Mechanisms Underlying Functional Changes in the Primary Motor Cortex Ipsilateral to an Active Hand

Monica A. Perez and Leonardo G. Cohen

Human Cortical Physiology Section and Stroke Neurorehabilitation Clinic, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892

Performance of a unimanual hand motor task results in functional changes in both primary motor cortices ($M1_{\text{ipsilateral}}$ and $M1_{\text{contralateral}}$). The neuronal mechanisms controlling the corticospinal output originated in $M1_{\text{ipsilateral}}$ and the resting hand during a unimanual task remain unclear. Here, we assessed functional changes within $M1_{\text{ipsilateral}}$ and in interhemispheric inhibition (IHI) associated with parametric increases in unimanual force. We measured motor-evoked potential (MEP) recruitment curves (RCs) and short-interval intracortical inhibition (SICI) in $M1_{\text{ipsilateral}}$, IHI from $M1_{\text{contralateral}}$ to $M1_{\text{ipsilateral}}$, and the influence of IHI over SICI using transcranial magnetic stimulation at rest and during 10, 30, and 70% of maximal right wrist flexion force. EMG from the left resting flexor carpi radialis (FCR) muscle was comparable across conditions. Left FCR MEP RCs increased, and SICI decreased with increasing right wrist force. Activity-dependent (rest and 10, 30, and 70%) left FCR maximal MEP size correlated with absolute changes in SICI. IHI decreased with increasing force at matched conditioned MEP amplitudes. IHI and SICI were inversely correlated at increasing forces. In the presence of IHI, SICI decreased at rest and 70% force. In summary, we found activity-dependent changes in (1) SICI in $M1_{\text{ipsilateral}}$, (2) IHI from $M1_{\text{contralateral}}$ to $M1_{\text{ipsilateral}}$, and (3) the influence of IHI over SICI in the left resting hand during force generation by the right hand. Our findings indicate that interactions between GABAergic intracortical circuits mediating SICI and interhemispheric glutamatergic projections between M1s contribute to control activity-dependent changes in corticospinal output to a resting hand during force generation by the opposite hand.

Key words: primary motor cortex; interhemispheric inhibition; transcallosal pathways; intracortical inhibition; transcranial magnetic stimulation; force

Introduction

The primary motor cortex contralateral ($M1_{\text{contralateral}}$) to a moving hand undergoes activity-dependent adaptations (Evarts, 1968; Lemon et al., 1986; Maier et al., 1993; Ashe, 1997). Functional magnetic resonance imaging (fMRI) studies have shown that blood oxygenation level-dependent signal activity in $M1_{\text{contralateral}}$ relates to the type and magnitude of the motor action (Dettmers et al., 1995; Dai et al., 2001), as does the amplitude of motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) (Flament et al., 1993; Hasegawa et al., 2001; Ni et al., 2006).

Task-related adaptations have also been reported in the $M1_{\text{ipsilateral}}$ to an active arm. In monkeys, activity in neurons within $M1_{\text{ipsilateral}}$ depends on the type of upper-limb movement (Tanji et al., 1988; Cisek et al., 2003). fMRI (Dettmers et al., 1995; Thickbroom et al., 1998; Dai et al., 2001; van Duinen et al., 2008) and TMS (Hess et al., 1986; Stedman et al., 1998;

Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Hortobagyi et al., 2003) studies in humans revealed functional changes in $M1_{\text{ipsilateral}}$ during parametric increases in unimanual force. Additionally, motor learning studies have demonstrated the involvement of $M1_{\text{ipsilateral}}$ during acquisition of unimanual motor skills (Chen et al., 1997; Davare et al., 2007; Duque et al., 2007; Perez et al., 2007). Although increasing evidence points to the involvement of $M1_{\text{ipsilateral}}$ during performance of a unimanual motor task, the neuronal mechanisms controlling the corticospinal output originated in the $M1_{\text{ipsilateral}}$ and the resting hand remain unclear. Gaining insight into these mechanisms may contribute to a better understanding of how unimanual and bimanual movements are controlled (Carson, 2005).

Activity in $M1_{\text{ipsilateral}}$ may be influenced by input from the opposite $M1_{\text{contralateral}}$ (Carson, 2005). In humans, interhemispheric inhibitory interactions between M1s can be measured using a paired-pulse TMS technique [interhemispheric inhibition (IHI)] (Ferbert et al., 1992). IHI is absent in patients with callosal lesions or agenesis of the corpus callosum, suggesting that they involve transcallosal pathways (Rothwell et al., 1991; Meyer et al., 1995). Transcallosal pathways between motor cortices and intracortical inhibitory circuits contribute to control the corticospinal output from the M1 (Avanzino et al., 2007; Lee et al., 2007). Therefore, we hypothesized that their interactions may contribute to control the corticospinal output from $M1_{\text{ipsilateral}}$ in an activity-dependent manner.

Received Jan. 9, 2008; revised April 20, 2008; accepted April 20, 2008.

This work was supported in part by the Intramural Research Program of the National Institutes of Health—National Institute of Neurological Disorders and Stroke.

Correspondence should be addressed to Dr. Leonardo G. Cohen, Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892-1430. E-mail: cohenl@ninds.nih.gov.

DOI:10.1523/JNEUROSCI.0093-08.2008

Copyright © 2008 Society for Neuroscience 0270-6474/08/285631-10\$15.00/0

The purpose of the present study was to gain insight into the mechanisms controlling the corticospinal output to a resting hand (originated in $M1_{\text{ipsilateral}}$) during performance of a force generation by the contralateral hand. We measured activity-dependent changes in motor cortical excitability [MEP recruitment curves (RCs)], short-interval intracortical inhibition (SICI) (Kujirai et al., 1993), IHI (Ferbert et al., 1992), and the influence of IHI over SICI (Daskalakis et al., 2002) as a function of parametric changes in unimanual wrist flexion. We found that SICI in $M1_{\text{ipsilateral}}$ and IHI from $M1_{\text{contralateral}}$ to $M1_{\text{ipsilateral}}$ as well as their interactions differed at different force levels, indicating that interhemispheric connections between $M1$ s provide one possible pathway by which $M1_{\text{ipsilateral}}$ is facilitated, whereas modulation of intracortical inhibition may provide a mechanism for the facilitation.

Materials and Methods

Subjects. Ten right-handed healthy volunteers (five women and five men) with an average age of 27.5 ± 4.2 years participated in the study. All subjects gave their informed consent to the experimental procedure, which was approved by the National Institute of Neurological Disorders and Stroke (NINDS) ethics committee. The study was performed in accordance with the Declaration of Helsinki. All subjects participated in three to four testing sessions separated by at least 2 d in the Human Cortical Physiology Section laboratory at NINDS, National Institutes of Health. On each session, subjects performed 10, 30, and 70% of their maximal right wrist flexion force in a randomized order with the right arm while the left arm remained at rest. Measurements of motor cortical function were acquired at the different force levels and at rest (see below, TMS measurements).

Motor task. Subjects were seated in an armchair with both arms flexed at the elbow by 90° and the wrist in a neutral position. The right arm was attached to a custom six-axis load cell (35-E15A; JR3), which measures the forces exerted by the subject (Fig. 1A). Custom software was written to acquire signals from the load cell and to display visual feedback corresponding to rest and 10, 30, and 70% of each subject maximal right wrist flexion force in real time (Matlab R14SP3; Mathworks). Subjects were instructed to respond to the GO signal (target signal) presented on a computer monitor by moving a cursor to a target box. Figure 1B illustrates the location of the target box showing that at 10% of force there is a small distance between the target signal and target box compared with 70% of force. Subjects had to maintain the cursor in the target box for 3–5 s by performing a right wrist flexion isometric contraction. The instruction for the subject was “When you see the GO signal, bend the right wrist and completely relax the left arm.” The maximal right wrist flexion force was measured three times at the beginning of each session, and measurements were averaged. Electrophysiological measurements were taken at rest and during 10, 30, and 70% of maximal right wrist flexion force. At the time the GO signal appeared on the computer screen, a trigger pulse was sent to a software program (Signal), which in turn triggered the TMS. Each TMS pulse was applied during the right flexor carpi radialis (FCR) voluntary muscle burst in all force trials. During testing, the left arm was immobilized by a custom brace to ensure that the same testing position was maintained in all experimental sessions. The left FCR electromyogram (EMG) was displayed as a continuous line on an oscilloscope during right wrist voluntary contraction, and feedback was constantly shown to participants and experimenters. In addition, verbal feedback was provided to the subjects to assure that the left FCR remained at rest at all times. In individual traces, EMG activity on the left FCR was analyzed 500 ms before the stimulus artifact. Trials in which left FCR activity exceeded the background noise level of $25 \mu V$ were excluded from additional analysis (Muellbacher et al., 2000). In $\sim 11.2\%$ of trials, subjects were unable to relax the left FCR completely; this is consistent with a previous report (Hortobagyi et al., 2003).

Electromyographic recordings. Surface electrodes were positioned bilaterally on the skin overlying the FCR muscles in a bipolar montage (interelectrode distance, 2 cm). The amplified EMG signals were filtered

Figure 1. Experimental set-up. **A**, Schematic of the experimental set-up. Subjects were instructed by the monitor to perform different levels of maximal right wrist flexion force while RC, SICI, IHI, and the influence of IHI on SICI were tested in the left, resting hand. The right forearm was immobilized in the manipulandum. The figure also illustrates the position of the TMS coils. **B**, Diagram showing the visual display presented to all subjects during testing. The black vertical line in the center is the cursor that subjects were instructed to move by performing right isometric wrist flexion force over the manipulandum. The “GO” signal (dark gray box located to the left of the cursor) was also the target to where subjects had to move the cursor, maintaining it in position for 3–5 s. The distance between cursor and target related to the magnitude of force required to accomplish each task, normalized to the maximal wrist flexion force determined in each participant.

(bandpass, 25 Hz to 1 kHz), sampled at 2 kHz, and stored on a personal computer for off-line analysis.

TMS measurements. TMS was delivered to the optimal scalp position for activation of the FCR muscles overlying left- and right-hand primary motor cortices (hot spot). The hot spot shows good correlation with stimulation of Brodmann’s area 4 (Mills et al., 1992). MEPs were elicited by transcranial magnetic stimuli delivered from a Magstim 200 stimulator (Magstim Company) through a figure-eight coil (loop diameter, 8 cm; type number SP15560) with a monophasic current waveform. The coil was held tangential 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 (Di Lazzaro et al., 2004). Measures of motor cortical excitability included the resting motor threshold (RMT), MEP RCs, maximal MEP size (MEP-max), SICI in the right $M1_{\text{ipsilateral}}$ and IHI from $M1_{\text{contralateral}}$ to $M1_{\text{ipsilateral}}$. Because of the length of the physiological measurements and to avoid excessive fatigue, all measurements were completed in three to four sessions. Four subjects were asked to return for an additional session to assess the effect of IHI on SICI at 70% of maximal right wrist flexion force and at rest.

MEPs RCs. RCs were measured in the left FCR while the right FCR was at rest and during 10, 30, and 70% of maximal right wrist flexion force in all subjects. At all times, the left FCR remained at rest. Stimulus intensities started at 5% below the RMT, defined as the lowest intensity of TMS output required to evoke MEPs of at least 50 μ V in peak-to-peak amplitude in at least three of five consecutive trials (Rossini et al., 1994). Stimulus intensities were increased in 5% steps of maximal device output until the MEP amplitude did not show additional increases (MEP-max, defined in all participants). Five MEPs were recorded at each stimulation intensity, and each RC determination was repeated twice. Therefore, 10 trials were available to determine MEP amplitudes at each stimulus intensity. TMS pulses were given every 10 s. Several periods of rest were given to subjects between trials to avoid muscle fatigue. MEP amplitudes were measured peak to peak, averaged off-line, and expressed as a percentage of the maximal peripheral motor response (M-max). To determine M-max, the median nerve was stimulated (1 ms rectangular pulse) with supramaximal intensity using bipolar surface electrodes placed at the elbow. Subsequently, data were normalized to the individual RMT of each participant.

SICI. SICI in M1_{ipsilateral} was measured in the left FCR while the right FCR was at rest and during 10, 30, and 70% of maximal right wrist flexion force in all subjects. At all times, the left FCR remained at rest. SICI was tested using the method described by Kujirai et al. (1993). A conditioning stimulus (CS) was set at an intensity of the RMT that elicited an amount of inhibition of ~50% at rest. In all subjects, the intensity used for the CS ranged from 33 to 53% of the stimulator output ($45.3 \pm 6.1\%$ of stimulator output) corresponding to 79.4% of the RMT. This low-intensity stimulus does not activate corticospinal fibers and does not produce changes in the excitability of spinal motoneurons (Di Lazzaro et al., 2001). The same stimulation intensity used for the CS at rest was used during trials in which 10, 30, and 70% of maximal right wrist flexion force was completed. The test stimulus (TS) was adjusted to produce an MEP of ~0.3–0.5 mV at rest. Test stimuli were delivered 2.5 ms after CS, an optimal interstimulus interval for eliciting SICI and to avoid mixture of the two phases of inhibition (Fisher et al., 2002). At this interval, SICI is prone to contamination by the second peak of short-interval intracortical facilitation (Ziemann et al., 1998), which may, to some extent, affect SICI. In cases in which TS size was facilitated by the right wrist flexion, the TS intensity was adjusted to match a size of 0.3–0.5 mV. Ten test stimuli and conditioning stimuli were presented randomly at each condition, and responses were recorded for off-line analysis. Stimuli were applied every 10 s. Several periods of rest were given to subjects between trials to avoid muscle fatigue. Measurements were repeated three times at rest until a consistent baseline was established. After the baseline was established, two measurements were done at each level of right wrist flexion and averaged.

IHI. IHI from M1_{contralateral} to M1_{ipsilateral} was measured in the left FCR during 10, 30, and 70% of maximal right wrist flexion force in all subjects. At all times, the left FCR remained at rest. IHI was tested after a randomized conditioning-test design reported previously (Ferbert et al., 1992). A suprathreshold CS was set at an intensity of the RMT that elicited an amount of inhibition of ~50%. In all subjects, the intensity used for the CS ranged from 58 to 76% of the stimulator output ($67.2 \pm 6\%$ of stimulator output) corresponding to 122.8% of the RMT. The same stimulation intensity was used for the CS during 10, 30, and 70% of force. Testing was also completed, when the intensity of the CS was adjusted to maintain similar conditioned MEP (the “conditioned MEP” is the MEP elicited by the CS and TS) amplitudes during right wrist flexion force (Chen, 2004). Here, the size of the CS was maintained around 1 mV during all levels of right wrist flexion (10% = 1.3 ± 0.8 mV; 30% = 1.4 ± 1 mV; 70% = 1.2 ± 0.8 mV) by decreasing the intensity of the CS pulse. We were not able, in all subjects, to match this MEP amplitude for the conditioned MEP when IHI was tested at rest (even increasing the stimulator output to 100%). Therefore, we completed a separate test to compare the magnitude of IHI with the right FCR at rest and during 10% of force with and without adjustments of the conditioned MEP amplitude.

During all testing, the CS was given 10 ms before a TS delivered to the contralateral side. The CS was always given to the left M1, and the TS was

Table 1. Stimulus conditions used to test the effect of IHI on SICI

Condition	Stimulus intensity		
	CCS10	CS2	TS
1A			0.3 mV
1B		80% RMT	0.3 mV
1C	120% RMT		0.3 mV
1D			TS 0.3 mV _{CCS10}
1E		80% RMT	TS 0.3 mV _{CCS10}
1F	120% RMT		TS 0.3 mV _{CCS10}
1G	120% RMT	80% RMT	TS 0.3 mV _{CCS10}

CCS10, CS applied over the left M1_{ipsilateral} delivered 10 ms before the TS applied over the right M1_{contralateral} for testing IHI; CS2, CS delivered 2.5 ms before TS for testing of SICI; TS 0.3 mV_{CCS10}, TS adjusted to produce a 0.3 mV MEP in the presence of a previous CCS10 pulse.

always given to the right M1. In all testing, the size of the TS was maintained at ~0.3–0.5 mV at rest and during all levels of right wrist flexion. The coil was positioned at the optimal location for activating the left and right FCR, respectively. The two coils were secured by straps and attached to a coil holder to ensure that the same area of the primary motor cortex was stimulated. The handle of the coils pointed backward and laterally ~45° to the midsagittal line. The order of the testing was randomized. Ten test stimuli and conditioning stimuli were averaged during off-line analysis. Stimuli were applied every 10 s. Several periods of rest were given to subjects between trials to avoid muscle fatigue. Measurements were repeated three times at rest until a consistent baseline was established. After the baseline was established two measurements were done at each level of right wrist flexion and averaged.

Effect of IHI on SICI. Previous evidence demonstrated that SICI is reduced in the presence of IHI when tested at rest (Daskalakis et al., 2002). Here, we investigated whether SICI tested in the right M1_{ipsilateral} was altered by IHI from the left M1_{contralateral} to the right M1_{ipsilateral} at rest and during 70% of maximal right wrist flexion force using an experimental paradigm similar to that used before (Daskalakis et al., 2002). Because our results demonstrated that SICI decreased at 70% of force, we asked four subjects who had incomplete decrease in SICI at 70% of force and in whom we were able to elicit reliable SICI by changing the CS intensity to return for an additional testing session. Seven conditions were tested and are listed in Table 1 as 1A–1G. Conditions 1A to 1C were used to determine SICI (1B/1A) and IHI (1C/1A) for a 0.3 mV test MEP. Because IHI inhibits the test MEP and SICI tested in M1_{ipsilateral} may be altered by an attenuated test MEP, for conditions 1D–1G the strength of the TS was adjusted to produce a 0.3 mV test MEP in the presence of an earlier conditioning pulse to M1_{contralateral} that occurred 10 ms before a TS (CCS10). Here, we refer to this TS as a “TS 0.3 mV_{CCS10}.” This adjustment allowed us to match MEP amplitudes to produce a similar degree of corticospinal activation with (1F) and without (1D) preceding a CCS10. We studied SICI in the presence of IHI using three pulses in condition 1G. We measured SICI (1E/1D) and IHI (1F/1D) with the increased TS strength (TS 0.3 mV_{CCS10}). In this experiment, we compared SICI in the presence of IHI (1G/1F) to SICI in the absence of IHI matched for test MEP amplitude (1B/1A) and TS intensity (1E/1D).

Data analysis. In the initial analysis, normal distribution was tested by the Kolmogorov–Smirnov tests for each variable, and Mauchly’s test of sphericity was followed by a repeated-measures ANOVA to determine the effect of TASK (rest and 10, 30, and 70%) on left FCR EMG activity and to determine the effect of TASK (rest and 10, 30, and 70%) and stimulus INTENSITY (1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9) on MEP RCs. We also tested the effect of TASK (rest and 10, 30, and 70%) on SICI and MEP-max. During IHI testing, we assessed the effect of TASK (10, 30, and 70%) on IHI and used a paired *t* test to compare IHI measurements at rest and during 10% of force. Repeated-measures ANOVA was used to test the effect of IHI on SICI. A Bonferroni *post hoc* test was used for multiple comparisons. Significance was set at $p < 0.05$. Variance is expressed as mean $\pm$ SD. Pearson correlation analysis was used to test correlations as needed.

Results

MEP RCs

Figure 2*A* illustrates left FCR MEPs recorded in a single subject while the right FCR was at rest and during 10, 30, and 70% of maximal right wrist flexion force. Repeated-measures ANOVA showed effect of TASK ($F = 23.2$; $p \leq 0.001$), INTENSITY ($F = 43.2$; $p \leq 0.001$), and their interaction TASK $\times$ INTENSITY ($F = 1.7$; $p = 0.02$) on left FCR MEP RCs in all subjects (Fig. 2*B*). *Post hoc* testing showed a significant increase in RC amplitude at 70% ($p \leq 0.001$) and 30% ($p \leq 0.001$) of force compared with rest. MEP RCs were significantly larger at 70% compared with 30% ($p \leq 0.001$) and 10% ($p \leq 0.001$) of force. MEPs RC were significantly larger at 30% compared with 10% ($p \leq 0.01$). No differences were observed between MEPs RC at rest and during 10% ($p = 0.2$) of force. RMTs remained unchanged across conditions ($F = 1.56$; $p = 0.2$). Repeated-measures ANOVA showed effect of TASK ($F = 8.9$; $p \leq 0.001$) on MEP-max. *Post hoc* testing showed a significant increase in MEP-max at 70% ($11.8 \pm 6.6\%$ of M-max; $p \leq 0.001$) compared with rest ($6.7 \pm 3\%$ of M-max; $p \leq 0.001$) and 10% ($7.2 \pm 2.9\%$ of M-max; $p \leq 0.01$) of force. No difference was observed between MEP-max at rest and 10% ($p = 0.9$) and 30% ($p = 0.2$) of force. MEP-max were larger at 70% compared with 30% ($p = 0.03$). EMG activity in the right FCR increased with increasing levels of right wrist flexion ($F = 7.2$; $p \leq 0.01$), while no changes were observed in EMG activity in the left FCR ($F = 0.2$; $p = 0.8$). In summary, left FCR MEPs RC amplitude increased with increasing levels of force generated by the right-hand.

SICI

Figure 3*A* illustrates changes in SICI in $M1_{\text{ipsilateral}}$ recorded in a single subject while the right FCR was at rest and during 10, 30 and 70% of force. Repeated-measures ANOVA showed a significant effect of TASK (rest and 10%, 30% and 70%; $F = 20.03$; $p \leq 0.001$) (Fig. 3*B*) on SICI. *Post hoc* analysis revealed a significant attenuation of SICI (Cond. MEP $\times$ 100)/Test MEP) at 70% ($89.6 \pm 24.6\%$; $p \leq 0.001$) and 30% ($62.2 \pm 23.8\%$; $p = 0.04$) compared with rest ($42.7 \pm 9.2\%$). SICI was decreased at 70% compared with 30% ($p \leq 0.001$) and 10% ($p \leq 0.01$) of force. SICI was decreased, although not significantly, at 30% compared with 10% ($p = 0.08$) of force. No difference was observed between SICI at rest and 10% (mean, $44.8 \pm 11.1\%$; $p = 0.9$). Test MEP amplitudes across conditions were comparable (rest = 0.34 ± 0.2 mV; 10% =

Figure 2. Recruitment curves. *A*, MEPs recorded from the left FCR of a representative subject during performance of different levels of maximal right wrist flexion force (rest and 10, 30, and 70%). In the left column, traces show burst of EMG activity across the different force levels, whereas in the right column, traces show 1 s of EMG activity within each burst. Calibration bars are shown for the left FCR at rest and the right FCR across force levels. Note the increasing levels of EMG activity in the right FCR (R FCR) while the left FCR (L FCR) remains at rest. *B*, Group data ($n = 10$) showing left FCR MEP RCs at rest and during 10, 30, and 70% of maximal right wrist flexion force. The abscissa shows transcranial magnetic stimulus intensity expressed relative to the RMTs in each subject, and the ordinate shows MEP amplitudes as a percentage of the left FCR M-max. Error bars indicate SEs. * $p < 0.05$. Note the progressive increment in RCs with increasing levels of maximal right wrist flexion force.

0.3 ± 0.15 mV; 30% = 0.32 ± 0.14 mV; 70% = 0.35 ± 0.22 mV; $F = 0.68$; $p = 0.57$). EMG activity in the right FCR increased with increasing levels of right wrist flexion ($F = 8.1$; $p \leq 0.01$), with no changes in EMG activity in the left FCR ($F = 0.9$; $p = 0.5$). In summary, SICI tested in $M1_{\text{ipsilateral}}$

Figure 3. SICI in $M1_{ipsilateral}$. **A**, SICI from the left FCR of a representative subject during performance of different levels of maximal right wrist flexion force (rest and 10, 30, and 70%). Solid lines, Test MEPs; dashed lines, conditioned MEPs. Note the well defined SICI at rest and 10% of maximal right wrist flexion force and the progressive disinhibition shown at 30 and 70% of maximal right wrist flexion force. **B**, Group data ($n = 10$). The abscissa shows all conditions tested (rest and 10, 30, and 70%). The ordinate indicates the magnitude of SICI in $M1_{ipsilateral}$. The size of the conditioned MEP is expressed as a percentage of the size of test MEP amplitude (horizontal dotted line). Note the progressive attenuation in SICI at 30 and 70% of maximal right wrist flexion force. **C**, Relationship between SICI in $M1_{ipsilateral}$ (abscissa, vertical dotted line shows complete absence of SICI) and left FCR MEP-max (ordinate) at all conditions tested. Note that subjects that showed less SICI are those that showed larger left FCR MEP-max. Error bars indicate SEs. * $p < 0.05$. Cond. MEP, Conditioned MEP.

decreased with increasing levels of force generated by the right hand.

IHI

With matched conditioned and test MEP amplitudes across force levels, Figure 4A illustrates changes in IHI from $M1_{contralateral}$ to $M1_{ipsilateral}$ recorded in a single subject during 10, 30, and 70% of force. Repeated-measures ANOVA showed a significant effect of TASK (10, 30, and 70%; $F = 9.5$; $p \leq 0.01$) (Fig. 4B) on IHI. *Post hoc* analysis revealed a significant attenuation of IHI (conditioned MEP $\times$ 100)/test MEP) at 70% ($82.7 \pm 26\%$) compared with 10% ($48 \pm 10\%$; $p \leq 0.001$) of force. IHI was decreased at 30% ($71.7 \pm 22.8\%$; $p = 0.04$) compared with 10% ($p = 0.02$), but no differences were observed between 70 and 30% ($p = 0.4$). Test (10% = 0.35 ± 0.2 mV; 30% = 0.40 ± 0.16 mV; 70% = 0.45 ± 0.3 mV; $F = 1.38$; $p = 0.27$) and conditioned MEP amplitudes (10% = 1.3 ± 0.8 mV; 30% = 1.4 ± 1 mV; 70% = 1.2 ± 0.8 mV; $F = 1.4$; $p = 0.3$) were comparable across conditions. EMG activity in the right FCR increased with right wrist flexion force ($F = 6.3$; $p \leq 0.01$), and no changes were observed in left FCR EMG activity ($F = 1.08$; $p = 0.4$). With matched conditioned and test MEP amplitudes in a different set of experiments, we compared IHI at rest and during 10% of force. Here, IHI (rest = $55 \pm 24\%$; 10% = $68 \pm 20.5\%$; $p = 0.36$) was comparable while the test (rest = 0.35 ± 0.21 mV; 10% = 0.41 ± 0.26 mV; $p = 0.2$) and conditioned MEP (rest = 0.35 ± 0.21 mV; 10% = 0.41 ± 0.26 mV; $p = 0.2$) amplitudes were matched. EMG activity in the right FCR increased at 10% compared with rest ($p = 0.01$) with no changes in EMG activity in the left FCR ($p = 0.43$).

Without adjusting for the size of the conditioned MEP amplitude, repeated-measures ANOVA showed a significant effect of TASK (10, 30, and 70%; $F = 12.8$; $p \leq 0.001$) on IHI. IHI (conditioned MEP $\times$ 100)/test MEP) was significantly increased (as seen by lower numbers) at 70% ($31.3 \pm 21\%$) compared with 30% ($64 \pm 21.5\%$; $p \leq 0.001$) and 10% ($52 \pm 11.8\%$; $p = 0.02$) of force. Test MEP amplitudes were comparable (10% = 0.46 ± 0.22 mV; 30% = 0.48 ± 0.2 mV; 70% = 0.53 ± 0.32 mV; $F = 0.26$; $p = 0.7$), whereas the size of the conditioned MEP increased with increasing force (10% = 1.0 ± 0.6 mV; 30% = 1.7 ± 1 mV; 70% = 3.4 ± 1.4 mV). EMG activity in the left FCR was comparable across conditions ($p = 0.51$). Without adjusting for the size of the conditioned MEP amplitude, we also compared IHI at rest and during 10% of force in a different set of experiments. IHI (conditioned MEP $\times$ 100)/test MEP) increased at 10% ($48 \pm 17.7\%$) compared with rest ($63.6 \pm 22\%$; $p = 0.04$) when test MEP amplitudes were comparable (rest = 0.28 ± 0.22 mV; 10% = 0.29 ± 0.19 mV; $p = 0.55$), and the size of the conditioned MEP increased at 10% (1.15 ± 0.56 mV) compared with rest (0.34 ± 0.32 mV; $p \leq 0.001$). EMG activity in the right FCR increased at 10% compared with rest ($p = 0.01$), whereas no changes were observed in EMG activity in the left FCR ($p = 0.73$).

In summary, IHI from $M1_{contralateral}$ to $M1_{ipsilateral}$ decreases with increasing levels of force generated by the right hand when the size of the conditioned MEP is matched across conditions. However, IHI from $M1_{contralateral}$ to $M1_{ipsilateral}$ increases with increasing levels of force generated by the right hand when the size of the conditioned MEP is not adjusted between force levels.

Correlation analysis

When all conditions (rest and 10, 30, and 70%) were tested, we found a significant correlation between SICI in $M1_{ipsilateral}$ and left FCR MEP-max ($r = 0.73$; $p \leq 0.001$) (Fig. 3C) and between SICI and force levels ($r = 0.75$; $p \leq 0.001$). Subjects who had larger MEP-max during right wrist flexion were also the ones with less SICI. The analysis of each separate condition revealed a significant correlation between MEP-max and SICI at 30% ($r = 0.68$; $p = 0.03$) and 70% ($r = 0.8$; $p \leq 0.001$) of force. In contrast, we found no correlation between MEP-max and IHI when tested with ($r = -0.1$; $p = 0.46$) (Fig. 4C) or without ($r = -0.06$; $p = 0.6$) adjustments of the conditioned MEP amplitude. SICI and IHI were correlated only when IHI was tested by adjusting the conditioned MEP amplitude (Fig. 5) (70%: $r = -0.68$, $p = 0.01$; 30%: $r = -0.52$, $p = 0.12$; 10%: $r = 0.14$, $p = 0.69$; rest: $r = 0.12$, $p = 0.7$).

Effect of IHI on SICI

Figure 6 illustrates the effect of IHI from $M1_{contralateral}$ to $M1_{ipsilateral}$ on SICI in $M1_{ipsilateral}$ at rest and during 70% of force. The experimental setting for this experiment is shown in Table 1. The MEP amplitude for TS 0.3 mV was 0.26 ± 0.17 mV (Table 1,

condition 1A) and for TS 0.3 mV_{CCS10} was 0.56 ± 0.43 mV (condition 1D). When a TS 0.3 mV_{CCS10} was preceded by CCS10, the test MEP amplitude was 0.3 ± 0.27 mV (Table 1, condition 1F). Then, the test MEP amplitudes for conditions 1A and 1F were matched ($p = 0.5$) (Table 1). Compared with a TS 0.3 mV_{CCS10} (Table 1, condition 1D), a preceding CS2 (Table 1, condition 1E) or CCS10 (Table 1, condition 1F) inhibited the test response. The nature of the test MEP had a significant effect on SICI ($F = 8.6$; $p = 0.01$). The *post hoc* test showed a significant reduction in SICI in the presence of IHI ($96 \pm 26\%$) (Table 1, conditions 1G/1F) compared with SICI alone ($52 \pm 14\%$; $p = 0.02$) (Table 1, conditions 1B/1A; Fig. 6D) and to SICI when comparisons were made using the TS 0.3 mV_{CCS10} ($46 \pm 5\%$; $p = 0.03$) (Table 1, conditions 1E/1D; Fig. 6D) during 70% of force. In all subjects, we observed the disinhibitory effect of IHI on SICI. In the same subjects at rest (TS 0.3 mV, 0.41 ± 0.33 mV; TS 0.3 mV_{CCS10}, 0.79 ± 0.41 mV), the test MEP had a significant effect on SICI ($F = 8.4$; $p = 0.01$). SICI was significantly reduced in the presence of IHI ($66.4 \pm 34\%$) (Table 1, conditions 1G/1F) compared with SICI alone ($41 \pm 24\%$; $p = 0.04$) (Table 1, conditions 1B/1A; Fig. 6C) and to SICI when comparisons were made using the TS 0.3 mV_{CCS10} ($36.3 \pm 23.7\%$; $p = 0.02$) (Table 1, conditions 1E/1D; Fig. 6C). Our results show that the inhibition from SICI (conditions 1B/1A, $52 \pm 14\%$; conditions 1E/1D, $46 \pm 5\%$) and IHI (conditions 1C/1A, $58.7 \pm 10\%$; conditions 1F/1D, $51.6 \pm 7\%$) do not add together, consistent with the idea that SICI is disinhibited by transcallosal input. In addition, the disinhibitory effect of IHI on SICI was significantly stronger at 70% of force compared with rest ($p = 0.03$). In summary, at rest and during 70% of force, IHI from M1_{contralateral} to M1_{ipsilateral} decreased SICI in M1_{ipsilateral}. However, the disinhibitory effect of IHI on SICI is stronger at 70% of force compared with rest.

Discussion

In the present study, we investigated the neuronal mechanisms contributing to control the corticospinal output to a resting hand during performance of a contralateral unimanual force generation task. We found activity-dependent changes in (1) SICI in M1_{ipsilateral}, which controls the resting hand, (2) IHI from M1_{contralateral} to M1_{ipsilateral}, and (3) the influence of IHI over SICI in the left resting hand during performance of a parametric force generation task with the right hand.

Previous studies showed that performance of high levels of force with one hand results in an increase in corticomotor excitability targeting the contralateral resting hand (Hess et al., 1986; Meyer et al., 1995; Stedman et al., 1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Hortobagyi et al., 2003), whereas performance of low levels of force led to conflicting results: facilitation, inhibition, or no changes (Hess et al., 1986; Stedman et al., 1998; Liepert et al., 2001; Sohn et al., 2003). These results raised the untested hypothesis that the mechanisms within the

Figure 4. IHI from M1_{contralateral} to M1_{ipsilateral}. **A**, IHI from M1_{contralateral} to M1_{ipsilateral} (10 ms) recorded from the left FCR of a representative subject during performance of different levels of maximal right wrist flexion force (10, 30, and 70%; gray squares). Solid lines, Test MEPs; dashed lines, conditioned MEPs. Recordings from the right FCR are shown to demonstrate with solid lines the MEP evoked by the CS (for eliciting IHI) and in light gray solid lines the raw EMG activity in the right FCR at the time of application of the TS alone. Note the well defined IHI at 10% and the progressive disinhibition shown at 30 and 70% of maximal right wrist flexion force. **B**, Group data ($n = 10$). The abscissa shows the three levels of maximal right wrist flexion force (10, 30, and 70%). The ordinate indicates the magnitude of IHI, in which the size of the conditioned MEP is expressed as a percentage of the size of test MEP amplitude. Note the progressive attenuation in IHI at 30 and 70% of maximal right wrist flexion force (bars approaching the horizontal dotted line). **C**, Relationship between IHI from M1_{contralateral} to M1_{ipsilateral} and left FCR MEP-max at all three levels of maximal right wrist flexion force. Error bars indicate SEs. * $p < 0.05$. Cond. MEP, Conditioned MEP.

primary motor cortex controlling corticospinal output to a resting hand may differ in an activity-dependent manner. To address this question, we evaluated various neurophysiological parameters including (1) RCs to TMS in M1_{ipsilateral}, which reflect excitability of high- and low-threshold motor cortical neurons to the stimulating magnetic coil (Siebner and Rothwell, 2003); (2) SICI in M1_{ipsilateral}, which reflects activity in intracortical GABAergic inhibitory interneurons (Kujirai et al., 1993; Ziemann et al., 1996) shown to contribute to control the output from contralateral corticospinal neurons (Ziemann et al., 1996; Reynolds and Ashby, 1999; Buccolieri et al., 2004); (3) IHI from M1_{contralateral} to M1_{ipsilateral}, mediated predominantly by transcallosal glutamatergic projections, acting through local GABAergic interneurons (Berlucchi, 1990; Ferbert et al., 1992; Meyer et al., 1995; Gerloff et al., 1998; Di Lazzaro et al., 1999; Chen, 2004); and (4) the influence of IHI over SICI (Daskalakis et al., 2002) controlling the resting hand with parametric changes in wrist force in the opposite hand.

MEP RCs

We found more prominent facilitation of MEPs elicited in the left resting FCR muscle at 30 and 70% of force than at rest and 10% of force when background EMG activity was comparable (see Results, MEP RCs). These findings are in agreement with previous studies demonstrating an increase in MEP size in a resting hand during higher levels of unimanual force generation by the opposite hand (Hess et al., 1986; Meyer et al., 1995; Stedman et al., 1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Hor-

Figure 5. Relationship between IHI from M1_{contralateral} to M1_{ipsilateral} and SICI tested in M1_{ipsilateral}. SICI in M1_{ipsilateral} and IHI from M1_{contralateral} to M1_{ipsilateral} at 10% (**A**), 30% (**B**), and 70% (**C**) of right wrist flexion force. In all graphs, the ordinate shows the magnitude of IHI from M1_{contralateral} to M1_{ipsilateral} in which the size of the conditioned MEP (Cond. MEP) is expressed as a percentage of the size of test MEP amplitude. The abscissa shows the magnitude of SICI tested in M1_{ipsilateral} in which the size of the conditioned MEP is expressed as a percentage of the size of test MEP amplitude. Note that at 70% of maximal right wrist flexion force the decrease in SICI is associated with an increase in IHI.

tobagyi et al., 2003). These results are also in agreement with Rau et al. (2003) demonstrating that during forceful phasic finger movements M1_{ipsilateral} is essentially facilitated.

SICI

We found that at 30 and 70% of right wrist force SICI tested in the left resting FCR was decreased compared with rest and to 10% of

force. Although a previous study showed that maximal voluntary contraction of one hand decreased SICI in the other hand (Muellbacher et al., 2000), our results, to our knowledge, are the first reporting the influence of parametric increases in unimanual force generation on SICI in the M1_{ipsilateral}. We found that the magnitude of the exerted force correlated with the magnitude of changes in SICI. These results document activity-dependent modulation of SICI that might contribute to facilitate corticospinal excitability in M1_{ipsilateral} (Ziemann et al., 1996; Reynolds and Ashby, 1999; Buccolieri et al., 2004), a proposal consistent with the strong correlation that we found between the size of left FCR MEP-max and SICI across conditions (Fig. 3C). Given that the instruction to our subjects was to avoid contracting the left resting arm (see Materials and Methods), it would be theoretically possible that the reduction in SICI might be related to “volitional inhibition” (i.e., to the intent to suppress unwanted voluntary movements in the resting arm) (Waldvogel et al., 2000). However, such interpretation seems unlikely because volitional inhibition results in increases in SICI and suppression of corticospinal excitability, opposite to our results (Waldvogel et al., 2000; Sohn et al., 2002; Coxon et al., 2006).

IHI from M1_{contralateral} to M1_{ipsilateral}

Our results also showed activity-dependent changes in IHI during performance of a force generation task by the opposite hand. Because in our experiment the conditioning transcranial magnetic stimulus was applied to the M1_{contralateral} to the active hand, there are some considerations that need to be taken into account. The activity of intracortical circuits in M1_{contralateral} changes with increasing levels of force (Zoghi and Nordstrom, 2007), and intracortical circuits influence IHI and corticospinal output originated from M1_{contralateral} (Lee et al., 2007). Therefore, we first tested IHI by matching the conditioned MEP amplitude to elicit the same level of corticospinal output across conditions (Chen, 2004). When the conditioned MEP amplitude was maintained constant, as required for IHI measurements (Chen, 2004), IHI at 30 and 70% force decreased compared with rest and to 10% force. Interestingly, the magnitude of left FCR MEP-max did not correlate with the changes in IHI, suggesting a less direct influence of IHI, compared with SICI, on MEP facilitation in M1_{ipsilateral}. When we did not correct for changes in CS MEP size, we found, as expected, that the same CS intensities resulted in much larger conditioned MEP amplitudes at higher levels of force. IHI tested in the left resting FCR increased at 10 and 70% of force, in agreement with previous results tested during mild voluntary contraction only (Ferber et al., 1992; Hamzei et al., 2002; Talelli et al., 2008). More importantly and similar to the results when conditioned MEP amplitudes were corrected for, the magnitude of changes in the left FCR MEP-max also did not correlate with the magnitude of increases in IHI. Altogether, results using both techniques to measure IHI pointed clearly toward a less direct influence of IHI on MEP facilitation observed in M1_{ipsilateral}. It is critical to note that, on one hand, by adjusting the size of the conditioned MEP (accomplished by decreasing the CS intensity), we normalized IHI to the increase in corticospinal excitability caused by voluntary contraction. On the other hand, the IHI results without adjusting the CS intensity (which caused larger MEPs in the right FCR muscle, as expected) might be interpreted as a “true” reflection of how IHI originating in the contralateral M1 changed with different degrees of contraction. Overall, these results indicate that changes in the state of the motor cortex re-

ceiving the CS should be carefully weighted in the interpretation of IHI results.

It should also be kept in mind that there are multiple interhemispheric effects that can be assessed by TMS at different stimulus intensities and time intervals (Reis et al., 2008). We designed and controlled this study to evaluate specifically IHI at an interstimulus interval and stimulus intensity accepted to elicit this particular effect (Ferbert et al., 1992; Chen et al., 2003). Changes in these parameters may elicit different effects such as interhemispheric facilitation (Hanajima et al., 2001) or might mediate IHI through other mechanisms (Chen et al., 2003), not tested under our experimental design.

Interactions between IHI and SICI

An important finding in our investigation was that, in the presence of IHI, SICI in M1_{ipsilateral} decreased at 70% of force. A first conclusion from these findings is that the influence of IHI over SICI appears to operate in behaviorally relevant settings (performance of a unimanual force generation task) as it does at rest (Daskalakis et al., 2002) (Fig. 6). These results suggest that our findings of a decreased SICI in M1_{ipsilateral} may be related to changes in IHI. This is supported by the stronger disinhibitory effect of IHI on SICI at 70% of force compared with rest. Also, the inverse correlation between IHI–SICI at 70% of force when we adjusted for the conditioned MEP amplitude (i.e., subjects with larger IHI were those who showed less SICI) suggest an activity-dependent link between both mechanisms. Although speculative, the strong disinhibitory effect of IHI on SICI during 70% of force may contribute to balance activity of corticospinal cells in M1_{ipsilateral}.

Our findings suggest that activity-dependent modulation of SICI, IHI, and their interactions contribute to control the corticospinal output to a resting hand during performance of a unimanual force generation task. This conclusion is in tune with the view that intracortical function associated with performance of unimanual motor tasks relies on an active and often discrete interaction between both M1s (Murase et al., 2004; Duque et al., 2005, 2007), although differences may be seen between movements of the dominant and nondominant hand (Liepert et al., 2001; Ziemann and Hallett, 2001; Vines et al., 2006; Duque et al., 2007). On one side, our results show that a strong unimanual movement provides extra excitation to the M1_{ipsilateral} in the absence of involuntary EMG activity in the contralateral resting arm. A possibility is that functional changes in SICI, IHI, and their interactions may be seen as processes tuning the corticospinal motor output from M1_{ipsilateral}. In our setting, at 10% of force the overall net interhemispheric effect targeting M1_{ipsilateral} is more inhibitory and similar to rest, whereas at 70%, there is an overall release of inhibition. This is consistent with findings showing that during a strong unimanual contraction it is more likely to have the presence of mirror EMG activity than during

Figure 6. Effect of IHI from M1_{contralateral} to M1_{ipsilateral} on SICI tested in M1_{ipsilateral} at rest and 70% of force. **A, B**, The first four traces (average of 10 single trials recorded from the left FCR) show test MEP amplitudes alone (Table 1, condition 1D), SICI tested in M1_{ipsilateral} alone (Table 1, condition 1E), IHI from M1_{contralateral} to M1_{ipsilateral} alone (Table 1, condition 1F), and the effects of the CS applied for IHI on SICI tested in M1_{ipsilateral} (IHI + SICI) (Table 1, condition 1G) at rest (**A**) and during 70% of force (**B**). The fifth trace (average of 10 single trials recorded from the right FCR) shows the MEP amplitude elicited by the CS required to induce IHI at rest (**A**) and during 70% of force (**B**). Note that at 70% of force, compared with a test MEP alone (first trace), a preceding CS at 2.5 ms (second trace, SICI) and at 10 ms (third trace, IHI) inhibited the test response. However, with IHI followed by SICI there was little additional inhibition (fourth trace, IHI + SICI). **C, D**, Group data ($n = 4$). The abscissa shows SICI tested in M1_{ipsilateral} in the absence of IHI matched for test MEP amplitude (Table 1, conditions 1B/1A) and TS intensity (Table 1, conditions 1E/1D) and SICI in the presence of IHI (Table 1, conditions 1G/1F). The ordinate shows the size of the conditioned MEP expressed as a percentage of the size of test MEP. Error bars indicate SDs. * $p < 0.05$.

small efforts (Zijdewind et al., 2006). In other unimanual tasks, the existence of disinhibition in the M1_{ipsilateral} may vary depending on the behavioral context: distal versus proximal muscles involved (Harris-Love et al., 2007), level of complexity of the movement (Avanzino et al., 2008) and learning related improvements (Chen et al., 1997; Davare et al., 2007; Duque et al., 2007; Perez et al., 2007). On the other side, the activity-dependent changes in IHI–SICI identified here may provide insights to better understand unwanted mirror EMG activity in the opposite limb, which is frequently reported during unimanual movements in patients with motor disorders (Hashimoto et al., 2001; Georgiou-Karistianis et al., 2004; Cincotta and Ziemann, 2008). Although it has been widely considered that mirroring may relate to IHI (Carson, 2005; Daffertshofer et al., 2005; Duque et al., 2005, 2007; Li et al., 2007), our results suggest a more complex relationship in which mirroring might relate to interactions between circuits, such as IHI and SICI in the M1_{ipsilateral} rather than only to IHI. These results raise the importance of considering interactions between multiple circuits and not only the state of individual pathways when we search for the neural underpinnings of a behavioral phenomenon-like mirroring. Then, it is theoretically possible that activity-dependent abnormalities in IHI–SICI interactions may influence behavioral deficits reported

in the “unaffected” limb after brain lesions such as stroke (Winstein and Pohl, 1995; Desrosiers et al., 1996; Yarosh et al., 2004; Murase et al., 2004; Ward and Cohen, 2004), an issue for future investigation. Finally, another possible functional role of these activity-dependent changes is that they operate when there is a need to control extended and bilateral overflow of high levels of motor activity, as during 70% of force. If so, IHI–SICI interactions targeting the M1_{ipsilateral} to a hand engaged in unimanual force generation may vary according to the need to control corticospinal output to a resting hand in different behavioral sets.

References

- Ashe J (1997) Force and the motor cortex. *Behav Brain Res* 87:255–269.
- Avanzino L, Teo JT, Rothwell JC (2007) Intracortical circuits modulate transcallosal inhibition in humans. *J Physiol (Lond)* 583:99–114.
- Avanzino L, Bove M, Trompetto C, Tacchino A, Ogliastro C, Abbruzzese G (2008) 1-Hz repetitive TMS over ipsilateral motor cortex influences the performance of sequential finger movements of different complexity. *Eur J Neurosci* 27:1285–1291.
- Berlucchi G (1990) Commissurotomy studies in animals. In: *Handbook of neurophysiology*, Vol 4 (Boller F, Grafman J, eds), pp 9–47. Amsterdam: Elsevier.
- Buccolieri A, Abbruzzese G, Rothwell JC (2004) Relaxation from a voluntary contraction is preceded by increased excitability of motor cortical inhibitory circuits. *J Physiol (Lond)* 558:685–695.
- Carson RG (2005) Neural pathways mediating bilateral interactions between the upper limbs. *Brain Res Brain Res Rev* 49:641–662.
- Chen R (2004) Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res* 154:1–10.
- Chen R, Gerloff C, Hallett M, Cohen LG (1997) Involvement of the ipsilateral motor cortex in finger movements of different complexities. *Ann Neurol* 41:247–254.
- Chen R, Yung D, Li JY (2003) Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 89:1256–1264.
- Cincotta M, Ziemann U (2008) Neurophysiology of unimanual motor control and mirror movements. *Clin Neurophysiol* 119:744–762.
- Cisek P, Crammond DJ, Kalaska JF (2003) Neural activity in primary motor and dorsal premotor cortex in reaching tasks with the contralateral versus ipsilateral arm. *J Neurophysiol* 89:922–942.
- Coxon JP, Stinear CM, Byblow WD (2006) Intracortical inhibition during volitional inhibition of prepared action. *J Neurophysiol* 95:3371–3383.
- Daffertshofer A, Peper CE, Beek PJ (2005) Stabilization of bimanual coordination due to active interhemispheric inhibition: a dynamical account. *Biol Cybern* 92:101–109.
- Dai TH, Liu JZ, Sahgal V, Brown RW, Yue GH (2001) Relationship between muscle output and functional MRI-measured brain activation. *Exp Brain Res* 140:290–300.
- Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R (2002) The mechanisms of interhemispheric inhibition in the human motor cortex. *J Physiol (Lond)* 543:317–326.
- Davare M, Duque J, Vandermeeren Y, Thonnard JL, Olivier E (2007) Role of the ipsilateral primary motor cortex in controlling the timing of hand muscle recruitment. *Cereb Cortex* 17:353–362.
- Desrosiers J, Bourbonnais D, Bravo G, Roy P-M, Guay M (1996) Performance of the “unaffected” upper extremity of elderly stroke patients. *Stroke* 27:1564–1570.
- Dettmers C, Fink GR, Lemon RN, Stephan KM, Passingham RE, Silbersweig D, Holmes A, Ridding MC, Brooks DJ, Frackowiak RSJ (1995) Relation between cerebral activity and force in motor areas of the human brain. *J Neurophysiol* 74:802–815.
- Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Exp Brain Res* 124:520–524.
- Di Lazzaro V, Oliviero A, Profice P, Meglio M, Cioni B, Tonali P, Rothwell JC (2001) Descending spinal cord volleys evoked by transcranial magnetic and electrical stimulation of the motor cortex leg area in conscious humans. *J Physiol (Lond)* 537:1047–1058.
- Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Mazzone P, Insola A, Tonali PA, Rothwell JC (2004) The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clin Neurophysiol* 115:255–266.
- Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG (2005) Transcallosal inhibition in chronic subcortical stroke. *NeuroImage* 28:940–946.
- Duque J, Mazzocchio R, Stefan K, Hummel F, Olivier E, Cohen LG (2007) Memory formation in the motor cortex ipsilateral to a training hand. *Cereb Cortex*, in press.
- Evarts EV (1968) Relation of pyramidal tract activity to force exerted during voluntary movement. *J Neurophysiol* 31:14–27.
- Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. *J Physiol (Lond)* 453:525–546.
- Flament D, Goldsmith P, Buckley CJ, Lemon RN (1993) Task dependence of responses in first dorsal interosseous muscle to magnetic brain stimulation in man. *J Physiol (Lond)* 464:361–378.
- Georgiou-Karistianis N, Hoy KE, Bradshaw JL, Farrow M, Chiu E, Churchyard A, Fitzgerald PB, Aramatas CA (2004) Motor overflow in Huntington’s disease. *J Neurol Neurosurg Psychiatry* 75:904–906.
- Gerloff C, Cohen LG, Floeter MK, Chen R, Corwell B, Hallett M (1998) Inhibitory influence of the ipsilateral motor cortex on responses to stimulation of the human cortex and pyramidal tract. *J Physiol (Lond)* 510:249–259.
- Hamzei F, Dettmers C, Rzanny R, Liepert J, Büchel C, Weiller C (2002) Reduction of excitability (“inhibition”) in the ipsilateral primary motor cortex is mirrored by fMRI signal decreases. *NeuroImage* 17:490–496.
- Hanajima R, Ugawa Y, Machii K, Mochizuki H, Terao Y, Enomoto H, Furubayashi T, Shiio Y, Uesugi H, Kanazawa I (2001) Interhemispheric facilitation of the hand motor area in humans. *J Physiol (Lond)* 531:849–859.
- Harris-Love ML, Perez MA, Chen R, Cohen LG (2007) Interhemispheric inhibition in distal and proximal arm representations in the primary motor cortex. *J Neurophysiol* 97:2511–2515.
- Hasegawa Y, Kasai T, Tsuji T, Yahagi S (2001) Further insight into the task-dependent excitability of motor evoked potentials in first dorsal interosseous muscle in humans. *Exp Brain Res* 140:387–396.
- Hashimoto T, Shindo M, Yanagisawa N (2001) Enhanced associated movements in the contralateral limbs elicited by brisk voluntary contraction in choreic disorders. *Clin Neurophysiol* 112:1612–1717.
- Hess CW, Mills KR, Murray NM (1986) Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neurosci Lett* 71:235–240.
- Hortobagyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC (2003) Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. *J Neurophysiol* 90:2451–2459.
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. *J Physiol (Lond)* 471:501–519.
- Lee H, Gunraj C, Chen R (2007) The effects of inhibitory and facilitatory intracortical circuits on interhemispheric inhibition in the human motor cortex. *J Physiol (Lond)* 580:1021–1032.
- Lemon RN, Mantel GW, Muir RB (1986) Corticospinal facilitation of hand muscles during voluntary movement in the conscious monkey. *J Physiol (Lond)* 381:497–527.
- Li JY, Espay AJ, Gunraj CA, Pal PK, Cunic DI, Lang AE, Chen R (2007) Interhemispheric and ipsilateral connections in Parkinson’s disease: relation to mirror movements. *Mov Disord* 22:813–821.
- Liepert J, Dettmers C, Terborg C, Weiller C (2001) Inhibition of ipsilateral motor cortex during phasic generation of low force. *Clin Neurophysiol* 112:114–121.
- Maier MA, Bennett KM, Hepp-Reymond MC, Lemon RN (1993) Contribution of the monkey corticomotoneuronal system to the control of force in precision grip. *J Neurophysiol* 69:772–785.
- Meyer BU, Roricht S, Graf von Einsiedel H, Kruggel F, Weindl A (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118:429–440.
- Mills KR, Boniface SJ, Schubert M (1992) Magnetic brain stimulation with a double coil: the importance of coil orientation. *Electroencephalogr Clin Neurophysiol* 85:17–21.

- Muellbacher W, Facchini S, Boroojerdi B, Hallett M (2000) Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. *Clin Neurophysiol* 111:344–349.
- Murase N, Duque J, Mazzocchio R, Cohen LG (2004) Influence of inter-hemispheric interactions on motor function in chronic stroke. *Ann Neurol* 55:400–409.
- Ni Z, Takahashi M, Yamashita T, Liang N, Tanaka Y, Tsuji T, Yahagi S, Kasai T (2006) Functional demanded excitability changes of human hand motor area. *Exp Brain Res* 170:141–148.
- Perez MA, Wise SP, Willingham DT, Cohen LG (2007) Neurophysiological mechanisms involved in transfer of procedural knowledge. *J Neurosci* 27:1045–1053.
- Rau C, Plewnia C, Hummel F, Gerloff C (2003) Event-related desynchronization and excitability of the ipsilateral motor cortex during simple self-paced finger movements. *Clin Neurophysiol* 114:1819–1826.
- Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love ML, Perez MA, Ragert P, Rothwell JC, Cohen LG (2008) Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol (Lond)* 586:325–351.
- Reynolds C, Ashby P (1999) Inhibition in the human motor cortex is reduced just before a voluntary contraction. *Neurology* 53:730–735.
- Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijević MR, Hallett M, Katayama Y, Lücking CH, Maertens de Noordhout AL, Marsden CD, Murray NMF, Rothwell JC, Swash M, Tomberg C (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 91:79–92.
- Rothwell JC, Colebatch J, Britton TC, Priori A, Thompson PD, Day BL, Marsden CD (1991) Physiological studies in a patient with mirror movements and agenesis of the corpus callosum. *J Physiol (Lond)* 438:34P.
- Siebner HR, Rothwell J (2003) Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Exp Brain Res* 148:1–16.
- Sohn YH, Wiltz K, Hallett M (2002) Effect of volitional inhibition on cortical inhibitory mechanisms. *J Neurophysiol* 88:333–338.
- Sohn YH, Jung HY, Kaelin-Lang A, Hallett M (2003) Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. *Exp Brain Res* 148:176–185.
- Stedman A, Davey NJ, Ellaway PH (1998) Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. *Muscle Nerve* 21:1033–1039.
- Talelli P, Waddingham W, Ewas A, Rothwell JC, Ward NS (2008) The effect of age on task-related modulation of interhemispheric balance. *Exp Brain Res* 186:59–66.
- Tanji J, Okano K, Sato KC (1988) Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. *J Neurophysiol* 60:325–343.
- Thickbroom GW, Phillips BA, Morris I, Byrnes ML, Mastaglia FL (1998) Isometric force-related activity in sensorimotor cortex measured with functional MRI. *Exp Brain Res* 121:59–64.
- Tinazzi M, Zanette G (1998) Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. *Neurosci Lett* 244:121–124.
- van Duinen H, Renken R, Maurits NM, Zijdwind I (2008) Relation between muscle and brain activity during isometric contractions of the first dorsal interosseus muscle. *Hum Brain Mapp* 29:281–299.
- Vines BW, Nair DG, Schlaug G (2006) Contralateral and ipsilateral motor effects after transcranial direct current stimulation. *NeuroReport* 17:671–674.
- Waldvogel D, van Gelderen P, Muellbacher W, Ziemann U, Immisch I, Hallett M (2000) The relative metabolic demand of inhibition and excitation. *Nature* 406:995–998.
- Ward NS, Cohen LG (2004) Mechanisms underlying recovery of motor function after stroke. *Arch Neurol* 61:1844–1848.
- Winstein CJ, Pohl PS (1995) Effects of unilateral brain damage on the control of goal-directed hand movements. *Exp Brain Res* 105:163–174.
- Yarosh CA, Hoffman DS, Strick PL (2004) Deficits in movements of the wrist ipsilateral to a stroke in hemiparetic subjects. *J Neurophysiol* 92:3276–3285.
- Ziemann U, Hallett M (2001) Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: further evidence for motor dominance. *Clin Neurophysiol* 112:107–113.
- Ziemann U, Bruns D, Paulus W (1996) Enhancement of human motor cortex inhibition by the dopamine receptor agonist pergolide: evidence from transcranial magnetic stimulation. *Neurosci Lett* 208:187–190.
- Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W (1998) Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. *J Physiol (Lond)* 511:181–190.
- Zijdwind I, Butler JE, Gandevia SC, Taylor JL (2006) The origin of activity in the biceps brachii muscle during voluntary contractions of the contralateral elbow flexor muscles. *Exp Brain Res* 175:526–535.
- Zoghi M, Nordstrom MA (2007) Progressive suppression of intracortical inhibition during graded isometric contraction of a hand muscle is not influenced by hand preference. *Exp Brain Res* 177:266–274.