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ABSTRACT

Purpose: Neural adaptations to strength training have long been recognized, but knowledge of mechanisms remains incomplete. Using novel techniques and a design which limited experimental bias, this study examined if 4 weeks of strength training alters voluntary activation and corticospinal transmission. **Methods:** Twenty-one subjects were randomized into strength training (n = 10; 7 females, 3 males; 23.5 ± 7.5 yr; mean ± SD) and control groups (n = 11; 2 females, 9 males; 23.0 ± 4.2 yr). Strength training involved 12 sessions of high-force isometric contractions of the elbow flexors. Before and after training, voluntary activation of the elbow flexors was assessed via transcranial magnetic stimulation. Also, for the first time, magnetic stimulation of corticospinal axons was used to examine spinal-level adaptations to training. The evoked responses, termed cervicomedullary motor evoked potentials (CMEPs), were acquired in resting biceps brachii in 3 arm postures. Muscle adaptations were assessed via electrical stimulation of biceps. **Results:** Compared to the control group, the strength training group exhibited greater increases in maximal strength (12.8 ± 6.8% vs 0.0 ± 2.7%; $p < 0.001$), biceps electromyographic activity (27.8 ± 25.9% vs -5.2 ± 16.8%; $p = 0.002$), and voluntary activation (4.7 ± 3.9% raw change vs -0.1 ± 5.2%; $p = 0.034$). Biceps CMEPs in all arm postures were unchanged after training. Biceps twitch characteristics were also unchanged. **Conclusion:** Four weeks of isometric strength training of the elbow flexors increased muscle strength and voluntary activation, without a change in the muscle. The improvement in activation suggests that voluntary output from the cortex was better able to recruit motoneurons and/or increase their firing rates. The lack of change in CMEPs indicates that neither corticospinal transmission nor motoneuron excitability was affected by training.

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Key Words: BICEPS; CERVICOMEDULLARY MOTOR EVOKED POTENTIAL; MOTONEURON; MOTOR CORTEX; SPINAL CORD; VOLUNTARY ACTIVATION

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INTRODUCTION

Strength training involves repeated bouts of high-force muscle contractions. After 2 – 5 weeks of strength training, muscle strength can improve *without* an increase in muscle thickness or cross-sectional area (3, 6, 28, 47), or *without* an increase in muscle twitch torque from peripheral nerve stimulation (7, 8, 23, 29, 33, 49). Adaptations in the nervous system likely explain these early strength gains; however, knowledge of mechanisms remains incomplete (9).

Recently, we demonstrated that cervicomedullary motor evoked potentials (CMEPs) in biceps brachii are facilitated for ~25 minutes after one session of high-force isometric contractions of the elbow flexors (35). CMEPs are muscle responses to subcortical stimulation of corticospinal axons at the cervicomedullary junction. These responses travel along the same corticospinal axons as motor evoked potentials (MEPs) from transcranial magnetic stimulation (TMS) (19); they have a large monosynaptic component in biceps (37); and unlike the H-reflex, they are not subject to conventional presynaptic inhibition (25, 34). We postulated that the increased CMEP after the single session of isometric exercise was due to increased efficacy of corticospinal-motoneuronal synapses, rather than increased motoneuron excitability (35). Support for chronic changes in transmission of excitatory input to motoneurons comes from a study in rats, which showed increased numbers of excitatory synapses onto motoneurons after 30 days of strength training (2, see also 18, 46). However, due to limitations in measurement techniques, it has not been possible to test changes in transmission after weeks of strength training in humans. MEPs from TMS can be used to compare the corticomotoneuronal pathway across days, but these responses cannot reveal the site of adaptation, because they reflect effects at both the cortex and spinal cord.

In our previous study, we used *electrical* stimulation to evoke CMEPs and gauge synaptic efficacy at a spinal level (35). However, CMEPs from electrical stimulation could be problematic for long-term training studies. The stimulus might not be reliable day-to-day because skin resistance to the

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electrical current could vary between assessment sessions, and the stimulating electrodes would need to be accurately repositioned. A solution is to acquire CMEPs with *magnetic* stimulation (32, 40, 41, 45). With this technique, a double-cone magnetic coil is held at the back of the head and used to identify the optimal site for stimulating corticospinal axons. In strength training studies, the same protocol has been used for identifying the optimal site at the top of the head for stimulating the motor cortex (7, 8, 27, 28). The issue with tissue resistance is avoided with magnetic stimulation because the method of stimulating the nerves does not rely on electrical current passing through skin (4). We have found CMEPs from magnetic stimulation to be reproducible across days (32). Yet, until the current study, CMEPs from magnetic stimulation have never been used to examine changes in the human spinal cord after weeks of training.

Physiological changes in the corticomotoneuronal pathway after training might increase muscle strength via enhanced voluntary activation (i.e., the nervous system's ability to drive the muscle to produce its maximal force). In strength training studies, voluntary activation has been tested with stimulation of the peripheral nerve during a maximal voluntary contraction (MVC) and measurement of the added torque produced by the stimulus (i.e., the superimposed twitch) (13, 21). A limitation of this technique is that it cannot provide insight about the *site* within the nervous system responsible for any change. Cortically-evoked superimposed twitches from TMS over the motor cortex can also be used to test voluntary activation (44). The benefit of the technique is that it allows inferences about voluntary output from the motor cortex during an MVC. This technique has rarely been used to examine changes in voluntary activation after weeks of strength training (29).

Thus, the purpose of the current study was to determine if 4 weeks of strength training alters responses to stimulation of corticospinal axons (i.e., CMEPs) and TMS-based voluntary activation. We expected no change in motoneuron excitability, because resting H-reflexes do not change with strength

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training (9, 16, 22). Thus, CMEPs served as an index of the efficacy of transmission of the corticospinal volley to the motoneurons, rather than a measure of motoneuron excitability. We hypothesized that strength training would increase muscle strength and sizes of CMEPs. Also, we tested CMEPs in three upper-limb postures, one of which was the posture used in training. The purpose of this procedure was to determine if changes in corticospinal transmission are specific to the posture used in training or if they "transfer" to other postures. To limit bias and improve study quality, the design included a control group, randomized group allocation, blinded assessors, and blinded data analysis.

METHODS

Ethical approval

The study protocol (HC14318) was approved by the Human Research Ethics Committee at the University of New South Wales and complied with the Declaration of Helsinki (2008). Subjects gave their written informed consent to participate and were paid for their time.

Subjects and study design

Figure 1A summarizes the design of the study. Subjects were recruited via advertisements, which were posted on bulletin boards at a university and at a research institute; telephone calls, which were made to individuals on the institute's volunteer registry; and word-of-mouth. Those who responded were assessed for eligibility via phone or email. Individuals were deemed eligible to participate in the study's screening session if they: (a) were available to attend all assessment and intervention sessions; (b) were not currently taking medications that may alter synaptic plasticity (e.g., anti-depressants); (c) did not report any contraindications to TMS (e.g., epilepsy) on a screening questionnaire (38); and (d) were not currently participating in any of the following activities more than once per week: upper-body strength training, boxing, rock climbing, or racquet sports.

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The primary purpose of the screening session was to identify individuals in whom CMEPs from magnetic stimulation could be acquired in resting biceps brachii. The evoked potentials needed to be adequate in size (peak-to-peak amplitude ≥ 0.5 mV) without inadvertent stimulation of cervical motor roots (onset latency ≥ 7.5 ms). Subjects sat with the shoulder flexed and forearm supinated during this procedure (see *Experimental Setup*; and Document, Supplemental Digital Content 1, experimental set-up, http://links.lww.com/MSS/A984). The secondary purpose of the screening session was to familiarize subjects with MVCs of the elbow flexors. If adequate CMEPs were obtained, subjects performed 5 MVCs. These MVCs served as practice trials to minimize learning in the pre-intervention assessment. Following the MVCs, subjects completed the short form version of the International Physical Activity Questionnaire (IPAQ) (14).

About a week after the screening session, eligible individuals participated in the pre-intervention assessment, in which a baseline was established for the study's outcomes. This session was conducted prior to group allocation. On Monday of the following week, subjects were randomly allocated to the strength training or control group. The randomization consisted of subjects reaching their hand into an envelope and drawing out a folded piece of paper that said either "training" or "control." Thus, subjects knew what group they were in. Subjects in both groups attended the laboratory for 4 consecutive weeks, 3 days per week (12 intervention sessions). Subjects returned for the post-intervention assessment within 3 to 7 days of the final intervention session.

Sample size was based on the anticipated effect size for changes in muscle strength after 4 weeks of strength training (11% increase, d = 0.35) (7). With this effect size, an alpha of 0.05, power of 0.80, and a repeated measures design, we determined that 20 subjects (10 per group) would be needed to observe a statistically significant increase in muscle strength (G*Power 3.1.7 software) (17). Sample sizes of ~10 subjects have been adequate to detect small to moderate effects in corticospinal excitability

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after acute strength training in our laboratory (35) and after 4 weeks of strength training in other laboratories (7, 8, 28). We increased our target sample to 12 per group to account for potential dropouts, but we were unable to identify this number of eligible participants.

Experimental setup

For the screening, assessment, and intervention sessions, subjects sat in an adjustable chair. Their right forearm was positioned against a vertical arm bar and strapped into place at the wrist. The arm bar was secured to a table, and a force transducer was attached at the back (Xtran S1W, Applied Measurement, Melbourne, Australia; sampling rate: 1,000 Hz). The right elbow and shoulder were flexed at 90˚, and the forearm was supinated. This was the primary arm posture used in the study (see Document, Supplemental Digital Content 1, experimental set-up, http://links.lww.com/MSS/A984). In the assessment sessions, CMEPs and maximal compound muscle action potentials (M_{max}) were acquired in two additional postures: shoulder flexed with the forearm pronated, and arm hanging with the forearm neutral (36). These 3 postures were incorporated into the study because they are associated with different levels of motoneuron excitability (36).

Electromyography. EMG activity was recorded from the right biceps and triceps brachii using surface electrodes (Ag-AgCl, Conmed Cleartrace, Conmed Corporation, Utica, USA). For biceps, the active electrode was placed over the motor point at the mid-belly of the muscle, and the reference electrode was placed over the distal tendon. For triceps, the active electrode was positioned half way between the humeral head and olecranon process, and the reference electrode was placed over the distal tendon. Signals were amplified (gain 100) and filtered (bandpass 20 – 1,000 Hz; NL844/820/135/144 Neurolog amplifier, isolator, and filters Digitimer, Welwyn Garden City, UK). The sampling rate was 2,000 Hz. Data were stored on a computer using a laboratory interface (CED Power3 1401 and Spike 2 software version 7; Cambridge Electronics Design, Cambridge, UK).

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Brachial plexus stimulation. Electrical stimulation (200 μs duration, DS7AH constant current stimulator, Digitimer, Welwyn Garden City, UK) of the brachial plexus was delivered at Erb's point to obtain M_{max} for the right biceps and triceps. The cathode was positioned in the supraclavicular fossa. The anode was positioned on the acromion. Stimulation intensity (range: 52.5 – 192 mA) was supramaximal. It was 50% above the level necessary to produce M_{max} in biceps or 20% above the level necessary to produce M_{max} in triceps, whichever was higher.

Cervicomedullary magnetic stimulation. Magnetic stimulation (BiStim^2, Magstim, Whitland, UK) at the cervicomedullary junction was used to obtain CMEPs in the right biceps at rest. Subjects wore earplugs to dampen the noise from the stimulator. Subjects also wore a polyester swimcap. The inion was palpated and its location was marked on the cap. A double-cone coil (11 cm outside diameter, Magstim), which was oriented with a downward current direction in the junction of the coil (32), was then used to identify the optimal site for evoking biceps CMEPs ("hot spot"). Identification of the hot spot involved moving the coil in a grid-like manner to various positions at the back of the head and assessing the resultant shapes and size of biceps CMEPs. The hot spot was defined as the site which produced biceps CMEPs that were largest in amplitude and free from inadvertent stimulation of cervical motor roots. Typically, the hot spot was right and caudal to the inion. The hot spot was marked on the cap to ensure reliable placement of the coil during the assessments. The investigator who held the magnetic coil was blind to group assignment.

Each subject was assigned a swimcap, which was worn in the screening session and the assessment sessions. The mark on the cap that represented the inion was used to realign the cap on the head in the post-intervention assessment. Marks of the hot spot also remained on the cap from the pre-intervention assessment. These marks were used as a guide when the hot spot was re-identified. In some cases, the hot spot in the post-intervention assessment differed from that in the pre-intervention

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assessment. If this was the case, the hot spot from the post-intervention assessment was also marked on the cap. The difference between the hot spot locations was later calculated (see Document, Supplemental Digital Content 2, position of the double-cone magnetic coil, http://links.lww.com/MSS/A985).

The two magnetic stimulators were set at the same intensity and discharged simultaneously. Stimulation intensity (range: 52 – 100% of BiStim output) was that which induced a biceps CMEP of ~1 mV in peak-to-peak amplitude during the pre-intervention assessment. For a given subject, the same stimulator output was used in the pre- and post-intervention assessments.

Transcranial magnetic stimulation. Magnetic stimulation (200^2, Magstim) of the left motor cortex was used to assess voluntary activation of the right elbow flexors (42-44). A circular coil (13.5 cm outside diameter) with an anticlockwise current direction (i.e, to induce a posterior-to-anterior current across left motor cortex) was placed with its center at the vertex then moved to identify the hot spot for evoking MEPs in the right biceps. This spot was marked on the cap. During post-intervention assessments, the hot spot was always re-identified.

An appropriate stimulus intensity for measurement of voluntary activation was identified. The intensity was that which: (a) during a 50% MVC contraction elicited a biceps MEP ≥ 70% of the amplitude of biceps M_{max}; and (b) during an MVC elicited a triceps MEP < 10% of the amplitude of triceps M_{max}. In some cases, criteria "a" and "b" could not be met simultaneously, so the intensity that led to the smallest triceps MEP, while still meeting criterion "a", was used. The range of intensities used was 45 – 100% of stimulator output. The same stimulus intensity was used in a given subject's pre- and post-intervention assessments for 18 of the 21 subjects. For 3 subjects in the strength training group, it was necessary to alter the intensity of stimulator output (-7, +4, +25%) in the post-intervention assessment, in order to meet criteria "a" and "b". As noted in Supplemental Digital Content 3, the subject in whom stimulator output was +25% in the post-intervention assessment was later excluded

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from the analysis of voluntary activation (see Document, Supplemental Digital Content 3, data excluded from statistical analysis, http://links.lww.com/MSS/A986).

Motor point stimulation. Electrical stimulation (200 μs duration, DS7AH constant current stimulator) over the muscle belly of biceps was used to evoke maximal twitches. As the cathode for the biceps recording electrode was placed over the motor point, the cathode for this stimulation was positioned proximal to the motor point, and the anode was positioned distal to the motor point (see Document, Supplemental Digital Content 1, experimental set-up, http://links.lww.com/MSS/A984). The stimulation intensity (range: 55 – 330 mA) was supramaximal. It was set at 10% above the level necessary to produce maximal twitch torque.

Assessment protocol

CMEPs and Mmax. An outline of the assessment protocol is provided in Fig. 1B. After setup, biceps CMEPs were obtained in 8 blocks of stimulation. Each block consisted of 5 CMEPs, with individual stimuli 10 s apart. Four blocks were obtained with the right shoulder flexed and forearm supinated (i.e., the study's primary arm posture; see Document, Supplemental Digital Content 1, experimental set-up, http://links.lww.com/MSS/A984), 2 blocks were obtained with the shoulder flexed and forearm *pronated*, and 2 blocks were obtained with the arm hanging to the side. Posture order was randomized, but for a given subject, the same order was used in the pre- and post-intervention assessments. All potentials were acquired with the subject at rest. EMG was monitored to ensure subjects were relaxed prior to each stimulus. One biceps M_{max} was acquired at the end of each of the 8 blocks of CMEPs.

Maximal strength. MVCs of the elbow flexors were performed in the study's primary arm posture. Subjects were given instruction on technique. They were also told: "This is the most important measure of the entire study. Please give an absolute maximal effort." Subjects performed 5 MVCs with a

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90-s rest between each trial. Each MVC lasted ~3 seconds. Feedback of elbow flexor torque was provided on a monitor. Once the first MVC was completed, a target, which represented the peak torque from the first MVC, was placed on the monitor. Within a given assessment session, subjects were instructed to try to beat their previous best performance by pulling their torque beyond the target. If, in subsequent MVCs, the subject pulled above the initial target, the target was raised, such that subjects were always attempting to beat their best performance. The investigator who provided verbal encouragement was blind to group assignment.

Voluntary activation and muscle twitch characteristics. Voluntary activation was assessed in five separate blocks. Each block began with an MVC, and TMS was delivered when the subject reached peak torque. Immediately following the MVC, a potentiated resting twitch was elicited by electrical stimulation of the motor point. This was followed by brief contractions at 75% and then 50% MVC, in which TMS was again delivered. Target torques were presented to subjects on a monitor. Blocks were separated by 90 s.

Intervention

Subjects in both groups attended the laboratory for 12 intervention sessions over four weeks. Sessions were conducted on Mondays, Wednesdays, and Fridays. Each one lasted ~15 minutes.

For subjects in the strength training group, intervention sessions consisted of high-force isometric contractions of the right elbow flexors. The arm posture used during training is depicted in Document, Supplemental Digital Content 1, experimental set-up, http://links.lww.com/MSS/A984. Each session consisted of 4 sets of 8 isometric contractions. Each contraction lasted 3 seconds and was followed by a 3-s rest. Target torques were presented to subjects via a monitor. With the aid of an auditory cue (3-s beep), subjects immediately contracted to the target and maintained that torque until the beep ended. A 2-min rest was provided between each set of contractions. Training intensity was

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progressively increased over the four weeks: week 1 (70% MVC), week 2 (75% MVC), week 3 (80% MVC), and week 4 (85% MVC) (i.e., MVC from the pre-intervention assessment).

For subjects in the control group, intervention sessions consisted of sitting with the right arm strapped into the arm bar for the same time required to complete the training. Control subjects heard the same audio cues as the training group, but instead of contracting, they sat with their arm relaxed. They were instructed: "Sit relaxed and count the number of beeps in your head." Torque traces were monitored to ensure subjects were not contracting their muscles.

Data analysis

Data files were renamed to blind the investigator who analyzed them. Peak torques from the 5 MVCs were measured, and the highest was taken to represent maximal strength. Root mean square (RMS) amplitudes of biceps and triceps EMG were measured across the torque plateau of each MVC. These EMG values were normalized to the peak-to-peak amplitude of biceps and triceps M_{max}, respectively. The average from the 5 MVCs was taken as the final EMG value.

For CMEP and M_{max} waveforms, areas and amplitudes were measured. All CMEPs acquired in a given arm posture were averaged into one value. This value was then normalized to the M_{max} value from the same posture. In the primary arm posture (shoulder flexed, forearm supinated), the CMEP was the average of 20 potentials (4 blocks x 5 CMEPs per block) and the M_{max} was the average of 4 potentials (4 blocks x 1 M_{max} per block). For the other two arm postures, the CMEP was the average of 10 potentials (2 blocks x 5 CMEPs per block) and the M_{max} was the average of 2 potentials (2 blocks x 1 M_{max} per block). For twitch torques that accompanied the CMEPs, the peaks of the responses were measured. The individual CMEP twitch torques were then averaged in the same way as the CMEPs.

Voluntary activation (%) was computed from the equation: (1 – MVC superimposed twitch / estimated resting twitch) × 100. Amplitudes of superimposed twitch torques at the three contraction

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intensities (i.e., MVC, 75% MVC, and 50% MVC) were measured as the differences between the pre-stimulus torque (mean over 100 ms prior to stimulation) and the peak flexion torques in the 200 ms after the stimulus. The estimated resting twitch torque was calculated by extrapolation of a single linear regression between voluntary torques and twitch torques at the three contraction intensities from the 5 voluntary activation blocks (42-44). Voluntary activation was computed for each of the 5 MVCs, with the same resting twitch used in each equation. The 5 voluntary activation values were then averaged.

For the twitch responses from motor point stimulation, peak torque, time to peak torque, and half-relaxation time were measured. Each number for each measure is the average from the 5 trials.

Statistical analysis

Statistical analyses were conducted with SPSS version 22 (IBM, Armonk, USA). Independent t-tests compared pre- to post-intervention change scores between the strength training and control groups. For MVC peak torque, biceps and triceps EMG, biceps M_{max} area and amplitude, and muscle twitch characteristics from peripheral nerve stimulation, the change scores were *percentage* differences from baseline. For voluntary activation, CMEPs (areas and twitch torques), and the x and y coordinates of the double-cone magnetic coil, the change scores were *raw* differences from baseline. Statistical significance was set at 0.05. Also, effect sizes (Cohen's *d*) compared the changes scores between the two groups. Data in text and tables are reported as mean ± SD, and figures present group means and individual data. Some data were excluded from statistical analysis (see Document, Supplemental Digital Content 3, data excluded from statistical analysis, http://links.lww.com/MSS/A986).

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RESULTS

Subjects. Figure 1C depicts the flow of individuals through the study. Of the 45 individuals screened for CMEPs, 22 exhibited responses that were adequate in size and free from inadvertent stimulation of cervical motor roots. These 22 subjects were randomized into the strength training and control groups. One subject in the training group withdrew after 7 training sessions due to pain in their biceps associated with the training. That individual did not complete the post-intervention assessment. Thus, twenty-one subjects completed both the pre- and post-intervention assessments and comprised the final sample (strength training, n = 10; control, n = 11). The randomization procedure led to a disproportionate number of males and females in the groups. The training group consisted mostly of females (n = 7), while the control group consisted mostly of males (n = 9). No differences existed between the groups for age (strength training: 23.5 ± 7.5 yr; control: 23.0 ± 4.2 yr), body mass index (21.6 ± 3.4 kg/m^2; 22.0 ± 2.6 kg/m^2), or level of physical activity (1952 ± 1595 MET-min/wk; 1583 ± 1127 MET-min/wk).

Compliance. All control subjects attended all 12 intervention sessions. For the strength training group, 8 of the 10 subjects completed all 12 sessions. One subject completed 11 sessions, while another completed 10. Data for the subject in the strength training group who withdrew due to pain in their biceps were removed from all analyses, and they are not a part of the final sample of 10 in the strength training group.

Strength, EMG, and voluntary activation. The strength training group increased MVC peak torque by 12.8% (Fig. 2A), biceps EMG by 27.8% (Fig. 2B), and voluntary activation (in raw units) by 4.7% (Fig. 2C). These changes (Table 1) were greater than in the control group (MVC peak torque: t = 5.574, $p < 0.001$, d = 2.523, 95% CI = 1.376 – 3.670; biceps EMG: t = 3.494, p = 0.002, d = 1.528, 95% CI = 0.555 – 2.501; voluntary activation: t = 2.299, p = 0.034, d = 1.05, 95% CI = 0.137 – 1.963). For

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the strength training group, the correlation between changes in strength and voluntary activation was r = 0.12 (p = 0.761). Changes in triceps EMG were not different (strength training: 11.0 ± 41.1%; control: 17.4 ± 43.5; t = -0.345, p = 0.734).

At baseline, MVC peak torque was 13.7 Nm less in the strength training group than in the control group (t = -1.962, p = 0.065). A difference at baseline between the two groups existed for biceps EMG (t = 2.343, p = 0.030), but not for voluntary activation (t = -0.134, p = 0.895).

Muscle twitch characteristics. No differences existed between the two groups' change scores for biceps twitch peak torque (t = 0.839, p = 0.412), time to peak torque (t = 1.038, p = 0.312), and half-relaxation time (t = 1.229, p = 0.234) from motor point stimulation (Table 2). Also, no difference existed between the two groups' change scores for the estimated resting twitch torque from TMS (t = 1.731, p = 0.101). But note, the estimated resting twitch increased in 6 of 9 individuals in the strength training group (19% mean increase) and only 3 of 11 individuals in the control group (0.2% mean increase). At baseline, no differences existed for biceps twitch characteristics between the two groups, although the estimated resting twitch torque from TMS was smaller in the strength training group (t = -2.13, p = 0.047). Also, as expected, the biceps twitch peak torque at baseline was smaller than the estimated resting twitch torque from TMS, in both the strength training (t = -4.114, p = 0.003) and control groups (t = -4.323, p = 0.002).

Biceps CMEPs and M_{max}. Figure 3A shows traces of biceps CMEPs in the supinated posture for one subject in the strength training group and one subject in the control group. Biceps CMEPs in all arm postures were unchanged by strength training (Table 3; Fig. 3B). No differences existed between the two groups' change scores for biceps CMEP area in the supinated (t = -1.346, p = 0.196), pronated (t = -0.497, p = 0.626), or hanging (t = -0.174, p = 0.864) arm postures. Moreover, no differences existed between the two groups' change scores for biceps CMEP twitch torques in the supinated (t = -1.152, p =

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0.266) or pronated (t = -1.085, p = 0.294) arm postures. At baseline, biceps CMEP area normalized to M_{max} area in the supinated (t = 2.877, p = 0.010) and pronated postures (t = 2.834, p = 0.011) was greater in the training than control group (see explanation below).

Biceps M_{max} in all arm postures was unchanged by strength training (Table 3). No differences existed between the two groups' change scores for biceps M_{max} amplitude in the supinated (t = -0.500, p = 0.623), pronated (t = -0.443, p = 0.663), or hanging (t = 0.466, p = 0.646) arm postures. Also, no differences existed between the two groups' change scores for biceps M_{max} area in the supinated (t = -0.550, p = 0.589), pronated (t = -0.374, p = 0.713), or hanging (t = -0.097, p = 0.923) arm postures. At baseline, biceps M_{max} amplitude (t = -2.385, p = 0.028) and area (t = -2.123, p = 0.047) in the supinated posture differed between the two groups.

DISCUSSION

The current study explored neural adaptations to strength training using novel techniques and a design which limited experimental bias. We found that four weeks of high-force isometric contractions of the elbow flexors increased muscle strength, voluntary activation, and biceps EMG, but did not change biceps twitch characteristics or responses to stimulation of corticospinal axons (i.e., biceps CMEPs at rest). The results imply that the improvement in strength was due to a neural mechanism. This mechanism was not identified, but the lack of change in the CMEPs suggests it was neither enhanced corticospinal transmission nor increased motoneuron excitability.

Muscle strength and biceps twitch. Strength training improved muscle strength by 13%. A change in the muscle was likely not the cause of this strength increase, because the biceps twitch – which should reflect any changes in muscle size or architecture that influence torque production – was unaltered by training. These results are consistent with studies that have used single electrical shocks (7,

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8, 23, 29, 33, 49) and *tetanic* stimulation of the muscle (15, 33, 39, 48). Thus, the increase in muscle strength in the current study was due, primarily, to adaptations in the nervous system. The improvements in voluntary activation and biceps EMG (normalized to M_{max}) are evidence of such adaptations.

Muscle strength was not well matched between the training and control groups at baseline, although there was no statistically significant difference. The lack of similarity can be attributed to the disproportionate number of males and females that were randomized into the two groups, as cross-sectional area of the elbow flexors is larger in males than females (24, 26). To account for this difference in muscle strength, we conducted our analysis on percentage change scores. Although not always the case (24), percentage increases in muscle strength from strength training are usually similar between males and females (1, 12, 30). Thus, we do not believe the disproportionate numbers of males and females in the two groups played a critical role in the observed changes in strength. Also, because of eligibility criteria, the two groups were otherwise homogenous. They had similar levels of physical activity, and they were comprised of individuals who were not undertaking upper-body exercise more than one time per week. Moreover, the training group improved muscle strength, while the control group did not. This result, irrespective of any underlying sex differences between groups, still provided the basis for examining our key question – is enhanced corticospinal transmission responsible for improvements in muscle strength after strength training?

Voluntary activation and biceps EMG. Strength training increased voluntary activation of the elbow flexors by 4.7% (raw, not percent change) and biceps EMG by 28%. Baseline levels of voluntary activation (~89%) were low compared to previous studies that have examined the measure in the same arm posture and with TMS (~94%) (42, 43). The lower levels of activation may be due to the subjects' lack of experience with strong voluntary contractions of the elbow flexors. That is, subjects were generally "untrained". None were participating in strength training or other upper-body exercises more

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than once per week, and the majority had no history of strength training. Nevertheless, no baseline differences in activation existed between groups. For the training group, the increase in activation suggests that voluntary output from the motor cortex was better able to recruit motoneurons and/or increase motoneuron firing rates to produce maximal muscle force.

TMS activates cortical areas for biceps and its synergists. This aspect of TMS-based voluntary activation is one of its benefits, because strength is the net sum of the torques created by *all* muscles about a joint. Thus, the improvement in voluntary activation could be due to enhanced neural drive to any of the muscles involved in elbow flexion (e.g., brachialis, brachioradialis) or reduced drive to antagonists. The increased biceps EMG provides evidence that part of the improvement in activation was due to enhanced drive to an agonist, while the lack of change in triceps EMG suggests that reduced drive to an antagonist was not a major contributor.

Cervicomedullary motor evoked potentials and potential mechanisms. Strength training did not alter sizes of CMEPs in resting biceps or CMEP twitch torques in any arm posture. We hypothesized that training would enhance corticospinal transmission in the training posture, and we wanted to test whether such an adaptation would "transfer" to other postures. However, we were unable to examine a transfer effect because CMEPs in the training posture did not change. The lack of change in CMEPs suggests that the increase in muscle strength was *not* due to increased motoneuron excitability, enhanced efficacy of corticospinal-motoneuronal synapses, or other long-term modifications in transmission of corticospinal signals to motoneurons. Taken together with previous findings of no change in motoneuron excitability (i.e., H-reflex) with strength training (9, 16, 22), there is little support for spinal-level changes when the motoneuron pool is at rest.

We acquired CMEPs at rest but not during voluntary contraction. This approach was taken for a few reasons. Primarily, if some underlying property of the corticomotoneuronal path were to be altered

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by training, we would expect this to be apparent at rest. We would also expect any such change to be present during voluntary contraction, but evoked responses measured during contraction are complicated by the uncertainty of the level of motoneuron excitability upon which the test stimulus is superimposed. Hence, measurement of altered corticospinal transmission could be confounded by altered motoneuron excitability. As motoneuron excitability is loosely related to motoneuron output, it can, to some degree, be controlled if subjects generate a matched torque or EMG level between assessment sessions. However, even this approach is problematic in training studies, because the intervention is likely to alter maximal torque and/or EMG and this makes the appropriate match unclear. A further difficulty is that the meaning of changes of size of CMEPs acquired during strong contractions is complex. The responsiveness of the biceps motoneuron pool declines with strong contractions and causes sizes of CMEPs (or MEPs) to decrease (31). Thus, increases in CMEP (or MEP) size during strong contractions might represent increased corticospinal input to the motoneurons, but alternatively could reflect a decrease in motoneuron firing.

Nevertheless, after 3 – 4 weeks of strength training, evoked responses have been reported to change when measured during voluntary contraction but not at rest (7, 8, 16, 22). The changes during contraction have been attributed to enhanced corticospinal transmission (7), increased motoneuron excitability and/or decreased presynaptic inhibition (22), increased motoneuron firing rates and/or increased duration or amplitude of the motoneuron afterhyperpolarization (8), and increased "supraspinal excitability" (16).

We cannot exclude spinal-level factors that would differ during contraction or that may not influence responses to synchronised synaptic input, as occurs with cervicomedullary stimulation. For example, spinal reflex pathways, whose inputs to the motoneurons change during contraction, might play a role. Another factor is the intrinsic state of the motoneurons. Two weeks of isometric strength

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training of the ankle dorsiflexors reduced the duration of the motoneuron afterhyperpolarization (10). Modifications in motoneuron firing properties could arise from altered neuromodulatory input. In rats, strength training of the tongue led to extra immunoreactivity for serotonin in the hypoglossal nucleus and suggests an increase in serotonergic inputs (5). Serotonin enhances persistent inward currents, which are critical for repetitive firing of motoneurons (20). Such a change would be important for motoneuron firing during voluntary contraction but not at rest.

A cortical mechanism that results in increased descending drive could also be responsible for the improvements in muscle strength and voluntary activation. Repetitive TMS over the motor cortex appears to attenuate gains in strength from strength training (23). The mechanism underlying this effect is unknown, and spinal-level mechanisms cannot be excluded, but perhaps the repetitive stimulation interfered with training-induced reductions in cortical inhibition (11, 27, 47).

In sum, if the mechanisms that give rise to enhanced voluntary activation and muscle strength are evident at rest, then our results suggest these are "upstream" from the corticomotoneuronal synapses. If the mechanisms are not evident at rest but are only evident during voluntary contraction, then they could be any of a number of factors that alter repetitive firing of motoneurons, such as, increased descending drive from the cortex or modifications in the intrinsic properties of the motoneurons.

Conclusion. For the first time, magnetic stimulation of corticospinal axons was used to investigate neural adaptations to strength training. Responses to the stimulation were unaltered after four weeks of high-force isometric contractions of the elbow flexors. Muscle strength and voluntary activation both improved, but muscle twitch characteristics were unchanged. Thus, a neural mechanism likely underpinned the improved muscle strength. However, the mechanism was not enhanced corticospinal transmission or increased motoneuron excitability.

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All authors affirm that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the study do not constitute endorsement by the American College of Sports Medicine.

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FIGURE CAPTIONS

FIGURE 1. A, Study overview. Subjects participated in 15 sessions: 1 screening session, 1 pre-intervention assessment, 12 intervention sessions, and 1 post-intervention assessment. Following the pre-intervention assessment, subjects were randomly allocated to a strength training or control group. All subjects undertook 12 intervention sessions over 4 weeks. Subjects in the strength training group completed high-force isometric contractions of the right elbow flexors. Subjects in the control group sat relaxed with their right arm strapped to the arm bar for the time required to complete the training (~15 min). B, Assessment protocol. Eight blocks of cervicomedullary motor evoked potentials (CMEPs) and maximal compound muscle action potentials (M_{max}) were acquired in resting biceps. Four blocks were obtained with the shoulder flexed and forearm *supinated* (S), 2 blocks were obtained with the shoulder flexed and forearm *pronated* (P), and 2 blocks were obtained with the arm hanging to the side (H). Subjects then performed 5 MVCs of the elbow flexors. Voluntary activation and muscle twitch characteristic were also assessed. These measures were obtained in 5 blocks. Each block began with an MVC, and the magnetic stimulator from transcranial magnetic stimulation (TMS) was discharged when the subject reached peak torque. Immediately following the MVC, a potentiated resting twitch was induced by motor point stimulation of biceps. This was followed by brief contractions at 75% and 50% MVC, in which the magnetic stimulator was discharged when subjects reached target torques. C, Flow diagram of subjects through the study.

FIGURE 2. A, Percentage change in maximal voluntary contraction (MVC) peak torque of the elbow flexors after the 4-wk intervention. The small circles on the left represent the individual subjects (filled circles = males; unfilled circles = females). The large circle on the right represents the group mean. The mean change in the strength training group (12.8%) was greater than in the control group (0%). B, Percentage change in biceps brachii electromyographic activity (EMG) after the 4-wk intervention. The

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mean change in the training group (27.8%) was greater than in the control group (-5.2%). C, Raw change in voluntary activation after the 4-wk intervention. The mean change in activation in the training group (4.7%) was greater than in the control group (-0.1%).

FIGURE 3. A, Traces of biceps brachii cervicomedullary motor evoked potentials (CMEPs) in one subject from the strength training group and one subject from the control group. These potentials were acquired at rest and with the shoulder flexed and forearm supinated. Each waveform is the average of 20 potentials. The stimulus artefact, which is indicated by the arrow, has been truncated in some instances. Dashed lines indicate amplitudes from the pre-intervention assessment. For both subjects, sizes of biceps CMEPs were unchanged after their respective interventions. B, Areas of biceps CMEPs before (Pre) and after (Post) the 4-wk intervention. These data were acquired at rest and with the shoulder flexed and forearm supinated. Gray lines represent individual subjects (solid lines = males; dashed lines = females) and black lines represent group data. CMEPs were unchanged after training. C, Elbow flexion twitch torques that accompanied the CMEPs were also unchanged after training.

Supplemental Digital Content

Supplemental Digital Content 1: Experimental set-up

Supplemental Digital Content 2: Position of the double-cone magnetic coil

Supplemental Digital Content 3: Data excluded from statistical analysis

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Figure 1

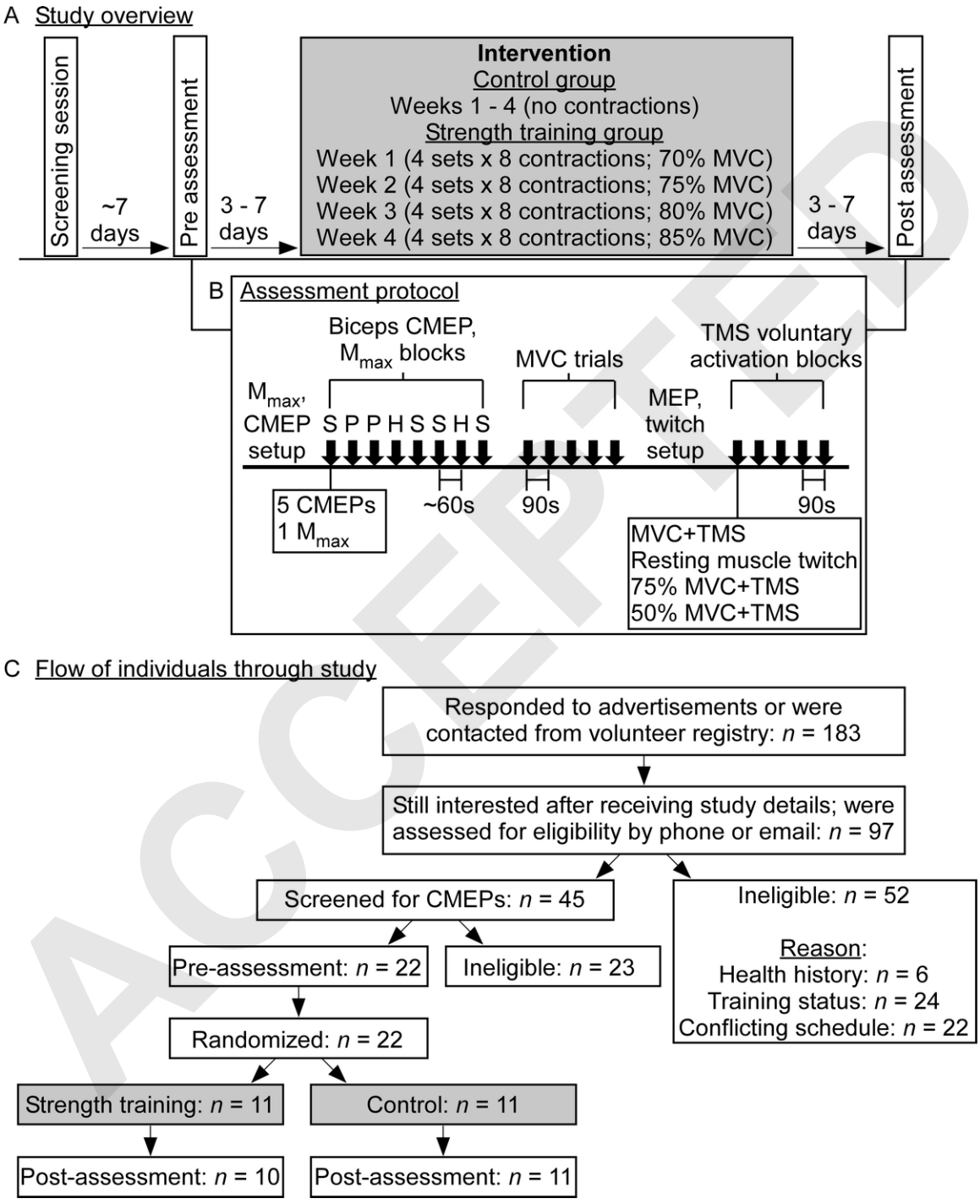

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Figure 2

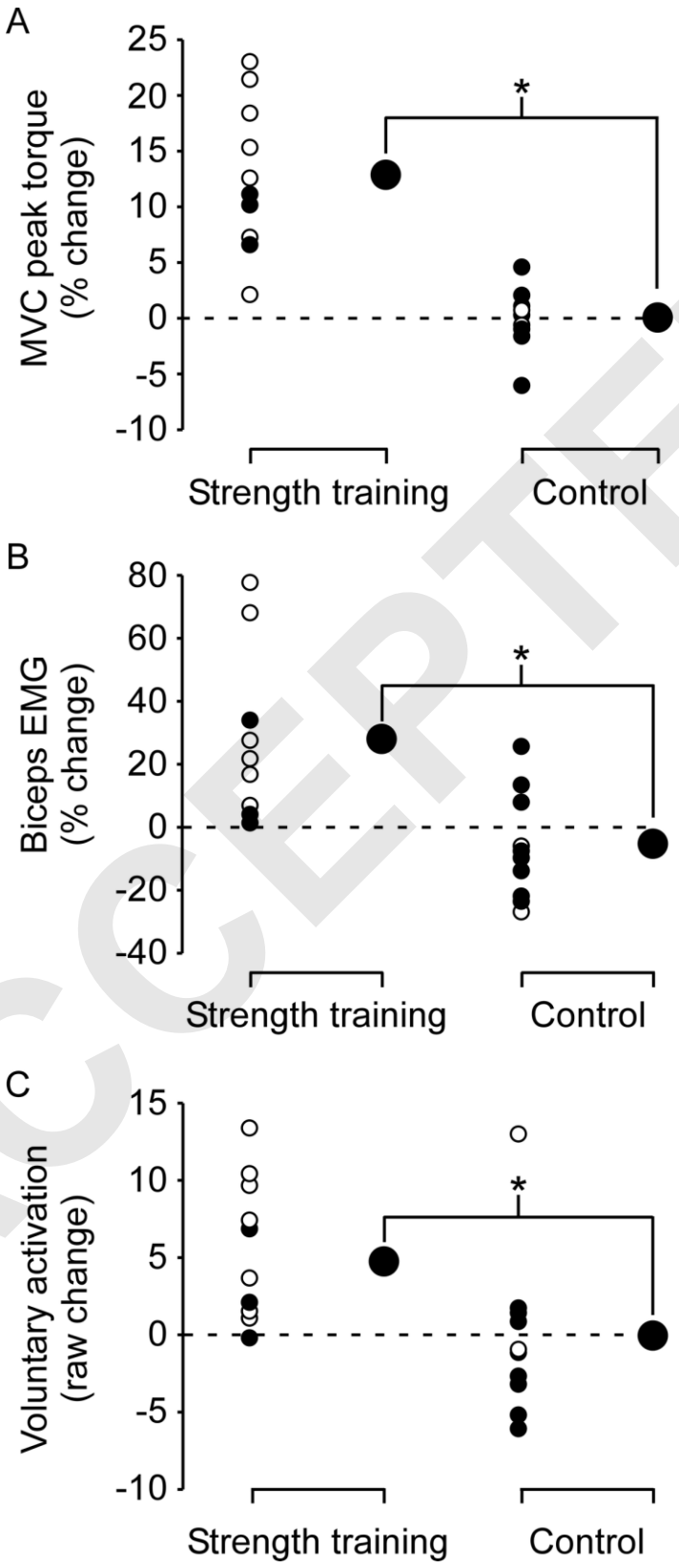

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Figure 3

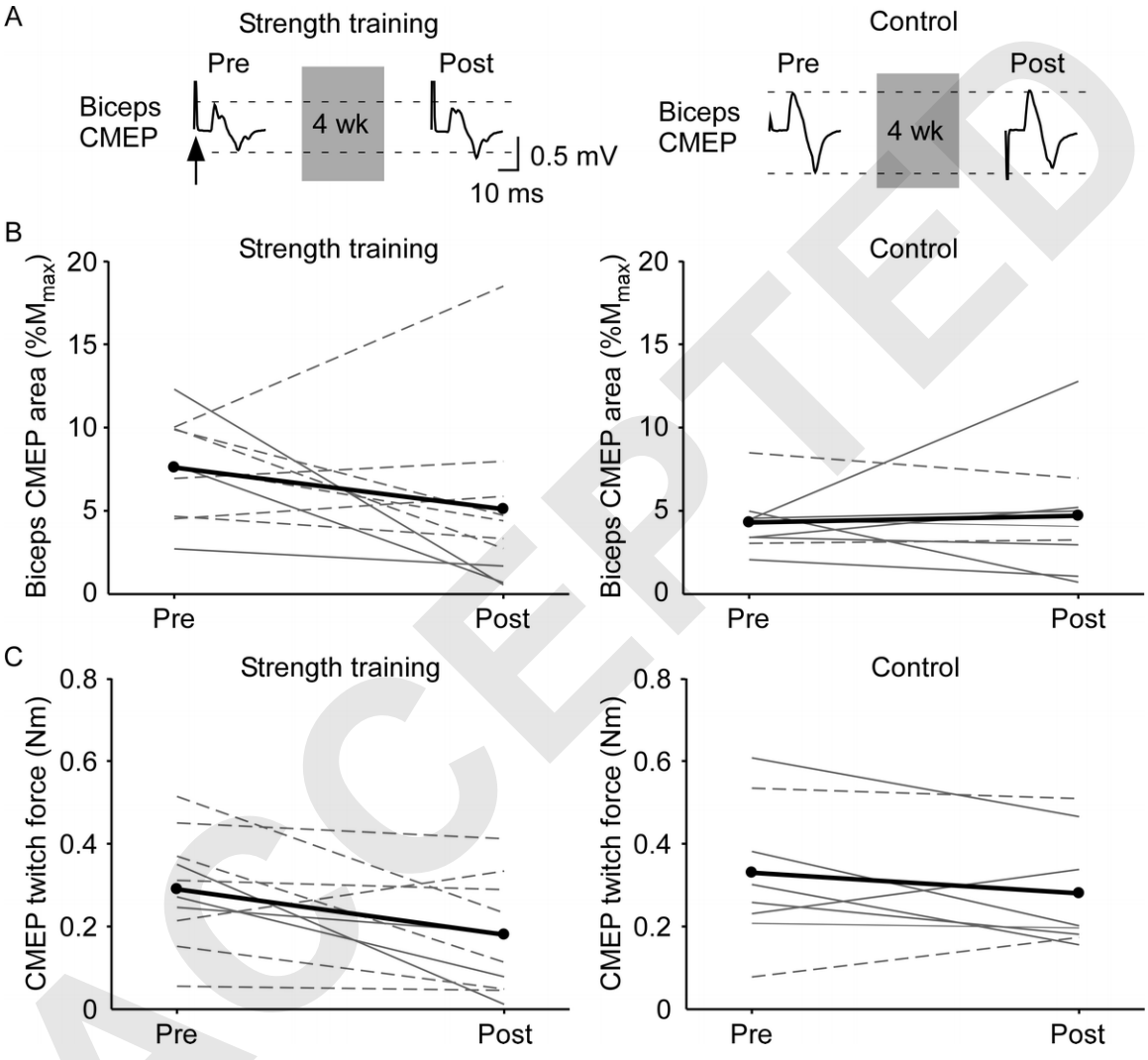

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Table 1. Measures acquired during maximal voluntary contractions of the elbow flexors with the shoulder flexed and forearm supinated.

	Strength training			Control		
Variable	Pre	Post	Change (%)	Pre	Post	Change (%)
Peak torque (Nm)	41.2 ± 17.0	46.2 ± 18.3	12.8 ± 6.8*	54.9 ± 15.0	54.9 ± 14.9	0.0 ± 2.7
Biceps (agonist) EMG (%Mmax)	10.8 ± 1.9	13.5 ± 2.5	27.8 ± 25.9*	8.5 ± 2.5	8.1 ± 2.9	-5.2 ± 16.8
Triceps (antagonist) EMG (%Mmax)	1.3 ± 0.5	1.5 ± 0.5	11.0 ± 41.1	0.6 ± 0.3	0.7 ± 0.3	17.4 ± 43.5
	Pre	Post	Change (raw)	Pre	Post	Change (raw)
Voluntary activation (%)	88.7 ± 6.3	93.4 ± 3.5	4.7 ± 3.9*	89.2 ± 7.1	89.1 ± 3.8	-0.1 ± 5.1

EMG = electromyography. Values are mean ± SD. *Statistically significant difference between the strength training and control groups (all $p \leq 0.034$).

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Table 2. Muscle twitch characteristics with the shoulder flexed and forearm supinated.

	Strength training			Control		
Variable	Pre	Post	Change (%)	Pre	Post	Change (%)
Biceps motor point stimulation						
Peak torque (Nm)	4.5 ± 1.9	4.7 ± 2.6	3.5 ± 25.9	5.8 ± 1.7	5.2 ± 1.8	-7.4 ± 32.8
Time to peak torque (ms)	66.0 ± 15.0	70.3 ± 11.7	8.9 ± 19.1	65.0 ± 12.2	64.0 ± 9.3	0.5 ± 18.1
Half-relaxation time (ms)	144.3 ± 28.4	149.6 ± 22.2	5.2 ± 12.3	130.0 ± 177.3	128.1 ± 17.8	-1.0 ± 10.9
Transcranial stimulation						
Estimated resting twitch torque (Nm)	7.5 ± 3.2	8.6 ± 3.4	19.0 ± 28.6	11.0 ± 3.9	11.1 ± 4.9	0.2 ± 20.0

Values are mean ± SD. No statistically significant differences existed for pre- to post-intervention change scores between the strength training and control groups for these variables.

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Table 3. Cervicomedullary motor evoked potentials (CMEP) and maximal compound muscle action potential (M_{max}) in resting biceps brachii.

	Strength training			Control		
Variable	Pre	Post	Change (raw)	Pre	Post	Change (raw)
Supinated						
Biceps CMEP area (%M_{max})	7.6 ± 3.0	5.1 ± 5.3	-2.6 ± 5.6	4.3 ± 1.8	4.7 ± 3.6	0.3 ± 3.4
Biceps CMEP twitch (Nm)	0.29 ± 0.14	0.18 ± 0.14	-0.12 ± 0.14	0.33 ± 0.18	0.28 ± 0.14	-0.05 ± 0.11
Pronated						
Biceps CMEP area (%M_{max})	5.7 ± 2.2	5.1 ± 5.8	-0.6 ± 6.2	3.0 ± 1.8	3.6 ± 2.5	0.5 ± 2.8
Biceps CMEP twitch (Nm)	0.28 ± 0.15	0.19 ± 0.13	-0.09 ± 0.18	0.32 ± 0.14	0.31 ± 0.12	-0.01 ± 0.12
Arm hanging to side						
Biceps CMEP area (%M_{max})	3.5 ± 1.6	2.6 ± 2.1	-0.9 ± 2.2	2.8 ± 3.0	2.0 ± 2.2	-0.7 ± 1.7
	Pre	Post	Change (%)	Pre	Post	Change (%)
Supinated						
Biceps M_{max} amplitude (mV)	13.6 ± 5.6	13.6 ± 6.3	0.0 ± 17.8	20.2 ± 7.0	20.8 ± 7.5	3.5 ± 14.2
Biceps M_{max} area (mV*s)	0.113 ± 0.047	0.112 ± 0.051	1.6 ± 27.8	0.168 ± 0.069	0.177 ± 0.069	7.3 ± 19.4
Pronated						
Biceps M_{max} amplitude (mV)	14.5 ± 6.1	14.0 ± 6.1	-0.4 ± 23.7	19.9 ± 6.5	20.5 ± 7.3	3.2 ± 13.1
Biceps M_{max} area (mV*s)	0.139 ± 0.061	0.134 ± 0.053	4.2 ± 35.5	0.184 ± 0.063	0.199 ± 0.067	8.7 ± 16.5
Arm hanging to side						
Biceps M_{max} amplitude (mV)	13.1 ± 5.2	13.2 ± 5.4	2.1 ± 16.6	16.5 ± 5.4	16.5 ± 6.0	-0.8 ± 11.0
Biceps M_{max} area (mV*s)	0.132 ± 0.053	0.132 ± 0.052	3.5 ± 23.0	0.165 ± 0.055	0.173 ± 0.063	4.3 ± 15.1

Values are mean ± SD. No statistically significant differences existed for pre- to post-intervention change scores between the strength training and control groups for these variables. CMEP twitch forces were not acquired with the arm hanging to the side, because the arm was not strapped to the force transducer.

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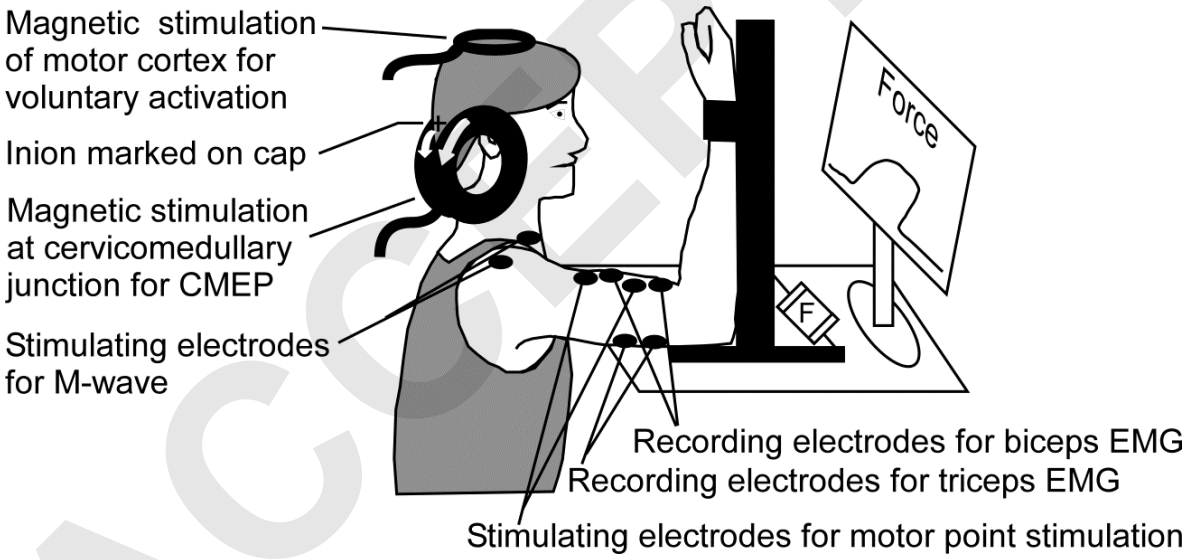
Supplementary digital content 1

Experimental setup. Depicted below is the study's primary arm posture (shoulder flexed, forearm supinated). This posture was used in the screening, assessment, and intervention sessions. Surface electrodes were placed over the right biceps and triceps brachii and captured maximal compound muscle action potentials from electrical stimulation of the brachial plexus at Erb's point, cervicomedullary motor evoked potentials (CMEPs) from magnetic stimulation at the cervicomedullary junction, and motor evoked potentials from transcranial magnetic stimulation over the motor cortex. Also, electrical stimulation over the biceps muscle belly (i.e., motor point stimulation) was used to evoke biceps twitches. Voluntary and evoked-twitch torques were measured with a force transducer (F).



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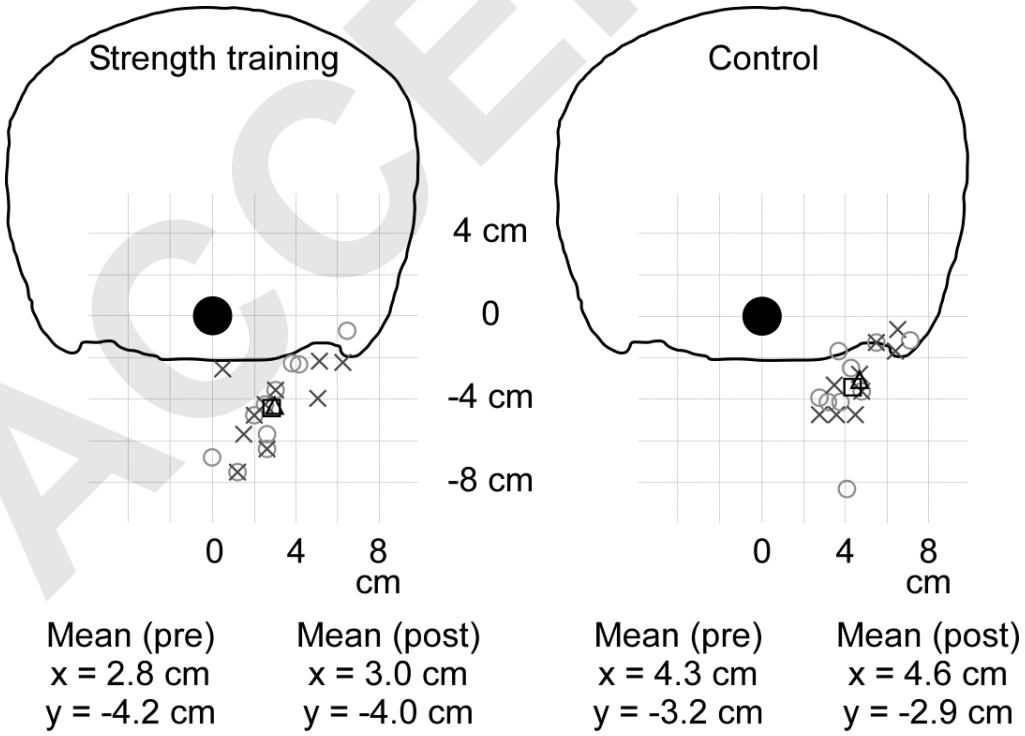
Supplementary digital content 2

Position of the double-cone magnetic coil. The change in position of the center of the double-cone magnetic coil (i.e., "hot spot") from the pre- to post-intervention assessments was analyzed. This involved placing each subject's swimcap on a model head and measuring the x and y coordinates from the inion to the hot spots marked on the cap. Means of the x and y coordinates were calculated for both the strength training and control groups. In the figure below, the large black circle is the inion, the open circles are the individual subjects during the pre-intervention assessments, and the "X" are the individual subjects during the post-intervention assessments. Typically, the hot spot was 2 – 5 cm lateral and 3 – 4 cm caudal to the inion. In both groups, the mean position of the coil changed little from the pre- (open square) to post-intervention (open triangle) assessment. No difference existed between the two groups for the change in the x (t = 0.511, p = 0.616) and y coordinates (t = 0.338, p = 0.739).



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Supplementary digital content 3

Data excluded from statistical analysis. Files were renamed shortly after collection. Thus, the investigators who made decisions on excluding individual data points were blind during the exclusion process. That is, the investigators were unaware of whether a given file was from a subject in the strength training group or control group, and whether the file was from a pre- or post-intervention assessment.

For one control subject, their entire CMEP data set was excluded due to an error in procedure (i.e., location of magnetic coil) noted immediately after an assessment. In addition, individual biceps CMEPs were excluded if the level of cervical root stimulation was ≥ 10% of the initial phase of the CMEP. A total of 141 CMEPs (of 1,760; 8%) were excluded for this reason. For one control subject, all 40 of their post-intervention CMEPs were excluded for this reason, and thus, their entire dataset of CMEPs was excluded from analysis. After these CMEPs were excluded, the total number of CMEPs in a given arm posture was calculated for each subject. For the primary arm posture (supinated), 10 of 20 CMEPs from a given assessment session needed to pass the above criterion in order to be averaged, and for the secondary arm postures (pronated and arm hanging), 3 of 10 CMEPs in each posture. The final sample sizes for biceps CMEPs in the strength training group were $n = 10$ for the supinated posture, $n = 10$ for pronated, and $n = 7$ for arm hanging. For the control group, the samples were $n = 9$ for all three arm postures. Also, in cases where peak-to-peak amplitude of an individual CMEP was not bigger than the amplitude of the biceps EMG signal in the 100 ms prior to stimulation (i.e., not bigger than noise), the size of the potential was considered zero and was included in analysis. A total of 33 CMEPs were zero.

Some voluntary activation trials were also excluded from statistical analysis. For one subject in the strength training group, data were excluded due to an error in procedure during the pre-intervention assessment. This was the subject in whom TMS output was 25% greater

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in the post-intervention assessment than in the pre-intervention assessment. For the remaining voluntary activation data, the following criteria were applied. First, data from maximal contractions were excluded if, during data collection, an investigator noted that the stimulus was delivered when the subject was at a submaximal torque. A total of 9 (of 200; 4.5%) maximal contractions were excluded for this reason. After these trials were excluded, the linear regression between voluntary torque and superimposed twitch torque was computed for each subject. If the correlation was < 0.90, which was the case for 2 of the 40 data sets, then the file was inspected further. In both cases, it was obvious that 1 or 2 outliers (of 15 points) were affecting the linearity of the regressions. As the purpose of the regression is to estimate the resting twitch, these individual data points were removed, to strengthen the relationship. A total of 3 contractions (of 600; 0.5%) were excluded for this reason, after which, correlations between voluntary torque and superimposed twitch torque became > 0.90 for all subjects.

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