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Muscle-specific modulation of indirect inputs to primary motor cortex during action observation

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Abstract

Single-pulse transcranial magnetic stimulation (spTMS) studies report that movement observation facilitates corticospinal excitability in primary motor cortex (M1) in a muscle-specific manner. However, motor evoked potentials (MEPs) elicited by spTMS are known to reflect the summation of several descending volleys in corticospinal neurons which are evoked via mono- and polysynaptic inputs (so-called indirect waves or I-waves). It is unclear which of these components contribute to the muscle-specific modulation of M1 during action observation. The interactions between different I-waves are reflected in the facilitatory peaks elicited with a short-intracortical facilitation (SICF) protocol when two pulses are sent to M1 at precise intervals (i.e., 1.3, 2.5 or 4.1 ms). Here, we explored the modulation of early and late SICF peaks during action observation by measuring highly specific MEP amplitude changes measured in two muscles (index, FDI and little finger, ADM) while participants observed two different actions (precision and whole-hand grip). Our results demonstrate that both early (1.3 ms) and late (2.5 and 4.1 ms)

SICF peaks are modulated in the context of movement observation. However, only the second peak (ISI 2.5 ms) was significantly associated with the muscle-specific modulation of corticospinal excitability as measured with spTMS. This late SICF peak is believed to reflect the activity cortico-cortical pathways involved in the facilitation of muscle-specific representations in M1. Thus, our findings suggest that movement observation leads to widespread activation of different neural circuits within M1, including those mediating cortico-cortical communication.

AQ1

AQ2

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Electronic supplementary material

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Introduction

Observing movements performed by another individual modulates the activity of primary motor cortex (M1). Previous studies using single-pulse transcranial magnetic stimulation (TMS) over M1 have demonstrated that corticospinal excitability changes during action observation as quantified by motor-evoked potentials (MEPs). The pattern of this facilitation closely “resonates” with the muscle activation pattern of the observed action (Fadiga et al. 1995, 2005; Strafella and Paus 2000; Alaerts et al. 2009b). However, the origin of this facilitation is still unknown. MEP amplitude measured with single-pulse TMS is a summary measure of repetitive waves of excitation reflecting the contribution of several trans-synaptically evoked activation bursts (so-called I-waves) of corticospinal neurons (Amassian et al. 1987; Day et al. 1989; Bestmann and Krakauer 2015). It has been speculated that different circuits generate early (I1) versus late (I2 onwards) I-waves. Late I-waves, in particular, may reflect complex cortico-cortical inputs, Please change comma with a fullstop here.For example, late I-waves may reflect complex cortico-cortical inputs that originate from premotor cortex (PMC) and project to M1 (Esser et al. 2005; Di Lazzaro and Ziemann 2013). I-wave interactions can be captured using paired TMS stimuli (i.e., short-interval intracortical facilitation; SICF) that result in marked facilitation peaks at specific interstimulus intervals (Young 1990).

Cattaneo et al. (2005), for instance, showed that the second SICF peak measured from M1 during grasp preparation was modulated in a muscle-specific manner

during movement preparation but not during object presentation alone, motor imagery, or before movements involving the same muscles but without an object. Accordingly, the authors speculated that the modulation of this peak reflects the activity of late I-waves which is driven by grasp-specific PMC–M1 interactions underpinning the transformation of object properties into motor output. This finding is in line with invasive measurements suggesting that ventral PMC can specifically facilitate the late I-wave peaks in M1 (Shimazu et al. 2004). In the context of action observation and motor resonance, it has been demonstrated that both dorsal and ventral PMC can exert a muscle-specific modulatory influence over M1 through cortico-cortical projections (Prabhu et al. 2009; Davare et al. 2010; Koch et al. 2010; Groppa et al. 2012; de Beukelaar et al. 2016; Vesia et al. 2018). Even though these regions were found to be critical for mediating visual-to-motor transformations during both action execution and observation it is currently unknown whether this modulation is relayed specifically via late SICF peaks during movement observation.

To investigate this question, we employed a paired-pulse TMS protocol targeting different SICF peaks while participants observed either precision grip or whole-hand grip movement which are known to evoke distinct muscle activation patterns (Lemon et al. 1995; Sartori et al. 2012; Cavallo et al. 2013). Our TMS protocol consisted of a supra-and a sub-threshold pulse to M1 separated by 1.3, 2.5 or 4.1 ms, i.e., targeting specifically the first, second or third SICF peak (Ziemann and Rothwell 2000).

Our results demonstrate that all MEPs, independent of the stimulation protocol (i.e., single- or paired-pulse TMS), are modulated in a muscle-specific manner by the observed movements. Interestingly, the modulation of single-pulse MEPs, which are thought to reflect a summation of complex early and late indirect inputs to M1, was statistically related to the modulation of MEPs elicited at an ISI of 2.5 ms (i.e., possibly reflecting the influence of late I-waves).

These findings suggest that muscle-specific facilitation is observed in various neural circuits within M1, including those mediating cortico-cortical communication.

Methods

Participants

Twenty-six participants (12 females, mean ± SD age 24.5 ± 6.6 years) were tested in the present experiment. All subjects were right-handed, as assessed with the Edinburgh Handedness Questionnaire (Oldfield 1971). Written informed consent was obtained before the experiment and all participants were screened for

potential contraindications to TMS (Rossi et al. 2009). The experiments were approved by the Kantonale Ethikkommission Zurich and conform to the Declaration of Helsinki (1964).

Action observation stimuli

Participants sat on a chair with their hand rested in a neutral position supported by foam pillows and observed static pictures depicting grasping movements. We chose to show static images presented in a succession to give the impression of movement rather than complete action videos to have better control over the TMS timing relative to the availability of grasp specific information (see Cattaneo et al. 2005; Prabhu et al. 2007a, b).

Stimuli showed the apparent motion of a hand reaching, grasping and lifting a round jar (9 cm diameter, 14.5 cm height, 1.5 kg weight) either using a precision-grip (PG) or a whole-hand grip (WHG). The apparent motion was induced by showing still pictures of a hand reaching, grasping and lifting the object which were each shown for 600 ms. During the WHG, all fingers were used to grasp the lid of the jar, whereas for the PG, only the thumb and index finger grasped a small knob mounted on the top of the jar. In the reach picture, the jar was visible in the middle of the screen together with the right hand of an actor positioned in the upper right corner as a clenched fist. Importantly, both WHG and PG conditions were identical at this phase. The grip type only became apparent in the second and third pictures which showed the hand grasping the jar and lifting it approximately 15 cm above the surface.

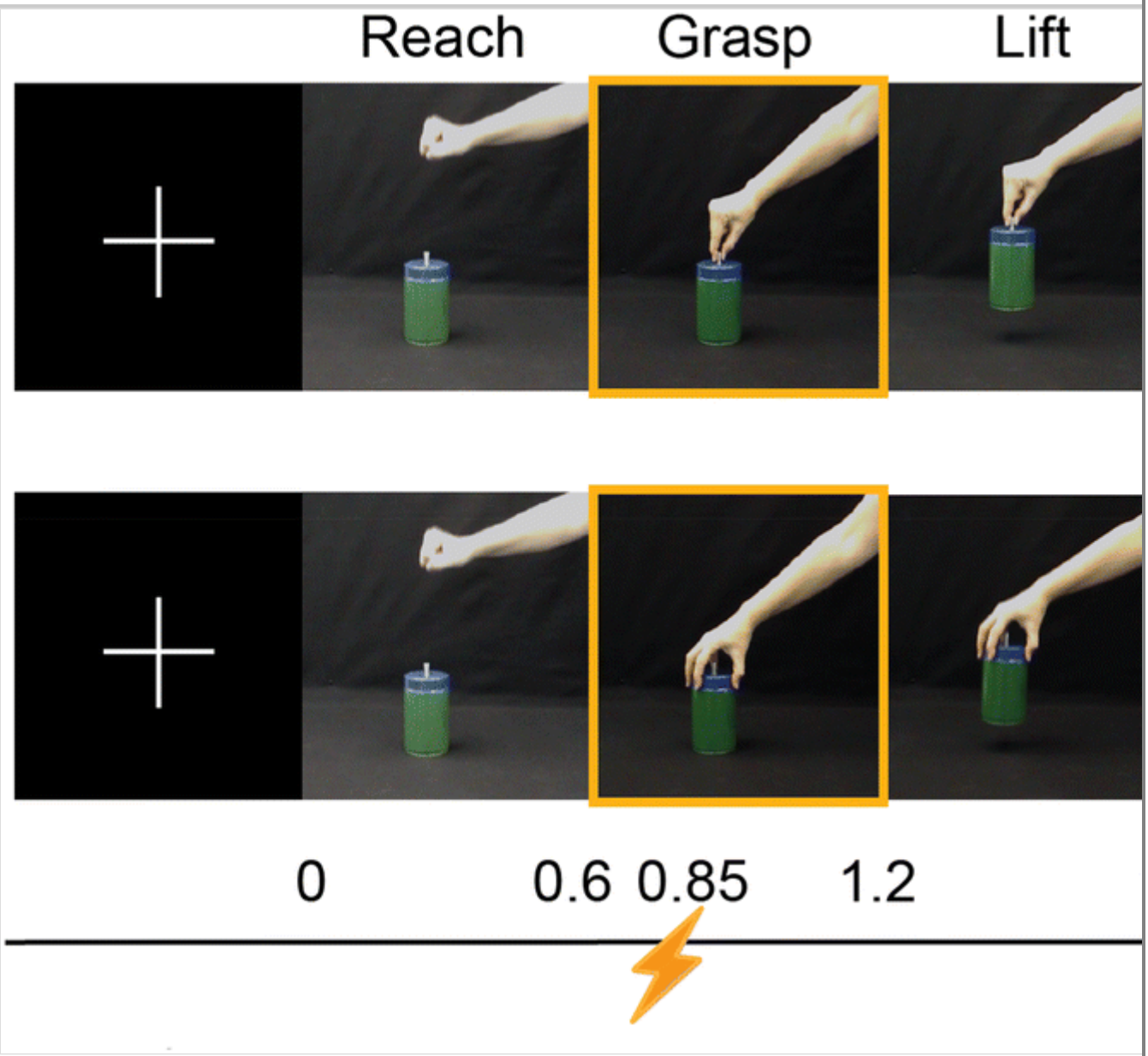
Each experimental session initiated with task instructions followed by a short training block (10 trials) in which participants could learn the general structure of the experiment.

They had to perform a counting task which ensured that they paid attention to the presented actions. Each block started with a screen showing a snapshot of one grasp type (i.e., WHG or PG) together with the instruction “Please count how many times you see this type of grasp”. They were asked to respond at the end of each block and were encouraged to be as relaxed as possible during the experiment.

All trials started with a fixation cross which stayed on the screen for a random duration between 1.5 and 3 s followed by the reach, grasp and lift pictures which only remained visible for 600 ms (Fig. 1). The occurrence of WHG and PG trials was randomized to avoid anticipation of the type of grasp. TMS pulses (either single or paired pulses) were administered 250 ms after the grasp snapshot appeared on the screen.

Fig. 1

Schematic of experimental task showing a precision-grip (PG) and a whole-hand grip (WHG) trial. Each trial started with a fixation cross followed by still shots depicting the reach, grasp and lift of a cylinder by the right hand of an actor. The orange boxes are surrounding the frame where the transcranial magnetic stimulation (TMS) pulses were sent (i.e., 250 ms after hand-object interaction)



The choice of the stimulation timing is in line with previous electrophysiological and TMS research showing that motor resonance can be observed around 200 ms after action onset (Urgesi et al. 2006, 2010; Barchiesi and Cattaneo 2013; Cavallo et al. 2014; Tucciarelli et al. 2015; Ubaldi et al. 2015).

In total, 10 blocks containing 20 trials were shown. For each of the 8 conditions [2 grasp types (PG, WHG) × 4 stimulation types (SP, PP1.3, PP2.5, PP4.1)], 25

MEPs were recorded, resulting in a total of 200 MEPs for each subject and each muscle (FDI, ADM).

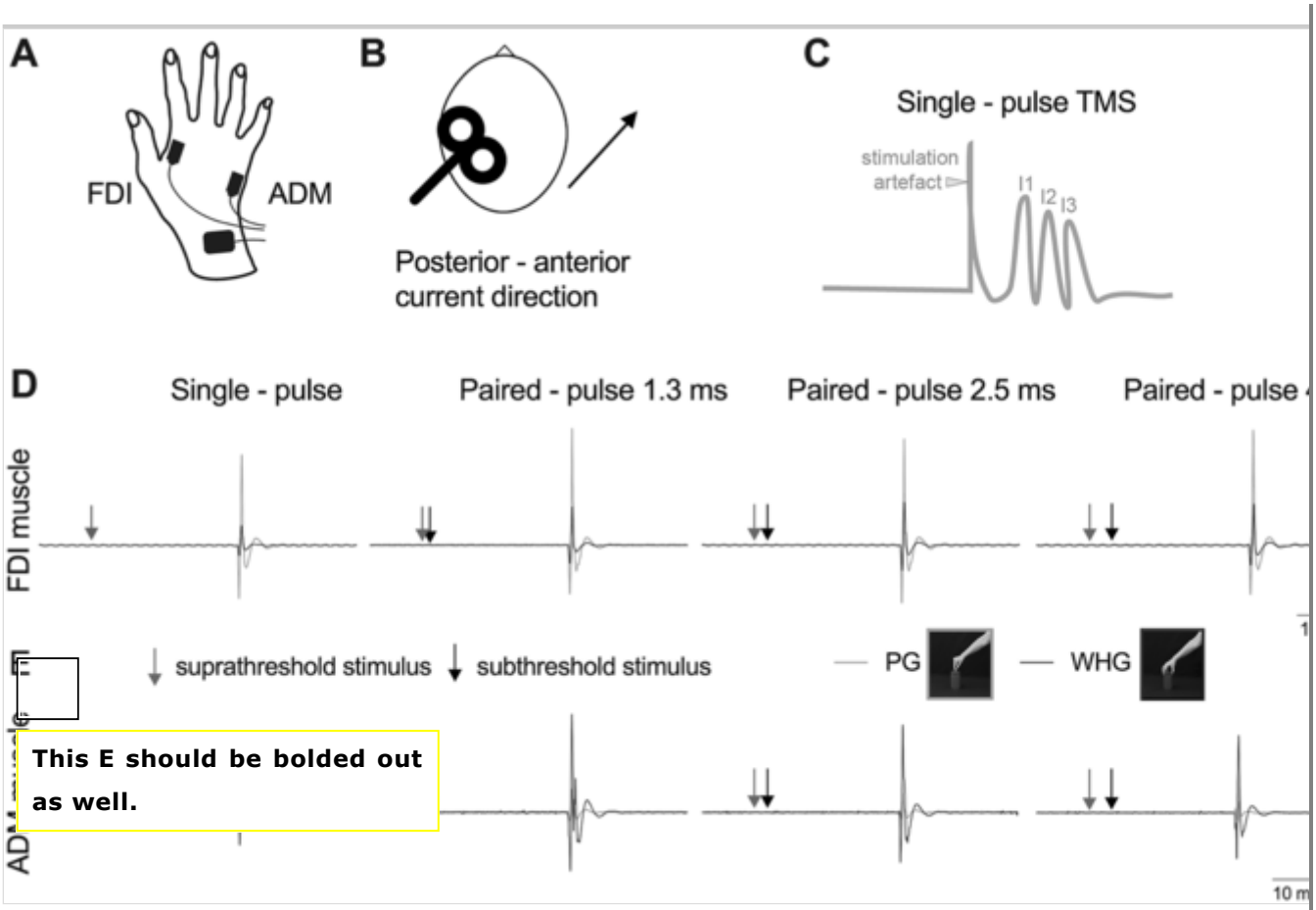
Additionally, baseline MEPs were measured while participants were fixating on a cross presented in the middle of the screen. These were obtained before and after the main experiment and consisted of 20 MEPs per stimulation type (i.e., randomized single and paired pulses separated by 1.3, 2.5 and 4.1 ms).

Electromyography recordings and TMS

Corticomotor excitability was measured using TMS during the observation of apparent motion. Motor evoked potentials (MEPs) were recorded simultaneously from the First Dorsal Interosseous (FDI) and Abductor Digiti Minimi (ADM) muscles of the right-hand using surface electromyography (EMG; Delsys Bagnoli DE-2.1; Fig. 2a). EMG data were recorded using Signal Software (Version 5.07, Cambridge Electronic Design, UK), sampled at 5000 Hz (CED Power 1401; Cambridge Electronic Design, UK), amplified, band-pass filtered (30–800 Hz with a 50 Hz notch filter), and stored on a PC for off-line analysis.

Fig. 2

Experimental setup and physiological underpinnings of motor-evoked potentials evoked by single- and paired-pulse TMS. **a** Schematic of electrode position. We recorded electromyographic (EMG) signals simultaneously from the first-dorsal intraosseous (FDI) and Abductor Digiti Minimi (ADM). **b** TMS coil position and induced current in the brain. **c** Graphic representation of the descending volleys evoked by single-pulse TMS recorded from the epidural space at moderate TMS intensities. TMS with a PA current direction evokes indirect descending waves (I-waves). Electromyography traces depicting motor-evoked potentials (MEP)s recorded in the **d** first dorsal interosseous (FDI) and **e** abductor digiti minimi (ADM) muscles during the observation of precision grasps (PG; grey traces) and whole-hand grasps (WHG; black traces) in a representative subject. MEPs were elicited using either single pulses or paired pulses with an interstimulus interval of 1.3, 2.5 or 4.1 ms. Arrows indicate the suprathreshold test (S1; grey) and subthreshold conditioning (S2; black) stimulus



Two Magstim 200 stimulators (Magstim, Whitland, UK) were used to deliver either one (i.e., single-pulse) or two (i.e., paired-pulse) magnetic pulses through the same 70-mm figure-of-eight coil. The coil was positioned over the primary motor cortex (M1) of the left hemisphere, tangentially to the scalp with the handle pointing backwards and laterally at 45° away from the mid-sagittal line, such that the induced current flow was in a posterior–anterior direction, i.e., approximately perpendicular to the central sulcus (Fig. 2b). Since we wanted to make sure that MEPs were consistently elicited in both muscles, we defined the optimal scalp position (hotspot) as the position from which responses were evoked in both the right FDI and ADM muscles. The resting motor threshold (rMT) was defined as the lowest stimulus intensity evoking MEPs in the right FDI and ADM with an amplitude of at least 50 µV in 5 out of 10 consecutive stimuli (Rossini et al. 2015). Subjects' rMT expressed as a percentage of the maximum stimulator output was on average 47.23% (35–57%). TMS triggering was controlled using Matlab 2013b (The MathWorks, Inc., Natick, USA) in combination with a Teensy 3.1 microcontroller.

Transcranial magnetic stimulation protocols

A single magnetic stimulation pulse with a PA-induced current in the brain produces a series of corticospinal descending volleys which can be recorded from the epidural space. These volleys mainly come from the direct (i.e., D-

wave) and indirect (i.e., I-waves) activation of the pyramidal tract neurons. Although a small D-wave can be observed at very high stimulation intensities, it is unlikely that D-waves were consistently evoked by our moderate TMS intensities, i.e., 130% rMT; Fig. 2c (Di Lazzaro 1998; Di Lazzaro et al. 2006, 2012). Therefore, the MEPs recorded in our study likely reflect the summation of these I-waves which are thought to result from the transsynaptic excitation of intracortical interneurons (Amassian 1961; Di Lazzaro et al. 2004).

To investigate the influence of action observation on the separate synaptic inputs to corticospinal neurons, we employed a short intracortical facilitation (SICF) protocol. This involves a suprathreshold (test stimulus; S1) followed by a subthreshold (conditioning stimulus; S2) pulse to the same hemisphere separated by specific interstimulus intervals (ISIs).

Using this protocol, facilitation can be observed at ISIs of 1.3, 2.5 or 4.1 ms, which is likely to reflect facilitatory I-wave interaction (Ziemann and Rothwell 2000).

Figure 2d, e illustrates the influence of action observation on exemplary MEPs recorded from the FDI (Fig. 2d) and ADM (Fig. 2e) muscles in a representative subject. MEPs were elicited via different stimulation protocols (i.e., single-pulse and paired pulses separated by 1.3, 2.5, and 4.1 ms) during the observation of precision (gray traces) and whole-hand grasps (black traces).

Participants received in every trial either single pulses (SP) at 130% rMT or paired pulses (PP) at 130% rMT for the first stimulus and 90% rMT for the second. Previous studies investigating the characteristics of SICF peaks using paired pulses demonstrated that three MEP peaks are clearly distinguishable using the same stimulation intensity (Ziemann et al. 1998; Cattaneo et al. 2005; Prabhu et al. 2007a, b).

Data analyses

Peak-to-peak amplitudes of the MEPs were calculated using custom Matlab scripts (Matlab 2015, Mathworks, Natick, MA, USA). Pre-TMS EMG was estimated by determining the root mean square (rms) for a window of 105–5 ms before TMS onset and trials with rms EMG greater than 10 μV were removed from further analysis. Furthermore, for each subject, the mean and standard deviation of the background EMG scores were computed and trials with rms EMG larger than the mean plus 2.5 SDs were excluded from the analysis. MEPs with a peak-to-peak amplitude smaller than 50 μV were also removed. Evoking MEPs smaller than 50 μV was most likely due to biological variability or due to technical failures of data recording. Following these criteria, a total of 3.48% of

all MEPs were removed. Missing trials were equally distributed across conditions. The mean peak-to-peak amplitude was calculated using the remaining data, separately for each muscle, grasp type and stimulation condition.

Inferential statistics were computed using linear mixed-effects models in SPSS (Version 25.0, IBM USA) which account for correlations between repeated measurements in the same subject (Gueorguieva and Krystal 2004). All models were fitted using a Compound Symmetry covariance structure and contained subjects as random effects to account for the high inter-individual variability of MEP measurements. The significance threshold alpha = 0.05 was chosen for all statistical tests and FDR corrections (Benjamini and Hochberg 1995) for multiple comparisons were applied when necessary. Results are reported in the figures as mean ± standard error of the mean (SEM). Additionally, we depicted the strength of the muscle-specific effects during action observation as Cohen's *d* bootstrapped sampling distributions employing the DABEST Matlab package (https://www.estimationstats.com; Ho et al. 2019). In the tables, partial eta-squared (small $\eta_p^2 = 0.01$, medium $\eta_p^2 = 0.06$, large $\eta_p^2 = 0.14$; Lakens and Bakker 2013) or Cohen's *d* (small $d = 0.20–0.49$, medium $d = 0.50–0.80$, large $d > 0.80$; Cohen 1988) values are reported as a measure of effect-sizes.

Baseline analyses

We first checked whether MEPs acquired before and after the action observation task were significantly different. For this reason, we employed a mixed-effects model with stimulation (SP, PP1.3, PP2.5, PP4.1), time (pre, post) and muscle (FDI, ADM) as fixed effects. Since no time effects were observed suggesting that baseline MEP amplitudes were stable, we pooled these measurements (pre, post) in all subsequent analyses.

To validate that we successfully targeted the SICF peaks, we calculated the ratio between average MEPs elicited during baseline using the paired-pulse and single-pulse protocols in each muscle. A ratio > 1 indicates facilitation by paired pulses while ratios ≤ 1 show that no facilitation or inhibition occurs. To quantify these effects, linear mixed-effects models using ISI (1.3, 2.5, 4.1 ms) and muscle (FDI, ADM) as fixed effects were employed. Post hoc *t* tests were used to probe the targeting of SICF peaks (i.e., ratios > 1).

General action observation effects

Second, we investigated whether MEPs were modulated by general action observation (both grasp types collapsed) compared to baseline. We did this by calculating the percentage difference between MEP amplitude during observation versus rest, separately for each muscle and stimulation condition:

$$\text{Baseline}_{\text{change}} = \frac{\text{MEP}_{\text{observation}} - \text{MEP}_{\text{rest}}}{\text{mean}\,(\text{MEP}_{\text{observation}}, \text{MEP}_{\text{rest}})} \times 100.$$

We employed a mixed-effects model on $\text{Baseline}_{\text{change}}$ with stimulation (SP, PP1.3, PP2.5, PP4.1) and muscle (FDI, ADM) as fixed effects. In line with our previous results (Cretu et al. 2019), we predicted that action observation will produce an increase in MEP amplitude compared to rest; therefore, one-sided *t* tests were performed for each condition to test specifically whether $\text{Baseline}_{\text{change}} > 0$.

Grasp-specificity effects

Finally, to provide a measure of grasp specificity, we assessed how observing a precision versus a whole-hand grip modulated the MEP amplitude:

$$\text{MEP}_{\text{mod}} = \frac{\text{MEP}_{\text{WHG}} - \text{MEP}_{\text{PG}}}{\text{mean}\,(\text{MEP}_{\text{WHG}}, \text{MEP}_{\text{PG}})}.$$

A value of 0 suggests that no grasp-specific modulation is present. Given that both action execution and action observation studies have specified a dissociation between the involvement of these two muscles in each grasp type (e.g., Cavallo et al. 2013; Lemon et al. 1995; Sartori et al. 2012), we expect positive MEPmod values for the ADM, indicating a stronger facilitation during WHG than PG observation, and negative MEPmod values for the FDI muscle, indicating a stronger facilitation during PG than WHG (also depicted in Fig. 2d, e).

Grasp-specific modulation index was calculated separately for each muscle (FDI, ADM) and stimulation protocol (SP, PP1.3, PP2.5, PP4.1). Since we are interested in whether the SICF peak amplitudes are modulated by the grip type, we report the MEPmod index calculated for both single-pulse and paired-pulse stimulation protocols. A similar approach was employed in previous studies investigating the influence of SICF peaks during movement preparation (Prabhu et al. 2007a, b; Marangon et al. 2013).

To assess whether action observation triggered a differential grasp-specific change depending on the stimulation protocol, we employed a linear mixed-effects model using muscle (FDI, ADM) and stimulation (SP, PP1.3, PP2.5, PP4.1) as fixed effects. Additionally, we employed one-sided *t* tests and asked whether the MEPmod values were significantly smaller than 0 for FDI and bigger than 0 for ADM, as expected for a grasp-specific modulation.

Contribution of SICF peaks to corticospinal excitability

To further explore the relationship between single- and paired-pulse MEPmod for each muscle (i.e., FDI, ADM) we employed a robust regression implemented by the Matlab fitlm function (with robust fitting option). This method uses iteratively reweighted least squares regression and is less sensitive to outlier data points than traditional regression models because less weight is assigned to extreme values. We aimed to describe the contribution of SICF peaks (i.e., the predictors: $\mathrm{MEPmod}_{\mathrm{PP1.3}}$, $\mathrm{MEPmod}_{\mathrm{PP2.5}}$ and $\mathrm{MEPmod}_{\mathrm{PP4.1}}$) to the grasp-specific corticospinal excitability as measured with single-pulse TMS (i.e., the dependent variable: $\mathrm{MEPmod}_{\mathrm{SP}}$). For this reason, we employed the following model:

$$\mathrm{MEPmod}_{\mathrm{SP}} = \beta_0 + \beta_1 \mathrm{MEPmod}_{\mathrm{PP1.3}} + \beta_2 \mathrm{MEPmod}_{\mathrm{PP2.5}} + \beta_3 \mathrm{MEPmod}_{\mathrm{PP4.1}} + \varepsilon,$$

where β_0 is the $\mathrm{MEPmod}_{\mathrm{SP}}$ intercept, while β_1, β_2, and β_3 are the slopes of the predictors (i.e., regression coefficients) and ε is the error term.

Prior to the regression analyses, the independence of residuals (i.e., Durbin–Watson tests), multicollinearity of predictors (i.e., Belsley collinearity diagnostics) and normality (i.e., using Lillefors tests) were assessed. Data from both muscles met all these assumptions.

Results

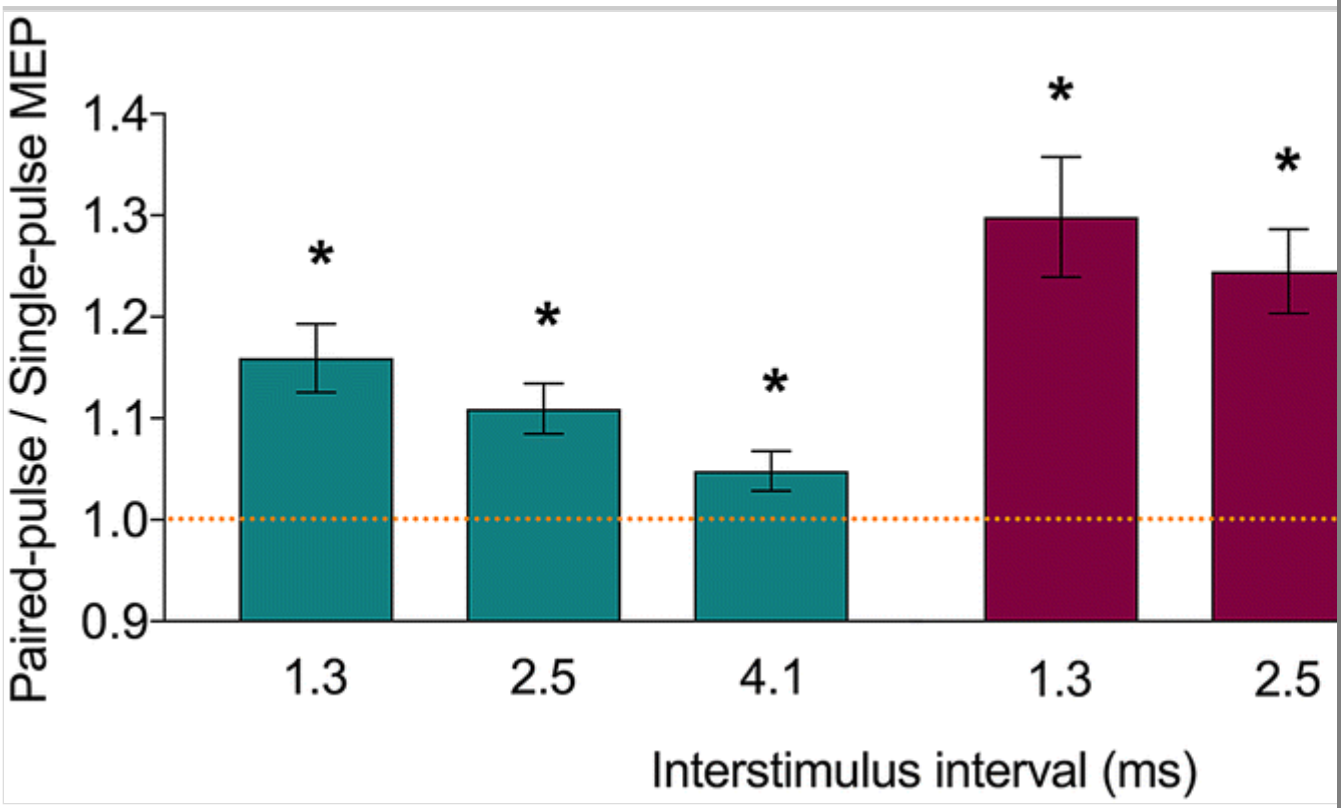
SICF peaks during rest (no action observation)

Baseline MEPs recorded at the beginning (pre) and the end (post) of the action observation task were not significantly different (main effect and interactions containing the factor time: $p \geq 0.43$), demonstrating no general change in corticospinal excitability during the experiment. Thus, all subsequent analyses using the baseline MEPs were performed with the average (pre, post).

Our results confirmed that the employed paired-pulse TMS protocols elicited the expected effects (Supplementary Table S1). All ISIs (i.e., 1.3, 2.5 and 4.1 ms) lead to a facilitation of MEPs (Fig. 3). More specifically, mixed-effects analyses with the factors muscle (FDI, ADM) and ISI (1.3, 2.5 and 4.1 ms) revealed a significant fixed effect of muscle ($F = 24.359$, $p < 0.0001$) and ISI ($F = 9.064$, $p < 0.0001$). Although facilitation of ADM MEPs was stronger than FDI MEPs, the same pattern of decreased facilitation from the first to the third SICF peak was present in both muscles ($\mathrm{PP/SP}_{\mathrm{FDI}}$: $1.159 > 1.11 > 1.048$; $\mathrm{PP/SP}_{\mathrm{ADM}}$: $1.298 < 1.245 < 1.148$), which is in line with the patterns observed in other studies (e.g., Cirillo et al. 2016). Importantly, post hoc t tests confirmed that the paired-pulse protocols elicited the expected facilitation in both muscles (all $p_{\mathrm{FDR}} < 0.011$).

Fig. 3

MEP amplitude ratio (paired-pulse MEPs divided by single-pulse MEPs; $n = 26$) during rest presented separately for the two muscles (FDI, ADM). A value higher than 1 indicates facilitation of paired-pulse MEPs compared to single-pulse MEPs. The range of interstimulus intervals (ISIs) employed for the paired-pulse stimulation is presented on the *x*-axis. The paired-pulse MEP amplitude increased significantly compared to the single-pulse for all the ISIs (1.3, 2.5 and 4.1 ms). *$p \leq 01$ (false discovery rate (FDR)-corrected one-sided t tests)



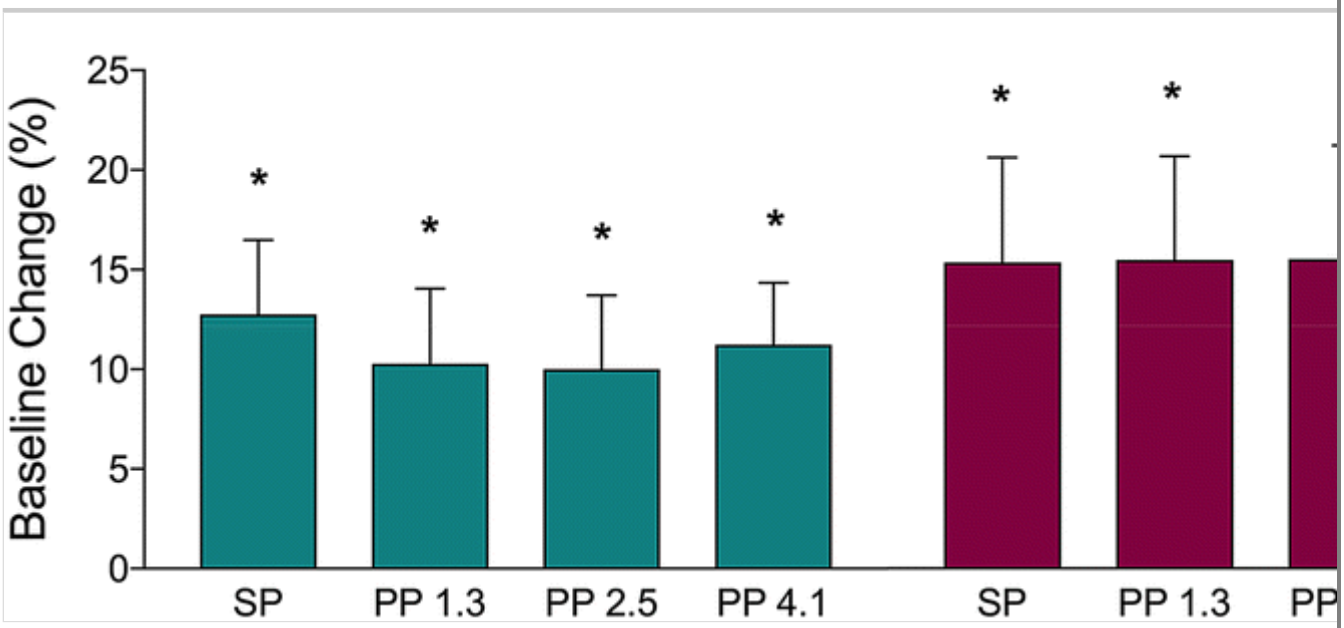
General action observation effects on single- and paired-pulse MEPs

We then investigated the changes in amplitude of MEPs acquired during the action observation task (collapsed across grasp types) and baseline by calculating an index of mirroring. The term 'mirroring' refers to neural activity within motor areas that is elicited by movement observation at rest (i.e., when the observer generates no motor activity). In both muscles, excitability was larger during action observation than during baseline, as it can be observed in Fig. 4. The results of *t* tests are summarized in Supplementary Table S2.

Fig. 4

Baseline change presented separately for each muscle [first dorsal intraosseous (FDI) and abductor digiti minimi (ADM)] and stimulation protocol [single-pulse (SP), paired-pulse ISI 1.3 ms (PP1.3), paired-pulse ISI 2.5 ms (PP2.5), paired-

pulse ISI 4.1 ms (PP4.1)]. Values > 0 indicate a stronger facilitation of corticomotor excitability during action observation versus rest. *$p \leq 0.006$ (false discovery rate (FDR)-corrected one-sided t tests)



Mixed-effects analyses showed a main effect of muscle ($p = 0.029$) indicating that general mirroring was on average higher in the ADM compared to FDI muscle. However, both muscles showed the same pattern of increased corticomotor excitability during movement observation versus rest, independent of the stimulation protocol (stimulation $p = 0.93$).

Grasp-specific observation effects on single- and paired-pulse MEPs

M1 was modulated in a grasp-specific manner for all stimulation protocols (main effect of muscle $p < 0.0001$; Supplementary Table S3). This indicates that FDI is facilitated more strongly when observing a precision versus a whole-hand grip while the opposite facilitation pattern is present for the ADM (stronger during whole-hand than precision grip).

The mixed-effects model with muscle (FDI, ADM) and stimulation (SP, PP1.3, PP2.5, PP4.1) as fixed effects yielded a significant fixed effect of muscle ($p < 0.001$), indicating that FDI and ADM muscles were differentially modulated by the observed grasp type (Fig. 5a; Table 1). Interestingly, no difference was found between the MEPmod elicited using the different TMS stimulation protocols ($p = 0.187$). When tested separately for each stimulation protocol, the pattern of grasp-specific modulation was highly significant for SP, PP1.3, and PP4.1 (muscle effect $p <= 0.011$), whereas it only showed a trend toward significance for PP2.5 ms ($p = 0.067$).

Fig. 5

Grip-specific facilitation ($n = 26$). **a** MEP modulation obtained in the FDI and ADM muscles during the observation of whole-hand (WHG) versus precision grasp (PG) stimuli. Values > 0 indicate higher facilitation during WHG observation, while values < 0 show increased facilitation during PG. **b** Effect sizes (Cohen's *d*) for the muscle effect (ADM–FDI difference) are plotted for each stimulation condition (SP, PP1.3, PP2.5, PP4.1) as dots. These can be interpreted as follows: small $d = 0.20–0.49$, medium $d = 0.50–0.80$, large $d > 0.80$ (Cohen 1988). Filled curves depict the resampled distribution of the muscle effect, given the observed data, and error bars depict 95% confidence intervals. $*p \leq 0.042$ [false discovery rate (FDR)-corrected one-sided *t* tests]

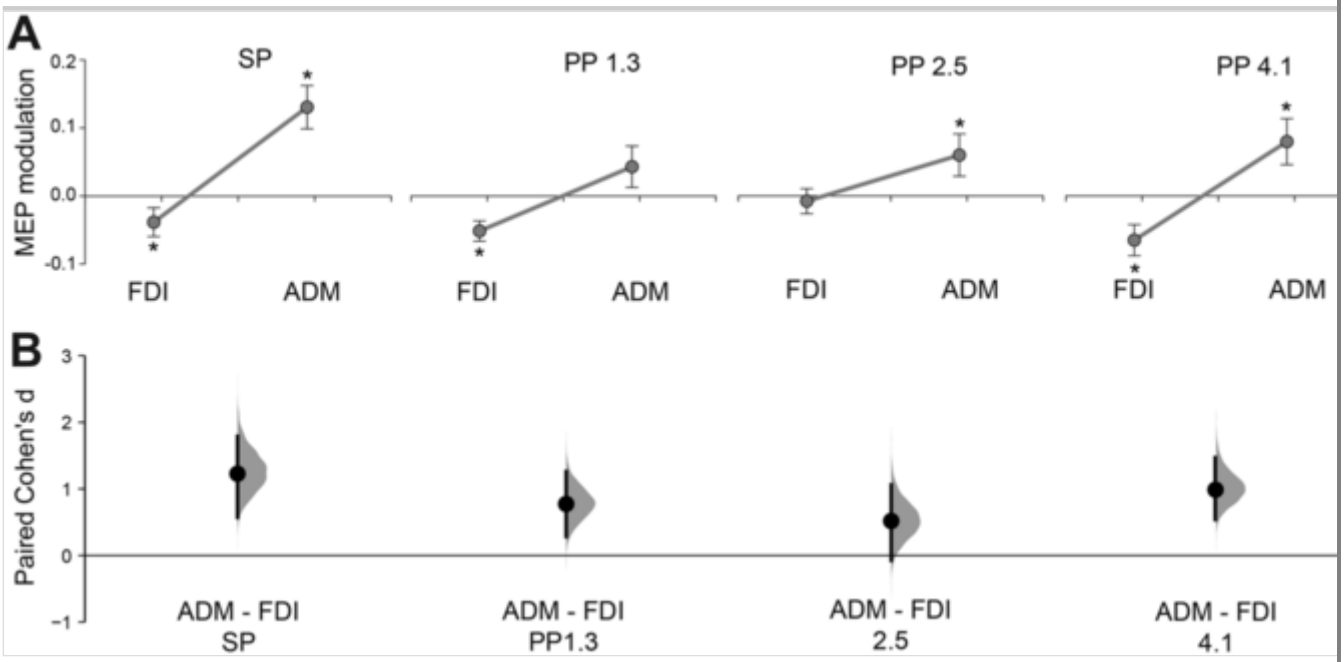


Table 1

Results of linear mixed-effects analyses performed with the MEPmod index ($N = 26$)

	***F* values**	***p* values**
Muscle (FDI, ADM)	**47.283**	< **0.0001**
Stimulation (SP, PP1.3, PP2.5, PP4.1)	1.619	0.187
Muscle × stimulation	1.76	0.157
Degrees of freedom	175	
FDI first dorsal intraosseous, *ADM* abductor digiti minimi, *SP* single-pulse, *PP1.3* paired-pulse ISI 1.3 ms, *PP2.5* paired-pulse ISI 2.5 ms, *PP4.1* paired-pulse ISI 4.1 ms		
p values that survived multiple comparisons correction are represented in bold		

One-sided *t* tests revealed that FDI MEPmod elicited by single-pulse as well as paired pulses at ISIs of 1.3 and 4.1 ms significantly deviated from 0 (all $p_{FDR} <= 0.04$). For the ADM muscle, this facilitation was present for MEPs elicited by single and paired pulses at ISIs 2.5 and 4.1 ms (all $p_{FDR} <= 0.013$). The strength of the muscle-specific effect (i.e., paired Cohen's *d* effect size for the ADM − FDI difference) is plotted in Fig. 5b for each stimulation condition as a bootstrap sampling distribution.

Contribution of SICF peaks to cortico-spinal excitability during action observation

A robust regression analysis was used to investigate whether the grasp-specific modulation of SICF peaks (i.e., MEPmod elicited using paired pulses separated by 1.3, 2.5 and 4.1 ms) significantly predicted the grasp-specific modulation (i.e., MEPmod) of single-pulse MEPs.

For FDI, we found that only the grasp-specific modulation observed in the second SICF peak ($\beta_2 = 0.91$, $p = 0.001$) was a significant predictor of the single-pulse grasp-specific modulation. The modulation evoked in the first ($\beta_1 = 0.44$, $p = 0.23$) and third SICF peaks ($\beta_3 = 0.29$, $p = 0.18$) were not significant predictors of the single-pulse MEPmod. The overall model fit was $R^2 = 0.415$ ($p = 0.007$). Similar results were found in the ADM muscle where only the second SICF peak (i.e., ISI 2.5 ms) significantly contributed to the single-pulse grasp-specific modulation ($\beta_2 = 0.65$, $p = 0.0008$), with an overall model fit of $R^2 = 0.436$ ($p = 0.005$).

Discussion

In this study, we aimed to investigate whether synaptic inputs to corticospinal neurons carry muscle-specific information during grasp observation. By delivering paired-pulse TMS at specific inter-stimulus intervals (ISIs) we aimed to isolate the contribution of early and late excitatory inputs (i.e., SICF peaks) to M1 and showed that all of them exhibit a muscle-specific modulation, at least at the trend level. Independent of the TMS protocol, MEPs recorded from FDI muscle were more strongly facilitated during the observation of precision versus whole-hand grip movements while the opposite pattern was found for the ADM muscle. Additionally, our regression results suggest that late SICF peaks (in particular the second one, i.e., with an ISI = 2.5 ms) are significantly related to MEP amplitudes modulation during action observation. This is consistent with theories proposing that motor resonance in M1 is at least partly driven via circuits that contribute to late SICF peaks such as premotor-to-M1 projections (Shimazu et al. 2004; Esser et al. 2005; Di Lazzaro and Ziemann 2013).

Our results concerning baseline (resting) data (i.e., without observing any actions) confirm that SICF peaks were successfully targeted by showing a significant facilitation of MEPs elicited at 1.3, 2.5 and 4.1 ms ISIs (all $p <= 0.011$). Action observation (i.e., collapsed across grasp type) facilitated the amplitudes of single-pulse MEPs as well as of all SICF peaks. Thus, the well-known effect that movement observation facilitates single-pulse MEPs (Fadiga et al. 1995; Strafella and Paus 2000; Gangitano et al. 2001; Alaerts et al. 2009a, b; Hannah et al. 2018) generalizes also to different sub-circuits reflected by SICF peaks.

Since these increases in MEP amplitudes can be rather unspecific (e.g., due to increased attention or arousal), we used a 'two action × two muscle' design (Cavallo et al. (2014)) to test action-specific observation effects. We identified a strong muscle-specific modulation (Cohen's *d* exp. 1 = 0.87 -- please correct text here, correct text in parathesis should be 'Cohen's d = 0.87'---and exp. 2 = 0.77) of MEPs elicited by single-pulse TMS in the FDI and ADM muscle when participants observed precision versus whole-hand grasping actions (Davare et al. 2008; Sartori et al. 2013; Bunday et al. 2016; de Beukelaar et al. 2016; Cretu et al. 2019). However, single-pulse MEPs provide only a summary measurement of several excitatory bouts descending via the corticospinal tract. SICF peaks as evoked by double-pulse TMS, by contrast, provide additional insights into the contribution of later activity bouts which might arise from upstream areas projecting to M1, from polysynaptic intracortical circuits formed by M1 different subpopulations of M1 interneurons or from cortico-spinal interactions (Rothwell et al. 1987; Reis et al. 2008; Di Lazzaro and Rothwell 2014; Bestmann and Krakauer 2015; Cirillo and Perez 2015). One previous study found the second SICF peak to be modulated in a muscle-specific manner during the observation of goal-directed actions (Koch et al. 2010). We extend these findings by showing that action observation facilitated MEP amplitudes for all SICF peaks in a muscle-specific manner (at least at the trend level). Additionally, our regression results showed that out of the three ISIs employed to test facilitatory SICF peaks, only ISI 2.5 ms was a significant predictor of the muscle-specific modulation observed in single-pulse MEPs. Assuming that SICF peaks have different neural generators, they all represent the observed action in a muscle-specific manner. However, circuits reflected by SICF peaks evoked for 2.5-ms ISI seem to provide a rather consistent input to M1 excitability across participants.

Identifying the exact neural substrates driving this modulation is challenging. It has been suggested that peaks elicited using the same SICF paired-pulse protocol as in our experiment could result from complex interactions of excitatory M1 networks (Di Lazzaro et al. 2004; Cash et al. 2011). Although the interstimulus

intervals of 1.3, 2.5, and 4.1 ms resemble the periodicity of I-waves, it is unlikely that there is a one-to-one correspondence with the resulting SICF peaks. However, previous research indicated that later SICF peaks (at ISI of 2.5 and 4.1 ms) seem to preferentially reflect the contribution of later I-waves (I2 and I3) (Lazzaro et al. 1999; Hanajima et al. 2002; Ilić et al. 2002). Additionally, there is evidence that different neural circuits are responsible for generating the early versus late I-waves. Day et al. (1989) found that later I-waves can be elicited on their own (i.e., independent from the early I-waves) and suggested that separate interneurons are responsible for the different I-wave peaks. Furthermore, Di Lazzaro et al. (2012) suggested that there is a connection between late I-waves and cortico-cortical inputs to M1, possibly arriving from premotor or parietal areas (i.e., mirror neuron areas). Alternatively, it is also possible that subcortical circuits (e.g., in the spinal cord) might contribute to the late I-wave peaks (Cirillo and Perez 2015). Thus, we cannot exclude the possibility that pathways downstream from M1 might have contributed to the modulation of MEPs at ISIs of 2.5 and 4.1 ms. We found no evidence that muscle-specific facilitation during movement observation is bound to specific intra-cortical circuits in M1 but it might arise at multiple levels of the sensorimotor system. This result is consistent with the observation that “mirror neuron” like properties have been reported for both pyramidal tract neurons in M1 (Tkach et al. 2007; Dushanova and Donoghue 2010; Vigneswaran et al. 2013; Kraskov et al. 2014) and neuronal population in ventral premotor cortex (di Pellegrino et al. 1992; Gallese et al. 1996; Rizzolatti et al. 1996).

AQ3

Given this finding, it is interesting to note that previous action execution research using the same paired-pulse protocols as in our study demonstrated that only MEPs at 2.5-ms ISI were modulated in a muscle-specific manner during grasp preparation (Cattaneo et al. 2005; Prabhu et al. 2007a, b). These authors suggested that prior to the initiation of movements, grasp-related information was transmitted to M1 via cortico-cortical pathways, possibly reflecting premotor cortex (PMC) inputs. Subsequent studies corroborated these findings and further strengthened the idea that during movement planning, object properties are transmitted to M1 via excitatory cortico-cortical inputs (Prabhu et al. 2007a; Marangon et al. 2013). Our study is not at odds with this finding but we showed that grasp-related modulation was present for all stimulation conditions.

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In summary, our findings suggest that movement observation of different grasp types causes muscle-specific activation patterns which are reflected by different

neural circuits within M1, including those mediating cortico-cortical communication.

AQ6

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary file1 (DOCX 126 kb)

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