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Cortico-cortical paired associative stimulation conditioning superficial ventral premotor cortex–primary motor cortex connectivity influences motor cortical activity during precision grip

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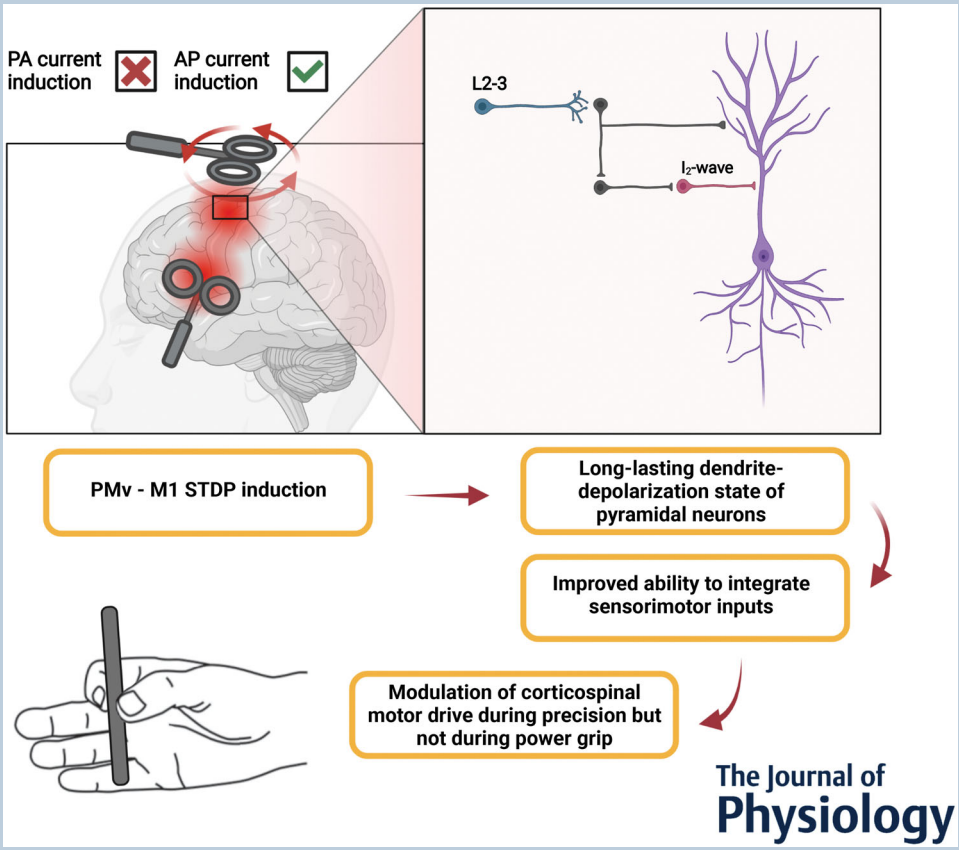

Abstract The ventral premotor cortex (PMv) and primary motor cortex (M1) represent critical nodes of a parietofrontal network involved in grasping actions, such as power and precision grip. Here, we investigated how the functional PMv–M1 connectivity drives the dissociation between these two actions. We applied a PMv–M1 cortico-cortical paired associative stimulation (cc-PAS)

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protocol, stimulating M1 in both postero-anterior (PA) and antero-posterior (AP) directions, in order to induce long-term changes in the activity of different neuronal populations within M1. We evaluated the motor-evoked potential (MEP) amplitude, MEP latency and cortical silent period, in both PA and AP, during the isometric execution of precision and power grip, before and after the PMv–M1 cc-PAS. The repeated activation of the PMv–M1 cortico-cortical network with PA orientation over M1 did not change MEP amplitude or cortical silent period duration during both actions. In contrast, the PMv–M1 cc-PAS stimulation of M1 with an AP direction led to a specific modulation of precision grip motor drive. In particular, MEPs tested with AP stimulation showed a selective increase of corticospinal excitability during precision grip. These findings suggest that the more superficial M1 neuronal populations recruited by the PMv input are involved preferentially in the execution of precision grip actions.

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Abstract figure legend Neural circuits presumably involved in the induction of plasticity after cortico-cortical paired associative stimulation from the ventral premotor cortex to primary motor cortex (PMv-to-M1) applied with an antero-posterior (AP) coil orientation. As can be seen in the upper part of the figure, the AP coil orientation preferentially targets the more superficial M1 layers and the late I-wave (I_2-wave) circuits. This specific induction of spike timing-dependent plasticity (STDP) could lead to a long-lasting state of dendrite depolarization in pyramidal neurons. The dendritic tree of layer V large pyramidal neurons (L5) is located in the superficial layers of M1. The long-lasting depolarization might improve the ability of neurons to integrate sensorimotor inputs from PMv, which are necessary for the execution of fine motor tasks. This effect is specific for the corticospinal motor drive during precision grip (and not during power grip), which, in turn, requires more sensorimotor integration for its execution.

Key points

- Ventral premotor cortex (PMv)–primary motor cortex (M1) cortico-cortical paired associative stimulation (cc-PAS) with different coil orientation targets dissociable neural populations.
- PMv–M1 cc-PAS with M1 antero-posterior coil orientation specifically modulates corticospinal excitability during precision grip.
- Superficial M1 populations are involved preferentially in the execution of precision grip.
- A plasticity induction protocol targeting the specific PMv–M1 subpopulation might have important translational value for the rehabilitation of hand function.

Introduction

The control of fine finger movements is driven by the primary motor cortex (M1; Muir & Lemon, 1983), which uses information provided by the activity of a more complex network in which it is integrated. Within M1, multiple neuronal populations are involved specifically in the control of precision grip rather than power grip (Muir & Lemon, 1983). These different neuronal populations might be targeted preferentially by specific coil orientations of transcranial magnetic stimulation (TMS). In fact, despite their indirect nature, there are several pieces of evidence supporting partial dissociation for circuits targeted by different

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coil orientations (Di Lazzaro & Rothwell, 2014; Fong et al., 2021; Ni et al., 2011; Spampinato, 2020). These orientations are believed to target partly dissociable neuronal populations projecting to the pyramidal layer V (L5) neurons, namely more superficial ones [layers 2–3 (L2–L3)] with antero-posterior (AP) and deeper ones with postero-anterior (PA) current directions (L5; Aberra et al., 2020; Sommer et al., 2013). Above all, circuits targeted by the two orientations might contribute in different ways to various motor tasks (Davis et al., 2022; Spampinato et al., 2020). Federico and Perez (2017) suggested that late synaptic input, targeted by AP TMS stimulation of M1, could be involved preferentially during power grip, whereas early synaptic input, targeted by the PA stimulation, might play a predominant role in precision grip. However, it has recently been shown that neuronal populations stimulated by AP coil orientation are more sensitive to primary somatosensory cortex (S1)–M1 interaction, via thalamocortical pathways, during the execution of precision grip rather than power grip (Davis et al., 2022).

The execution of a grasping action recruits a complex parietofrontal network, in which ventral premotor cortex (PMv)–M1 connections represent a critical node. In humans, PMv activity is crucial for the transformation of object-related visual properties into an appropriate motor plan (de Beukelaar et al., 2016; Koch, Versace et al., 2010; Murata et al., 1997; Prabhu et al., 2009; Raos et al., 2006), and previous studies on PMv–M1 connectivity have shown how the PMv exerts an important influence on M1 during different grasping movements (Davare et al., 2008; de Beukelaar et al., 2016; Koch, Versace et al., 2010). In addition, modulation of PMv–M1 connectivity via cortico-cortical paired associative stimulation (cc-PAS), a TMS protocol that promotes Hebbian spike timing-dependent plasticity (STDP) (Hebb, 1949; Markram et al., 2011), influences the performance in several motor tasks (Buch et al., 2011; Fiori et al., 2018; Turrini, Bevacqua et al., 2023). Nevertheless, little is known about the possibility of sustained modulation of corticospinal motor drive during the execution of specific actions. The aim of the present work was to investigate the cortical contribution of different M1 neural populations influenced by PMv input in precision and power grasping actions.

In two different sessions, we applied a PMv–M1 cc-PAS protocol with different M1 coil orientations (PA *vs.* AP current induction) to condition preferentially the neuronal populations that might be involved predominantly in precision or power grip. We assessed corticospinal excitability (CSE) and inhibition [cortical silent period (cSP)], in addition to motor-evoked potential (MEP) latency during isometric execution of precision and power grip, before and 30 min after the PMv–M1 cc-PAS protocol applied in the PA direction (*Session 1*, cc-PAS_{PA}) or the AP direction (*Session 2*, cc-PAS_{AP}). Considering the dense connections from PMv and S1 to the superficial M1, L2–L3; (Ghosh & Porter, 1988; Mao et al., 2011), we hypothesized that the cc-PAS_{AP} might be more effective in modulating the corticospinal motor drive in grasping actions and, in particular, during precision grip, which might require the integration of more sensorimotor signals than power grip (Davis et al., 2022).

Methods

Ethical approval

All the participants were informed about the experimental procedure and gave their written consent according to the last update of the *Declaration of Helsinki*, except for the registration in a database. The experiment was approved by the ethical committee 'Comitato Etico Unico della Provincia di Ferrara' (approval no. 170592). The participants were compensated for their participation with €30.00 for their first TMS session and with an additional €15.00 if they also took part in the second experimental session.

Participants

A total of 31 healthy volunteers (mean ± SD age, 23.33 ± 2.37 years; 14 males) took part in this study (Table 1). The first experimental session was completed by 18 participants (*Session 1*, cc-PAS_{PA}), and 17 subjects took part in the second experimental session (*Session 2*, cc-PAS_{AP}). Four of 31 volunteers took part in both experimental sessions.

Experimental task

At the beginning of the experimental session, subjects performed three short abductions of the right index finger, each separated by 30 s, in which they were asked to express the maximal voluntary contraction (MVC) for 3 s. Later, during the experiment, participants were asked to perform and maintain precision grip and power grip in randomized order, with their right hand. In the precision grip, participants were asked to grasp a cylinder (diameter, 1.18 cm; length, 10.9 cm; weight, 86 g) between the thumb and index finger. While performing the power grip, subjects were instructed to grasp the same cylinder with the whole hand, with all fingers flexed against the palm. During both these actions, the forearm and wrist were maintained in a natural position. Subjects were instructed to maintain ∼10% of maximal voluntary contraction in the first dorsal interosseous (FDI) muscle (Davare et al., 2008) and to keep the cylinder in a vertical position. Before the start of each experiment, some practice trials

Table 1. For each experimental session is shown the number of subjects, their age, the resting motor threshold and the active motor threshold (means ± SD) in both postero-anterior and antero-posterior directions

Session	Subject (males)	Age (years)	M1 rMT_{PA} $coil_1$	M1 rMT_{AP} $coil_1$	M1 rMT_{PA} $coil_2$	M1 aMT_{PA} $coil_2$	M1 aMT_{AP} $coil_2$
1	18 (8)	22.7 ± 1.7	48.3 ± 7.0	60.2 ± 8.5	51.6 ± 6.8	45.1 ± 5.5	54.6 ± 7.0
2	17 (7)	24 ± 3.0	46.1 ± 4.6	56.7 ± 4.5	49.2 ± 5.2	43.4 ± 4.0	53.0 ± 4.5

During the cortico-cortical paired associative stimulation (cc-PAS) protocol, $coil_1$ was positioned on the primary motor cortex, while $coil_2$ was positioned on the ventral premotor cortex. During the pre-PAS and post-PAS acquisition, $coil_1$ was used to acquire the neurophysiological indices at rest (baseline), while $coil_2$ was used to assess the neurophysiological indices during the execution of the action. The use of two coils during the acquisition of motor-evoked potentials was necessary to prevent them from overheating. Abbreviations: aMT, active motor threshold; AP, antero-posterior; PA, postero-anterior; rMT, resting motor threshold.

ensured that participants were able to complete the tasks using the requested level of EMG activity. In addition, during all the experimental sessions, the EMG activity was monitored visually by the experimenter to provide verbal feedback about the correct level of muscle contraction. The FDI muscle was selected because it is consistently involved in both the examined actions and it is highly sensitive to task-dependent changes in corticospinal drive (Bunday et al., 2014; Federico & Perez, 2017; Tazoe & Perez, 2017). Both motor tasks were performed before and 30 min after the application of the cc-PAS protocols (Fig. 1).

EMG recording

Surface EMG was recorded from the right FDI muscle by means of a wireless system (Zerowire EMG, Aurion, Italy) with a tendon–belly montage. EMG signals were digitized (2 kHz) and acquired by a CED Micro Power1401 mk *II* board (Cambridge Electronic Design, Cambridge, UK).

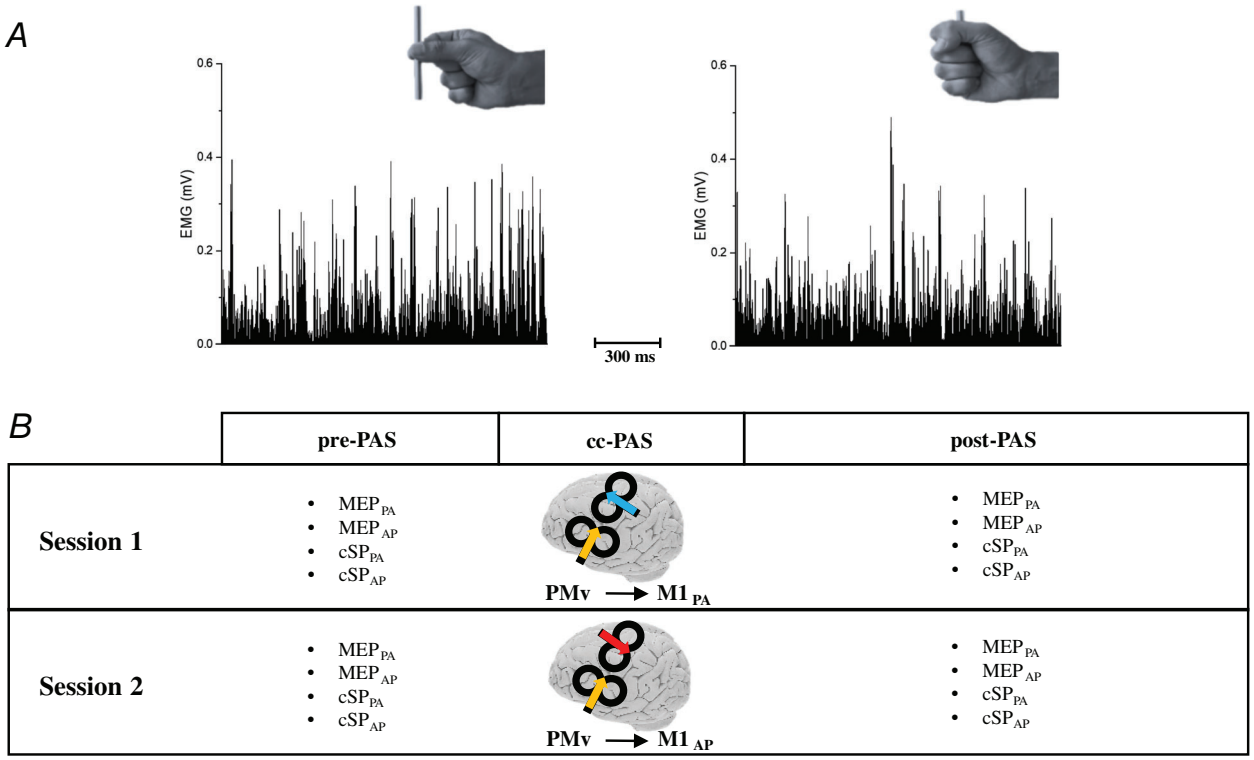

Figure 1. Table summarizing the experimental procedures
A, representative hand posture during precision and power grip, with rectified EMG traces for the first dorsal interosseous (FDI) in a representative subject. *B*, summary of the experimental procedures. The cortico-cortical paired associative stimulation (cc-PAS) was preceded by the pre-PAS acquisition and followed by the post-PAS re-acquisition. All neurophysiological indices were acquired at rest (baseline) and during the precision and power grips. In the middle column, illustrating cc-PAS, the coil positions and induced current directions (arrows) are shown. [Colour figure can be viewed at wileyonlinelibrary.com]

All the acquired data were stored for offline analysis using the software Signal 6.05 (Cambridge Electronic Design).

Transcranial magnetic stimulation

Participants were seated on a comfortable armchair during all the experimental sessions. Single-pulse TMS and cc-PAS protocols were administered through a 50 mm figure-of-eight focal coil connected to a Magstim BiStim^2 monophasic stimulator (The Magstim Company, Whitland, UK).

The FDI optimal scalp position (OSP) was found by moving the coil in 0.5 cm steps over the left primary motor cortex hand area and using a slightly supra-threshold stimulus. Resting motor threshold (rMT) was defined as the lowest intensity that evoked a MEP with >50 μV amplitude in 5 of 10 consecutive trials while the participants kept the FDI muscle relaxed (Rossi et al., 2009; Rossini et al., 2015). Likewise, the active motor threshold (aMT) was determined as the minimum intensity required to elicit MEPs of >200 μV (peak to peak) above the background EMG activity ($\sim$10% of maximal voluntary contraction), in $\geq$5 of 10 consecutive trials (Davis et al., 2022). The individual OSP, rMT and aMT were defined for each coil used in each experiment, and separately for the different coil orientations (PA *vs*. AP). Table 1 gives a summary of rMT and aMT in each experiment and coil.

A total of 90 trials were acquired before (pre-PAS) and 30 min (post-PAS) after the end of the cc-PAS protocol. Specifically, we recorded 15 MEPs for each action (precision grip *vs*. power grip) and for each coil orientation (PA *vs*. AP). In addition, 15 MEPs were also acquired at rest, with the coil in both PA and AP orientation.

Cortico-cortical paired associative stimulation. In the cc-PAS protocol, dual-sites TMS repeatedly activated the connection between the left PMv and left M1. One hundred couples of pulses were delivered at a frequency of 0.25 Hz for $\sim$6 min. The left PMv was stimulated at 90% of individual rMT, while the left M1 was stimulated at 120% of rMT (Koch et al., 2013; Casarotto et al., 2022). In each pair, the M1 stimulation followed the PMv stimulation by 6 ms (Davare et al., 2008, 2009; Koch et al., 2010; Casarotto et al., 2022). The coil over the left M1 was placed tangentially to the scalp on the FDI OSP, at $\sim$ 45° with respect to the midline, to induce a PA current flow (*Session 1*, cc-PAS$_{PA}$); from this position, the coil was rotated 180° to induce an AP current flow (*Session 2*, cc-PAS$_{AP}$). To estimate the position of the left PMv, we used the SofTaxic Navigator System (Electro Medical System, Bologna, Italy). The skull landmarks (nasion, inion, right and two preauricular points) and 23 points on the scalp were digitalized through a Polaris Vicra optical tracker (Northern Digital, Canada). To stimulate the left PMv, the coil was placed over a scalp region corresponding to the Montreal Neurological Institute (MNI) coordinates $x = -52.8$, $y = 11.6$, $z = 25.1$ (Koch, Versace et al., 2010).

Data analysis

As a first data check, we tested whether EMG activity was different before and after the cc-PAS protocol (pre-PAS *vs*. post-PAS) and across actions (precision *vs*. power), before the stimulus onset. We computed the root mean square (RMS) of the 100 ms pre-TMS window and, for each experimental session, we conducted a 2 $\times$ 2 repeated-measures ANOVA, with action (precision grip *vs*. power grip) and time (pre-PAS *vs*. post-PAS) as factors. The ANOVAs did not show any main effect or interaction between factors (*Session 1*, all $P > 0.24$; *Session 2*, all $P > 0.33$).

We then extracted the peak-to-peak amplitude of MEPs, the MEP latency and the duration of the cSP. The duration of the cSP was calculated, for each trial, from the offset of the MEP to the return of EMG activity according to literature standards (Hupfeld et al., 2020). One participant was excluded from the cSP analysis in *Session 1* owing to a technical problem in calculating the duration of the cSP. The MEP latency was extracted from each trial as the time from the TMS pulse release to the MEP onset. The MEP amplitude was defined as the peak-to-peak difference of the first two major positive and negative deflections after MEP onset. We excluded from the analysis all trials that presented a peak-to-peak MEP amplitude of $\leq$0.05 mV. Then, we calculated for each subject the mean and SD of the background pre-TMS EMG (100 ms) over all trials. We removed from the analysis those trials in which mean EMG activity was $\pm$2 SD of the mean EMG. In *Session 1*, we excluded an average of 8.59% of the trials; in *Session 2*, 11.34%. At the single subject level, in *Session 1*, we excluded a minimum of 0% and a maximum of 17.7% of trials; in *Session 2*, we excluded a minimum of 2.22% and a maximum of 17.2% of trials. A minimum of 10 valid trials per condition was set to consider the data acquisition valid. All trials were inspected visually for artefacts.

The different trans-synaptic input engaged in PA *vs*. AP results in a constantly delayed MEP latency of $\sim$1.5 ms, attributable to the recruitment of different M1 neural circuits in different layers (Federico & Perez, 2017; Ni et al., 2011). Therefore, as a second data check, we verified that this effect was also present in our data. We analysed the latencies of resting MEPs elicited by the PA and AP TMS stimulation before application of the cc-PAS protocol. In *Session 1*, Student's two-tailed paired-sample *t* test showed a significantly shorter latency ($t_{18} = -4.38$, $P = 0.0004$) for MEP$_{PA}$ (mean = 0.021 s, SD = 0.001 s)

Table 2. Complete results of mixed ANOVA on corticospinal excitability data

Effect	*F*	*P*-value
cc-PAS protocol	$F_{1,33} = 0.50$	0.48
Action condition	$\mathbf{F_{2,66} = 35.80}$	**<0.0001**
Action condition × cc-PAS protocol	$F_{2,66} = 0.93$	0.40
Coil orientation	$\mathbf{F_{1,33} = 20.95}$	**<0.0001**
Coil orientation × cc-PAS protocol	$F_{1,33} = 0.46$	0.50
Time	$F_{1,33} = 0.39$	0.53
Time × cc-PAS protocol	$F_{1,33} = 0.25$	0.62
Action condition × coil orientation	$F_{2,66} = 0.05$	0.95
Action condition × coil orientation × cc-PAS protocol	$F_{2,66} = 1.46$	0.24
Action condition × time	$F_{2,66} = 0.69$	0.51
Action condition × time × cc-PAS protocol	$\mathbf{F_{2,66} = 17.47}$	**<0.0001**
Coil orientation × time	$F_{1,33} = 1.57$	0.22
Coil orientation × time × cc-PAS protocol	$F_{1,33} = 0.11$	0.75
Action condition × coil orientation × time	$F_{2,66} = 1.83$	0.17
Action condition × coil orientation × time × cc-PAS protocol	$\mathbf{F_{2,66} = 4.72}$	**0.01**

Abbreviation: cc-PAS, cortico-cortical paired associative stimulation. Significant results are shown in bold.

with respect to MEP_{AP} (mean = 0.023 s, SD = 0.002 s). The same result was obtained in the *Session 2* ($t_{17} = -6.66$, $P < 0.0001$; MEP_{PA}, mean = 0.020 s, SD = 0.002 s; MEP_{AP}, mean = 0.022 s, SD = 0.001 s).

To investigate the effects induced by different PMv–M1 cc-PAS protocols and the contributions of different M1 circuits (activated by single pulse PA or AP stimulation) during the execution of precision and power grip, we computed a 2 × 3 × 2 × 2 mixed ANOVA, with "cc-PAS protocol" (cc-PAS_{PA} *vs.* cc-PAS_{AP}) as a between factor and with "Action condition" (rest *vs.* precision grip *vs.* power grip), "Coil orientation" (PA *vs.* AP) and "Time" (pre-PAS *vs.* post-PAS) as within factors, on MEP amplitude and MEP latency data. Likewise, we computed a 2 × 2 × 2 × 2 mixed ANOVA, with "cc-PAS protocol" (cc-PAS_{PA} *vs.* cc-PAS_{AP}) as a between factor and "Action condition" (precision grip *vs.* power grip), "Coil orientation" (PA *vs.* AP) and "Time" (pre-PAS *vs.* post-PAS) as within factors, on cSP duration data. This analytical approach allowed us to compare the effect of different cc-PAS protocols on the three action conditions. Please note that the rest condition corresponds to the experimental scenario reported in our previous study (Casarotto et al., 2022) and thus can be used also to test the reliability of cc-PAS protocols. Any significant interaction was analysed further by Newman–Keuls corrected *post hoc* analysis. All analyses were conducted in STATISTICA 12 (StatSoft).

Results

Corticospinal excitability

The ANOVA on the MEP amplitude showed a significant main effect of "Action condition" ($F_{2,66} = 35.80$; $P < 0.0001$) and "Coil orientation" ($F_{1,33} = 20.95$; $P < 0.0001$). The interaction between "Action condition", "Time" and "cc-PAS protocol" was also significant ($F_{2,66} = 17.48$; $P < 0.0001$). Furthermore, the interaction between "cc-PAS protocol", "Action condition", "Coil orientation" and "Time" was significant ($F_{2,66} = 15.87$; $P < 0.0001$). All the other interactions were not significant; for the complete ANOVA results, see Table 2. The *post hoc* analyses showed, that after the cc-PAS_{PA}, there was a significant increment of MEP_{PA} (pre-PAS, mean = 1.49 mV, SD = 0.69 mV; post-PAS, mean = 2.15 mV, SD = 1.23 mV; $P = 0.0003$) at rest. No significant differences emerged for the MEP_{PA} during precision grip (pre-PAS, mean = 3.09 mV, SD = 1.30 mV; $P = 0.07$) and power grip (pre-PAS, mean = 2.35 mV, SD = 1.23 mV; post-PAS, mean = 2.19 mV, SD = 1.16 mV; $P = 0.44$) execution. Moreover, after the cc-PAS_{PA}, the MEP_{AP} did not show any significant modulation at rest (pre-PAS, mean = 1.33 mV, SD = 1.20 mV; post-PAS, mean = 1.36 mV, SD = 0.97 mV; $P = 0.83$), during the execution of precision grip (pre-PAS, mean = 2.19 mV, SD = 1.09 mV; post-PAS, mean = 2.12 mV, SD = 1.01 mV; $P = 0.94$) and the power grip (pre-PAS, mean = 1.80 mV, SD = 0.97 mV; post-PAS, mean = 1.64 mV, SD = 0.86 mV; $P = 0.47$, Fig. 2).

After the cc-PAS_{AP}, we found a significant reduction of the MEP_{PA} at rest (pre-PAS, mean = 2.00, SD = 1.05 mV; post-PAS, mean = 1.68; SD = 0.88 mV; $P = 0.05$). Differently, there was no significant modulation of the MEP_{PA} during the execution of precision grip (pre-PAS, mean = 2.79 mV, SD = 0.98; post-PAS, mean = 3.15 mV; SD = 0.86 mV; $P = 0.06$) and power grip (pre-PAS, mean = 2.38 mV, SD = 0.94 mV; post-PAS, mean = 2.68 mV, SD = 1.03 mV; $P = 0.06$). In this case, the

MEP_{AP} was modulated selectively during the execution of precision grip (pre-PAS, mean = 2.48 mV, SD = 1.04 mV; post-PAS, mean = 2.84 mV; SD = 1.12 mV; $P = 0.04$). No significant modulation was observed in the MEP_{AP} at rest (pre-PAS, mean = 1.37 mV, SD = 0.64 mV; post-PAS, mean = 1.14 mV, SD = 0.46 mV; $P = 0.35$) and during the power grip execution (pre-PAS, mean = 2.09 mV, SD = 1.08 mV; post-PAS, mean = 2.04 mV, SD = 0.98 mV; $P = 0.66$; Fig. 3).

Cortical silent period

The 2 × 2 × 2 × 2 ANOVA on the cSP duration showed a significant main effect of "Action condition" ($F_{1,32} = 11.71$; $P = 0.002$; precision grip, mean = 0.09 s, SD = 0.02 s; power grip, mean = 0.08 s, SD = 0.02 s) and "Coil orientation" ($F_{1,32} = 6.45$; $P = 0.02$; PA, mean = 0.08 s, SD = 0.02 s; AP, mean = 0.09 s; SD = 0.02 s). The interaction between "Coil orientation" and "cc-PAS protocol" was significant ($F_{1,32} = 4.26$; $P = 0.04$). The *post hoc* analyses revealed a significant difference between the cSP_{PA} and the cSP_{AP} (PA, mean = 0.07 s, SD = 0.02 s; AP, mean = 0.08 s, SD = 0.03 s; $P = 0.003$) in *Session 2* (Fig. 5), in other words when the cc-PAS_{AP} was applied. This difference was not present when the cc-PAS_{PA} was applied (PA, mean = 0.08 s, SD = 0.03 s; mean = 0.08 s; SD = 0.02 s; $P = 0.74$ Fig. 4). Considering that no main effect or interaction with the factor "Time" was present, these results will not be discussed further. The complete results of ANOVA are reported in Table 3.

Motor-evoked potential latency

The 2 × 3 × 2 × 2 ANOVA conducted on the latency data showed a significant main effect of "Action condition" ($F_{2,66} = 41.31$; $P < 0.0001$) and "Coil orientation" ($F_{2,66} = 109.94$; $P < 0.0001$). A significant interaction emerged between "Coil orientation", "Time" and "cc-PAS protocol" ($F_{1,33} = 6.85$ $P = 0.01$). We found no other significant interactions or main effect; the complete results are reported in Table 4.

The *post hoc* analyses on the interaction showed a significant difference in the latencies of the MEPs acquired with a PA coil orientation after the cc-PAS_{PA} (pre-PAS, mean = 0.020 s, SD = 0.001 s; post-PAS, mean = 0.021 s, SD = 0.002 s; $P = 0.01$; Fig. 6). No difference was observed in the latencies of the MEPs acquired with the AP coil orientation (pre-PAS, mean = 0.022 s, SD = 0.001 s; post-PAS, mean = 0.022 s, SD = 0.001 s; $P = 0.99$). After the cc-PAS_{AP}, a significant difference was present in the latencies of the MEPs acquired with an AP coil orientation (pre-PAS, mean = 0.020 s, SD = 0.001 s; post-PAS, mean = 0.021 s, SD = 0.001 s; $P = 0.02$; Fig. 7). No difference was present in the latencies of the MEPs acquired with a PA coil orientation (pre-PAS, mean = 0.020 s, SD = 0.001 s; post-PAS, mean = 0.020 s, SD = 0.001 s; $P = 0.85$).

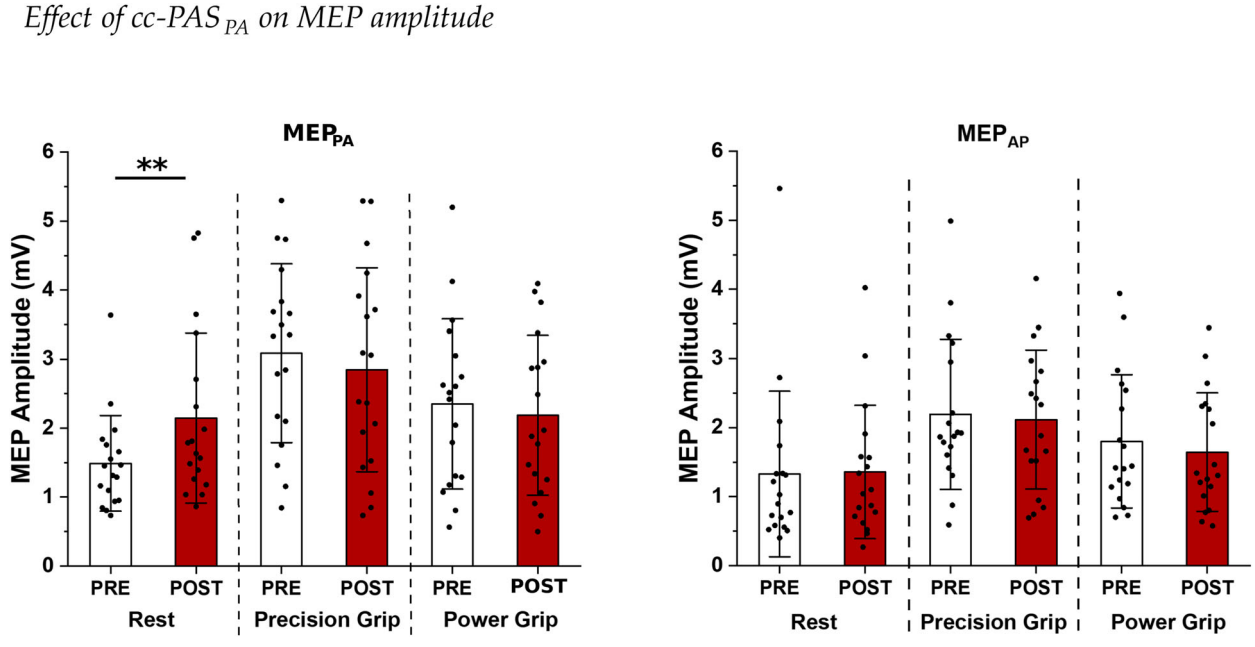

Figure 2. Motor-evoked potential results in *Session 1*
The left panel shows the effects of the PMv-to-M1 cc-PAS_{PA} protocol on motor-evoked potentials (MEPs) tested with a postero-anterior (PA) coil orientation; the right panel reports the results of the MEP data acquired with an antero-posterior (AP) coil orientation. The error bars represent the SD; $^{**}P < 0.01$. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3. Complete results of mixed ANOVA on cortical spinal period duration data

Effect	*F*	*p*
cc-PAS protocol	$F_{1,32}$ = 1.86	0.18
Action condition	**$F_{1,32}$ = 11.71**	**0.002**
Action condition × cc-PAS protocol	$F_{1,32}$ = 0.21	0.65
Coil orientation	**$F_{1,32}$ = 6.45**	**0.02**
Coil orientation × cc-PAS protocol	**$F_{1,32}$ = 4.26**	**0.05**
Time	$F_{1,32}$ = 3.10	0.09
Time × cc-PAS protocol	$F_{1,32}$ = 0.56	0.46
Action condition × coil orientation	$F_{1,32}$ = 3.56	0.07
Action condition × coil orientation × cc-PAS protocol	$F_{1,32}$ = 0.0004	0.98
Action condition × time	$F_{1,32}$ = 1.56	0.22
Action condition × time × cc-PAS protocol	$F_{1,32}$ = 0.51	0.48
Coil orientation × time	$F_{1,32}$ = 1.53	0.23
Coil orientation × time × cc-PAS protocol	$F_{1,32}$ = 3.82	0.06
Action condition × coil orientation × time	$F_{1,32}$ = 0.30	0.58
Action condition × coil orientation × time × cc-PAS protocol	$F_{1,32}$ = 0.44	0.51

Abbreviation: cc-PAS, cortico-cortical paired associative stimulation. Significant results are shown in bold.

Discussion

In the present work, we applied a PMv–M1 cc-PAS protocol with two coil orientations (PA *vs.* AP on M1) to investigate the possibility of modulating specific PMv–M1 connections during the execution of different grasping actions. We found that PMv–M1 cc-PAS with an AP direction resulted in a preferential modulation of precision grip motor drive. Notably, at rest we replicated some of the key results obtained earlier (Casarotto et al., 2022), whereas in activation, we showed that the cc-PAS protocols modulated MEP latency only when elicited with the same coil orientation used during the cc-PAS stimulations, thus lending additional consistency to our present manipulations and results.

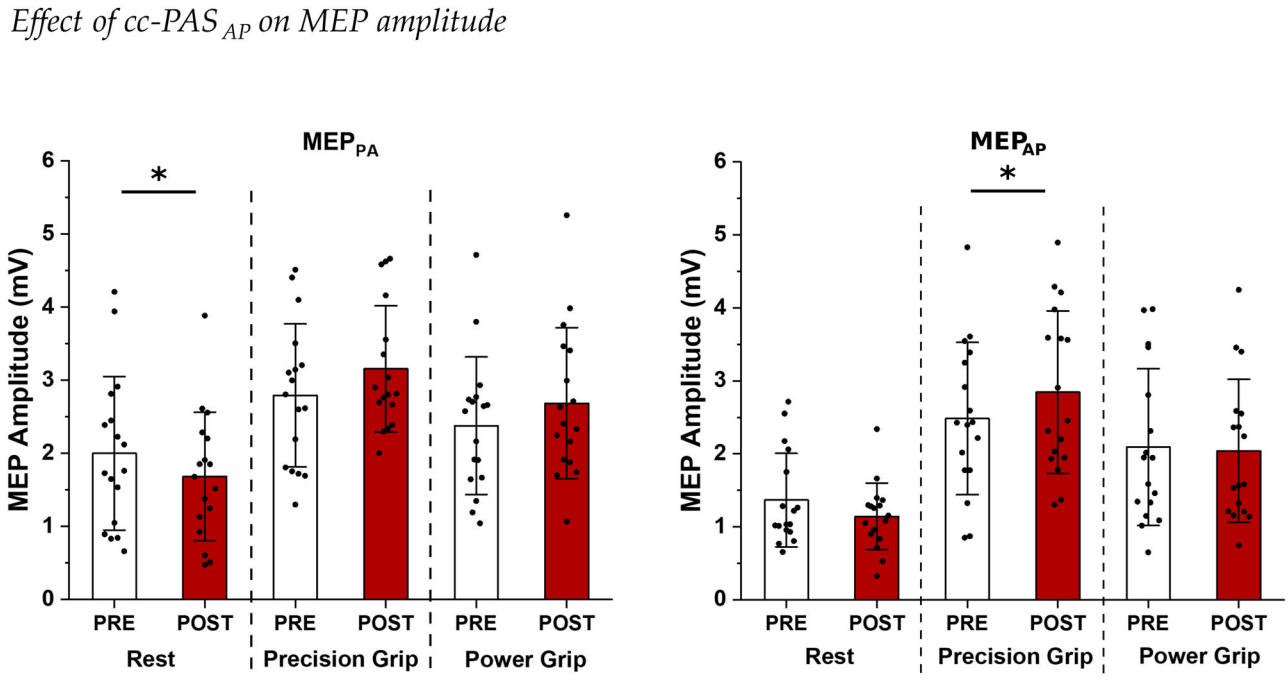

Figure 3. Motor-evoked potential results in *Session 2*
The left panel shows the effects on motor-evoked potentials (MEPs) amplitude tested with a postero-anterior (PA) coil orientation; the right panel reports the results of MEPs acquired with an antero-posterior (AP) coil orientation. The error bars represent the SD; $^*P < 0.05$. [Colour figure can be viewed at wileyonlinelibrary.com]

Effects of PMv-to-M1 cc-PAS on corticospinal motor drive

Visually guided grasping actions recruit an extended network, in which different parietal and frontal areas provide key contributions. Previous studies highlighted the visuomotor nature of PMv and its crucial role in grasping actions; in particular, during the precision grip (Davare et al., 2008, 2009; Koch, Versace et al., 2010; Prabhu et al., 2009). Although several parietal areas offer

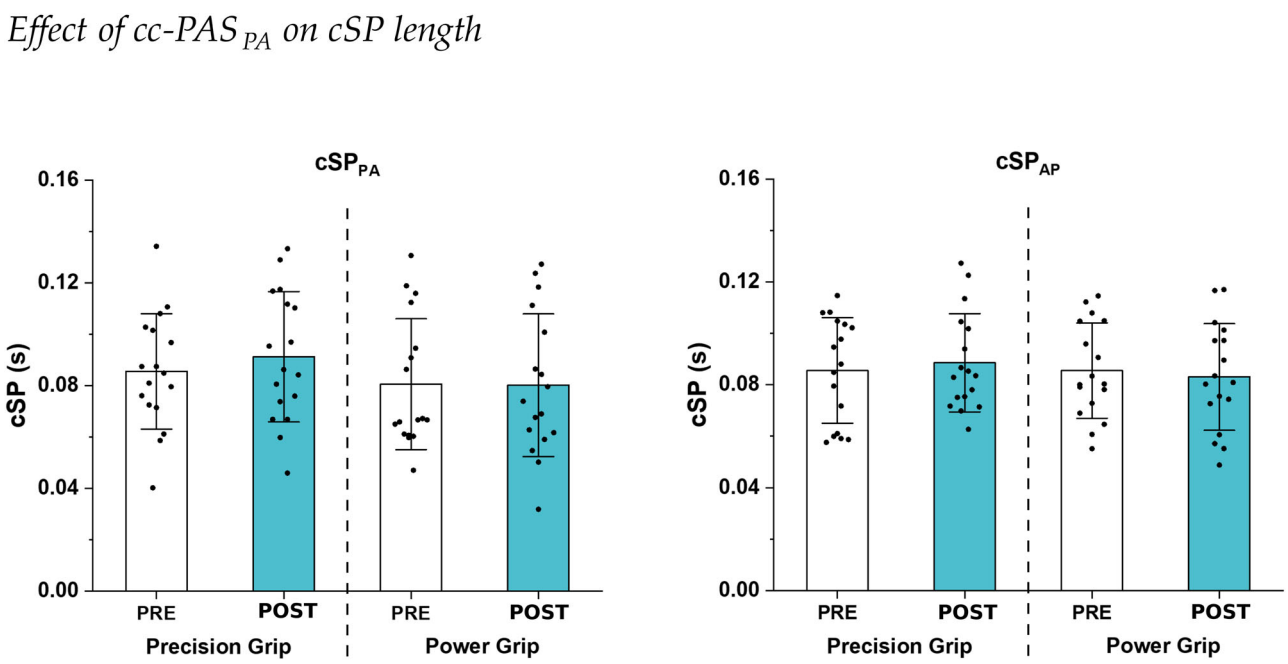

Figure 4. Cortical spinal period results in *Session 1*
The left panel shows the effects of the PMv-to-M1 cc-PAS$_{PA}$ protocol on cortical spinal period (cSP) tested with a postero-anterior (PA) coil orientation; the right panel report the results on cSP acquired with an antero-posterior (AP) coil orientation. Error bars represent the SD. [Colour figure can be viewed at wileyonlinelibrary.com]

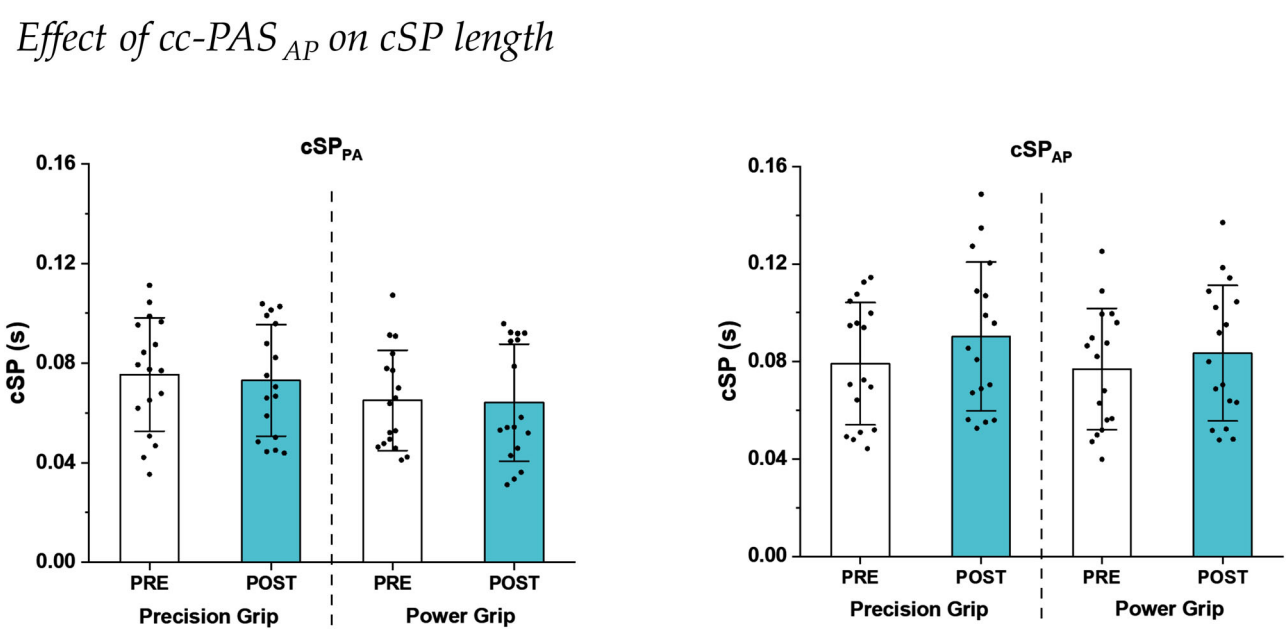

Figure 5. Cortical spinal period results in *Session 2*
The left panel shows the effects of the PMv-to-M1 cc-PAS$_{PA}$ protocol on the cortical spinal period (cSP) tested with a postero-anterior (PA) coil orientation; the right panel reports the results on cSP recorded with an antero-posterior (AP) coil orientation. Error bars represent the SD. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 4. Complete results of ANOVA on motor-evoked potential latency data

Effect	*F*	*P*-value
cc-PAS protocol	$F_{1,33}$ = 3.49	0.07
Action condition	**$F_{2,66}$ = 41.31**	**<0.0001**
Action condition × cc-PAS protocol	$F_{2,66}$ = 0.25	0.78
Coil orientation	**$F_{1,33}$ = 109.94**	**<0.0001**
Coil orientation × cc-PAS protocol	$F_{1,33}$ = 0.62	0.44
Time	$F_{1,33}$ = 3.36	0.07
Time × cc-PAS protocol	$F_{1,33}$ = 0.04	0.84
Action condition × coil orientation	$F_{2,66}$ = 1.18	0.31
Action condition × coil orientation × cc-PAS protocol	$F_{2,66}$ = 1.56	0.22
Action condition × time	$F_{2,66}$ = 0.36	0.70
Action condition × time × cc-PAS protocol	$F_{2,66}$ = 1.72	0.19
Coil orientation × time	$F_{1,33}$ = 0.01	0.94
Coil orientation × time × cc-PAS protocol	**$F_{1,33}$ = 6.85**	**0.01**
Action condition × coil orientation × time	$F_{2,66}$ = 0.43	0.65
Action condition × coil orientation × time × cc-PAS protocol	$F_{2,66}$ = 0.79	0.46

Abbreviation: cc-PAS, cortico-cortical paired associative stimulation. Significant results are shown in bold.

key contributions to the fine execution of grasping actions, these seem to be mediated by the activity of premotor areas (Koch, Cercignani et al., 2010). The PMv thus represents a converging node for several inputs which, unlike parietal and frontal areas, is connected monosynaptically to M1 (Makris et al., 2005; Matelli et al., 1998; Rozzi et al., 2006).

This extended network converges towards M1 for the control of precision and power grip, possibly involving partially non-overlapping neural populations. Single-unit recordings clearly show that some cortical motor neurons appear to be more active during precision grip. whereas others are more active during power grip (Muir & Lemon, 1983). Precision and power grip are not the two ends of the same action continuum (i.e. grasping), but represent two qualitatively different motor plans. At least in part, these actions engage different PMv and M1 intracortical circuits (Bennett & Lemon, 1996; Muir & Lemon, 1983; Umilta et al., 2007) and descending systems (Baker & Perez, 2017; Federico & Perez, 2017; Tazoe & Perez, 2017).

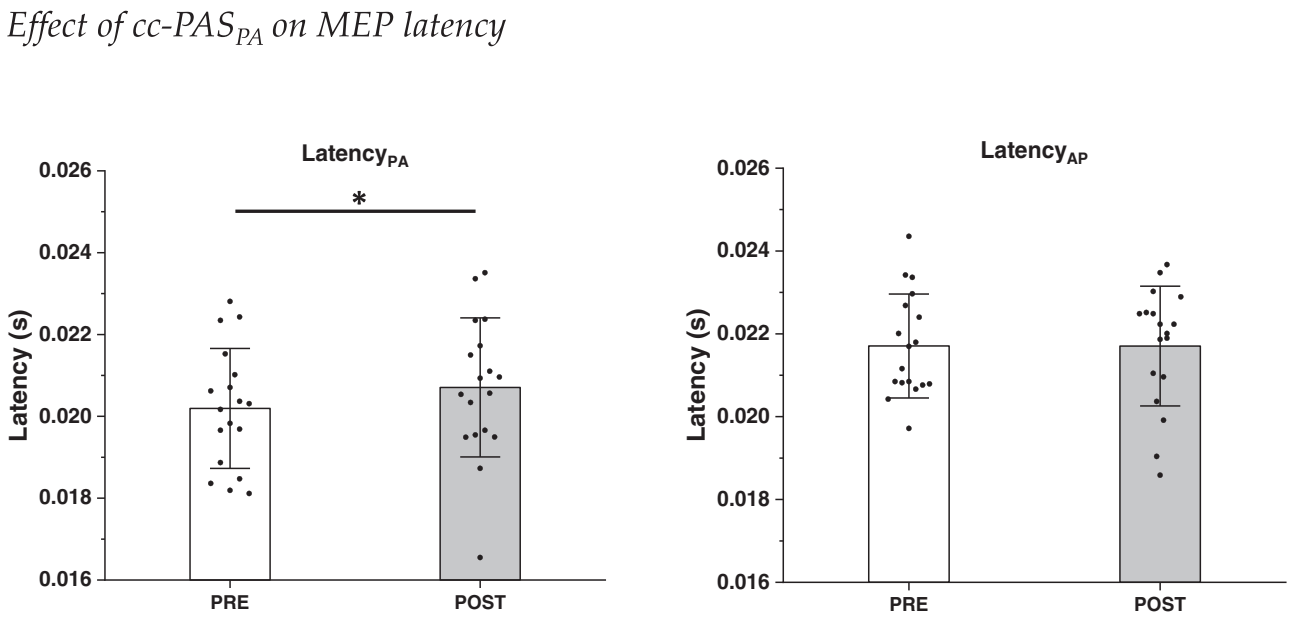

Figure 6. Main effect results for motor-evoked potential latencies in *Session 1*
The left panel highlights the significant main effect of time on latency$_{PA}$. The right panel shows no significant main effect of time on latency$_{AP}$. In experiment 1, the PMv–M1 cc-PAS was applied with a postero-anterior (PA) orientation. Error bars represent the SD; *$P < 0.05$.

Although the origin of the various descending volleys that compose the M1 output remains largely unclear, it is assumed that different neuronal populations might be targeted preferentially by TMS with different coil orientations (Aberra et al., 2020; Fong et al., 2021; Hamada et al., 2014; Ni et al., 2011). Our results confirm this hypothesis, showing that by varying the coil orientation of a PMv–M1 cc-PAS protocol, we preferentially conditioned M1 neural populations activated or not during the execution of precision grip.

After the cc-PAS_{PA}, we replicated previous results showing that PMv–M1 cc-PAS_{PA} led to an increase of CSE at rest (Casarotto et al., 2022; Turrini, Fiori et al., 2023). However, the PMv–M1 cc-PAS_{PA} did not produce any significant modulation of the corticospinal motor drive during muscle activation (for both the precision and power grip), as indicated by the absence of modulation of both MEP amplitude and cSP duration. Also, in the cc-PAS_{AP} session we replicated our previous results at rest, showing a significant reduction of CSE after the PMv–M1 cc-PAS_{AP} (Casarotto et al., 2022). More importantly, the specific activity of the neural populations involved in precision or power grip were also modulated differentially by the PMv–M1 cc-PAS_{AP} protocol. Indeed, the populations recruited by PA single pulse stimulation showed no significant modulation but only a generalized trend to a higher excitability during both precision and power grip. Instead, the neural populations recruited by the AP current direction showed a selective increase for precision grip only. Hence, M1 populations, preferentially recruited by the AP stimulation and influenced by PMv input (Casarotto et al., 2022), seem to be more involved in the execution of precision grip than power grip (Fig. 8).

The AP stimulation is believed to induce currents flowing from layer VI to layer I that are likely to generate significant depolarizations in dendrites, hence in more superficial layers (Sommer et al., 2013). Given that most synaptic input occurs on dendrites, signalling to the synapse that the neuron has generated an output is believed to be mediated by back-propagating action potentials (Magee & Johnston, 1997). These provide the depolarization that allows relief of the Mg^{2+} block of NMDA receptors (Kampa et al., 2004; Vargas-Caballero & Robinson, 2003), which is essential for induction of STDP (Bi & Poo, 1998; Debanne et al., 1998; Kampa et al., 2007). Here, the depolarization of the dendritic arbor of pyramidal neurons would improve their ability to integrate various input signals. The combined effect of AP M1 stimulation paired with the PMv stimulation, as in cc-PAS_{AP}, would induce a long-lasting state of dendrite depolarization, specifically strengthening the integration of PMv inputs. In this regard, effective input integration in the superficial layers of M1 might be mediated by the I_2-wave intracortical circuits that interact with projections coming from the PMv (Cattaneo et al., 2005; Koch, Versace et al., 2010; Shimazu et al., 2004). As previously demonstrated, the PMv–M1 cc-PAS specifically modifies the activity of I_2-wave circuits at rest (Casarotto et al., 2022).

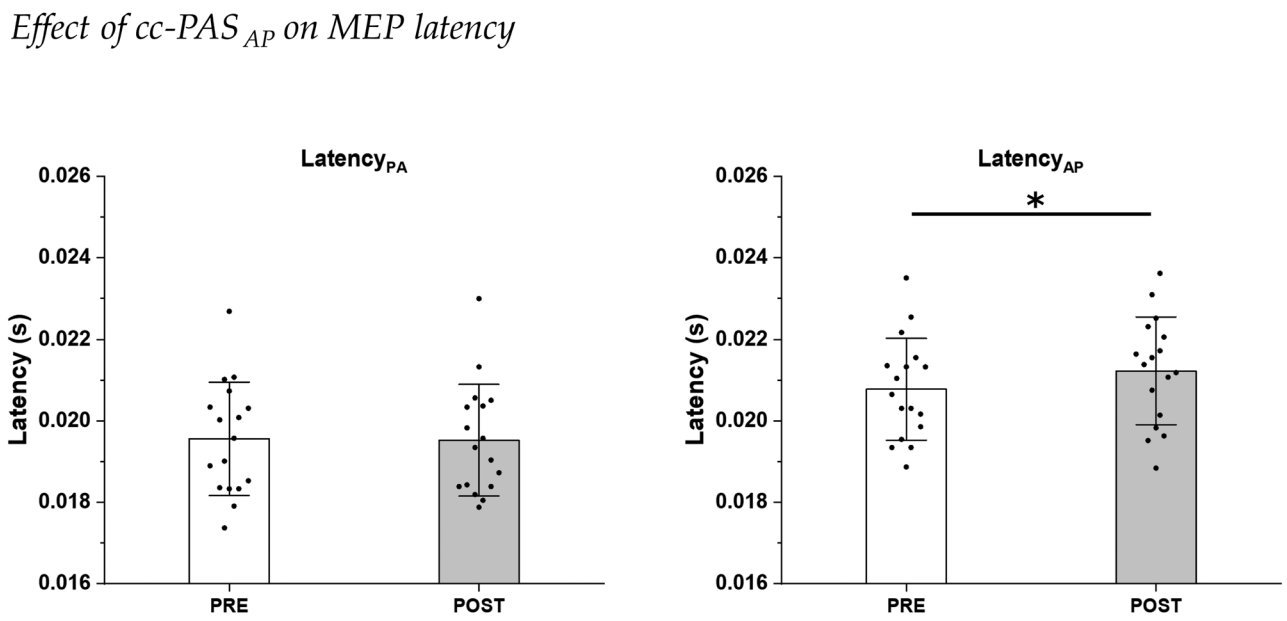

Figure 7. Main effect results for motor-evoked potential latencies in *Session 2*
The left panel shows no significant main effect of time on $latency_{PA}$. The right panel highlights the significant main effect of time on $latency_{AP}$. In *session 2*, the PMv–M1 cc-PAS was applied with an antero-posterior (AP) orientation. Error bars represent the SD; $^*P < 0.05$.

From a functional perspective, the PMv is more involved in the control of precision grip, as opposed to power grip (Davare et al., 2008; Ehrsson et al., 2000). Integration of a larger variety of signals is also the hallmark of refined motor control, and the precision grip is configured as a finer action than the power grip (Fig. 8; Iturrate et al., 2018; Witney et al., 2004). In line with this idea, previous work has highlighted a stronger influence of thalamocortical connections on M1 superficial layers during the precision grip than the power grip (Davis et al., 2022), further supporting the need for stronger sensorimotor integration. In our case, previous direct and indirect evidence has shown that the I_2-wave is influenced by the activity of premotor areas (Casarotto et al., 2022; Cerri et al., 2003; Koch et al., 2010; Shimazu et al., 2004). It is then reasonable to propose that the effects obtained here, after the cc-PAS_{AP}, are mediated by the late I-wave circuits and that these circuits represent the site of interaction of PMv with M1 specifically for the control of precision grasping actions (Fig. 8). Conversely, PA stimulation, preferentially targeting the M1 deep layers, might somewhat cloud the contribution of the superficial neuronal populations, providing a more general readout of M1 activity. The contribution of M1 superficial layers could be hidden by the lower threshold for the recruitment of populations targeting the M1 pyramidal neurons closer to the soma with PA stimulations.

Effects of PMv-to-M1 cc-PAS on MEP latency

Further support in favour of a partial separation of neuronal populations recruited with the AP *vs.* PA current direction can be derived from the results on MEP latencies. The application of the cc-PAS protocol induces specific latency modulation of MEPs elicited with the same coil orientation used for the plasticity-inducing protocol. More specifically, in the *Session 1*, when the cc-PAS was applied with a PA coil orientation, the MEP_{PA} showed a longer latency in the post-PAS acquisition with respect to the pre-PAS acquisition. The MEP_{AP} latency was not affected. In a similar way, after the cc-PAS_{AP} (*Session 2*), only the MEPs elicited with an AP coil orientation presented an altered latency.

The PA and AP stimulations engaged different trans-synaptic sets of inputs (Ni et al., 2011), probably involving more deep and superficial neural populations, respectively (Aberra et al., 2020; Koch et al., 2013; Sommer et al., 2013). More precisely, the cortical motoneuronal cells, connected monosynaptically with α-motor neurons, were found predominantly in the anterior bank of the central sulcus (Rathelot & Strick, 2009), which appears to be the portion most activated by the induction of PA current flow. This would justify MEPs with shorter latencies in PA stimulation. In contrast, AP current flow would activate the rostral M1 portion, where the

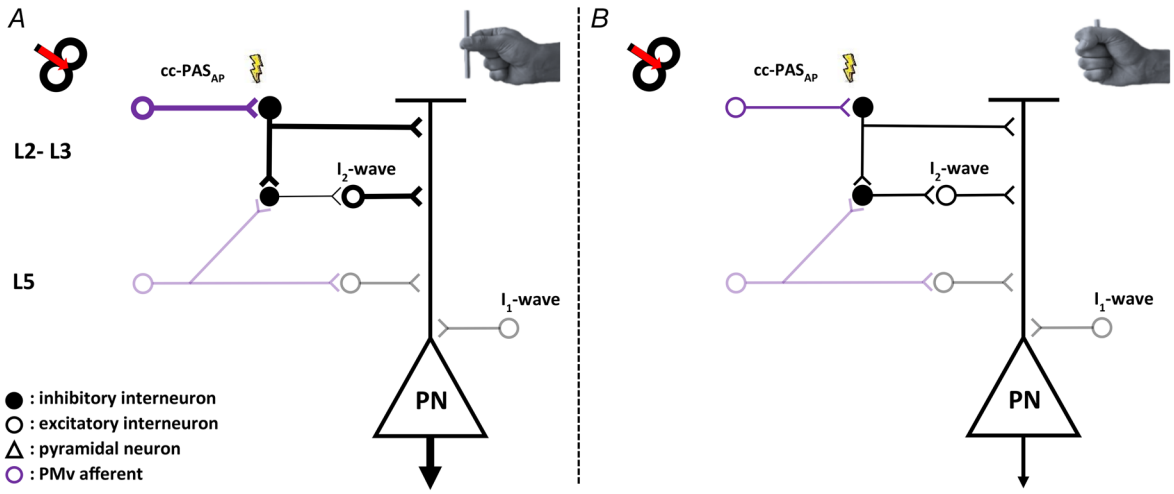

Figure 8. Proposed activity of primary motor cortex superficial layers, involving the I_2-wave circuit, during the precision and power grips after cc-PAS_{AP}
This figure focuses on the preferential contribution of the superficial primary motor cortex (M1) population [layer 2–3 (L2–L3)] to the precision grip (*A*, left) rather than the power grip (*B*, right). After the cc-PAS_{AP}, the superficial M1 neuronal populations (L2–L3) lead to an increase in corticospinal excitability (CSE) only during the precision grip. The precision grip requires finer programming than the power grip, which is likely to be supported by a stronger integration of sensorimotor input. This integration process, after the cc-PAS_{AP}, might be supported by a long-lasting state of dendritic depolarization of the pyramidal neurons and probably occurs in the superficial M1 layers, where dendritic arborizations of layer 5 (L5) pyramidal neurons are located. The effects of PMv–M1 cc-PAS_{AP} on M1 superficial layers are likely to be mediated by the late I-wave circuits, most probably located in these layers. The line thickness indicates increased or decreased motor output. [Colour figure can be viewed at wileyonlinelibrary.com]

premotor pyramidal cells are located, leading to MEPs with longer latencies (Aberra et al., 2020). According to this view, inputs to M1 from the premotor cortex, with conduction latencies matching late descending I-waves, have been identified in monkeys (Maier et al., 2013; Shimazu et al., 2004; Tokuno & Nambu, 2000) and humans (Casarotto et al., 2022; Groppa et al., 2012; Liao et al., 2023), suggesting that they could be recruited by AP stimulation (Di Lazzaro & Rothwell, 2014).

In this study, modulation of MEP latencies congruent with the cc-PAS orientation support the idea that different coil orientations activate different sets of cortical neurons. Moreover, we demonstrate here that it is possible to apply plasticity-inducing protocols separately to different M1 intracortical circuits. The cc-PAS_{PA} might have conditioned the deep M1 populations specifically, whereas the cc-PAS_{AP} might have modulated the activity of superficial M1 neuronal populations.

Limitations and future perspectives

A limit of the present study might be the isometric execution of grasping actions. Future work should investigate the effects of the induction of plasticity on ecological execution of reaching and grasping actions. In addition, an ecological visually guided grasping action would probably be more suitable to disentangle the differential contributions of premotor and parietal areas.

Here, although the FDI muscle is recruited in a similar manner in both the explored actions, it might play a more important role in precision grip than in power grip. For this reason, future work could explore similar mechanisms in different muscles to understand the generalizability of our results. Finally, the contribution of distinct populations in different M1 layers during specific tasks is far from established, and TMS-based methods are certainly not optimal in solving this issue. However, Kurz et al. (2019) demonstrated recently how the temporal combination of single-pulse TMS protocol with elicitation of the H reflex could provide an interesting tool to investigate the contribution of different M1 layers during specific tasks. Future research might use this procedure to provide further insight into the contribution of different M1 layers during the execution of precision and power grip.

Conclusion

These results provide useful insight into the cortical contribution of isolable neuronal populations to different grasping actions. These findings can be used to induce an action-specific PMv–M1 network plasticity by means of the cc-PAS protocol. Although deep M1 neuronal populations appear to be involved unspecifically in the implementation of precision and power grip, more superficial M1 populations have been shown to play a more prominent role in precision grip. Application of a cc-PAS protocol directed preferentially to these more superficial populations could be particularly suitable for designing specific interventions to improve precision grip performance in various clinical populations. Enhanced synaptic input from PMv, a crucial hub in the grasping parietofrontal network, combined with targeted dendrite depolarization in M1 (Koch, Versace et al., 2010; Sommer et al., 2013), might thus represent an important physiological basis for the rehabilitation of fine and independent control of the fingers.

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Additional information

Data availability statement

Data from this study will be made available to qualified investigators upon reasonable request to the corresponding author.

Competing interests

None declared.

Author contributions

A.C.: Conceptualization; Methodology; Software; Data curation; Formal analysis; Investigation; Writing – original draft, Writing – review & editing; Visualization. E.D.: Conceptualization; Methodology; Software; Data curation; Formal analysis; Investigation; Writing – review & editing; Visualization. L.F.: Writing – review & editing; Funding acquisition; Resources; Supervision. G.K.: Conceptualization; Methodology; Writing – review & editing; Supervision; Project administration. A.D.: Conceptualization; Methodology; Writing – review & editing; Funding acquisition; Resources; Supervision; Project administration. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated

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Keywords

cortico-cortical paired associative stimulation, Hebbian-like plasticity, power grip, precision grip, primary motor cortex, ventral premotor cortex

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Statistical Summary Document
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