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Absence of cross-limb transfer of performance gains following ballistic motor practice in older adults

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Hinder MR, Schmidt MW, Garry MI, Carroll TJ, Summers JJ. Absence of cross-limb transfer of performance gains following ballistic motor practice in older adults. *J Appl Physiol* 110: 166–175, 2011. First published November 18, 2010; doi:10.1152/japplphysiol.00958.2010.—The phenomenon of cross-limb transfer, in which unilateral strength training can result in bilateral strength gains, has recently been tested for ballistic movements. Performance gains associated with repetitive motor practice, and the associated transfer, occur within a few minutes. In this study, young and older adults were trained to perform ballistic abductions of their dominant (right) index finger as quickly as possible. Performance was assessed bilaterally before, during, and after this training. Both groups exhibited large performance gains in the right hand as a result of training ($P < 0.001$; young 84% improvement, older 70% improvement), which were not significantly different between groups ($P = 0.40$). Transcranial magnetic stimulation revealed that the performance improvements were accompanied by increases in excitability, together with decreases in intracortical inhibition, of the projections to both the trained muscle and the homologous muscle in the contralateral limb ($P < 0.05$). The young group also exhibited performance improvements as a result of cross-limb transfer in the left (untrained) hand ($P < 0.005$), equivalent to 75% of the performance increase in the trained hand. In contrast, there were no significant performance gains in the left hand for the older group ($P = 0.23$). This was surprising given that the older group exhibited a significantly greater degree of mirror activity than the young group ($P < 0.01$) in the left first dorsal interosseus muscle (FDI) during right hand movements. Our findings suggest that older adults exhibit a reduced capacity for cross-limb transfer, which may have implications for motor rehabilitation programs after stroke.

aging; motor learning; plasticity; transcranial magnetic stimulation

MANY FORMS of unilateral motor practice result in performance improvements when the training task is performed with either the trained or the untrained limb. One candidate mechanism for mediating cross-limb transfer is the so-called "cross-activation hypothesis." It is predicated on the assumption that performance of a unilateral task generates cortical activation not only in the contralateral motor cortex but also in the ipsilateral motor cortex. Indeed, imaging studies support the concept of bilateral activation during unilateral tasks (9, 10, 20). The degree of activation in the ipsilateral hemisphere has been shown to vary as a function of forcefulness of the contraction (10), task complexity (32, 42), the handedness of the participant (43), the hand that executes the task (9), and age (45). (See Ref. 42 for a useful review on influences on the degree of ipsilateral cortical activation.) Transcranial magnetic stimulation (TMS) studies also provide evidence that unilateral contractions have the ability to increase ipsilateral corticomotor excitability during tonic (15, 26, 37) and ballistic (6, 16, 17) contractions. The cross-activation hypothesis suggests that performance gains in the untrained limb are mediated by changes within the ipsilateral cortex that occur as a result of the bilateral cortical activity during unilateral task performance (see Ref. 6).

During later life there is an exaggerated propensity to exhibit muscle activity in both hands when unimanual activation is desired (Refs. 2, 3; see Ref. 19 for a review). Recent imaging studies indicate that this so-called mirror activity is a result of exaggerated bihemispheric activation of the motor cortices during unimanual tasks. That is, aging (and specifically the neurophysiological changes that occur as a resulting of increasing age—see Ref. 39) is associated with an increased activation of the primary motor cortex ipsilateral to the moving limb (Ref. 43; for a review see Ref. 44). This additional cortical activity may be due to a breakdown in the ability to modulate some (40) but not all (17, 40) interhemispheric inhibitory mechanisms during different volitional tasks. The cross-activation hypothesis may predict that the greater bilateral cortical activation often observed in older adults during unilateral tasks could induce more pronounced cross-limb transfer of performance gains than that exhibited for young adults. As far as we are aware, this proposition has not been systematically tested.

Strength training is one form of unilateral practice that induces reliable performance improvements in the opposite (untrained) limb. It has been known since the late nineteenth century (36) that unilateral strength training can result in increases in strength in both the trained and untrained (contralateral) limb. Meta-analysis suggests that the extent of the strength increases observed in the untrained (contralateral) limb is ~35–50% of the improvements seen in the trained limb (5, 28). Recent studies have extended the concept of cross-limb transfer to tasks requiring fast-as-possible (ballistic) movements of the fingers or thumb (e.g., Refs. 6, 23). Experimentally, these tasks are appealing because large performance improvements can be observed in both the trained and untrained limb in a single session of several hundred repetitive movements lasting less than half an hour (e.g., Refs. 6, 8, 27, 33). Accordingly, it has been possible to use techniques such as electromyographic (EMG) recordings and TMS mechanisms mediating the cross-limb transfer of performance gains associated with unilateral practice of a motor task in a single experimental session.

Because changes in the ipsilateral cortex are generally most pronounced in tasks requiring substantial drive (16, 17, 31), strength training or fast-as-possible dynamic tasks provide a good platform to test the cross-activation theory. For example, Carroll et al. (6) demonstrated bilateral increases in cortico-

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motor excitability as a result of unilateral, fast-as-possible training, together with cross-limb transfer of the performance gain. The same research group (23) subsequently used repetitive TMS to induce a virtual lesion and show that adaptations within the left (trained) hemisphere mediated performance improvements in the (trained) right hand and changes within the right (untrained) hemisphere mediated those performance gains (as a result of cross-limb transfer) in the (untrained) left hand. That is, while bilateral increases in excitability were observed as a result of performance improvements in a unilateral task, the adaptations within each hemisphere specifically mediated performance improvements of the respective contralateral limb (as a result of practice or cross-limb transfer). These findings are consistent with the cross-activation hypothesis.

While it is well established that unilateral motor practice can lead to excitability increases in the trained (contralateral) cortex and that these practice-induced excitability changes can be associated with a change in the level of inhibition [short-interval intracortical inhibition (SICI)] within in the trained cortex (24, 34), it is unknown whether excitability increases in the untrained (ipsilateral) cortex (6, 23) are also (at least in part) a result of changes in SICI. Furthermore, recent work has suggested that mirroring (i.e., bilateral activation during a unilateral task, which we suggest may facilitate cross-limb transfer in older adults) may be mediated not only by interhemispheric inhibition (IHI) but by IHI and SICI in the cortex ipsilateral to the contraction (31). As such, investigating changes in SICI in both hemispheres during a unilateral training task may provide additional insights into the processes responsible for cross-limb transfer.

To address some of the aforementioned issues, the present study required young and older adults to practice a fast-as-possible index finger movement with their dominant hand. Motor performance, corticomotor excitability, and intracortical inhibitory mechanisms were assessed bilaterally before, during, and upon completion of the unilateral training in order to identify any age-dependent differences in the expression and mechanisms of cross-limb transfer.

METHODS

Participants

A total of 30 right-handed adults (29) were recruited from the university and local community and were either <33 yr old ("young") or >62 yr of age ("older"). Participants gave written informed consent before beginning the experiment, which had received ethical approval from the University of Tasmania's Human Research Ethics Committee. Participants were screened for contraindications to TMS, had normal or corrected-to-normal vision, and were free from neurological and neuromuscular disorders. Initially, two groups of 12 participants (young group: mean ± SD age 22.3 ± 4.4 yr, range 18–32 yr; older group: 67.8 ± 3.3 yr, 63–74 yr) were recruited. There were 8 women and 4 men in each group. A second group of young participants [n = 6 (5 women, 1 man), 20.2 ± 2.6 yr, range 18–25 yr] were subsequently recruited and underwent an identical behavioral experimental protocol with some additional neurophysiological testing.

Experimental Design

The study was designed to assess cross-limb transfer of performance gains attributable to the practice of a unilateral motor task in young and older adults. Figure 1 outlines the experimental procedure. Initially, corticomotor excitability and intracortical inhibition were assessed in both hemispheres using TMS. Assessment of performance in both the left and right hands (10 trials per hand) was also conducted without visual feedback (Pre testing). All participants then undertook 150 trials of motor practice with their dominant right hand (R training *block 1*; 15 sets of 10 trials), after which corticomotor excitability and intracortical inhibition and performance were reassessed in both hemispheres and hands (Mid testing). Participants then completed a second training block (150 trials, R training *block 2*) before measures of excitability, inhibition, and performance were assessed for a final time (Post testing). The order of TMS testing (left/right cortex) and performance testing (left/right hands) was randomized.

Movement Task

While seated, participants placed their forearms on a horizontal board mounted onto a table. The palms faced down and the elbows were bent at ~120°. The hands were restrained with vertical pegs inserted into the board. These restraints were designed to restrict movements to the second metacarpophalangeal joint (6, 23) and helped to maintain a consistent posture throughout the experiment. The movement task required participants to perform isolated abductions of the index finger "as quickly as possible." They were instructed to move in the horizontal plane by skimming across the surface of the low-friction board and asked to isolate the movements to the second metacarpophalangeal joint of the index finger. Triaxial accelerometers (Dytran Instruments, Chatsworth, CA; Endevco, San Juan Capistrano, CA) were mounted to plastic splints and taped to the top of the left and right index fingers such that one of the orthogonal axes of each accelerometer was aligned to measure horizontal acceleration (the positive axes were orientated to measure index finger abduction of each finger).

Initially we tested performance in both the left and right hands (Pre testing). Testing involved 10 trials in which performance feedback and verbal encouragement were not provided. Participants were simply reminded to make isolated abduction movements as quickly as

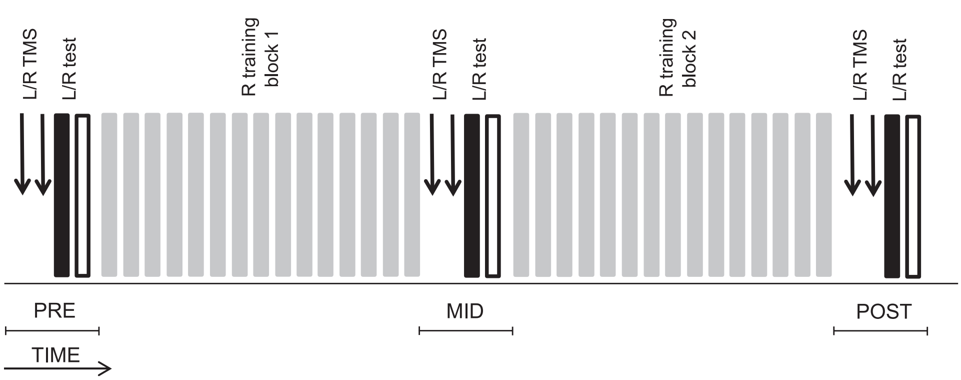

Fig. 1. Experimental timeline. For more detail regarding behavioral testing/training and transcranial magnetic stimulation (TMS) neurophysiological testing refer to the appropriate sections. L, left; R, right.

possible. An audio tone ("go" signal) was used to prompt subjects to perform a ballistic index finger abduction movement every 2 s (0.5 Hz). After the Pre tests, participants underwent unilateral training with their right hand (2 blocks of 150 trials, 300 movements total). During this practice, verbal encouragement and visual feedback of the peak abduction acceleration attained were provided. Feedback from each trial was presented in the form of a data point on a graph on which the *y*-axis represented peak acceleration and the *x*-axis represented trial number. Participants were encouraged to raise the line (created by joining all previous trials) as high as possible up the screen, i.e., they aimed to increase the peak acceleration of the ballistic finger abduction over the course of the training period. After every 10 movements of the training, a short rest period (~30 s) was inserted to minimize fatigue effects. Upon completion of the first and second unilateral training blocks, we assessed performance in the left and right hands in the absence of feedback or encouragement (Mid and Post tests; 10 trials per hand).

Recording of Muscle Activity

EMG activity was recorded with Ag/AgCl electrodes (Meditrace 130, Tyco Healthcare, Mansfield, MA) from the first dorsal interosseus muscle (FDI) and abductor digiti minimi muscle (ADM) in both hands in a belly-tendon montage (as per Ref. 23) during execution of the task and during corticomotor excitability measurements (see below). EMG signals were fed into a CED 1401 amplifier (Cambridge, UK), where a notch filter (50 Hz) was applied before amplification (gain 300–1,000). Data were recorded on a computer for later off-line analysis.

Transcranial Magnetic Stimulation

TMS was delivered with two Magstim 200 units (Magstim, Whitland, UK) connected via a Bistim unit and a single figure-of-eight coil (external diameter of each loop 70 mm). The optimal coil positions for eliciting motor evoked potential (MEPs) from the left and right FDI (with posterior-to-anterior current direction, i.e., coils at ~45° to the midline and in a plane tangential to the scalp surface) were determined in the initial setup phase of the experiment and marked on the scalp with a nonpermanent marker pen. Participants relaxed both their limbs during the period in which TMS measures were acquired, with their hands in the same posture as that assumed during the movement task (see above). They were provided with visual feedback of muscle activity and asked to keep background activity at a minimum. Resting motor thresholds (RMTs) were determined as the minimum intensities required to elicit MEPs >50 μV in the right and left FDI in three of five consecutive trials when stimulating at the predetermined hotspots (4, 14).

A block of 20 stimulations (at a rate of 0.2 Hz) was administered before (Pre) and after (Mid) the first training block and after completion of the second training block (Post) to the left (trained) and right (untrained) cortex. The order in which the cortices were stimulated was randomized. Accordingly, the Mid and Post TMS blocks commenced ~1.5 (first cortex tested) or 4 (second cortex tested) min after completion of the preceding training block. Ten of the twenty stimulations applied to each cortex within each block involved a single "test" stimulus, applied to the predetermined FDI motor hotspot at 130% RMT. These trials were used to assess the net excitability of the corticomotor projections to the trained/untrained hand. In the other 10 trials, a subthreshold conditioning stimulus was delivered through the same coil at 70% RMT 3 ms before the same suprathreshold test stimulus, i.e., paired-pulse stimulation (22). The 10 single-pulse stimulations and 10 paired-pulse stimulations were pseudorandomly intermingled. The ratio of the MEP evoked after paired-pulse stimulation to the MEP amplitude evoked in the single-pulse stimulation is referred to as the short-interval intracortical inhibition (SICI) ratio (22) and is used as an indication level of activity of the inhibitory circuits (within the trained or untrained hemisphere).

In six of the young participants two other stimulation blocks were also administered in the Pre, Mid, and Post testing blocks. These blocks were undertaken to determine whether the excitability measures obtained during the initial stimulation block (described above) were affected in any way by the intensity of the test pulse or because of the intermingling of single- and paired-pulse trials (e.g., hysteresis effects, see Ref. 25). The first of these additional stimulation blocks (again applied to the FDI hotspot in the left and right cortices) involved 10 single-pulse stimulations at 130% RMT, while the second block involved 10 single-pulse stimulations at 150% RMT (to each cortex). These two additional stimulation blocks were undertaken in a random order, but always followed the stimulation block containing single- and paired-pulse stimulations.

At each time point where corticomotor excitability and movement performance were assessed (i.e., Pre, Mid, and Post), the TMS procedures always preceded the performance testing. In this manner we ensured that any changes in MEP amplitude and/or SICI were a result of the preceding training phase and could not be a result of any changes in corticomotor excitability as a result of the test phase.

Data Acquisition and Analysis

Kinematic and EMG data associated with each of the volitional finger movements were sampled at 2 kHz from 500 ms before the "go" tone for 1,500 ms with custom-written CED (Cambridge, UK) Signal programs. Data analysis was performed off-line with custom-written Signal routines. Acceleration data were low-pass filtered at 20 Hz before analysis. For each movement, peak abduction acceleration was determined as the first peak in the horizontal acceleration.

To assess performance, peak acceleration was determined in the 10 trials of the Pre, Mid, and Post for the left and right hands and then averaged across the 10 trials. Values were then normalized (for each participant) to the Pre acceleration for each hand (i.e., left hand values were normalized to average acceleration in left Pre test block, while right hand accelerations were normalized to the right Pre test block) for the purposes of statistical comparisons and graphic representation. We quantified cross-limb transfer in the untrained left hand as a percentage of the normalized performance gain in the trained right hand. Specifically, we divided the normalized performance gain in the left hand Post test by the normalized performance gain in the right hand Post test and multiplied the result by 100. Mean cross-limb transfer was then determined for each participant group.

EMG data were analyzed to quantify the movement-related muscle activity in each trial. For each left and right hand test movement, EMG data were rectified and low-pass filtered (20 Hz) before further analysis. The peak EMG amplitude in the FDI of the hand undertaking the ballistic task was then determined. Movement onset was determined as the time at which FDI activity in the active hand first increased above a threshold level equivalent to 4 times background EMG determined before movement onset. Movement offset was determined as the time at which FDI activity in the active hand first dropped below 0.2 times the peak amplitude. In this manner we were able to consistently determine a movement offset even if (low level) contraction was present at the end point of the finger abduction (cf. Ref. 6). We then determined the average EMG of the FDI in the hand executing the ballistic action within this time window, minus the average value of (background) EMG in the same muscle during the period 50–100 ms before movement onset. In a similar manner we determined the average FDI EMG in the contralateral hand during the same time window. Accordingly, EMG signals of both muscles represent muscle activity associated with the ballistic actions and do not include any ongoing activity that could have been present for postural maintenance/stabilization. As with the kinematic (acceleration) data, we then averaged these EMG values across the 10 trials of the Pre, Mid, and Post tests. The values for the right FDI (in left and right hand test trials) were normalized to the EMG value obtained for the right FDI during the right hand PRE test. Values for left FDI activity (during left and right hand trials) were normalized to the left FDI EMG value obtained for the left hand PRE test. This normalization procedure enabled us to assess changes in the FDI of the hand undertaking the task relative to that activity exhibited before training and permitted the extent of mirror activity to be expressed as a proportion of the level of activity observed when that hand was actively undertaking the task (e.g., mirror activity of 0.05 indicates that the level of activity in the hand contralateral to that undertaking the task was 5% of the level of activity in that same hand when it was undertaking the volitional action).

Line plots were also constructed to qualitatively compare the proportion of trials exhibiting specific levels of mirror activity for the young and older groups. The Pre, Mid, and Post test trials were combined, and we assigned each trial to 1 of 20 bins on the basis of the level of mirror activity in that trial (0–5%, 5–10%, 15–20%, . . . 95–100% of that activity seen when the hand undertook the volitional action).

Responses to the cortical stimulations were sampled at 10 kHz from 3 s before to 2 s after the suprathreshold TMS pulse. Accordingly, we were able to observe any undesired volitional activity in any of the muscles of interest before the TMS stimulations and remove these trials from further analysis (see below). The peak-to-peak amplitude of MEP evoked as a result of the stimulation was measured in the two muscles of the limb contralateral to the cortex being stimulated in the period 15–50 ms after stimulation. Average MEP amplitudes were derived for each muscle for trials in the single- and paired-pulse trials of each stimulation block separately. For each muscle, MEP amplitudes were normalized to the Pre value before statistical analyses. Normalized MEP amplitudes are referred to here as nMEP. The SICI ratio for each muscle was determined as the average (nonnormalized) MEP amplitude in the paired-pulse stimulations divided by the average MEP amplitude in the single-pulse stimulations (SICI < 1 indicates inhibition was present). To assess training-induced changes in SICI, we divided the SICI ratio in the Mid and Post test trials by the SICI ratio in the Pre test and refer to this value as nSICI. nSICI values < 1 indicate increased inhibition relative to the Pre test, while values > 1 indicate a release of inhibition (reduced SICI) relative to the Pre test SICI ratio.

The normalization procedure we undertook for all dependent variables is beneficial because it removes possible confounds in the statistical results that may otherwise exist because of the inherent intergroup variability in the Pre test values, i.e., statistical analyses of normalized values are not biased by the data of any one participant who has a particularly low, or high, Pre test value.

Statistical Analysis

Data from all 18 young and 12 older participants were included in statistical analyses of task performance, activity of both FDI muscles during unilateral task performance, and changes in MEP amplitude and SICI. Additional analyses of neurophysiological measures were undertaken on the six young participants who were exposed to supplementary TMS stimulation blocks (see APPENDIX).

Task performance. To assess any pretraining differences in performance, nonnormalized (raw) peak accelerations in the Pre test were compared by ANOVA with hand (left, right) as a within-subjects factor and age (young, older) as a between-subjects factor. To assess changes in performance of the right and left hands relative to the respective Pre tests, we compared normalized peak accelerations in the Mid and Post tests by ANOVA with hand (left, right) and time (Mid, Post: repeated measures) as within-subject factors and age (young, older) as a between-subjects factor. Subsequent post hoc tests were undertaken to further investigate any significant main effects and interactions.

Statistical analyses were also conducted on cross-limb transfer (see *Data Acquisition and Analysis* above) exhibited in the untrained left hand. Independent-samples *t*-test was used to compare the extent of cross-limb transfer across the two age groups, and single-sample *t*-tests were used to determine whether cross-limb transfer for each group was statistically different from zero.

Muscle activity during task performance. We assessed changes in the levels of muscle activity in the FDI of the hand instructed to undertake the task by ANOVA with hand (left, right) and time (Mid, Post: repeated measures) as within-subject factors and age (young, older) as a between-subjects factor. The extent of the mirror activity in the FDI of the contralateral hand was assessed by ANOVA with hand (left, right) and time (Pre, Mid, Post: repeated measures) as within-subject factors and age (young, older) as a between-subjects factor.[1] Finally, regression analyses were undertaken to assess any relationship between the degree of mirror activity observed in the left FDI (during right hand test trials) and the extent of cross-limb transfer exhibited in left hand test trials.

TMS measures. Corticomotor excitability was assessed by using nMEP from the single-pulse stimulation trials within the 20-pulse stimulation block. We assessed excitability in the FDI (i.e., the muscle primarily engaged in index finger abductions) in both the trained (right) and untrained (left) hands. SICI was assessed in the right and left FDI by evaluating SICI ratio in the Mid and Post tests relative to SICI in the Pre test. For nMEP and nSICI we undertook ANOVA with hand (right, left) and time (Mid, Post) as (repeated measures) within-subject factors and age group as a between-subjects factor.

For all ANOVAs, Huynh-Feldt corrections were applied if the assumption of sphericity was violated ($\varepsilon < 0.7$). Partial η-squared (η_p^2) values are presented as a measure of effect size to aid the interpretation of the tests of significance. Statistical significance was set at $P < 0.05$.

RESULTS

Performance of Trained (Right) and Untrained (Left) Hands

Pretraining performance, as assessed by nonnormalized accelerations, of the right hand (young: 21.9 ms^{-2}; older: 23.2 ms^{-2}) was significantly faster than that recorded in the left hand Pre test (young: 14.3 ms^{-2}; older: 13.4 ms^{-2}) [$F_{(1,28)} = 19.25$, $P < 0.001$, $\eta_p^2 = 0.41$], but pretraining performance did not vary as function of age [$F_{(1,28)} < 0.01$, $P = 0.96$, $\eta_p^2 < 0.01$]. Accordingly, any group differences in normalized performances for either hand cannot be attributed to baseline (untrained) performance capabilities.

Figure 2 shows normalized performance in the test trials for the left and right hands in which performance was tested without the benefit of visual feedback of performance or verbal encouragement. For the right hand (Fig. 2*B*), the young group exhibited a 53% and 84% improvement in performance in the Mid and Post tests, respectively, relative to the Pre test, while the older group exhibited 40% and 70% improvements in the Mid and Post tests, respectively. In the left hand test phases (Fig. 2*A*), the young group exhibited 29% and 54% improvement (relative to the left Pre test) in the Mid and Post tests, respectively. In contrast, for the older group performance in the Pre and Mid (2% increase) and Post (6% increase) tests for the left hand were similar.

Three-way ANOVA revealed a significant time effect [$F_{(1,28)} = 22.18$, $P < 0.001$, $\eta_p^2 = 0.44$] indicating that, averaged across both age groups and hands, there was a

[1] Because the extent of mirror activity is reported relative to the level of activity in that same hand when it undertook the task (i.e., mirror activity in the left hand during right hand movements is reported relative to the activity in the left hand during left hand movements), Pre values are not unity and, as such, are included in the ANOVA.

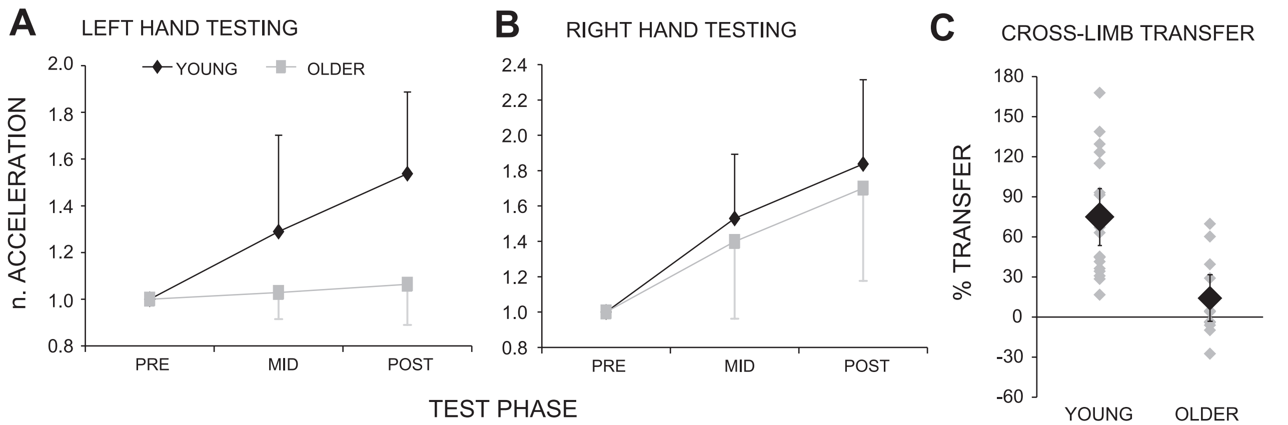

Fig. 2. Normalized (n) performance of the left (*A*) and right (*B*) hands in the Pre, Mid, and Post tests for the young and older groups. *C*: performance gain in the left limb as % of performance gain in the right limb (cross-limb transfer). Data are shown for all individuals (gray diamonds) and averages (black diamonds) for the young (*left*) and older (*right*) groups. Error bars denote SD.

significant improvement in performance from Mid to Post training. Significant main effects for hand [$F_{(1,28)} = 18.60$, $P < 0.001$, $\eta_p^2 = 0.40$] and age [$F_{(1,28)} = 6.44$, $P < 0.05$, $\eta_p^2 = 0.19$] denote that, averaged across all other variables, right hand performance was faster than left hand performance and performance of the young group was faster than that of the older group. Significant interactions between time and hand [$F_{(1,28)} = 10.31$, $P < 0.005$, $\eta_p^2 = 0.27$] and the three-way interaction between time, hand, and age [$F_{(1,28)} = 4.12$, $P < 0.05$, $\eta_p^2 = 0.13$] allude to the fact that improvements in performance over time varied as a function of both hand and age. Inspection of Fig. 2 reveals that the three-way interaction is driven by the fact that both groups improved performance in the right hand, while only the young group improved performance in the left hand. This observation was confirmed by post hoc analyses: for the young group performance in the Mid and Post tests for both the right and left hands was significantly greater than 1 (both $P < 0.005$), i.e., performance improvements had occurred in both hands relative to the Pre test. While statistically significant performance improvements were also observed in the Mid and Post tests of the right hand for the older group ($P < 0.005$), performances in the left hand (in both Mid and Post tests) did not differ significantly from 1 ($P > 0.23$ in both cases). In summary, the behavioral data clearly indicate that unilateral training of the right hand resulted in significant performance gains in both the right and (untrained) left hands for the young group, but for the older group left hand performance was unaffected by unilateral right hand training.

Performance Gains in Left Hand As Function of Right Hand Performance Gains

Figure 2*C* presents normalized performance gains in the left hand as a percentage of the normalized performance gain observed in the right hand, i.e., cross-limb transfer (see METHODS). All young participants exhibited cross-limb transfer of at least 16% and up to 168%. On average, cross-limb transfer was 75% (Fig. 2*C*, *left*). In contrast, cross-limb transfer for the older participants ranged from −32% to 67%, with 8 of the 12 participants in the range −12% to 26% (Fig. 2*C*, *right*). Across all older participants, the cross-limb transfer averaged only 11%. An independent-samples *t*-test indicated that the cross-limb transfer for the young group was significantly greater than the cross-limb transfer observed for the older group ($t_{28} = 4.32$, $P < 0.001$). Furthermore, single-sample *t*-tests revealed that for the young group cross-limb transfer was significantly greater than zero ($t_{17} = 7.10$, $P < 0.001$) while for the older group cross-limb transfer did not differ from zero ($t_{11} = 1.29$, $P = 0.22$).

Volitional Muscle Activity During Right and Left Hand Test Phases

Overall, there was an increase in the level of FDI activity during the volitional muscle burst in the Mid (9% increase) and Post (18% increase) tests relative to the Pre test [$F_{(1,28)} = 9.02$, $P < 0.01$, $\eta_p^2 = 0.24$; Fig. 3]. The FDI EMG burst increased from Mid to Post test [time main effect: $F_{(1,28)} = 8.04$, $P < 0.01$, $\eta_p^2 = 0.22$] but did not vary between the right and left hands [$F_{(1,28)} = 0.05$, $P = 0.82$, $\eta_p^2 < 0.01$] or between age groups [$F_{(1,28)} = 0.06$, $P = 0.81$, $\eta_p^2 < 0.01$]. All two- and three-way interactions were not significant (all $P > 0.40$).

Mirror Activity During Ballistic Actions

The level of mirror activity was significantly greater for the older group than for the younger group [young: 4%; older: 9%; $F_{(1,28)} = 8.85$, $P < 0.01$, $\eta_p^2 = 0.24$; Fig. 3] and was found to increase with time [$F_{(2,56)} = 7.48$, $P < 0.005$, $\eta_p^2 = 0.21$]. Mirror activity was also somewhat higher in the right FDI during left hand testing compared with mirror activity in the left FDI during right hand testing [$F_{(1,28)} = 4.55$, $P < 0.05$, $\eta_p^2 = 0.14$]. The interactions between hand and time [$F_{(2,56)} = 3.76$, $P < 0.05$, $\eta_p^2 = 0.12$] and hand, time, and age [$F_{(2,56)} = 5.20$, $P < 0.05$, $\eta_p^2 = 0.16$] were also significant. Bonferroni-adjusted post hoc tests suggest that the two-way interaction can be interpreted by the fact that (averaged over both groups) mirror activity increased significantly from Pre to Post tests in the left FDI during right hand movements (post hoc $P < 0.001$), but a similar comparison did not quite reach significance for the right FDI mirror activity during left hand movements ($P = 0.056$). The three-way interaction was predominantly driven by the fact that marginal Pre to Post increases in mirror activity in right FDI activity during right hand movements occurred for both groups (both $P < 0.03$); however, for the right FDI during left hand movements activity levels

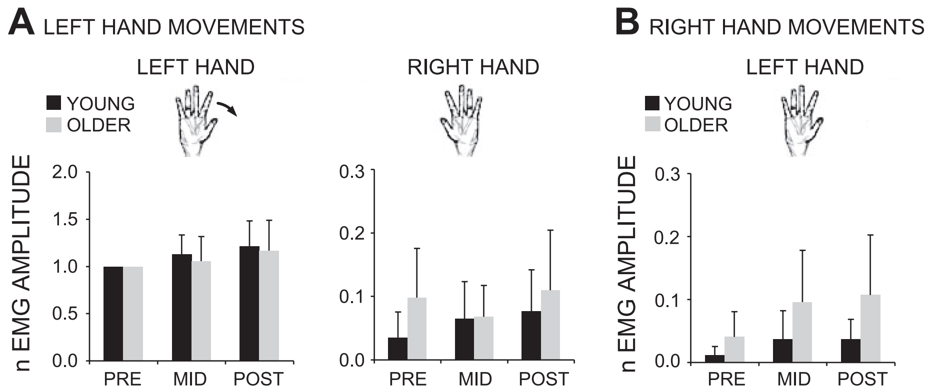

Fig. 3. Muscle activity of the right and left first dorsal interosseus muscle (FDI) during ballistic movements. *A*: left hand movements. *Left*: activity in the moving left hand (FDI). *Right*: mirror activity in the right FDI. *B*: right hand movements. *Right*: activity in the right FDI during the movement. *Left*: mirror activity in the left FDI. Data are shown for the Pre, Mid, and Post tests for the young and older groups. Error bars denote SD. Arrows next to each hand denote the moving hand.

increased for the young ($P < 0.01$) but not the older ($P = 0.75$) group (see Fig. 3).

Figure 4 shows line plots that indicate the proportion of trials in which varying degrees of mirror activity were observed for each participant group. For movements of the right (trained) hand (Fig. 4*B*) 80% of trials for the young group show little, or no, mirror activity (i.e., activity in left FDI during right hand movements ≤5% of left FDI activity observed during left hand movements). For the older group, ~50% of trials exhibit little or no mirror activity. However, it can be seen that the distributions for each group intersect in the second bin (5–10% mirror activity) such that the older group show a higher proportion of trials with >10% mirror activity than the young. Overall, ~35% of trials for the older group have mirror activity of at least 10%, while for the younger group <10% of trials have mirror activity of >10%. A similar age effect is observed for the mirror activity in the right hand during left hand movements (Fig. 4*A*). However, it can be seen that for both groups a smaller proportion of trials have little or no activity compared with the right hand movements.

Finally, we used regression analyses to test whether the degree of cross-limb transfer exhibited was correlated to the observed level of mirror activity. This was found not to be the case, as the regressions undertaken either for each group separately, or for all participants combined, were not statistically significant (all $P > 0.20$).

Changes in Corticomotor Excitability with Training

Average (±SD) RMTs for the younger group were 45.1 ± 6.5% and 45.4 ± 7.0% of maximum stimulator output for the left and right hands, respectively. For the older group, average RMTs were 49.1 ± 7.1% and 47.1 ± 6.4% for the left and right hands, respectively. ANOVA revealed that there was no significant difference in RMT between hands [$F_{(1,28)} = 0.81$, $P = 0.38$, $\eta_p^2 = 0.03$] or age groups [$F_{(1,28)} = 1.19$, $P = 0.29$, $\eta_p^2 = 0.04$] and no hand by age interaction [$F_{(1,28)} = 1.48$, $P = 0.23$, $\eta_p^2 = 0.05$]. MEP amplitudes measured in the quiescent right FDI during the Pre test were 0.98 ± 0.56 and 0.87 ± 0.91 mV for the young and older participants, respectively. MEP amplitudes measured in the left FDI during the Pre test were 1.08 ± 0.15 mV for the young and 0.77 ± 0.18 mV for the older group. ANOVA (hand × age group) indicated that there was no significant difference in MEP amplitude measured in each hand [$F_{(1,28)} < 0.01$, $P = 0.96$, $\eta_p^2 < 0.00$] or across age groups [$F_{(1,28)} = 0.90$, $P = 0.35$, $\eta_p^2 = 0.03$].

ANOVA was conducted on the average pretrigger EMG calculated for each participant in the period 50–100 ms prior to the TMS pulse. Averaged over all conditions, average pretrigger EMG was 0.006 ± 0.002 mV, well below the cutoff of 0.015 mV we used to remove trials that could potentially contain a low level of volitional muscle activity before TMS stimulation (see *Data Acquisition and Analysis*). ANOVA indicated that EMG was very slightly, but significantly, lower in the left FDI (0.0055 mV) compared with the right FDI (0.0066 mV) [$F_{(1,28)} = 6.73$, $P < 0.05$, $\eta_p^2 = 0.19$]. However, given the extremely low values observed for both hands, it is extremely unlikely that this value reflects subliminal muscle activity, and it is most likely a result of different levels of noise across the two hands. Pretrigger EMG did not differ between the single-pulse and paired-pulse trials, did not differ as a function of time, and did not differ between age groups (all $P > 0.15$). All interactions were also nonsignificant (all $P >$

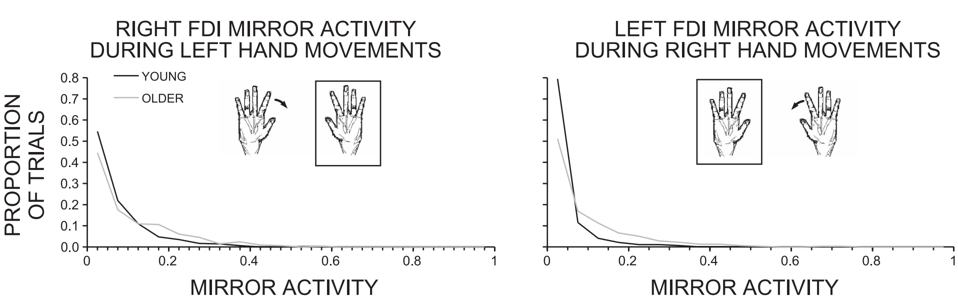

Fig. 4. Plots showing the proportion of trials that exhibit varying degrees of mirror activity. *A*: mirror activity of the right FDI during left hand movements. *B*: mirror activity of the left FDI during right hand movements. Pre, Mid, and Post test trials were combined to yield 1 distribution for each participant group. Hand diagrams and arrow indicate for each panel which hand was moving and in which hand mirror activity was recorded.

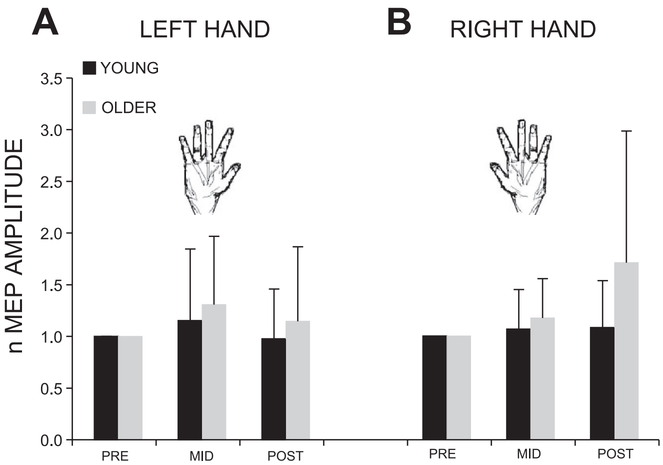

Fig. 5. Normalized motor evoked potential (MEP) amplitude evoked in the FDI of the quiescent left (untrained; *A*) and right (trained; *B*) hand during the Pre, Mid, and Post TMS stimulation sessions. Data are shown for the young and older groups. Error bars denote SD.

0.16). Accordingly, any changes in MEP amplitudes are most likely to be associated with the motor task and are not confounded by pretrigger EMG.

MEP amplitudes in response to single pulses of TMS were used as an indication of how corticomotor excitability of the right and left FDI muscles varied as a result of unilateral training of the right hand. Figure 5 presents normalized MEP sizes measured in the left (Fig. 5*A*) and right (Fig. 5*B*) FDI muscle for the young and older groups. Values > 1 indicate potentiation of MEP relative to the Pre test MEP.

Averaged over both participant groups, excitability of the right FDI was 12% and 40% higher in the Mid and Post tests, respectively, compared with the Pre test, while excitability increases for the left FDI averaged 23% and 6% in the Mid and Post tests, respectively. ANOVA revealed that, averaged over the Mid and Post tests for the left and right hands for both age groups, there was a significant increase in the amplitude of the MEP evoked in the FDI muscle relative to the Pre test [i.e., nMEP > 1; $F_{(1,28)} = 6.812$, $P < 0.05$, $\eta_p^2 = 0.20$]. This potentiation did not vary as a function of hand or time (both main effects $P > 0.4$). The effect of age group did not reach the conventional level of statistical significance [$F_{(1,28)} = 2.93$, $P = 0.098$, $\eta_p^2 = 0.10$], but the marginal P value suggests that, if anything, there was a tendency for the older group to exhibit greater increases in excitability than the younger group. Finally, a hand by time interaction [$F_{(1,28)} = 6.01$, $P < 0.05$, $\eta_p^2 = 0.18$] indicates that, averaged over both age groups, excitability of the right hand tended to increase from Mid to Post test while excitability of the left hand was slightly diminished in the Post test relative to the Mid test.

Changes in SICI

SICI ratios for right FDI during the Pre test were 0.42 ± 0.21 and 0.79 ± 0.83 for the young and older participants, respectively. SICI ratios for left FDI during the Pre test were 0.47 ± 0.23 and 0.63 ± 0.36 for the young and older participants, respectively. ANOVA with hand as a within-subject factor and age group as a between-subjects factor revealed that pretraining SICI did not vary between hands [$F_{(1,28)} = 0.44$, $P = 0.51$, $\eta_p^2 = 0.02$]. The tendency for greater SICI (lower ratio) in the young compared with the older group did not quite reach significance [$F_{(1,28)} = 3.86$, $P = 0.06$, $\eta_p^2 = 0.12$].

To investigate how SICI in both FDIs changed as a result of the right hand training, we normalized SICI ratio to the Pre condition (i.e., nSICI, see METHODS) (Fig. 6). A ratio >1 indicates less pronounced inhibition in the Pre or Mid test relative to the Post test.

ANOVA revealed that, averaged over both hands, time points, and groups, nSICI was >1 [$F_{(1,28)} = 2.43$, $P < 0.05$, $\eta_p^2 = 0.15$]. This result indicates a generalized release of inhibition (i.e., less inhibition) in the Mid and Post tests relative to the Pre test. The main effect of time [$F_{(1,28)} = 2.38$, $P = 0.14$, $\eta_p^2 = 0.09$] did not reach significance, suggesting that no significant change in nSICI occurred between the Mid and Post tests. The main effects of hand and age ($P > 0.48$) and all two- and three-way interactions ($P > 0.38$) were not significant.

DISCUSSION

This study was designed to assess cross-limb transfer of performance gains attributed to the practice of a unilateral ballistic task in a group of young and older adults. We hypothesized that the increased bilateral cortical activity that is typically observed when older adults undertake unilateral tasks (43–45) might increase neural adaptations within the untrained hemisphere, and thereby permit a greater degree of cross-limb transfer compared with that observed in young adults. In contrast to our hypothesis, the young adults exhibited considerable transfer of performance gains to the untrained left hand, while the older group failed to exhibit any significant gains in the untrained left hand (Figs. 2 and 3). This absence of transfer for the older group occurred despite their ability to improve performance in the trained hand to a degree similar to that seen in the younger adults.

Mirror Activation During Task Performance Does Not Facilitate Cross-Limb Transfer for Older Adults

In agreement with the body of evidence indicating greater overflow in older adults (2, 3, 19), we observed greater muscle

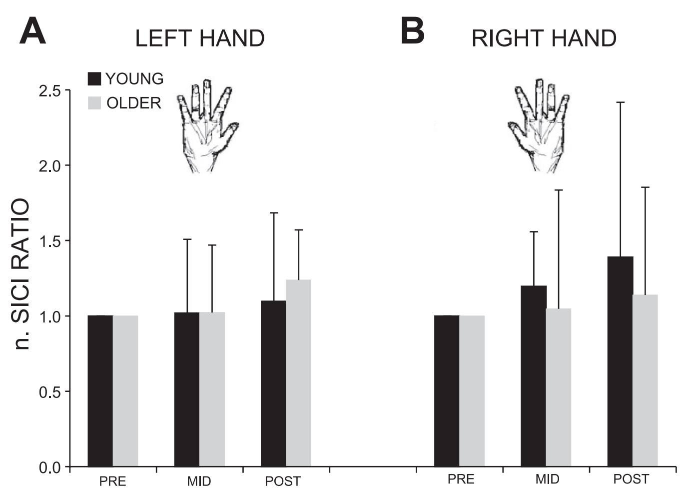

Fig. 6. Normalized short-interval intracortical inhibitor (SICI) ratio measured in the FDI of the quiescent left (untrained; *A*) and right (trained; *B*) hand during the Pre, Mid, and Post TMS stimulation sessions. Data are shown for the young and older groups. Error bars denote SD.

activity in the left FDI during right hand movements for the older compared with the young adults (Fig. 3, *A* and *B*). Mirror activation was not observed in an intrinsic muscle that was not primarily involved in the movement task (ADM; data and analyses not shown), suggesting that the FDI mirror activity was specifically related to the task undertaken. We postulated that this task-specific mirror activity may have resulted in greater cross-limb transfer for our older participants compared with the young group. However, the absence of cross-limb transfer for the older group argues against this postulate. Indeed, the evidence suggests that the increased drive to the nonengaged hand for the older group does not aid in the cross-limb transfer.

Regression analyses failed to reveal a statistically significant relationship between the degree of mirror activity and cross-limb transfer. However, it is conceivable the lack of significance is due, in part, to the restricted number of data points in the regressions and the fact that the range of cross-limb transfer (especially for the older group) was rather restricted. Previous work has shown that increases in net excitability of the untrained corticomotor pathways play a critical role in the performance gains in the untrained limb (23). Both younger and older adults in the present study exhibited excitability increases of the untrained pathways; indeed, the increase in excitability for the older group, if anything, tended to be greater than that exhibited by the younger group, although this failed to reach significance (Fig. 5*B*; $P = 0.098$). It is tempting to speculate that the increased mirror activation (i.e., greater descending drive) observed in the older adults that accompanied the increased corticomotor excitability may, in fact, interfere with the cross-limb transfer process. It is conceivable that active inhibition/suppression of this mirror activity is an integral part of the mechanism facilitating cross-limb transfer. An alternative speculation would be that corticomotor plasticity becomes more "use dependent" with age such that cross-limb transfer, mediated by the cross-activation hypothesis, is less evident. That is, with age the circuitry mediating movement control on one side of the body becomes more reliant upon volitional movements to permit plastic changes to occur and, as such, cannot benefit as freely from crossed effects such as cross-limb transfer. Further research would be warranted to test these speculations.

Pretraining Performance and Ability to Improve with Training Is Unaffected by Age

We observed that the older adults showed no deficits in initial performance—as indicated by similar peak acceleration (before normalization) values in both the left and right hands for the young and older groups. Furthermore, we showed that the ability to improve task performance in the right hand during a single session of training was unaffected by advancing age, a finding contrary to previous work (8, 33). Task differences could account for these differing results: we constrained the finger movements to the horizontal plane, whereas others (8, 33) had participants make thumb accelerations in "free space." Moreover, Cirillo and colleagues (8) recently showed that older participants were able to improve performance in the left thumb during a ballistic thumb abduction task to an extent similar to that observed in a younger group. Accordingly, in the present study, the substantial cross-limb transfer for the young group but lack thereof for the older group is not due to deficits in initial performance in either hand, is not due to intergroup differences in the extent of the performance improvements achieved during the right hand training, and is very unlikely to be due to diminished ability of older adults to improve performance in the left hand in the task we employed (8).

Measurements of Net Corticomotor Excitability and Inhibitory Mechanisms

Consistent with previous work (6, 8, 23, 26), the performance improvements induced by repetitive motor practice in the present study were accompanied by significant increases in corticomotor excitability of the FDI representation within the trained and untrained hemispheres (Fig. 5). Work from another group (12) has shown decreases in the excitability of the cortical representation of the homologous muscle in the nontrained limb. However, it is conceivable that differences in the intensity or timing of TMS stimulation, or differences in the task itself (affecting whether participants allocated attention predominantly to their hands or the computer screen), could reconcile differences between the results.

Single pulses of suprathreshold TMS are able to reveal changes in net corticomotor excitability; however, they are not capable of determining whether such changes are a result of task-induced modulation of inhibitory or facilitatory circuitry. To this end, we utilized a paired-pulse TMS procedure (22) and investigated SICI of the trained and untrained cortices as well as net excitability. We observed a generalized release in inhibition (i.e., greater SICI ratio in the Mid and Post tests compared with the Pre test) across the task-specific FDI of the trained and untrained hand (Fig. 6). There are a limited number of studies that have investigated how SICI may be affected by repetitive motor learning, and these have produced varying results. Liepert et al. (24) and Rosenkranz et al. (34) report a reduction in SICI (i.e., disinhibition) in the trained cortex following motor learning. In contrast, Rosenkranz and Rothwell (35), Rogasch et al. (33), and Cirillo et al. (8) all observed that no significant changes in SICI occurred as a result of motor practice. The studies undertaken by Rogasch et al. (33) and Cirillo et al. (8) are particularly relevant to the present investigation as they tested both young and older adults in a ballistic movement paradigm similar to that used here. Interestingly, no study that we are aware of has assessed the effect of repetitive motor practice on SICI in the ipsilateral (untrained) cortex. The release of inhibition that we observed in both the trained and the untrained FDI (Fig. 6*A*) is therefore a novel finding of the present work. It could be suggested that the increased excitability as measured in the right and left FDI was due, at least in part, to a release of inhibition in both hemispheres resulting from unilateral training, and that SICI could therefore be involved in the process of cross-limb transfer. This postulation is consistent with our working hypothesis that much of the cross-limb transfer is mediated at a cortical level (see Refs. 6, 23), although the present data do not rule out a spinal contribution. However, the fact that older adults did not exhibit transfer indicates that, at least for older adults, other factors, such as mirror activity, may also influence the degree of transfer. We found that averaged over both hands the older group exhibited a reduced level of SICI compared with the younger group in the Pre test, although this did not quite reach statistical significance ($P = 0.06$). Previous research has reported mixed findings with respect to SICI and age, suggesting increases with age (21), decreases with age (30), or no age-related change (8, 33). Of potentially more relevance to cross-limb transfer is that our finding that the modulation of SICI (i.e., the release of inhibition in both hemispheres) and the increases in overall corticomotor excitability as a result of the training did not vary as a function of age, suggesting that in this particular case age was not associated with a reduced capacity for cortical plasticity. This finding contrasts some previous work (e.g., Ref. 33) indicating reduced capacity of cortical plasticity in older adults.

Can Further Insights for Cross-Limb Transfer Be Gained from Interhemispheric Inhibition Studies?

Consistent with the view that we need to suppress mirror activity during unilateral actions, previous studies have reported an increase in the extent of IHI from the responding (active) cortex to the nonresponding (passive) cortex during the preparation (11) and early execution (17) of ballistic actions. Two recent studies indicate that older adults maintain this ability to modulate IHI at a short (10 ms) interstimulus interval (ISI) during steady state (40) and relatively low-force ballistic contractions (17). Accordingly, the increased neural drive to the contralateral limb observed in the older adults in the present study (resulting in mirror activity) is unlikely to be due to a breakdown of this specific inhibitory mechanism. However, IHI at a longer ISI (40 ms) is mediated by a different mechanism (7), which appears to be affected by age (40). Further work is warranted to examine the roles of IHI at long and short ISIs and SICI (see Ref. 31) with respect to suppression of mirror activity and how this may impact on cross-limb transfer in different age groups.

Implications and Future Directions

The absence of cross-limb transfer in older adults in the present study suggests that aging-related changes in brain function affect the efficacy of the mechanisms that underlie cross-limb transfer. It is not clear whether the increased propensity for mirror activity with age is related to the impairment in cross-transfer. Thus, although the finding that older people displayed exaggerated mirror activity but weaker transfer appears in conflict with the cross-activation hypothesis, it is possible that independent changes in brain function that occur with advancing age prevent transfer despite considerable bilateral cortical activity. Alternatively, the possibility exists that mirror activity per se interferes with cross-limb transfer, which might suggest a role for the circuits involved in suppressing ipsilateral corticomotor output in the transfer effect. In this case, there should be evidence that even in younger adults mirror activity interferes with cross-limb transfer. Although the lack of correlation between mirror activity and transfer argues against this interpretation, the present data do not allow a definitive discrimination between the various possibilities. It would be interesting to investigate whether controlling the level of mirror activity through specific verbal instructions and/or biofeedback of muscle activity in the contralateral hand alters the degree of cross-limb transfer observed in a group of older or younger adults. Specifically, do young and older adults with similar mirror activity show similar cross-limb transfer?

The present study provides initial findings with regard to cross-limb transfer in older adults. The results have potential implications for rehabilitation programs for recovery from stroke, where the nonparetic limb (i.e., the contralesional hemisphere) can be actively exercised while the paretic limb either is passive or is assisted to make a similar movement (e.g., Ref. 38). Although the average age of a person suffering a stroke is ~70 yr (1), it is not uncommon for people of a much younger age to suffer a stroke. It is important, therefore, that we fully understand the brain mechanisms involved in cross-limb transfer and how these may be affected by age to enable determination of the most efficient and productive rehabilitation program for each person.

APPENDIX

Additional Neurophysiological Testing in Subset of Young Participants

As alluded to in METHODS, 6 of the 18 young participants were exposed to additional TMS measures to determine the robustness of our findings with respect to corticomotor excitability measurements. ANOVA to compare excitability measured in the 130% RMT single-pulse trials within the mixed-trial block to excitability determined in the single-pulse-only block (at 130% RMT) revealed a nonsignificant effect of block type [mixed block vs. single-pulse block: $F_{(1,5)} = 0.06$, $P = 0.81$, $\eta_p^2 = 0.01$] and no (2 or 3 way) interactions with block type as a factor (all $P > 0.32$). Accordingly, possible hysteresis effects (see Ref. 25) as a result of interspersing single- and paired-pulse trials did not affect the magnitude of single-pulse MEPs, nor did the alternating trials alter, or mask, any time-varying changes in excitability (measured in single-pulse trials) that occurred as a result of the training paradigm. Changes in excitability assessed through the single-pulse trials within the mixed-trials block therefore provide an accurate assessment of changes in net corticomotor excitability as a result of the unilateral training.

Additionally, we compared the MEP amplitudes in the 130% RMT single-pulse trials to the MEP amplitudes attained in 150% RMT single-pulse trials. ANOVA revealed a marginal effect of stimulation intensity [$F_{(1,5)} = 5.18$, $P = 0.07$, $\eta_p^2 = 0.51$], with the more intense stimulations, as expected, yielding somewhat larger MEPs. However, the absence of statistically significant interactions with stimulation intensity as a factor ($P > 0.14$ for all interactions) indicates that trends in MEP amplitudes between the hands or over time were not significantly affected by stimulation intensity. This particular finding indicates that the conclusions we draw regarding corticomotor excitability changes/trends from stimulation at 130% RMT (i.e., the stimulation intensity used for all participants) can be generalized to higher stimulation intensities when more cortical circuits are stimulated and increased descending commands are evoked.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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