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This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Jacquet, P.O., Avenanti, A. (2015). Perturbing the Action Observation Network During Perception and Categorization of Actions' Goals and Grips: State-Dependency and Virtual Lesion TMS Effects. CEREBRAL CORTEX, 25(3), 598-608 [10.1093/cercor/bht242].

Availability:

This version is available at: <https://hdl.handle.net/11585/184134> since: 2015-11-10

Published:

DOI: <http://doi.org/10.1093/cercor/bht242>

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<https://doi.org/10.1093/cercor/bht242>

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Perturbing the Action Observation Network during perception and categorization of actions' goals and grips: state-dependency and virtual lesion TMS effects

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Abstract Watching others grasping and using objects activates an action observation network (AON), including inferior frontal (IFC), anterior intraparietal (AIP), and somatosensory cortices (S1). Yet, causal evidence of the differential involvement of such AON sensorimotor nodes in representing high- and low-level action components (i.e., end-goals and grip type) is meager. To address this issue, we used transcranial magnetic stimulation-adaptation (TMS-A) during 2 novel action perception tasks. Participants were shown adapting movies displaying a demonstrator performing goal-directed actions with a tool, using either power or precision grips. They were then asked to match the end-goal (Goal-recognition task) or the grip (Grip-recognition task) of actions shown in test pictures to the adapting movies. TMS was administered over IFC, AIP, or S1 during presentation of test pictures. Virtual lesion-like effects were found in the Grip-recognition task where IFC stimulation induced a general performance decrease, suggesting a critical role of IFC in perceiving grips. In the Goal-recognition task, IFC and S1 stimulation differently affected the processing of “adapted” and “nonadapted” goals. These “state-dependent” effects suggest that the overall goal of seen actions is encoded into functionally distinct and spatially overlapping neural populations in IFC–S1 and such encoding is critical for recognizing and understanding end-goals.

Keywords: action observation network, action perception, somatosensory cortex, state dependency, transcranial magnetic stimulation, virtual lesion

Introduction

Observing another individual manipulating an object (e.g., a wine bottle) with the aim of achieving a specific purpose may involve the processing of low- and high-level components of the observed motor behavior, namely the specific grip used to grasp the object (e.g., power or precision grip) and the end-goal achieved via object manipulation (e.g., pouring a glass or placing the bottle in the ice bucket). It has been suggested that the ability to perceive and understand others' actions depends on resonance mechanisms that map observed motor acts onto one's own action representations (Rizzolatti and Craighero 2004; Wilson and Knoblich 2005; Keysers et al. 2010; Urgesi et al. 2010; Avenanti and Urgesi 2011; Kilner 2011; Borgomaneri et al. 2012) and are implemented in a widespread cortical network, usually referred to as the action observation network (AON). Classically, the inferior frontal cortex (IFC, including the ventral premotor cortex and the posterior part of the inferior frontal gyrus) and the anterior intraparietal cortex (AIP) have been considered important nodes of the AON, mediating action perception through motor simulation (di Pellegrino et al. 1992; Gallese et al. 1996; Fogassi et al. 2005; Chong et al. 2008; Etzel et al. 2008; Kilner et al. 2009; Oosterhof et al. 2010). In addition, mounting evidence suggests that the somatosensory cortices may also be involved in perceiving and internally simulating others' behavioral states (Keysers et al. 2004; Bufalari et al. 2007; Ebisch et al. 2008; Valeriani et al. 2008; Avenanti et al. 2009; Aziz-Zadeh et al. 2012; Gazzola et al. 2012). In particular, the primary somatosensory cortex (S1) is consistently active during action perception and execution (Avikainen et al. 2002; Rossi et al. 2002; Costantini et al. 2005; Avenanti et al. 2007; Gazzola and Keysers 2009; Turella et al. 2012) and may thus be considered an additional sensorimotor node of the AON (Keysers et al. 2010).

One unresolved issue is whether, and how, low- and high-level components of actions—namely the type of hand grip and end-goals—are differentially represented in sensorimotor regions of the AON and what is the respective contribution of such regions to action perception. Imaging and neurophysiological studies have suggested that the IFC is involved in processing both low- and high-level components of seen actions, whereas parietal nodes of the AON may be more involved in processing high-level components (e.g., end-goals) (Iacoboni et al. 2005; Hamilton and Grafton 2006, 2008; Grafton and Hamilton 2007; Lestou et al. 2008; Grafton 2009; Majdandzic et al. 2009; Bonini et al. 2010, 2012; Urgesi et al. 2010). However, as AIP and S1 are often co-activated (Keysers et al. 2010), it is unclear whether these 2 regions play any differential role in action perception. Moreover, although several studies using imaging and neurophysiological techniques have suggested activation of IFC, AIP, and S1 during observation of others' actions (Caspers et al. 2010; Molenberghs et al. 2012), it should be noted that these techniques provide correlational evidence and cannot establish a direct causal link between brain and function (Silvanto and Pascual-Leone 2012).

The precise aim of the present study is to test the causal influences of IFC, AIP, and S1 in the perception of different action components. To test the hypothesis that IFC has a major role in processing grips and end-goals while parietal regions would be mainly devoted to processing goals, we used transcranial magnetic stimulation-adaptation (TMS-A).

The TMS-A paradigm is based on the well-established notion of “state-dependency”, i.e. that TMS effects depend on the context and the initial state of the stimulated neurons (Lang et al. 2004; Siebner et al. 2004, 2009; Bestmann et al. 2010). Specifically, TMS is thought to differentially modulate neurons that are activated by a given perceptual or cognitive process relative to neurons that are not activated by such a process (Cattaneo et al. 2008; Silvanto et al. 2008; Silvanto and Pascual-Leone 2012). In the TMS-A paradigm, the state of the neurons prior to the TMS pulse is manipulated in a controlled way by means of perceptual adaptation. Although the underlying neurophysiological mechanisms are not entirely understood (Ruzzoli et al. 2011; Schwarzkopf et al. 2011; Perini et al. 2012), the phenomenology of TMS-A is very robust. Stimulation time locked

to the cognitive task and delivered over the cortical area representing the adapted stimulus features typically produces an improvement in processing the adapted stimulus features relative to the nonadapted ones (Silvanto and Muggleton 2008; Cattaneo et al. 2009, 2012; Cohen Kadosh et al. 2010). These behavioral changes unambiguously indicate the presence of neurons encoding the adapted feature in the stimulated area and can disclose their organization into spatially overlapping, but functionally distinct, populations that are critical for perceptual processing.

Relevant to the present research, studies have suggested that TMS after-effects are not only related to the activation state of the stimulated neurons. In some circumstances, depending on the intensity of the magnetic pulses and task difficulty, brain stimulation in TMS-A protocols may also lead to disruption of neural functions, that is “virtual lesions” effects, consisting of a “state-independent” reduction of behavioral performance (Burton et al. 2009; Ruzzoli et al. 2010, 2011; Schwarzkopf et al. 2011; Perini et al. 2012).

The TMS-A approach was recently used by Cattaneo et al. to investigate the action perception mechanisms (Cattaneo et al. 2010). In that study, participants were exposed to adapting movies of grasping or pulling actions performed with either the hand or the foot. Then, test pictures depicting the same or different actions were presented and subjects were asked to provide similarity judgments. When TMS was applied over the IFC and another visuo-motor node of the AON, namely the inferior parietal lobule, response times (RTs) to adapted actions were shorter. This state-dependent RT improvement was independent of the type of effector that was involved in the adapting movies, suggesting that visuo-motor nodes of the AON represent seen actions in an abstract goal-related manner. However, in that study, RTs and accuracy measures were analyzed separately and thus it is not entirely clear whether speed accuracy trade-off effects were at play. Most importantly, the conclusion drawn by Cattaneo and colleagues applies only to a very basic level of the action hierarchy, that is, the motor goal level (Jacob and Jeannerod 2005; Grafton and Hamilton 2007). Indeed, action stimuli that were used in the task present a “one-to-one” mapping problem as only one observed motor behavior (e.g., flexing the fingers) was used to achieve one goal (grasping an object). Yet, the broad set of actions that we are confronted with in our everyday lives present a “many-to-one” mapping problem as a particular complex goal can be achieved through many different movements (Jacob and Jeannerod 2005; Grafton and Hamilton 2007; Kilner 2011; Jacquet et al. 2012).

The experiments performed in the present study are inspired by Cattaneo et al.'s paradigm (2010), but focus on actions whose goals can be decoupled from specific sensorimotor correlates—that is, goals that can be achieved through different types of grips of the same effector. Participants were repeatedly exposed to complex hand actions in which the end-goal (i.e., lifting an object to open a box vs. turning an object to switch-on a light; see Fig. 1) and the type of grip (i.e., power vs. precision grip) were manipulated, in such a way that either end-goal could be achieved with either grip (presenting a “many-to-one” mapping problem). In addition, subjects had to perform 2 tasks. In the “Goal-recognition task,” participants had to provide similarity judgments on the end-goal of the action, independently of the type of grip being used to achieve it. In the “Grip-recognition task,” similarity judgments were provided on the grip used, independently of the end-goal. In both tasks, active TMS was applied to the left IFC, left AIP, and left S1. To rule out any speed-accuracy trade off, the effect of TMS on behavioral performance was assessed by merging both RTs and accuracy into a single measure of performance [inverse efficiency (IE) index]. In this way, we were able to test the active involvement of key sensorimotor nodes of the AON in the neural representation of grips and complex action end-goals. Moreover, by highlighting state-dependent effects on action perception, our approach can provide behavioral evidence of spatially overlapping, but functionally distinct, neural populations which: 1) code specific grips and end-goals; and 2) play a critical role in the visual recognition of these low- and high-level action components.

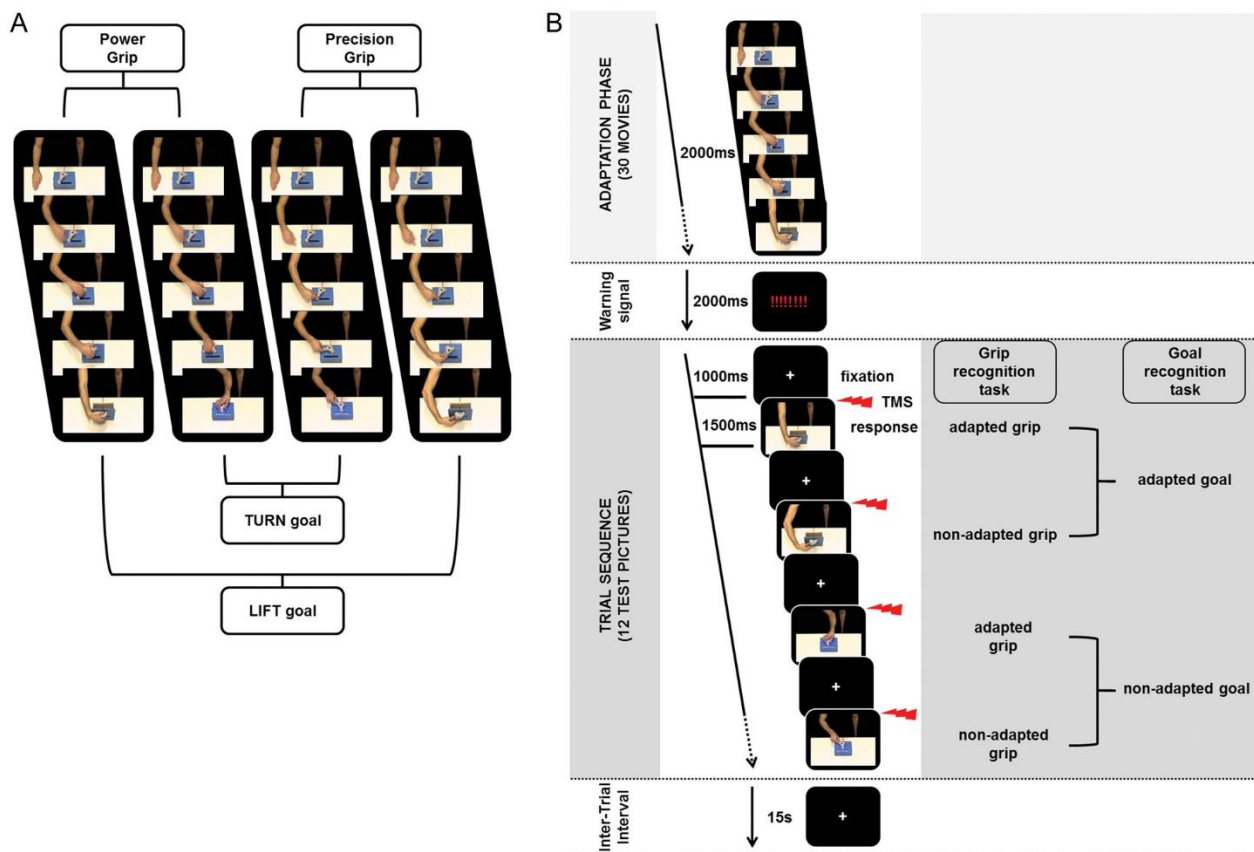


Figure 1. (A) Example of the 4 adapting movies. The actor could use either a power or a precision grip to either “lift” the object to open the box or “turn” the object to switch on the light. (B) Example of an experimental trial. On each trial, participants were first presented with 30 adapting movies repeatedly showing one of the 4 actions. This perceptual adaptation phase was followed by a series of 12 test pictures (3 exemplars of each of the 4 actions). Test pictures lasted 1500 ms each and were separated by a fixation cross of 1000 ms duration. At the onset of each test picture, a TMS pulse was delivered. Participants were first required to carefully watch the series of adaptation movies and then they were asked to compare the test pictures to the movies (Grip-recognition task vs. Goal-recognition task). Behavioral responses to test pictures were coded relative to the goal and the grip represented in the preceding adapting movie. In the example provided in the figure, the adapting movies showed “lifting with power grip” actions and thus response to the first picture (lifting with power grip) was coded as “adapted goal, adapted grip,” response to the second picture (lifting with precision grip) was coded as “adapted goal,” “nonadapted grip,” etc. For each stimulation condition—sham, IFC, S1, and AIP—subjects performed 4 experimental trials. Experimental trials were separated with a 15 s interval. Hence, a total of 48 responses were collected in each stimulation condition (4 trials × 12 test pictures).

Materials and Methods

Participants

Twenty-seven healthy adults [16 females, 11 males; mean age \pm standard deviation (SD) = 25.8 \pm 5.18 years] volunteered to participate in the study. All participants were right handed according to a standard handedness inventory (Briggs and Nebes 1975), reported normal or corrected-to-normal vision acuity, and were naïve to the purpose of the experiment. None of them reported evidence of neurological or psychiatric diseases. The experimental setting was approved by the ethics committee of the Bologna University's Department of Psychology and was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki. All participants gave written and informed consent and were remunerated 24 euros for participating in the study.

Stimuli

Participants were seated in a comfortable chair in front of a 19-inch computer screen on which a series of video clips (adapting movies) and pictures (test pictures) were displayed. Adapting movies consisted of 2000 ms video clips (30 frames per second, subtending 35° of visual angle) showing a male actor operating on an unfamiliar tool. The tool consisted of a handle designed to make possible 2 different goal-oriented actions using 2 different types of hand grips. More specifically, the actor could either 1) lift the handle to open the box or 2) turn the handle to switch-on the light. These 2 actions could be performed using either 1) a power (whole-hand) or 2) a precision (pinch) grip (see Fig. 1A). Thus, 4 types of videos were created following a 2 (types of goal: lifting, turning) × 2 (types of grip: power, precision) design, namely lifting with precision grip, lifting with power grip, turning with precision grip, and turning with power grip. For each action category, a set of 24 videos was created. All movies were equalized for temporal homogeneity such that the initial (from still hand to tool grasping) and last phase of the action (tool manipulation) involved the same number of video frames and lasted 1000 ms each (see also Jacquet et al. 2012).

Test pictures consisted of single frames extracted from the adapting movies. For each action category, 24 test pictures were created, one for each adapting movie. Pictures presented the actor in the 4 possible postures corresponding to the end-state of the 4 actions (i.e., lifting with power grip, lifting with precision grip, turning with power grip, turning with precision grip). Each test picture lasted 1500 ms.

Tasks

Subjects performed 2 tasks (Goal-recognition and Grip-recognition) in 2 separate sessions on the same day. In both tasks, subjects were presented with a series of adapting movies showing one of the 4 actions (lifting with power grip, lifting with precision grip, turning with power grip and turning with precision grip) followed by a series of 12 test pictures (3 exemplars for each action). In the Goal-recognition task, participants were asked to identify, for each test picture, whether the overall goal of the action (lift vs. turn the handle) implied in the picture was similar to or different from that shown in the preceding adapting movies (independent of the type of grip used). In the Grip-recognition task, they had to report whether the grip depicted in the picture (power vs. precision grip) was similar or different relative to that shown in the preceding adapting movies (independent of the type of goal being achieved). Responses were made with the index and middle finger of the left hand (ipsilateral to the stimulated hemispheres) on a keyboard. Response buttons were counterbalanced across participants. RTs and accuracy (proportion of correct responses) were recorded and analyzed off-line.

Procedure

Participants performed the 2 tasks in 2 sessions separated by a 15 min pause. The order of the tasks was counterbalanced across subjects. Eprime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) was used to collect both RTs and correct responses.

Goal- and Grip-recognition tasks were performed in 4 different TMS blocks (Sham, IFC, S1, and AIP) whose order was counterbalanced across subjects. Each block included 4 trials. On each trial, participants were first presented with a set of 30 adapting movies displaying one of the 4 possible actions (the set included 24 different exemplars of the action, 6 of which were repeated twice). Movies were presented in a random order and were separated by a white fixation cross of 250 ms

duration. The series of adapting movies (lasting 67.5 s in total) was followed by a warning signal (i.e., a pattern of 8 exclamation points) lasting 2000 ms after which a series of 12 test pictures (3 exemplars of each of the 4 action types) was shown. Test pictures lasted 1500 ms each and were separated by a fixation cross of 1000 ms duration. At the onset of each test picture, a single-pulse TMS was delivered (Silvanto et al. 2007; Cattaneo et al. 2010). Participants were first required to carefully watch the series of adapting movies and then to compare the test pictures to the movies (see Fig. 1B). A fixation cross was shown in the inter-trial interval (15 s duration). The order of the trials and of the test pictures was randomized. In each block, 48 behavioral responses were collected (4 trials \times 12 test pictures), with 12 responses for each action category. In both tasks, half of the test pictures showed adapted Goal/Grip configurations and half showed nonadapted Goal/Grip configurations.

Transcranial Magnetic Stimulation

TMS pulses were delivered with a figure-of-eight coil (70 mm) and a Magstim Rapid2 stimulator (Magstim, Whitland, Dyfed, UK). The individual resting motor threshold (rMT) of each participant was identified as the minimal stimulation intensity producing motor evoked potentials (MEPs) of a minimum amplitude of 50 μ V in the right first dorsal interosseous (FDI) muscle, with 50% probability (Rossini et al. 1994). MEPs were recorded by means of a Biopac MP 36 electromyograph (Biopac Systems, Inc., USA). EMG signals were band-pass filtered (30–1000 Hz) and digitized (sampling rate at 5 kHz). Pairs of silver/silver chloride surface electrodes were placed over the right FDI muscle using a belly/tendon montage. The intensity of stimulation used during the experiments was set at 110% of the individual rMT. The experiment was programmed using Eprime 2.0 software (Psychology Software Tools, Inc.) to control stimuli presentation and trigger the magnetic stimulator.

Prior to the experimental session, coil position was identified on each participant's scalp using the SofTaxic Navigator system (EMS, Bologna, Italy) or anatomo-functional methods as in our previous TMS research (Bertini et al. 2010; Serino et al. 2011; Avenanti et al. 2012a, 2013a). In a first step, skull landmarks (nasion, inion, and 2 preauricular points) and about 60 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra Optical Tracking System (Northern Digital, Inc., Waterloo, ON, Canada). Coordinates in Talairach space were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template. Then, we selected the scalp sites corresponding to IFC, AIP, and S1 hand region in the left hemisphere.

Scalp positions corresponding to IFC and AIP were identified by means of the SofTaxic Navigator system. The IFC was targeted in the anterior–ventral aspect of the precentral gyrus (ventral premotor cortex) at the border with the pars opercularis of the inferior frontal gyrus (coordinates: $x = -52$, $y = 10$, $z = 24$), corresponding to Brodmann's area 6/44 (Urgesi et al. 2007; Van Overwalle and Baetens 2009; Caspers et al. 2010; Avenanti et al. 2012a, 2013a). The selected frontal area is thought to be just 1 synapse away from the motor cortex as suggested by dual-coil TMS (Davare et al. 2009; Cattaneo and Barchiesi 2011) and thus can mainly be considered a premotor region. The AIP region was targeted in the anterior sector of the intraparietal sulcus ($x = -40$, $y = -40$, $z = 45$), corresponding to Brodmann's area 40; Van Overwalle and Baetens 2009; Caspers et al. 2010; Avenanti et al. 2012a). The IFC and AIP scalp sites were marked on the bathing cap with a pen. Then, the neuronavigation system was used to estimate the projections of the scalp sites on the brain surface (see Fig. 2).

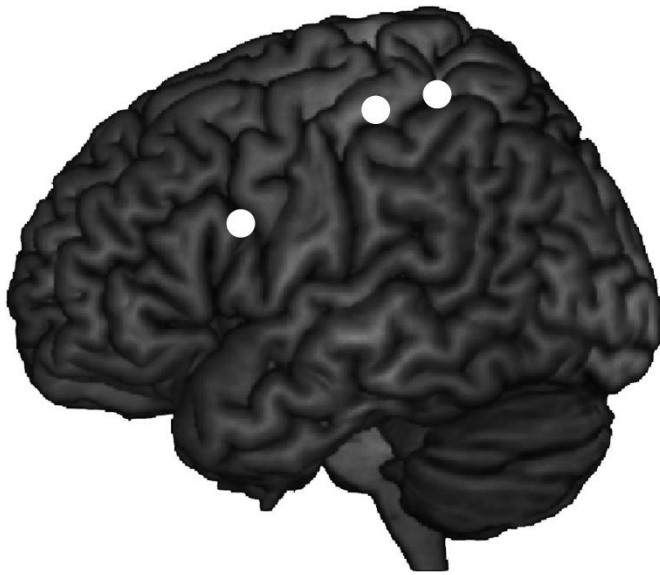


Figure 2. Schematic representation of the 3 stimulation sites. The IFC and AIP sites were localized based on brain-imaging meta-analyses and marked on the scalp. The hand representation in S1 was localized by moving the coil 2 cm backward with respect to the representation of the FDI muscle in the motor cortex. Coordinates in Talairach space corresponding to the projection of the IFC, AIP, and S1 scalp sites on the brain surface were estimated through the neuronavigation system and later transformed to the MNI space for visualization with the MRICron software (IFC mean surface MNI coordinates \pm SEM: $x = -60.4 \pm 0.4$, $y = 10.8 \pm 0.3$, $z = 24.1 \pm 0.2$; AIP: $x = -44.2 \pm 0.4$, $y = -44.2 \pm 0.2$, $z = 60.4 \pm 0.4$; S1: $x = -50.7 \pm 0.9$, $y = -30.4 \pm 1.3$, $z = 56.7 \pm 0.7$).

To select the scalp region corresponding to the hand area in S1, we used anatomo-functional methods. TMS studies that have successfully targeted this area (and interfered with hand somatosensory processing) position the TMS coil 1–4 cm posterior to the motor hotspot (Balslev et al. 2004; Avenanti et al. 2007; Azañón and Haggard 2009). In keeping with this, we identified S1 using a two-step procedure. We first localized the hand region in the motor cortex (corresponding to the optimal scalp position for evoking MEPs in the FDI muscle) and then moved the coil 2 cm backward. This site was marked on the bathing cap and then the neuronavigation system was used to confirm that brain surface coordinates fell within the hand region of S1 (Figure 2). Moreover, to ensure that stimulation from this position would not influence the motor system (Avenanti et al. 2007), we checked that TMS pulses at 110% rMT did not elicit any detectable MEP.

Stimulation of IFC, AIP, and S1 was carried out by placing the coil tangentially over the marked scalp sites. Sham stimulation was performed by placing the coil tilted at 90° over the vertex, so that no current was induced in the brain.

Data Analysis

The proportion of correct responses and RTs was analyzed off-line. In both tasks and in all TMS blocks, behavioral responses to test pictures were grouped and averaged relative to 2 factors: 1) adaptation of grip and 2) adaptation of goal (see Fig. 1B). For each condition, RTs deviating more than 2 SDs from the individual mean were discarded. During the IFC stimulation block, 3 participants reported being surprised by the stimulation in the first trial, resulting in an absence of response during 12 test pictures. This was actually a side effect of the stimulation which brought about facial muscle contractions and slight movements of the mandible. Accordingly, responses collected during this trial were removed from the analyses. No similar effects were found in the remaining blocks or in the other participants.

Statistical analyses were conducted on the IE index (Townsend and Ashby 1982; Heed et al. 2010; Pernigo et al. 2012), obtained by dividing the median RT by the proportion of correct responses, calculated for each experimental condition and for each subject separately. In principle, TMS over a target region may improve RT and reduce accuracy and vice versa. By combining response latencies and accuracy into a single measure, the IE index allows to discount possible criterion shifts or speed accuracy tradeoffs in the different TMS conditions. A lower value on IE indicates a

better recognition performance, whereas a higher value on IE indicates a lower recognition performance. For the Goal-recognition task, IE scores were submitted to a $4 \times 2 \times 2$ repeated-measures ANOVA with Stimulation (Sham, IFC, S1, and AIP), Goal (adapted and nonadapted) and Grip (adapted and nonadapted) as within-subject factors. A similar Stimulation \times Grip \times Goal ANOVA was conducted on IE scores of the Grip-recognition task.

Before reporting the 2 ANOVAs, a preliminary Task (Goal task, Grip task) \times Stimulation \times Grip \times Goal ANOVA was performed. This analysis revealed a main effect of Task ($F_{1,26} = 321.41$, $P < 0.0001$) with greater IE values (lower performance) for the Grip-recognition (mean \pm SD: 677 ± 76 ms) relative to the Goal-recognition task ($493 \text{ ms} \pm 64$). Moreover, the analysis showed higher order interactions, including a marginally significant quadruple interaction ($F_{3,78} = 2.67$, $P = 0.053$) which provided further ground to run separate ANOVAs for the 2 tasks (Keppel and Wickens 2004). Post-hoc analyses were carried out using the Newman–Keuls test. For all analyses, $P < 0.05$ was taken as the criterion for significance. Main effects and interactions in the ANOVAs on IE values were also interpreted by analyzing RTs and accuracy (see Tables 1–3). Statistical analyses were performed using Statistica 9 (www.statsoft.com).

Results

Goal-recognition Task

The ANOVA on the IE index computed during the Goal-recognition task showed a main effect of Goal ($F_{1,26} = 4.35$, $P = 0.047$; greater IE for nonadapted relative to adapted goals) and a main effect of Stimulation ($F_{3,78} = 4.27$, $P = 0.0008$; greater IE for IFC relative to all the other stimulation conditions). See Table 1 for IE, RTs, and accuracy data indexing this virtual lesion effect of IFC stimulation. Exploratory analyses reported in Table 1 suggest that such an effect was due to an increase in RTs during IFC stimulation, but not to changes in accuracy.

	Inverse efficiency (ms)	RT (ms)	Accuracy (%)
Sham	$496 \pm 14^*$	$482 \pm 13^\#$	97.5 ± 0.4 n.s.
IFC	512 ± 16	499 ± 16	97.7 ± 0.4
S1	$480 \pm 13^*$	$464 \pm 12^*$	96.9 ± 0.6 n.s.
AIP	$484 \pm 12^*$	$472 \pm 11^*$	97.8 ± 0.4 n.s.

Table 1 Mean values \pm SEM for inverse efficiency (IE), RT and accuracy in the Goal-recognition task: main effect of Stimulation.

The main effect of Stimulation in the ANOVA on the IE index was accounted for by the greater IE values (lower performance) for stimulation of IFC relative to the other stimulation conditions. This state-independent virtual lesion-like effect was due to an increase of RTs (on average +27 ms) during active stimulation of IFC. No change in accuracy was detected. Symbols indicate significant planned comparison ($*P < 0.05$), tendency toward significant comparison ($^\#P < 0.09$), or nonsignificant comparison (n.s.) between the IFC and the other stimulation conditions.

	Inverse efficiency (ms)			RT (ms)			Accuracy (%)		
	Adapted goal	Non adapted goal		Adapted goal	Nonadapted goal		Adapted goal	Nonadapted goal	
Sham	493 ± 15	498 ± 14	n.s.	478 ± 14	487 ± 15	n.s.	97.1 ± 0.6	98.0 ± 0.5	n.s.
IFC	500 ± 15	525 ± 18	*	492 ± 15	507 ± 17	#	98.6 ± 0.5	96.9 ± 0.5	*
S1	468 ± 13	492 ± 14	*	452 ± 12	476 ± 14	*	96.9 ± 0.9	97.0 ± 0.7	n.s.
AIP	483 ± 14	486 ± 11	n.s.	465 ± 12	480 ± 12	*	96.7 ± 0.8	98.9 ± 0.4	*

Table 2. Mean values ± SEM for inverse efficiency (IE), RT and accuracy in the Goal-recognition task: interaction Stimulation × Goal. The interaction found in the ANOVA on the IE index was due to the lower IE values for adapted relative to the nonadapted goals in the IFC and S1 conditions only. Planned comparisons performed on raw RT and accuracy indices indicate that state-dependent effects of IFC stimulation (greater performance for the adapted relative to the nonadapted goals) were consistently detected on both RT (mean advantage of 15 ms) and accuracy (mean increase of 2%). State-dependent effects of S1 stimulation on IE were mainly due to changes of RTs (mean advantage of 24 ms) but not of accuracy. The stimulation of AIP yielded an increase of response speed and a decrease of accuracy for adapted relative to nonadapted goals (speed accuracy trade-off) and thus no difference in IE were detected during stimulation of AIP. Symbols indicate significant (* $P < 0.05$), marginally significant (# $P < 0.055$), tendency toward significant (# $P < 0.09$) and nonsignificant planned comparisons (n.s.) between adapted and nonadapted goal conditions.

Importantly, the ANOVA on the IE index also showed a significant Stimulation × Goal interaction ($F_{3,78} = 3.12$, $P = 0.031$) (Fig. 3A; see also Table 2). Post-hoc analysis of the interaction suggested that no clear behavioral correlate of adaptation was present when Sham stimulation was administered: comparable IE scores were seen for adapted relative to nonadapted goals (mean IE ± SD: 493 ± 78 vs. 498 ± 74 ms, $P = 0.48$). Similarly, no difference between adapted and nonadapted goals were found in the AIP block (483 ± 71 vs. 486 ± 58 ms, $P = 0.67$). In striking contrast, when IFC or S1 stimulation was administered a clear “state change” was induced in the subject's perceptual system as a function of prior exposure to the adapting movies. In the IFC block, we found that nonadapted goals were associated with higher IE (worst performance) relative to adapted goals (525 ± 92 vs. 500 ± 80 ms, $P = 0.0004$) and to all the other conditions in the other blocks (all IE values < 498 ms, all $P < 0.0006$). An exploratory analysis suggested that the state-dependent effects of IFC stimulation were due both to differences in RTs and to accuracy for adapted relative to nonadapted goals (Table 2).

In the S1 block, we found that adapted goals were associated with lower IE (better performance) relative to nonadapted goals (468 ± 69 vs. 492 ± 75 ms, $P = 0.004$) and to all the other conditions in the other blocks (all IE values > 483 ms, all $P < 0.032$). Such state-dependent effect of S1 stimulation on IE was almost due to a reduction in RTs for adapted goals (Table 2). No other significant post-hoc differences were found (all $P > 0.13$). Moreover, no other main effects or interactions were significant in the ANOVA on IE (all $P > 0.18$).

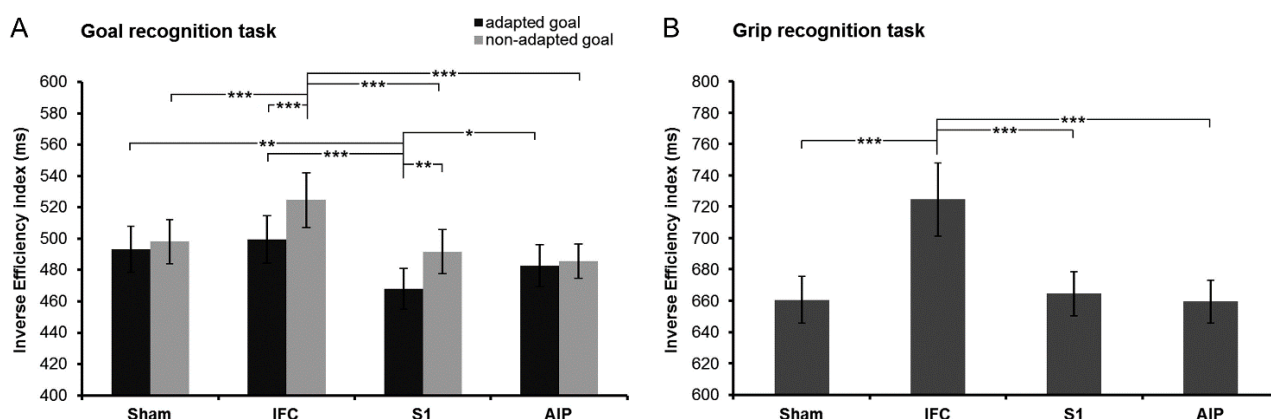


Figure 3. (A) Goal-recognition task: interaction effect Stimulation × Goal. The vertical axis reports the mean IE index, with greater IE values representing lower performance. The horizontal axis represents the 4 stimulation condition. Dark and light grey columns represent IE indices calculated for the adapted and nonadapted goals, respectively. (B) Grip-recognition task: main effect of the “Stimulation” factor. The vertical axis reports the mean IE index and the horizontal axis represents the 4 stimulation conditions. Error bars denote standard errors of mean. Asterisks indicate significant comparisons (*P < 0.05; **P < 0.01; ***P < 0.001).

Grip-recognition Task

The ANOVA on the IE index computed on the Grip-recognition task revealed a main effect of Grip ($F_{1,26} = 20.30$, $P = 0.0001$), with greater IE scores for nonadapted (701 ± 80 ms) relative to adapted grips (654 ± 81 ms); and a main effect of Stimulation ($F_{3,78} = 8.81$, $P < 0.0001$), accounted for by the higher IE scores in the IFC block relative to the other blocks (all $P < 0.0004$) which, in turn, did not differ from one another (all $P > 0.80$) (Figure 3B; see also Table 3). No Grip × Stimulation interaction was found ($F_{3,78} = 1.57$, $P = 0.20$), suggesting that TMS did not induce any state-dependent effects in the Grip-recognition task, but only a strong virtual lesion effect (lower performance detected mostly on RT but also on accuracy; see Table 3) when applied over the IFC. No other significant main effects or interactions were found (all $P > 0.18$).

	Inverse efficiency (ms)	RT (ms)	Accuracy (%)
Sham	$661 \pm 15^*$	$635 \pm 15^*$	$96.3 \pm 0.7^{\S}$
IFC	725 ± 24	683 ± 22	94.9 ± 0.8
S1	$664 \pm 14^*$	$639 \pm 15^*$	$96.7 \pm 0.6^*$
AIP	$659 \pm 14^*$	$636 \pm 14^*$	$96.7 \pm 0.6^{\#}$

Table 3 Mean values ± SEM for inverse efficiency (IE), RT and accuracy in the Grip-recognition task: main effect of stimulation. The effect of Stimulation in the ANOVA on the IE index was accounted for by the greater IE values (lower performance) for stimulation of IFC relative to the other stimulation conditions. This state-independent virtual lesion-like effect of IFC stimulation was clearly seen on RTs (mean increase of +47 ms) and, less consistently, on accuracy (mean decrease of −2%). Symbols indicate significant (*P < 0.05), marginally significant (#P < 0.055), and tendency toward significance comparison (§P < 0.1).

Discussion

In the present study, we used the TMS-A paradigm with the aim of testing the causal relationships between 3 sensorimotor nodes of the AON—namely IFC, AIP, and S1—and the ability of humans to represent the overall goal and the specific grip of observed complex hand actions. We tested the hypothesis that IFC is causally involved in processing both the grip and the end-goals of seen actions while parietal regions are mainly involved in processing high-level action components. To this aim, we designed 2 novel tasks in which participants were presented with adapting movies of an actor performing goal-directed actions on a tool by using a specific grip and were asked to categorize test pictures as showing similar or different end-goal/grip relative to the adapting movie.

Results of the Goal-recognition task revealed that applying TMS over S1 and IFC induced state-dependent effects on action recognition. TMS over S1 induced a selective decrease in the IE index for pictures presenting the adapted end-goal, indicating that stimulation of S1 improved the behavioral response to end-goals to which participants have previously been adapted. Similarly, TMS over IFC resulted in greater performance for adapted relative to nonadapted end-goals (see below for a further discussion of the behavioral effect of IFC stimulation), while no difference between adapted and nonadapted goals was found with sham or AIP stimulation. Such a pattern of findings suggests that TMS over S1 and IFC specifically enhanced the activity of the neural subpopulations that respond to a specific invariant feature, i.e., the end-goal of the action, between the adapting stimulus and the test stimulus. The TMS-induced behavioral enhancement occurred when subjects had to explicitly attend to such invariant feature (i.e., in the Goal-recognition task) and was absent when processing of the same feature was task-irrelevant (i.e., in the Grip-recognition task).

In the Grip-recognition task, TMS over IFC brought about a general virtual lesion effect, with reduced performance relative to the sham TMS or active TMS over S1 and AIP. Here, TMS did not change performance for adapted relative to nonadapted actions, indicating that stimulation of IFC altered the discrimination of grips in a general, “state-independent” manner.

Overall, these findings provide direct evidence to the notions that the anterior node of the AON is required for visual perception of both high- and low-level action components, whereas parietal regions—S1 in particular—are involved in processing the goal of seen actions. In addition, by showing both virtual lesion and state-dependent effects, our findings provide insights into the functional mechanisms of action perception in the AON.

TMS-A highlights the causal role of goal representation in the human IFC and S1 on action recognition

The state-dependent effects of TMS over S1 and IFC are well in keeping with the notion that repeated visual presentation of motor acts may induce action-specific adaptation phenomena in the human AON (Hamilton and Grafton 2006, 2008; Chong et al. 2008; Lingnau et al. 2009), and in particular in S1 (Dinstein et al. 2007) and IFC (Kilner et al. 2009). The results observed in the Goal-recognition task expand this notion by highlighting the behavioral consequences of such neural adaptation in the AON. Taken together, these findings indicate that TMS over key nodes of the AON may influence action recognition mechanisms through modulating the neural representation of the adapted relative to the nonadapted action features (i.e., the end-goal).

Notably, both state-dependent effects of S1 and IFC stimulation were obtained for the adapted versus nonadapted end-goals, regardless of the type of grip used by the demonstrator to achieve them. This suggests that IFC and S1 possess neural populations that are critically involved in encoding the meaning of seen actions at a relatively abstract level of representation in which low-level components (i.e., the particular way the action is performed) are less relevant. Our study is in

line with previous action observation studies reporting goal-related state-dependent effects after stimulation of IFC (Cattaneo 2010; Cattaneo et al. 2010). Importantly, our results significantly expand previous evidence by demonstrating that state-dependent effects due to IFC stimulation are detected not only when observing simple grasping actions, but also with much more complex actions in which the end-goal can be decoupled from the specific grip being used to achieve it.

Seminal studies have shown that the monkey motor system contains neurons encoding the goal of an action, independent of specific features of the movement (Alexander and Crutcher 1990; Kakei et al. 2001; Umiltà et al. 2008), and this property holds true for observed actions (di Pellegrino et al. 1992; Gallese et al. 1996; Fogassi et al. 2005). Our study supports this notion and provides causal evidence that stimulation of motor areas involved in representing action goals in the monkey brain (i.e., IFC) can bias action recognition in humans.

Another key point of novelty of our study is the demonstration that similar bias is found when stimulating S1, suggesting that this region actively participates in understanding the meaning of seen actions and contains distinct neural populations encoding action goals. These findings provide direct causal support to the increasing number of studies suggesting that S1 also represents a key node of the AON (Avenanti et al. 2007; Keysers et al. 2010) and suggest a role of S1 in understanding action goals. The somatosensory cortices are reciprocally connected with frontal and posterior parietal nodes of the AON (Keysers et al. 2010). Somatosensory activity is strongly increased, for example, when seeing hands grasping objects (Gazzola and Keysers 2009; Pierro et al. 2009) or extreme joint stretching (Costantini et al. 2005; Avenanti et al. 2007). Moreover, the somatosensory cortices are modulated when seeing tactile or noxious stimulations on the body of others (Keysers et al. 2004; Bufalari et al. 2007; Ebisch et al. 2008; Valeriani et al. 2008; Lamm et al. 2011) and recently, Bolognini et al. (2011) have shown that TMS over the hand region in S1 reduces the ability to judge whether an observed hand was touched or not. These findings have suggested that the S1 recruitment during action observation may be linked to the simulation of sensory components of observed motor acts (Avenanti et al. 2007; Gazzola and Keysers 2009; Keysers et al. 2010). Our findings that IFC and S1 stimulations may similarly affect the processing of end-goals are not in contrast with the proposal that IFC and S1 may perform simulations of motor and somatosensory components of observed actions, respectively (Avenanti et al. 2007). Indeed, goal processing may involve the prediction of both motor and somatic afferent action components (Christensen et al. 2007; Etzel et al. 2008; Gazzola and Keysers 2009; Schippers and Keysers 2009). Rather, our results further expand the notion that S1 and IFC are functionally coupled not only during action planning and execution, but also when perceiving the actions of others (Keysers et al. 2010).

A possible differential role of IFC and S1 in goal processing: state-dependent versus virtual lesion effects

It should be noted that in the Goal-recognition task, stimulation of S1 resulted in a performance increase (reduction of IE index) for test pictures showing the adapted relative to the nonadapted end-goal and relative to sham conditions. Similarly, performance was better for adapted than for nonadapted end-goals with IFC stimulation. However, relative to the sham condition, stimulation of IFC revealed a decrease in performance (increase of IE index) for test pictures showing the nonadapted end-goal. While both IFC and S1 stimulation effects reflect state-dependent modulations due to goal encoding, the apparently different trends of the IE index require further examination. Inspection of raw data (RTs and accuracy) suggests that, in addition to state-dependent effects (Table 2), after stimulation of IFC there was also a general state-independent increase of RTs relative to the other stimulation conditions (+27 ms on average, see Table 1) that may explain the greater IE values in the IFC relative to the S1 stimulation condition. This suggests

that changes in the IE index after stimulation of IFC reflect a summation of state-dependent and virtual lesion effects.

Several other studies have found that TMS over IFC impairs performance in tasks requiring visual discrimination between similar actions (Pobric and Hamilton 2006; Avenanti et al. 2013b; Tidoni et al. 2013). Although these studies did not directly investigate whether IFC stimulation specifically impairs the processing of high- or low-level components of seen actions, they provided causal evidence that IFC is critical for action perception. Since TMS was delivered at the onset of test pictures, it is unlikely that virtual lesion effects following IFC stimulation in our experiment were due to the deterioration of the test picture perception. Notably, our tasks required maintenance of an active representation of the adapting movie and a comparison of this representation with the test picture. Following this, it is more likely that TMS impaired the maintenance of action-related information concerning the adapting movie in working memory. Hence, our findings suggest that the AON, and the IFC in particular, is not only causally involved in action perception (Avenanti et al. 2013b) but possibly also in the short-term storage and manipulation of action-related information. On the other hand, the finding that S1 stimulation brought about state-dependent but not virtual lesion effects suggests that this region encodes the end-goal but is less involved in its short-term maintenance.

Of note is that state-dependent effects during the Goal-recognition task appeared to be more robust when TMS was applied to IFC relative to S1. While stimulation of S1 brought about a change in RTs, stimulation of IFC significantly affected both RTs and accuracy in a state-dependent manner (Table 2). This suggests that the neural representation of observed goals in IFC has a major role in action perception and, moreover, that TMS modulation of such representation may be particularly effective in biasing visual perception.

IFC stimulation disrupts grip recognition

As already mentioned, IFC stimulation induced not only state-dependent, but also virtual lesion-like effects, as shown by the general increase in RTs during the Goal-recognition task. State-independent virtual lesion effects were even clearer in the Grip-recognition task. Here, IFC stimulation brought about a general IE index increase which was due to an increase in RTs and a decrease in accuracy (Table 3). Similar impairment in performance was found for adapted and nonadapted stimuli, as evidenced by the lack of significant Stimulation × Grip interaction.

Several prior studies suggested that the IFC may be involved in processing not only high- but also low-level aspects of action perception. For example, it is well known that seeing an action triggers a simulation of the specific motor features of the observed movement in the motor cortex (Gangitano et al. 2001; Fadiga et al. 2005; Urgesi et al. 2010; Tidoni et al. 2013) and studies have shown that such motor resonance effects are due to computations carried out in IFC (Avenanti et al. 2007, 2013a; Koch et al. 2010; Catmur et al. 2011) rather than in the motor cortex itself (Avenanti et al. 2007). Moreover, paying attention to how an action is done (i.e., to the particular movement used to perform the action) robustly increases IFC activity (Hesse et al. 2009) and IFC stimulation impairs the ability to discriminate between 2 images showing slightly different upper and lower limb postures (Urgesi et al. 2007; Candidi et al. 2008).

Our study expands these prior findings by providing causal evidence that IFC is also critical for processing (and possibly maintaining in working-memory) observed grips. However, according to the classical logic of the TMS-A approach (Silvanto et al. 2007, 2008; Silvanto and Pascual-Leone 2012), the general state-independent impairment of behavioral performance after IFC stimulation and the lack of state-dependent effects suggest that the observed grips are less likely encoded into distinct neural populations.

It is important to note that performance was lower in the Grip-recognition task than in the Goal-recognition task. This difference may be related to the different visual analyses of action scenes required by the 2 tasks. The Grip-recognition task requires a focus on more local information (the specific finger configuration on the tool), whereas recognition of end-goals in the Goal-recognition task could require a more global analysis of the hand/arm spatial configuration as well as nonbodily contextual information (Jacquet et al. 2012). Consequently, one cannot rule out that task difficulty may have contributed to the lack of state-dependent effects in the Grip-recognition task due to a floor effect (Ruzzoli et al. 2010, 2011; Schwarzkopf et al. 2011; Perini et al. 2012). Nevertheless, our study suggests that a clear distinction in different neuronal populations tuned to a specific action-related feature is more likely to occur for the processing of the end-goal than for the grip.

Behavioral correlates of neural adaptation in the AON

The state-dependent effects obtained with IFC and S1 stimulation during the processing of action goals are in keeping with repetition priming studies, suggesting that observed actions are mainly represented in terms of their goal (Costantini et al. 2008). They are also in keeping with behavioral and neurophysiological evidence in humans and monkeys, showing that repeated exposure to others' actions can induce perceptual after effects (Barraclough et al. 2009). However, similar to the study of Cattaneo et al. (2010), a clear correlate of adaptation was not evident in the sham condition of our Goal-recognition task (i.e., no reduction in performance to repeated/adapted stimuli was observed). Nevertheless, the clear state-dependency of the effects induced by TMS over IFC and S1 suggests that we did induce a “state change” in the subjects' perceptual system by means of repeated visual exposure to actions even in the absence of clear behavioral effects with sham TMS. It has been suggested that the lack of behavioral manifestation of adaptation in sham or no-TMS conditions does not imply the absence of neural adaptation: for example, phosphenes induced from the stimulation of the early visual cortex after color adaptation can appear with the color of the adapting stimulus even after the perceptual afterimage induced by adaptation has faded (Silvanto et al. 2007). In accordance with this perceptual evidence, several other studies reported clear state-dependent effects of active TMS in spite of a weak (or absent) behavioral effect of adaptation in the sham or no-TMS conditions (Cattaneo et al. 2008, 2009, 2010; Cohen Kadosh et al. 2010).

It should be noted that the effect of IFC or S1 stimulation may be at least partially due to the spread of the TMS-induced excitation along neural connections (Valero-Cabré et al. 2005, 2007). It is well known that brain stimulation can modulate activity not only in the neurons under the coil but also in remote interconnected regions (Siebner et al. 2009; Arfeller et al. 2013; Avenanti et al. 2012b, 2013a). Thus, although we centered our stimulation over IFC and S1 sites found to be active during action observation, it is possible that additional interconnected sectors of the AON (e.g., the inferior parietal lobule) were influenced by TMS and may have contributed to the observed state-dependent and/or virtual lesion effects. In addition, it should be noted that the AIP and S1 sites were very close and thus it is possible that stimulation on either site may not have been entirely selective and rather may have influenced activity in the other site. At any rate, our study shows a clear dissociation between the anterior (IFC) and more posterior (AIP, S1) nodes of the AON in the processing of grip during action observation; and between the IFC-S1 circuit and AIP when action goals are processed.

Finally, the lack of behavioral effects after AIP stimulation may seem in contrast with the well-accepted view that the parietal regions, possibly containing mirror neurons, play an important role in action perception (Rizzolatti and Craighero 2004). Indeed, brain-imaging studies have shown adaptation effects in the parietal cortex and, in particular, in AIP (Hamilton and Grafton 2006, 2008; Chong et al. 2008; Lingnau et al. 2009) and lesions occurring in this region may impair action perception in patients with acquired brain injury (Buxbaum et al. 2005; Weiss et al. 2008; Kalénine

et al 2010). The apparent discrepancy between previous correlational and lesion studies and the present experiment may be related to technical issues. While we localized the AIP scalp site based on previous imaging studies (Van Overwalle and Baetens 2009), it is possible that task-relevant neurons in AIP lay in the depth of the intraparietal sulcus and thus brain stimulation was unable to modulate such neurons (Bertini et al. 2010; Serino et al. 2011; Avenanti et al. 2012a). Conversely, more superficial parietal sites within the AON may be more accessible to TMS and indeed evidence indicates that stimulation of the left supramarginal gyrus in the inferior parietal lobule affects action perception and can reveal state-dependent effects (Cattaneo et al. 2010). Thus, 1 aim of future research will be to map the role of specific parietal sites in action perception.

In conclusion, our study provides causal evidence for a role of the AON in the processing of overall goals and grip during observation of complex actions and highlights the functional organization of seen actions into distinct and overlapping goal-specific neural populations in the human IFC and S1.

Funding This work was supported by the FP7 European project “ROSSI – emergence of communication in RObots through Sensorimotor and Social Interaction” (contract number: 216125) and by grants from the Istituto Italiano di Tecnologia (SEED 2009, protocol number: 21538), Ministero della Salute (Bando Ricerca Finalizzata Giovani Ricercatori 2010, protocol number: GR-2010-2319335), Ministero Istruzione Università e Ricerca (Futuro in Ricerca 2012, protocol number: RBFR12F0BD) and Cogito Foundation (research projects 2013) awarded to A.A.; P.O.J. is also supported by Fyssen Foundation (post-doctoral fellowship 2013).

Notes We thank Anna M. Borghi and Alessia Tessari for the generous sharing of facilities, Michelangelo Bottura for technical help, Cosimo Urgesi and Neil Dundon for their comments on an early version of the manuscript. Conflict of Interest: None declared.

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