Neurophysiological correlates of aging-related muscle weakness

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1Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio; 2Department of Physical Medicine and Rehabilitation, Neurological Institute, Cleveland Clinic, Cleveland, Ohio; 3Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, New Jersey

Submitted 19 March 2013; accepted in final form 10 September 2013

Plow EB, Cunningham DA, Bonnett C, Gohar D, Bayram M, Wyant A, Varnerin N, Mamone B, Siemionow V, Hou J, Machado A, Yue GH. Neurophysiological correlates of aging-related muscle weakness. J Neurophysiol 110: 2563–2573, 2013. First published September 11, 2013; doi:10.1152/jn.00205.2013.—Muscle weakness associated with aging implicates central neural degeneration. However, role of the primary motor cortex (M1) is poorly understood, despite evidence that gains in strength in younger adults are associated with its adaptations. We investigated whether weakness of biceps brachii in aging analogously relates to processes in M1. We enrolled 20 young (22.6 ± 0.87 yr) and 28 old (74.79 ± 1.37 yr) right-handed participants. Using transcranial magnetic stimulation, representation of biceps in M1 was identified. We examined the effect of age and sex on strength of left elbow flexion, voluntary activation of biceps, corticospinal excitability and output, and short-interval intracortical and interhemispheric inhibition. Interhemispheric inhibition was significantly exaggerated in the old (P = 0.047), while strength tended to be lower (P = 0.075). Overall, women were weaker (P < 0.001). Processes of M1 related to strength or voluntary activation of biceps, but only in older adults. Corticospinal excitability was lower in weaker individuals (r = 0.38), and corticospinal output, intracortical inhibition and interhemispheric inhibition were reduced too in individuals who poorly activated biceps (r = 0.43, 0.54 and 0.38). Lower intracortical inhibition may reflect compensation for reduced corticospinal excitability, allowing weaker older adults to spread activity in M1 to recruit synergists and attempt to sustain motor output. Exaggerated interhemispheric inhibition, however, conflicts with previous evidence, potentially related to greater callosal damage in our older sample, our choice of proximal vs. distal muscle and differing influence of measurement of inhibition in rest vs. active states of muscle. Overall, age-specific relation of M1 to strength and muscle activation emphasizes that its adaptations only emerge when necessitated, as in a weakening neuromuscular system in aging; transcranial magnetic stimulation; strength; muscle weakness; primary motor cortex

AGING IS ACCOMPANIED BY SIGNIFICANT LOSS of muscle strength, ranging from 20% to 50% (Doherty 2003). Muscle weakness is one of the most significant factors limiting mobility, independence and quality of life in frail older adults (Giampaoli et al. 2003; Faulkner et al. 2007), but recently, changes within the central nervous system have received attention. This is because degenerative changes, such as reduction in gray matter volume (Good et al. 2001), number of motor cortical (Henderson et al. 1980) and spinal motor neurons (Doherty 2003), synaptic density (Haug and Eggers 1991), white matter integrity (Davis et al. 2009), and descending commands for voluntary activation (Yue et al. 1999), exaggerate effects of peripheral degeneration to perpetuate weakness.

Although evidence implicating central neural degeneration in age-related weakness is established (Semmler et al. 2006), the role of the primary motor cortex (M1), its associated motor regions and corticospinal output have received limited attention. This gap can be ascribed to the fact that M1 and associated corticospinal neurons are traditionally believed to be critical for individuated movement control of fingers and skilled use of the hand (for review, see Porter and Lemon 1993) rather than muscle force/strength (Remple et al. 2001).

Classical and growing evidence, however, suggests that, besides skill/precision, M1 and corticospinal system also contribute to modulating forces and muscle strength. In nonhuman primates, frequency of discharge of cells in M1 increases monotonically with forces (Cheney and Fetz 1980; Evarts 1968). Functional imaging (Dai et al. 2001; Siemionow et al. 2000) data in humans demonstrate a strong linear relationship between M1 activation and incremental forces in humans. Neurophysiological evidence, using transcranial magnetic stimulation (TMS), a noninvasive approach examining cortical and corticospinal excitability, similarly suggests that excitability varies strategically across contexts in which force is applied (Flament et al. 1993). Besides cross-sectional evidence, M1 and its processes have been linked to serial improvements in muscle strength as well. In young adults, corticospinal output and excitability increase (Beck et al. 2007; Griffin and Carelli 2007; Lee et al. 2009; Weier et al. 2012), and short-interval intracortical inhibition lowers (Goodwill et al. 2012; Weier et al. 2012). Gains in strength may also implicate interhemispheric interactions because unilateral training is shown to influence processes in M1 ipsilateral to the trained limb (Goodwill et al. 2012). Therefore, role of M1 in strength is now being recognized by virtue of classical evidence and recent evidence of its adaptations with training in young adults.

As a corollary, is it possible that adaptations in M1 also relate to loss of muscle strength with aging? Evidence using
TMS documents age-related adaptations, but findings are conflicting. For instance, corticospinal excitability is believed to diminish with advancing age (McGinley et al. 2010; Peinemann et al. 2001; Pitcher et al. 2003; Sale and Semmler 2005), but, on the other hand, there is evidence suggesting that it may not remarkably change (Oliviero et al. 2006; Talelli et al. 2008b). Similarly, with regards to short-interval intracortical physiology, some have claimed that aging has little effect (Oliviero et al. 2006), while others report a reduction (Marneweck et al. 2011; Peinemann et al. 2001), and still some others note exaggeration (Kossev et al. 2002; McGinley et al. 2010). There is also no consensus on whether interhemispheric interactions remain unchanged (Hinder et al. 2010) or become less inhibitory (Talelli et al. 2008b). Thus, even after several years of investigations, it remains unclear whether any of these processes ultimately explain age-related muscle weakness.

The present exploratory study aimed to address the debate by defining processes in M1 that specifically relate to age-based changes in strength and the direction of such relationships. Across older and younger participants, using TMS, we examined the representation of biceps brachii, a key elbow flexor. We examined its excitability at corticospinal, intracortical and interhemispheric levels because these mechanisms interact to define motor output (Chen 2004; Daskalakis et al. 2011; Peinemann et al. 2001), and still some others note exaggeration (Kossev et al. 2002; McGinley et al. 2010). There is also no consensus on whether interhemispheric interactions remain unchanged (Hinder et al. 2010) or become less inhibitory (Talelli et al. 2008b). Thus, even after several years of investigations, it remains unclear whether any of these processes ultimately explain age-related muscle weakness.

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the upper limbs, cognitive decline [tested using the Mini Mental State Examination (Folstein et al. 1983)] and established contraindication to TMS (Rossi et al. 2009). All subjects provided written, informed consent prior to participation. The experimental protocol was approved by the Institutional Review Board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Procedures**

We measured isometric strength of left elbow flexion and processes within M1 that could potentially explain strength, including corticospinal, short-interval intracortical and interhemispheric influences, within the representation of biceps brachii in right M1. The reason for choosing to investigate nondominant biceps was that a previous study had discussed greater differences in corticospinal excitability between aged and young for the nondominant side (Sale and Semmler 2005).

**Assessment of strength.** Subjects were seated in a chair with the left arm in abduction (~10°), elbow flexion (90°) and forearm supination. Upon verbal reinforcement, they generated maximal isometric elbow flexion force briefly (3–5 s) against a wrist cuff attached to a force transducer (universal force-moment sensor system; JR3, Woodland, CA), while feedback about the level of force was displayed on an oscilloscope (TDS 460 digitizing oscilloscope, Tektronix, Beaverton, OR). They performed five trials of maximal isometric elbow flexion with a rest period of 45–60 s between trials. Force signals were amplified (~1,000–3,000), digitized at 200 Hz (CED 1401, Cambridge Electronic Design, Cambridge, UK), and recorded on computer for offline analysis.

Surface electromyographic (EMG) signals were recorded from the left biceps brachii using bipolar electrodes (silver-silver chloride, 8 mm diameter) positioned over the middle of the muscle belly and a reference electrode over the lateral epicondyle. EMG signals were amplified (~500–5,000), band-pass filtered (10 Hz to 1 kHz; model CED 1902, Cambridge Electronic Design), and digitized (2,000 Hz). EMG data were analyzed offline using Spike2 (1401, Cambridge Electronic Design).

**TMS recordings.** TMS was applied using figure-of-eight coils (70 mm) connected to one or two Magstim devices (200° and Bistim device, Magstim, Dyfed, UK). The coil was placed tangential to the scalp with the handle oriented backwards and laterally at 45° from the midsagittal axis. Positioning of the coil was guided by frameless stereotaxy (Brainsight, Rogue Research, Montreal, Quebec, Canada) that defined the online relationship between the position of the subject’s head, the coil and the cortical target and updated this information with high spatial resolution. Surface EMG electrodes overlying the left and right biceps recorded muscle responses evoked by TMS, also known as motor evoked potentials or MEPs. MEP data were amplified, band-pass filtered (10 Hz-2 kHz), digitized (4 kHz; PowerLab 4/25T, AD Instruments, Salt Lake City, UT), and stored on a computer for offline analysis (Scope Software, version 4.0.8).

Using single-pulse TMS, we identified the optimal site in right M1 devoted to left biceps. We determined this site based on a criterion: its ability to evoke MEPs of ≥ 50 μV (peak-to-peak) amplitude in 3 out of 5 trials. The lowest intensity of TMS pulse used to evoke these consistent, minimally perceptible MEPs in resting biceps was called the resting motor threshold, serving to define bias of excitability within the corticospinal system (Devanne et al. 1997). We also noted corticospinal output. For this, suprathreshold intensity of TMS was used to evoke large, supramaximal MEPs in resting biceps in 3 out of 5 trials. Intensity ranging up to 95% of maximum stimulator output was delivered to generate a criterion MEP (0.1–0.5 mV peak-to-peak amplitude). The criterion range was set lower than that generally adopted for study of distal hand muscles (~1 mV) because it is difficult to evoke larger MEPs from biceps (Chen et al. 1998; Harris-Love et al. 2007). Furthermore, MEPs elicited in biceps are more variable (Brasil-Neto et al. 1992) than those in the muscles of hand (van Kuijk et al. 2009). In fact, older adults show even greater inconsistency of their MEPs (Pitcher et al. 2003).

Using paired-pulse TMS, we investigated short-interval intracortical excitability in the representation of biceps in right M1. When paired pulses are delivered at short interpulse intervals (1–5 ms), MEP amplitude is inhibited, a phenomenon termed as short-interval intracortical inhibition. At long intervals (7–15 ms), the MEP size is facilitated, termed as short-interval intracortical facilitation (Ziemann et al. 1996). The subthreshold conditioning pulse was set to deliver TMS at intensity of 90% of resting motor threshold, while the subsequent suprathreshold test pulse was delivered at TMS intensity evoking supramaximal MEP (0.1–0.5 mV peak-to-peak amplitude).

To define short-interval intracortical inhibition, we delivered paired pulses at intervals of 1 through 5 ms, and we examined short-interval intracortical facilitation at intervals of 7 through 15 ms (Perez et al. 2004) across 3 out of 5 trials each. However, since most individuals in our study demonstrated peak inhibition and facilitation at 2 and 10 ms, respectively, and since these intervals have been most commonly used in both young and older subjects (Chen et al. 1998; Marneweck et al. 2011; Ziemann et al. 2002), we only report inhibition and facilitation at these intervals.

We used paired-pulse TMS to evaluate interhemispheric inhibition. Paired suprathreshold pulses when delivered to bilateral M1s at interpulse intervals of 10–20 ms can test interhemispheric inhibition (Ferbert et al. 1992); conditioning pulse over one hemisphere can inhibit MEP elicited by subsequent test pulse delivered to the other, arguably reflecting transcallosal interactions (Chen et al. 2003; Ferbert et al. 1992; Fling and Seidl 2012; Irbacher et al. 2007; Udupa et al. 2010). We tested inhibition exerted by dominant upon nondominant M1 by first delivering a conditioning pulse to left M1, which was followed 12 ms later by a test pulse given to the right. Both pulses were delivered at suprathreshold intensities, i.e., intensities evoking large (0.1–0.5 mV) supramaximal MEPs from respective hemispheres.

**Data Analysis**

**Strength of elbow flexion.** Over five trials of maximal isometric elbow flexion on the left, we noted average and maximal force in Newtons (N). Voluntary EMG signals generated in left biceps during trials of maximal isometric elbow flexion were full-wave rectified. EMG was averaged over a 1-s period when maximal force was generated during a trial. Over five trials, we noted (in millivolts, mV) the mean and maximal EMG generated in biceps brachii. The levels of EMG in biceps could not be normalized because we did not collect the compound muscle action potential. Evoking such a potential in biceps brachii using electrical stimulation of Erb’s point or musculocutaneous nerve could be uncomfortable for older adults.

**TMS analysis.** Outcome measures related to TMS included the following.

1. **Corticospinal excitability:** we defined the resting motor threshold for biceps representation in right M1 as the bias of corticospinal excitability (Devanne et al. 1997). Resting motor threshold was the lowest intensity of TMS pulse, expressed as percentage of maximum stimulator output, that was required to evoke the smallest MEPs in biceps (peak-to-peak amplitude of at least 50 μV) in 3 of 5 trials.

2. **Corticospinal output** was expressed as the size of MEP (in mV) elicited with suprathreshold intensity of TMS pulse that generally evoked large (0.1–0.5 mV) responses.

3. **Short-interval intracortical inhibition,** short-interval intracortical facilitation and interhemispheric inhibition were each expressed as a percentage. The size of the conditioned MEP was expressed as a percentage of the test MEP (Chen et al. 1998; Harris-Love et al. 2007; Marneweck et al. 2011; Ziemann et al. 2002).

**Statistical analyses.** Statistical analysis was performed using Statistical Package for the Social Sciences (version 18, SPSS, Chicago, IL). A two-way multivariate analysis of variance (MANOVA) was used to examine the effect of age group (younger or older) and sex.
upon dependent measures. Sex was included because it was unequally distributed across both age groups, which may affect outcome variables, such as strength. A MANOVA was chosen for two reasons. First, dependent measures of strength (force or voluntary activation of muscle) may relate to intracortical excitability (Zoghbi and Nordstrom 2007), and intracortical excitability may relate to cortico-spinal output and interhemispheric interactions (Chen et al. 2003). Using a MANOVA allowed us to study effect of independent variables upon potentially related dependent measures. Second, using a single two-way MANOVA rather than multiple two-way ANOVAs was preferred so as to reduce the study-wise type I error rate that could become inflated if multiple inferential tests are used across several variables (Leech et al. 2011). Normality of all dependent variables was assessed with Kolmogorov-Smirnov tests and analysis of normality curves because normal distribution is an important assumption for MANOVA. Correlations were assessed to meet its next assumption. Homogeneity of covariance matrixes was examined using the Box’s M test. To meet the assumptions of the MANOVA (e.g., including a limited number of moderately-related variables that are normally distributed, with homogenous covariance matrixes), we had to exclude mean and maximal EMG of biceps generated in isometric elbow flexion, mean force of elbow flexion, short-interval intracortical facilitation and corticospinal output from the MANOVA. Since the sample size in our present exploratory study was limited, MANOVA was finally conducted for the following dependent variables: maximal elbow flexion force, short-interval intracortical inhibition and interhemispheric inhibition. However, since intensity of TMS can affect intensities of conditioning and test pulses, affecting results of paired pulse TMS (Peurala et al. 2008), we included resting motor threshold as a covariate. Finally, to examine correlates of strength of elbow flexion, expressed as mean force and as voluntary activation of biceps muscle, we examined within each age group, the bivariate relation with measures of corticospinal excitability, intracortical excitability and interhemispheric inhibition using Pearson’s $r$.

**RESULTS**

Details of subjects enrolled in both groups are presented in Table 1. The total number of subjects included in the MANOVA was 33. This reduction is due to the fact that MANOVA removed participants who had a missing value on any single dependent variable. Three older participants could elicit neither short-interval intracortical inhibition, nor interhemispheric inhibition; two older adults and four young individuals each could not elicit either intracortical inhibition or interhemispheric inhibition. The two-way MANOVA revealed a significant multivariate main effect for sex (Wilks’ $\lambda = 0.484, F_{3,26} = 9.25, P < 0.001$) and a trend toward main effect for age group (Wilks’ $\lambda = 0.77, F_{3,26} = 2.58, P = 0.075$), but there was no significant effect for age group-by-sex interaction. Although the $F$-test was not significant for the multivariate main effect of group, we investigated its trend ($P = 0.075$). This is because our study represents a pilot exploratory approach and knowing how age and sex affect dependent measures would allow us to create homogenous samples in future studies. We noted a trend toward a main effect for age group on the maximal force of elbow flexion. Older adults tended to be weaker at generating maximal force of elbow flexion compared with the younger participants ($130.01 \pm 12.97$ N vs. $102.21 \pm 6.56$ N; $F_{1,28} = 3.4, P = 0.075$) (Figs. 1A and 2, A and B). We also found a significant main effect of age group on interhemispheric inhibition; older individuals showed increasingly conditioned MEPs that were $32.17 \pm 4.7$% of test MEPs compared with their younger counterparts ($48.48 \pm 5.55$%, $F_{1,28} = 4.3, P = 0.047$) (Fig. 3, A and B).

Since the overall omnibus $F$ was significant for multivariate effect of sex, we continued to examine its univariate main effects. We found a significant univariate main effect of sex for maximal force of elbow flexion. Women were significantly weaker than men ($90.10 \pm 5.47$ N vs. $153.28 \pm 10.62$ N; $F_{1,28} = 20, P < 0.001$) (Fig. 1B). A univariate main effect of sex could also be noted for short-interval intracortical inhibition, but this was not significant. Men tended to have greater short-interval intracortical inhibition than women ($22.09 \pm 5.15$% vs. $35.14 \pm 4.1$%; $F_{1,28} = 2.97, P = 0.096$) (Fig. 3C).

We found that measures of strength and voluntary muscle activation were related to corticospinal excitability, intracortical excitability and interhemispheric inhibition only in older adults. Mean force of elbow flexion was negatively related with motor threshold ($r = -0.38, P = 0.044, n = 28$) (Fig. 4A). Again, in older adults alone, mean EMG of biceps during elbow flexion was positively related to corticospinal output ($r = 0.43, P = 0.024, n = 28$), and short-interval intracortical inhibition ($r = -0.54, P = 0.008, n = 23$) (Fig. 4B), and showed a trend toward association with interhemispheric inhibition ($r = -0.38, P = 0.073, n = 23$) (Fig. 4C). Younger adults showed no relation between force or voluntary activation of biceps and corticospinal, intracortical or interhemispheric measures.

**Table 1. Subject characteristics by age and sex**

<table>
<thead>
<tr>
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<th>Age Group</th>
<th>Sex</th>
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<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Old</td>
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<tr>
<td>$n$</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Age, yr</td>
<td>22.6 ± 0.87</td>
<td>74.79 ± 1.37</td>
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<tr>
<td>Sex (no. women)</td>
<td>10</td>
<td>20</td>
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<tr>
<td>Hand dominance</td>
<td>Right</td>
<td>Right</td>
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<tr>
<td>Hand dominance</td>
<td>Right</td>
<td>Right</td>
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<tr>
<td>Grip force (left), lbs</td>
<td>59 ± 5.82</td>
<td>30.02 ± 3.65</td>
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<tr>
<td>Maximal force of left elbow flexion, N</td>
<td>130.01 ± 12.97</td>
<td>102.21 ± 6.56</td>
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<tr>
<td>Maximal EMG of biceps in left elbow flexion, mV</td>
<td>0.89 ± 0.18</td>
<td>0.49 ± 0.06</td>
</tr>
<tr>
<td>Resting motor threshold, %maximum stimulator output</td>
<td>63.42 ± 5.65</td>
<td>64.76 ± 2.65</td>
</tr>
<tr>
<td>Intensity of test pulse, %resting motor threshold</td>
<td>128.20 ± 6.19</td>
<td>126 ± 1.94</td>
</tr>
<tr>
<td>Corticospinal output, mV</td>
<td>0.45 ± 0.12</td>
<td>0.51 ± 0.09</td>
</tr>
<tr>
<td>Short-interval intracortical inhibition (conditioned), %test MEP</td>
<td>30.09 ± 5.28</td>
<td>28.89 ± 4.73</td>
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<tr>
<td>Interhemispheric inhibition (conditioned), %test MEP</td>
<td>48.48 ± 5.55</td>
<td>32.17 ± 4.7</td>
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Values are means ± SD; $n$, no. of subjects. Characteristics of study participants are arranged by age (younger and older) and by sex, and how subgroups differed with respect to strength/force and processes of primary motor cortex (M1) studied with transcranial magnetic stimulation (TMS) are shown. MEP, motor evoked potential.

J Neurophysiol • doi:10.1152/jn.00205.2013 • www.jn.org
activity to recruit adjacent muscles, in compensation for lower corticospinal output. Aged individuals show exaggerated interhemispheric inhibition imposed from dominant upon nondominant M1. Since association of M1 processes with strength were manifest here in a sample of elderly who tended to be only slightly weaker than young adults, study of more impaired cohorts of older individuals, or longitudinal investigations, would best confirm our projections in the future, so novel therapeutic interventions can be developed to delay/alleviate weakness in aging. Albeit preliminary, our cross-sectional approach carries significance as it harmonizes evidence in the field of aging and TMS by demonstrating the specific nature of associations between M1 mechanisms and strength/muscle activation. In doing so, we further reinforce the role of M1 in representing muscle strength, extending it beyond its traditionally viewed scope in dexterity. We, however, present an important caveat. By noting an age-based divergence in the relationship of M1 to strength, we suggest that changes in strength, than its maintenance, may invoke M1’s role. Its adaptations may manifest with increasing demands, such as in a weakening neuromuscular system in aging, or even with intensive strength training in younger, healthier system.

Regarding age-related differences in M1 processes, we found that interhemispheric inhibition is exaggerated with age. Although our finding conflicts with that of Talelli et al. (2008b), differences can be understood when considering study populations. Average age of our older participants was 75 (range 65–93 yr), while it was ~43 in the study by Talelli et al., with only 5 or 6 participants being between 60 and 78 yr of age. Callosal damage may have, thus, been more extensive in our subjects since its white matter reaches peak maturity only in the 4th decade (Kochunov et al. 2012; Sullivan et al. 2010). Greater damage may have exaggerated interhemispheric inhibition in our study, in line with recent evidence using diffusion tensor magnetic resonance imaging in aging adults (Fling and Seidler 2012).

Methodological variance also affects direct comparison of our results with those of Talelli et al. (2008b) and Fling and Seidler (2012). We examined inhibition at the level of a proximal muscle, employing higher TMS intensities than generally used for distal, as in the study of Talelli et al. (66% vs. 45%). Higher intensities excite callosal pathways projecting to inhibitory interneurons than ones facilitating pyramidal (Schnitzler et al. 1996; Ugawa et al. 1993). Furthermore, since we measured inhibition during rest, unlike Talelli et al., who examined it during a motor task, results are less relatable because MEPs in the context of a task are complex and disproportionately reflective of alterations in spinal than cortical excitability (Clark et al. 2010; Di Lazzaro et al. 1998; Smith et al. 2011).

Nevertheless, study of interhemispheric interactions during task and rest may be complementary. In unilateral movement, older subjects demonstrate increased ipsilateral besides contralateral activity (Talelli et al. 2008a; Ward et al. 2008), attributed to diminishing inhibition exerted by “active/contralateral” upon ipsilateral M1 (Fling and Seidler 2008b; 2012). Our findings, although converse, in a state of bilateral rest, could still add to such evidence if a temporal sequence through rest and movement were to be investigated as in stroke (Murase et al. 2004). It may be that older adults who show greater ipsilateral to contralateral inhibition at rest also show reduced
ability to overcome it during contralateral movement (Fling and Seidler 2012; Talelli et al. 2008a; 2008b; Ward et al. 2008), showing greater bilateral than contralateral activity.

Intracortical inhibition, unlike interhemispheric, was not affected by aging, in line with evidence presented by some others (Oliviero et al. 2006; Smith et al. 2009), but also contradictory to evidence of reduction (Marneweck et al. 2011; Peinemann et al. 2001) or exaggeration (Kossev et al. 2002; McGinley et al. 2010). We may have witnessed lower intracortical inhibition due to differing choice of muscles compared with others (Kossev et al. 2002; Marneweck et al. 2011; McGinley et al. 2010; Peinemann et al. 2001). Inhibition within networks devoted to proximal vs. distal muscles is dissimilar (Chen and Garg 2000; Chen et al. 1998). Since proximal muscles elicit smaller, variable MEPs, they may be prone to lower intracortical excitability (Saisanen et al. 2011), a relation that was apparent in our study (not shown: r = 0.48, P = 0.002). Also, since use of proximal muscle in our study warranted use of higher conditioning stimulus intensities than generally used for distal muscles, we potentially activated more facilitatory interneurons (Peurala et al. 2008; Ziemann et al. 1996).

Importantly, however, association of intracortical inhibition with voluntary biceps’ activation was significant in older adults. Increased intracortical inhibition with increasing activation of biceps may reflect long-term adaptation. Rosenkranz et al. (2007) demonstrated that skilled musicians show increased intracortical inhibition, representing a braking mechanism to stop unwanted spread of activation (Rosenkranz et al. 2007) to antagonists (Hortobagyi et al. 2006) and coactivated muscles (Sohn and Hallett 2004). Neuroimaging comparably discusses that, as incrementally greater force is generated, intensity of M1 activation increases linearly (Benwell et al. 2007; Dai et al. 2001; Post et al. 2009), suggesting focusing.

On the other hand, as an individual fatigues, intracortical inhibition lowers so activity in M1 spreads to representations of neighboring muscles that may be recruited (Maruyama et al. 2006; Takahashi et al. 2009). In our present study, older adults who generated greater biceps activity showed higher intracortical inhibition, potentially, as a marker of their ability to focus output from biceps, while weaker older adults relied upon lower inhibition to spread activation to agonist muscles.

The direction of association between intracortical inhibition and biceps activity in older adults conflicts, however, with evidence in young adults where inhibition lowers with increases in force or strength (Goodwill et al. 2012; Weier et al. 2012; Zoghi and Nordstrom 2007). Although dissimilarities can be attributed to age-specific differences, as also discussed by Fling and Seidler (2012) recently, we believe the association between intracortical inhibition and muscle activity presents differently with duration or maturity of training. For instance, with acute, serial increases in force (Zoghi and Nordstrom 2007) or early strength training (Goodwill et al. 2012; Weier et al. 2012), individuals may rely upon reduced intracortical inhibition to spread activity to synergists. Over time, however, as perhaps in our stronger older individuals, the association changes. With better ability to activate prime muscles in long term, individuals may now use higher inhibition to focus output from trained muscles and disengage irrelevant activation (Hortobagyi et al. 2006; Rosenkranz et al. 2007; Sohn and Hallett 2004).

We have noted that low corticospinal excitability also related with elbow flexion weakness in the aged. Lower threshold of corticospinal excitation in stronger aged individuals aligns with evidence that excitability increases with training-associated strength gains (Beck et al. 2007; Griffin and Cafarelli 2007; Lee et al. 2009; Weier et al. 2012). We, however, failed to note age-associated differences. Corticospinal degen-
eration with age may manifest strongly for hand muscles (Oliviero et al. 2006; Peinemann et al. 2001; Rossini et al. 1992; Sale and Semmler 2005; Talelli et al. 2008b). And since our older subjects were not remarkably weaker (differences of ∼19% vs. >30% cited previously) (Lindle et al. 1997; Yue et al. 1999), alterations in corticospinal properties may have not yet been apparent.

In our report, strength was strongly influenced by sex too. Women were weaker by about 40%, arguably based on lower proportion of lean tissue in upper body, lower muscle mass and cross-sectional area (Frontera et al. 1991; Kanehisa et al. 1994; Miller et al. 1993), reduced slow-twitch fibers and less efficient neuromuscular output (Komi and Karlsson 1978). Sex did not interact with age though, suggesting sex-based differences are maintained at all ages (Vandervoort and McComas 1986). Future studies may benefit from exploring confound of sex in study of strength training.

Certain issues require deliberation. Our findings may have been affected by small sample size, influencing assumptions of MANOVA. Overall, our older group was ∼21% weaker, which although in the range (20–40%) discussed classically (review, see Doherty 2003), is still not as dramatic. A wider range of ages in our older cohort (65–93 yr) and an unequal distribution of sexes potentially introduced greater within-group variability. Study of distal than proximal muscles may have shown a more pronounced deficit because loss of skill is apparent much earlier (Soer et al. 2012). We find hints of such a divergence in our data because both age and sex significantly affected grip strength on nondominant

Fig. 3. Differences in paired pulse transcranial magnetic stimulation (TMS) parameters. A: older subjects show significantly greater interhemispheric inhibition from the left to right primary motor cortex (M1) compared with young participants (*P < 0.05). B: representative examples from one young and one old subject illustrating the difference in their interhemispheric inhibition. Whereas the top traces represent original test motor evoked potentials (MEPs) evoked at suprathreshold TMS, the bottom traces show reduction in their amplitude when preceded by a suprathreshold conditioning pulse delivered to opposite M1. The young subject showed lower interhemispheric inhibition (% of conditioned MEP/test MEP = 88.3%) than the older subject (% of conditioned MEP/test MEP = 5.33%). C: in the right (nondominant M1), old and young subjects do not differ significantly with respect to short-interval intracortical inhibition. D: representative examples of intracortical inhibition across two older male subjects, one who is able to generate greater EMG activation of biceps (on the left) than the other (on the right). Whereas the top traces represent original test MEPs evoked at suprathreshold TMS, the bottom traces show reduction in their amplitude when preceded by a paired subthreshold conditioning pulse delivered 2 ms prior to the test pulse. Individual showing high EMG activation of biceps shows greater short-interval intracortical inhibition than the weaker counterpart on the right.
side (data not shown, $P < 0.001$ and $P < 0.001$). Furthermore, our results of intracortical and interhemispheric inhibition may have been affected by the nature of the muscle we tested. With biceps, we encountered smaller, variable MEPs (Brasil-Neto et al. 1992), an issue that was more pronounced in older individuals who show variable responses anyway (Pitcher et al. 2003). Smaller MEPs relate to lower inhibition (Saisanen et al. 2011). But choosing a high value of criterion MEP ($1 \text{ mV}$) as defined for distal (Brasil-Neto et al. 1992; Chen et al. 1998) was infeasible for a proximal muscle. Finally, correlations of intracortical and interhemispheric substrates were noted with volitional EMG of biceps, which can be confounded by unrelated nonphysiological effects. To account for them, use of compound muscle action potential as a normalization strategy was, however, beyond the scope of our study. Future longitudinal designs involving long-term training of strength, or larger cross-sectional cohorts of weaker older adults, can best confirm relation of M1 processes with strength or EMG activation of muscle.

Still, the significance of our pilot, cross-sectional study emerges strongly at two levels. First, we have attempted to harmonize evidence in the field of aging and TMS that has thus far been contradictory (Hinder et al. 2010; Kossev et al. 2002; Marneweck et al. 2011; McGinley et al. 2010; Oliviero et al. 2006; Peinemann et al. 2001; Pitcher et al. 2003; Sale and Semmler 2005; Talelli et al. 2008b). We show the specific direction of association between corticospinal, intracortical and interhemispheric excitability and strength or activation of proximal musculature. Second, we demonstrate an age-based diver-
gence in these relationships, as has been recently observed by others as well (Bernard and Seidler 2012). The dichotomy in roles of M1 in young vs. old may be related to the fact that young individuals show near-maximal neural drive (Yue et al. 1999), so M1 may not need to adapt, but, in older individuals, where almost 35% of corticomotor neurons are lost by age 50 (Eisen et al. 1996), adaptations in M1 may become critical (Doherty 2003; Henderson et al. 1980; Kapur et al. 2010). Substrates of M1 may thus not play a critical role in maintaining strength in an efficiently performing young nervous system, while they may be significant in adapting with “increasing” demands as in age-related weakness or strength training in younger individuals (Beck et al. 2007; Goodwill et al. 2012; Griffin and Cafarelli 2007; Kidgell and Pearce 2010; Lee et al. 2009). While we suggest an intimate relation between M1 processes and strength/muscle activation, we also recommend caution and suggest the relation be strategically considered with regard to age of population (young, old), type of muscle, TMS intensities, methods used to titrate intensities and set criterion MEPs, nature of MEPs (variability, amplitude), content of testing, task vs. rest, and metrics of strength (force or EMG), besides anthropomorphic differences.

In summary, we have shown that age and sex, both, affect strength of elbow flexion, although they do not interact. More importantly, we have found that aging exaggerates interhemispheric inhibition in homologous motor cortical representations of biceps brachii. Although different from previous evidence, these results are reconcilable when considering that the sample of elderly in the present study was older than in previous; a greater loss of callosal integrity may have manifested as exaggerated interhemispheric inhibition in our sample. We also found a fundamental shift with age in the relationship between intracortical properties in M1 and strength. Stronger older adults show greater intra-cortical inhibition, perhaps to stop unwanted muscle activation as in antagonists or synergists, but that such a relation is only present in old indicates that M1 adaptations for strength are apparent only when demands upon neuromuscular system increase. Finally, although several studies in aging have explored changes in M1 physiology, our study, to the best of our knowledge, is the first exploratory attempt to quantify their relationship with strength, so we can realize which direction of changes in physiology are indeed adaptive, helping harmonize conflicting evidence, and create new opportunities to delay or alleviate weakness.

ACKNOWLEDGMENTS

We acknowledge support from Daniel Janini for study coordination and analysis.

GRANTS

This work was supported by National Institutes of Health (NIH) Grant R01-NS-35130 (to G. H. Yue). NIH grants supporting investigator roles included Career Development Award K01-HD-069504 (to E. B. Plow), and R01-HD-061363 and New Innovator’s Award OD00646 (to A. Machado).

DISCLOSURES

A. Machado has the following conflicts of interest to disclose: IntElect Medical, Inc., Cleveland, OH (co-founder, scientific advisory board, consultant, shareholder), ATI, and CardioNomic.

AUTHOR CONTRIBUTIONS


REFERENCES


