Age-related differences in corticospinal control during functional isometric contractions in left and right hands

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Sale, Martin V., and John G. Semmler. Age-related differences in corticospinal control during functional isometric contractions in left and right hands. J Appl Physiol 99: 1483–1493, 2005. First published June 9, 2005; doi:10.1152/japplphysiol.00371.2005.—The purpose of the study was to examine age-related differences in electromyographic (EMG) responses to transcranial magnetic stimulation (TMS) during functional isometric contractions in left and right hands. EMG responses were recorded from the first dorsal interosseus muscle following TMS in 10 young (26.6 ± 1.3 yr) and 10 old (67.6 ± 2.3 yr) right-handed subjects. Muscle evoked potentials (MEPs) and silent-period durations were obtained in the left and right hands during index finger abduction, a precision grip, a power grip, and a scissor grip, while EMG was held constant at 5% of maximum. For all tasks, MEP area was 30% (P < 0.001) lower in the left hand of old compared with young subjects, whereas there was no age difference in the right hand. The duration of the EMG silent period was 14% (P < 0.001) shorter in old (150.3 ± 2.9 ms) compared with young (173.9 ± 3.0 ms) subjects, and the age differences were accentuated in the left hand (19% shorter, P < 0.001). For all subjects, the largest MEP area (10–12% larger) and longest EMG silent period (8–19 ms longer) were observed for the scissor grip compared with the other three tasks, and the largest task-dependent change in these variables was observed in the right hand of older adults. These differences in corticospinal control in the left and right hands of older adults may reflect neural adaptations that occur throughout a lifetime of preferential hand use for skilled (dominant) and unskilled (nondominant) motor tasks.

THE MUSCLES OF THE HAND THAT move the fingers are governed by a unique and exquisite control system. Unlike other muscles of the human body, these muscles can be activated in a fractionated manner to accomplish remarkable motor tasks involving precise and selective use of individual digits. The neural mechanism responsible for this exceptional ability is the lateral corticospinal pathway, which projects from the motor cortex to various levels of the spinal cord. Most of the axons in the lateral corticospinal tract originate in the regions of the primary motor cortex that control the distal parts of the limbs. They form synapses directly, or via interneurons, with motoneurons in the spinal cord. These connections provide the motor cortex with direct access to the motoneurons and the ability to perform remarkably skilled tasks requiring independent control of the fingers (38).

Transcranial magnetic stimulation (TMS) is a noninvasive technique that allows indirect assessment of human corticospinal neuron activity during voluntary contractions in humans. Recent experiments using TMS indicate that there are age-related changes in corticospinal control to upper limb muscles in healthy, older adults. For example, there is a shift to the right of the corticospinal input-output curve in older adults at rest (37) and an age-related decline in the amplitude of motor-evoked potentials (MEPs) during simple isometric contractions (13, 14), suggesting a reduced ability to activate corticospinal cells by TMS in older adults. Furthermore, there is increasing evidence from TMS studies of reduced cortical inhibitory mechanisms with advancing age, as shown using the paired-pulse technique (25, 36, 55) and the duration of the electromyogram (EMG) silent period (14, 40). The reduced cortical inhibition in older adults may explain the findings of an increased cortical activation in the elderly using other techniques, such as functional magnetic resonance imaging (fMRI; Ref. 30) and electroencephalography (42), which cannot distinguish between excitatory and inhibitory mechanisms within the cortex.

None of these previous TMS studies in the elderly have examined the differences in corticospinal control between left and right hands, to determine whether there are chronic adaptations in the corticospinal pathway with a lifetime of preferential use of the hand for fine-motor tasks. In young subjects, several studies have reported hemispheric differences in corticospinal control that are related to hand preference. For example, there is a larger cortical representation for the left hemisphere controlling the dominant hand (18), and there are asymmetries in corticospinal excitability during voluntary contractions with the left or right hands, depending on the extent of laterality (3, 47). In contrast, lateral differences in cortical inhibition are less clear, with some studies reporting a difference in paired-pulse intracortical inhibition (21), whereas others do not (6, 7), although there does seem to be decreased cortical inhibition measured from EMG silent periods in the dominant hand of left- and right-handed subjects (39). Nonetheless, it is not currently known if corticospinal control is influenced by a lifetime of preferential use of the hand for skilled (dominant) and unskilled (nondominant) motor tasks.

In healthy young adults, several lines of evidence using TMS suggest that corticospinal excitability is modulated, depending on the demands of the task that is performed. For example, MEPs in the first dorsal interosseus (FDI) muscle following TMS are larger during the performance of a precision grip compared with a power grip (9) or with a simple index finger abduction task (15). The use of transcranial electrical stimulation (TES), which activates corticospinal neurons directly to assess spinal (motoneuron) excitability, indicates that these task-related variations did not occur at the site of TMS.
spinal level (9, 46). These findings indicate that the performance of more complex tasks is associated with increased cortical excitability and suggest that the efficient modulation of corticospinal activity between tasks may provide a mechanism for accurate and skilled motor performance of the hand and fingers. To date, changes in corticospinal function in the elderly have been assessed at rest or during simple isometric contractions involving nonfunctional tasks. Although these findings are of interest, it is of greater functional importance to establish the contribution of the corticospinal neurons during voluntary activation of their target muscles when performing more demanding tasks, which necessitate greater involvement of the corticospinal pathway (15). It is currently not known how corticospinal responses are modulated during different tasks in left and right hands of older adults.

The purpose of this study was to quantify the age-related differences in EMG responses (MEP size and silent period duration) to TMS during functional isometric contractions in left and right hands. Based on previous studies in young subjects, we expect to see reduced MEP amplitudes (47) and shorter EMG silent periods (39) in the dominant hand of right-handed older subjects. Furthermore, we expect to see reduced modulation of EMG responses during more functional tasks in older adults. This expected finding is based on indirect evidence that functional losses in motor performance of older adults are associated with a diminished task-related modulation of descending (excitatory and inhibitory) input to motoneurons during rhythmic isometric contractions (50) and movements (48). Preliminary results have been published in abstract form (43).

METHODS

Experiments were performed on the left and right hands of 10 young (5 women, 5 men; means ± SD, 26.6 ± 1.3 yr; range 19–31 yr) and 10 old (5 women, 5 men; 67.6 ± 2.3 yr; range 60–79 yr) subjects with no known history of peripheral or neurological impairment. All subjects were right handed, as identified by the Edinburgh Handedness Inventory (33), with laterality quotients >0.85 (strongly right-hand dominant). Subjects were administered the Paffenbarger Physical Activity Questionnaire (34) to obtain information on daily activity levels, and all subjects were no more than moderately active and did not regularly participate in unique skilled activities (e.g., playing a musical instrument). The study was approved by the Deakin University ethics committee, and all subjects gave informed consent to participate in the study.

Experimental Arrangement

Both hands were tested in a single experimental session, and the hand to be tested first was randomly selected. Subjects were seated comfortably in an experimental chair such that their shoulder was abducted ~45° and the elbow was flexed at 90° so that the forearm rested on a manipulandum. The hand was positioned such that the proximal interphalangeal joint of the index finger was aligned with a compression load cell (Sensotec model 13, Columbus, OH) that measured index finger abduction force. The third to fifth digits were flexed around a handle located on the manipulandum, and the thumb was kept extended by support. The surface EMG was recorded from the FDI muscle using two AgCl electrodes (4-mm diameter) that were placed 1–2 cm apart in a bipolar configuration. A reference electrode was placed over a bony prominence on the dorsal aspect of the hand. The signals were amplified (~100–1,000) and band-pass filtered (13–1,000 Hz). The surface EMG was rectified and integrated (1-s time constant) and was displayed on an oscilloscope for subject feedback. Both the original and integrated EMG were digitized online (2 kHz/channel) via a CED 1401 interface (Cambridge Electronic Design).

Experimental Procedures

Manual performance. Subjects performed three tests in each hand to assess manual performance. The Purdue pegboard was used to assess manual dexterity. The task involved picking up small pegs from a well and placing them as quickly as possible in a vertical array of holes covering only the index finger and thumb. Subjects used one hand at a time, and the number of holes filled over a 30-s period was recorded. Both hands were tested in random order, and each hand was tested three times. The total score for the three trials from each hand was recorded. The second manual performance assessment was termed a single-tap task and involved subjects tapping the number 2 key on a standard computer keyboard with their index finger as fast as possible with their eyes closed. The number of taps performed over a 15-s period was recorded. Each hand was tested three times, and the cumulative score from the three trials in each hand was obtained. The final dexterity task was an alternate-tap task, where subjects were required to alternately tap the number 1 and 3 keys on the keyboard with their index and middle fingers while their eyes were closed. Three trials on each hand were performed, and the cumulative score from each hand was recorded.

Maximum voluntary contractions. The force exerted by the index finger during a maximum voluntary contraction (MVC) was measured at the beginning of every session. The task involved a gradual increase in the abduction force to its maximum value over 2–3 s, after which the maximal force was maintained for another 2–3 s. Subjects were aided in this task by visual feedback of the index finger force on an oscilloscope positioned ~1.4 m in front of them at eye level. Two to four MVC trials were recorded at the start of each session. Rest periods of at least 60 s were given between each MVC trial. FDI EMG (original and integrated) and force were digitized online during the MVCs, and maximum force and integrated EMG were measured with Spike 2 software (Cambridge Electronic Design).

M-waves. The maximum compound muscle action potential (M-wave) was obtained in resting FDI by supramaximal electrical stimulation of the ulnar nerve at the wrist by using a Digitimer (Hertfordshire, UK) DS7A constant-current electrical stimulator (pulse duration 100 μs). An increasing current strength was applied to the ulnar nerve until there was no further increase in the amplitude of the EMG response. To ensure maximal responses, the current was increased a further 20%, and the average M wave was obtained from five stimuli delivered at <0.5 Hz.

TMS. TMS was applied by using a Magstim 200 (Magstim, Dyfed, UK) stimulator with a standard 9-cm circular coil. The coil was positioned at the optimal scalp site for evoking an MEP in the contralateral resting FDI muscle. The coil was orientated such that the current flowed in a clockwise direction (viewed from above) for activating the right motor cortex (left side muscles) or a counterclockwise direction for activating the left motor cortex (right-side muscles). The threshold stimulus strength was determined as the lowest intensity required to produce ~10/15 responses of >50 μV in the resting FDI muscle. The optimal coil position was marked on the scalp to ensure a constant position throughout the experiment.

Subjects were required to perform a series of tasks while TMS was applied to the appropriate hemisphere. The tasks were as follows: 1) index finger abduction: isolated index finger abduction against a force transducer; 2) power grip: a 5-cm-diameter cylinder was held such that all digits exerted force at an equivalent strength; 3) precision grip: pressing the thumb and index finger against a standard staple remover (maximum opening width 4 cm), with the wrist extended at ~40°; and 4) scissor grip: pressing the thumb and index finger against spring-loaded (compression) gardening shears, with the wrist flexed at ~10°.

Task 1 was considered a simple task because it involved isolation of
a single muscle, whereas tasks 2–4 were considered functional tasks because they involved natural hand movements requiring activation of multiple hand muscles. Subjects were required to perform each task while maintaining their integrated FDI EMG at 5% of maximum, which was provided by a target line on the feedback oscilloscope. TMS was then applied for each task at 80, 100, and 120% of resting threshold intensity, delivered in random order. Fifteen stimuli (~0.2 Hz) were delivered at each intensity for the four different tasks. Once all combinations of TMS intensity and task were completed, the other hand was tested by altering the direction of current flow to activate the other hemisphere (by flipping the coil), and the same tasks and stimulus protocol were repeated.

Data Analysis

The maximum EMG during index finger abduction was calculated over a 1-s duration centered around the peak force obtained during each MVC contraction. All MEPs in a trial (n = 15) were full-wave rectified, and the MEP area was obtained from each individual stimulus. For consistency, the area for each MEP was calculated for a triphasic EMG response. The mean MEP area from all trials was normalized as a percentage of the area of the maximal FDI M wave in that hand. The latency of the MEP was measured from the averaged and rectified EMG recordings. The silent period was measured for TMS intensities of 100 and 120% of resting threshold from each trial and then averaged over the 15 stimuli. The commencement of the silent period was calculated from the onset of the stimulus, and the cessation of the silent period was measured at the resumption of consistent EMG to prestimulus levels. This was obtained by placing horizontal cursors on the maximum and minimum prestimulus EMG levels and determining the time when the EMG crossed these threshold levels following the silent period.

Task-related changes in MEP area were investigated by normalizing MEP areas obtained for power, precision, and scissors grips with that obtained for index finger abduction. For each subject, the normalization procedure involved dividing the average MEP area of each task by the mean value obtained for abduction in that subject group and hand and multiplying by 100. A task-related increase in the MEP would result in a normalized MEP area >100% (abduction), and a task-related decrease would result in a normalized MEP area <100%.

Statistical Analysis

A two-factor ANOVA was used to determine the influence of age (young, old) and hand (left, right) on the dependent variables of Purdue score, single-tap score, alternate-tap score, MVC (N), MVC EMG (mV), M wave (mV/ms), and MEP threshold (%stimulator output). For MEP area (% M wave), MEP latency (ms), and silent period duration (ms) for all tasks, a three-factor ANOVA was used to assess the effect of age, hand, and stimulus intensity (80, 100, and 120% of threshold, 100 and 120% for silent period). Differences between tasks, a four-factor repeated-measures ANOVA was used to assess the effect of age, hand, stimulus intensity, and task (abduction, power, precision, scissors). Scheffe’s post hoc test was used when significant main effects or interactions were observed in the ANOVA.

Linear regression analysis was used to examine the association between manual performance (single tap, alternate tap, Purdue score, and MVC strength), MEP area, and silent period duration. For all comparisons, P < 0.05 was regarded as significant. Data are shown as means ± SE.

RESULTS

The age- and hand-related differences in MVC, MVC EMG, M-wave area, resting MEP threshold, and manual performance are shown in Table 1. The older adults showed significantly reduced manual performance scores than young subjects, with 29% lower scores for the Purdue pegboard [F(1,36) = 98.2, P < 0.001], 20% less for single-tap scores [F(1,36) = 15.1, P < 0.001], and a 44% reduction in alternate-tap scores [F(1,36) = 32.9, P < 0.001]. Maximum force and EMG measures were also reduced in older adults, with a 36% lower MVC strength [F(1,36) = 18.2, P < 0.001], a 31% smaller M-wave [F(1,36) = 15.1, P < 0.001], and 47% lower maximum EMG values [F(1,36) = 10.0, P < 0.001]. Despite these performance effects, there was no difference in the stimulus intensity needed to induce a MEP in resting muscle between young and old adults. No differences between left and right hands existed for any of these measures in young or old adults, other than the Purdue scores, which were four pegs greater [10%, F(1,36) = 8.9, P = 0.005] for the right compared with the left hand for all subjects combined.

Representative examples of EMG responses following TMS in the left and right hands of one young (22-yr-old male) and one old (78-yr-old male) adult are shown in Fig. 1. Data are shown on two time scales to emphasize the subject differences in MEP area (Fig. 1, A and B) and silent period durations (Fig. 1, C and D). EMG responses are displayed following TMS at resting threshold intensity and are shown as an average of 15 trials in Fig. 1, A and B, and a superimposition of 15 trials in Fig. 1, C and D. The silent period duration was measured from the onset of the stimulus (dashed vertical line) to the resumption of prestimulus EMG levels (arrow). These data show that the MEP areas were approximately twofold larger in the young subject (relative to M wave) and were ~20% larger in a scissors grip compared with index finger abduction. Furthermore, the EMG silent periods were ~100 ms longer in the young compared with the old subjects and were unchanged with the different tasks.

Table 1. Manual performance scores and subject responses in left and right hands of young and old adults

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th></th>
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<th>Old</th>
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<th>All</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Both</td>
<td>Left</td>
<td>Right</td>
<td>Both</td>
<td>Left</td>
<td>Right</td>
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<td>Purdue score</td>
<td>46±1</td>
<td>51±2</td>
<td>48±1*</td>
<td>32±1</td>
<td>36±2</td>
<td>34±1</td>
<td>39±2</td>
<td>43±2†</td>
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<tr>
<td>Single tap</td>
<td>255±10</td>
<td>283±8</td>
<td>269±7*</td>
<td>210±17</td>
<td>220±17</td>
<td>215±12</td>
<td>230±11</td>
<td>251±12</td>
</tr>
<tr>
<td>Alternate tap</td>
<td>291±28</td>
<td>338±29</td>
<td>314±20*</td>
<td>169±19</td>
<td>186±16</td>
<td>177±13</td>
<td>230±22</td>
<td>262±24</td>
</tr>
<tr>
<td>MVC, N</td>
<td>403±3.5</td>
<td>399±4.7</td>
<td>401±2.8*</td>
<td>24.0±2.2</td>
<td>27.7±2.5</td>
<td>25.8±1.7</td>
<td>32.2±2.7</td>
<td>33.8±2.9</td>
</tr>
<tr>
<td>Maximum EMG, mV</td>
<td>0.47±0.08</td>
<td>0.55±0.12</td>
<td>0.51±0.07*</td>
<td>0.24±0.03</td>
<td>0.31±0.04</td>
<td>0.27±0.03</td>
<td>0.35±0.05</td>
<td>0.43±0.07</td>
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<tr>
<td>M-wave, mV/ms</td>
<td>99.5±7.1</td>
<td>94.6±9.1</td>
<td>97.0±5.7*</td>
<td>60.5±6.6</td>
<td>73.6±7.8</td>
<td>67.1±5.2</td>
<td>80.0±6.5</td>
<td>84.1±6.3</td>
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<td>MEP threshold, %</td>
<td>44±1</td>
<td>40±1</td>
<td>42±1</td>
<td>44±1</td>
<td>42±1</td>
<td>43±1</td>
<td>44±1</td>
<td>41±1</td>
</tr>
</tbody>
</table>

Values are means ± SE. MVC, maximum voluntary contraction; EMG, electromyogram; MEP, motor-evoked potential. *P < 0.001 compared with both hands of old subjects. †P = 0.005 compared with the left hand.
Effect of Age and Hand on MEP Responses

To examine the effect of age and hand on MEP area, data were collapsed across task conditions, and a three-way ANOVA (age group, hand, stimulus intensity) was performed. This analysis revealed significant main effects for age \( F(1,468) = 20.6, P < 0.001 \) and stimulus intensity \( F(2,468) = 497.2, P < 0.001 \) on MEP area but no main effect for hand \( F(1,468) = 0.2, P = 0.7 \). These MEP responses following TMS are summarized for all subjects in Fig. 2. When both hands were included, the MEP area of old subjects was 17% smaller than that of young subjects at all stimulus intensities (Fig. 2A). Although no main hand effect was observed in the ANOVA, there was an age \( \times \) hand interaction \( F(1,468) = 17.4, P < 0.001 \). Post hoc analysis revealed that the age differences in MEP area were primarily associated with responses in the left hand, where the MEP area was 30% lower \( (P = 0.007) \) in old compared with young subjects, whereas there were no age-related differences in MEP area for the right hand \( (P = 0.99) \). Furthermore, the MEP responses were 23% greater in the right compared with the left hand in old subjects, but this difference just failed to reach statistical significance \( (P = 0.07, \text{Fig. 2A}) \).

As expected, increasing stimulus intensity resulted in significantly larger MEP response in all subjects. However, there was a significant age \( \times \) stimulus intensity interaction \( F(2,468) = 8.6, P < 0.001 \), and post hoc analysis revealed that MEP area was significantly smaller \( (35%, P < 0.001) \) in old compared with young subjects at resting threshold (100%) stimulus intensity (Fig. 2B). No significant differences in MEP responses were observed at 80 and 120% of threshold between young and old adults. Although nearing statistical significance, there was no age \( \times \) hand \( \times \) stimulus intensity interaction \( F(2,468) = 2.6, P = 0.08 \).

The mean latency of the MEP was significantly longer in older adults \( F(1,468) = 22.6, P < 0.001 \), and this was consistent between hands \( F(1,468) = 0.04, P = 0.8 \) and stimulus intensities \( F(2,468) = 2.1, P = 0.1 \). The mean latency of the MEP was 22.3 \( \pm \) 0.1 ms in young subjects and 23.1 \( \pm \) 0.1 ms in old subjects.

Effect of Age and Hand on Silent Period Durations

The duration of the silent period following the MEP was quantified for stimulus intensities of 100 and 120% of resting threshold. These data are pooled for all tasks and summarized in Fig. 3. A three-way ANOVA revealed significant main effects for age \( F(1,312) = 45.3, P < 0.001 \) and stimulus intensity \( F(1,312) = 118.1, P < 0.001 \), whereas there was no difference between hands \( F(1,312) = 0.9, P = 0.34 \). For both hands combined, the duration of the EMG silent period following TMS was 14% \( (P < 0.001) \) shorter in old \( (150.3 \pm 2.9 \text{ ms}) \) compared with young \( (173.9 \pm 3.0 \text{ ms}) \) subjects. A significant age \( \times \) hand interaction \( F(1,312) = 9.0, P = 0.003 \) revealed a 34-ms (19%) shorter silent period for the left hand in old subjects \( (P < 0.001) \) and a 13-ms (8%) shorter silent period in the right hand of old subjects \( (P = 0.03, \text{Fig. 3A}) \). Furthermore, there was a 14-ms (9%) shorter silent period in
the left compared with the right hand of older adults ($P = 0.02$), with no difference between hands for young subjects ($P = 0.22$). Finally, there was a significant age by stimulus intensity interaction [F(3,324) = 6.7, $P = 0.01$], which revealed significantly shorter silent periods in older adults for the 100% (15 ms shorter, $P = 0.04$) and 120% (33 ms, $P < 0.001$) resting threshold stimulus intensity (Fig. 3B).

Relation Between MEP Size and Silent Period Duration

Because of the differences in the size of the MEP responses and silent period durations in left and right hands in young and old adults, it was necessary to determine the association between the size of the MEP and the duration of the silent period. For stimulus intensities at 100% threshold, there was a significant correlation between MEP area and silent period duration for all subjects ($r^2 = 0.21$, $P < 0.001$), which was greatest in the left ($r^2 = 0.25$, $P < 0.001$) compared with the right hand ($r^2 = 0.19$, $P < 0.001$). The strongest correlation was observed for the left hand in young subjects ($r^2 = 0.31$, $P < 0.001$), whereas the weakest correlation was observed for the right hand in young subjects ($r^2 = 0.07$, $P = 0.08$). In contrast, the correlations between MEP area and silent period duration were substantially weaker at 120% of resting threshold ($r^2 = 0.08$, $P < 0.001$, all subjects), and these data are shown for left and right hands in Fig. 4. There was a weak but significant association for the left hand in all subjects ($r^2 = 0.14$, $P < 0.001$, Fig. 4A), which was strongly influenced by the data in old subjects ($r^2 = 0.22$, $P = 0.002$). The only significant correlation in the right hand was observed for the young subjects ($r^2 = 0.11$, $P = 0.04$, Fig. 4B).

Effect of Task and Age on MEP Area

For the MEP area data from all 20 subjects, a four-factor repeated-measures ANOVA revealed significant main effects for task [F(3,324) = 6.2, $P < 0.001$], age [F(1,324) = 16.0, $P < 0.001$], and stimulus intensity [F(2,324) = 154.9, $P < 0.001$], whereas there was no main effect for differences between hands [F(1,324) = 0.05, $P = 0.8$]. The effect of task on MEP area is shown for young and old adults in Fig. 5. For all subjects combined (Fig. 5A), the MEP area was significantly greater in the scissor grip compared with index finger abduction (12%, $P = 0.005$), power grip (10%, $P = 0.003$), and precision grip (12%, $P < 0.001$).

To more closely examine the task-dependent changes in MEP area within each subject group and hand, we needed to...
account for the differences in MEP responses in young and old adults. Therefore, the MEP area for the three functional tasks (power, precision, and scissors) in each subject were normalized to the average MEP area obtained for abduction (control condition) in that age group and hand. These data are shown for the left hand in Fig. 5B and for the right hand in Fig. 5C. For the left hand, there was no significant task-dependent modulation of the MEP response in young or old adults (Fig. 5B). In contrast, there was a significant (22%, \( P = 0.04 \)) facilitation of responses for the scissor grip compared with index finger abduction in the right hand of old subjects (Fig. 5C). No significant differences were observed with any of the functional tasks compared with index finger abduction in the right hand of young subjects, although there were significantly larger MEP responses with a scissor grip compared with a precision grip (15% larger, \( P = 0.04 \)). Therefore, these data suggest that the increased size of the MEP response for the scissor grip in all subjects (Fig. 5A) was due largely to the responses obtained in the right hand of old adults (Fig. 5C).

**Effect of Task and Age on Silent Period Duration**

For all subjects, there was a task-related change in the duration of the silent period (Fig. 6A). The longest silent period was observed during the scissor grip, with a duration 19 ms longer than the power grip (\( P < 0.001 \)), 10 ms longer than the precision grip (\( P = 0.003 \)), and 8 ms longer than index finger abduction (\( P < 0.05 \)). Furthermore, the duration of the silent period during the power grip was 11 ms (\( P = 0.002 \)) shorter than abduction and 8 ms (\( P = 0.03 \)) shorter than the precision grip. To examine the contribution of each hand, the data were normalized to the group and hand mean for index finger abduction in young and old adults. For the left hand (Fig. 6B), there was a significantly longer silent period for the scissor grip (13% longer, \( P < 0.001 \)) and abduction (10% longer, \( P = 0.005 \)) compared with the power grip in young subjects, whereas there was no significant task-dependent change in the left hand of older adults. For the right hand (Fig. 6C), there was a significantly longer silent period in the scissor grip compared with the power grip in older adults (16%, \( P < 0.001 \)), whereas there was no task-dependent change for the right hand in young subjects. These data show that the largest relative change in silent period duration was observed in the right hand of old adults.

**Relations Between Manual Performance, MEP Size, and Silent Period Durations**

In an effort to establish any fundamental association between MEP responses, silent periods, and manual performance, it was necessary to perform linear regression analysis between these dependent variables. Manual performance measures consisted of single- and alternate-tap scores, Purdue scores, and MVC strength, and each of these was correlated with MEP area (80, 100, and 120% of threshold) and silent period duration (100 and 120% of threshold) in young and old adults. Given that the correlations were not substantially different between tasks and hands, all comparisons were performed by using index finger abduction in both hands.

There was a weak but significant correlation between MEP area at all intensities and alternate-tap score (\( r^2 = 0.03, P = 0.05 \)), which was most prominent at a 100% threshold stimulus intensity (\( r^2 = 0.2, P = 0.004 \)). There was also a weak but significant association between MEP area and MVC strength at all intensities (\( r^2 = 0.04, P = 0.037 \)), with the strongest correlation observed at 100% threshold (\( r^2 = 0.19, P = 0.005 \)). These data indicate that there is a weak, positive association between the size of the MEP response at 100% threshold and alternate-tap performance and maximal strength of the FDI muscle. No significant correlations were observed between MEP area and single-tap score or Purdue score (\( r^2 \) from 0.006 to 0.009). Furthermore, there were weak but significant correlations between silent period duration and alternate-tap score and Purdue score (\( r^2 = 0.07–15 \)). No substantial differences were observed for any of these variables between young and old adults.

**DISCUSSION**

The purpose of the study was to quantify the age-related differences in EMG responses to TMS during functional isometric contractions in left and right hands of right-handed subjects. We have confirmed the findings of previous studies, by showing smaller MEP responses and shorter EMG silent periods following TMS in older adults. There were three new
findings in this study. First, the MEP size was reduced in the left but not the right hand of old compared with young subjects. Second, differences in the silent period duration between young and old adults were greatest in the left hand. Third, the largest task-dependent changes in MEP responses and silent period durations were observed in the right hand of older adults. We suggest that these differences in the cortical and spinal control of functional isometric contractions in left and right hands of older adults reflect adaptive properties of the nervous system related to preferential hand use with advancing age.

Age and Hand Differences in Motor Cortex Excitability

Healthy aging is associated with a marked decline in neuromuscular performance capabilities. Changes in neuromuscular function that are often observed in older adults include a loss of strength, a reduction in the magnitude of reflex responses, an increased postural instability, a greater kinematic variability of simple movements, and impaired performance of fine-motor skills (17). Many of these changes in movement capabilities can be attributed to a marked alteration of the neuromuscular system with advancing age. The most frequently studied neuromuscular adaptation is the loss of muscle mass (sarcopenia) and the associated reduction in maximal muscle strength. Sarcopenia is primarily due to a decrease in the number of muscle fibers (28) that is caused by the death of spinal motoneurons and an incomplete reinnervation of the abandoned muscle fibers by the surviving motoneurons (12). This results in a decline in the number of motor units and an
increase in the innervation ratio of the motor units in the muscles of older individuals (10).

Along with the alterations in the peripheral neuromuscular system, neurons in the motor cortex appear to be modified with advancing age. For example, ~40% of motor cortex neurons are lost or become nonfunctional after 60 yr of age (19), but the extent of corticospinal neuron loss with age is not known. Similar maximal MEPs in young and old adults (37) suggest that the specific loss of large-diameter corticospinal neurons may not be substantial. Using submaximal stimulus intensities, electrophysiological evidence indicates that there is a reduction in the amplitude of MEPs (13) and an alteration of the input-output properties of the corticospinal pathway (37) in older adults. These findings suggest that the number of corticospinal neurons may be the same in young and old adults, but the ability to activate these cells with TMS is reduced in older subjects. We have shown that the MEP responses are 30% smaller in the left (nondominant) hand of older adults during a variety of isometric contractions, whereas no difference was observed in the right (dominant) hand. These data suggest that long-term preferential use of a muscle for skilled daily activities, such as handwriting, may alleviate some of the detrimental neural adjustments that occur in the corticospinal and peripheral nervous system with advancing age.

Because EMG responses are recorded from the muscle following TMS, the differences in MEP size between young and old adults must reflect differences in spinal motoneuron excitability as well as cortical excitability. No measures of spinal motoneuron excitability were obtained in the present study, because TES (direct corticospinal activation) is too uncomfortable to be performed in older subjects, H-reflex measurements are inconsistent in the FDI muscle, and mastoid stimulation is not appropriate for intrinsic hand muscles (52). Nonetheless, there is some evidence in lower limb muscles of a decline in the H reflex with advancing age (26, 41, 45), although others have found no age-related effect (1, 11). However, limited information exists on spinal excitability changes with age for upper limb motoneurons, although it has previously been shown that the F-wave-to-M-wave ratio and F-wave persistency measures are similar in the abductor pollicis brevis muscle of young and old adults (29). Taken together, these findings indicate that there may be a small decline in upper limb motoneuron excitability with advancing age, but this probably occurs in the left and not the right hand in older subjects, based on our present finding of a smaller MEP in the left hand of older adults, and no difference with age in the right hand (Fig. 2A).

Aside from a possible decline in spinal excitability, smaller MEPs in older adults may be due to dispersion and EMG amplitude cancellation when recorded from the muscle, if there is conduction velocity slowing in the central or peripheral nervous system. In order for this to occur, there would need to be slowing of neural conduction velocities that is not consistent among the pool of active motor units, leading to a greater within-subject variability in the latency of the single motor unit responses to TMS, and an increased cancellation of the summed potential at the surface of the muscle. Although the latencies for evoked single motor unit responses are usually 1 ms longer in older adults, there does not seem to be any difference in the variability of this latency measured from single motor units between young and old subjects (14). Alternatively, there could be increased jitter within single motor units of older adults, but this is not likely to be substantial enough to influence EMG cancellation (24). Furthermore, these effects would have to be observed in the left and not the right hand to be consistent with present findings, and there is no evidence to suggest that this is a likely scenario. We, therefore, conclude that the smaller MEP responses observed in the left hand of older adults at resting threshold intensity reflects, in part, reduced corticospinal excitability with advancing age. This could be due to altered cortical neuronal properties, a change in the balance of the reduced excitation and inhibition in cortical networks acting on corticospinal cells, or a reduced ability to engage the corticospinal system by the motor commands with advancing age.

**Decreased Cortical Inhibition in Older Adults**

Approximately 25–30% of the neurons in the primate neocortex use GABA as their neurotransmitter, and these inhibitory neurons are important in influencing input-output properties and for cortical reorganization and plasticity (23). These GABAergic systems within the human motor cortex are studied with paired-pulse TMS or with suprathreshold single-pulse TMS. Paired-pulse TMS uses a subthreshold conditioning stimulus to activate an intracortical inhibitory circuit, which reduces the size of a suprathreshold TMS delivered up to 5 ms later (27). In contrast, a single suprathreshold TMS over the motor cortex suppresses voluntary muscle activation for up to 300 ms and has been termed the EMG silent period. Spinal mechanisms contribute to EMG suppression for the first 60 ms, but later effects are attributed to cortical inhibitory mechanisms (22). Recent evidence indicates that these two types of inhibition are distinct: paired-pulse intracortical inhibition is mediated by GABA_A receptors, whereas silent period inhibition is mediated by GABA_B receptors (Ref. 49, see Ref. 5).

Several reports have shown reduced intracortical inhibition by using the paired-pulse technique (25, 36, 55) and the EMG silent period duration (14, 40) in older adults. We have confirmed the finding of a reduced silent period in both hands of older adults, providing supporting evidence for an age-related decline in GABAergic inhibition in the human motor cortex. Furthermore, we have shown that the age-related differences in silent period duration are nearly three times larger in the left hand (34-ms reduction) compared with the right hand (13-ms reduction) in these subjects, which is contrary to our original hypothesis based on data in young subjects (39). These findings suggest that long-term use of the dominant hand for skilled tasks may preserve some of the loss of GABA-mediated inhibition within the motor cortex hemisphere controlling the dominant hand. These findings also have important implications for other imaging techniques that cannot distinguish between excitatory and inhibitory cortical mechanisms. For example, differences in cortical activation between young and old adults measured with fMRI are largest when the nondominant hand is used to perform a simple motor task (20), and this finding could be due to the reduced silent period inhibition that was observed in the nondominant hand of older adults. The interpretation of fMRI data is further complicated by the finding of a differential modulation of agonist and antagonist muscles at both the cortical and spinal level (2) and...
the evidence that these parallel excitatory and inhibitory pathways can be altered with advancing age (26).

In the present study, we found reduced cortical excitability (measured with MEP size) and silent period inhibition in the left hand of old compared with young subjects. The reduced silent period duration in the left hand of older adults is not due to smaller MEPs, because silent period duration is sensitive to stimulus intensity rather than MEP size (56) and the current findings were obtained with equivalent stimulus intensities between subject groups and hands (Table 1). Furthermore, there was no difference in MEP size at 120% of resting threshold intensity between young and old adults (Fig. 2B), but the silent period was still significantly shorter (33 ms, \( P < 0.001 \)) in older adults at this intensity. The correlations between MEP size and silent period duration within each subject and hand were only weakly related (Fig. 4), suggesting that these excitatory and inhibitory mechanisms are likely to impinge on separate neural populations (see also Ref. 54). Nonetheless, these data suggest that the shorter silent periods, particularly in the left hand, are due to a reduction in GABA\(_B\)-mediated cortical inhibition during all tasks in older adults.

**Task-dependent Changes in Left and Right Hands**

TMS produces short-latency contractions of contralateral muscles, with the amplitude of the response a reflection of the strength and excitability of cortical and spinal control to the target muscle. Responses following TMS, but not TES, are larger during the performance of more complex tasks (9, 46), which reflect the increased excitability of the corticospinal pathway during fine control of the digits. In support of this, we have shown that MEP responses were increased in the scissor grip task compared with index finger abduction (Fig. 5A), but this was observed predominantly in the right hand of older adults (Fig. 5C), with no task-dependent change in the left hand of young or old subjects. The scissor grip task involved the independent activation of the index finger and thumb to control the levers against a compliant load (spring). Given that there is relatively little change in spinal excitability during the performance of similar tasks in young subjects (9, 46), these data suggest that the scissor grip is performed with increased corticospinal excitability in the right hand of older adults.

The reduced task-dependent facilitation for functional tasks in young subjects is contrary to the findings of Flament et al. (15), who used a variety of similar tasks and found that they were all facilitated with respect to index finger abduction. The most likely reason we did not see MEP facilitation in young subjects is due to the use of different stimulus intensities, given that intensities of 35–80% of maximum stimulator output were used by Flament et al., which are greater than those used in the present study (range 26–64% for young subjects). In contrast, task-related changes in EMG responses were largest in the right hand of older adults, suggesting that the pathways involved in modulating the MEP response are utilized more with advancing age, particularly in the right (dominant) hand. This was a somewhat unexpected result, given that functional losses in older adults have been associated with a diminished ability to modulate descending (excitatory and inhibitory) input to motoneurons during rhythmic isometric contractions (50) and slow movements (48) and with a reduced task-dependent modulation of the soleus H-reflex (26). The task-dependent plasticity in the right hand of older adults suggests an intact ability to modulate the descending corticospinal and spinal inputs to motoneurons with altering task demands, which may be due to a lifetime of preferential use of that hand for skilled tasks. Alternatively, it may suggest that older adults have a greater need to use direct as opposed to indirect descending pathways with increasing task demands with the dominant hand. Minimal task-dependent modulation of the MEP response was observed in either hand in young subjects, and it is possible that this modulation would be present when confronted with more demanding tasks where feedback on task performance is provided.

The possibility exists that the different MEP sizes between tasks arose due to the different hand postures associated with the performance of each of the tasks. Subjects were asked to maintain a set level of EMG (5%) that was normalized to the maximum EMG that was obtained during an index finger abduction MVC. Because the FDI muscle is primarily responsible for index finger abduction (4), the maximum possible EMG is likely to be less during the three functional tasks, and the 5% EMG contribution of the FDI muscle used in the present study is likely to be greater (relative to the possible maximum) during the three functional tasks. The most likely result would be an increase in the size of the MEP response during the functional tasks due to an increased cortical and spinal excitability with increased contraction intensity (see Ref. 47). However, the precision and scissor grips involve almost identical hand postures, with the only difference for the scissor grip relating to the variable load on the levers induced by the spring. There were substantial differences in the MEP responses between these two tasks in all subjects, and this effect was not consistent between hands (Fig. 5). Therefore, although we cannot exclude this as a possible confounding factor, the variable MEP responses between subject groups and hands suggest that an increased relative activation of the FDI muscle during the functional tasks does not account for the current findings.

It has previously been shown that there is a task-dependent change in the EMG silent period in young subjects, with a shorter silent period in a precision and power grip task compared with index finger abduction (53). Minimal task-related change in the silent period induced by TES suggests that a reduced cortical inhibition was involved in the performance of the more complex precision and power grips (53). We found that the duration of the silent period was shorter during the power grip compared with index finger abduction, which supports the previous findings. In contrast, the silent period was prolonged during the scissor grip compared with index finger abduction, indicating that the scissor grip task is performed with an increased (GABA\(_B\)-mediated) cortical inhibition to corticospinal neurons involved in controlling the FDI muscle. Furthermore, similar to the MEP response, we found that the greatest change in the silent period was observed in the right hand of older subjects. These findings suggest that the pathways that modulate the MEP and silent period responses are relatively well preserved with a lifetime of preferential use of the dominant hand for fine-motor tasks.

**Cortical Control and Motor Performance in Older Adults**

The older adults examined in the present study had significantly lower motor performance scores than young subjects,
with reduced strength and manual dexterity assessments. Between-hand differences were only observed for the Purdue pegboard task (Table 1), suggesting that the different size of the MEP response between hands may not be directly associated with muscle strength or the ability to control the digits. Linear regression analysis showed significant associations between MEP size and alternate-tap performance and maximum strength, but the effect was relatively weak, suggesting that it is of minimal physiological significance. Several studies have shown that task-induced MEP facilitation is positively correlated with improvements in motor performance (31, 35, 57), and it is likely that the ability to modulate motor cortex excitability, depending on the task, is more important for learning a new motor skill (32, 44). Similarly, there were only weak associations between the EMG silent period duration and the Purdue pegboard score, and it may be that the manual performance tests used in the present study were not sensitive enough to establish any association between the measured EMG responses (MEP area, silent period) and motor performance. It is interesting to note, however, the substantial impairment in the alternate-tap score (44% lower) compared with the single-tap score (20% lower) in older adults, which involves the selective switching between the index and middle finger and is more likely to be influenced by deficits in intracortical inhibition (see Refs. 51, 58). There is increasing evidence that both silent period (GABA_A) inhibition (8) and paired-pulse intracortical (GABA_A) inhibition (16) play an important role in motor performance, but it is yet to be determined how a reduction in these types of inhibition influences skilled motor performance in older adults.

In conclusion, we have shown in right-handed subjects that the cortical control of a hand muscle during functional isometric contractions is differentially altered in left and right hands with advancing age. For the left (nondominant) hand in older adults, we found reduced motor cortex excitability and cortical inhibition and minimal task-related modulation of these corticospinal responses compared with the left hand in young subjects. In contrast, age-related differences in motor cortex excitability and cortical inhibition were less obvious in the right hand, with increased task-dependent modulation of the corticospinal pathway in the dominant hand of older adults. We suggest that these differences in the corticospinal control in the left and right hands of older adults reflect neural adaptations that occur throughout a lifetime of preferential use of the hand for skilled (dominant) and unskilled (nondominant) motor tasks. It remains to be determined how these age-related differences in corticospinal control influence the performance of motor tasks during more demanding contractions.

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