Physiological changes underlying bilateral isometric arm voluntary contractions in healthy humans

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Abstract

Many bilateral motor tasks engage simultaneous activation of distal and proximal arm muscles, but little is known about their physiological interactions. Here, we used transcranial magnetic stimulation to examine motor evoked potentials (MEPs), interhemispheric inhibition at a conditioning-test interval of 10 (IHI$_{10}$) and 40 ms (IHI$_{40}$) and short-interval intracortical inhibition (SICI) in the left first dorsal interosseous (FDI) muscle during isometric index finger abduction. The right side remained at rest or performed isometric voluntary contraction with the FDI, biceps or triceps brachii, or the tibialis anterior. Left FDI MEPs were suppressed to a similar extent during contraction of the right FDI, biceps and triceps brachii but remained unchanged during contraction of the right tibialis anterior. IHI$_{10}$ and IHI$_{40}$ were decreased during contraction of the right biceps and triceps brachii compared to contraction of the right FDI. SICI was increased during activation of the right biceps and triceps brachii and decreased during activation of the right FDI. The present results indicate that an isometric voluntary contraction with either a distal or a proximal arm muscle, but not a foot dorsiflexor, decreases corticospinal output in a contralateral active finger muscle. Transcallosal inhibitory effects were strong during bilateral activation of distal hand muscles and weak during simultaneous activation of a distal and a proximal arm muscle; whereas GABAergic intracortical activity was modulated in the opposite manner. These findings suggest that in intact humans crossed interactions at the level of the motor cortex involved different physiological mechanisms when bilateral distal hand muscles are active and when a distal and a proximal arm muscle are simultaneously active.
Most bilateral motor tasks involve simultaneous activation of distal and proximal muscles in both arms (for review see Scott 2000). While distal hand muscles are more involved in performance of fine movements, proximal arm muscles play an important role in posture and stabilization (Hasan 2005; Gurfinkel et al. 2006). Such combination of mobility and stability in everyday motor activities relies largely on a precise and coordinated activation of different muscles groups. At the behavioral level, bilateral interactions between distal and proximal arm segments have been extensively examined (Kelso 1984; Carson et al. 2000; Swinnen 2002; Li et al. 2005; Dounskaia et al. 2010), but their physiological connections during voluntary activity remain poorly understood.

In non-human primates, anatomical inputs (Tokuno and Tanji 1993) and outputs (Fetz and Cheney 1980; Humphrey 1986; Donoghue et al. 1992; McKiernan et al. 1998; Jackson et al. 2003) from the forelimb representation of the primary motor cortex (M1) have been well characterized (for review see Schieber 2001). A few studies have demonstrated the existence of intrinsic connections between distinct regions within the M1 forelimb representation (Gould et al. 1986; Huntley and Jones 1991). Additional observations revealed the presence of interhemispheric interactions between M1 forelimb representations. Studies have shown an uneven distribution of callosal connections in M1s, being more pronounced in cortex representing movements of proximal compared to distal body parts (Gould et al. 1986; Roullier et al. 1994). Also, some of the representations of the distal limbs including the digits have dense callosal connections and some have sparse callosal projections (Gould et al. 1986), which might contribute to functional specialization of upper-limb movements. In agreement, functional magnetic resonance imaging (fMRI) (Grafton et al. 1993) and transcranial magnetic stimulation
(TMS) studies in humans have demonstrated that motor tasks that involve distal and proximal arm muscles engage overlapping motor cortical regions (Devanne et al. 2002; Dominici et al. 2005; Ginanneschi et al. 2005).

Transcallosal connections are a major candidate for mediating interactions between distal and proximal arm muscles during bilateral contractions (Franz et al. 1996; Cardoso de Oliveira et al. 2001; Diedrichsen et al. 2003; Ridderikhoff et al. 2005). Callosal projections between arm-related motor cortical representations exist (Pandya et al. 1971; Jenny, 1979; Pappas and Strick 1981; Roullier et al. 1994). Evidence suggests that inhibitory interhemispheric effects are not strictly homotopic (Dimond 1977; Ni et al. 2009) while callosal fibers can excite restricted areas a more diffuse inhibitory effect is observed in surrounding regions (Asanuma and Okuda 1962).

Previous evidence supports the view that transcallosal pathways from one hemisphere interact with intracortical inhibitory circuits in the contralateral hemisphere in animals (Fisken et al. 1975; Martin et al. 1983; Voight et al., 1988; Houzel and Milleret 1999) and humans (Kukaswadia et al. 2005; Perez and Cohen 2008) which might contribute to control the corticospinal output from the M1. Therefore, we hypothesized that interactions between distal and proximal arm muscles during bilateral isometric voluntary contractions will take place at the cortical level by involving transcallosal and intracortical inhibitory pathways.

We first examined whether an isometric voluntary contraction with either a distal or a proximal arm muscle affected corticospinal output to a contralateral active hand. Corticospinal output was measured by the size of motor evoked potentials in the first dorsal interosseous muscle (FDI) during activation of the contralateral FDI, biceps or triceps brachii. Then, transcallosal and intracortical function was assessed by a paired-pulse TMS protocol (Ferbert et al. 1992; Kujirai et al. 1993).
Methods

Subjects

Eleven right handed healthy volunteers (2 female, 9 male) with an average age of 26±7.2 years participated in the study. Handedness was confirmed by the Edinburgh inventory (Oldfield, 1971) (mean laterality index 83, range 59-100). We tested right handed subjects since the magnitude of IHI is stronger from the dominant M1 to the non-dominant M1 (Netz et al. 1995; Bäumer et al. 2007). All subjects gave their informed consent to the experimental procedure, which was approved by the local ethics committee. The study was performed in accordance with the Declaration of Helsinki.

EMG recordings

EMG was recorded bilaterally from the first dorsal interosseous (FDI), biceps and triceps brachii and right tibialis anterior muscle by surface electrodes secured to the skin over the belly of each muscle (Ag–AgCl, 10 mm diameter). The signals were amplified, filtered (16–1000 Hz), and collected at 2 kHz for off-line analysis using customized software (CED 1401 with Signal software; Cambridge Electronic Design, Cambridge, UK). Forces exerted at the proximal interphalangeal joint of the index finger and at the elbow were measured bilaterally by two load cells (Honeywell, Ltd, range ±111.2 N, voltage ±5V, high-sensitivity transducer 0.045 V/N). Force was sampled at 200 Hz and stored on a computer for off-line analysis.

Experimental setup
Subjects were seated in an armchair with both arms flexed at the elbow by 90° with the forearm pronated and the wrist and forearm restrained by straps with the shoulder at 0° of abduction (Fig. 1A). In this position, the left and right index fingers were attached to a custom two-axis load cell (Honeywell, Ltd), which measures abduction (ABD) force (refers to force exerted by the index finger towards the body midline). During testing subjects performed 10% of left maximal isometric index finger ABD while the right index finger remained at rest or performed 30% of maximal isometric ABD. In addition, testing was completed with the left arm maintained in the same position as described above while the right shoulder was flexed at 90° and the elbow flexed at 90° with the forearm supinated and the wrist restrained by straps (Fig. 1B). Here, a custom device was used to maintain the position of the right arm with a two-axis load cell (Honeywell, Ltd) attached to measure elbow flexion and extension forces. During this part of the testing subjects performed 10% of left maximal isometric index finger ABD while the right arm remained at rest or performed 30% of maximal isometric elbow flexion or elbow extension by activating the biceps and triceps brachii muscles, respectively. We used different levels of isometric force in both sides because the magnitude of transcallosal inhibition is stronger during asymmetric forces compared to a unilateral force (Yedimenko and Perez 2010). For reasons of clarity we will refer to the condition in which the right index finger remained at rest to ‘baseline’ and to the muscle activated in the right arm as FDI, biceps and triceps brachii. At the start of each respective testing, all subjects performed 2-3 brief maximal voluntary contractions (3–5 s) with left and right index fingers into ABD or right elbow flexion or extension separately with 30 s rest between contractions. The maximal forces were used to set targets for subsequent submaximal contractions. During maximal contractions subjects were verbally encouraged to perform maximally with the relevant muscle, and visual feedback was
provided (Gandevia 2001). Custom software was written to acquire signals from the load cell and to display visual feedback corresponding to rest and 10 and 30% of each subject’s maximal left and right index finger abduction force and right elbow flexion and extension force in real time (LabView, California). Subjects were instructed to respond to the GO signal (target signal, black bar) presented on a computer monitor at a comfortable speed by moving a cursor to a target box. Figures 1A and B illustrates the location of the target box (gray bar) showing that at 10% of force there is a small distance between the target signal and target box compared with 30% of force. Subjects had to maintain the cursor in the target box for 3–5 s by performing an isometric contraction. It is important to consider that during activation of a finger muscle subjects were instructed to relax elbow flexor and extensor muscles and vice versa. EMG activity was monitored visually by the experimenters to provide online feedback during testing. During unilateral contractions, trials in which the mean rectified EMG was above 2 SD of the mean resting EMG were excluded from further analysis. During bilateral contractions, we monitored for co-contraction of elbow flexor/extensor muscles. A familiarization trial was completed at the beginning of each experiment to ensure that subjects were able to complete the task with minimal activation of the antagonistic muscle. Based on our preliminary data, trials in which the mean rectified EMG in the antagonistic muscle was > 3% of their MVC were excluded from further analysis (Hunter et al. 2003). A total of 16.1% of trials were excluded from the analysis consistent with previous reports in related tasks (Muellbacher et al. 2000; Hortobagyi et al. 2003; Perez and Cohen 2008). Additional verbal feedback was provided to the subjects to assure that both arms performed the correct task at all times.

In an additional control experiment the left arm was maintained in the same position as described above while the right foot was attached to a footplate connected to a custom two-axis
load cell (Honeywell, Ltd) to measure dorsiflexion forces. Subjects performed 10% of left ABD while the right side remained at rest or performed 30% of maximal isometric ankle dorsiflexion.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimuli were delivered from a Magstim 200 stimulator (Magstim Company) through a figure-eight coil (loop diameter, 7 cm; type number SP15560) with a monophasic current waveform. The centre of the junction of the TMS coil was placed at the optimal scalp position (hot spot) to elicit MEPs in the left and right FDI muscles and the right biceps and triceps brachii in each respective experiment. To identify the optimal scalp position for each muscle the coil was held tangential to the scalp with the handle pointing backward and 45° away from the midline. With this coil position the induced current in the brain flowed in an anterior-medial direction and probably produced D and early I wave activation of corticospinal neurones (Werhahn et al. 1994; Sakai et al. 1997; Di Lazzaro et al. 1998, 2001). Measures of motor cortical excitability included resting (RMT) and active (AMT) motor threshold, motor evoked potentials (MEPs), MEP-max, interhemispheric inhibition (IHI) from left M1 to right M1 and short-interval intracortical inhibition (SICI). Because of the length of the physiological measurements and to avoid fatigue, all measurements were completed in two to four testing sessions separated by at least two days. MEPs were tested in a randomized order in the first session. IHI, SICI and the additional control experiment (right foot dorsiflexion) were tested in consecutive randomized sessions. To maximize consistency of the stimulated area between sessions subjects wear a cap where we marked the vertex (Cz) and the hot spot for each of the stimulated muscles. The TMS coil was held to the head of the subject by a coil holder (Magstim Company) while the head was firmly secured to a headrest with two straps to limit head
movements. Localization of the hot spot for the right FDI, biceps and triceps brachii was necessary only for IHI measurements and these measurements were completed within the same session. The hotspot for the biceps and triceps brachii was located 1.6±0.4 posterior and 1.4±0.5 cm medial from the hot spot for the FDI muscle. Localization of the hot spot for the left FDI was completed in every session. No differences were observed in the left FDI RMT (F(3,21)=0.2, p=0.8) between sessions. Additionally, for each measurement the comparison of the effects of distal and proximal muscle contraction was completed within the same session.

202 **Motor evoked potentials (MEPs)**

According to the IFCN guidelines (Rossini et al. 1994; Rothwell et al. 1999), RMT was defined as the minimum stimulus intensity require to elicit MEPs greater than 50 μV peak-to-peak amplitude in at least 5 out of 10 consecutive trials in the relaxed muscle, and the AMT was defined as the minimal stimulus intensity able to evoke MEPs bigger than 200 μV peak-to-peak amplitude in at least 5 out of 10 consecutive trials during 10% of left ABD. MEP-max was defined in all participants during 10% of left ABD. Here stimulus intensities were increased in 5% steps of maximal device output until the MEP amplitude did not show additional increases. TMS intensity used for testing was adjusted in each subject to elicit an MEP of ~2 mV. Thirty MEPs were averaged in each condition. TMS pulses were given when subject successfully reach one (unilateral contraction) or both targets (bilateral contraction) in a randomized order.

214 **Interhemispheric inhibition (IHI)**

IHI from the left to the right M1 was tested using a randomized conditioning-test design reported previously (Ferbert et al. 1992). Testing was completed at a conditioning-test interval of
10 (IHI\textsubscript{10}) and 40 (IHI\textsubscript{40}) ms, the time between the conditioning stimulus (CS) and test stimulus (TS), which likely reflect activity from different GABAergic neuronal populations (Irlbacher et al. 2007; Ni et al. 2009). The CS was delivered to the optimal scalp position for activating the right FDI, biceps and triceps brachii. All trials at a given CS interval were collected together and randomized with the TS. The order for testing IHI\textsubscript{10} and IHI\textsubscript{40} during different right muscle contractions was randomized. At baseline, a suprathreshold CS was set at an intensity that elicited 50% of each subject’s maximal IHI\textsubscript{10} and IHI\textsubscript{40}. This approach was used to ensure that during voluntary activity we have the possibility to increase and/or decrease the magnitude of IHI. This CS intensity during right voluntary activity elicited an MEP ~20% of the MEP-max of each respective muscle (see Table 1). The comparisons to the baseline condition were not included in the study since we were not able to match the amplitude of the MEP elicited by the CS when the right FDI was at rest and during 30% of voluntary activity of the biceps and triceps brachii (even increasing the stimulator output to 100%) since MEP-max for these muscles are smaller. The intensity of the TS was adjusted for each subject to elicit a Test MEP in the left FDI of ~2 mV. The TS was always delivered to the optimal scalp position for activation of the left FDI muscle. IHI\textsubscript{10} and IHI\textsubscript{40} during unilateral and bilateral contractions were calculated by expressing the size of the conditioned MEP as a percentage of the size of the Test MEP \[\frac{\text{Conditioned MEP} \times 100}{\text{Test MEP}}\]. A total of 25 Test MEPs and 25 Conditioned MEPs were tested in each condition.

\textbf{Short-interval intracortical inhibition (SICI)}

SICI was tested using the method described by Kujirai et al. (1993). A CS was set at an intensity of around 70% of AMT. This low-intensity stimulus can test SICI independently of the
effects on short-intracortical facilitation (SICF) at low contraction levels (Ortu et al. 2008). The 
same stimulation intensity was used for the CS in all conditions tested (see Table 2). The TS was 
adjusted to produce an MEP of ~2 mV. Test stimuli were delivered 2.5 ms after CS, an optimal 
interstimulus interval for eliciting SICI and to avoid a mixture of the two phases of inhibition 
(Fisher et al. 2002). SICI measurements were also tested by adjusting the size of the Test MEP 
across conditions. SICI was calculated by expressing the size of the conditioned MEP as a 
percentage of the size of the Test MEP \[\frac{\text{Conditioned MEP} \times 100}{\text{Test MEP}}\] in all conditions 
tested. A total of 25 Test MEPs and 25 Conditioned MEPs were tested in each condition. 

**Data analysis**

Normal distribution was tested by the Kolmogorov–Smirnov tests and sphericity by the 
Mauchly's sphericity test. One way repeated-measures ANOVA were performed to determine the 
effect of activation of right side arm muscles (Baseline, FDI, biceps and triceps brachii) 
(independent variable) on the size of left FDI MEPs, SICI and L FDI mean rectified EMG 
activity (dependent variables). Two-way repeated-measures ANOVA were performed to 
determine the effect of right side arm muscles (FDI, biceps and triceps brachii) and conditioning-
test interval (10 ms and 40 ms) (independent variables) on IHI, the size of Test MEP and the 
MEP elicited by the CS (dependent variables). Statistical analysis was performed using 
SigmaPlot 11.0. Tukey *post hoc* analysis was used to test for significant comparisons. Paired t-
test was used to compare IHI_{10} and IHI_{40} at baseline, TMS intensity and MEPs during activation 
of the left FDI and right tibialis anterior. Significance was set at p<0.05. Group data are 
presented as means ± standard deviations (SD) in the text.
Results

Motor evoked potentials (MEPs)

Figure 2A illustrates left FDI MEPs recorded in a single subject during unilateral and bilateral isometric voluntary contractions. Left FDI MEP size was decreased in all subjects during contraction of the right FDI (range: 3% to 37% of the baseline; significant effect in 8/11 subjects) and in 9 subjects during contraction of the right biceps and triceps (range: 5% to 33% of the baseline; significant effect in 7/11 subjects). Repeated-measures ANOVA showed that the size of left FDI MEPs was decreased during voluntary contraction of right side arm muscles (F(3,30)=8.2, p<0.001, n=11) (Fig. 2B). Post hoc testing showed a significant decrease in left FDI MEP size during activation of the right FDI (81.8±11% of baseline MEP, p<0.001), biceps (90±11% of baseline MEP, p<0.01) and triceps (84.1±14% of baseline MEP, p<0.001) brachii compared to trial in which the right FDI remained at rest (baseline condition). No difference was observed in the magnitude of left FDI MEP suppression during activation of the right FDI and biceps (p=0.15) and triceps (p=0.47) brachii or between right biceps and triceps (p=0.48) brachii. Mean background rectified EMG activity in the left FDI was similar across conditions (F(3,30)=1.3, p=0.26). In an additional control experiment, a paired t-test showed no changes in left FDI MEPs when the right side was at rest or when the right foot performed 30% of dorsiflexion (p=0.34, n=8) at similar background EMG activity in the left FDI (t=0.1, p=0.9).

Interhemispheric inhibition (IHI10 and IHI40)

Figure 3A illustrates changes in IHI10 and IHI40 recorded in a single subject during activation of the right FDI, biceps and triceps brachii. The size of the test MEP and the size of
the MEP elicited by the CS were similar across conditions (see Table 1). IHI\textsubscript{10} was decreased in all subjects during contraction of the right biceps (range: 15\% to 33\%; significant effect in 8/9 subjects) and in 8 subjects during activation of the right triceps (range: 7\% to 34\%; significant effect in 6/9 subjects). While IHI\textsubscript{40} was decreased in 8 subjects during contraction of the right biceps (range: 10\% to 47\%; significant effect in 7/9 subjects) and triceps (range: 5\% to 49\%; significant effect in 6/9 subjects). Repeated-measures ANOVA showed an effect of voluntary contraction of right arm muscles (F(2,16)=9.1, p<0.01, n=9) (Fig. 3B) but not the conditioning-test interval (F(1,8)=0.2, p=0.7) nor their interaction (F(2,16)=0.6, p=0.5) on IHI. Post hoc analysis revealed a significant decrease on IHI\textsubscript{10} during activation of the right biceps (82±8\%, p<0.01) and triceps (83±11\%, p<0.01) brachii compared to trials in which the right FDI was active (63.3±10\%, p<0.001). In addition, IHI\textsubscript{40} was decreased during activation of the right biceps (84±14\%, p<0.01) and triceps (80±8\%, p<0.01) brachii compared to trials in which the right FDI was active (68.3±15\%, p<0.01). Overall, these results indicate that IHI\textsubscript{10} and IHI\textsubscript{40} targeting the left FDI were weaker when the right biceps and triceps brachii were activated compared to trials in which the right FDI was active. Mean background EMG activity in the left FDI was similar across conditions (F(2,16)=1.8, p=0.2). At baseline, the magnitude of IHI\textsubscript{40} was stronger than IHI\textsubscript{10} when the coil for the CS was located at the hot spot for the FDI (p<0.01), biceps (p<0.01) and triceps brachii (p<0.01). During activation of the right FDI IHI\textsubscript{10} was increased (baseline=81.1±12\%, right FDI active=63.3±12\%, p<0.01) and IHI\textsubscript{40} remained unchanged (baseline=64.6±11\%, right FDI active=68.3±15\%, p=0.5) compared to trials in which the right FDI was at rest.

**Short-interval intracortical inhibition (SICI)**
An illustration of changes in SICI recorded in a single subject during bilateral isometric forces is shown in figure 4A. SICI was decreased in all subjects during contraction of the right FDI (range: 4% to 22%; significant effect in 6/8 subjects) and increased during activation of the right biceps and triceps (range: 5% to 26%; significant effect in 5/8 subjects). Repeated-measures ANOVA showed an effect of voluntary contraction of right arm muscles on SICI ($F_{(3,21)}=53.2$, $p<0.001$; $n=8$) (Fig. 4B). The magnitude of SICI was increased during activation of the right biceps ($53.3\pm7.8\%$, $p<0.001$) and triceps ($49.3\pm9.1\%$, $p<0.001$) brachii and decreased during activation of the right FDI ($79.8\pm12\%$, $p<0.001$) compared to trials in which the right FDI remained at rest ($65.4\pm9.5\%$, $p<0.001$). The magnitude of SICI was increased during activation of the right biceps ($p<0.001$) and triceps ($p<0.001$) brachii compared to trials in which the right FDI was active. No differences were observed in SICI during activation of the right biceps and triceps brachii ($p=0.2$). Mean rectified EMG activity in the left FDI remained similar across conditions ($F_{(3,21)}=2.4$, $p=0.3$).

When SICI was tested by maintaining the size of the Test MEP similar in all conditions (see Table 2), repeated-measures ANOVA showed an effect of right arm muscles on SICI ($F_{(3,15)}=33.2$, $p<0.001$, $n=6$). Post hoc analysis revealed a significant increase in SICI (Conditioned MEP x 100)/Test MEP) during activation of the right biceps ($54.3\pm11\%$, $p<0.01$) and triceps ($51.3\pm8.4\%$, $p<0.01$) brachii and decreased during activation of the right FDI ($71.6\pm9.1\%$, $p<0.001$) compared to trials in which the right FDI remained at rest ($60.3\pm12\%$, $p<0.001$). SICI was also increased during activation of the right biceps ($p<0.01$) and triceps ($p<0.001$) brachii compared to trials in which the right FDI was active. No differences were observed in SICI during activation of the right biceps and triceps brachii ($p=0.28$). Mean rectified EMG activity in the left FDI remained similar across conditions ($F_{(3,15)}=1.6$, $p=0.4$).
Our findings demonstrate that an isometric voluntary contraction involving an intrinsic finger muscle or an elbow flexor or extensor muscle, but not a foot dorsiflexor, reduces corticospinal output from M1 to the contralateral active hand. These results indicate that finger muscles respond to volitional activity of contralateral arm-related motor cortical regions during bilateral isometric voluntary contractions. We show that these interactions take place, at least in part, through the corpus callosum likely by accessing different mechanisms. IHI\textsubscript{10} and IHI\textsubscript{40} were decreased during activation of the right biceps and triceps brachii compared to activation of the right FDI, whereas SICI was increased during activation of the right biceps and triceps brachii and decreased during activation of the right FDI. This is the first evidence for crossed interactions at the level of the motor cortex between distal and proximal flexor and extensor arm muscles during bilateral voluntary activity in intact humans.

Changes in corticospinal output during bilateral isometric arm voluntary contractions

A previous study demonstrated a decrease in MEP size during bilateral voluntary contraction of wrist flexor muscles compared to a unilateral contraction (Stinear and Byblow 2004a). Our findings agree with those results and suggest that a similar phenomenon can be observed during bilateral voluntary activation of a distal and a proximal arm muscle. This also agrees with a previous demonstration of a decrease in MEP size in a distal and in a proximal arm
muscle during a small voluntary contraction of the contralateral finger (Sohn et al. 2003). We found that right dorsiflexion did not affect the size of MEPs elicited in the left active FDI. Interactions between upper and lower limb muscles have been demonstrated during motor tasks such as walking (Dietz et al. 2001), but not during standing and sitting (Dietz et al. 2001; Haridas and Zehr 2003). These studies and our results support the view that neuronal coupling between upper and lower limbs occurs in a flexible task-dependent manner (Dietz and Michel 2009).

The suppression of the left FDI MEPs size was evoked by voluntary contraction of the right FDI, biceps and triceps brachii muscles. This finding is consistent with the existence of callosal connections between different M1 forelimb representations (Pandya et al. 1971; Jenny, 1979; Pappas and Strick 1981; Roullier et al. 1994). Furthermore, previous observations have shown that the digits are represented in areas of the M1 that have dense callosal connections and some that have sparse callosal connections (Gould et al. 1986). One advantage of these multiple representations within M1 can be their contribution to functional specialization of upper-limb movements. Studies in humans have also suggested that at rest interhemispheric inhibitory effects between different M1 body representations interact closely (Ni et al. 2009). Our results agree with those findings and suggest that during bilateral isometric voluntary contractions corticospinal output of an area controlling distal hand muscles can be accessed by activation of adjacent arm-related cortical representations.

It is important to consider that bilateral isometric voluntary contractions have been associated with inhibitory effects such as the phenomenon of bilateral deficit (Koh et al. 1993; Oda and Moritani 1995; Häkkinen et al. 1997) and with facilitatory effects such as overflow or mirror activity (Lazaruous et al. 1999; Giovanelli. 2009). It is less likely that these phenomenons affected our results since our subjects maintained a constant and monitored level of EMG during
We observed similar effects on left MEP size during contralateral distal and proximal voluntary contractions, suggesting that symmetrical aspects of the task might have a lesser influence in the present results as it is the case in bilateral deficit (Li et al. 2001, 2002). This is consistent with the view that M1 is concerned, at least in part, with the generation of actions in terms of an "extrinsic" space related to the limb action (Kakei et al. 1999; Mechsner et al. 2001; Yedimenko and Perez 2010). Our results suggest that the suppression of the left FDI MEPs size is related to an increased inhibitory effect during bilateral isometric voluntary contractions involving arm muscles. An increased inhibitory effect might help to coordinate the arms during actions that require some degree of bimanual coupling (Rokni et al. 2003). This is in agreement with a recent study demonstrating that an increase in the magnitude of transcallosal inhibition between M1s during bilateral compared to unilateral index finger voluntary contractions might contribute to suppress unwanted muscle activity (Giovannelli et al. 2009). Since the size of an MEP might be influenced by changes at multiple levels within the central nervous system (Petersen et al. 2003), we assessed if these interactions might take place through the corpus callosum and by changes on intracortical inhibitory activity (Kukaswadia et al. 2005; Perez and Cohen 2008).

Mechanisms contributing to control corticospinal output

Transcallosal inhibitory function can be examined by using a paired-pulse TMS protocol (Ferbert et al. 1992). The direct evidence of the cortical origin of the inhibition induced by the paired-pulse TMS protocol was provided by Di Lazzaro et al. (1999) by showing a suppression of the later I-waves (I3) in recordings of descending volleys with epidural electrodes. Two main phases of interhemispheric inhibition have been reported, one at a short-interval of 10 ms (IHI_{10})
and another at a long-interval of 40 ms (IHI\textsubscript{40}) (Chen et al. 2003). Significant differences exits between IHI\textsubscript{10} and IHI\textsubscript{40} (Chen et al. 2003; Kukaswadia et al. 2005; Lee et al. 2007; Ni et al. 2009), including that IHI\textsubscript{40} is mediated by postsynaptic gamma-aminobutyric acid type B (GABA\textsubscript{B}) receptors. The transmitter system mediating IHI\textsubscript{10} remains inconclusive (Irlbacher et al. 2007).

We found that IHI\textsubscript{10} and IHI\textsubscript{40} were decreased by contralateral activation of the biceps and triceps brachii compared to trials in which the FDI was active. To our knowledge this is the first demonstration that activation of a proximal arm muscle influences trancallosal inhibitory function targeting the contralateral active hand to a different extent that activation of a distal finger muscle. This contralateral inhibitory influence in a hand muscle appears widespread, as it was evoked (although to a different extent) by activating either a distal or a proximal arm muscle. This widespread effect is in agreement with our MEP results (Fig. 2) and consistent with the view that interhemispheric inhibitory effects are diffuse (Dimond 1977). In the cat brain, callosal fibers excite restricted homotopic areas but exhibit diffuse inhibitory effects in surrounding regions (Asanuma and Okuda, 1962).

An intriguing question is why IHI\textsubscript{10} and IHI\textsubscript{40} decreased to a larger extent during activation of contralateral proximal arm muscles compared to activation of a distal hand muscle? Despite the undoubted importance of callosal pathways in inter-hemispheric communication, their functional role during bimanual actions remains unknow (Cardoso de Oliveira et al. 2001; Diedrichsen et al. 2003; Ridderikhoff et al. 2005). Similarly, the functional role of IHI\textsubscript{10} and IHI\textsubscript{40} is unclear (Ni el al. 2009). The low baseline rate of callosal neurons in awake monkeys leads to the suggestion that these cells might signal the discrete time of a motor event to the opposite hemisphere (Soteropoulos and Baker 2007). The strong IHI\textsubscript{10} and IHI\textsubscript{40} during bilateral
activation of finger muscles might reflect the involvement of inhibitory pathways to suppress unwanted muscle activity (Duque et al. 2005; Giovannelli et al. 2009) to ensure greater bilateral coupling between hands (Rokni et al. 2003). Since proximal muscles play a role in posture and stabilization, their effect on contralateral hand muscles might be different. Indeed, even less activity is observed in callosal neurons during a postural stabilization task (Beloozerova et al. 2003). The weaker IHI_{40} and IHI_{10} during distal-proximal activation points towards the contribution from other pathways, if changes in interhemispheric inhibition were solely responsible for MEP changes, then all contractions should result in increased inhibition. A voluntary contraction of biceps or triceps might activate a greater cortical area compared to distal hand activation, consistent with evidence showing that the size of muscle representations is larger for proximal than distal muscles (Donoghue et al. 1992; Devanne et al. 2002). It is also important to consider that IHI from one hemisphere can affect the excitability of intracortical inhibitory circuits, which together might contribute to control corticospinal output from M1. Indeed previous evidence has demonstrated that less intracortical inhibition in one hemisphere might result from an increased in the magnitude IHI from the contralateral hemisphere (Kukaswadia et al. 2005; Perez and Cohen 2008). We observed stronger IHI_{10} and IHI_{40} during contralateral activation of a distal muscle when SICI was decreased. In contrast, we observed weaker IHI_{10} and IHI_{40} during contralateral activation of the biceps and triceps brachii when SICI was increased. Since in all conditions corticospinal output in the left hand was decreased our results suggest that a combination of the effects of IHI and SICI might contribute, at least in part, to modulate corticospinal output from a contralateral active hand (Perez and Cohen 2008). An important question is if changes in coil position across stimulation sessions might have affected our results (Gugino et al. 2001). To minimize variability between the stimulated areas across
sessions we examined the distal and proximal effects for each physiological measurement within
the same session, therefore, although possible it is less likely that this factor might have
contributed to differences in distal-proximal interactions. Another important factor to consider in
future research is if similar results will be observed in left and right-handed subjects considering
differences in hemisphere specialization (Stinear and Byblow 2004b). Our study does not allow
identifying the precise route by which distal and proximal cortical areas interact, but differences
in time (i.e. IHI_{10} and IHI_{40}) and strength (i.e. increased or decreased) of the transcallosal and
intracortical inhibitory effects suggest that activation of distal-distal and distal-proximal arm
muscles convey information through at least partly different neuronal pathways.

Functional significance

The present findings open the possibility of accessing the distal finger motor cortical
representation by activating a contralateral arm-related cortical region during bilateral isometric
voluntary contractions. This is in agreement with the view that the neural control of the hand can
be influenced by activity originating at proximal joints (Kalaska et al. 1997). This might be of
interest for patients with CNS injuries. The recovery of control of finger movement is one of the
main problems after a lesion of the corticospinal tract in humans and non-human primates (Perez
and Cohen 2009). The understanding of physiologically relevant interactions between different
arm muscles might contribute to a better design of future rehabilitation strategies involving
bilateral arm movements. Additionally, our results suggest that a possible functional role for
IHI_{10} and IHI_{40} is to converse different information to a finger muscle from a contralateral active
distal or proximal arm muscle.
References


Kelso JA. Phase transitions and critical behavior in human bimanual coordination.

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Figure legends

**Figure 1.** Experimental set-up. *A and B, upper figures,* Diagram showing the visual display presented to all subjects during testing. Subjects were instructed by the monitor to perform 10% of index finger abduction by using the FDI muscle (10% FDI) while the right side was at rest (0% Rest) or performed a 30% contraction with the right hand (right index finger abduction, 30% FDI), right elbow flexion (30% Biceps) or elbow extension (30% Triceps). The condition in which the right hand remained at rest was used as baseline. The black vertical bar is the cursor that subjects was instructed to move by performing left and right isometric voluntary contractions. *A and B, lower figures,* Schematic of the experimental set-up showing the posture of both hands and the right arm during testing.

**Figure 2.** Motor evoked potentials (MEPs). *A,* MEPs recorded from the left FDI of a representative subject during 10% of left ABD while the right index finger remained at rest.
or performed 30% of ABD or elbow flexion or extension. The specific muscle activated in the right arm is indicated as FDI, biceps and triceps. B, Group data (n=11). The abscissa shows the muscle activated in the right arm. The ordinate shows left FDI MEP amplitudes as a percentage of the baseline left FDI MEPs measured with the right arm at rest. The horizontal dashed line represents the left FDI MEP baseline measure with the right index finger at rest. Note the decrease in left FDI MEPs size during activation of the right FDI, biceps and triceps brachii compared to baseline. Error bars indicate SEs. *p < 0.05.

Figure 3. IHI$_{10}$ and IHI$_{40}$. **A**, IHI$_{10}$ (left column) and IHI$_{40}$ (right column) recorded from the left FDI of a representative subject during 10% of L ABD while the right side performed 30% of ABD or elbow flexion or extension. The specific muscle activated in the right arm is indicated as FDI, biceps and triceps. Test MEP and conditioned MEP (Cond. MEP) are indicated by the arrows. **B**, Group data (n=9). The abscissa shows the muscle activated in the right arm during testing of IHI$_{10}$ (black bars) and IHI$_{40}$ (white bars). The ordinate indicates the magnitude of the conditioned MEP expressed as a percentage of the Test MEP during bilateral isometric voluntary contractions. The horizontal dashed line represents the size of the Test MEP. Note that IHI$_{10}$ and IHI$_{40}$ were decreased during activation of the right biceps and triceps brachii compared to trials in which the right FDI was active. Also note there are no differences in the magnitude IHI$_{10}$ and IHI$_{40}$ during activation of any of the right arm muscles tested. Error bars indicate SEs. *p < 0.05.

Figure 4. Short-interval intracortical inhibition (SICI). **A**, SICI recorded from the left FDI of a representative subject during 10% of left ABD while the right index finger remained at rest (baseline) or performed 30% of ABD or elbow flexion or extension. The specific muscle activated in the right arm is indicated as FDI, biceps and triceps. Test MEP and conditioned MEP...
(Cond. MEP) are indicated by the arrows. \textit{B}, Group data (n=8). The abscissa shows all
conditions tested during the assessment of SICI. The ordinate indicates the magnitude of the
conditioned MEP expressed as a percentage of the Test MEP. The horizontal dashed line
represents the size of the Test MEP. Note that the magnitude SICI was decreased during
activation of the right FDI and increased during activation of the right biceps and triceps
compared to the baseline condition. Also note that SICI was significantly increased during
activation of the right biceps and triceps compared to trials in which the right FDI was active.
Error bars indicate SEs. *p < 0.05.

Table 1. Mean stimulus intensity (±SD) used for the test stimulus (TS) and conditioning
stimulus (CS) during IHI$_{10}$ and IHI$_{40}$ testing during voluntary contraction of the right FDI, biceps
and triceps brachii. The intensity of the TS was maintained similar across conditions. Note that
the size of the Test MEP elicited in the left FDI was similar when IHI$_{10}$ and IHI$_{40}$ were tested.
Since the FDI, biceps and triceps brachii have different input-output excitability curves, the CS
intensity was expressed as a percentage of the MEP-max elicited on each respective muscle
during 30% of their maximal voluntary activity. Note that the CS intensity used during testing of
IHI$_{10}$ and IHI$_{40}$ was similar across conditions.

Table 2. Mean stimulus intensity (±SD) used for the test stimulus (TS) and conditioning
stimulus (CS) during SICI testing. Measurements were completed without adjusting
(Unadjusted) or adjusting (Adjusted) the size of the Test MEP while the right side remain at rest
(baseline) or performed voluntary contraction with the right FDI, biceps or triceps brachii. In the
unadjusted condition, the same stimulus intensity was used across conditions. Note there was a
significant decreased in the size of the Test MEP during activation of the right FDI, biceps and
triceps brachii compared to baseline. In the adjusted condition, the intensity of the TS was increased to acquire a similar Test MEP across conditions. Note there were no differences in the size of the adjusted Test MEP when SICI was tested across conditions.
A  LEFT HAND   RIGHT HAND
10% FDI  0% Rest (Baseline)

10% FDI  30% FDI

LEFT HAND   RIGHT ARM
10% FDI  0% Rest (Baseline)

10% FDI  30% BICEPS

10% FDI  30% TRICEPS
A. Baseline, FDI, Biceps, Triceps

B. Response size (% of baseline MEP)

- FDI
- Biceps
- Triceps
A

Baseline

Test MEP

Cond. MEP

BICEPS

FDI

TRICEPS

B

Cond. MEP (% of Test MEP)

Baseline

FDI

Biceps

Triceps

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<td></td>
<td>45.3±6.3%</td>
<td>43.8±6.5%</td>
<td>43.8±6.5% (F=0.54, p=0.6)</td>
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<tr>
<td>TS</td>
<td>59±13%</td>
<td>60.1±11%</td>
<td>61.4±10% (F=0.13, p=0.8)</td>
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<td>CS</td>
<td>2.1±0.53 mV</td>
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<td>MEP elicited by the CS (% of MEP-max)</td>
<td>24.2±11%</td>
<td>21.1±10%</td>
<td>19.4±18% (F=0.3, p=0.7)</td>
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<td>45.6±6.6%</td>
<td>44.1±5.1%</td>
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<td>23.5±18%</td>
<td>18±19% (F=0.2, p=0.8)</td>
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