Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults

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Rogasch NC, Dartnall TJ, Cirillo J, Nordstrom MA, Semmler JG. Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. J Appl Physiol 107: 1874–1883, 2009. First published October 15, 2009; doi:10.1152/japplphysiol.00443.2009.—This study examined changes in corticomotor excitability and plasticity after a thumb abduction training task in young and old adults. Electromyographic (EMG) recordings were obtained from right abductor pollicis brevis (APB, target muscle) and abductor digiti minimi (ADM, control muscle) in 14 young (18–24 yr) and 14 old (61–82 yr) adults. The training task consisted of 300 ballistic abductions of the right thumb to maximize peak thumb abduction acceleration (TAAcc). Transcranial magnetic stimulation (TMS) of the left primary motor cortex was used to assess changes in APB and ADM motor evoked potentials (MEPs) and short-interval intracortical inhibition (SICI) before, immediately after, and 30 min after training. No differences in corticomotor excitability (resting and active TMS thresholds, MEP input-output curves) or SICI were observed in young and old adults before training. Motor training resulted in improvements in peak TAAcc in young (177% improvement, P < 0.001) and old (124%, P = 0.005) subjects, with greater improvements in young subjects (P = 0.002). Different thumb kinematics were observed during task performance, with increases in APB MEP amplitude related to improvements in peak TAAcc in young (r² = 0.46, P = 0.008) but not old (r² = 0.09, P = 0.3) adults. After training, APB MEPs were 50% larger (P < 0.001 compared with before) in young subjects, with no change after training in old subjects (P = 0.49), suggesting reduced use-dependent corticomotor plasticity with advancing age. These changes were specific to APB, because no training-related change in MEP amplitude was observed in ADM. No significant association was observed between change in APB MEP and improvement in TAAcc with training in individual young and old subjects. SICI remained unchanged after training in both groups, suggesting that it was not responsible for the diminished use-dependent corticomotor plasticity for this task in older adults.

Address for reprint requests and other correspondence: J. G. Semmler, School of Molecular and Biomedical Science, Univ. of Adelaide, Adelaide, South Australia 5005 Australia (e-mail: john.semmler@adelaide.edu.au).
with advancing age. The second aim of this study was to examine training-related changes in SICI after a ballistic thumb abduction task in young and old adults.

METHODS

Fourteen young (8 male, age 21.3 ± 1.8 yr; 6 female, age 20.3 ± 1.9 yr) and fourteen older (8 male, age 70.5 ± 7.7 yr; 6 female, age 65.3 ± 2.7 yr) subjects participated in the study. Subjects were neurologically healthy, had no family history of epilepsy, and were right handed according to the Edinburgh Handedness Inventory [laterality quotient (LQ) > 0; young: median LQ = 0.75, range = 0.4–1; old: median LQ = 1, range = 0.6–1] (27). All experimental procedures were approved by the Human Research Ethics Committee at the University of Adelaide in accordance with the Declaration of Helsinki, and all subjects gave informed consent to participate in the study.

Experimental Arrangement

Subjects were seated comfortably with their right arm resting on a table in front of them. For all measures other than training, the forearm was pronated and the palm was facing down on the table surface. EMG recordings were obtained from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles throughout the experiment with bipolar surface electrodes (Ag–AgCl, 4-mm diameter) placed ~2 cm apart in a belly-tendon montage. A grounding strap located around the elbow served as a common reference for all electrodes. The EMG signals were amplified (100–1,000×), band-pass filtered (high pass at 13 Hz, low pass at 1,000 Hz), digitized at 2 kHz with a CED interface system (Cambridge Electronic Design), and recorded on computer for offline analysis. EMG signals from both muscles were displayed on an oscilloscope for subject feedback.

Experimental Procedures

At the beginning of each experiment, baseline measures of maximal thumb strength [maximum voluntary contractions (MVCs)] were obtained and resting (RMT) and active (AMT) motor thresholds were determined with TMS. To determine the effect of aging on training-induced neuroplasticity, M1 excitability [input-output (IO) curves] and SICI curves were assessed by TMS before, immediately after, and 30 min after a motor training task. To examine the possibility of training-induced changes in peripheral neuromuscular processes, maximum compound muscle action potentials (M waves) were also recorded at these time points. A schematic representation of the protocol is shown in Fig. 1.

MVC. For MVC measurements, the right hand was positioned with the palm facing down and the proximal phalanx of the thumb was placed in a metal ring attached to a load cell (LC1205-K020, A&D Mercury). The subject’s task was to exert maximum isometric force against the force transducer for 3 s while verbal encouragement was provided by the experimenters. Visual feedback of the force was provided to the subject on an oscilloscope positioned in front of him/her at eye level. Throughout the MVC, subjects were visually monitored to ensure that activation was restricted to thumb muscles and that muscles of the upper arm and shoulder were relaxed as much as possible. Subjects continued to perform MVCs until the peak forces from two trials were within 10% of each other. The maximum peak force was considered the MVC force. Force signals were amplified (1,000–3,000×), digitized at 200 Hz with a CED 1401 interface (Cambridge Electronic Design), and recorded on computer for offline analysis.

TMS. TMS was performed with a figure eight-shaped coil (external wing diameter of 9 cm) with two Magstim 200\u2002 stimulators connected through a Magstim Bistim\u2002 unit (Magstim). This arrangement allowed the output of both stimulators to be directed through the same coil. The coil was held tangentially over the scalp with the handle pointing ~45° backwards and laterally to the sagittal plane in the optimum position to evoke MEPs in relaxed right APB and ADM. With this coil orientation, current flow within the cortex was induced in a posterior-anterior direction. The optimal coil position was marked, and the coil was held in this position by hand during each stimulus block. TMS was delivered at 0.2 Hz for all conditions. RMT in APB was determined as the TMS intensity required to elicit MEPs of ≥50 μV in three of five consecutive trials, expressed as percent maximum stimulator output (% MSO). AMT in APB was determined as the TMS intensity required to elicit MEPs of ≥200 μV in three of five consecutive trials while the subject maintained a tonic abduction force of 10% MVC (see Ref. 37). TMS intensity was altered in 1% increments of MSO throughout this process.

IO curve. MEPs in APB and ADM were recorded at nine different TMS intensities increasing in 10% increments from RMT to 180% of RMT (100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180% RMT). A single block of 72 stimuli (8 stimuli at each intensity), with TMS intensities delivered in random order, was used to obtain the IO

Fig. 1. Schematic representation of the experimental protocol with measures obtained before, immediately after (0 min), and 30 min after training. Baseline measures include assessments of maximum voluntary contraction (MVC), resting motor threshold (RMT), and active motor threshold (AMT). The input-output (IO) curve involved single-pulse transcranial magnetic stimulation (TMS) at 9 different intensities (72 stimuli) from 100% to 180% RMT. Short-interval intracortical inhibition (SICI) was performed as close as possible to training (before and after) and involved a total of 40 single and paired-pulse TMS (70%, 80%, 90% AMT conditioning; 3-ms interstimulus interval) trials. Training consisted of 2 blocks, with each block involving 15 × 10 ballistic thumb abduction movements (total of 300 trials) and a 5-min rest between blocks. Each black vertical bar in training indicates where a more detailed analysis of motor performance was undertaken (see METHODS).
MEP of test TMS pulse by 3 ms. The test TMS intensity was set to provide a subthreshold conditioning TMS pulse that preceded a suprathreshold pulse TMS technique described previously (20). This consisted of a triggered a recording sweep of calculated during the MVC, and the mean rectified APB EMG each block to quantify the effectiveness of SICI. Maximum force was averaged for each condition. For paired-pulse TMS, conditioned the peak-to-peak amplitudes of MEPs and M waves were obtained and ms before stimulation) were discarded from analysis. For each trial, Data Analysis Data in the abduction and flexion planes, along with EMG from the 1876 TRAINING, AGING, AND HUMAN CORTICOMOTOR PLASTICITY

Subjective motor training task was a modified version of a previously described paradigm, which has been shown to produce changes in MEP amplitude that are associated with improvements in motor performance (6, 46). The task required subjects to maximize peak thumb abduction acceleration (TAAcc) during ballistic movements of the right thumb. Subjects sat with their right arm adducted at the shoulder and bent at ~90° at the elbow. The forearm was in a neutral position (between pronation and supination) with the thumb free to move while the fingers were immobilized with a custom-designed splint. Subjects performed two blocks of 150 ballistic thumb abduction movements for a total of 300 trials. Trials were paced at 0.5 Hz with an audible tone from a metronome. To avoid fatigue, subjects rested for 30 s after every 10 trials and for 5 min between changes in motor performance 

Motor Training Task

The motor training task was a modified version of a previously described paradigm, which has been shown to produce changes in MEP amplitude that are associated with improvements in motor performance (6, 46). The task required subjects to maximize peak thumb abduction acceleration (TAAcc) during ballistic movements of the right thumb. Subjects sat with their right arm adducted at the shoulder and bent at ~90° at the elbow. The forearm was in a neutral position (between pronation and supination) with the thumb free to move while the fingers were immobilized with a custom-designed splint. Subjects performed two blocks of 150 ballistic thumb abduction movements for a total of 300 trials. Trials were paced at 0.5 Hz with an audible tone from a metronome. To avoid fatigue, subjects rested for 30 s after every 10 trials and for 5 min between blocks 1 and 2 (see Fig. 1). Thumb acceleration in both the abduction/adduction (hereafter referred to as abduction) and flexion/extension (hereafter referred to as flexion) planes was recorded with a biaxial accelerometer (sensitivity ±6 g; LISS106AL, STMicroelectronics) fastened over the interphalangeal joint of the thumb. For each movement, a thumb acceleration greater than +3 m/s² in the abduction plane triggered a recording sweep of ±500 ms that recorded acceleration data in the abduction and flexion planes, along with EMG from the APB and ADM muscles. Subjects were provided with visual feedback of their abduction acceleration trace via a computer screen, and subjects were verbally encouraged to continually improve their maximum acceleration of thumb abduction throughout training. Acceleration signals were digitized at 2 kHz with a CED interface system and recorded on computer for offline analysis.

Data Analysis

All MEPs and M waves that contained any prestimulus EMG (100 ms before stimulation) were discarded from analysis. For each trial, the peak-to-peak amplitudes of MEPs and M waves were obtained and averaged for each condition. For paired-pulse TMS, conditioned MEPs were expressed as a percentage of the mean test-alone MEP in each block to quantify the effectiveness of SICI. Maximum force was calculated during the MVC, and the mean rectified APB EMG (maximum EMG) was calculated for the period 500 ms before and after the maximum force.

For the motor training task, the first 10 movements (movements 1–10; start) and final 10 movements (movements 141–150; middle) of block 1 and the final 10 movements of block 2 (movements 291–300; end) were used for a detailed analysis of task performance (Fig. 1). For each acceleration trace, a baseline period from 400 to 200 ms before the movement was used to calculate the mean baseline acceleration in the abduction and flexion planes. The mean acceleration over this baseline period was subtracted so that baseline acceleration equaled 0 m/s² in both planes. The time and magnitude of peak TAAcc were then obtained, along with the magnitude of the flexion acceleration at the time of peak TAAcc. Furthermore, three additional measurements were obtained from the movement trials: 1) time of APB EMG onset, 2) time of abduction onset, and 3) the resultant acceleration vector (magnitude and direction) for the abduction and flexion planes combined at the time of peak abduction acceleration. APB EMG onset was calculated as the earliest time at which EMG became three times greater than the SD of EMG during the baseline period. Abduction onset was determined visually as the time when acceleration exceeded baseline (0 m/s²). From these data points, the time from EMG onset to peak abduction acceleration and the time from abduction onset to peak abduction acceleration were calculated. The magnitude and direction of the resultant acceleration were also calculated from the acceleration vector in the abduction and flexion planes (at the time of peak abduction) by trigonometry. Resultant direction values of 0° represent pure abduction, values >0° represent abduction with movement into extension, and values <0° represent abduction with movement into flexion. APB EMG during training was quantified as the mean rectified APB EMG between EMG onset and peak abduction acceleration.

Statistical Analysis

An unpaired t-test was used to examine differences between young and old adults for age, MVC force, maximum EMG, RMT, AMT, SICI test TMS intensity, and M-wave data, before training. A Mann-Whitney U-test was used to compare the nonparametric handedness scores. A two-factor ANOVA with a repeated-measures design (for intensity) was used to examine MEP amplitude (age, TMS intensity) and SICI (age, conditioning intensity) before training. A two-factor ANOVA with a repeated-measures design was used to determine the influence of age and training (start, middle, end) on peak abduction acceleration, resultant acceleration vector magnitude at time of peak abduction, resultant peak acceleration vector direction, mean rectified EMG during acceleration, time of EMG onset to peak abduction, and time of abduction onset to peak abduction. A two-factor ANOVA with a repeated-measures design was used to determine the effect of age and time (before, after, 30 min) on M-wave amplitude. A three-factor ANOVA with a repeated-measures design was used to assess the influence of age, time, and IO curve TMS intensity (100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180% RMT) or SICI conditioning intensity (70%, 80%, 90%) on APB and ADM MEP amplitude and SICI (expressed relative to test MEP amplitude). Significant main effects and interactions in the ANOVAs were further analyzed with a Fisher’s paired least significant difference post hoc test. Linear regression analysis was used to examine the association between changes in motor performance [(end peak acceleration/start peak acceleration) × 100] and changes in mean APB EMG during training [(end APB EMG/start APB EMG × 100) – 100], MEP amplitude after training [(pooled MEP amplitude after/before × 100) – 100], and SICI after training [(SICI at 70%, 80%, and 90% AMT after/before × 100) – 100. Furthermore, linear regression analysis was performed between change in APB EMG and change in MEP amplitude after training. Statistical significance was set at $P < 0.05$ for all comparisons. All values are reported as means ± SD in the text and means ± SE in Figs. 3–6.
Table 1. Subject characteristics and baseline excitability measures before training in young and old adults

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Old</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>20.7 (1.9)</td>
<td>68.3 (6.5)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Handedness, LQ</td>
<td>0.74 (0.2)</td>
<td>0.92 (0.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>MVC, N</td>
<td>21.9 (8.6)</td>
<td>19.9 (9.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>M wave, mV</td>
<td>14.3 (4.7)</td>
<td>11.3 (4.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Maximum EMG, mV</td>
<td>0.79 (0.3)</td>
<td>0.51 (0.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum EMG, %M wave</td>
<td>5.5 (1.3)</td>
<td>5.2 (1.8)</td>
<td>0.73</td>
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<tr>
<td>RMT, % MSO</td>
<td>44 (7.2)</td>
<td>44 (3.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>AMT, % MSO</td>
<td>36 (6.8)</td>
<td>38 (5.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>APB IO curve, pooled mV</td>
<td>1.3 (0.6)</td>
<td>1.5 (0.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>SICI, pooled % test alone</td>
<td>65.3 (18.7)</td>
<td>52.9 (32.3)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are shown as means (SD). LQ, laterality quotient [from −1 (left handed) to +1 (right handed)]; MVC, maximum voluntary contraction; EMG, electromyogram; RMT, resting motor threshold; AMT, active motor threshold; MSO, maximum stimulator output; APB, abductor pollicis brevis. Input-output (IO) and short-interval intracortical inhibition (SICI) were analyzed with a 2-way ANOVA [age × transcranial magnetic stimulation (TMS) intensity] on data obtained before training, with P value representing the main effect for age. There were significant TMS intensity main effects for motor evoked potential (P < 0.001) and SICI (P < 0.001) but no significant age × TMS intensity interactions. *Significantly different between young and old adults. M-wave data were obtained from 10 young and 9 old adults.

RESULTS

Age-related differences in subject characteristics and baseline excitability measures before training are shown in Table 1. Most notably, the older subjects were more strongly right handed and had reduced APB EMG during MVC, although there was no difference in EMG between young and old adults when normalized to maximum M wave. There was no difference in either RMT or AMT between young and older adults. Furthermore, there were no age-related differences in APB IO curve or SICI between young and old adults before training and there were no age × TMS intensity interactions (IO curve, P = 0.7; SICI, P = 0.1). Normalizing the MEPs to maximum M wave did not alter these findings (data not shown).

Effect of Age on Motor Performance

Original data of TAAcc and rectified APB EMG from the start and end of the motor training task are shown for a young man (24 yr) and an older man (81 yr) in Fig. 2. Peak TAAcc was similar between the young and old subject at the start of training (young: 9.92 m/s², old: 8.80 m/s²). Both the young and the old subject were able to increase peak abduction acceleration over the training task, although the improvement for the young subject was greater (264%) than that of the older subject (212%). This improvement in motor performance was accompanied by an increase in the mean rectified APB EMG in the young (89%) but not the old (0%) subject.

Peak TAAcc was quantified for young and old adults for each block of 10 ballistic thumb movements throughout training, and these data are shown in Fig. 3A. There was a progressive increase in peak acceleration for the young subjects throughout the full duration of training, whereas the peak acceleration reached a plateau after ~150 contractions in old subjects. For the first (movements 1–10), middle (movements 141–150), and last (movements 291–300) training blocks there was a significant age × training interaction (P < 0.001), and these data are shown in Fig. 3B. Peak thumb acceleration was similar between young and old adults at the start of training but was significantly greater in young compared with old subjects at the middle (51% greater in young, P = 0.01) and end (63% greater, P = 0.002) of training. In young subjects, there was a 144% increase in peak acceleration from the start to the middle of training (P < 0.001) and a 177% increase at the end of training (P < 0.001). For the old subjects, there was an 113% increase in peak acceleration from the start to the middle of training (P = 0.01) and a 124% increase at the end of training (P = 0.005).

There was no significant effect of time (time effect: P = 0.34) or age (age effect: P = 0.14) or age × time interaction (P = 0.9) on APB M-wave amplitude. APB M-wave amplitude remained unchanged after training in both young (before: 14.2 ± 4.7 mV, after: 13.8 ± 4.2 mV, 30 min: 14.8 ± 4.6 mV) and old (start: 0.44 mV, end: 0.44 mV).
but not old (r = 0.46). *P < 0.05 compared with young start; †P < 0.05 compared with old start; $P < 0.05 compared with old middle; ‡P < 0.005 compared with old end.

The mean rectified EMG from the APB muscle was quantified from EMG onset to the peak TAAcc during trials performed at the start, middle, and end of training. For this analysis, the EMG from one older adult was removed because of inadvertent electrode lead disconnection during training. A significant age × training interaction (P = 0.03; Fig. 3C) and subsequent post hoc analysis indicated that there was no age-related difference in APB EMG at the start of training (P = 0.23), but it was significantly greater in young subjects at the middle (43% greater in young, P = 0.004) and end (40% greater, P = 0.008) of training. In young subjects, there was a 30% increase in APB EMG from the start to the middle of training (P = 0.02), which just failed to reach statistical significance for the end of training (25% increase from start, P = 0.06). No significant increase in APB EMG was observed throughout training in older adults (middle, 8% increase, P = 0.62; end, 6% increase, P = 0.70). The association between change in APB EMG with training (start to end) and change in peak TAAcc with training (start to end) in individual young and old subjects is shown in Fig. 3D. There was a significant positive association between change in APB EMG and change in peak TAAcc with training in young (r² = 0.46, P = 0.008) but not old (r² = 0.09, P = 0.3) adults. The training-related changes in EMG and the linear correlations between EMG and peak TAAcc shown above were similar when the EMG was normalized to the maximum M wave (data not shown).

Although the purpose of the training task was to maximize peak TAAcc, subjects achieved this goal with different thumb kinematics. From the abduction and flexion accelerations at the time of peak TAAcc, we were able to calculate the magnitude and direction of the resultant acceleration vector (Fig. 4). A significant age × time interaction (P = 0.002) showed that the magnitude of the resultant thumb acceleration was similar between young and old adults at the start of training but was significantly greater in young subjects at the middle (48% greater in young, P = 0.02) and end (56% greater, P = 0.003; Fig. 4A) of training. For the direction of the resultant acceleration, a significant age × training interaction (P = 0.04) showed greater thumb flexion in young versus old subjects at the start of training (−14° vs. 0°; P = 0.006), with both subject groups moving to similar amounts of flexion at the middle (−12° vs. −10°) and end (−9° vs. −6°) of training (Fig. 4B).

Effect of Training and Age on MEP Amplitudes

For all subjects, APB MEP amplitudes increased with increasing TMS intensities (TMS intensity effect: P < 0.0001; Fig. 5, A and B). For APB MEP amplitudes there was a significant age × time interaction (P = 0.03) in the ANOVA, indicating that the effect of training on the APB MEP was different for young and old subjects. Post hoc analysis revealed that APB MEP amplitude in young subjects was 50% larger immediately after training (P = 0.001) and 38% larger 30 min after training (P = 0.004) compared with before training (Fig. 5A). In contrast, there was no significant MEP facilitation in old subjects immediately after training (P = 0.95) or 30 min later (P = 0.43; Fig. 5B). When APB MEPs were normalized to M-wave amplitude (10 young and 9 old adults) there was no age × time effect in the ANOVA (P = 0.32), but this nonsignificant result was likely due to reduced statistical power because the findings were similar for absolute MEPs (mV) in the ANOVA using the same 19 subjects (age × time interac-
Fig. 4. Resultant thumb acceleration magnitude and direction at the start, middle, and end of training in young and old adults. A: peak resultant thumb acceleration magnitude was greater in young adults at the middle and end of training. B: resultant thumb direction was more flexed in young compared with old adults at the start but not at the middle or end of training. **P < 0.05 compared with young start; †P < 0.05 compared with old start; ‡P < 0.05 compared with old middle; ††P < 0.005 compared with old end.

DISCUSSION

The purpose of this study was to examine age-related changes in use-dependent corticomotor plasticity and performance of a repetitive thumb abduction task. There were several new findings in this study. First, MEP amplitudes in the target muscle (APB) were facilitated after training in young but not old adults. Second, the extent of improvement in task-specific ballistic motor performance was diminished in older adults, although we could not identify any linear association between thumb acceleration and changes in APB MEP amplitudes in individual subjects. Third, different thumb kinematics were observed during task-specific motor performance, with in-

Effect of Training and Age on SICI

APB SICI remained unchanged after training across both groups (time effect: P = 0.84), and there was no difference between young and old adults (age effect: P = 0.06). Furthermore, there was no interaction with time × age (P = 0.65), time × conditioning intensity (P = 0.31), or time × conditioning intensity × age (P = 0.7; Fig. 6). When data before and after training were combined, a significant age × conditioning intensity effect (P = 0.03) and subsequent post hoc analysis indicated that SICI was reduced at 70% conditioning intensity compared with 80% (P = 0.001) and 90% (P = 0.002) conditioning intensity (but was not different between 80% and 90% conditioning intensities; P = 0.83) in old adults, whereas SICI increased progressively from 70% to 90% AMT in young adults. On an individual subject basis, linear regression analysis indicated that the extent of APB SICI at each conditioning intensity (70%, 80%, 90% AMT) was not related to the improvement in motor performance in young (r² values from 0.001 to 0.22, P > 0.05) or older (r² values from 0.03 to 0.17, P > 0.05) adults.

For the unconditioned (test alone) APB MEP during the SICI trials, there was no difference in TMS intensity (young: 60 ± 10%; old: 60 ± 11%; P = 0.96) or MEP amplitude between young and old adults (age effect: P = 0.4), although MEP amplitude was influenced by training (time effect: P = 0.046). Post hoc analysis indicated that there was a significant increase in unconditioned MEP amplitude 30 min after training (1.43 ± 0.6 mV) compared with before training (1.10 ± 0.4 mV, P = 0.02), with the change in MEP amplitude immediately after training just failing to reach statistical significance (1.35 ± 0.6 mV, P = 0.07). The test-alone MEP amplitude was consistent between age groups at each time point relative to training (time × age interaction: P = 0.11).

For the SICI analysis of a muscle not directly involved in the training (ADM), two older adults were excluded because of persistent prestimulus EMG in ADM. As with APB, conditioned MEP amplitude decreased in ADM as the conditioning intensities approached AMT (conditioning intensity effect: P < 0.0001). However, there was no significant effect of age or time on either ADM SICI (age effect: P = 0.7; time effect: P = 0.5) or ADM test-alone MEP amplitude (age effect: P = 0.89; time effect: P = 0.4).

Using linear regression of data from individual subjects, we examined whether the training-related change in the pooled APB MEP amplitude (averaged over all TMS intensities) was associated with any change in EMG or peak TAACC in young and old subjects (Fig. 5, C and D). For young subjects, there was no association between change in APB MEP amplitude and change in APB EMG (r² = 0.001, P = 0.96) or peak TAACC (r² = 0.02, P = 0.6) with training. In contrast, there was a significant positive association in old adults between change in APB MEP amplitude and change in APB EMG (r² = 0.45, P = 0.01) with training and also between change in APB MEP and change in TAACC (r² = 0.38, P = 0.02) with training. However, these significant relations were largely influenced by one old subject who demonstrated large changes in APB MEPs after training. Without this subject, the associa-

tion between the change in pooled MEP and EMG in old adults was weakened (r² = 0.28, P = 0.08) and there was no significant association between the change in pooled MEP and peak TAACC (r² = 0.001, P = 0.92).

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For the unconditioned (test alone) APB MEP during the SICI trials, there was no difference in TMS intensity (young: 60 ± 10%; old: 60 ± 11%; P = 0.96) or MEP amplitude between young and old adults (age effect: P = 0.4), although MEP amplitude was influenced by training (time effect: P = 0.046). Post hoc analysis indicated that there was a significant increase in unconditioned MEP amplitude 30 min after training (1.43 ± 0.6 mV) compared with before training (1.10 ± 0.4 mV, P = 0.02), with the change in MEP amplitude immediately after training just failing to reach statistical significance (1.35 ± 0.6 mV, P = 0.07). The test-alone MEP amplitude was consistent between age groups at each time point relative to training (time × age interaction: P = 0.11).

For the SICI analysis of a muscle not directly involved in the training (ADM), two older adults were excluded because of persistent prestimulus EMG in ADM. As with APB, conditioned MEP amplitude decreased in ADM as the conditioning intensities approached AMT (conditioning intensity effect: P < 0.0001). However, there was no significant effect of age or time on either ADM SICI (age effect: P = 0.7; time effect: P = 0.5) or ADM test-alone MEP amplitude (age effect: P = 0.89; time effect: P = 0.4).
creases in APB EMG related to improvements in peak thumb acceleration in young but not old adults. Finally, there was no age-related difference in SICI before training, and it was not altered by training in young or old adults, suggesting that the age-related differences in corticomotor plasticity and performance in this thumb training task were not due to differences in GABAergic intracortical inhibition between age groups.

In the present study, the magnitude of baseline corticomotor excitability in APB before training was similar in this population of young and old adults, with no age-related differences in resting and active TMS thresholds, MEP IO curves, or SICI. Similar TMS thresholds between young and older adults have been observed previously (28, 34), which supports the present findings. However, previous studies have shown some age-related differences in SICI, but these findings have not been consistent. For example, it has been reported previously that SICI is decreased in older adults (32), but other studies have shown no difference (28, 44) or an increase in SICI (19) with advancing age. It is possible that differences in experimental design in these studies, such as the subject population (age, activity levels), muscle investigated (hand or wrist), or limb tested (dominant or nondominant) are important factors in determining age-related differences in corticomotor excitability.

Several lines of evidence suggest that short-term training (<30 min) on the thumb abduction task induces reorganization of circuits within the central nervous system (CNS). For example, the improvements in ballistic motor performance with short-term (<30 min) training are unlikely to be due to changes within the muscle, because unilateral practice of this movement results in substantial improvements in ballistic motor performance and corticomotor excitability of both the trained and the untrained hand (6). More specifically, several lines of evidence in young subjects provide strong support that learning of a ballistic motor task induces plasticity in human M1. For example, the increase in MEP size after ballistic thumb movements is larger with TMS than with transcranial electrical stimulation [with the latter largely reflecting changes in spinal excitability (8)]. Furthermore, learning of a ballistic motor task is disrupted with repetitive TMS over M1, but not when administered over other brain areas (25). Although changes in spinal circuits are possible, results from these studies in young subjects support a significant contribution from M1 during these ballistic motor tasks.

Training-Induced Corticomotor Plasticity in Young but Not Old Adults

Since the early 1990s, numerous studies using TMS in young subjects have demonstrated corticomotor plasticity following motor learning, motor practice, or training. These interventional studies have shown that the performance of skilled motor tasks results in an increase in MEP amplitude that can last for up to an hour after the intervention (24, 33, 45). However, the ability of M1 to adapt to a period of motor training in older adults is less well established. Neuroimaging studies have shown that older adults produce less focused task-related cortical activation in a wider network of brain regions (43), and there is reduced structural plasticity of cortical gray matter in older adults when learning a novel motor skill (3). Similarly, studies involving TMS have shown a progressive decline in TMS-induced thumb movements in the training direction with advancing age (39), which can be improved by concurrent video observation of the training movement (7). Using a training intervention with instantaneous performance feedback, we found that MEP amplitudes in the
target muscle (APB) were significantly facilitated for at least 30 min after training in young but not old adults, despite significant improvements in motor performance in both subject groups. These changes were specific to the trained muscle, because there was no change in MEP amplitude in an unrelated control muscle (ADM) in young or old adults. These findings suggest that the ability of M1 to reorganize in response to training with a ballistic thumb abduction task decreases in older adults.

Despite the relatively robust MEP facilitation after motor skill training in young subjects, the functional implications of this increased corticomotor excitability are unclear. Several studies have shown that use-dependent MEP facilitation is associated with an improved behavioral outcome under some circumstances. For example, increased training-related agonist MEP amplitude has been positively correlated with increased finger acceleration during a pinch grip (24), increased forearm acceleration during ballistic elbow flexor contractions (45), and improvements in Purdue pegboard performance (10). However, using a linear regression analysis in individual subjects, we could not identify any strong association between changes in APB MEP and TAAcc after training in young or old adults. It may be that the relation between MEP changes and performance improvement with training is more complex than the simple linear association assessed here, and may need a larger subject population to detect it. Alternatively, it may be that factors other than the magnitude of performance improvement during this task are more important in mediating changes in corticomotor excitability, such as differences in thumb kinematics throughout the task (see below), attentional focus required (23), or factors that are unrelated to the movement commands, such as extent of cognitive processing (17) or emotional state of the subjects (41).

The lack of MEP facilitation in older adults could be due to the different thumb kinematics observed throughout training to improve task performance in these subjects. For young subjects, the greater TAAcc with training was achieved by increased APB EMG throughout training, accompanied by a small reduction in thumb flexion (from 14° to 9° flexion). In contrast, the greater TAAcc with training in older subjects was achieved without an increase in APB EMG but a small increase in thumb flexion (from 0° to 6° flexion). These findings suggest that young and old subjects maximize TAAcc throughout training with different kinematic strategies, which may involve alterations in synergistic (12) and antagonist muscle activation (see Ref. 15) with training. The lack of change in EMG with training in older adults could be due to neuromuscular changes that occur in the elderly, because the proportion of muscle occupied by type II fibers declines with advancing age (18) and these fast-twitch fibers are likely to make the biggest contribution to the surface EMG, particularly at the end of training when TAAcc is maximized. This lack of change in EMG and the plateau in motor performance are unlikely to be due to fatigue in older adults, because no recovery was observed in motor performance after the 5-min rest between blocks (see Fig. 3A) and no difference in M-wave duration was observed between young and old adults throughout training.

**Mechanisms for Reduced Use-Dependent Plasticity in Older Adults**

M1 is equipped with numerous mechanisms that are capable of facilitating reorganization and plasticity in response to short-term training. One powerful mechanism that could alter M1 function is a change in GABAergic intracortical inhibition. Modulation of GABA and SICI in young subjects appears to play a critical role in use-dependent plasticity in human M1 (45). Several studies have shown reduced SICI in young subjects after repetitive unidirectional thumb movements (21, 35), although others have found no change in SICI with this task (36), which supports the findings of the present study. It is possible that factors related to task performance may contribute to these inconsistent findings, because selective activation of the target muscle may be important in mediating training-related changes in SICI (21, 47). Subjects were provided with no instructions during task performance other than to maximize thumb abduction acceleration, so selective muscle activation was not required in the present study. In addition to task performance, the method for testing SICI following altered corticomotor excitability may influence the estimate of SICI. Previous studies using this task in young subjects have adjusted the TMS intensity to match MEP amplitudes before and after training but have produced mixed results (21, 35, 36). We tested SICI with a constant test TMS intensity before and after training as previous work from our group has shown that measures of SICI are sensitive to test TMS intensity, because of the balance of D (direct) waves and early and late I (indirect) waves evoked in corticospinal neurons by the
stimulus (47). More recently, Garry and Thomson (11) systematically examined the effect of MEP size and test TMS intensity on SICI and found that estimates of SICI are affected by the intensity of the test TMS pulse, regardless of MEP size. On the basis of this evidence, we maintained a constant test TMS intensity throughout the experiment at an intensity (~135% RMT for both groups) shown to produce moderate inhibition in young subjects (11). Using this technique, we found no change in SICI after training in both young and old subjects, suggesting that M1 inhibitory tone as assessed by SICI in the resting state before and after training is not a primary factor responsible for reduced use-dependent plasticity during this ballistic thumb task in older adults.

Other mechanisms that could be responsible for reduced use-dependent plasticity in older adults include an age-related decline in LTP and a reduction in neurotransmitters, gene expression, or proteins important for synaptic plasticity. For example, experimental observations show that aged rats have deficits in LTP induction and maintenance (see Ref. 4), possibly caused by a reduction in the number of functional synaptic contacts (1), a decrease in NMDA receptors (9), and deficits in calcium regulation (see Ref. 2). Furthermore, normal aging is accompanied by diminished brain dopamine activity (22), which has been shown to play an important role in the task-dependent modulation of LTP (16) and is associated with a decline in cognitive and motor function in humans (42). Finally, the reduced use-dependent plasticity could be due to an age-related decline in neurotransmitter factors important for cortical function, synaptic plasticity, and learning. For example, brain-derived neurotrophic factor (BDNF) is known to enhance learning, memory, and LTP (30) and improves use-dependent plasticity (40). There is evidence that a decreased production or secretion of BDNF may contribute to age-related cognitive impairments (29), and this may also contribute to reduced use-dependent plasticity and motor skill learning in older adults.

In conclusion, we have examined corticomotor plasticity and motor learning after a repetitive thumb abduction task in young and old adults. Despite substantial improvements in task performance in both subject groups, different thumb kinematics were observed that resulted in greater improvements in motor performance (learning) in young adults. These differences in training-related improvements in task performance were accompanied by greater activation of APB during the trained movement, and increased APB MEP amplitudes at rest, in young but not old subjects. These differences reflect diminished use-dependent corticatomotor plasticity of the CNS network controlling the prime-mover muscle with advancing age. No changes in SICI were observed after training in young and old adults, suggesting that differences in resting-state GABAergic inhibition do not contribute to impaired corticomotor plasticity for this task in older adults.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

REFERENCES


