the neuron response tested in the VDm and ADm, separately. Note that in order to verify a possible activity change “specifically” induced by the second cue, neuronal activity during cue presentation (target in VDm and sound in ADm) was compared with that of the 500-ms period before stimulus onset. Furthermore, paired-samples t-test ( $P < 0.05$ , Bonferroni corrected) were used to compare significant sensory responses evoked by the presentation of each stimulus as second (cued by the first stimulus), with those evoked by the presentation of the same stimulus as first (un-cued).



Based on the results provided by the analyses described earlier, we distinguished 2 main types of neurons: purely motor neurons, which responded during the execution of grasping actions but not to target presentation, and visuo-motor neurons, activated during both target presentation and grasping execution.

Population analyses were performed on specific sets of neurons, classified on the basis of the results of single-neuron analyses. Population vectors were computed by normalizing each neuron's response across all the compared task conditions and epochs, averaged in 20-ms bins (see Bonini et al. 2010). The same epochs and analyses employed for single-unit data were also used for population analyses, except for motor-related responses (analyzed on a trial-by-trial basis in single neurons), which have been analyzed in 2 fixed 300-ms epochs, one (hand-shaping) preceding, the other (grasping/holding) following, the hand-target contact.

In order to identify the start/end of population selectivity for specific variables (i.e., target or condition), paired sample t-tests were used to establish the first/last of a series of at least 5 consecutive 80-ms bins (slid forward in steps of 20 ms) in which the activity significantly differed (uncorrected  $P < 0.05$ ) between the 2 compared conditions.

## Results

We isolated 330 single neurons. Some of them ( $N = 23$ ) activated mainly during the introduction of the food into the mouth or following reward delivery, thus being likely related to mouth actions (see Maranesi et al. 2012): These neurons have not been included in the present data set. The great majority of the recorded cells ( $N = 307$ ) discharged significantly during grasping execution. Based on the criteria defined earlier (see Materials and Methods), 173 (56.3%) were purely motor neurons, whereas the remaining 134 (43.7%) were visuo-motor (see Table 1). About half of the recorded visuo-motor neurons (69/134, 51.5%) showed a differential activation during grasping execution depending on the action (grasp-to-eat or grasp-to-place) in which grasping was embedded. The same behavior was found in a similar proportion of purely motor neurons (76/173,  $\chi^2 = 1.73$ ,  $p = 0.18$ , see examples in Supplementary Fig. 1). Since the properties of F5 purely motor neurons during grasp-to-eat and grasp-to-place actions have been previously described in detail elsewhere (Bonini et al. 2010), here we specifically focus on the properties of visuo-motor neurons.

Figure 2 shows examples of the different response patterns of visuo-motor neurons. Neuron 1 discharged stronger to the visual presentation of the food than of the object and subsequently showed a coherent motor preference for grasp-to-eat relative to grasp-to-place. It might be interesting to note that although the presentation of the cue sound by itself did not evoke any modulation of the neuron discharge, its visual response exhibited significant target selectivity only when it occurred following the go-cue in the VDM, whereas it was weaker and devoid of any target selectivity in the un-cued context (ADm). Neuron 2 showed

the opposite visuo-motor selectivity: It discharged to the visual presentation of the object whereas it was inhibited during the presentation of the food and then showed coherent motor preference for grasp-to-place. Even in this example, the visual selectivity was limited to the cued context (VDM), particularly during go-trials. Finally, Neuron 3 exemplifies the response of a visuo-motor neuron showing no target preference during both visual presentation and action execution epochs.

Table 2 summarizes the properties of the visual response of visuo-motor neurons. Although none of these neurons responded to the auditory cues by itself, the great majority of them (86/134) discharged stronger in the VDM than in the ADm. In addition, most of visual selective neurons (37/44) showed target preference in the VDM. Thus, even if the auditory contextual information cannot trigger F5 neurons activity by itself, it exerts strong influence on their firing rate and visual target selectivity.

## Visuo-Motor Congruence for the Target Object

Figure 3A illustrates the percentage of visuo-motor neurons with visual selectivity for the target as a function of their motor selectivity. It is clear that visuo-motor neurons discharging stronger during grasp-to-eat ( $N = 35$ ) or grasp-to-place ( $N = 34$ ) showed either congruent visual preference for the food (54%) or the object (47%), respectively (congruent visuo-motor neurons), or no significant visual preference: Indeed, only one neuron exhibited incongruent visuo-motor preference. Furthermore, figure 3B evidences that the visual and motor preference of congruent visuo-motor neurons were positively correlated ( $r = 0.92$ ,  $P < 0.001$ ).

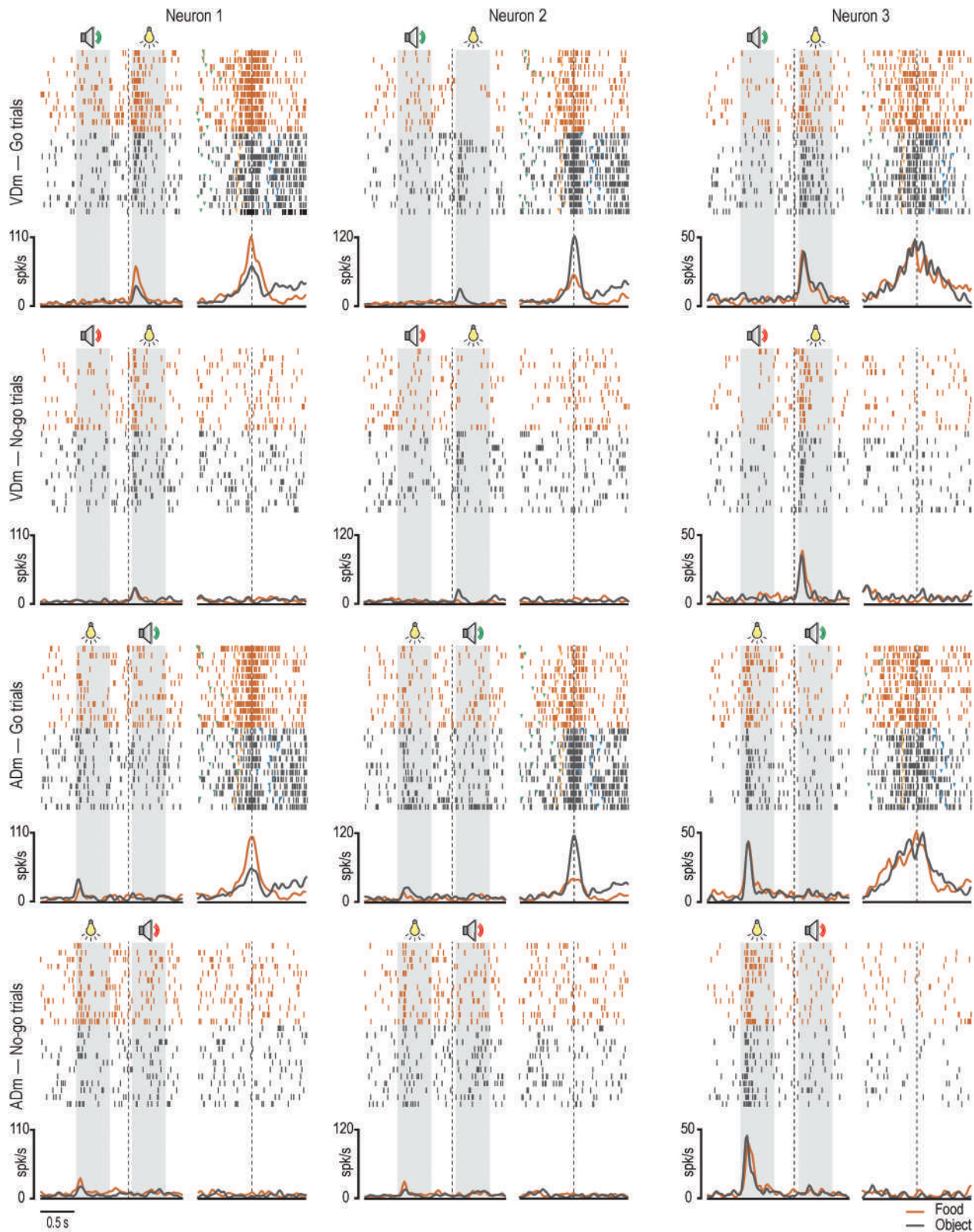
Population analyses (see Fig. 4) have been performed in order to assess the visual preference for the target of visuo-motor neurons in the different contexts (i.e., go and no-go VDM trials, and uncued ADm trials). We carried out  $2 \times 2 \times 3$  repeated-measures ANOVAs (factors: target, epoch, and context) on congruent visuo-motor neurons with visual and motor preference for the food ( $N = 19$ ) or the object ( $N = 16$ ), separately. The results showed significant main effects for all factors and their interaction ( $F_{2,36} = 12.85$ ,  $P < 0.001$  for food selective neurons;  $F_{2,30} = 32.02$ ,  $P < 0.001$  for object-selective neurons). In particular, Bonferroni post hoc comparisons revealed that the visual preference for the target was exclusively present, in both subpopulations of food- ( $P < 0.001$ ) and object-selective neurons ( $P < 0.001$ ), during instructed go-trials of the VDM. In addition, the analysis of the population response (see Materials and Methods) evidenced that target selectivity started shortly after target presentation (120 ms for the food and 80 ms for the object) and lasted until 460 ms after target presentation for both food and object trials: Thus, target preference did not remain sustained during the delay period, and it appeared again during grasping execution prior to hand-target contact (320 ms before hand-food contact and 260 ms before hand-object contact).

## Multimodal Modulation of Grasping Neurons Discharge Reflects the Action Goal

Previous studies demonstrated that F5 visuo-motor neurons encode potential motor representations of the grip type required for grasping objects of different size and shape (see Maranesi et al. 2014). Likewise, it might be hypothesized that a similar mechanism may exist to extract the action goal afforded by objects with the same size and shape but different identity/behavioral relevance (i.e., edible vs. inedible objects). If this is indeed the case, then one would expect to find similar target-induced modulations regardless of the sensory modality (i.e., visual or somatosensory) conveying the information on object identity.

**Table 1** Target selectivity of the motor response of all the recorded neurons

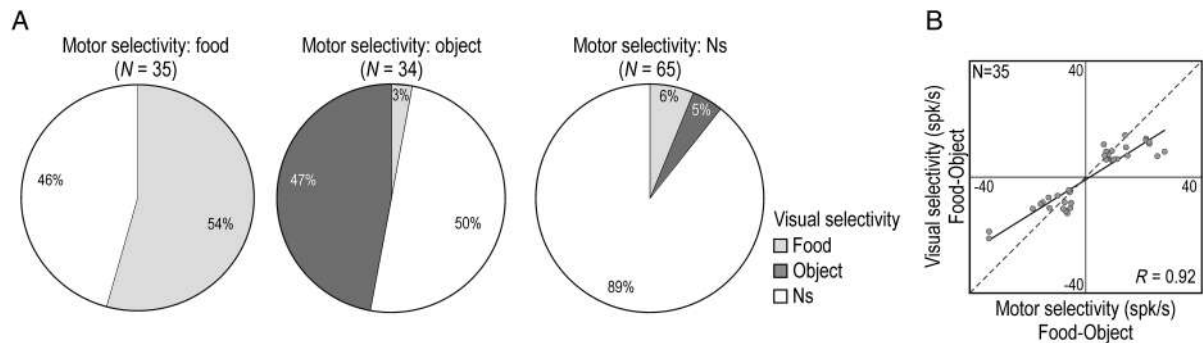
	Target selectivity			Total
	Food > Object	Object > Food	Food = Object	
Purely motor neurons	40	36	97	173
Visuo-motor neurons	35	34	65	134
Total	75	70	162	307



**Figure 2.** Examples of 3 area F5 visuo-motor neurons recorded during VDM and ADM. Rasters and histograms of each example neuron are aligned on target presentation and cue sound onset, which were separated by a fixed interval of 800 ms. Single-neuron responses during trials with different targets are shown in different colors (red for food, black for object). The gray-shaded areas indicate the time windows used for statistical analysis of neuronal sensory responses during (symbols) 1) target presentation (light bulb), 2) high cue tone (green speaker), and 3) low cue tone (red speaker). Rasters and histograms of go trials are aligned (dashed lines) on the hand-target contact (grasping), whereas those of No-go trials are aligned on the no-go signal. Markers color code: green, go-signal; orange, detachment of monkey's hand from the starting position (movement onset); light blue, contact of the monkey's hand with the border of the jar (placing).

**Table 2** Task mode (VDM/ADM), condition (go/no-go), and target (food/object) selectivity of the visual response of visuo-motor neurons

	Go > No-go			No-go > Go			Go = No-go			Total
	Food	Object	NS	Food	Object	NS	Food	Object	NS	
VDM>ADM	17	17	45	0	0	0	3	0	4	86
VDM = ADM	0	0	2	0	0	0	4	3	39	48
Subtotal	17	17	47	0	0	0	7	3	43	
Total		81			0			53		134



**Figure 3.** Visuo-motor congruence of target selectivity in visuo-motor neurons. (A) Visual selectivity for the target of the 3 categories of visuo-motor neurons characterized by motor selectivity for the food, the object, or no selectivity. (B) Scatter-plot showing the relationship between the visual and motor selectivity for the target in congruent visuo-motor neurons. The selectivity has been calculated in terms of differential discharge by simply subtracting, for each neuron, the average response to food and object trials (Food–Object) during the visual presentation epoch (visual selectivity) and during the grasping execution epoch/s (motor selectivity). Therefore, on each axis, positive values indicate stronger discharge during food relative to object trials, whereas negative values indicate stronger discharge during object trials. The dashed line represents the function  $x = y$ .

We addressed this issue by studying visuo-motor neurons activity in the HDm (see Fig. 1C). Behavioral data collected during neuronal recordings demonstrate that, in the HDm, the monkey could not know what the target of the ongoing trial was before touching it (Supplementary Fig. 2A,B). Figure 5A shows the example of a visuo-motor neuron recorded during all task modes. Its pattern of discharge in the VDM and ADM is the same as of the other example neurons shown in Figure 2: It showed a congruent visuo-motor preference for the food during both target presentation and grasping execution in the VDM, and no visual selectivity in the ADM. Interestingly, during HDm, this neuron showed a significant motor selectivity for the food, but only after hand-target contact. Of the 35 congruent visuo-motor neurons tested in the HDm, 29 showed postcontact target selectivity during grasping in the VDM (13 were selective for the food, and 16 for the object): The great majority of them ( $N = 23$ , 79.3%) exhibited post-contact target selectivity in the HDm as well, whereas the remaining 6 (20.7%) did not show any selectivity based on haptic feedback only (Fig. 5B). Figure 5C shows the population activity of all the 23 visuo-motor neurons with haptic-induced target selectivity. A  $2 \times 2 \times 3$  repeated-measures ANOVA (factors: task mode, target, and epoch) revealed a significant interaction of all factors ( $F_{2,44} = 12.13$ ,  $P < 0.001$ ), and Bonferroni post hoc comparisons indicated that target preference occurred during hand-shaping ( $P < 0.001$ ) and grasping/holding ( $P < 0.001$ ) epochs of the VDM, but only during the grasping/holding epoch ( $P < 0.001$ ) of the HDm. The same analyses have been performed on purely motor neurons recorded during the HDm (Supplementary Fig. 3), indicating that also in this set of neurons the haptic feedback can play an important role in generating target-selective responses.

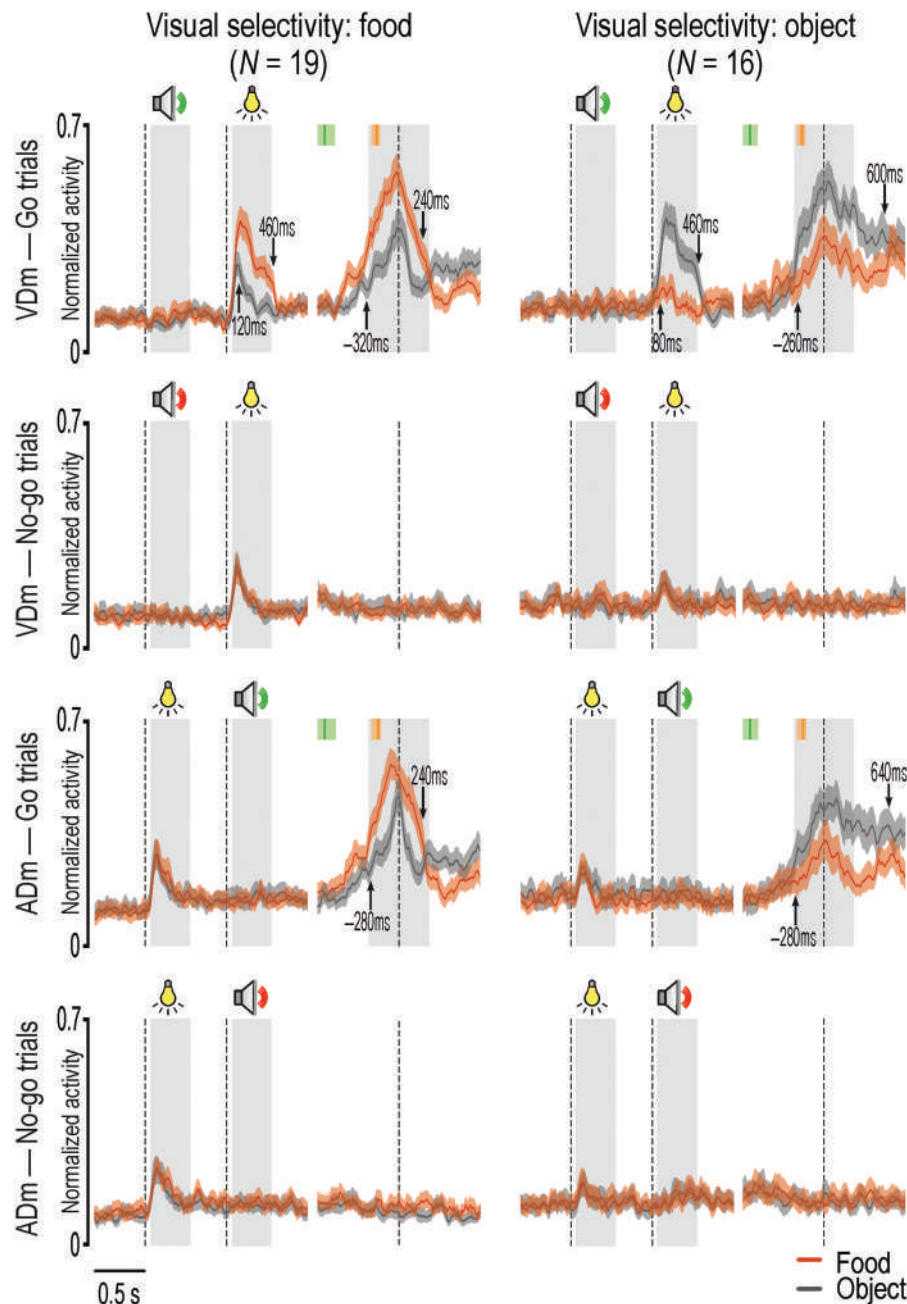
In order to investigate in more detail the relationship between visual and haptic target selectivity in F5 visuo-motor neurons, we looked for possible correlation between visually and haptically induced differential activity: Figure 5D shows that the target

preference conveyed by visual and haptic information is positively correlated ( $r = 0.88$ ,  $P < 0.001$ ). Furthermore, Figure 5E shows the temporal profile of the differential activity induced by the visual and haptic information: It is clear that target selectivity starts as early as 80 ms from the visual presentation of the target and 60 ms from hand-target contact.

## Discussion

It is well established that observed objects are processed in parallel by multiple, reciprocally connected, cortical areas: High-order visual areas belonging to the ventral stream contribute a “semantic” description of “what” an object is and underlie its perceptual recognition, whereas posterior parietal areas belonging to the dorsal stream generate a “pragmatic” representation of “how” the observer could motorically interact with it (Rizzolatti and Matelli 2003; Goodale and Westwood 2004). The parieto-frontal circuit formed by inferior parietal areas AIP/PFG and the ventral premotor area F5 provides a paradigmatic example of how the physical properties of observed objects are transformed into pragmatic representations of the grip types afforded by them (see Maranesi et al. 2014). Single-neuron studies also showed that both parietal (Fluet et al. 2010) and premotor (Baumann et al. 2009) neurons can selectively encode specific pragmatic affordances (i.e., precision or power grip) cued by abstract visual information (i.e., white or green light) even when the monkey faced the same target (a handle), which was graspable with both types of grip. However, what a potential target is (e.g., an edible or inedible object) constitutes crucial information allowing an agent to decide what to do with it (e.g., eating or placing it, respectively). The present study provides the first evidence that F5 visuo-motor neurons can discharge differently depending on the “identity” of visually presented objects having the same pragmatic features, and their visual selectivity matches the motor





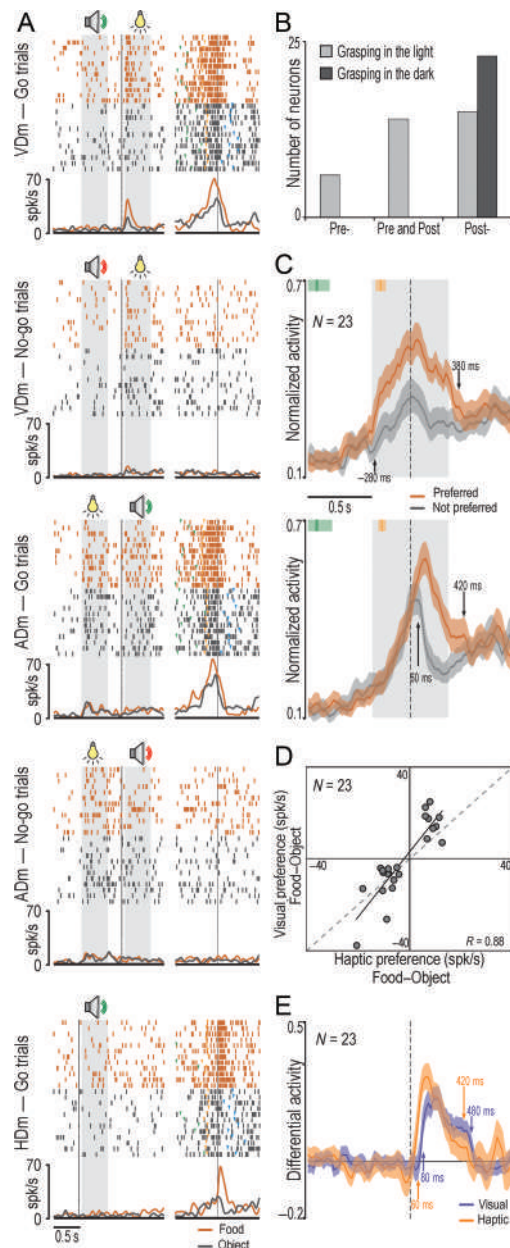
**Figure 4.** Population responses of congruent visuo-motor neurons. For each population, the left part of each panel illustrates the response aligned (dashed line) to the presentation of the sensory cues in the Vdm and Adm, whereas the right part (after the gap) illustrates the motor response aligned on hand-target contact (go trials) and the activity during no-go trials aligned to the no-go signal. The colored-shaded regions around each line indicate 1 SEM. The gray-shaded regions evidence the time periods used for statistical analyses of population response. The symbols over each region indicate the event characterizing each epoch, as described in Figure 2. The median times of go-signal onset and movement onset are indicated with the green and orange markers, respectively, above each population plot. Shaded areas around each marker represent the 25th and 75th percentile times of other events of the same type. The black arrows indicate the time of onset (upward arrow) and end (downward arrow) of significant separation of the activity between the 2 compared conditions.

preference they exhibit during grasping execution. Interestingly, when grasping occurs in complete darkness and the monkey can recognize the target only based on haptic information, visuo-motor neurons lose their precontact motor selectivity, but in most of them the selectivity shows up again within ~60 ms after hand-target contact.

Before discussing in more detail the interpretation and the possible implications of the present findings, it is worthwhile to address some possible criticisms. It might be claimed that target selectivity depends on attentional/motivational factors: For

example, the food could induce higher arousal/attention than the object. Several pieces of evidence allow to safely excluding this possibility. First, it is known from previous studies that the action rewarding value does not affect grasping neurons motor selectivity (Bonini et al. 2011). In addition, in the present study, we kept constant the overall rewarding value of all trials by delivering as a reward at the end of each trial the same food pellet the monkey ate during eating actions. Second, many neurons with selectivity for one of the 2 targets, or no target selectivity, have been recorded simultaneously through different electrodes of





**Figure 5.** Multimodal target selectivity evoked by visual and haptic information. (A) Example of a visuo-motor neuron recorded during the VDM, ADm, and HDm. Conventions for the first 4 panels as in Figure 2. Note that in the HDm (fifth panel) the response is aligned (dashed lines) on the cue sound and then on hand-target contact, as all trials occurred in complete darkness. (B) Target selectivity during the precontact, postcontact, or both epochs of grasping execution in congruent visuo-motor neurons recorded during grasping in the light (VDM) and in the dark (HDm). (C) Population response of visuo-motor neurons with haptic target selectivity during grasping in the light (VDM, upper panel) and in the dark (HDm, lower panel). Other conventions as in Figure 4. (D) Scatter-plot showing the relationship between the visual and haptic selectivity for the target in the neuronal population shown in C. Visual selectivity was calculated by taking into account the target presentation epoch of the VDM, whereas the haptic selectivity was calculated by taking into account the grasping/holding epoch of the HDm. The calculation was performed as described in Figure 3B. Other conventions as in Figure 3B. (E) Time course of the differential activity between the preferred and not preferred target in the same neuronal subpopulation considered in C and D. Note that the dashed line represents 2 different alignment points for the 2 curves, namely, the visual presentation of the target (blue line—visual), and the hand-target contact (orange line—haptic). Colored arrows indicate, for each curve, the time of onset (upward arrow) and end (downward arrow) of significant differential activity.

the same probe (see [Supplementary Fig. 4](#)), thus allowing to exclude that general internal factors, such as attention or motivation, can cause the modulation of neuronal activity. Third, if the target by itself deployed different attentional/motivational resources, which could differently affect the response of individual neurons, then this effect should be evident whenever the object is presented: In contrast, the great majority of target-selective visual responses occurred during the VDM, that is, when target presentation occurred within a cued context, not in the ADm when the target was presented prior to any go/no-go instruction. Although contributing to rule out attentional/motivational interpretations, this latter observation may introduce a further caveat, namely, that the visual target selectivity constitutes the neural correlate of motor preparation to perform a given action. However, the great majority of visuo-motor neurons, as well as their population response, encoded phasically the presented object and did not show sustained activation or smooth increase of firing rate during the delay period, which are typically associated with preparatory activity ([Cisek 2007](#); [Shenoy et al. 2011](#)). Based on these considerations, it might be confidently excluded that the multimodal target preference reported in this study was due to a different degree of attention, motivation, or rewarding value of food and object trials. Furthermore, although the relevance of the behavioral context (go/no-go) in which target presentation occurred appears to be crucial to generate visual target selectivity, this latter seems hardly reducible to preparatory activity preceding the execution of a specific action.

A further caveat is that the small differences (i.e., color and texture) between the 2 targets used by the monkey to recognize them and to select the action to perform could be sufficient to induce a differential discharge in some neurons. This possibility appears extremely unlikely. Indeed, previous studies with similar paradigms carried out on F5 grasping neurons showed that neuronal motor preference did not change when a food morsel, rather than an object, was used as a target for placing actions ([Bonini et al. 2011](#)). Even when eating and placing actions were performed using targets of different sizes and shapes, the neurons selectivity remained the same ([Bonini et al. 2012](#)). Thus, visual and haptic differences between the targets, per se, cannot account for eating or placing selectivity. Of course, we do not have similar information concerning object presentation responses, and it might be argued that they can derive from some overlearned sensorimotor association (see for example [Fluet et al. 2010](#)). Even this possibility appears, however, unlikely, because while the plastic sphere needs to be associated with placing actions by means of explicit training, this is not the case for the link between food and eating actions. Thus, if a cue-to-response association was responsible of the observed selectivity, the great majority of the visual responses should show selectivity for the object, whereas we found a similar proportion of visual responses selective for the 2 targets. Furthermore, the fact that the visual, motor, and haptic selectivity of the same neuron appears to be tuned to the same target strongly suggests that F5 grasping neurons discharge represents some more general property of the target, which is accessible through multiple modalities. On these bases, we suggest that area F5 possesses a multimodal access to semantic information on objects, which is transformed into motor representations of the potential goal-directed actions afforded by them.

### Sensorimotor Integration Underlies the Organization of Natural Goal-Directed Actions

Several pieces of evidence have been accumulated indicating that sensory-motor integration in PMv is particularly crucial for the

emergence of smoothly organized goal-directed actions. First, the organization of somatosensory receptive field in PMv neurons suggested the existence of functional links between the neuronal representations of different body parts: For example, neurons have been described having both proprioceptive responses during elbow flexion and tactile responses on the face/mouth (Rizzolatti et al. 1981a). Second, PMv hosts bimodal neurons that respond to both tactile and visual (Rizzolatti et al. 1981b; Graziano et al. 1994; Fogassi et al. 1996; Guipponi et al. 2015) or tactile and auditory (Graziano et al. 1999) stimuli delivered within peripersonal space sectors linked with specific body parts (e.g., arm or mouth), suggesting that sensory-motor integration plays a role in the organization of specific multi-joints movements in space. Third, intracortical microstimulation studies employing long stimulation trains (Graziano et al. 2002) revealed stimulation-induced complex multi-joint movements, often involving even multiple effectors (i.e., the forelimb and the mouth), and resembling the motor sequences of primates' foraging behaviors (e.g., grasping and bringing food to the mouth). Finally, direct evidence of the role of PMv in action organization came from single-unit recordings carried out in area F5 during the execution of simple (Bonini et al. 2010, 2012) and complex (Bonini et al. 2011) goal-directed actions. These latter studies revealed that grasping neurons in the monkey ventral premotor area F5 can discharge differently depending on the goal (i.e., eating or placing) of the action in which grasping was embedded, likely due to the connections of area F5 with the inferior parietal lobule (Rozzi et al. 2006; Bonini et al. 2010), in which similar properties were originally identified (Fogassi et al. 2005). A crucial point of these latter studies concerned what was the source of information underlying motor selectivity: Although it was clear that the context played a crucial role in the emergence of neuronal selectivity (Bonini et al. 2011), all these studies focused on the neuronal properties "during" grasping execution.

The present data demonstrate that the visual presentation of a potential target object can trigger neuronal pools providing internal representations of the specific goal-directed action (i.e., grasp-to-eat or grasp-to-place) afforded by the object. Importantly, since the size and shape of the 2 targets employed in this study were exactly the same, their identity appears to be the key factor inducing visuo-motor differential discharge. Just as the tridimensional, pragmatic features of an object can trigger the internal representation of the hand configuration most suitable to pick it up (Rizzolatti et al. 1988; Murata et al. 1997; Raos et al. 2006; Bonini et al. 2014b), so too the features allowing an observer to recognize what an object is automatically trigger the potential action he/she could perform on it. It is important to note, however, that single neuron and population activity of the visuo-motor neurons described in this study clearly show transient activation to the visual presentation of the target, but not the sustained activity during the delay period reported in previous studies on F5 visuo-motor neurons (see Murata et al. 1997; Raos et al. 2006; Bonini et al. 2014b). One possibility is that the effect observed here depends on some feature of the task (e.g., it included only 2 alternative decisions and only one possible grip type, whereas previous studies typically involved at least 3 alternative types of grip), in line with the recent finding of similar phasic activation pattern of ventrolateral prefrontal (VLPF) neurons tested with the same task (Bruni et al. 2015). Another, not mutually exclusive, possibility is that the strong anatomical connection of area F5 with VLPF accounts for their functional similarity in this type of phasic activation pattern and that other brain regions, such as dorsal premotor cortex (PMd) or basal ganglia (see Hoshi 2013), intervene to generate sustained context-dependent activation during the delay period of this task.

These results fit well with previously proposed models of action selection and specification, which maintain that information arriving from the world is continuously used to specify several currently available potential actions and then select among them the one that will be turned into overt execution (Cisek 2007; Cisek and Kalaska 2010). Indeed, our findings show that when a small sphere was visually presented in an un-cued context, neurons activate in the same way regardless of whether the sphere was edible or inedible: In this case, neuronal activity appears to reflect just the potential motor act afforded by the object (i.e., "grasping"), and hence its "graspability." In contrast, when additional go/no-go cues are provided prior to target presentation, then the visual information enables the monkey to make a decision, and the neuronal visual selectivity reflects the selection of a specific action (i.e., grasp-to-eat or grasp-to-place). The involvement of target-selective neurons in the representation of specific goal-directed actions is confirmed by their motor selectivity, which becomes significant already hundreds of milliseconds before hand-target contact, in line with previous studies (Bonini et al. 2010). Crucially, when no information on the target is provided and grasping actions have to be initiated in the dark, neuron motor activity shows a comparable increase during all trials before hand-target contact but suddenly reflects the selected action once haptic information on target identity becomes available. The short latency of haptically induced target selectivity (60 ms) fits well with the results of recent transcranial magnetic stimulation studies in humans (Schettino et al. 2015), indicating that the reprogramming of neural activity in PMv based on haptic perturbation occurs in a window of 50–100 ms from perturbation onset. Altogether, these findings suggest that a fast, multimodal access to sensory information could be at the basis of a dynamic selection of goal-directed actions in area F5.

Anatomical data make a useful contribution to understand the circuitry underlying the multimodal processing of sensory information in area F5. Indeed, area F5 possesses rich reciprocal connections with inferior parietal area AIP, which is the source of visual information not only on object physical properties but likely also on object identity, by virtue of its connections with inferotemporal regions (Borra et al. 2008). Both AIP and area F5 are also strongly connected with the secondary somatosensory cortex (Borra et al. 2008; Gerbella et al. 2011), which is known to play a crucial role in haptic recognition of familiar objects (Binkofski et al. 1999; Grefkes et al. 2002; Ishida et al. 2013). In addition, neuropsychological data (Jeannerod et al. 1994) suggested that routes different from the classical pragmatic parieto-frontal pathway may exist to implement premotor representations of actions with semantic information on objects: Recent connectional data indicate that an important role in this function could be played by the VLPF cortex (Borra et al. 2011). Thus, this evidence point to the existence of a wide network of reciprocally connected areas in which the multimodal processing of pragmatic and semantic information on potential targets of manual actions is exploited for action selection and specification.

## Conclusions

In this study, we explored for the first time the capacity of visuo-motor neurons of the ventral premotor cortex to encode visually presented object in terms of the action afforded by them. An extremely interesting possibility would be to directly compare, in the same single neurons, the encoding of both pragmatic and semantic information on objects, for example by employing edible and inedible objects (to be eaten or placed, respectively) presented in various sizes and shapes. This would enable one to directly compare grip and behavioral affordance processing.

A similar study is technically difficult to perform with a visuo-motor paradigm. However, in a previous study with an execution task, we recorded grasping neurons of the inferior parietal area PFG and ventral premotor area F5 showing that their motor discharge can reflect both pragmatic (grip type) and semantic (action goal) information on objects (Bonini et al. 2012). Although in this latter study we did not investigate visual presentation responses, it is plausible that the integration of pragmatic and semantic information occurs in visuo-motor neurons as well, intervening in the organization of manual actions.

The multimodal integration of multiple information on object likely constitutes a basic and phylogenetically ancient mechanism, widely represented in the parieto-frontal system of many primate species (Kaas et al. 2013). Its higher exploitation in humans might be exemplified by the capacity to use tools, by integrating semantic information on “what” objects are with the pragmatic information on “how” to use them to achieve a distal goal (see Johnson-Frey 2004; Orban and Caruana 2014).

## Supplementary Material

Supplementary Material can be found at <http://www.cercor.oxfordjournals.org/> online.

## Funding

The work was supported by the Italian PRIN (2010MEFN7), Istituto Italiano di Tecnologia, and the European Commission Grant Cogsystem FP7-250013.

## Notes

We thank Marco Bimbi for his assistance in software implementation. *Conflict of Interest:* None declared.

## References

- Baumann MA, Fluet MC, Scherberger H. 2009. Context-specific grasp movement representation in the macaque anterior intraparietal area. *J Neurosci.* 29:6436–6448.
- Belmalih A, Borra E, Contini M, Gerbella M, Rozzi S, Luppino G. 2008. Multimodal architectonic subdivision of the rostral part (area F5) of the macaque ventral premotor cortex. *J Comp Neurol.* 512:183–217.
- Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H. 1999. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur J Neurosci.* 11:3276–3286.
- Bonini L, Maranesi M, Livi A, Bruni S, Fogassi L, Holzhammer T, Paul O, Ruther P. 2014a. Application of floating silicon-based linear multielectrode arrays for acute recording of single neuron activity in awake behaving monkeys. *Biomed Tech.* 59:273–281.
- Bonini L, Maranesi M, Livi A, Fogassi L, Rizzolatti G. 2014b. Space-dependent representation of objects and other's action in monkey ventral premotor grasping neurons. *J Neurosci.* 34:4108–4119.
- Bonini L, Rozzi S, Serventi FU, Simone L, Ferrari PF, Fogassi L. 2010. Ventral premotor and inferior parietal cortices make distinct contribution to action organization and intention understanding. *Cereb Cortex.* 20:1372–1385.
- Bonini L, Serventi FU, Simone L, Rozzi S, Ferrari PF, Fogassi L. 2011. Grasping neurons of monkey parietal and premotor cortices encode action goals at distinct levels of abstraction during complex action sequences. *J Neurosci.* 31:5876–5886.
- Bonini L, Ugolotti Serventi F, Bruni S, Maranesi M, Bimbi M, Simone L, Rozzi S, Ferrari PF, Fogassi L. 2012. Selectivity for grip type and action goal in macaque inferior parietal and ventral premotor grasping neurons. *J Neurophysiol.* 108:1607–1619.
- Borra E, Belmalih A, Calzavara R, Gerbella M, Murata A, Rozzi S, Luppino G. 2008. Cortical connections of the macaque anterior intraparietal (AIP) area. *Cereb Cortex.* 18:1094–1111.
- Borra E, Gerbella M, Rozzi S, Luppino G. 2011. Anatomical evidence for the involvement of the macaque ventrolateral prefrontal area 12r in controlling goal-directed actions. *J Neurosci.* 31:12351–12363.
- Bruni S, Giorgetti V, Bonini L, Fogassi L. 2015. Processing and integration of contextual information in monkey ventrolateral prefrontal neurons during selection and execution of goal-directed manipulative actions. *J Neurosci.* 35:11877–11890.
- Cisek P. 2007. Cortical mechanisms of action selection: the affordance competition hypothesis. *Philos Trans R Soc Lond B Biol Sci.* 362:1585–1599.
- Cisek P, Kalaska JF. 2010. Neural mechanisms for interacting with a world full of action choices. *Annu Rev Neurosci.* 33:269–298.
- Fluet MC, Baumann MA, Scherberger H. 2010. Context-specific grasp movement representation in macaque ventral premotor cortex. *J Neurosci.* 30:15175–15184.
- Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. 2005. Parietal lobe: from action organization to intention understanding. *Science.* 308:662–667.
- Fogassi L, Gallese V, Fadiga L, Luppino G, Matelli M, Rizzolatti G. 1996. Coding of peripersonal space in inferior premotor cortex (area F4). *J Neurophysiol.* 76:141–157.
- Gerbella M, Belmalih A, Borra E, Rozzi S, Luppino G. 2011. Cortical connections of the anterior (F5a) subdivision of the macaque ventral premotor area F5. *Brain Struct Funct.* 216:43–65.
- Goodale MA, Westwood DA. 2004. An evolving view of duplex vision: separate but interacting cortical pathways for perception and action. *Curr Opin Neurobiol.* 14:203–211.
- Graziano MS, Reiss LA, Gross CG. 1999. A neuronal representation of the location of nearby sounds. *Nature.* 397:428–430.
- Graziano MS, Taylor CS, Moore T. 2002. Complex movements evoked by microstimulation of precentral cortex. *Neuron.* 34:841–851.
- Graziano MS, Yap GS, Gross CG. 1994. Coding of visual space by premotor neurons. *Science.* 266:1054–1057.
- Grefkes C, Weiss PH, Zilles K, Fink GR. 2002. Crossmodal processing of object features in human anterior intraparietal cortex: an fMRI study implies equivalencies between humans and monkeys. *Neuron.* 35:173–184.
- Guipponi O, Cléry J, Odouard S, Wardak C, Ben Hamed S. 2015. Whole brain mapping of visual and tactile convergence in the macaque monkey. *Neuroimage.* 117:93–102.
- Herwik S, Paul O, Ruther P. 2011. Ultrathin silicon chips of arbitrary shape by etching before grinding. *J Microelectromech Syst.* 20:791–793.
- Hodges JR, Bozeat S, Lambon Ralph MA, Patterson K, Spatt J. 2000. The role of conceptual knowledge in object use evidence from semantic dementia. *Brain.* 123(Pt 9):1913–1925.
- Hoshi E. 2013. Cortico-basal ganglia networks subserving goal-directed behavior mediated by conditional visuo-goal association. *Front Neural Circuits.* 7:158. Review.
- Hoshi E, Tanji J. 2006. Differential involvement of neurons in the dorsal and ventral premotor cortex during processing



- of visual signals for action planning. *J Neurophysiol.* 95:3596–3616.
- Ishida H, Fornia L, Grandi LC, Umiltà MA, Gallese V. 2013. Somato-motor haptic processing in posterior inner perisylvian region (SII/pIC) of the macaque monkey. *PLoS One.* 8:e69931.
- Jeannerod M, Decety J, Michel F. 1994. Impairment of grasping movements following a bilateral posterior parietal lesion. *Neuropsychologia.* 32:369–380.
- Johnson-Frey SH. 2004. The neural bases of complex tool use in humans. *Trends Cogn Sci.* 8:71–78.
- Kaas JH, Gharbawie OA, Stepniewska I. 2013. Cortical networks for ethologically relevant behaviors in primates. *Am J Primatol.* 75:407–414.
- Maranesi M, Bonini L, Fogassi L. 2014. Cortical processing of object affordances for self and others' action. *Front Psychol.* 5:538.
- Maranesi M, Roda F, Bonini L, Rozzi S, Ferrari PF, Fogassi L, Coudé G. 2012. Anatomic-functional organization of the ventral primary motor and premotor cortex in the macaque monkey. *Eur J Neurosci.* 36:3376–3387.
- Murata A, Fadiga L, Fogassi L, Gallese V, Raos V, Rizzolatti G. 1997. Object representation in the ventral premotor cortex (area F5) of the monkey. *J Neurophysiol.* 78:2226–2230.
- Orban GA, Caruana F. 2014. The neural basis of human tool use. *Front Psychol.* 5:310.
- Pardo-Vazquez JL, Leboran V, Acuna C. 2008. Neural correlates of decisions and their outcomes in the ventral premotor cortex. *J Neurosci.* 28:12396–12408.
- Raos V, Umiltà MA, Murata A, Fogassi L, Gallese V. 2006. Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. *J Neurophysiol.* 95:709–729.
- Rizzolatti G, Camarda R, Fogassi L, Gentilucci M, Luppino G, Matelli M. 1988. 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.
- Rizzolatti G, Matelli M. 2003. Two different streams form the dorsal visual system: anatomy and functions. *Exp Brain Res.* 153:146–157.
- Rizzolatti G, Scandolara C, Matelli M, Gentilucci M. 1981a. Afferent properties of periarculate neurons in macaque monkeys. I. Somatosensory responses. *Behav Brain Res.* 2:125–146.
- Rizzolatti G, Scandolara C, Matelli M, Gentilucci M. 1981b. Afferent properties of periarculate neurons in macaque monkeys. II. Visual responses. *Behav Brain Res.* 2:147–163.
- Romo R, de Lafuente V. 2013. Conversion of sensory signals into perceptual decisions. *Prog Neurobiol.* 103:41–75.
- Rozzi S, Calzavara R, Belmalih A, Borra E, Gregoriou GG, Matelli M, Luppino G. 2006. Cortical connections of the inferior parietal cortical convexity of the macaque monkey. *Cereb Cortex.* 16:1389–1417.
- Ruther P, Herwik S, Kisban S, Seidl K, Paul O. 2010. Recent progress in neural probes using silicon MEMS technology. *IEEJ Trans Elec Electron Eng.* 5:505–515.
- Schettino LF, Adamovich SV, Bagce H, Yarossi M, Tunik E. 2015. Disruption of activity in the ventral premotor but not the anterior intraparietal area interferes with on-line correction to a haptic perturbation during grasping. *J Neurosci.* 35:2112–2117.
- Shenoy KV, Kaufman MT, Sahani M, Churchland MM. 2011. A dynamical systems view of motor preparation: implications for neural prosthetic system design. *Prog Brain Res.* 192:33–58.
- van Elk M, van Schie H, Bekkering H. 2014. Action semantics: a unifying conceptual framework for the selective use of multimodal and modality-specific object knowledge. *Phys Life Rev.* 11:220–250.
- Yamaguchi K, Nakamura K, Oga T, Nakajima Y. 2014. Eating tools in hand activate the brain systems for eating action: a transcranial magnetic stimulation study. *Neuropsychologia.* 59:142–147.