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The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice

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Although it has long been known that practicing a motor task with one limb can improve performance with the limb opposite, the mechanisms remain poorly understood. Here we tested the hypothesis that improved performance with the untrained limb on a fastest possible (i.e. ballistic) movement task depends partly on cortical circuits located ipsilateral to the trained limb. The idea that crossed effects, which are important for the learning process, might occur in the 'untrained' hemisphere following ballistic training is based on the observation that tasks requiring strong descending drive generate extensive bilateral cortical activity. Twenty-one volunteers practiced a ballistic index finger abduction task with their right hand, and corticospinal excitability was assessed in two hand muscles (first dorsal interosseus, FDI; adductor digiti minimi, ADM). Eight control subjects did not train. After training, repetitive transcranial magnetic stimulation (rTMS; 15 min at 1 Hz) was applied to the left (trained) or right (untrained) motor cortex to induce a 'virtual lesion'. A third training group received sham rTMS, and control subjects received rTMS to the right motor cortex. Performance and corticospinal excitability (for FDI) increased in both hands for training but not control subjects. rTMS of the left, trained motor cortex specifically reduced training-induced gains in motor performance for the right, trained hand, and rTMS of the right, untrained motor cortex specifically reduced performance gains for the left, untrained hand. Thus, cortical processes within the *untrained* hemisphere, ipsilateral to the trained hand, contribute to early retention of ballistic performance gains for the untrained limb.

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Abbreviations ADM, adductor digiti minimi; FDI, first dorsal interosseus; MEP, motor evoked potential; rTMS, repetitive transcranial magnetic stimulation.

Introduction

Most healthy humans have the ability to learn new skills given the opportunity to practice. When learning is accomplished with one limb through task repetition, the ability to perform the same task with the opposite, untrained limb can also improve. This type of skill acquisition is known as interlateral or cross-limb transfer, or 'cross education' in older literature. For more than 100 years, cross-limb transfer has been demonstrated for a wide range of motor tasks including mirror tracing (Cook, 1933), pursuit tracking (Hicks *et al.* 1983), the serial reaction time task (Perez *et al.* 2007*a*), sequential finger tapping (Parlow & Dewey, 1991), maze tracing (van Mier & Petersen, 2006), reaching while exposed to force perturbations (Dizio & Lackner, 1995), and pointing or aiming tasks with distorted vision (Elliot & Roy, 1981; Imamizu & Shimojo, 1995). The magnitude of cross-limb transfer varies depending on the nature of the task and the learning environment (e.g. availability of visual feedback, training period) (Imamizu & Shimojo, 1995; Teixeira, 2000; Teixeira & Caminha, 2003).

Hypotheses to explain cross-limb transfer can be classified into two broad categories. The first suggests that, as a precursor to successful transfer, the practice-induced motor engrams underlying improved performance with the trained limb must reside at a central nervous system (CNS) site that is also accessible for the control of the opposite, untrained limb (Imamizu & Shimojo, 1995; Anguera *et al.* 2007) (i.e. the 'bilateral access' hypothesis;

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see Fig. 1*A*). An example is the so called 'callosal access' hypothesis (Taylor & Heilman, 1980), in which it has been proposed that motor engrams developed in the dominant hemisphere can be accessed by the opposite hemisphere via the corpus callosum to facilitate task performance with the untrained limb (see Fig. 1*A*).

The second category of possible mechanisms is based on the observation that the execution of many unilateral tasks generates cortical activity both contralateral and ipsilateral to the trained limb (i.e. crossed activation). According to the 'cross-activation' hypothesis (Fig. 1*B*), the bilateral cortical activity produced by unilateral training leads to adaptations in both hemispheres. Thus, unilateral training causes task-specific changes in the organization of motor circuits normally associated with the control of the opposite, homologous muscles (Davis, 1898; Hellebrandt, 1951; Parlow & Kinsbourne, 1989). The hypothesis is supported by imaging evidence that there is bilateral activation of several cortical areas during various types of unilateral motor tasks (Kawashima *et al.* 1994; Dettmers *et al.* 1995; Cramer *et al.* 1999; Lee *et al.* 2003; Koeneke *et al.* 2006), and studies involving transcranial magnetic stimulation (TMS) showing acute changes in the excitability of corticospinal pathways projecting to the opposite, homogolous muscles during unilateral muscle contractions (Hess *et al.* 1986; Stedman *et al.* 1998; Tinazzi & Zanette, 1998; Muellbacher *et al.* 2000*a*; Stinear *et al.* 2001; Hortobagyi *et al.* 2003; Perez & Cohen, 2008). Furthermore, unilateral motor practice and voluntary muscle contractions can also influence inter-hemispheric inhibitory interactions between the motor cortices (Muellbacher *et al.* 2000*a*; Perez *et al.* 2007*b*; Perez & Cohen, 2008). Critically, for simple movements, the magnitude of the crossed cortical effects is related to the force of contraction (e.g. Dettmers *et al.* 1995; Hortobagyi *et al.* 2003; Perez & Cohen, 2008), suggesting that the cross-activation hypothesis might be especially relevant for tasks requiring strong descending drive. It is also

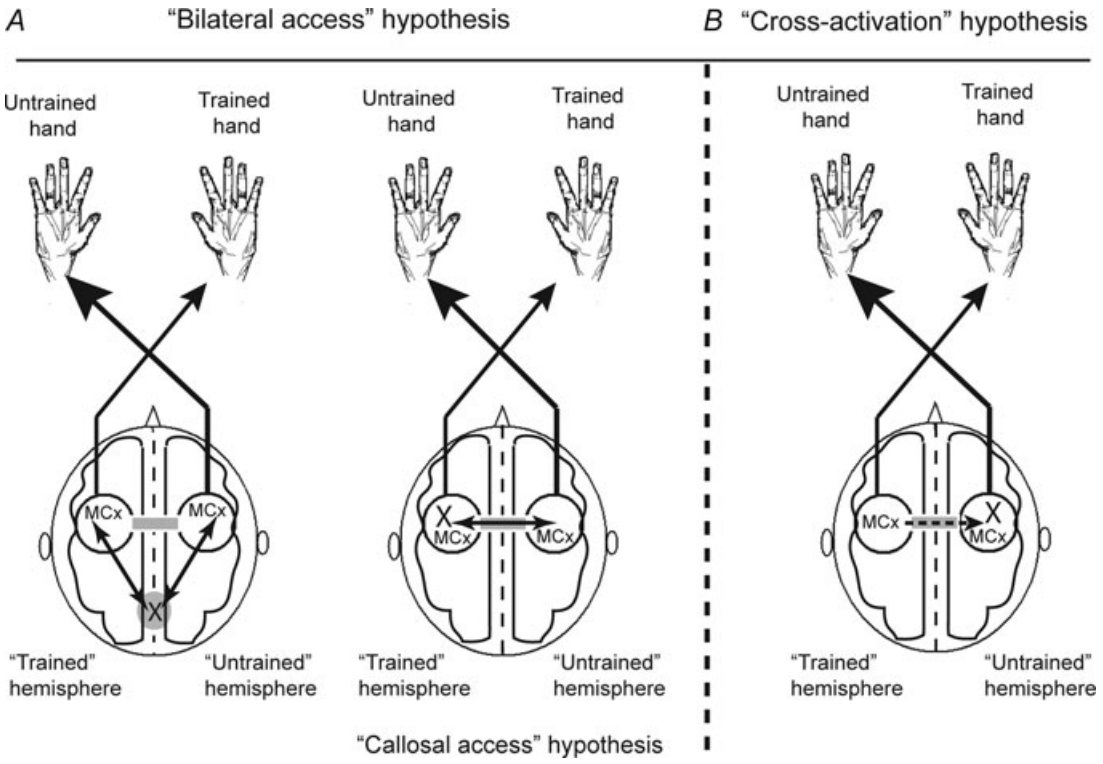


Figure 1. A schematic representation of the two main classes of mechanism that could underlie cross-limb transfer of motor skill

The 'X' represents the site of adaptation that contributes to improved performance with the untrained hand. *A* shows two versions of the 'bilateral access' hypothesis. According to this hypothesis, adaptations occur in motor areas that are typically involved in the control of the trained hand but are accessible to the untrained hand during task execution. The shaded circle represents cortical, or sub-cortical, motor areas that project bilaterally. Adaptations that mediate cross-limb transfer may reside in high order motor areas that project bilaterally (left panel), or in the contralateral ('trained') motor cortex (MCx), which is accessible to the untrained motor cortex during task execution via the corpus callosum, depicted as a grey bar (i.e. the callosal access hypothesis; right panel). *B* illustrates the 'cross-activation' hypothesis, according to which bilateral motor activity generated during unilateral training induces adaptations in the 'untrained' hemisphere that contribute to improved performance with the untrained hand.

important to recognize that despite the clear distinctions between the bilateral access and cross-activation hypotheses, they are not mutually exclusive (Parlow & Kinsbourne, 1989; Parlow & Dewey, 1991; Carroll *et al.* 2006; Lee & Carroll, 2007).

In accordance with the cross-activation hypothesis, we showed recently that unilateral practice of a ballistic finger abduction task is accompanied by bilateral increases in corticospinal excitability (Carroll *et al.* 2008). The purpose of the current study was to determine whether adaptations in the motor cortex ipsilateral to the trained hand contribute to the early retention of performance improvements in the untrained hand after unilateral training. For simplicity, the sides of the brain contralateral and ipsilateral to the trained hand are referred to, respectively, as the 'trained' and 'untrained' hemisphere throughout the text. We used repetitive transcranial magnetic stimulation (rTMS) as a non-invasive method of inducing short-term interruption of local cortical function in the human cortex (Chen *et al.* 1997*a*; Siebner & Rothwell, 2003). At low frequency, rTMS causes transient depression in cortical excitability (Muellbacher *et al.* 2000*b*, 2002) which persists beyond the duration of stimulation (Hallett *et al.* 1999). In accordance with the view that motor learning is a time-dependent process in which motor memories are initially fragile after acquisition, but are consolidated to a more stable form over time (see Krakauer & Shadmehr, 2006; Nader & Hardt, 2009), rTMS protocols that interfere with normal patterns of cortical activity shortly after motor practice can impair the retention of training-induced improvements in motor performance (Muellbacher *et al.* 2002; Baraduc *et al.* 2004; Hadipour-Niktarash *et al.* 2007). Here we studied the effects of low-frequency rTMS on the motor performance of both limbs, when applied shortly after training to the motor cortex in either the trained or untrained hemisphere. If unilateral ballistic training affects both the trained and untrained motor cortices, we should observe a bilateral increase in corticospinal excitability. If there is a causal link between untrained hemisphere effects and performance improvement with the untrained hand, motor performance should be susceptible to rTMS. In other words, rTMS of the untrained hemisphere should disrupt the early retention of any improvements in ballistic performance that transfers between limbs.

Methods

Ethical approval

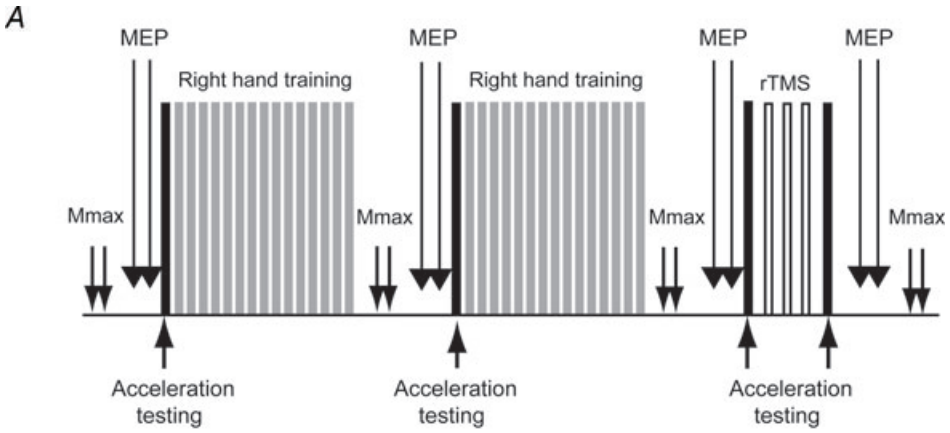
A total of 29 healthy right-handed (Oldfield, 1971) people (19 males and 10 females, aged 18–50, mean age of 25.8 ± 7.6 years) with no previous neurological disorders participated in the study after providing written, informed consent. Participants were recruited in two cohorts. The first 15 people were randomly assigned to either a training group ($n = 7$) or a control group (no training) ($n = 8$). Fourteen more subjects were recruited 3 months later, and randomly allocated to two additional training groups (see below). The experimental procedures conformed to the *Declaration of Helsinki* and were approved by the Human Research Ethics Committee at the University of New South Wales.

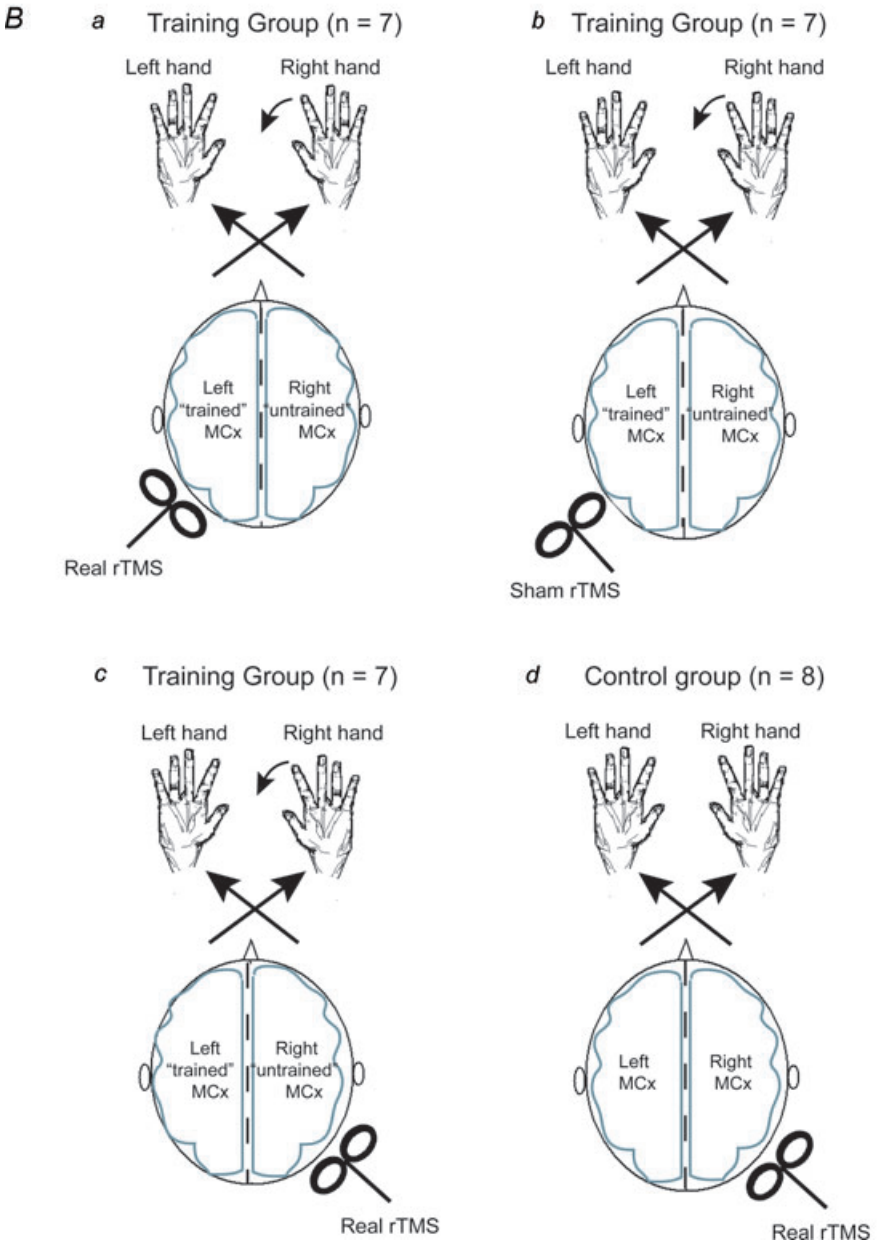
Experimental design

The experiments were designed to assess whether a 'virtual lesion', induced in either the trained or the untrained motor cortex by rTMS, interferes with retention of cross-limb performance gains after unilateral ballistic motor training. Figure 2*A* schematically depicts the testing protocol. Briefly, initial (pre-training) testing of corticospinal excitability was performed bilaterally, followed by (pre-training) assessment of ballistic task performance for both hands. Subjects in all training groups subsequently performed two blocks of training with the right hand (150 movements in each block), whereas the control group rested for an equivalent period (12 min). After each training block (or rest period for the control group), motor performance and corticospinal excitability were re-assessed bilaterally. After the final training block, and subsequent excitability and performance testing, rTMS was applied to the left or right motor cortex at 1 Hz and 1.1 times the resting motor threshold for 15 min (i.e. 3 blocks of 5 min with a 2 min rest between blocks) (Fig. 2*B*). Subjects in the training groups received rTMS to the left trained hemisphere ($n = 7$), to the right untrained hemisphere ($n = 7$), or 'sham' rTMS to the left trained hemisphere ($n = 7$). The non-training control group ($n = 8$) received rTMS to the right hemisphere (see TMS and nerve stimulation section for details). The rTMS protocol was followed by a final assessment of motor performance and corticospinal excitability bilaterally.

Motor training

The motor task required subjects to produce maximal acceleration during ballistic abduction of the index finger with the hand pronated and the forearm resting on a desk. Both hands were secured in a custom-built rig that isolated motion to the second metacarpo-phalangeal joint. Tri-axial accelerometers (Dytran Instruments, Chatsworth, CA, USA) were attached to the index fingers and secured via plastic splints and tape to record peak acceleration. Subjects were cued to perform movements via a visual stimulus (green 'GO' symbol on a computer monitor) paced at 0.5 Hz. A 30 s rest was provided after every 10 movements. We instructed the subjects to perform isolated abduction movements at the second





metacarpophalangeal joint while keeping the rest of the hand relaxed. During right hand training, digital feedback of peak acceleration from the previous two trials was provided after every movement. We provided standard verbal encouragement 'to move as fast as you can' throughout the experiment. Acceleration feedback was not provided during performance testing for either hand.

Recording of EMG activity

We recorded EMG from the first dorsal interosseus (FDI) and abductor digiti minimi (ADM) muscles of both hands via 1 cm^2 self-adhesive electrodes (Ag–AgCl) using a belly-tendon arrangement with the active electrode on the motor point and the reference electrode on the metacarpo-phalangeal joint. EMG signals were amplified (gain 200–500; P511 Grass Instruments, AstroMed) and band-pass filtered (10–1000 Hz).

TMS and nerve stimulation

TMS was delivered through a figure-of-eight coil (outside diameter of each loop 70 mm) connected to a Magstim rapid stimulator, which generates biphasic pulses of 250 μs duration. The stimulating coil was positioned over the motor cortex to elicit motor evoked potentials (MEPs) in the FDI and ADM muscles. The coil handle was oriented posterior-laterally, to produce an anterior to posterior induced current direction for the first stimulation phase. The optimal coil position for activating FDI was established, and resting motor threshold was determined for each hemisphere as the lowest intensity to produce MEPs ($\sim$50 μV) in at least three out of five consecutive trials (Carroll *et al.* 2001). The position of the coil (a 'V' shaped mark at the junction of the figure-of-eight coil) was marked directly on the scalp with a whiteboard marker. Ten stimuli were delivered to each hemisphere at 20% of the stimulator output range above threshold at the beginning of the experiment, after each training block and after the rTMS intervention. The experimental procedures were identical for the second cohort of subjects (i.e. the groups that received rTMS of the right, untrained motor cortex, and 'sham' rTMS to the left, trained motor cortex) except that the optimal stimulating coil position was recorded with a frameless stereotactic guidance system (StealthStation Treon, Medtronic USA) to provide feedback of coil position throughout testing. We recorded the amplitude of maximal M-wave responses (Mmax) to supramaximal ulnar nerve stimulation at the wrist from both the FDI and ADM muscles. A Digitimer DS7A stimulator applied currents (0.2 ms pulse width) via bipolar surface electrodes at an intensity 20% higher than that necessary to elicit Mmax in the relaxed FDI. All MEPs were normalized to mean amplitude of three corresponding Mmax responses recorded at the same time point.

rTMS and sham stimulation

rTMS was performed in accordance with the current international safety guidelines (Wassermann, 1998). The Magstim Rapid stimulator delivered pulses to the FDI motor hot-spot at 110% of resting motor threshold at 1 Hz. Three blocks of 5 min were applied (total of 900 stimuli), with a rest period of 2 min between blocks to prevent over-heating of the coil. Sham rTMS was performed according to the same parameters, except the side of the coil formed a 90 deg angle with the surface of the scalp. This arrangement mimicked the sound, skin pressure and postural requirements associated with 'actual' rTMS, but rendered the stimulation ineffective for activating the cortex.

Data acquisition and analysis

For index finger acceleration trials, data collection was triggered for each movement when acceleration exceeded 0.5 m s^{-2}. Data were sampled at 1000 Hz with a 12-bit National Instruments A/D board, interfaced with a computer running a custom-written Labview program,

Figure 2. A schematic illustration of the experimental design
A shows a schematic illustration of the experimental protocol. Maximal M-waves (Mmax) and motor evoked potentials (MEP) were recorded bilaterally at the beginning of each session, after each training block, and after the rTMS intervention. The order of testing between hands was randomized. The black bars represent trials in which movement acceleration was assessed. Visual feedback of performance was not provided during these trials. The grey bars represent training trials, performed with the right hand in the presence of visual feedback, and the light (unshaded) bars represent the rTMS intervention. *B* illustrates the training and stimulation procedures for each of the four experimental groups. At the completion of right hand training, subjects received real rTMS to either the left, 'trained' motor cortex (MCx) (*a*), real rTMS to the right, 'untrained' motor cortex (*c*), or sham rTMS to the left, 'trained' motor cortex (*b*). Subjects in the control group received real rTMS to the right motor cortex (*d*). Black arrows represent 'crossed' corticospinal projections. The terms trained and untrained refer, respectively, to the sides of the brain contralateral and ipsilateral to the trained hand. The curved arrows indicate the abduction movement practiced during training.

and collected from 100 ms before to 300 ms after the trigger. Data analysis was performed off-line using a custom-written Labview program (National Instruments, Austin, TX, USA). Acceleration data were low-pass filtered at 50 Hz prior to analysis. For each acceleration trace, peak acceleration was measured as the maximum acceleration minus baseline acceleration. Baseline acceleration was specified as the average value between two cursors set prior to the movement and a second set of cursors was used to specify a window that captured the maximum acceleration. The magnitude and time to peak acceleration were calculated. MEP and Mmax data were sampled at 10 kHz. The peak-to-peak amplitude of MEP and Mmax responses was measured between cursors set at the beginning and end of each waveform.

Statistical analysis

To examine the effects of unilateral training on peak acceleration and MEP amplitude in each hand, data from all subjects in the three training groups were pooled and subjected to two-way (group × time) ANOVAs (i.e. 2 groups: training *versus* control, 3 times: pre-training *versus* mid-training *versus* post-training) with repeated measures on the time factor. An additional two-way ANOVA (4 groups, 2 times: post-training *versus* post-rTMS), with repeated measures on the time factor, was also conducted to assess the effect of rTMS (or sham) on post-training values for peak acceleration and MEP amplitude across conditions. Planned contrast analyses were used to assess changes from post-training to post-rTMS within each group (Keppel, 1982). Statistical significance was set at $P < 0.05$.

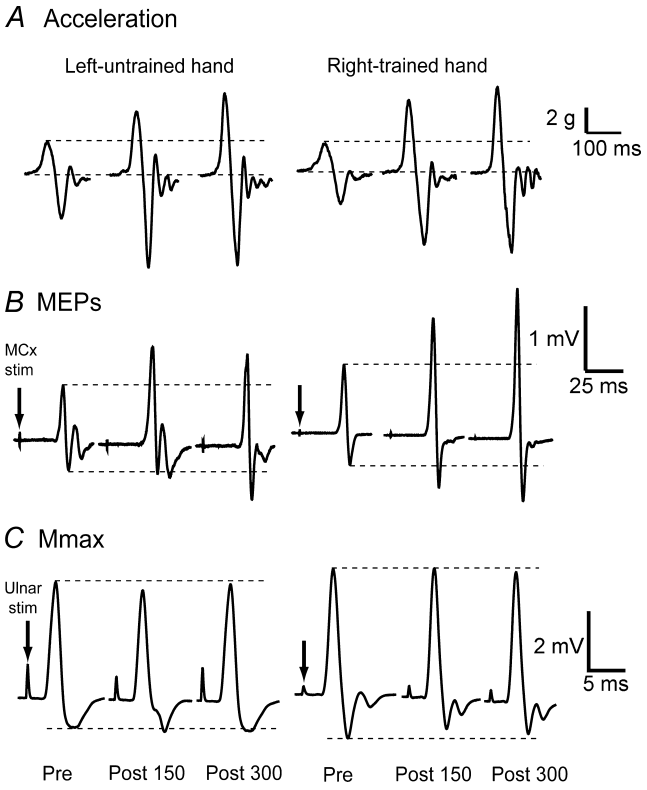


Figure 3. Examples of raw records of index finger acceleration (*A*), FDI MEP (*B*) and FDI Mmax (*C*)
Data were taken from a representative subject before training (Pre), and after 150 (Post 150) and 300 (Post 300) practice trials. Black arrows in *B* and *C* indicate motor cortical stimulation (MCx stim) and ulnar nerve stimulation (Ulnar stim), respectively.

Results

Acceleration of the index finger

Raw acceleration traces from a representative subject show the typical increase in peak acceleration with training in Fig. 3*A*. For the group ($n = 21$), practice of the ballistic task significantly improved peak abduction acceleration of the right index finger after 150 (+64% above pre-training acceleration, $P < 0.001$) and 300 (+93%, $P < 0.001$) training movements (Fig. 4*A*). Peak acceleration of the left, untrained index finger also increased significantly after right-hand training (after 150 right finger movements: +37%, $P < 0.001$; after 300 right finger movements: +62%, $P < 0.001$; Fig. 4*A*). The extent of transfer observed in the three training groups was positively correlated with the degree to which performance improved in the trained hand ($r = 0.44$, $P = 0.04$). There was no significant change in finger acceleration for the control group in either the right ($P = 0.976$) or left hand ($P = 0.768$).

Corticospinal excitability

MEP data from the left and right FDI muscles of a representative subject in the training group are shown in Fig. 3*B*. MEP amplitudes (normalized to Mmax) were larger in both hands after ballistic training for this subject. For the group ($n = 21$), mean FDI MEP amplitude in the right, trained hand increased significantly after 150 (+43%, $P < 0.01$) and 300 training movements (+63%, $P < 0.001$), whereas there was no significant change for the control group (Fig. 4*B*, $P = 0.784$). MEPs recorded from the left, untrained FDI were also significantly larger at the completion of right hand training (+35%, $P < 0.01$; Fig. 4*B*). There were no significant changes in left FDI MEP amplitude for the control group ($P = 0.808$), nor were there significant changes in the amplitude of MEPs recorded from the left or right ADM in any group ($P > 0.3$; Fig. 4*C*).

Effects of real and sham rTMS

No subjects reported adverse effects of the rTMS procedures other than temporary, mild discomfort localized to the site of stimulation. Fifteen minutes of rTMS of the left, trained motor cortex significantly decreased subsequent movement acceleration of the right, trained index finger (−13.1%, $P = 0.017$). Mean MEP amplitude of the right FDI was reduced by 28% ($P = 0.014$), whereas neither peak acceleration of the left, untrained finger, nor left FDI MEP amplitude were affected ($P > 0.29$, Fig. 5). In contrast, rTMS of the right, untrained motor cortex significantly decreased peak acceleration of the left, untrained index finger (−15.5%, $P < 0.001$). Peak acceleration of the right, trained index finger was unchanged ($P = 0.59$), and the amplitude of MEPs evoked in both the right and left FDI muscles were also unaffected by repetitive stimulation of the right motor cortex ($P = 0.17$ and $P = 0.72$, respectively). The reduction in performance induced by rTMS was not related to the amount of initial learning (or transfer) for either group in which disruptive effects were observed. That is, neither the reduction in untrained hand performance due to rTMS of the untrained hemisphere, nor the reduction in trained hand performance due to trained hemisphere rTMS, were significantly correlated to the degree of learning (or transfer). We interpret this as evidence that any apparent differences in the size of training effects between groups did not influence the within-group responses to rTMS. Sham stimulation over the left, trained hemisphere did not affect peak acceleration ($P > 0.18$) or MEP size in either hand ($P > 0.7$, Fig. 5). Similarly, there was no significant change in peak acceleration ($P > 0.1$) or MEP size ($P > 0.44$) for subjects in the control group, who received real rTMS to the right motor cortex. There were no significant changes in mean ADM MEP amplitude in either hand after real or sham rTMS for any group ($P > 0.4$, Fig. 5*C*).

Discussion

Practice of a ballistic finger abduction task with the right hand produced a rapid improvement in performance that generalized to the untrained, left hand. The behavioural improvement was accompanied by a bilateral increase in corticospinal excitability. Thus, practice of ballistic contractions with one hand increases cortical excitability ipsilateral to the moving hand. The data add to evidence that the ipsilateral motor cortex is involved during unilateral motor learning (e.g. Chen *et al.* 1997*b*; Davare *et al.* 2007; Perez *et al.* 2007*b*) and during strong, unilateral muscle contractions (Hess *et al.* 1986; Stedman *et al.* 1998; Muellbacher *et al.* 2000*a*). The training-induced improvement in peak finger acceleration in each hand was reduced by repetitive stimulation of the motor cortex in the contralateral, but not the ipsilateral, hemisphere. That is, rTMS of the left, trained motor cortex specifically reduced peak acceleration of the right, trained hand; and rTMS of the right, untrained motor cortex specifically reduced peak acceleration of the left, untrained hand. Hence, our data suggest that part of the neural mechanism responsible for the early retention of ballistic performance improvements in an untrained limb (i.e. obtained via cross-limb

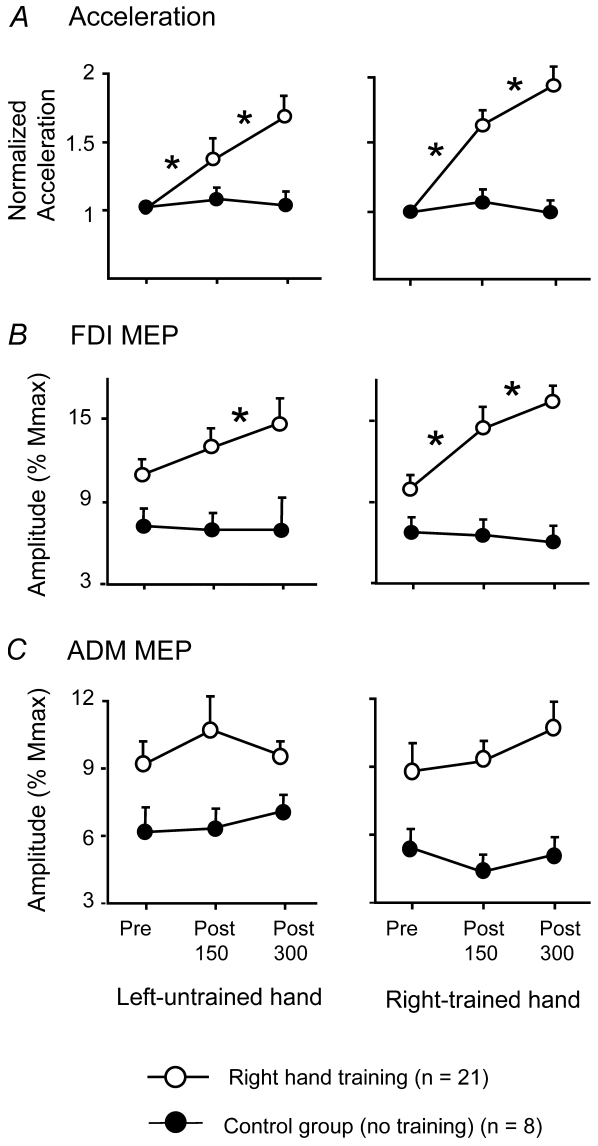


Figure 4. *A* shows average training (open circles) and control (filled circles) group data for peak acceleration (normalized to initial acceleration); *B* shows mean MEP amplitudes (normalized to Mmax) recorded from the left and right FDI; and *C* shows average MEP amplitudes for the left and right ADM muscles
Data were taken before training (Pre), and after 150 (Post 150) and 300 (Post 300) practice trials. Data were pooled from all three training groups for the right hand training values. Error bars indicate S.E.M. *denotes statistically significant changes ($P < 0.05$).

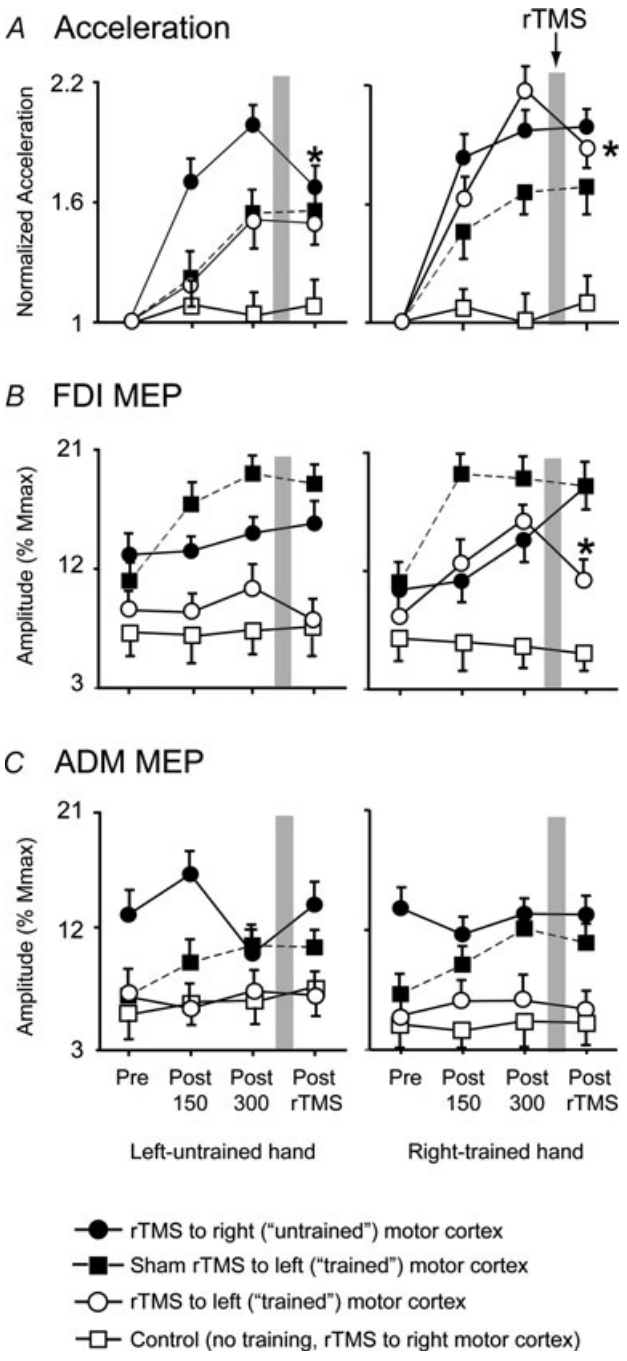


Figure 5. Group mean data for peak acceleration (normalized to initial acceleration) (*A*), and mean MEP amplitudes (normalized to Mmax) recorded from the left and right FDI (*B*) and ADM (*C*) muscles

Filled circles represent the training group that received rTMS to the right (untrained) motor cortex; open circles represent the group that received rTMS to the left (trained) motor cortex; filled squares represent the training group that received sham rTMS; and open squares represent the control group (no training) that received rTMS to the right motor cortex. Data were taken before and after two blocks of right hand training and after the rTMS intervention. The shaded bars represent periods of rTMS. Error bars indicate S.E.M. *denotes statistically significant changes ($P < 0.05$).

transfer) resides in the *untrained* motor cortex (i.e. the motor cortex ipsilateral to the trained limb).

The motor cortex has long been implicated in human motor learning (Pascual-Leone *et al.* 1994; Karni *et al.* 1995; Muellbacher *et al.* 2001), and there is recent evidence from TMS studies that improvement in ballistic motor performance is particularly dependent on adaptations in the motor cortex (Muellbacher *et al.* 2001, 2002; Baraduc *et al.* 2004; Jancke *et al.* 2004; Carroll *et al.* 2008). For example, rTMS of the trained motor cortex disrupts the early retention of performance gains in ballistic tasks (Muellbacher *et al.* 2002; Baraduc *et al.* 2004), whereas the evidence is mixed for force field tasks (Baraduc *et al.* 2004; cf. Cothros *et al.* 2006). Similarly, Jancke and co-workers (2004) demonstrated that rTMS reduced the maximum (ballistic) index finger tapping speed but did not affect self-paced (submaximal) tapping performance when applied to the contralateral motor cortex shortly after training. Our current results support the evidence that early retention of ballistic performance improvements are impaired by application of a virtual lesion to the contralateral motor cortex, and show additionally that cross-limb transfer of ballistic performance improvements are reduced *only* by disruptive rTMS to the untrained motor cortex. This suggests that processes in the *untrained* motor cortex (rather than the trained motor cortex) contribute to the early retention of ballistic performance improvements in the untrained limb.

Although the current findings indicate that the untrained motor cortex contributes to the early stages of the cross-limb transfer process, they do not provide information about the involvement of the untrained motor cortex in the consolidation, or long-term retention, of ballistic skill. Current understanding of the neuronal mechanisms that underlie motor learning is incomplete, but it is likely that multiple brain regions and synaptic (and/or intracellular) processes operate in a time-dependent fashion (see Krakauer & Shadmehr, 2006; Nader & Hardt, 2009). Thus, it is possible that training-induced processes in the untrained motor cortex contribute to the early retention of ballistic performance improvements with the untrained hand, but are not involved in the process of motor memory consolidation which mediates the long-term retention of skill. Studies that track the retention of ballistic skill for several hours after disruption of the motor cortex (via rTMS) are necessary to address this issue.

While adaptations in the untrained motor cortex appear to be involved in the early stages of the cross-limb transfer process for ballistic motor skills, they may not be as relevant to other types of learning that can result in cross-limb transfer. An example is implicit learning of finger tapping sequences, which results in cross-limb transfer of performance and an increase in

the excitability of the trained motor cortex, but does not affect the untrained motor cortex (Pascual-Leone *et al.* 1995; Perez *et al.* 2007*b*). Further, functional magnetic resonance imaging (fMRI) and rTMS data suggest that the supplementary motor area and basal ganglia are involved in the cross-limb transfer of sequence learning (Perez *et al.* 2007*a*). Hence, the mechanisms underlying cross-limb transfer of motor learning may differ depending on the task. While our current data suggest that mechanisms consistent with the cross-activation hypothesis contribute to cross-limb transfer of simple ballistic tasks, this does not exclude the possibility that bilateral access mechanisms are also involved. Furthermore, it is likely that the bilateral access model may be more relevant for tasks which require complex sequencing or sensorimotor integration.

The bilateral increases in corticospinal excitability observed after unilateral training in this study, and previously (Carroll *et al.* 2008), are also consistent with the cross-activation hypothesis. The increase in excitability was specific to the FDI representation in the current study (c.f. Carroll *et al.* 2008), perhaps due to the instruction for subjects to isolate movements to the second metacarpo-phalangeal joint, and to relax other parts of the hand. Surprisingly, Duque and colleagues (2008) recently showed that repetition of brisk index finger abduction movements decreased FDI MEP amplitude in the untrained hand, and shifted the direction of TMS-evoked twitches (at rest) towards finger adduction. However, there was no assessment of voluntary motor behaviour in the trained or untrained hand. The contrasting MEP results in the opposite, homologous muscles following unilateral 'ballistic' practice are probably due to differences in the nature of the training task, such as the intensity and duration of training, and the availability of visual feedback. Nevertheless, both studies indicate that unilateral motor practice can cause task-specific plastic changes in the untrained (ipsilateral) motor cortex.

An important consideration when interpreting rTMS data is that the effects of the stimulation can spread to brain areas distant to those directly targeted (e.g. Lee *et al.* 2003; Siebner & Rothwell, 2003). Since areas with strong connections to the motor cortex (e.g. the supplementary motor area) can be activated by suprathreshold stimulation (Gerschlager *et al.* 2001; Reis *et al.* 2008), we cannot exclude the possibility that adaptations in these areas contribute to the early retention of cross-limb transfer of ballistic performance improvements. The application of rTMS to 'control' brain areas has been used previously to infer that the effects of the stimulation are specific to the targeted area (e.g. Muellbacher *et al.* 2002; Hadipour-Niktarash *et al.* 2007). However, this approach only excludes the targeted 'control' areas from the observed effects. Given the wide range of cortical and subcortical sites that receive synaptic inputs from the motor cortex, such approaches provide only partial evidence to exclude non-specific spatial effects (Lee *et al.* 2003; Siebner & Rothwell, 2003). Low-frequency rTMS can also affect motor cortical excitability in the opposite hemisphere (Gilio *et al.* 2003; Kobayashi *et al.* 2004; Heide *et al.* 2006). In the current study, the application of rTMS to either hemisphere failed to modify early retention of performance gains in the hand ipsilateral to stimulation. Since it is unlikely that rTMS would exert its effect transcallosally without affecting local circuits beneath the stimulating coil, the data suggest that the cortical circuits involved in cross-limb transfer, in which the early retention of performance was disrupted by rTMS, lie within the *untrained* hemisphere.

The intensity of rTMS used in the current experiment was above resting motor threshold, and therefore sufficient to evoke descending corticospinal volleys and occasional, small finger movements (Di Lazzaro *et al.* 1999). Part of the rTMS effects could therefore have been mediated either at the spinal level via descending impulses, or at spinal or cortical levels via the influence of afferent feedback associated with small finger movements (Bestmann *et al.* 2004; Perez *et al.* 2005). However, any contribution to the impairment in motor learning from these mechanisms is likely to be small since reductions in MEP amplitude induced by rTMS are likely to be largely generated by cortical mechanisms (Di Lazzaro *et al.* 2008). Furthermore, peripheral nerve stimulation designed to mimic the afferent feedback produced by suprathreshold rTMS does not appear to produce major cortical effects (Gilio *et al.* 2003), and extended periods of peripheral nerve stimulation (>1 h at 10 Hz) are typically required to alter corticospinal excitability (Ridding *et al.* 2000).

It is interesting that rTMS of the untrained hemisphere disrupted performance in the untrained hand without affecting MEP amplitude in either hand. Muellbacher and colleagues (2002) attributed a similar lack of altered excitability for the trained hand to an interaction between learning-related excitatory effects and rTMS-related inhibitory effects. However, in the current study, rTMS to the right hemisphere also failed to significantly reduce corticospinal excitability for the right hand of control subjects. While a suppression of MEP amplitude is expected after low-frequency rTMS, scrutiny of the literature reveals considerable variability in the effects of rTMS on cortical excitability. While many studies have reported significant reductions in MEP amplitude (Chen *et al.* 1997*a*; Muellbacher *et al.* 2000*b*; Siebner & Rothwell, 2003; Fitzgerald *et al.* 2006), some have found no effect (Siebner *et al.* 1999; Gilio *et al.* 2003), and others have highlighted large inter-individual variability (Maeda *et al.* 2000; Gangitano *et al.* 2002; Romero *et al.* 2002). It is also possible that the specific protocol employed (i.e. 3 bouts of stimulation for 5 min), targeted hemisphere (most previous studies have stimulated left motor cortex) or type of stimulation used for excitability testing (i.e. biphasic rather

than monophasic TMS waveform) influenced the results. Whatever the reason, the crucial point for interpretation of the current results is that the rTMS protocol disrupted the training-induced improvement in maximal acceleration in both hands, but had no effect on basal motor behaviour in the control subjects who did not train. Thus, rTMS did not interfere with motor performance on the ballistic task per se (i.e. in either hand), but rather suppressed the training-induced performance gains. We conclude that rTMS impaired the early retention of ballistic performance gains in the untrained hand by specifically disturbing the neural circuits in the untrained (i.e. contralateral to the untrained hand) hemisphere, suggesting that the untrained hemisphere is involved in the early stages of the process by which ballistic skill transfers between limbs.

In summary, our data contribute to the evidence that the contralateral motor cortex contributes to initial improvements in ballistic motor performance, whether obtained through direct training or transfer from the opposite limb. The results suggest that adaptations in the 'untrained' motor cortex contribute to the early retention of ballistic performance gains for the untrained limb. We speculate that these 'crossed' adaptations are associated with the extensive bilateral cortical activity generated by unilateral high-force tasks.

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M.L. was involved in conception, design, interpretation of results and drafting the article. M.R.H. was involved in analysis and interpretation of data, and critical revision of the article. S.C.G. was involved in conception, design, interpretation of results and drafting the article. T.J.C. was involved in conception, design, interpretation of results and drafting the article.

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