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Modulatory Effects of the Ipsi and Contralateral Ventral Premotor Cortex (PMv) on the Primary Motor Cortex (M1) Outputs to Intrinsic Hand and Forearm Muscles in Cebus apella

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Abstract
The ventral premotor cortex (PMv) is a key node in the neural network involved in grasping. One way PMv can carry out this function is by modulating the outputs of the primary motor cortex (M1) to intrinsic hand and forearm muscles. As many PMv neurons discharge when grasping with either arm, both PMv within the same hemisphere (ipsilateral; iPMv) and in the opposite hemisphere (contralateral; cPMv) could modulate M1 outputs. Our objective was to compare modulatory effects of iPMv and cPMv on M1 outputs to intrinsic hand and forearm muscles. We used paired-pulse protocols with intracortical microstimulations in capuchin monkeys. A conditioning stimulus was applied in either iPMv or cPMv simultaneously or prior to a test stimulus in M1 and the effects quantified in electromyographic signals. Modulatory effects from iPMv were predominantly facilitatory, and facilitation was much more common and powerful on intrinsic hand than forearm muscles. In contrast, while the conditioning of cPMv could elicit facilitatory effects, in particular to intrinsic hand muscles, it was much more likely to inhibit M1 outputs. These data show that iPMv and cPMv have very different modulatory effects on the outputs of M1 to intrinsic hand and forearm muscles.

Key words: cortical network, interaction, interhemispheric, motor-evoked potential, stimulation

Introduction
The ventral premotor cortex (PMv) is an area of the frontal lobe with a large representation from which hand movements can be evoked (Gentilucci et al. 1988; Preuss et al. 1996; Dancause et al. 2006). In visually guided grasping movements, neuronal activity in PMv is initiated in the early, preparatory stages (Godschalk et al. 1985; Kurata and Wise 1988) and neurons discharge selectively for specific types of hand configurations.
murata et al. 1997
Tanji et al. 2011
Koch et al. 2007
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Deffeyes et al. 2015
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modulating the activity of neurons in the primary motor cortex (M1) (tokuno and nambu 2000; Kraskov et al. 2011) or the outputs of M1. Several studies using double or paired-pulse stimulation protocols have investigated the modulatory effects of the PMv ipsilateral to M1 on the outputs of M1 to intrinsic hand muscles of the contralateral arm. They showed that conditioning stimulations in the ipsilateral PMv (iPMv) can have both facilitatory and inhibitory effects, depending on the phase of movements or the configuration of the hand required for the task. For example, in humans at rest, PMv has inhibitory effects on M1 outputs to intrinsic hand muscles (Davare et al. 2008). During power grip, inhibitory effects are decreased and during precision grip, PMv becomes facilitatory. Furthermore, during the preparatory period prior to grasp, facilitatory effects of PMv are specific to the muscle that will be used (Davare et al. 2009).

However, hand configuration to grasp objects requires the coordinated activation of intrinsic hand as well as forearm muscles (Brochier et al. 2004) and the pattern of activity in these two muscles groups varies in function of the type of grasping movement being performed (Long et al. 1970). Accordingly, PMv may have different patterns of modulatory effects on intrinsic hand and forearm muscles in order to configure the hand into a desired shape. Supporting this hypothesis, recordings of cervical motoneurons from anesthetized macaque monkeys have revealed that facilitatory effects from PMv conditioning are more frequent in intrinsic hand than forearm muscles (Shimazu et al. 2004). A more systematic comparison of the impact of PMv on outputs to intrinsic hand and forearm muscles would improve our understanding of its range of modulatory effects.

In addition to its involvement in the control of the contralateral hand, PMv is also active during ipsilateral movements. For example, many neurons in PMv discharge when monkeys perform tasks with either hand (Rizzolatti et al. 1988; Tanji et al. 1988). In humans, sequential finger movements are associated with increased hemodynamic activity in the hemisphere ipsilateral to the moving hand, most likely centered in PMv (Hanakawa et al. 2005). The extensive network of interhemispheric connections between PMv and M1 (Boussaoud et al. 2005; Dancauce et al. 2007) could certainly allow the contralateral PMv (cPMv) to modulate M1 outputs. To date, transcranial magnetic stimulation (TMS) studies that have investigated interhemispheric interactions from contralateral premotor areas on M1 outputs have largely focused on the contralateral dorsal premotor cortex (PMd) (Mochizuki et al. 2004; Baumer et al. 2006; Koch et al. 2007; Liuzzi et al. 2010, 2011). To our knowledge, no study has yet investigated the modulatory effects of cPMv on M1. Given the pattern of neural activity in PMv during movements of the ipsilateral hand and the numerous interhemispheric connections of cPMv with M1, cPMv is likely to also have substantial modulatory effects on M1 outputs. A study of cPMv’s modulatory effects would thus provide much needed insight into interhemispheric interactions from this premotor area on M1.

To address some of these issues, we conducted paired-pulse stimulation protocols using intracortical microstimulation techniques (ICMS) in sedated cebus monkeys. We compared the modulatory effects of a conditioning stimulus (Cstim) applied either to iPMv or cPMv at the same time as or prior to a test stimulus (Tstim) in M1. Modulatory effects of the Cstim were quantified in electromyographic (EMG) activity recorded in intrinsic hand and forearm muscles.

Materials and Methods

Subjects
Four adult female capuchin monkeys (Cebus apella) were used in this study (CB1: 1.9 kg, CB2: 1.25 kg, CB3: 1.4 kg, CB4: 1.2 kg). Monkeys were group housed and supplied with food and water ad libitum. The experimental protocol followed the guidelines of Canadian Council on Animal Care and was approved by the Comité de Déontologie de l’Expérimentation sur les Animaux (CDEA) of the Université de Montréal.

Surgical Procedures
Data were collected in a terminal procedure. Anesthesia was induced with an intramuscular injection of 15 mg/kg of ketamine hydrochloride (Ketaset; Pfizer, Inc, New York, NY, USA). The animal was transitioned to ~2% isoflurane (Furane; Baxter, Deerfield, IL, USA) in 100% oxygen and placed in ventral decubitus in a stereotaxic apparatus. To help prevent inflammation and swelling of the brain, the animal received an intramuscular injection of Dexamethasone 2 (Vetoquinol; 0.5 mg/kg) and intravenous injection of Mannitol 20% (1500 mg/kg) at the beginning of the surgery. Proper hydration was maintained through a continuous intravenous infusion of lactated ringer’s solution (10 ml/kg/h). The animal’s body temperature was maintained near 36.5°C throughout the surgery using a homeothermic blanket (Harvard Apparatus, Holliston, MA). Blood oxygen saturation and heart rate were continuously monitored.

Figure 1A illustrates our experimental setup. Insulated, multistranded microwires (Cooner Wire, Chatsworth, CA, USA) were implanted intramuscularly for the recording of EMG signals. For CB1, six muscles in each arm were implanted (flexor pollicis brevis (FPB), extensor carpi ulnaris (ECU), extensor digitorum communis (EDC), palmaris longus (PL), biceps brachii (BB), and triceps brachii (TB)). For the other 3 monkeys, the same muscles were implanted as well as the abductor pollicis brevis (APB) and the flexor digitorum superficialis (FDS). Accurate placement of the EMG wires was confirmed by electrical stimulation of the muscle using the implanted wires and observation of the evoked movements. Once the EMG electrodes were implanted, craniotomies and durectomies were performed to expose the M1 in one hemisphere as well as both the ipsilateral and contralateral ventral premotor areas (iPMv and cPMv, respectively).

Paired-Pulse Stimulation and EMG Recording
At the end of the surgical procedures, gas anesthesia was turned off and the animal was kept deeply sedated with intravenous injections of ketamine (~10 mg/kg/10 min) and Diazepam (Valium; 0.01 mg/kg/h) for electrophysiological data collection. In order to facilitate the search for suitable stimulation sites to use in the paired-pulse protocols, we first located the hand representation in M1, iPMv, and cPMv using standard ICMS trains (Mansoori et al. 2014; Deffeyes et al. 2015; Dea et al. 2016; Touvykine et al. 2016). All cortical sites retained for the paired-pulse protocols evoked clear digit or wrist movements in the contralateral arm with ICMS trains.

Two glass-coated tungsten microelectrodes (~1 MΩ impedance; FHC Bowdoin, ME, USA) were used for the paired-pulse stimulations. They were lowered perpendicular to the cortex with a micromanipulator to depths of ~1800 μm (layer V) below
the surface. The electrode for $T_{\text{stim}}$ was positioned in M1 of the right hemisphere with a micromanipulator. The electrode for $C_{\text{stim}}$ was placed in either the iPMv (right hemisphere) or cPMv (left hemisphere) with a second manipulator (see Fig. 1A). Both the $C_{\text{stim}}$ and $T_{\text{stim}}$ were cathodal single square pulses of 0.2 ms duration. The stimulation intensities for the $C_{\text{stim}}$ and $T_{\text{stim}}$ were determined independently online based on evoked EMG activity in muscles of the arm contralateral to the stimulation. If EMG activity was present in more than one muscle, the muscle with the lowest threshold was used to determine the
desired current intensity. The intensity for the Cstim was set at 75% of the EMG threshold (range = 95–225 µA, mean = 197 µA). If no EMG response could be observed with up to 300 µA, the intensity of the Cstim was arbitrarily set to 225 µA. The current intensity used for the Tstim in M1 was typically set to 125% of threshold (range = 40–300 µA, mean = 170 µA). In some cases, if the evoked activity was too small or too big with this value, the intensity was adjusted to a level producing clear but submaximal response.

Once the locations of the 2 electrodes and the proper stimulation intensities were selected, a paired-pulse stimulation protocol was initiated. In a protocol, stimulations could be delivered through the conditioning electrode only (C-only), the test electrode only (T-only), or through both with 6 different interstimulus intervals (ISIs). When the Cstim was in iPMv, the paired stimulations (C + T) could be delivered simultaneously (ISI0) or with Cstim preceding the Tstim by 1 ms (ISI1), 2 ms (ISI2), 4 ms (ISI4), 6 ms (ISI6), or 10 ms (ISI10). When the Cstim was in cPMv, we presented both stimulations simultaneously (ISI0) or with ISIs of 2.5 ms (ISI2.5), 5 ms (ISI5), 10 ms (ISI10), 15 ms (ISI15), or 20 ms (ISI20). A total of 150 trials per condition were collected (8 conditions per protocol; total stimulations = 1200).

For monkeys CB1 and CB2, data for each condition were recorded in three blocks of 50 trials delivered at 3 Hz and the stimulation condition of subsequent blocks was randomized (Deffeyes et al. 2015). For monkeys CB3 and CB4, the condition of each subsequent trial was randomly selected until a total of 150 trials delivered at 3 Hz for each condition were collected. We confirmed that the responses were stable across the recording. For all recorded protocols, we performed a two-sample t-test and verified that the response evoked with the T-only from the first 75 trials was not different to the response from the last 75 trials (t = −0.68; p = 0.50).

After completion of data collection for a protocol, the two electrodes were moved to different cortical locations and another protocol was initiated. In the 4 monkeys, we collected a total of 22 protocols, 11 with the Cstim electrode in iPMv and 11 with the cPMv electrode in cPMv. As EMG signals were simultaneously recorded from 6 muscles protocols in CB1 or 8 muscles 16 protocols in the other 3 monkeys, we thus collected 164 EMG signals under 8 conditions yielding 656 recordings for iPMv conditioning and 656 for cPMv conditioning.

Both the paired-pulse stimulations and EMG data recording were controlled with an RZ5 real-time processor (Tucker Davis Technologies (TDT), Alachua, FL, USA) running custom software designed for this procedure. Part of the software controlled the stimulations that were produced by an IZ2 stimulator (Tucker Davis Technologies (TDT), Alachua, FL, USA). Another part controlled the data acquisition. Each EMG channel was recorded at 4.9 kHz. Raw EMG data were stored for offline processing.

**EMG Data Analysis**

Offline data analyses were done using custom written Matlab (Version R2014a; Nantick, MA, USA) code. The continuously recorded raw EMG data were separated into individual trials and aligned to the end of the Cstim for the C-only condition, and to the end of the Tstim for the T-only and for the 6 paired-pulse conditions. The EMG signal in a window of 30 ms after the end of the stimulation was analyzed. The raw EMG was full-wave rectified, and smoothed using a 5-point moving average (window = 1.02 ms). Note that no additional filters were used to remove the stimulus artifacts. Traces presented show the extent of the artifact, when present, along with the EMG responses.

For each of the 164 EMG signals, we first established whether the Tstim evoked a detectable motor-evoked potential (MEP) (T-only condition) and that this response was large enough for us to detect either increases or decreases of activity by the Cstim. To do this, the T-only trials were averaged and the MEP response was compared to the baseline activity in the 30 ms prior to the first stimulus. If the average MEP peak amplitude was greater than 3 standard deviations (SD) above the average baseline, it was considered significant and kept for subsequent analyses.

In this study, we focused our analyses on the modulation of peak amplitude by the Cstim. For each significant average MEP evoked with the Tstim only, the first step was to generate a population of predicted responses based on the summation of responses in C-only and T-only trials (Fig. 1A,E). We performed all possible combinations of single C-only traces (n = 150) with single T-only traces (n = 150) and linearly summed them to produce predicted traces (n = 22,500). Because the target current intensity for the Cstim was subthreshold, the major contribution of these combined responses are from the Tstim. However, we preferred the predicted MEPs to account for any potential small EMG response from the Cstim that may have occurred over many trials (Deffeyes et al. 2015). Out of the population of predicted traces, we randomly drew samples of 150 trials and averaged them to produce average predicted MEPs (Fig. 1D). For each average predicted MEP, we calculated the peak amplitude according to the following formula:

\[
\text{Peak amplitude} = \text{peak maximum} - \text{peak minimum}
\]

where the MEP peak maximum is defined as the maximum voltage value within a 30 ms window after the end of the stimuli and the peak minimum is the voltage value at the peak onset time. Our algorithm searched for the peak onset from a point clearly within the peak (10% of the peak maximum voltage) and marching back toward the beginning of the trial (time = 0). The voltage value of each data point was compared to the one of the next point on that backward march. The first point with a voltage value of less than 5% higher than the following point was considered as not being part of the response and thus the previous point in the backward march was defined as the peak onset time (Fig. 1D). We chose this approach, instead of simply using prestimuli baseline for example, because we found it yielded more accurate results. This was especially obvious when the signal was small in comparison to baseline, something that often occurred when the conditioning stimulus had inhibitory effects (see “Results” section).

This process was repeated 10,000 times to generate a probability distribution of predicted peak amplitudes (Fig. 1E) (Stanford et al. 2005). This probability distribution describes the range of responses that could be obtained if there were no interactions between neurons stimulated by the Cstim and Tstim electrodes. Then, responses of all trials with the paired-pulse (C + T) with each ISI were averaged (n = 150) and the MEP peak amplitude was obtained similarly as described above. The responses obtained when conditioning iPMv or cPMv with the different ISIs were compared to the probability distribution to evaluate the direction (facilitation, inhibition, or no modulation) and the normalized strength of modulatory effects from PMv on M1 output by calculating the Z-score of the MEP peak amplitude (Fig. 2). The modulation of M1 output by PMv conditioning was deemed significant when the Z-score of a C + T
MEP peak amplitude differed by more than 1.96 SD from the mean of the distribution of predicted peak amplitudes \((p \leq 0.05)\). Consequently, an MEP peak amplitude \(Z\)-score value \(\leq -1.96\) was considered a significant inhibition while a \(Z\)-score value \(\geq 1.96\) was considered a significant facilitation.

Although we collected a limited number of cortical sites per area in each animal \((n = 2-4)\), we verified that the general modulatory effects of iPMv and cPMv conditioning were comparable across monkeys. An ANOVA comparing the peak amplitude of the MEPs across monkeys showed no significant difference for either iPMv \((F = 2.4; \ p = 0.83)\) or cPMv \((F = 1.1; \ p = 0.36)\) conditioning. It is also worth noting that because stimulations are applied at the cortical level and effects are recorded in the EMG signals, these techniques do not provide clear information about the locus of interactions, which may occur not only at the cortical level but also at other places along the neural axis.

Results

We conducted a total of 22 paired-pulse protocols in 4 cebus monkeys. Figure 3 shows the cortical location of the Cstim and Tstim electrodes for these protocols in relation to cortical
vasculature and sulci as well as movements evoked with ICMS trains. Mapping was more extensive in M1 to provide some information about the extent of the hand representation. Additional mapping was done in the opposite hemisphere to locate the cPMv hand representation. The iPMv was then easily located by stimulating cortical sites in the homotopic area in the ipsilateral hemisphere. For both the Cstim and Tstim electrodes, all cortical sites retained for the paired-pulse protocols evoked clear digit or wrist movements in the contralateral arm with ICMS trains. As such, our study focuses on interactions of outputs from cortical areas involved in the generation of distal forelimb movements.

For each of the 22 protocols, the T-only condition evoked a significant MEP (> 3 SD above baseline; see “Methods” section)
in at least one and up to seven muscles of the contralateral arm (total = 87 MEPs). These MEPs were more common in the FPB (n = 22), ECU (n = 17), APB (n = 16), and EDC (n = 14). They were less common in FDS (n = 9) and PL (n = 8). Only 1 Tstim site in M1 induced a clear MEP in BB and none produced MEPs in TB. This is not surprising as we specifically placed our Cstim and Tstim electrodes at cortical sites that evoked digit or wrist movements with ICMS trains. The overall mean onset latency for all muscles was 14.87 ± 2.5 ms (mean ± SD). Because only one MEP was found in the BB we excluded it from further analyses. Comparing latencies of the MEPs evoked with T-only trials, a one-way ANOVA confirmed that there was a main effect of muscle (F = 8.93, p < 0.01). Post hoc pairwise comparisons using Bonferroni method to correct for multiple comparisons confirmed that the MEPs in the two intrinsic hand muscles (APB and FPB) had similar latencies (p > 0.05; combined mean = 16.6 ± 2.2 ms), which were significantly longer (p < 0.001) than those of MEPs in forearm muscles (combined mean = 13.5 ± 1.7 ms). There was no difference in MEP latencies between forearm muscles (p > 0.05).

We analyzed the effects of iPMv and cPMv conditioning on the MEPs evoked in intrinsic hand and forearm muscles. Figure 4 shows different examples of modulations of the MEP with the various ISIs used in our protocols for both iPMv (Fig. 4A–C) and cPMv (Fig. 4D–F) conditioning. For some cortical sites, when the conditioning stimulation had an effect, the peak amplitude of the MEPs recorded with the C+T trials was greater than the mean predicted response regardless of the ISI (Fig. 4A, D). For other cortical sites, the peak amplitude of the MEPs recorded with the C+T trials was smaller than the predicted...
Finally, there were also cases in which the conditioning of iPMv or cPMv could have an inhibitory effect with some ISIs and a facilitatory effect with other ISIs (Fig. 4B, E).

All individual MEPs collected in our experiments are presented as an intensity plot in Figure 5. In general, the T-only trials produced a clear response while the C-only did not evoke any MEP. The plot shows the MEPs with the different ISIs normalized to the peak value of the MEPs obtained with the T-only condition. As indicated by the frequent dark red areas, the conditioning in iPMv (Fig. 5A) led to strong facilitation of the MEPs and these occurred much more often in intrinsic hand (top plot) than in forearm muscles (bottom plot). Conditioning of cPMv (Fig. 5B), as indicated by the common blue areas, led more often to inhibition of MEPs in both intrinsic hand and forearm muscles.

Effects of iPMv Conditioning on MEPs in Intrinsic Hand and Forearm Muscles

For protocols in which we applied the Cstim in iPMv, the T-only condition induced a total of 19 MEPs in intrinsic hand muscles (APB = 8; FPB = 11) and 23 MEPs in forearm muscles (ECU = 9; EDC = 8; FDS = 3; PL = 3). For intrinsic hand muscles, when...
conditioning of iPMv modulated the outputs of M1, most often it was facilitatory (Fig. 6A; white bars). Across studied ISIs, of the 74 significant modulation of MEPs we found, 62 were facilitatory (83.8%) and they were most common when the Cstim preceded the Tstim by 1 ms (ISI1 \( n = 13 \)), 2 ms, or 4 ms (ISI2 and ISI4 \( n = 12 \)). Facilitatory effects were least common when the Cstim and Tstim were delivered simultaneously (\( n = 7 \)). We also studied the magnitude of the modulation of M1 outputs produced by iPMv conditioning using the relative measure of the intensity of modulatory effect (Z-score) (Fig. 6B). Note that in order to give a more faithful representation of the intensity of the modulatory effect of the conditioning pulse, we used all intrinsic hand muscle MEPs for this analysis and not only the MEPs significantly modulated by the conditioning stimulus with the different ISIs (Fig. 6A). This analysis shows that facilitation tended to be most powerful with ISI10. Strong facilitations were also evoked with ISI2 and ISI1. Overall, this pattern of facilitation across ISIs is quite similar to what has previously been described in sedated macaque monkeys (Cerri et al. 2003).

We also found incidences of significant inhibitory effects with some tested ISIs (Fig. 6A; black bars). These inhibitory effects were much less common than facilitatory effects and represented only 16.2% of the significant modulations (\( n = 12 \)). They were more likely to occur when the Cstim preceded the Tstim by longer delays (ISI6 \( n = 5 \) and ISI10 \( n = 4 \)). When the Cstim in iPMv preceded the Tstim in M1 by 2 or 4 ms, we found no significant inhibitory effects. The magnitude of inhibitory
effects from iPMv conditioning on intrinsic hand muscles (Fig. 6B; black bars) was also much weaker in comparison to facilitatory effects. Inhibitory effects tended to be slightly more powerful with longer ISIs. Together, these data support that for intrinsic hand muscles involved in thumb movements, iPMv is much more likely to have facilitatory than inhibitory effects on M1 outputs and the facilitatory effects are much more powerful.

Modulatory effects of iPMv conditioning on forearm muscles were quite different. Across all ISIs, only 23 cases of significant modulations were facilitatory (33.8%) and their incidence increased with longer ISIs (Fig. 6C). The magnitude of the facilitation induced by iPMv conditioning was also much smaller for forearm muscles (Fig. 6D) and tended to increase with longer ISIs. Significant inhibitory effects were twice as common as facilitatory effects (n = 45; 66.2%). Most cases of inhibitory effects were found with ISI6 (n = 10) but many were found with all tested ISIs. The magnitude of the inhibitory effects on forearm muscles induced by iPMv conditioning did not vary much across ISIs but it was slightly more powerful when the Cstim preceded the Tstim by 6 ms (ISI6). In contrast to intrinsic hand muscles, inhibitory and facilitatory effects in forearm muscles were of comparable magnitude. Overall these results support that iPMv is more likely to have inhibitory than facilitatory effects on forearm muscles and that the magnitude of the facilitatory effect on forearm muscles is weaker than on intrinsic hand muscles.

Effects of cPMv Conditioning on MEPs of Intrinsic Hand and Forearm Muscles

For protocols where cPMv was the source of conditioning, we found a total of 19 significant MEPs in intrinsic hand muscles (APB = 8; FDP = 11) and 25 MEPs in forearm muscles (ECU = 8; EDC = 6; FDS = 6; PL = 5) with the T-only trials. For MEPs in intrinsic hand muscles, out of the significant modulations, cPMv conditioning facilitated M1 outputs in only 20 cases (26.7%), more of them occurring when the Cstim preceded the Tstim by 10 ms (ISI10 n = 6) or 5 ms (ISI5 n = 5) (Fig. 6E; light gray bars). The magnitude of the facilitatory effect was also greater with these two ISIs (Fig. 6F). The number of inhibitory effects induced by cPMv conditioning was much greater than the number of facilitatory effects (n = 55; 73.3%). Inhibitory effects were more common across most ISIs, in particular with ISI15 (n = 13) and ISI20 (n = 13) and inhibition was also most powerful with these two ISIs (Fig. 6F; dark gray bars). Although inhibition was predominant, it is worth noting that several facilitatory effects were also found with ISI5 and ISI10. In fact, in intrinsic hand muscles, facilitation of MEPs was more common than inhibition with ISI5 (facilitation n = 5 and inhibition n = 4).

The pattern of modulatory effects caused by cPMv conditioning in forearm muscles followed similar trends, although it tended to be even more inhibitory. Out of the significant modulation of MEPs, the proportion of facilitatory effects in forearm muscles was smaller than in intrinsic hand muscles (n = 9; 9.6%) (Fig. 6C). The highest number of facilitatory effects was evoked with ISI5 (n = 4) and the magnitude of facilitation was also the greatest at this ISI (Fig. 6H). No case of significant facilitation was found at ISI15 and ISI20. In sharp contrast, we found 85 cases (90.4%) in which conditioning of cPMv caused an inhibition of MEPs in forearm muscles, and inhibitory effects were much more common than facilitatory effects with all tested ISIs. The greatest numbers of inhibitory effects were induced with long delays between the Cstim and the Tstim (ISI15 n = 17 and ISI20 n = 15) or when the two stimuli were applied simultaneously (ISI0 n = 16). The inhibitory effects of cPMv on MEPs in forearm muscles were also generally more powerful than facilitatory effects. The magnitude of inhibitory effects was comparable across ISIs, but inhibition was slightly more powerful with ISI15. Together these results support that cPMv is much more likely to have inhibitory than facilitatory effects on the outputs of M1 and that these inhibitory effects are more powerful. In contrast to iPMv, cPMv has comparable effects on M1 outputs to both intrinsic hand and forearm muscles.

Comparison of the General Modulatory Effects of iPMv and cPMv Conditioning

After combining all ISIs, we compared the incidence of facilitation and inhibition induced by iPMv and cPMv conditioning (Fig. 7A). We used a chi-square test (χ²) followed by a post hoc two-proportion Z-test. For intrinsic hand muscles, the distribution of modulatory effects produced by iPMv conditioning was different from that produced by cPMv (χ² = 49.12; p < 0.001). Conditioning of iPMv induced more facilitatory effects (54.4%) than cPMv (17.5%) (p < 0.001), and cPMv induced more inhibitory effects (48.3%) than iPMv (10.5%) (p < 0.001). Similarly, although less pronounced effects were found for forearm muscles (χ² = 19.52; p < 0.001). The conditioning of iPMv induced more facilitatory effects (17.5%) than cPMv (6.0%) (p = 0.004), and cPMv conditioning induced more inhibitory effects (56.7%) than iPMv (32.6%) (p < 0.001).

We then compared the magnitude of the modulation produced by iPMv and cPMv conditioning (Fig. 7B). A two-way ANOVA was used to compare the facilitatory effects and a second to compare the inhibitory effects using the location of the conditioning stimulus (iPMv or cPMv) and muscle group (intrinsic hand or forearm) as factors. The magnitude of facilitatory effects was strongly influenced by the location of the conditioning stimulus (F = 9.68, p = 0.002). However, arm muscles and hand muscles were not affected equally as indicated by a significant “location of conditioning x muscle group” interaction. Pairwise comparisons with Bonferroni correction revealed that the magnitude of the facilitatory effects induced with iPMv conditioning was significantly greater than with cPMv only for the intrinsic hand muscles (p < 0.001). The magnitude of inhibitory effects was also significantly affected by the location of the conditioning stimulus (F = 38.77, p < 0.01). The inhibitory effects induced by cPMv were greater than those from iPMv for both intrinsic hand and forearm muscles. Thus, iPMv conditioning induced more facilitatory effects than cPMv for both intrinsic hand and forearm muscles, and the magnitude of the facilitatory effects in hand muscles induced by iPMv was greater than cPMv. In contrast, following cPMv conditioning there were more numerous and powerful inhibitory effects in both intrinsic hand and forearm muscles than after iPMv conditioning.

Categories of Modulatory Effects Across ISIs Induced by iPMv and cPMv Conditioning

We analyzed how individual MEPs were modulated across ISIs and if there were differences between iPMv and cPMv conditioning (Fig. 8A). To do so, we pooled together the MEPs from
the intrinsic hand muscles (left bars), the number of facilitatory effects was greater when the conditioning was in iPMv (white; \( n = 62; 54.4\% \)) than in cPMv (light gray; \( n = 20; 17.5\% \)). Conversely, inhibitory effects were more common when the conditioning was delivered in cPMv (dark gray; \( n = 55; 48.3\% \)) than in iPMv (black; \( n = 12; 10.5\% \)). The modulatory effects on MEPs of forearm muscles followed a similar pattern (right bars). Facilitatory effects were more common when the conditioning stimulus was in iPMv (\( n = 23; 16.7\% \)) than in cPMv (\( n = 9; 6.0\% \)). In contrast, inhibitory effects were more common when the conditioning stimulus was in cPMv (\( n = 85; 56.7\% \)) than in iPMv (\( n = 45; 32.6\% \)).

Figure 7. General modulatory effects of iPMv and cPMv conditioning. (A) Incidence of facilitatory and inhibitory effects induced by iPMv and cPMv conditioning on the two muscle groups for all ISIs combined. The incidence of facilitation and inhibition was affected by the cortical location of the conditioning and the muscle group. For the intrinsic hand muscles (left bars), the number of facilitatory effects was greater when the conditioning was in iPMv (white, \( n = 62; 54.4\% \)) than in cPMv (light gray, \( n = 20; 17.5\% \)). Conversely, inhibitory effects were more common when the conditioning was delivered in cPMv (dark gray, \( n = 55; 48.3\% \)) than in iPMv (black, \( n = 12; 10.5\% \)). The modulatory effects on MEPs of forearm muscles followed a similar pattern (right bars). Facilitatory effects were more common when the conditioning stimulus was in iPMv (\( n = 23; 16.7\% \)) than in cPMv (\( n = 9; 6.0\% \)). In contrast, inhibitory effects were more common when the conditioning stimulus was in cPMv (\( n = 85; 56.7\% \)) than in iPMv (\( n = 45; 32.6\% \)). (B) Magnitude of modulatory effects induced by iPMv and cPMv conditioning on the two muscle groups across all ISIs. For the intrinsic hand muscles (left bars), facilitation was much stronger with iPMv conditioning than with cPMv conditioning (mean \( Z \)-scores: iPMv \( = 10.4; \) cPMv \( = 3.0 \)). In contrast, the magnitude of inhibitory effects in intrinsic hand muscles induced by conditioning of cPMv (mean \( Z \)-score \( = −3.8 \)) was greater than iPMv (mean \( Z \)-score \( = −1.9 \)). For forearm muscles, the magnitude of facilitatory effects was comparable when the conditioning stimulus was in iPMv or cPMv (mean \( Z \)-scores: iPMv \( = 2.9; \) cPMv \( = 1.8 \)). For inhibitory effects, conditioning of cPMv induced greater inhibitory effects (mean \( Z \)-score \( = −2.9 \)) than iPMv (mean \( Z \)-score \( = −2.2 \)). Asterisks show significant differences.

We found that the source of the conditioning influenced the proportion of MEPs in each group (\( χ^2 = 18.2; p < 0.003 \)). Post hoc two-proportion \( Z \)-tests revealed that a greater proportion of MEPs modulated by iPMv conditioning were in Group Pure Facilitation (35.7\%) in comparison to MEPs modulated by cPMv conditioning (13.6\%) (\( p = 0.02 \)). In contrast, a greater proportion of MEPs modulated by cPMv conditioning were in Group Pure Inhibition (54.5\%) in comparison to iPMv conditioning (31.0\%) (\( p = 0.03 \)). Similar proportions of MEPs modulated by iPMv and cPMv were in Group Opposite (28.6\% and 29.5\%, respectively) (\( p = 0.90 \)). However, very few of these MEPs were facilitated and inhibited with an equal number of ISIs (16.7\% and 15.4\% for iPMv and cPMv, respectively).

The larger proportion of MEPs conditioned by iPMv (66.6\%) showed a predominance of facilitatory effects across ISIs and a much lower proportion showed a predominance of inhibitory effects (16.7\%). For cPMv conditioning, a larger proportion of MEPs showed a predominance of inhibitory effects across ISIs (76.9\% vs. 7.7\% with a predominance of facilitatory effects). Altogether, these analyses show that pure facilitatory (Group Pure Facilitation) or predominantly facilitatory (Group Opposite) effects on MEPs across ISIs were much more common when the conditioning stimulus was applied in iPMv. In contrast, pure inhibitory (Group Pure Inhibition) or predominantly inhibitory (Group Opposite) effects on MEPs across ISIs were much more common when the conditioning stimulus was applied in cPMv.

Simultaneous Modulation of Recorded Muscles with iPMv and cPMv Conditioning

We also inspected the effects of iPMv and cPMv conditioning on the MEPs across muscles (Fig. 8B). To do so, we pooled the MEPs with all 6 ISIs together and counted occurrences of facilitation and inhibition for each of the 6 muscles. Since \( T_{stim} \) alone did not evoke any MEPs in the TB and only one in BB, these muscles were excluded from analyses. For both iPMv and cPMv protocols, we analyzed effects with each ISI separately (11 protocols × 6 ISIs = 66 total cases for iPMv and for cPMv). In one protocol with a given ISI, the conditioning of PMv could be only facilitatory on the MEPs of up to all 6 muscles (Group Pure Facilitation), could be only inhibitory on the MEPs (Group
Pure Inhibition), or simultaneously facilitate and inhibit different combinations of muscles (Group Mixed) (Deffeyes et al. 2015). Out of the 66 cases with the conditioning stimulation in iPMv, we found 30 cases in Group Pure Facilitation (45.5%), and in 23 of these (34.8%), more than one muscle was simultaneously facilitated. Most often, however, MEPS in only 2 or 3 muscles were simultaneously facilitated. We found considerably fewer cases in Group Pure Inhibition (n = 13; 22.7%), and in 8 of these, more than 1 muscle was simultaneously inhibited (12.1%). Finally, there were few cases in Group Mixed (n = 11; 16.7%).

The profile of activation across muscles was quite different when the conditioning stimulation was in cPMv. There were many fewer cases in Group Pure Facilitation (n = 13; 19.7%) and many more cases in Group Pure Inhibition (n = 38; 57.6%). In 4 of the cases with Pure Facilitation (6.1%) and 29 of the cases with Pure Inhibition (43.9%), the effect was observed in more than one muscle simultaneously. Simultaneous inhibitory effects occurred most often in 4 or 5 muscles. As for iPMv, we found fewer cases in which simultaneous facilitation and inhibition were observed in the different muscles (Mixed; n = 6; 9.0%). The number of effects in each category was significantly different if the conditioning was done in iPMv or cPMv (χ² = 18.2; p < 0.001). Post hoc two-proportion Z-tests revealed that the incidence of cases of Pure Facilitation was greater after iPMv conditioning (p = 0.002) and the proportion of Pure Inhibition was greater after cPMv conditioning (p < 0.001). However, conditioning stimulation in both iPMv and cPMv induced comparable proportions of Mixed effects across muscles. Together, these results show that although both iPMv and cPMv can induce complex patterns of facilitation and inhibition across muscles, iPMv conditioning more frequently induces only facilitation and cPMv conditioning more frequently induces only inhibition across muscles of the hand and forearm.

We then wondered if simultaneous facilitation and inhibition of M1 outputs were specific to functional muscle groups. For example, if iPMv facilitates outputs to forearm flexors, is it simultaneously inhibiting only outputs to forearm extensors or can it have opposite effects on any one muscle from which it simultaneously inhibits? For all the protocols that resulted in Mixed Effects in two or more muscles (Fig. 8B; n = 11 for iPMv and n = 6 for cPMv), we counted the incidence of cases in which conditioning produced significant modulations in opposite directions for all six ISIs (i.e., significant facilitation in one muscle and significant inhibition in another). Figure 9 shows these results with the muscles divided into intrinsic hand (FPB; APB), forearm flexor (PL; FDS), and forearm extensor (EDC; ECU) categories.

When iPMv affected the MEP in a muscle (Fig. 9A), it never simultaneously had opposite effects on the other muscle of the same category. Similarly, when iPMv affected the MEP in a forearm muscle, it rarely had opposite effects on MEPs in other forearm muscles, either flexors or extensors (≤6%). In contrast, when iPMv affected MEPs in intrinsic hand muscles, it could have an opposite effect on MEPs in forearm muscles, and this was more common for forearm flexors (mean = 27%) than
extensors (mean = 17%). Altogether, these data suggest that the simultaneous modulation of iPMv on M1 outputs is always in the same direction for muscles within the same functional group and very often has similar effects on forearm flexors and extensors. However, it can simultaneously have opposite effects on intrinsic hand and forearm muscles. In comparison to iPMv, when cPMv affected the MEP in a muscle there were fewer instances of opposite effects in other muscles (<8% in all cases) (Fig. 9B). Similar to iPMv, opposite effects of cPMv on the MEPs of muscles within the same category were quite uncommon. Opposite effects between intrinsic hand and forearm muscles were also infrequent (flexors, mean = 6%; extensors, mean = 5%). This suggests that cPMv conditioning typically affects M1 outputs to all muscles in the same direction, regardless of their function.

Discussion

Our objective was to study the influence of iPMv and cPMv on M1 outputs to intrinsic hand and forearm muscles in C. apella using paired-pulse protocols with ICMS techniques. We found that iPMv has predominantly facilitatory effects that are powerful. Facilitatory effects to intrinsic hand muscles were, however, much more common and stronger than to forearm muscles. The profile of modulation from cPMv was strikingly different. Conditioning stimulations in cPMv were much more often inhibitory. The inhibitory effects were stronger than facilitatory effects and the differences between intrinsic hand and forearm muscles were smaller than for iPMv. Nevertheless, the effects of both iPMv and cPMv were not homogeneous. Conditioning stimuli in iPMv could also inhibit, and those in cPMv could also facilitate M1 outputs. Our results provide new insights into the complex interactions occurring between PMv of the ipsi and contralateral hemisphere and M1. They show that iPMv and cPMv have very different patterns of modulatory effects on M1 outputs, predominantly facilitating for iPMv and inhibitory for cPMv. The use of ICMS techniques, however, revealed complex neural populations within iPMv and cPMv, which may allow both these cortical areas to have facilitatory or inhibitory effects on M1 outputs that may be used depending on the requirements of the task.

The Effect of iPMv on the Outputs of M1 to Intrinsic Hand and Forearm Muscles

We found that stimulation of iPMv evoked mostly facilitatory effects on M1 outputs to the intrinsic hand muscles. The magnitude of facilitatory effects across the tested ISIs, with the most powerful effects evoked when the Cstim was delivered 10 ms prior to the Tstim, is quite similar to that reported in sedated macaques (Cerri et al. 2003). However, in contrast to our findings, no inhibitory effects were reported in that study. In cebus monkeys, whereas inhibitory effects were much less frequent and less powerful than facilitatory effects, the conditioning of iPMv could also inhibit M1 outputs to intrinsic hand muscles. These inhibitory effects were induced with several ISIs, in particular when the Cstim in iPMv preceded the Tstim in M1 by 6 or 10 ms. These results are more in line with reports in awake macaques performing a reach-to-grasp task (Prabhu et al. 2009). During reach, iPMv tends to facilitate M1 outputs when shorter ISIs are used, i.e., 0–1 ms and to be inhibitory with longer ISIs (5–6 ms). In humans, studies using TMS have also reported that iPMv conditioning can induce both facilitatory and inhibitory effects (Civardi et al. 2001; Munchau et al. 2002; Davare et al. 2008, 2009). It is therefore unlikely that the inhibitory effects from iPMv we found in cebus monkeys are due to interspecies
differences. Rather, the wider range of modulatory effects may be explained by the higher number of cortical sites tested and the number of MEPs analyzed in comparison to previous studies in ketamine-sedated macaques (Cerri et al. 2003).

In contrast to intrinsic hand muscles, conditioning stimulations in iPMv induced many more inhibitory effects and less powerful facilitatory effects on forearm muscles. No studies have yet systematically compared effects of iPMv on MEPs in these different muscles. However, results from intracortical recordings of spinal motoneurons also suggest that iPMv affects intrinsic hand and forearm muscles differently (Shimazu et al. 2004). In these experiments, the conditioning of iPMv often induced a facilitation of the late excitatory postsynaptic potentials evoked by M1 stimulations. The incidence of facilitatory effects was significantly greater in intrinsic hand motoneurons than in forearm flexor or extensor motoneurons.

It is not clear why the modulatory effects of iPMv on intrinsic hand and forearm muscles in cebus monkeys are so distinct. However, considering the magnitude of the discrepancies it is tempting to suggest that iPMv assumes different roles for the production of hand movements, depending on the function of the targeted muscle. Predominant and powerful facilitation of intrinsic hand muscles may allow iPMv to consolidate M1 outputs for the production of grasping forces required to squeeze objects. In contrast, the combination of facilitatory and inhibitory effects on M1 outputs to forearm muscles could be used to refine the coordination of simultaneous contractions of antagonist muscles necessary for the production of complex hand posture (Long et al. 1970; Brochier et al. 2004). One caveat that should be kept in mind is that the two intrinsic hand muscles recorded in this study, like in many others, were from the thumb. It is not yet clear if iPMv has the same pattern of modulatory effects on other intrinsic hand muscles, for example, the dorsal interosseous muscles, which have a very different impact on hand configuration.

The Effects of cPMv on the Outputs of M1 to Intrinsic Hand and Forearm Muscles

To our knowledge, this is the first study to analyze the influence of cPMv on the outputs of M1. Conditioning stimulations in cPMv induced inhibitory effects much more often than facilitatory effects in both intrinsic hand and forearm muscles, and inhibition was most common with longer ISIs (15–20 ms). This finding is in line with several studies demonstrating interhemispheric inhibition between other motor regions of the cortex. In cats, inhibitory responses in pyramidal tract neurons can be elicited from cortical sites spreading over a large territory in the contralateral M1 (Asanuma and Okuda 1962). In contrast, facilitatory effects are only evoked with the stimulation of a focal region homotopic to the recorded neuron. In humans, a number of paired-pulse TMS studies have also showed that M1 can exert robust inhibitory effects on its contralateral counterpart (Ferbert et al. 1992; Gerloff et al. 1998; Di Lazzaro et al. 2008). Although some studies have reported that interhemispheric facilitation can occur between the two M1s, these effects were weaker and only present under specific stimulation conditions (Ugawa et al. 1993; Hanajima et al. 2001).

The predominance of inhibitory effects across the hemispheres has also been suggested in several clinical and lesion studies. For example, small cortical lesions in one hemisphere in mice induce rapid increases of sensory evoked responses in the contralusional hemisphere (Mohajerani et al. 2011). Similarly, in humans, there are many reports of increased cerebral blood flow and hyperexcitability in the contralusional hemisphere after stroke (Liepert et al. 2000; Marshall et al. 2000; Butefisch et al. 2003). Like what has been proposed for M1, inhibitory effects from cPMv may favor unilateral hand movements by restricting the outputs from the other hemisphere (Duque et al. 2005; Grefkes et al. 2008; Reis et al. 2008). This could be of particular importance when skilled, precise, and often unilateral grasping movements are generated. The prevalent inhibitory effects of cPMv for both intrinsic hand and forearm muscles and with almost all ISIs suggest that this may be the primary role of interhemispheric interactions from the cPMv and that it occurs during several stages of the preparation and production of hand movements.

It is however worth noting that we also found many cases in which cPMv facilitated the outputs of M1. This was particularly common with ISIs of 5 and 10 ms. In intrinsic hand muscles, facilitatory effects were even more numerous and more powerful than inhibitory effects with ISIs of 5 ms. In humans, while the contralateral PMd has predominant inhibitory effects on M1 outputs at rest (Mochizuki et al. 2004; Koch et al. 2007), it is mainly facilitatory in the early stage of movement preparation (Iuzzì et al. 2010, 2011). This early facilitation appears to favor the coordination of independent, antiphase movements of the two hands. It is also possible that the facilitatory effects from cPMv are predominant in the early phases of movement preparation, something that should be tested in awake monkeys or humans.

The greater facilitatory effects to intrinsic hand muscles with ISIS and ISI10 highlight another potential role of cPMv more closely related to movement production. Again for PMd, the interhemispheric modulatory effects were also shown to change during the production of movements. For example, whereas the left PMd has inhibitory effects on the right M1 at rest, it becomes facilitatory during voluntary movements of the left hand (Bestmann et al. 2008). Facilitatory effects from premotor areas of the hemisphere ipsilateral to the moving limb may be specifically used in more complex and challenging tasks. In this context, instead of exerting interhemispheric inhibition to prevent undesirable movements, these premotor areas could play a more active role in the production of outputs to the moving hand (Horenstein et al. 2009). Alternatively, facilitatory effects from cPMv may be of particular use to coordinate bilateral contraction of distal muscles.

Effects of iPvM and cPMv Conditioning Across Tested ISIs

For both iPvM and cPMv, we found cases where the conditioning stimulation only facilitated M1 outputs, only inhibited or could both facilitate and inhibit M1 outputs across tested ISIs. These results support that there are small populations of neurons within iPvM and cPMv that systematically either facilitate or inhibit the outputs of M1 to a given muscle, even if more or less time is given for the conditioning stimulus to affect different neural pathways. Perhaps these populations can be used when outputs to a given muscle must be strictly inhibitory or facilitatory, independently of the stage of movement preparation or production. This could be the case when a finite hand position is intended and produced for a specific grasp.

In both iPvM and cPMv, we also found a comparable number of cases that could have both facilitatory and inhibitory effects on the same muscles, depending on the timing of the conditioning stimulus. These changes of effects across ISIs could be due to the pathway taken by the conditioning stimulus to exert
its effect on M1 output. For example, some stimulated neurons in iPmV may have direct facilitatory connections onto M1 pyramidal neurons and, yet, other nearby iPmV neurons excite GABAergic interneurons that then connect onto the same M1 pyramidal neurons (Ghosh and Porter 1988). Such complex patterns of modulation may help with the rapid phasic contractions of muscles when changes of hand configurations is the intended goal, as required by skilful dexterous manipulation of objects.

Effects of iPmV and cPmV Conditioning Across Recorded Muscles

Stimulus-triggered averaging of EMG studies in primates have shown that any given M1 site generally has consistent effects, either only facilitatory or only inhibitory, on the arm and hand muscles in its field (Kasser and Cheney 1985; McKernan et al. 1998). However, simultaneous facilitation and inhibition of different muscles can also occasionally be observed. With paired-pulse stimulations, similarly we found that both iPmV and cPmV most often had consistent effects across the muscle field targeted by the M1 outputs.

In both iPmV and cPmV, we also found cases with mixed effects within the muscle field of the M1 site. A closer look at the muscles in which these opposite effects occurred also suggests a more specific pattern of modulation from iPmV than cPmV. The incidence of simultaneous modulation of MEPs in opposite directions following cPmV conditioning was comparable for the different categories of muscles (intrinsic hand, forearm flexors, or forearm extensors). In contrast, the conditioning of iPmV induced many more opposite effects on M1 outputs to intrinsic hand and forearm muscles. This suggests a potentially different modulatory role of iPmV for these two muscle groups. Perhaps when the final hand configuration is obtained, iPmV favors powerful facilitation of M1 outputs to intrinsic hand muscles to exert the grasping forces while limiting the modulation of M1 outputs to the forearm muscles that only need to maintain the hand’s posture.

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Notes

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