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Evidence of motor resonance in stroke patients with severe upper limb function impairments

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Abstract

For the past fifteen years, observation of actions has proved to be effective in the motor rehabilitation of stroke. Despite this, no evidence has ever been provided that this practice is able to activate the efferent motor system of a limb unable to perform the observed action due to stroke. In fact, transcranial magnetic stimulation cannot easily be used in these patients, and the fMRI evidence is inconclusive. This creates a logical problem, as the effectiveness of action observation in functional recovery is attributed to its ability to evoke action simulation, up to sub-threshold muscle activation (i.e., motor resonance), in healthy individuals. To provide the necessary proof-of-concept, patients with severe upper limb function impairments and matched control participants were submitted to a verified action prediction paradigm. They were asked to watch videos showing gripping movements towards a graspable or an ungraspable object, and to press a button the instant the agent touched the object. The presence of more accurate responses for the graspable object trials is considered an indirect evidence of motor resonance. Participants were required to perform the task in two sessions which differed in the hand used to respond. Despite the serious difficulty of movement, 8 out of 18 patients were able to perform the task with their impaired hand. We found that the responses given by the paretic hand showed a modulation of the action prediction time no different from that showed by the non-paretic hand, which, in turn, did not differ from that showed by the matched control participants. The present proof-of-concept study shows that action observation involves the efferent motor system even when the hand used to respond is unable to perform the observed action due to a cortical lesion, providing the missing evidence to support the already established use of Action Observation Training (AOT) in motor rehabilitation of stroke.

Keywords: action observation; motor resonance; action prediction; stroke; AOT; paresis

1. Introduction

For fifteen years Action Observation Training (AOT) has been proposed as an intervention to improve the motor functions of the upper limbs in people with stroke. It consists of a treatment period, typically lasting four weeks (5 days a week), divided into sessions during which patients observe a daily action and afterwards execute it in context (Buccino, 2014) (for reviews see Borges et al., 2018; Buchignani et al., 2019; Rizzolatti et al., 2021). The first study was a randomized controlled study in patients with chronic ischemic stroke in the territory of the middle cerebral artery (Ertelt et al., 2007). Compared with the stable pre-treatment baseline, and compared with the control group, the scores of the AOT group at the stroke impact scale, the Wolf motor function test, and the Frenchay arm test showed a significant improvement of motor functions. Moreover, functional magnetic resonance imaging (fMRI) data in the same patients indicated a significant increase in activity after therapy in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, the supplementary motor area and the contralateral supramarginal gyrus. The authors concluded that action observation has a positive impact on recovery of motor functions after stroke by reactivation of motor areas within the “action observation–action execution matching system”, a network of cortical motor regions that are active when we perform an action and when we observe similar actions being performed by others (Rizzolatti & Craighero, 2004). In other words, action observation is hypothesized to rebuild motor function despite impairments by engaging similar brain regions to action execution (Garrison et al., 2010; Liew et al., 2012).

After this first paper was published, about 40 works appeared in literature that investigated the effects of AOT in stroke rehabilitation, generally reporting improvements on functional scales. A recent systematic review and meta-analysis (Zhang et al., 2019) considered randomized controlled trials about the effects of this treatment in stroke patients with residual upper limb function impairments, without the limitation in types and stage of stroke. Seven studies of 276 patients were included, and the results of the meta-analysis showed a significant effect favouring AOT on improving upper limb motor functions (see also Ryan et al., 2021). A further conclusion of this review was that the neural mechanism addressed by AOT in stroke patients was rarely investigated. As far as we know, aside from the fMRI data by Ertelt and colleagues (Ertelt et al., 2007), only one other study considered the neural response to action observation in these patients (Brunner et al., 2014). Specifically, the results of this longitudinal fMRI study showed an overlap of neuronal activation when observing and executing a bimanual movement task both in control participants and subacute stroke patients. One of the main limitations of the study, however, was that only patients with mild to moderate deficits were considered. Because of this limitation, these results are not useful in answering the not trivial question regarding the use of AOT in patients with severe paresis. That is, if it is true that the observation of the action activates the neural structures necessary for the execution of that action, what happens in an individual who cannot perform that action due to a stroke affecting these structures? In other words, does the inability to perform an action due to damage to the cortical motor system change the way the observed action is processed? A partial positive answer to this question was given by an fMRI study investigating brain activity during hand action observation in stroke (Garrison et al., 2013). Results indicated that cortical motor activity was taken up by intact tissue adjacent to the damaged brain regions typically activated by action observation in the healthy brain. Activating different areas does not guarantee that the processing of the action will be the same.

It is necessary to note that fMRI is not the best technique to describe the effects of action observation on the activity of the motor system. In fact, fMRI can determine if the blood oxygen–level dependent (BOLD) signal within a certain voxel is augmented both during action observation and execution. However, the signal may be determined by the presence of two distinct populations of neurons, one responding only during motor execution and one only during action observation. For this reason the term *shared voxels* has been proposed to describe voxels active during both action perception and execution (Gazzola & Keysers, 2009). Consequently, the presence of shared voxels is not proof that a perceptual task such as action observation automatically recruits the motor system. A more direct evidence of this phenomenon is given by transcranial magnetic stimulation (TMS) studies. When TMS is applied to the motor cortex (M1), at appropriate stimulation intensity, motor-evoked potentials (MEPs) can be recorded from contralateral extremity muscles. The modulation of MEPs amplitude can be used to assess changes in corticospinal (CS) excitability induced by the activity of various brain regions connected with M1 and involved in the concomitant task. Many experiments showed that perception of others' actions is constantly accompanied by motor facilitation of the observer's CS system (Buccino et al., 2004; Fadiga et al., 1995, 2005; Fadiga & Craighero, 2004). This motor activation, referred to as *motor resonance*, occurs in a muscle-specific fashion according to somatotopic rules (Alaerts et al., 2009; Fadiga et al., 1995; Urgesi et al., 2006), it is time-locked to the movement phases (Alaerts et al., 2012; Borroni et al., 2005; Gangitano et al., 2001), it follows the pattern of facilitation or inhibition of motor activity involved in selecting or refraining from performing a particular action (Craighero et al., 2014; Craighero & Mele, 2018; Romani et al., 2005; Schütz-Bosbach et al., 2009), and it may reflect the co-presence of multiple motor encodings (i.e., internal replication and predictive activation; see for example Sartori et al., 2015). Therefore, the proof-of-concept would consist of a TMS experiment in paretic patients after stroke that shows the presence of motor resonance. Unfortunately, this experimental procedure is not easily applicable to these patients as cortical damage compromises corticospinal excitability and the presence of MEPs. Indeed, the presence of MEPs is considered a reliable tool for predicting motor recovery of the upper extremity and general functional outcome (Bembenek et al., 2012; Hoonhorst et al., 2018; Stinear et al., 2017; Straudi et al., 2020). Motor resonance, however, can be also indirectly assessed by considering the influence that the action has on its execution or evaluation (e.g., facilitated mimicry of corresponding actions; motor interference during the simultaneous observation and execution of incompatible actions; influence on accuracy or time of action prediction) (Aglioti et al., 2008; Bisio et al., 2014; Castiello et al., 2002; Craighero et al., 2002, 2008, 2014, 2015; Craighero & Zorzi, 2012; Decety & Chaminade, 2005; Kilner et al., 2003; Saygin & Stadler, 2012). The interpretation is that the motor system is geared up to execute the observed movement, and this involvement congruently modulates any motor response.

The present proof-of-concept study was designed to address the lack of basic studies on the presence of motor resonance after stroke. Here, we provided support for the use of action observation in rehabilitation by demonstrating that action observation after stroke modulates action prediction time, an evidence of the recruitment of the motor system. We capitalized on the behavioural version of a robust paradigm from the same laboratory originally tested in a combined TMS and reaction time study (Craighero et al., 2014). Stroke patients with severe upper limb function impairments and matched controls were presented with videos showing grasping movements and requested to press a key at the contact time between the hand and the object. In half of the trials the kinematics of the videos was kept unchanged and the object replaced with an ungraspable one. The instant in which the hand touched the object in the different videos was always the same. This experimental paradigm has proved capable of providing neurophysiological and behavioural indices of the presence of motor resonance in healthy individuals. Specifically, corticospinal activation was present only when the observed movement was suitable to grasp the object, and in the same trials the response times were more accurate (i.e., the time lag between the instant the agent touched the object and the response was shorter), an index of action prediction (Craighero et al., 2014). These data, both neurophysiological and behavioural, indicate that motor resonance depends on the observer’s sensorimotor knowledge. Such knowledge, forged by experience, allows the observer to subliminally re-enact only suitable actions. It is assumed that a modulation of detection times in this experimental paradigm is an indirect evidence of motor resonance (Craighero et al., 2008, 2014, 2015; Craighero & Zorzi, 2012; Gentile et al., 2022). On the contrary, the lack of detection time modulation indicate that the task is performed without involving the motor system, in the absence of motor resonance.

The stimuli presented and the raw data recorded are archived in the research data repository Mendeley Data at the link http://doi.org/10.17632/h2tvxc7svd.2

No part of the study procedures and of study analyses was pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2. Materials and Methods

2.1. Participants

Eighteen individuals with stroke and 18 matched nondisabled individuals (Table 1) gave informed consent for the study. To determine the sample size of the present research we referred to the sample size of previous studies using the same experimental paradigm (Craighero et al., 2008, 2014, 2015; Craighero & Zorzi, 2012; Gentile et al., 2022). The study was approved by local Ethics Committee (protocol 359/2018/Sper/UniFe). All procedures were conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The privacy rights of human subjects were observed. Patients inclusion criteria were men and women aged 18-80 years with diagnosis of unilateral stroke verified by brain imaging. As the benchmark review and meta-analysis on AOT effects in stroke patients (Zhang et al., 2019), we set no limitation in types and stage of stroke. However, only patients with arm paresis were included. To be enrolled in the study, patients had to have a score at the Pinch grip test of the Motricity index ≤ 22 (0 = No movement; 11 = Beginnings of prehension; 19 = Grips cube but unable to hold against gravity; 22 = Grips cube, held against gravity but not against weak pull; 26 = Grips cube against pull but weaker than other/normal side; 33 = Normal pinch grip) (Demeurisse et al., 1980). Patients were excluded if they presented impaired cognitive functioning (score<21 on the Mini Mental Status Examination, https://salute.regione.emilia-romagna.it/assistenza-ospedaliera/file-cci/scala-mmse-mini-mental-state-examination-cartella-clinica-integrata/@@download/file/24%20MMSE.pdf), syndrome of hemispatial neglect, or language comprehension deficits. All participants were right-handed and had normal or corrected vision.

Patient	Age (Years)	Gender	Side of lesion	Motricity Index	Duration of illness (Months)	Task with 1 or 2 hands	Control	Age (Years)	Gender
11	28	F	left	0	19	1	**24**	26	F
27	49	F	left	11	2,5	1	**32**	48	F
6	58	M	left	0	7,6	1	**33**	59	M
16	62	M	left	11	7	1	**35**	63	F
38	71	F	left	11	4	1	**36**	68	F
7	78	F	left	0	2	1	**41**	70	F
12	42	F	right	0	120	1	**22**	47	F
20	45	F	right	0	48	1	**29**	51	F
13	46	F	right	11	12	1	**25**	56	F
19	75	M	right	0	2,3	1	**17**	66	F
10	53	M	left	19	0,9	2	**40**	57	M
18	73	F	left	11	1,4	2	**34**	77	F
3	73	M	left	11	1,2	2	**26**	64	M
14	73	M	left	22	3	2	**37**	65	M
21	77	M	left	22	4	2	**30**	69	M
202	78	M	left	22	1,6	2	**39**	73	M
201	63	F	right	22	1,6	2	**42**	72	F
28	78	F	right	19	1,2	2	**15**	79	F
Mean	62,33				13,29			61,67	
St. dev.	15,29				28,90			12,88	

Table 1. Demographic (age, gender) and clinical (side of lesion, score of the affected hand at the Pinch grip test of the Motricity index, duration of illness in months) characteristics of the experimental group (column Patient: numbers refer to the identification code), and demographic (age, gender) characteristics of the matched control group (column Control: number refer to the identification code). While the control group performed the task with both hands, 10 participants of the experimental group performed the task only with the non-paretic hand, given that they were unable to perform it with the paretic one.

2.2. Stimuli and procedure

The stimuli consisted of videos showing an agent in a third-person perspective sitting at a desk. The agent used her right hand to reach and grasp an object with a natural velocity, with the fingers opposition space parallel to her frontal plane, without lifting the object. Two were the possible objects. In the “flat object video” the object consisted of a parallelepiped, a square cuboid having 2 square and 4 rectangular faces (width: 7 cm; height: 3 cm; length: 3 cm) (Fig.1, top right side). The parallelepiped was placed with its longer axis facing the agent. In the “sharp-tip object video”, using software for video editing, the parallelepiped was artificially replaced with a polyhedron (i.e., a geometric solid in three dimensions with flat faces and straight edges) of the exact dimensions as the parallelepiped (7 cm × 3 cm × 3 cm) (Fig.1, bottom right side). In this way, the video showed the agent grasping the polyhedron with her fingers precisely at the sharp tips, moving with the same kinematic parameters present in the flat object video. The two videos had the same time duration (2640 ms), and the instant at which the agent’s index finger touched the object was the same for both (1880 ms, Frame 47). We used Adobe Premiere Pro 1.5 to edit the two videos (25 frames/second; duration of 1 frame = 40 ms; frame size: 720 × 576 pixels).

The two objects used in the videos were present in the lab, and participants were familiarized with them before the experimental session. Specifically, participants were asked to grab and lift the two objects once, one at a time, with the same grip shown in the videos. This test allowed the participants to realize that the high weight of the object (240 g), and the presence of sharp tips right at the point of contact with the fingers, made it impossible to grasp the sharp-tip object that way. On the contrary, even if the weight was the same as the other object, they were easily able to grab and lift the flat object.

The two videos were further manipulated to obtain two catch-trial videos in which the agent’s hand stopped before touching the objects (1520 ms after the beginning of the video, Frame 38). The last frame was repeatedly presented to obtain the same time duration as the experimental trial videos, i.e., 2640 ms (Fig. 1). For more technical details, see Craighero et al. (Craighero et al., 2014).

Each session consisted of 72 trials randomly presented: 60 experimental trials (30 flat object videos, and 30 sharp-tip object videos) and 12 catch trials (6 flat object catch videos and 6 sharp-tip object catch videos).

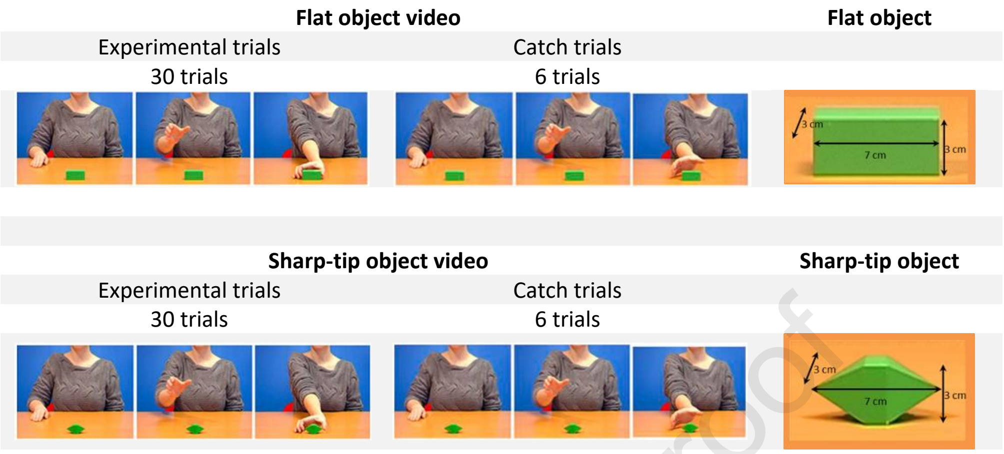

Fig.1 - Three frames extracted from the flat object video (top left side) and the sharp-tip object video (bottom left side). Specifically, for each video, three frames (Frame 1; Frame 25; Frame 66) extracted from the Experimental trial (number of repetitions: 30), and three frames (Frame 1; Frame 25; Frame 38. Frame 38 was repeated 28 times to obtain the same duration as that of the experimental videos, 66 frames) extracted from the Catch trial (number of repetitions: 6) are shown. The sharp-tip object videos were obtained by video editing the flat object videos. By means of a graphic software, the Flat object (top right side) was replaced by the Sharp-tip object (bottom right side) having the same size, but with sharp tips at the fingers opposition space.

The experiment was conducted in a quiet room. The participants were seated on a comfortable chair, or in their wheelchair, in front of a table on which there were a monitor (placed 60 cm far from the participant) and a keyboard. They were instructed to watch the videos and press the space bar on the keyboard at the same instant the agent touched the to-be-reached object (experimental trials); conversely, they had to refrain from tapping the space bar when the agent's hand stopped before touching the object (catch trials). If the number of responses to catch trials was equal to or greater than 6, the participant was discarded from the analysis. A low number of responses to catch trials ensured that the response was actually given at the moment of touch and not as the result of other clues. Therefore, the role of catch trials was to force participants to constantly pay attention to video content.

Participants were required to perform the task in two sessions which differed in the hand used to respond and to use their index finger to press the bar. The order of the sessions was balanced in the control group. As for the patients, everyone was asked to perform the experiment also with the paretic hand. Cushions and supports were used to keep the hand above the keyboard as comfortably as possible. Consistent with the Motricity index score, some patients were able to press the bar by moving the index finger, others using the proximal arm muscles, still others were unable to perform the task. Of the 8 patients who performed the task with both hands, 5 used their paretic hand in the first session.

2.3.Data analysis

The statistical analysis was performed by using an open-source statistics program (JASP, https://jasp-stats.org/).

We were interested in evaluating the action prediction time, and, therefore, we considered as dependent variable the time lag between the instant at which the agent's index finger touched the object (*Instant of Touch*), i.e., 1880 ms from the beginning of each video, and the participant's key pressing (*Response*). For each participant, for each trial, we calculated the time lag as *Instant of Touch - Response*. For each participant, for each session, values that were more or less than two standard deviations away from mean were discarded (clean data: 95.26%, SD = 2.19%) in the experimental group and 96.60%, SD = 1.20%) in the control group).

The purpose of the experiment was to verify the presence of a modulation of the action prediction time according to the graspability of the object. Specifically, in the present experimental protocol, shorter time lags for responses given to the flat object video than to the sharp-tip object video are considered an index of motor resonance (Craighero et al., 2008, 2014, 2015; Craighero & Zorzi, 2012; Gentile et al., 2022).

Although this experimental protocol was used in many studies, for the first time in the present work the task was performed with both hands. Therefore, we first checked whether there was any difference between the two sessions of the control group, as the hand acting in the video was anatomically congruent with the participant's right hand and spatially congruent with his/her left hand (Koski et al., 2003). The time lag was submitted to a repeated-measures analysis of variance (ANOVA) with hand (right hand vs left hand) and object (flat object vs sharp-tip object) as within-subject variables.

We then considered the responses given by the non-paretic hand of the experimental group (6 right hand and 12 left hand), and, since all participants were right-handed, we compared the data with those of the corresponding hand of the matched members of the control group. The time lag was submitted to an ANOVA with group (experimental vs control) as between-subjects variable, and object (flat object vs sharp-tip object) as within-subject variable.

Finally, and more critically for the proof-of-concept, we were interested in checking whether there was any difference between the paretic and the non-paretic hand of the experimental group. The time lag was submitted to an ANOVA with hand (paretic vs non-paretic) and object (flat object vs sharp-tip object) as within-subject variables.

For all the statistical tests, a *p*-value lower than 0.05 was considered statistically significant. Effect sizes were estimated using the partial eta squared measure (ηp^2). The data are reported as the mean ± standard error of the mean (SEM).

3. Results

The average of responses to the catch trials was 3.52% (SD = 4.74%) in the experimental group, and 4.16% (SD = 3.42%) in the control group, indicating that participants constantly paid attention to video content, and that the response was actually given at the moment of touch and not as the result of other clues.

The results of the ANOVA performed on the time lag between the right and the left hand in the control group showed that the object main effect was significant ($F_{1,17}$ = 114,18, $p < 0.001$, ηp^2 = 0.87, observed power = 1.0), since the time lag during sharp-tip object trials (mean = 310.91 ms, SEM = 43.60) was longer than during flat object trials (mean = 204.09 ms, SEM = 39.06). The hand main effect ($F_{1,17} = 3.71$, $p = 0.07$, $\eta p^2 = 0.179$, observed power = 0.44), and the 2-way interaction hand × object ($F_{1,17} = 2.14$, $p = 0.16$, $\eta p^2 = 0.111$, observed power = 0.28) were not significant. These results replicate those obtained in many experiments (Craighero et al., 2008, 2014, 2015; Craighero & Zorzi, 2012; Gentile et al., 2022), and reveal that neither the anatomical nor the spatial congruency between the agent's and the participant's hand modulates the action prediction time (Fig. 2, graph A).

The ANOVA to compare the performance of the experimental and control group showed that the object main effect was significant ($F_{1,34} = 113,18$, $p < 0.001$, $\eta p^2 = 0.77$, observed power = 1.0): the time lag during sharp-tip object trials (mean = 358.58 ms, SEM = 33.36) was longer than during flat object trials (mean = 244.86 ms, SEM = 29.06). Furthermore, the group main effect ($F_{1,34} = 2.61$, $p = 0.12$, $\eta p^2 = 0.07$, observed power = 0.35) and the 2-way interaction hand × object ($F_{1,34} = 0.21$, $p = 0.65$, $\eta p^2 = 0.01$, observed power = 0.07) were not significant, indicating that action prediction time in paretic patients responding with the non-paretic hand did not differ from that of healthy participants (Fig. 2, graph B).

Finally, the results of the ANOVA to compare responses given by patients with their paretic and non-paretic hand showed that the object main effect was significant ($F_{1,7} = 54,58$, $p < 0.001$, $\eta p^2 = 0.89$, observed power = 0.99): the time lag during sharp-tip object trials (mean = 493.31 ms, SEM = 64.97) was longer than during flat object trials (mean = 353.05 ms, SEM = 58.40). The hand main effect was also significant ($F_{1,7} = 54,58$, $p < 0.001$, $\eta p^2 = 0.89$, observed power = 0.99), indicating a delay in the response of the paretic hand (mean = 490.23 ms, SEM = 79.01) compared to the non-paretic one (mean = 356.12 ms, SEM = 53.02). However, the 2-way interaction hand × object was not significant ($F_{1,7} = 2,06$, $p = 0.19$, $\eta p^2 = 0.23$, observed power = 0.24), suggesting that motor resonance was evident not only when responses were given by the unaffected hand but also when they were given by the motor impaired hand (Fig. 2, graph C).

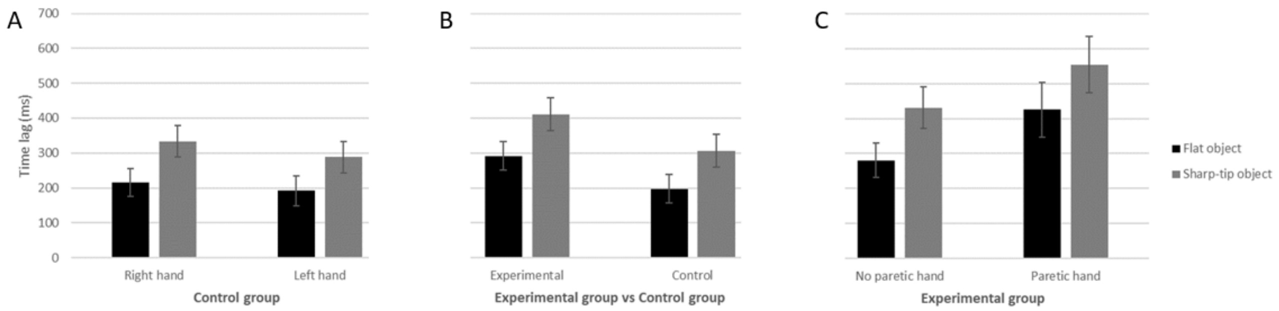

Fig.2 – Action prediction time results. Time lag between the instant at which the agent touches the object and participant's response time. Data for flat object trials (black bars) and sharp-tip object trials (grey bars) are presented. Graph A shows results for responses given by the right and the left hand of the Control group. Graph B shows results for responses given by the non-paretic hand of the Experimental group and by the corresponding hand of the matched members of the Control group. Graph C shows results for responses given by the non-paretic and the paretic hand of the Experimental group. Thin lines above histograms indicate standard error of the mean. Ordinates are in milliseconds.

4. Discussion

Our proof-of-concept study provided support for the use of action observation in motor rehabilitation of patients with upper limb function impairments, demonstrating that action observation modulates action prediction time, an evidence of the recruitment of the motor system, even when their responding hand is paretic and unable to perform the action.

Since the action observation - action execution matching system, also called mirror neuron system, was discovered (Buccino et al., 2006; Cattaneo & Rizzolatti, 2009; Kilner et al., 2007; Rizzolatti & Craighero, 2004), one of the most frequently asked question to experts has been "what if a person is unable to perform the observed action?". In fact, this system consists of a network of cortical motor regions in humans that are active both when we perform an action and when we observe similar actions being performed by others, indicating that an observed action is online subliminally re-enacted (i.e., motor resonance). This system is attributed a central role in action understanding and in imitative learning. Furthermore, it is strongly argued that observation of actions can be an effective strategy in motor rehabilitation. Logic, however, suggests that if an individual is unable to replicate the action seen, then all the benefits of this system must be lacking, including those in rehabilitation. On the contrary, evidence confirms the efficacy of action observation treatment (Buccino, 2014) in functional recovery (Ertelt et al., 2007; Zhang et al., 2019), even in the absence of the proof showing the involvement of the efferent motor system in those who cannot move that part of the body. The only evidence comes from an fMRI study indicating that action observation activates the intact tissue adjacent to the damaged brain regions typically activated by action observation and execution in the healthy brain (Garrison et al., 2013). Two were the main limitations of this proof. The first concerns the participants who had a minor motor limitation, since all were able to replicate the observed actions, albeit with varying degrees of motor capability. The second, and more important, concerns the significance of the results in relation to the involvement of the efferent motor system. In fact, fMRI can determine if the blood oxygen–level dependent (BOLD) signal within a certain voxel is augmented both during action observation and execution. However, this finding can be the consequence of the presence of two distinct populations of neurons, one responding only during motor execution and one only during action observation (Dinstein et al., 2008; Gazzola & Keysers, 2009). Consequently, the presence of shared voxels is not definitive evidence for the presence of motor resonance in either healthy people, or patients with motor difficulties. Unfortunately, TMS, the neurophysiological technique that can provide direct evidence of motor resonance (Buccino et al., 2004; Fadiga et al., 1995, 2005; Fadiga & Craighero, 2004), cannot easily be used in stroke patients due to cortical damage.

To solve this puzzle, in the present study we used a robust behavioural paradigm from the same laboratory, known to be effective in providing indirect evidence for the presence of motor resonance (Craighero et al., 2008, 2014, 2015; Craighero & Zorzi, 2012; Gentile et al., 2022). Participants watched videos showing gripping movements towards a graspable or an ungraspable object, and were asked to press a button the instant the agent touched the object. A constant result of this paradigm is that the time interval between the agent's touch of graspable objects and the response is shorter than simple reaction time (Geis et al., 2010), indicating that to accomplish the task participants base their response on an internal simulation of the action, and thus on the prediction of the event. This possibility is reflected by TMS results showing corticospinal activation during observation of the same videos (Craighero et al., 2014). On the contrary, the time interval when the agent acts towards an ungraspable object is longer, suggesting either that subjects are reacting and not predicting the event, or that the sensorimotor system is inhibited during observation of unsuitable actions. TMS results are congruent with both possibilities, showing that during observation of these videos corticospinal activation is absent, and therefore the efferent motor system is not involved or it is suppressed/inhibited (Craighero et al., 2014). In the present study, a group of stroke patients with upper limb function impairments and a group of matched control participants were submitted to the task, and asked to perform it with both hands. Of the 18 patients only 8 were able to perform the task with the paretic hand, thanks to the aid of cushions and supports and, often, using the proximal musculature to press the button. Despite the very serious difficulty of movement that prevented them from performing the action seen, the responses given by the paretic hand showed a modulation of the action prediction time (i.e., faster responses to the flat object video) no different from that showed by the non-paretic hand, which, in turn, did not differ from that showed by the corresponding hand of the matched control participants. It is to note that the hand used by the agent (i.e., right hand) was anatomically congruent with the right hand and spatially congruent with the left hand of the observer. In the control group, however, the responses given with the two hands were not different from each other. It is deduced that, in this paradigm, the effect of modulation of the action prediction times does not depend on the effector observed.

These results indicate the presence of motor resonance and constitute proof that the observation of the action activates the motor system even in those who are unable to perform that action. But how can this happen if the shared idea is that motor activation depends on the ability to perform the action?

The answer is quite simple if we consider that the sensorimotor system does not encode the movements but the goal of the action (Rizzolatti & Sinigaglia, 2010), as suggested by the data reporting that the effect found in the present study is independent of the observed effector. This evidence comes both from monkey (Ferrari et al., 2005; Gallese et al., 1996; Rochat et al., 2010; Umiltà et al., 2001), and human (Betti et al., 2019; Cattaneo et al., 2009; Gazzola et al., 2007; Peeters et al., 2009; Shimada, 2010) studies. As an example, in humans the same cortical activation occurred during observation of motor acts performed by a human hand, a robot hand or a tool (Peeters et al., 2009), therefore, regardless of the effector. Two studies in particular are interesting. The first one is an fMRI study (Gazzola et al., 2007) in which two aplasic participants, born without arms and hands, were asked to watch video clips showing hand actions. They also performed actions with their feet and mouth. The results showed that the same areas of aplasic individuals that were active during movements of the feet and mouth were also recruited by the observation of hand motor acts that they have never executed, but the motor goals of which they could achieve using their feet or mouth. Therefore, even in subjects who have never used an effector, because they were born without it, the observation of an action performed with it evokes an activation of the action observation - action execution matching system. As we said before, however, this does not guarantee the presence of an effect at the level of the efferent motor system. Specifically, in this case the proof would be the evidence of an internal simulation of the observed hand action but performed with the foot or with the mouth. This evidence was provided by the second study (Craighero & Zorzi, 2012) which used a behavioural paradigm similar to the one of the present work. In detail, healthy participants were required to detect the time-to-contact of a hand grasping an object either with a suitable or a less suitable movement, and to respond either with the hand or the foot, while having free or bound hands. As in the present paradigm, the time lag was shorter in response to suitable movements, and this occurred both when the response was given with the hand and when it was given with the foot. This suggests that the internal simulation of the observed action is not limited to the effector used by the agent, and that motor resonance is present even when the observer is unable to use that effector, even temporarily. This result is confirmed by a TMS study (Bassolino et al., 2014) showing that action observation prevented the corticospinal depression induced by immobilization in a group of participants who could not use their arm and hand for 10 hours due to a bandage (see also De Marco et al., 2021). Overall, these results demonstrate the existence of a visuomotor mechanism in humans that links action observation and execution, which is able to influence cortical plasticity in a beneficial way. However, the results of present study are in conflict with the interpretation given by Bassolino et al. (Bassolino et al., 2014) to their results. In fact, their interpretation was that that the movement performed by the others would have an access to observer's motor system not mediated by the explicit simulation of the action, which is at odds with the presence of motor resonance in the paretic hand found here.

By concluding, the present proof of concept study shows a modulation of action prediction time in stroke patients with upper limb function impairments, demonstrating that the observation of the actions has effects on the efferent motor system even when the hand used to respond is unable to perform the observed action. These results provide evidence that the AOT is effective in recruiting the paretic limb in the simulation of action. This is probably due to the involvement of intact tissue adjacent to the damaged brain regions that functionally replace them (Garrison et al., 2013).

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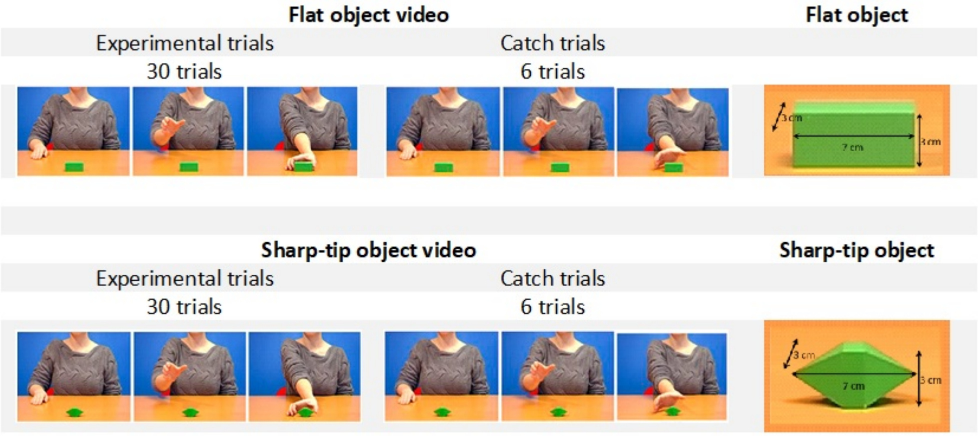
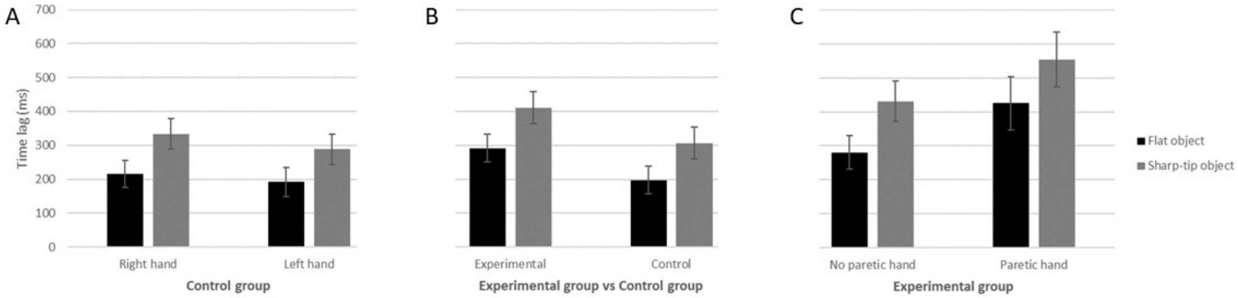
Patient	**Age (Years)**	**Gender**	**Side of lesion**	**Motricity Index**	**Duration of illness (Months)**	**Task with 1 or 2 hands**	**Control**	**Age (Years)**	**Gender**
11	28	F	left	0	19	1	**24**	26	F
27	49	F	left	11	2,5	1	**32**	48	F
6	58	M	left	0	7,6	1	**33**	59	M
16	62	M	left	11	7	1	**35**	63	F
38	71	F	left	11	4	1	**36**	68	F
7	78	F	left	0	2	1	**41**	70	F
12	42	F	right	0	120	1	**22**	47	F
20	45	F	right	0	48	1	**29**	51	F
13	46	F	right	11	12	1	**25**	56	F
19	75	M	right	0	2,3	1	**17**	66	F
10	53	M	left	19	0,9	2	**40**	57	M
18	73	F	left	11	1,4	2	**34**	77	F
3	73	M	left	11	1,2	2	**26**	64	M
14	73	M	left	22	3	2	**37**	65	M
21	77	M	left	22	4	2	**30**	69	M
202	78	M	left	22	1,6	2	**39**	73	M
201	63	F	right	22	1,6	2	**42**	72	F
28	78	F	right	19	1,2	2	**15**	79	F
Mean	62,33				13,29			61,67	
St. dev.	15,29				28,90			12,88	


Flat object video
Flat object
Experimental trials
30 trials
Catch trials
6 trials
3 cm
7 cm
3 cm
Sharp-tip object video
Sharp-tip object
Experimental trials
30 trials
Catch trials
6 trials
3 cm
7 cm
3 cm


A
B
C
Time lag (ms)
700
600
500
400
300
200
100
0
Right hand
Left hand
Control group
Experimental
Control
Experimental group vs Control group
No paretic hand
Paretic hand
Experimental group
■ Flat object
■ Sharp-tip object