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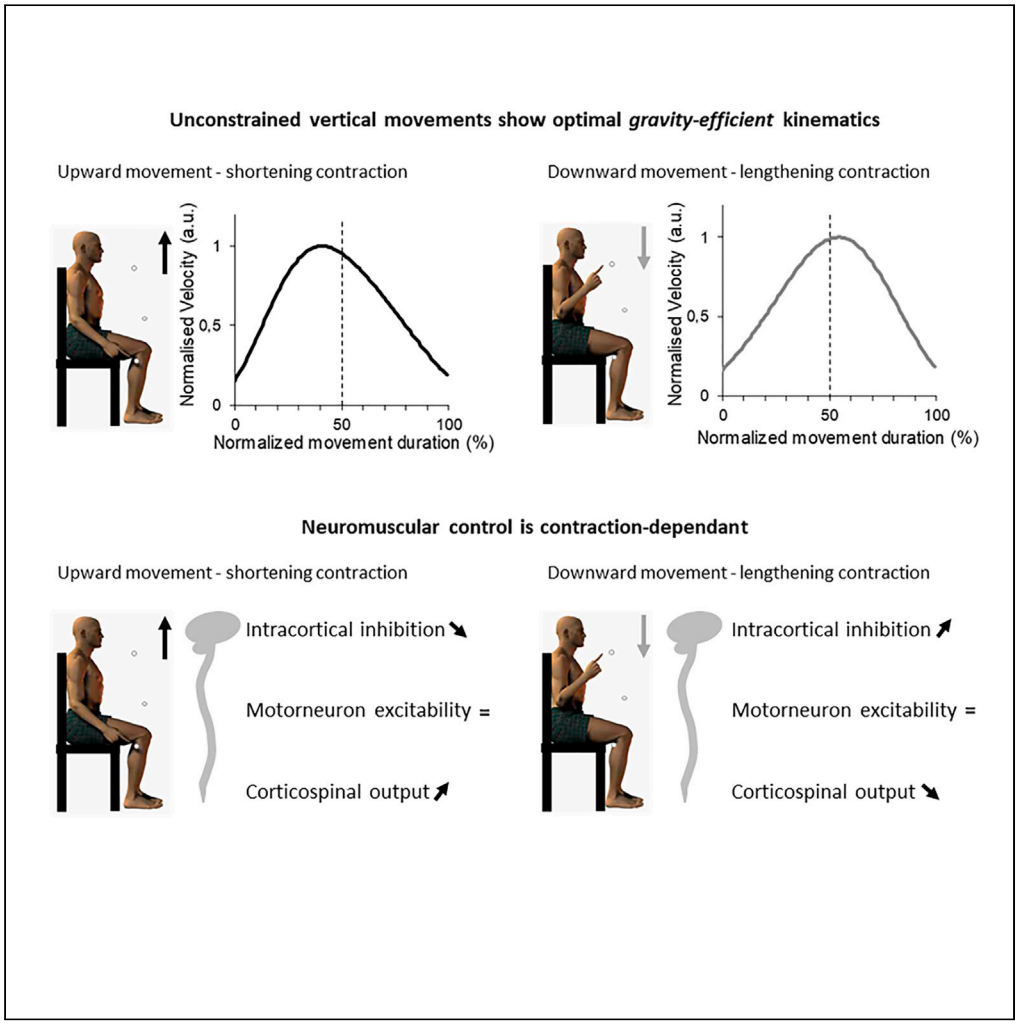

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Highlights

Unconstrained vertical, gravity-oriented, movements show *optimal* kinematics

Upward and downward movements rely on shortening and lengthening contractions

Neuromuscular control of such vertical movements is contraction-dependent

Intracortical – rather than spinal – mechanisms subserve this control

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Gravity-efficient motor control is associated with contraction-dependent intracortical inhibition

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SUMMARY

In humans, moving efficiently along the gravity axis requires shifts in muscular contraction modes. Raising the arm up involves shortening contractions of arm flexors, whereas the reverse movement can rely on lengthening contractions with the help of gravity. Although this control mode is universal, the neuromuscular mechanisms that drive gravity-oriented movements remain unknown. Here, we designed neurophysiological experiments that aimed to track the modulations of cortical, spinal, and muscular outputs of arm flexors during vertical movements with specific kinematics (i.e., optimal motor commands). We report a specific drop of corticospinal excitability during lengthening versus shortening contractions, with an increase of intracortical inhibition and no change in spinal motoneuron responsiveness. We discuss these contraction-dependent modulations of the supraspinal motor output in the light of feedforward mechanisms that may support gravity-tuned motor control. Generally, these results shed a new perspective on the neural policy that optimizes movement control along the gravity axis.

INTRODUCTION

From sensory perception to movement control, the central nervous system (CNS) has developed efficient strategies to cope with our surrounding *gravity-oriented* environment.[1] Whether we stand up or sit on a chair, draw, or reach to grasp an object, the trajectories of unconstrained movements systematically show directional asymmetries. Precisely, upward movements have a shorter time to peak velocity, greater peak acceleration, and larger path curvature than downward movements.[2–8] Previously, we demonstrated that this behavior is optimal to save muscle effort.[9] In addition, it suggests that such efficient control emerges from high-level processes, likely at the motor planning level.

The shift in muscle contraction modalities according to movement direction is also a basic feature of movement control in the gravity field. Indeed, naturally paced upward and downward arm movements required specific activations of the flexors/antigravity muscles, i.e., shortening contraction when moving upwards (against gravity) and lengthening contraction when moving downwards (with gravity). Such a control scheme is not possible in the horizontal plane, where the activation of both agonist and antagonist muscles is necessary to move leftwards or rightwards.[4,6,10] We recently scrutinized muscular activation patterns during single-degree-of-freedom arm movements in various directions. Using a well known decomposition method of tonic (i.e., isometric muscle activity needed to keep the arm still against gravity) and phasic (i.e. dynamic muscle activity needed to accelerate and decelerate the arm) electromyographic (EMG) activities,[11,12] we demonstrated that phasic electromyograms present systematic negative phases – i.e., phases where the amplitude of the EMG signal is less than necessary to compensate gravity torque. These short negativity phases are precisely time-locked to the acceleration and deceleration phases of downward and upward movements, respectively. This is systematically reported for many antigravity muscles, and very likely reveals an optimal motor plan where the motor system "harvests" the mechanical effects of gravity to accelerate downward and decelerate upward movements.[4,13]

Previous studies modeled these robust kinematic and EMG patterns as an optimal motor planning policy by which the central nervous system purposely takes advantage of the gravity force to save muscle effort.[3,4,13–15] Such models, deriving from neurophysiological data obtained in human and non-human

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primates, assume that the brain computes a gravity internal model[16–19] to support optimal motor planning and control. However, despite the abundant behavioral evidence for optimal control of gravity-oriented movements, its neural implementation remains unknown. The contribution of supraspinal and spinal neural mechanisms subserving the shortening and lengthening muscle patterns in the gravity field is unknown.

In *constrained* motor tasks, such as maximum or guided force generation tasks, shortening and lengthening muscle contractions result from specific neuromuscular control strategies,[20] as well as sensory processing.[21,22] For instance, it has been shown that spinal mechanisms contribute to partially inhibit the neural drive originating from the motor cortex (measured by the size of motor evoked potential, MEP) during lengthening compared with shortening contractions.[23–27] Gruber et al.[25] demonstrated a greater reduction of CMEP amplitude (cervicomedullary motor evoked potential) than MEP amplitude during lengthening contractions of the elbow flexor muscles. As CMEP does not involve the motor cortex, whereas MEP includes both intracortical and spinal neurons, it provides a direct assessment of spinal cord motoneurons' responsiveness to synaptic inputs.[28,29] Yet, the neural inhibition of the motor pathways during voluntary lengthening contractions is still debated,[30] as some data did not reveal specific modulations of MEP and CMEP amplitudes during such contractions in conditions of high force levels.[31]

During *unconstrained* motor tasks, such as naturally paced pointing tasks, the neural drive of shortening and lengthening muscle contractions has not been investigated. It is known that the control of arm dynamics involves both spinal and supraspinal mechanisms. For example, Gritsenko et al.[32] found that transcranial magnetic stimulation (TMS) responses in shoulder and elbow muscles changed when interaction torques were resistive but not assistive to arm movements, suggesting that the descending motor command includes compensation for passive limb dynamics. Kurtzer et al.,[33] during perturbed arm movements, found that short-latency reflexes of shoulder muscles were exclusively linked to shoulder motion, whereas long-latency reflexes were sensitive to both shoulder and elbow motion. They concluded that long-latency reflexes possess an internal model of limb dynamics, a degree of motor sophistication that was previously reserved for voluntary motor control. For postural control of the upper limb, recent work shows that even short latency feedback loops (20ms, i.e., eminently spinal even though under cortical control) are tuned to the motor context, thereby producing sophisticated efficient motor control.[34,35]

The main purpose of the study is to disentangle the neuromuscular mechanisms that subserve the control of lengthening and shortening muscular contractions during unconstrained gravity oriented movements. To do so, we investigated how supraspinal and/or spinal mechanisms contribute to the kinematic and EMG features of arm movements performed along the vertical axis. We therefore conducted two experiments where participants performed upward and downward arm pointing movements. Non-invasive neurophysiological methods were used (i.e., TMS and Cervicomedullary Stimulation (CMS)) to finely track the modulations of cortical, spinal, and muscular outputs of arm flexors during the lengthening and shortening contraction phases of arm motion along the vertical axis.

RESULTS

Arm kinematics

Sixteen healthy participants performed single-joint, visually guided pointing movements in the parasagittal plane with their right forearm (rotation around the elbow; see Figure 1, left panels). We used 1° of freedom movements to isolate the mechanical effects of gravity.[3,36,37] Precisely, during single-joint vertical forearm movements, inertia (i.e., the distribution of the forearm mass around the elbow joint in a body-fixed coordinate system) remains constant, and inertial torque is only related to joint acceleration. All participants accomplished downward and upward movements at a comfortable speed by mobilizing the elbow joint (no rotation at the other joints) without deviating from the sagittal plane. Motion capture techniques were used to track movement kinematics (see STAR Methods-data analysis) and revealed that velocity profiles were single-peaked and bell-shaped (Figure 1, right panels).

Average values ($\bar{x} \pm$ SE) of the main forearm kinematics are shown in Table 1. Movement amplitude, duration, and mean velocity did not show any significant difference between upward and downward movements, whereas peak velocity and acceleration were higher (acceleration was close to significance; $p = 0.050$) during upward compared to downward movements. Also, we observed significant differences in the relative time to peak acceleration (rTPA) and the relative time to peak velocity (rTPV), with lower values for upward movement compared to downward movements. Overall, these specific directional asymmetries

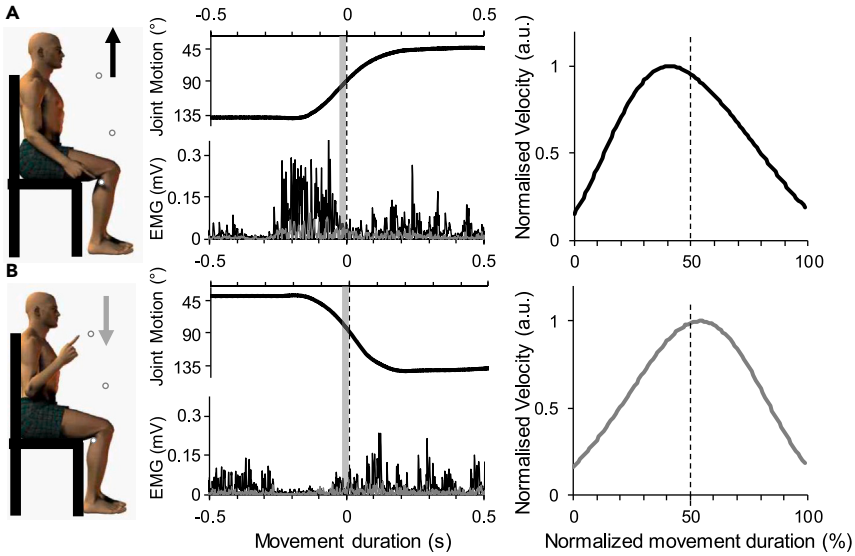

Figure 1. Kinematic and EMG determinants of the motor task

(A) Schematic representation of a participant executing an upward movement (left panel), with the corresponding temporal evolution of joint motion and EMG activity (middle panel). Joint motion is represented as the upper arm-forearm angle, and EMG activity is represented as the rectified EMG signal for the biceps brachialis (BB) and the triceps brachialis (TB), black and gray trace respectively. Typical normalized velocity profile (right panel). Data are from a typical trial.

(B) Same as (A), but for a typical downward movement. For the middle panels, the vertical dotted lines show the time of electrophysiological stimulations, and the shaded gray area indicates the time window during which the pre-stimulus EMG activity was quantified (see data analysis). For the right panel, the vertical dotted line indicates the mid-movement time and allows us to appreciate the directional asymmetry, with a clear shift of peak velocity toward the beginning and the end of the motion, for upward and downward movements, respectively.

confirm previous results from the literature that were shown to reveal an optimal motor control process minimizing muscle effort in the vertical plane.[4,9,13,14]

Neurophysiological parameters – Experiment A

Corticospinal excitability was evaluated by using single-pulse TMS, short intracortical inhibition (SICI) by paired-pulse TMS, and silent period (SP). Spinal excitability was evaluated by CMS, whereas muscle excitability was assessed through M_{max} recordings. The stimulations were applied when the elbow joint reached 90° during upward or downward movements. This allowed us to precisely target the potential neuromuscular modulations induced by contraction modalities (i.e., lengthening or shortening) of the BB whereas the elbow reach the same configuration during the movement course. The complete procedure is detailed in STAR Methods-neuromuscular stimulation methods.

At the muscular level, the motor task allowed us to focus on the BB, which was activated in the two contraction modalities according to movement direction; i.e., lengthening and shortening contractions for downward and upward movements, respectively. Electromyographic signals (EMG) from both the BB and the TB of the right arm were recorded during the whole movement course. Figure 1 (middle panels) qualitatively illustrates the activation patterns of both muscles during the motor task. It could be noticed that upward and downward forearm movements are mainly produced by the activation of the BB (note, however, that synergist muscles like brachialis and brachioradialis were not recorded). BB and TB muscle activity patterns were also characterized by computing the root-mean-square (RMS) of the EMG signals. Figure 2 thus shows the time-varying modulation of EMG RMS from both muscles during upward and downward movements right before the electrophysiological stimulation.

Average values ($\bar{x} \pm$ SE) for the main neurophysiological parameters during downward and upward movements are depicted in Table 2 (upper part). M_{max}, RMS/M_{max}, and muscle coactivation were not significantly different between the two movement directions (in all, $p > 0.05$). To directly test the equivalence

Table 1. Effect of movement direction on forearm movement kinematics, and direction ratios (i.e., invariant parameters)

	Movement *Type of muscle contraction*			
	Downward *Lengthening*	Upward *Shortening*	p value	Cohen's *d*
Kinematic features				
Movement Amplitude	0.52 ± 0.11	0.51 ± 0.12	0.178	0.08
Movement Duration (s)	0.5 ± 0.03	0.49 ± 0.03	0.972	<0.001
Mean Velocity (m/s)	1.16 ± 0.09	1.15 ± 0.07	0.963	0.12
Peak Velocity (m/s)	1.72 ± 0.11*	1.83 ± 0.15	0.040	0.83
Peak Acceleration (m/s^2)	9.25 ± 1.26	9.76 ± 1.19	0.050	0.41
Movement direction ratios				
rTPV	0.54 ± 0.04*	0.49 ± 0.04	0.035	1.11
rTPA	0.21 ± 0.02*	0.17 ± 0.01	0.036	0.97

Data are mean ± SE.
rTPV, relative time to peak velocity; rTPA, relative time to peak acceleration.

hypothesis, we performed a Bayesian analysis on the RMS/M_{max} parameter. For the overlapping hypothesis, we obtained a Bayes Factor BF^{OH}_{01} = 3.54 and, for the non-overlapping hypothesis, we obtained a Bayes Factor BF^{NOH}_{01} = 12.56. These analyses indicate that, at an elbow angle of 90°, the muscular activity was of comparable magnitude between movement directions. Note that RMS/M_{max} reflects the net EMG signal (i.e., the level of central motor command without considering peripheral factors.[38] Notably, this implies that further spinal and supraspinal modulations could not result from differences in muscle activation state between the two movement directions. Our EMG examination also confirms that forearm motion was actively controlled by the BB during both lengthening (downward movement) and shortening (upward movement) contractions, as revealed by similar values of coactivation.

Of interest, both MEP and CMEP amplitudes were significantly lower for downward versus upward movements (for both, $p < 0.05$). Figure 3A shows typical MEP and CMEP for downward and upward contractions, whereas Figures 3B and 3C shows normalized MEP and CMEP amplitudes for the same conditions. Though normalized MEP amplitudes were significantly reduced for downward compared to upward movements ($p = 0.001$; $d = 1.07$), no significant difference was found for CMEP amplitudes ($p = 0.89$; $d = 0.12$). The SP was significantly shorter during upward movements compared to downward movements. Because the SP duration can be influenced by the size of the MEP, we normalized the SP duration values by computing the ratio SP/MEP. Again, the normalized SP duration (Figure 3D) was significantly shorter during upward compared to downward movements ($p < 0.001$; $d = 2.46$).

Finally, SICI was more pronounced during upward compared to downward movements (Figure 3E; respectively −22.85 ± 9.25% and −42.45 ± 8.64% for downward and upward movements; $p = 0.04$; $d = 0.69$). The same result was obtained while expressing SICI with M_{max} normalization, a procedure that allows us to consider the proportion of spinal motoneurones activated by the test stimulus (i.e., $SICI_{Mmax}$, see STAR Methods-data analysis). Precisely, $SICI_{Mmax}$ reached −2.99 ± 1.78% and −31.74 ± 8.90% for downward and upward movements respectively ($p = 0.008$; $d = 9.75$).

Figure 4A shows typical $CMEP_{unconditioned}$ and $CMEP_{conditioned}$ signals during both downward and upward movements. Figure 4B shows both individual responses' amplitudes for all participants and the normalized $CMEP_{conditioned}$ amplitudes for the same conditions (high and low panel respectively). Normalized $CMEP_{conditioned}$ amplitudes were not significantly different between contractions ($p = 0.83$; $d = 0.09$). These data come from a paired-pulse TMS-CMS protocol that was specifically designed to evaluate the potential influence of the conditioning (sub-threshold) TMS pulse on spinal motoneuronal excitability (see Methods).

In summary, Experiment A showed a decrease in corticospinal excitability during lengthening (downward movement) versus shortening (upward movement) contractions, as evidenced by clear modulations of MEP

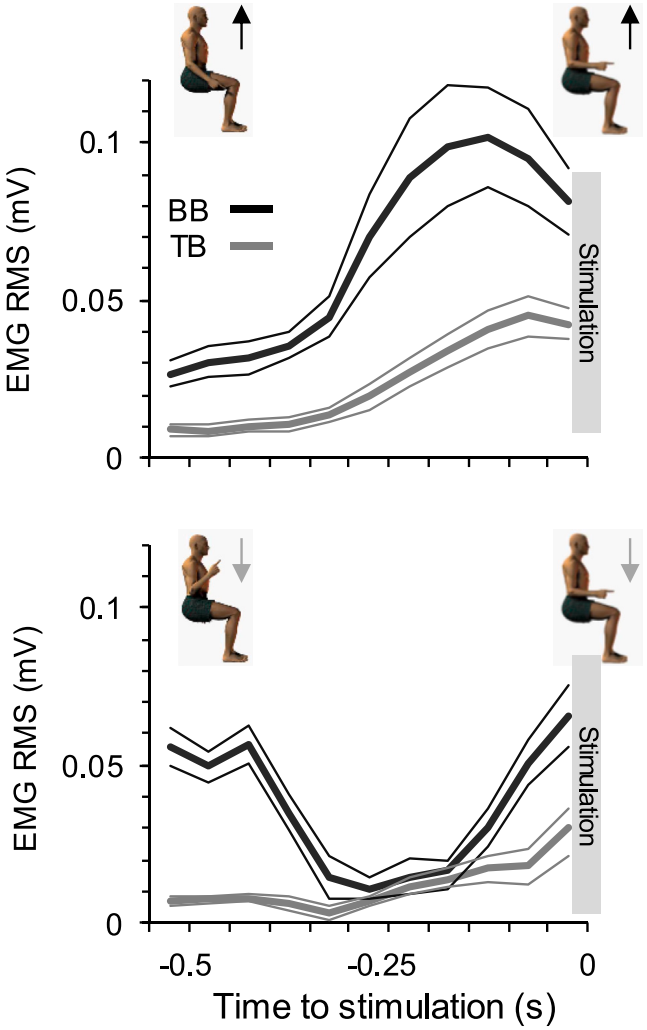

Figure 2. Time-varying modulation of muscle activity during upward (high panel) and downward movements (low panel)

RMS of the EMG signal (50 ms time window) for BB and TB - black and gray traces respectively - are shown for the 0.5 s preceding electrophysiological stimulation. Thick and thin lines represent mean and SE values for all subjects in experiment A (n = 10). Corresponding arm configurations are illustrated in the small figurines.

amplitudes; whereas spinal motor neuron excitability remained similar during both contraction types (no CMEP variation when normalized to M_{max}). However, intracortical inhibition showed paradoxical results whether it was assessed by SP or paired-pulse protocol (SICI). It increased during lengthening versus shortening contractions as measured by SP duration, whereas it showed the opposite pattern when measured by SICI.

Neurophysiological parameters – Experiment B

Because the size of the test MEP, in SICI protocols, can bias the magnitude of intracortical inhibition,[39,40] normalization methods are to be employed to control this size effect and better characterize SICI mechanisms in motor control tasks.[41,42] Accordingly, experiment B was designed to assess intracortical inhibition while precisely adjusting TMS intensities across the experimental conditions, where test MEP in the SICI protocol were carefully matched between shortening and lengthening contractions.

Average ($\bar{x} \pm$ SE) values for the main neurophysiological measures during downward and upward movements are given in Table 2 (lower part). As in experiment A, M_{max}, RMS/M_{max}, and muscle coactivation were not significantly different between movement directions (in all, $p > 0.05$), further confirming a comparable muscular

Table 2. Effect of movement direction on the neurophysiological parameters for experiment A (upper part) and B (lower part)

	Movement *Type of muscle contraction*			
	Downward *Lenghtening*	Upward *Shortening*	p value	Cohen's *d*
Experiment A				
Muscle activity				
M_{max} (mV)	4.75 ± 1.35	5.31 ± 1.31	0.14	0.19
RMS (mV)	0.032 ± 0.005*	0.054 ± 0.006	0.003	1.11
RMS/M_{max} (a.u. x 10^{-3})	12.23 ± 3.65	14.30 ± 3.42	0.47	0.22
Coactivation (%)	48.96 ± 7.60	47.76 ± 6.96	0.91	0.05
Corticospinal activity				
MEP (mV)	0.84 ± 0.15*	2.61 ± 0.39	<0.001	2.45
MEP/RMS (mV)	30.67 ± 6.76*	51.27 ± 8.41	<0.001	2.71
$MEP_{Conditioned}$ (mV)	0.69 ± 0.18*	1.49 ± 0.35	0.01	1.46
SP (ms)	149.73 ± 10.77*	121.36 ± 8.49	0.003	1.01
CMEP (mV)	1.78 ± 0.31*	2.75 ± 0.40	0.007	0.77
CMEP/RMS (mV)	55.54 ± 8.06	51.81 ± 7.88	0.48	0.16
$CMEP_{Conditioned}$ (mV)	1.81 ± 0.37*	2.94 ± 0.41	0.004	0.92
Experiment B				
Muscle activity				
M_{max} (mV)	6.57 ± 1.07	6.81 ± 1.12	0.60	0.07
RMS (mV)	0.034 ± 0.004*	0.051 ± 0.006	0.009	0.96
RMS/M_{max} (a.u. x 10^{-3})	7.92 ± 2.33	9.08 ± 1.95	0.29	0.18
Coactivation (%)	45.87 ± 6.61	48.36 ± 7.24	0.34	0.12
Corticospinal activity				
MEP (mV)	0.51 ± 0.10	0.52 ± 0.07	0.76	0.03
$MEP_{Conditioned}$ (mV)	0.27 ± 0.04*	0.39 ± 0.05	0.006	0.72
SP (ms)	123.35 ± 9.05*	88.47 ± 3.77	0.015	1.81

Data are mean ± SE.
* indicates a significant difference between conditions with a $p < 0.05$.

activity during both movement directions, and a similar agonist/antagonist strategy (as revealed by similar values of coactivation). Again, to directly test the equivalence hypothesis, we performed a Bayesian analysis on the RMS/M_{max} parameter. For the overlapping hypothesis, we obtained a Bayes Factor $BF^{OH}_{01} = 3.23$ and, for the non-overlapping hypothesis, we obtained a Bayes Factor $BF^{NOH}_{01} = 10.41$. These results further support the conclusion that RMS/M_{max} were equivalent between movement directions. No significant difference was found for MEP amplitudes during downward and upward movements, indicating an appropriate methodology for matching corticospinal excitability between conditions; yet, $MEP_{conditioned}$ amplitudes were significantly lower during downward compared to upward movements (see Table 2).

Figure 5A shows typical MEP during downward and upward movements, whereas Figure 5B shows normalized MEP amplitudes. The latter were not significantly different between movement directions ($p > 0.05$; $d = 0.08$). The SP was significantly shorter during upward versus downward movements ($p = 0.015$; $d = 1.81$). Also, the normalized SP duration (Figure 5C) was significantly shorter during upward compared to downward movements ($p = 0.03$; $d = 0.73$). SICI here showed a similar pattern, therefore opposite to what was observed in experiment A, as it was more pronounced during downward compared to upward movements (Figure 5D). The inhibition was −24.35 ± 4.68% and −45.01 ± 5.12% for upward and downward movements respectively ($p = 0.03$; $d = 1.48$). $SICI_{Mmax}$ gave comparable results with −4.73 ± 1.18% and −1.70 ± 0.38% for downward and upward movements, respectively ($p = 0.01$; $d = 6.91$).

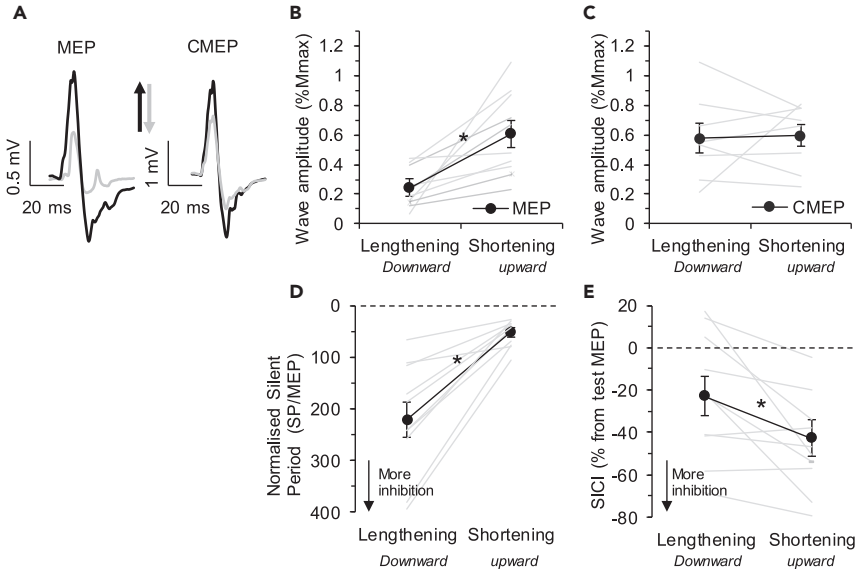

Figure 3. Changes in corticospinal responses and intracortical inhibition during downward (lengthening contraction) and upward (shortening contraction) movements

(A) Typical MEP and CMEP for downward and upward movements (gray and black traces, respectively).

(B and C) Mean normalized MEP amplitudes (±SE) of MEP and CMEP for downward and upward movements.

(D) Normalized SP duration (±SE) for downward and upward movements.

(E) Mean SICI values (±SE) for downward and upward movements. *Significant difference at $p < 0.05$. Thin gray traces show individual values.

To summarize, when controlling for test MEP amplitude between directions, experiment B revealed similar patterns of intracortical inhibition whether it was assessed by SP or paired-pulse protocol (SICI). Precisely, intracortical inhibition was more pronounced during downward (lengthening contractions) than upward movements (shortening contractions).

DISCUSSION

We investigated the neural mechanisms underlying the control of unconstrained gravity-oriented forearm movements. The main purpose of the study was to unravel the neuromuscular mechanisms of lengthening and shortening muscular contractions in a context of unconstrained vertical movements. We designed two experiments that allowed tracking the modulations of cortical, spinal, and muscular outputs of arm flexors whereas healthy adults accomplished movements along the vertical axis. We confirmed, in line with previous studies, that velocity profiles revealed consistent direction-dependent asymmetries (upward versus downward). In addition, forearm movements were performed by activating the flexor muscles only: downward movements (with gravity) were generated by lengthening (eccentric) contraction whereas upward movements (against gravity) were generated by shortening contraction (concentric). These kinematic and muscular patterns have been shown to reflect optimal solutions that take advantage of gravity torque to minimize muscle effort during vertical movements of the upper limb.[3,4,9,13,15] More interestingly, we found that the overall cortical output was reduced during lengthening compared to shortening contractions. This neural organization was produced by supra-spinal intracortical inhibition mechanisms as motoneuronal responsiveness remained unchanged between lengthening and shortening contractions. These data highlight a specific involvement of intracortical circuits during the neuromuscular control of vertical arm movements.

Neural mechanisms implicated in vertical arm movements

Neurophysiological data from experiment A showed a significant reduction of MEP amplitude in BB during downward (lengthening contraction) as compared to upward (shortening contraction) movements. This result copes with those of studies using force-generation tasks that systematically show a downregulation of corticospinal excitability during lengthening contractions – whether the task involved maximal or submaximal contractions of upper or lower limb muscles.[23–27,43] It is important to note that the drop in

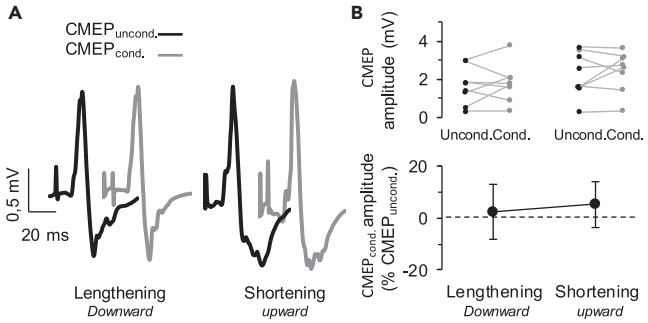

Figure 4. Effect of a conditioning TMS-pulse on CMEP response (paired-pulse TMS-CMS protocol)

(A) Typical unconditioned and conditioned CMEP (black and gray traces, respectively) during downward (lengthening contraction) and upward (shortening contraction) movements.

(B) Individual unconditioned and conditioned CMEP amplitudes (upper panel), and mean (±SE) normalized conditioned CMEP amplitudes (lower panel) for both movement directions.

corticospinal output could not be because of muscular mechanisms *per se* because both the coactivation and the RMS/M_{max} ratio in BB right before the stimulation remained comparable between the two contraction modalities. Instead, it must have relied on supraspinal and/or spinal mechanisms.

To assess changes at the spinal level, we measured the responses to CMS and found that normalized CMEP amplitudes did not differ between downward and upward movements, thus indicating that motoneuron responsiveness to synaptic inputs remained similar across lengthening and shortening contractions. Consequently, the drop in global corticospinal excitability without any modulation of CMEP indicates the involvement of cortical mechanisms. The CMS is the most direct method to test motoneuron responsiveness to synaptic input in conscious humans.[44] The CMEP has a large monosynaptic component in the upper limb[45] and the descending tracts are not subject to presynaptic inhibitory mechanisms.[46,47] Note, so far, that the contribution of spinal mechanisms acting pre- or postsynaptically of the motoneuron could not be excluded from our protocol.[48,49]

Our results reveal that the neural commands responsible for opposite movement orientations in the vertical plane are tuned by intracortical mechanisms. Indeed, in experiment B, both the SP and SICI indicated an increase in intracortical inhibition during lengthening contractions. The SP was longer in this contraction mode, even when MEP amplitudes were controlled – eliminating potential biases regarding the SP dependency on MEP size.[49,50] As shown by Inghilleri et al.,[51] TMS-evoked silent periods longer than 80–100 ms are indeed mainly produced by cortical mechanisms. It has to be noted, however, that some data suggested that spinal motoneuronal excitability might also be involved during silent periods longer than 80 ms; see.[52,53] Yet, our analysis of SICI, which similarly showed a higher inhibition during lengthening contractions, further points out a significant implication of intracortical circuits. Importantly, our paired-pulse protocol allowed us to assess SICI without confounding effects from the size of test MEP, as corticospinal output was matched between conditions by adjusting TMS intensity (experiment B). Without this procedure, the systematic variations in test MEP amplitude because of the muscle contraction mode[54] make SICI protocols unreliable,[41,42] which may confound the interpretation of data. In fact, Experiment A – without TMS adjustments – revealed higher levels of intracortical inhibition during shortening contractions compared to lengthening ones; whereas the opposite pattern of results was found while matching test MEP amplitude; i.e., higher inhibition during lengthening contractions (experiment B). This result copes with studies showing a robust influence of the magnitude of corticospinal output on SICI level.[39,40] For instance, an increased muscle force or test MEP intensity – both leading to higher test MEP amplitudes – significantly rise up SICI; notably when normalized to M_{max}.[41,42,55] Increasing muscle force or test MEP intensity led to a greater proportion of large spinal motoneurones activated by TMS (cf. Henneman's principle). Because of their higher threshold – compared to smaller low-threshold motoneurones, these large motoneurones are more sensitive to a decrease in corticospinal input induced by the conditioning pulse.[55,56] Consequently, SICI data from experiment A likely result from a contraction-dependent modulation of the test MEP size (~3x bigger during shortening contractions; see Figure 3B), rather than a *true* variation of the activity of intracortical inhibitory circuits. TMS adjustments from experiment B allow to assess the activity of inhibitory interneurons in standardized conditions (i.e., comparable corticospinal output), and strongly suggest a specific increase of SICI during lengthening contractions.

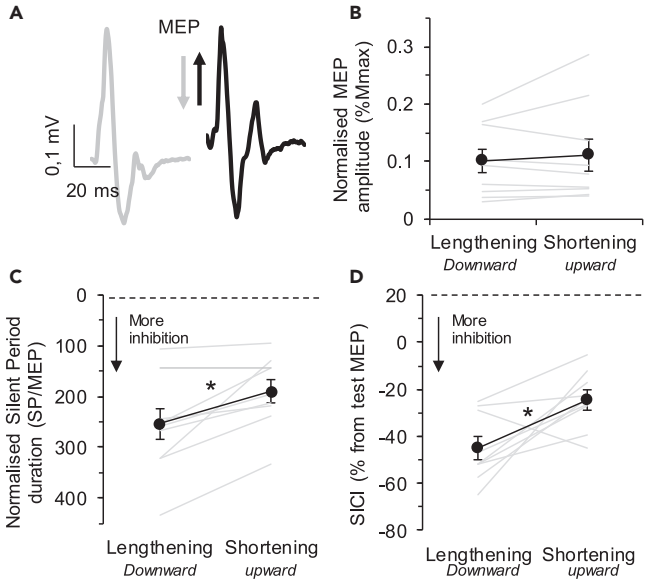

Figure 5. Changes in intracortical inhibition while adjusting TMS intensity

(A) Typical MEP for downward and upward movements (gray and black traces, respectively).

(B) Mean normalized MEP amplitudes (±SE) for downward and upward movements.

(C) Normalized SP duration (±SE) for downward and upward movements.

(D) Mean SICI values (±SE) for downward and upward movements. *Significant difference at $p < 0.05$.

Moreover, as our conditioning CMEP protocol showed that conditioning (subthreshold) MEP did not reach the spinal level, SICI data can be safely considered as an accurate assessment of intracortical inhibitory circuits. SP and SICI are thought to reflect the contribution of $GABA_B$-mediated and $GABA_A$-mediated inhibition, respectively.[57,58] Of interest, modulations of GABAergic inhibitory neurotransmission have been reported in the control of finger tracking tasks implying anisometric contractions, with a specific augmentation of both SP and SICI during lengthening contractions of intrinsic hand muscles.[43,59] Our findings provide strong evidence for a contraction-dependent modulation of intracortical inhibition in the control of vertical arm movements, where the neural command is specifically downregulated at the cortical level during lengthening contractions.

Neural control of muscle contraction modalities is task-dependent

The characteristics of the motor task (e.g., type of muscle contraction, range, speed of motion, level of external and/or internal forces) are a central issue when trying to identify the neural mechanisms of movement control. In many experiments, these mechanisms were evaluated through isokinetic actions where muscular contractions are induced by resisting a torque imposed by an ergometer, or by displacing a load to match a trajectory.[20,54] In such tasks, lengthening contractions specifically reveal spinal inhibitions,[23–25,59,60] which led to the interpretation that a relative increase in cortical excitability would compensate for it. Duclay et al.[23,24] have indeed shown that the SP in the ongoing EMG recorded after a MEP was shorter during lengthening compared with shortening contractions of ankle flexors, suggesting a specific release of cortical inhibition. Moreover, Gruber et al.[25] hypothesized greater cortical excitability in lengthening contractions, because of larger MEP-to-CMEP ratios during lengthening compared with shortening contractions in the elbow flexors. It could be noted, however, that under conditions of supra-maximal force levels, whereas subjects developed enhanced torques during lengthening contractions as compared to isometric maximal voluntary contractions, some authors could not find any contraction-dependent modulations of corticospinal or spinal excitabilities.[31] These data led the authors to suggest that the inhibition of the major motor pathways might be specific to lengthening contractions that did not produce significant torque enhancements.[30]

Generally, the majority of studies suggest that the overall drop in corticospinal output during lengthening contractions arises from an interaction between spinal and cortical mechanisms, where an extra excitatory drive from the motor cortex may be downregulated by spinal inhibitory mechanisms.[20,23–25] In this context, the spinal modulations may highlight peripheral control loops that are required for the online regulation of

the motor output, e.g., force and position.[61] Of interest, Hahn[30] suggests that spinal inhibition might be responsible for the "reduced" force enhancement during lengthening contractions in studies that did not report supra-maximal force levels. Also, low reflex gain favors the stability of muscle activation,[62] notably by mitigating the augmentation of Ia afferent activity because of proprioceptive inputs.[47]

Our study highlights a distinct control strategy for natural, unconstrained vertical movements. It is worth mentioning that the modulation of intracortical circuits in the control of shortening and lengthening contractions we report in our motor task may be related to the integration of gravity force, supporting predictive mechanisms of motor control.[63,64] In fact, many behavioral and computational studies have proposed that the kinematic and EMG features of upward and downward movements are set at the motor planning stage.[2–4,6,36] A striking example of this is the persistence of directional asymmetries during early adaptation to a microgravity environment.[7,9] Although the load force is absent, it takes several trials before directional asymmetries progressively disappear, thereby converging toward newly optimal motor patterns.[9] This result has been taken as the demonstration that a gravity internal model is recalibrated and that deterministic optimal motor control is set predictively. Of interest, these findings further support those of previous studies showing that the gravity internal model is supposed to be stored at the supra-spinal level, involving computations of the cerebellum, the anterior thalamus, the vestibular nuclei, and the vestibular cortex.[16–18,65] Yet, we cannot totally rule out the effect of sensory afferents in the regulation of intracortical circuits during such motor tasks. In fact, although the role of inhibitory feedback from sensory receptors (e.g., Golgi tendon organs) in motorneuron responsiveness have been discarded for lengthening contractions[20,66]; the precise influence of a contraction-dependent sensory signal over cortical inhibition remains to be evaluated - e.g., sensory gating via indirect pathway between the somatosensory cortex and M1.[67]

At last, many works in motor control has undeniably demonstrated that differences between upward and downward movements results from a central integration of gravity effects, and not just a loading effect on the upper-limb. For example, although horizontal movements with full vision do not show directional differences,[36,37] they do show similar directional asymmetries as vertical ones when one performs head/feet horizontal movements (i.e., lying on the side) with no vision.[37] Also, differences between upward and downward motor patterns precedes movement initiation.[4] These results and those of Gaveau et al.[9] suggest that the anticipation of gravity effects shapes motor control, and strongly refutes the hypothesis that the simple effect of arm loading produces directional differences.

Conclusion

The neural policy we identified in the present study, i.e., a consistent direction-dependent modulation of the intracortical inhibition whereas spinal excitability remained unchanged, well supports the hypothesis that gravity-related optimal motor commands are mainly processed upstream to the muscle and spinal levels, within brain intracortical circuits.

Limitations of the study

The vertical pointing movements used in our study present specific time-varying EMG patterns of the BB, which imply that the neuromuscular stimulations were delivered while muscle activity is *decreasing* during lengthening contractions, while it is *increasing* during shortening contractions (Figure 2). Hence, we cannot totally rule out the fact that the corticospinal responses also result from the muscle activity pattern per se, or immediate "muscle history" (e.g., change of activity level) and not solely from the contraction modality (lengthening versus shortening). Time-varying EMG signals - during the time window used to evaluate the neural circuits - are also reported in other experiments focusing on neuromuscular mechanisms during constrained force tasks[23,24,43,68]; yet, there reveal different results than ours; e.g., an increased cortical signal and/or a decreased spinal excitability. This makes questionable the 'muscle history' hypothesis as a potential mechanism to explain our data. Our team is however working on a follow-up study where neural modulations will be tested during isometric contraction ramps (i.e., static task), while reproducing the muscle activity patterns of upward and downward arm movements.

Nonetheless, the present findings undeniably show that, in the context of unconstrained "optimized" vertical arm movements, the changes within the motor command between lengthening and shortening contractions actually emerged from supra-spinal modulations. These modulations provide a first neurophysiological understanding of long hypothesized supra-spinal mechanisms that would underlie optimal motor control in the gravity field.[20]

From a clinical perspective, the present work also may contribute to the literature on motor deficits; e.g., spinal cord injuries,[69,70] aging.[71] By improving our comprehension of the neural organization that subserves simple motor actions of daily life, these data may help designing rehabilitation settings.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND PARTICIPANT DETAILS
- METHOD DETAILS
  - Study design
  - Motor tasks
  - Kinematics recording
  - Electromyography
  - Neuromuscular stimulation methods
  - Experiment A
  - Experiment B
  - Experimental conditions and recording procedure
  - Data analysis
- QUANTIFICATION AND STATISTICAL ANALYSIS

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AUTHOR CONTRIBUTIONS

N.G., A.M., and C.P. designed the experiment. N.G. and A.M. conducted the experiment. N.G. and J.G. analyzed the data. N.G. prepared figures. N.G., A.M., and C.P. wrote the manuscript. J.G., A.M., and C.P. provided feedback on the manuscript. All authors read and approved the current version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Analyzed data	This paper	https://doi.org/10.17605/OSF.IO/G89CF

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Nicolas Gueugneau (nicolas.gueugneau@univ-fcomte.fr).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Anonymized data have been provided at Open Science Framework and are publicly available as of the date of publication. The DOI is listed in the key resources table.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND PARTICIPANT DETAILS

Sixteen healthy right-handed adults participated in this study (13 males and 3 females, aged between 23 and 48, mean age = 33.11 $\pm$ 6.34 years old). Participants were white, according to the National Science Foundation. All were volunteers without any neurological or muscular disorders. Informed consents were signed, and the study was approved by the Regional Ethics Committee of Bourgogne and performed in accordance with the Declaration of Helsinki. The influence of gender on the data was not specifically tested in this study.

METHOD DETAILS

Study design

Two experiments were completed to assess corticospinal and spinal excitability during single-joint (elbow anatomical angle) vertical movements in the sagittal plane. Ten participants were involved in experiment A and nine in experiment B (3 participants took part in both experiments with at least one-week interval between them). The number of participants was determined based on previous studies from our lab using similar experimental tasks.[3,9,13] Also, based on previously published values of relative time to peak velocities (rTPV) equal to 0.42 $\pm$ 0.02 and 0.53 $\pm$ 0.04 for upward and downward directions respectively,[13] 8 participants would allow detecting significant differences in movement kinematics, with a level of $\alpha = 0.05$ and power of 0.8 (Biostatgv software). The motor task was strictly identical in both experiments; only the stimulation parameters for the neurophysiological measurements differed. Durations were ~2h30 and ~1h30 for experiments A and B, respectively. The experiments were carried out during the afternoon (between 1:00 p.m. and 5:00 p.m.) to control potential circadian effects.[72] On the day of the experiments, participants were required not to practice any sport or physical activity that could have altered their neuromuscular system; and no caffeine had to be consumed.

Motor tasks

Participants performed single-joint, visually guided pointing movements in the parasagittal plane with their right forearm (rotation around the elbow; see Figure 1, left panels). We chose one degree of freedom (DOF) movements to isolate the mechanical effects of gravity.[3,36,37] Precisely, during single-joint vertical forearm

movements, inertia (i.e., the distribution of the forearm mass around the elbow joint in a body-fixed coordinate system) remains constant, and inertial torque is only related to joint acceleration. Conversely, the work of gravity torque significantly changes according to the movement direction. Note that during single-joint movements, interaction torque may also influence motion dynamics. For example, during the motion of the elbow joint, inertial interaction torques may arise at the shoulder and wrist joints because of elbow acceleration and deceleration. We confirmed that joint motion was restricted to the elbow joint only (see data analysis below). At the muscular level, the task allowed us to focus on the Biceps Brachii (BB), which was activated in the two contraction modalities, according to the direction of the movement; i.e., lengthening (downward movement) and shortening contraction (upward movement). Figure 1 (right panels) qualitatively illustrates activity patterns from the BB and TB (triceps brachii) muscles. It is noticeable that upward and downward forearm movements are mainly realized by the activation of the BB (see the co-activation levels in Table 2). Besides, although very unlikely due to the low force level required by the motor task (also not measured) and the stiff nature of the biceps tendon,[73] complex behavior of the muscle-tendon unit during lengthening contractions could not be totally excluded, e.g. stretch of the tendon with isometric muscle fascicle contraction. Generally, this paradigm make it possible to apprehend the neural mechanisms of lengthening and shortening contractions, in the context of voluntary movements showing kinematic features that are reminiscent of optimal motor commands.

Participants sat in a comfortable chair with their trunks vertically aligned and supported by the back of the chair. Their right upper-arm was in the vertical plane during the whole experiment. Three targets (1 cm diameter plastic spheres) were centered on the participants' right elbow and positioned at a distance slightly superior to their forearm segment's length. The initial target (IT) was horizontally aligned with the elbow. The other two targets were placed at an angle of 45° upward (UT) and -135° downward (DT), taking as reference the elbow-IT horizontal line (0°). We considered three different actions: one static and two dynamics. During the static action, the participants pointed towards the IT; the upper arm-forearm angle was 90°. This action involved an isometric contraction of elbow flexor muscles against gravity (i.e., the muscle was contracted without changing its length; muscle torque was equal to gravity torque) and was chosen to adjust parameters for magnetic and electrical stimulations (see details below). The dynamic actions comprised downward (with gravity) and upward (against gravity) movements. For the downward movements, the participants initially pointed to the UT during 2-3 seconds (the elbow was flexed at 45° and the semi-pronated hand was aligned with the forearm) before performing a movement to the DT. Note that this movement involved an eccentric contraction of elbow flexor muscles (i.e., the muscle is contracted and lengthened; its torque was inferior to gravity torque allowing downward motion of the forearm). For the upward movements, the participants initially pointed to the DT during 2-3 seconds (the elbow was flexed at -135° and the semi-pronated hand was aligned with the forearm) before performing a movement to the UT. Note that this movement involved a concentric contraction of elbow flexor muscles (i.e., the muscle is contracted and shortened; its torque was superior to gravity torque allowing upward motion of the forearm). For both movement directions, participants were informed that final accuracy was not the primary goal of the task. We trained participants (~ 10 trials) to carry out upward and downward movements of ~0.5 s. An electronic metronome was used during the experiment to help them maintain it. We chose this speed because previous studies from our laboratory showed that at this velocity, participants accomplished movements at a natural and comfortable speed.[2,3]

Kinematics recording

Kinematics was recorded using an optoelectronic device (VICON, Oxford, UK). Three cameras (100 Hz sampling frequency) were used to record the displacements of five reflective markers (1 cm in diameter) placed on the shoulder (acromion), elbow (lateral epicondyle), wrist (in the middle of the wrist joint between the cubitus and radius styloid processes), hand (first metacarpophalangeal joint), and the nail of the index fingertip.

Electromyography

We recorded the electromyographic signals (EMG) from both the BB and the TB of the right arm. Two silver chloride (AgCl) surface electrodes (8 mm diameter; inter-distance 2cm) were positioned on both muscles after shaving and cleaning the skin. The electrodes were centered over the muscle bellies (lateral head of the TB; and medial part of the BB, ~2 cm above the elbow radial tendon). The EMG electrodes were placed while the elbow joint angle was at 90°. A common reference electrode was placed over the medial epicondyle of the left arm. EMG signals were amplified with a bandwidth frequency ranging from 15 to 5

kHz (gain: 1000), then digitized online (sampling frequency: 2 kHz), and stored on a personal computer for offline analysis using the MP150 acquisition system (BIOPAC Systems Inc., Santa Barbara, CA, USA).

Neuromuscular stimulation methods

We used different stimulation methods in experiments A and B to evaluate distinct neurophysiological processes. In experiment A, we evaluated corticospinal excitability using single-pulse TMS, short intracortical inhibition (SICI) by paired-pulse TMS, and spinal motor neuron excitability through cervicomedullary stimulation (CMS). In experiment B, corticospinal excitability and SICI were evaluated by single-pulse and paired-pulse TMS, respectively, but with specific stimulation parameters allowing to match motor evoked potentials amplitude (MEP) across conditions (see details below). In both experiments, BB muscle excitability was assessed through M_{max} recordings, which allowed us normalizing the other electrophysiological variables.

Experiment A

M_{max} recordings - Brachial plexus stimulation

Single electrical stimuli were delivered to the brachial plexus to evoke M_{max} in BB (pulse duration 1 ms; provided by a Digitimer stimulator - model DS7; Hertfordshire, UK). The cathode was placed in the supraclavicular fossa and the anode on the acromion. To induce M_{max}, the intensity was progressively increased (0.5-mA steps) from the perceptual sensory threshold to M_{max}. Then, this intensity was further increased by ~20% to ensure supramaximal stimulation. Once determined at rest, the M_{max} intensity was then used to record M-waves during vertical forearm movements. Four M_{max} were recorded for each direction (upwards and downwards).

MEP and SICI recordings - Transcranial magnetic stimulation

TMS was delivered to the optimal scalp position over the left motor cortex (M1) to activate the right BB. MEP was elicited by magnetic stimuli provided from a Bistim module combining two Magstim 200 stimulators (Magstim Company Ltd., Whitland, UK) through a figure-eight coil (loop diameter, 8 cm) with a monophasic current waveform. The coil was held tangentially to the scalp with the handle pointing backward and 45° away from the midline to activate the corticospinal system preferentially trans-synaptically via horizontal corticocortical connections.[74] The cortical representation of the BB was initially assessed with the stimulator intensity at 70% of its maximum stimulator output (MSO; 2.2 T). The optimal location was searched by slightly moving the coil over the M1 area until MEP of maximal amplitude and lowest threshold were recorded in the right BB. The optimal coil location was then marked on the participants' scalp. As resting motor threshold (RMT) in proximal muscles could be hard to find in some participants, we used active motor threshold (AMT) to set TMS intensity. AMT was defined as the minimum intensity to produce a MEP amplitude of $\geq$ 300 μV in three out of five trials during weak muscle contractions.[75] To do so, TMS was given while the participants pointed to the IT, thus producing a slight isometric contraction of the right BB. We confirmed in pre-experiment that the force developed during this postural configuration corresponded to ~3–5% of maximal voluntary contraction. Stimulation intensity was then set at 120% of the AMT to record a single MEP during vertical arm movements (TMS intensity ranged from 51% to 78% of MSO; mean 62.1 $\pm$ 7.2%). The SICI protocol used a subthreshold conditioning pulse set at 80% of AMT given before the test stimulus (120% AMT) with an interstimulus interval (ISI) of 3 ms.[76] SICI settings (intensity of subthreshold conditioning pulse and test stimulus, and ISI) were based on previous works focusing on intracortical mechanisms of neuromuscular control.[41,42,77] Importantly, we confirmed during isometric contractions (static position) that the paired-pulse method effectively reduced MEP amplitude. Indeed, the mean MEP amplitude of the conditioned responses (0.33 $\pm$ 0.05 mV) was significantly lower ($P < 0.05$, $t(9) = 10.99$) than the unconditioned responses (0.61 $\pm$ 0.09 mV). Corticospinal excitability and SICI were evaluated by recording unconditioned and conditioned MEP during vertical forearm movements. Ten unconditioned MEP and 10 conditioned MEP were recorded for each direction (upwards and downwards).

Cervicomedullary stimulation (CMS)

CMS was used to directly measure spinal motoneuron excitability by eliciting a single volley in descending axons at the pyramidal decussation level.[29] It is known that CMEP is challenging to record in some participants, due to the discomfort induced by the stimulation.[78] Here, we discarded two participants as they presented noise in the EMG signal (i.e., slight visually detectable EMG activities at rest) due to apprehension and general discomfort. CMS was given by placing two AgCl (2 cm diameter) electrodes over the mastoid

processes on both sides with the cathode placed on left. We used a DS7AH current stimulator (Digitimer, Hertfordshire, UK) to elicit 200 μs-width pulses. The RMT was determined individually as the minimal intensity to evoke peak-to-peak CMEP amplitude of 50 μV in the resting BB. The intensity was then set to 120% of the participant's RMT (mean intensity: 195.5 ± 65 mA; range: 110–270 mA) to record CMEP during vertical forearm movements. Four CMEP were recorded for each direction (upwards and downwards).

We also provided a complementary measure of spinal excitability by conditioning CMS with a TMS pulse over M1. When provided in close temporal proximity, CMS and TMS interact at the spinal level and give rise to a complex motor response in a target muscle. Precisely, when a supra-threshold TMS pulse precedes CMS by 5 ms, responses to paired stimuli are larger than the responses to individual stimuli.[78] This indicates that the signal from TMS interacts with the spinal motoneuron pool before the arrival of the volley from CMS and thus induces a facilitatory motor response. More, we have previously shown that a sub-threshold M1 magnetic stimulation could modulate spinal excitability during a force-generation task.[79] These data are crucial when one considers SICI set-ups, as the conditioning TMS pulse may influence spinal excitability, biasing thus the interpretations about the underlying neural mechanisms. To tackle this issue, we recorded CMEP during a paired-pulse TMS-CMS protocol,[78] where a sub-threshold TMS pulse (80% AMT, as in our SICI protocol) was given 5 ms before CMS. So, supposing that paired stimuli and single CMS induce motor responses of similar size, it could be concluded that the sub-threshold TMS pulse does not affect spinal excitability and that our SICI protocol does properly assess intracortical mechanisms. TMS coil manipulation and CMS arrangement were the same as detailed above. Four conditioned CMEP were recorded for each forearm movement (upwards and downwards).

Experiment B

Experiment B was specifically designed to assess intracortical inhibition while controlling the TMS intensity across the experimental conditions, where test MEPs in the SICI protocol were carefully matched between shortening and lengthening contractions.

M_{max} recordings - Brachial plexus stimulation

The procedure was identical to experiment A, with M_{max} being recorded during vertical arm movements (stimulation intensities ranged from 3.2 to 19.4 mA). Four M_{max} have been recorded for each upward and downward arm movement.

MEP and SICI recordings - Transcranial magnetic stimulation

Coil location and AMT were similar as in experiment A. MEP and SICI were first recorded during isometric contractions (as in experiment A), with stimulation intensities at 120% and 80% of AMT for test and conditioning pulses, respectively. At the group level, unconditioned and conditioned MEP amplitudes in isometric condition were 0.51 ± 0.07 mV and 0.28 ± 0.04 mV, respectively ($P < 0.05$, $t(8) = 11.7$). Then, TMS intensity was adjusted to produce unconditioned (test) MEP of similar amplitudes (~0.5 mV; as in isometric condition) for upward and downward movements. Stimulation intensity thus had to be slightly lowered for both upward (shortening contractions) and downward movements (lengthening contractions) compared to isometric contractions; i.e., 62.3 ± 7.2% of MSO in isometric contraction vs. 58.1 ± 5.2% and 61.4 ± 5.2% for shortening and lengthening contractions, respectively. The conditioning TMS pulse remained at 80% of AMT during the whole experiment. Thanks to this procedure, unconditioned and conditioned MEP were recorded during upward and downward movements, while the strength of the conditioning volley was matched across conditions. Ten unconditioned MEP and 10 conditioned MEP were recorded for each arm movement (upward and downward).

Experimental conditions and recording procedure

Before performing the trials including neurophysiological stimulations, 8 of the participants performed 24 trials (12 upwards, 12 downwards) without any stimulation. This procedure allowed us to evaluate the arm kinematics and EMG signals without the stimulation artifact. Then, the neurophysiological measures were carried out in a block design. The recording order of the variables was counterbalanced across participants. For instance, for a given participant in experiment A, the order of data collection could be: $M_{max,}$ unconditioned MEP, conditioned MEP, CMEP, and conditioned CMEP for upwards and downwards arm movements; and then changed for the next participant. experiment B included the same variables except for CMEP. Sixty-four trials with neurophysiological measures were performed in experiment A [(4 M_{max}, 10

unconditioned MEP, 10 conditioned MEP, 4 CMEP, 4 conditioned CMEP) x 2 (upwards, downwards movements)], and 48 in experiment B [(4 M_{max}, 10 unconditioned MEP, 10 conditioned MEP) x 2 (upwards, downwards movements)]. Among these trials, one trial free from any stimulation for 4 trials with neurophysiological measures was added. These trials were inserted randomly to prevent potential habituation and anticipation effects due to electrical/magnetic stimulations. A ten min break was included approximately in the middle of each experimental session to prevent any fatigue effect. The setting of stimulation parameters also introduced *de facto* delays between recording blocks. None of the subjects reported physical fatigue of muscle discomfort throughout the experiments.

Stimulations for both upwards and downwards movements were given when the arm and forearm reached a 90° angle. This guaranteed that arm configuration and muscle length were similar whatever the movement direction. The timing of stimulations was precisely triggered using a two-axis electronic goniometer (Biometrics Ltd, SG110) attached to the participants' right elbow (epicondyle). Arm/forearm angular displacements in the sagittal plane were recorded and monitored online (signal sampling frequency: 2 kHz). The goniometer calibration was undertaken before each experimental session and cautiously checked throughout the experiments. The triggering delay was ~1 ms (BIOPAC Systems Inc., Santa Barbara, CA, USA).

Data analysis

Movement kinematics

This analysis concerned trials free from any stimulation. Data processing was processed using custom MATLAB programs (MathWorks, Natick, MA). Kinematic signals were low-pass filtered (5-Hz cutoff frequency) using a digital fifth-order Butterworth filter (zero-phase distortion, "butter" and "filtfilt" MATLAB functions, Mathworks). Three-dimensional velocity signals were inspected to ensure that they were single-peaked. Angular displacements were inspected to verify that participants performed one DOF movement with the elbow joint. Joint movements were discarded from further analysis when they showed multiple local maxima and/or a rotation ($\geq 3°$) to other than the elbow joint (~2% of all trials). Movement onset and offset were defined with a threshold of 10% of the maximal angular velocity.[2]

We calculated the following kinematic parameters from the index fingertip: movement amplitude and duration, mean and peak velocity, time to peak velocity, peak acceleration, and time to peak acceleration. From these variables, *invariant* parameters were computed: i) relative time to peak velocity (rtPV = time to peak velocity / movement duration) and ii) relative time to peak acceleration (rtPA = time to peak acceleration / movement duration). These parameters are termed *invariant* because they could remain constant across experimental conditions and are theoretically independent of movement direction, speed, and amplitude.[9,80] Here, they were used as behavioural markers to examine whether participants produce physiological patterns during vertical movements, as previously revealed by specific kinematics for upward and downward movements.[7,9] Besides, to make qualitative comparisons between directions, we normalized the velocity profiles in time (cubic spline function; Math- Works) and amplitude (velocity time series divided by maximal velocity). Normalization guarantees that velocity profiles are independent of joint amplitude, time, and maximal velocity.

EMG activity

The procedure was identical for both experiments. The EMG signal was used to i) characterize the EMG activity of BB and TB during upward and downward movements and ii) quantify the electrophysiological responses to neuromuscular stimulations; i.e. M_{max}, MEP, silent period (SP), and CMEP.

BB and TB EMG activity patterns were characterized by computing the root mean square (RMS) of the EMG signal. Then, BB RMS values of the EMG signal over a 30 ms period before the stimulation were normalized to the mean amplitude of the M_{max} (RMS/M_{max}) for both movement directions. This time-period was chosen after careful inspections of the EMG signals, we rationally estimated that such a duration represents a reasonable proxy of muscle activity at the precise moment of stimulation. The M_{max} normalization procedure was used to control contraction-related changes at the muscle level.[23] Muscular coactivation was expressed as a ratio of antagonist to agonist muscle activity,[81,82] by normalizing TB RMS value to BB RMS value within the 30 ms preceding the stimulation. For each experiment, a mean value of coactivation was computed over all trials for each movement condition and participant. The distance between electrode

pairs for BB and TB (>~9cm) and careful visual inspections of EMG traces during weak contractions before data acquisition, allow discarding potential crosstalk phenomena.

Evoked potentials

For each electrophysiological measure, we considered the peak-to-peak amplitude of the EMG response. M_{max}, MEP, and CMEP amplitudes from BB were averaged for each movement, condition, and participant. Considering MEP, trials in which MEP amplitude was more prominent than two SDs were considered as outliers (see Methods in Gueugneau et al.[83]). On average 0.9 (SD: 1.2) out of 10 MEP were excluded. SICI was expressed as a difference between the conditioned and unconditioned test MEP and quantified in percentage: SICI = $[(MEP_{conditioned} - MEP_{unconditioned} / MEP_{unconditioned}) \times 100]$. We also provided a complementary estimation of SICI by calculating the difference between conditioned and unconditioned test MEP and then expressed as a percentage of the $M_{max:}$ $SICI_{Mmax} = [(MEP_{conditioned} - MEP_{unconditioned} / M_{max}) \times 100]$. This procedure has been proposed by methodological works and allow to estimate the level of inhibition while taking into account the proportion of spinal motoneurones involved in MEP generation.[41,42,55]

Thus, high and low negative values indicate strong and weak SICI, respectively, while positive values would indicate facilitation. The same formula was then used to quantify the conditioned CMEP amplitude in our paired-pulse TMS-CMS trials (Experiment A). Changes in intracortical inhibition were also evaluated by measuring SP in the ongoing EMG following TMS. The SP duration was taken as the time interval from the stimulus artifact to the return of continuous EMG.[84] The end of the SP was determined when the corresponding rectified EMG activity reached a value within two SD of the rectified mean EMG signal recorded during 1 s when the participant was at rest. Because the duration of the SP can be influenced by the size of the MEP,[50] we also computed the relation between the two parameters (SP/MEP ratios) for both shortening and lengthening contractions. Finally, for both experiments and contraction types, MEP and CMEP amplitudes of the BB were normalized to the corresponding Mmax amplitude obtained in the same condition, to reduce inter-subject variability and to reliably evaluate contraction-dependent changes in the corticospinal network.[41]

QUANTIFICATION AND STATISTICAL ANALYSIS

All data are presented as means ± standard error (SE). The normality of the data was confirmed using the Shapiro-Wilks W test ($P > 0.05$). First, our study aimed to confirm the kinematic differences between upward and downward arm movements previously described in the literature. For that reason (unilateral hypothesis), all kinematics variables were submitted to one-tailed paired *t-tests* (upward vs. downward). Direction-dependent differences in electrophysiological variables were the second step in our analyses. All electrophysiological variables were submitted to two-tailed paired *t-tests* (upward vs. downward). Multi-factor repeated measures analysis of variance (ANOVA) was used when necessary. The effect size was evaluated by calculating the Cohen's *d*. Significance was set at $P < 0.05$. To directly test the equivalence hypothesis on RMS/M_{max} data we also performed Bayesian equivalence tests using a region of practical equivalence ROPE = [-0.1,0.1] and a prior Cauchy scale of 0.707.[85]