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RESEARCH ARTICLE

Changes in spinal but not cortical excitability following combined electrical stimulation of the tibial nerve and voluntary plantar-flexion

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Abstract Unilateral training involving voluntary contractions, neuromuscular electrical stimulation (NMES), or a combination of the two can increase the excitability of neural circuits bilaterally within the CNS. Many rehabilitation programs are designed to promote such "neuroplasticity" to improve voluntary movement following CNS damage. While much is known about this type of activity-dependent plasticity for the muscles that dorsi-flex the ankle, similar information is not available for the plantar-flexors. Presently, we assessed the excitability of corticospinal (CS) and spinal circuits for both soleus (SOL) muscles before and after voluntary contractions of the right plantar-flexors (VOL; 5 s on–5 s off, 40 min), NMES of the right tibial nerve (tnNMES; 5 s on–5 s off, 40 min), or both together (V + tnNMES). CS excitability for the right (rSOL) and left SOL (lSOL) muscles was assessed by quantifying motor evoked potentials elicited by transcranial magnetic stimulation. Spinal excitability was assessed using measures from the ascending limb of the M-wave versus H-reflex recruitment curve. CS excitability did not change for rSOL (the activated muscle) or lSOL following any condition. In contrast, there was a marked increase in spinal excitability for rSOL, but only following V + tnNMES; the slope of the M-wave versus H-reflex recruitment curve increased approximately twofold (pre = 7.9; post = 16.2) and H-reflexes collected when the M-wave was ~5 % of the maximal M-wave (M_{max}) increased by ~1.5× (pre = 19 % M_{max}, post = 29 % M_{max}). Spinal excitability for lSOL did not change following any condition. Thus, only voluntary contractions that were coupled with NMES increased CNS excitability, and this occurred only in the ipsilateral spinal circuitry. These results are in marked contrast to previous studies showing NMES-induced changes in CS excitability for every other muscle studied and suggest that the mechanisms that regulate activity-dependent neuroplasticity are different for SOL than other muscles. Further, while rehabilitation strategies involving voluntary training and/or NMES of the plantar-flexors may be beneficial for producing movement and reducing atrophy, a single session of low-intensity NMES and voluntary training may not be effective for strengthening CS pathways to the SOL muscle.

Keywords Neuromuscular electrical stimulation · Motor cortex · H-reflex · Neuroplasticity · Human · Rehabilitation

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Introduction

Transmission across synapses and through neural circuits that control human movement changes throughout one's life in an activity-dependent manner, an effect known as "neuroplasticity." This neuroplasticity is driven by voluntary activation of the cortex in conjunction with feedback from sensory receptors activated by the movement (Pascual-Leone et al. 2005). In a similar way, the sensory

volley generated during neuromuscular electrical stimulation (NMES) can also induce activity-dependent plasticity in neural circuits. Such neuroplasticity generally manifests as an increase in the excitability of corticospinal (CS) circuits which, over time, strengthens the connectivity of the CS pathways. This strengthening of CS pathways is associated with improved motor learning (McDonnell and Ridding 2006), as well as improved motor function following stroke (Powell et al. 1999; Conforto et al. 2002), spinal cord injury (Hoffman and Field-Fote 2007), and other CNS damage (Everaert et al. 2010). Thus, promoting activity-dependent neuroplasticity has become a goal of many rehabilitation programs designed to help individuals relearn motor skills following CNS damage (Kleim 2011).

Plasticity in CS circuits induced by voluntary contractions or NMES has been demonstrated for almost every muscle tested thus far. CS excitability increases after voluntary contractions of muscles of the fingers and hand (Pascual-Leone et al. 1995) Caramia et al. 2000, Muellbacher et al. 2001), thumb (Rogasch et al. 2009), wrist extensors (Hauptmann et al. 1997), elbow flexors (Ziemann et al. 2001), and ankle flexors (Perez et al. 2004; Khaslavskaia and Sinkjaer 2005). Likewise, after a session of NMES, CS excitability increases for muscles associated with swallowing (Hamdy et al. 1998) and for muscles of the hand (Ridding et al. 2000; Charlton et al. 2003; Beekhuizen and Field-Fote 2005; Barsi et al. 2008) and leg (Khaslavskaia et al. 2002; Knash et al. 2003; Kido-Thompson and Stein 2004). Most of the evidence indicates that this plasticity is limited to cortical circuits (Ridding et al. 2000; Stefan et al. 2000; Charlton et al. 2003); however, for the muscles of the ankle, Khaslavskaia et al. (2002) reported increases in both cortical and spinal excitability when NMES was applied over the dorsi-flexors, and Kitago et al. (2004) found an increase in spinal excitability when NMES was applied over the plantar-flexors. Kitago et al. (2004) also tested CS excitability for the plantar-flexors and showed that after NMES, motor evoked potentials (MEPS) were 133 % of those evoked before the stimulation; however, these experiments were performed on only 3 participants and *t* tests identified no significant effect of the NMES on CS excitability. We suggest that these CS excitability experiments of Kitago et al. (2004) were markedly underpowered with inconclusive results; thus, whether NMES alters CS excitability for the ankle plantar-flexors remains to be determined. The goal of the present experiments was to provide a comprehensive evaluation of activity-dependent changes in CNS excitability for SOL by assessing CNS excitability on both the left and right legs, before and after a period of repetitive voluntary contractions, NMES, or a combination of the two.

While both voluntary training and NMES alone can increase CS excitability, their combination increases CS excitability even further for the ankle dorsi-flexors (Thompson and Stein 2004; Khaslavskaia and Sinkjaer 2005) and finger flexors/extensors (Barsi et al. 2008). Interestingly, for the upper limb, voluntary training and/or NMES interventions do not alter only the circuitry of the activated muscle, but changes also occur in circuits controlling homologous muscles on the contralateral side of the body. Studies utilizing imaging techniques (Kristeva et al. 1991), electroencephalography (Cramer et al. 1999), and transcranial magnetic stimulation (TMS; Stedman et al. 1998; Muellbacher et al. 2000) indicate that both left and right motor cortices are simultaneously activated during unilateral muscle activity. Accordingly, 5-s wrist flexion contractions generated voluntarily and/or by NMES altered the excitability of spinal and supraspinal circuits controlling the ipsilateral and contralateral limbs (Hortobagyi et al. 2003). Such changes in neural circuits are thought to underlie the strength gains that occur in the uninvolved limb following unilateral training (Hortobagyi et al. 2003; Hortobagyi 2005; Lee et al. 2010). A 5-week training program involving unilateral voluntary plantar-flexion of the ankle enhanced the strength of the ipsilateral and contralateral plantar-flexors; however, spinal excitability increased only for the ipsilateral plantar-flexors and cortical excitability was not evaluated (Lagerquist et al. 2006a).

Activity-dependent plasticity is well documented for the muscles that dorsi-flex the ankle; however, much less information is available for the plantar-flexors. The dorsi-flexors are commonly stimulated to assist in toe clearance during the swing phase of gait for people with "foot-drop" resulting from a stroke or incomplete spinal cord injury (Liberson et al. 1961; Thompson and Stein 2004; Sabut et al. 2010a, b; Thompson et al. 2011). Although NMES is not as commonly applied to the plantar-flexors during rehabilitation programs, NMES has been used to activate these muscles to increase step clearance (Bajd et al. 1997) and the plantar-flexors are important postural muscles that contribute considerably to balance and propulsion during gait (Winter 1983, Neptune et al. 2001). Thus, there is increasing interest in including these muscles in future NMES programs (Bajd et al. 1999; Nadeau et al. 1999; Kesar et al. 2009). The present study is the first designed to investigate the influence of voluntary plantar-flexion contractions and/or NMES of the tibial nerve on one side of the body on the excitability of CS and spinal circuits bilaterally. The contractions were intermittent (5 s on–5 s off for 40 min) and were designed to represent a protocol that could be used in a rehabilitation program. Given that NMES (Khaslavskaia et al. 2002; Kitago et al. 2004) or voluntary contractions (Lagerquist et al. 2006a) increase spinal excitability for the ankle dorsi-flexors and plantar-

flexors, respectively, we predicted that they would increase spinal excitability when delivered separately or together in the present study. Similarly, since voluntary training and NMES increase CS excitability when applied separately, and have an additive effect when applied together for other muscles (Khaslavskaia and Sinkjaer 2005; Barsi et al. 2008), we predicted that the same would be true for the plantar-flexors. Specifically, we hypothesized that spinal and CS excitability for the right soleus muscle (rSOL) would be enhanced following voluntary contractions of the right plantar-flexors (VOL) and NMES of the right tibial nerve (tnNMES) alone, and would be enhanced to an even greater extent by the combination of the two (V + tnNMES). CS excitability and spinal excitability were also evaluated for circuits controlling the contralateral SOL muscle (lSOL) before and after each condition to determine whether acute crossed effects on CNS excitability were evoked by any of the conditions, as occurs for muscles of the arms (Hortobagyi et al. 2003; Lee et al. 2010). The results of these experiments provide novel information about activity-dependent plasticity in circuits that control the SOL muscles and have implications for the development of rehabilitation protocols for these muscles.

Materials and methods

Ten persons with no known neuromuscular disorder (22–44 years old; 7 males) participated with written informed consent. This study was approved by the Health Research Ethics Board at the University of Alberta.

Experimental procedure

All subjects were right foot dominant as determined by asking subjects which leg they preferred to use to kick a soccer ball. Subjects were seated in the chair of a Biodex System 3 Dynamometer (Biodex Medical Systems, Shirley, NY, USA) with the hip, knee, and ankle at 90°, 120°, and 90°, respectively. The ankle and foot were tightly secured to the footplate of the Biodex to measure isometric plantar-flexion torque. Subjects were asked to abstain from caffeine consumption for 12 h prior to and for the duration of each experimental session to eliminate the possible effects of caffeine on CNS excitability (Walton et al. 2003). Each subject participated in 4 experimental sessions (~3–4 h per session). Data were collected before and after one of the following four conditions in each session. In three of the four sessions, contractions were intermittent (5 s on, 5 s off) for 40 min. The four conditions were as follows: (1) voluntary isometric contractions (~20 % MVC) of the right plantar-flexors (VOL); (2) NMES (1-ms pulse widths, 100 Hz) of the right tibial nerve (tnNMES); (3) VOL in conjunction with tnNMES (V + tnNMES); and (4) a control condition (CON) involving no contraction and no stimulation. The intensity of tnNMES was set to generate approximately 2–3 % of each subject's maximal, voluntary, isometric plantar-flexion torque (MVC). If necessary, stimulation intensity was adjusted in order to stay within this range. Thus, the net torque produced during V + tnNMES trials was ~22–23 % MVC. To ensure that tnNMES elicited contractions of 2–3 % MVC during V + tnNMES trials, subjects were asked to remain relaxed and not generate any volitional torque for 1–2 cycles of stimulation every 5 min. Subjects were provided with feedback via a monitor that displayed their plantar-flexion torque. All experimental sessions were separated by a minimum of three days and were collected at the same time of day for each subject to account for diurnal variations in CNS excitability (Lagerquist et al. 2006b; Tamm et al. 2009). The order of data collection trials during an experimental session was randomized on the first day of testing for every subject and kept constant for each individual during subsequent experimental sessions. An example of the order of trials for one subject is illustrated in Fig. 1. MVCs of the right and left plantar-flexors were always performed first because those data were used to set the target electromyography (EMG) levels for background contractions during subsequent TMS and H-reflex testing. The time at which CS excitability and spinal excitability were assessed after each 40-min condition varied between subjects but was the same for a given subject across the four conditions. SOL MEPs were collected for both legs using TMS applied over the right and left motor cortices to assess CS excitability. SOL H-reflexes were collected for both legs using electrical stimulation over the right and left tibial nerves at the popliteal fossa to assess spinal excitability.

Electromyography

Surface EMG was recorded from the rSOL and lSOL muscles using bipolar (2.25 cm^2) recording electrodes (Vermed Medical, Bellows Falls, Vermont). EMG signals were pre-amplified (500–2,000×) and band-pass filtered at 30–3,000 Hz (NeuroLog system; Digitimer, Welwyn Garden City, Hertfordshire, England). All data were sampled at 2,000 Hz using a 12-bit A/D converter (National Instruments, Austin, TX, USA).

Peripheral nerve stimulation

The right tibial nerve was stimulated using bipolar (2.25 cm^2) surface electrodes (Vermed Medical Inc.) placed over the popliteal fossa at the site that evoked a response (M-wave or H-reflex) at the lowest stimulation intensity. Rectangular pulses of 1 ms were delivered from a Digitimer (DS7A)

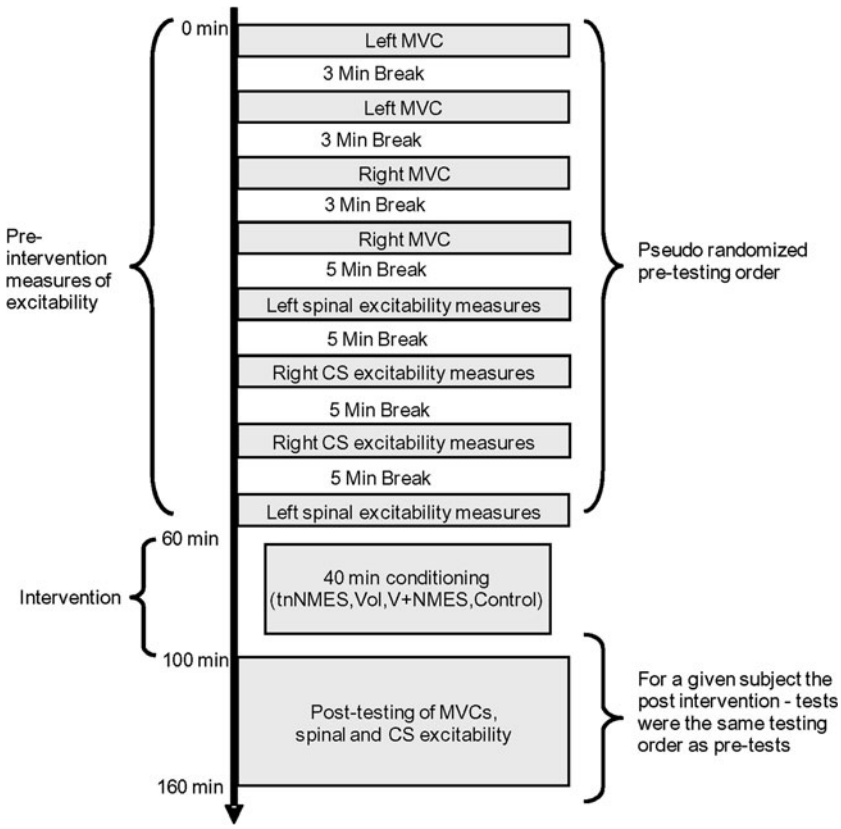

Fig. 1 Example of randomized testing order for one subject. MVC is maximum voluntary isometric contraction, and TMS/MEP is transcranial magnetic stimulation used for collecting motor evoked potentials. MVC trials were always pseudo-randomized first since subjects were required to hold a 5 % of maximum SOL EMG background contraction during H-reflex and TMS testing. The identical testing order was used before and after each 40-min condition

constant current stimulator. Stimulation current was measured using a current probe (mA-2000 Non-contact Milliammeter, Bell Technologies) to confirm that M-wave amplitudes plateaued with increasing levels of stimulation.

Maximum voluntary isometric contractions

Subjects performed between 2 and 5 MVCs of the right and left plantar-flexors at the beginning of each testing session and upon completion of each 40-min condition. Subjects performed MVCs until consistent maximal contractions were achieved (less than 5 % variability on two successive trials). Each MVC lasted approximately 3 s and was separated from the previous maximal effort by at least 3 min. Subjects were provided with visual feedback of their torque production and received verbal encouragement to perform maximally. MVC torque and the root mean square of the SOL EMG were calculated over a 500-ms interval centered around the region of maximal torque produced during each MVC.

Measures of CS excitability

MEPs were elicited using a magnetic stimulator (Magpro R30; Medtronic Inc., Minneapolis, Minnesota) with a figure-of-eight coil (Medtronic MC-B70, Minneapolis, Minnesota). The position and orientation of the coil was adjusted over the left and right motor cortices to find the two locations at which clear rSOL and lSOL MEPs were generated at the lowest stimulus intensity, respectively. The coil position and orientation was guided and recorded using a magnetic resonance imaging–guided TMS system (Brainsight; Rogue Research, Montreal, QC, Canada). The same stimulation site for each subject was stimulated during all experimental sessions, and we placed the TMS coil to within 3 mm of its optimal position for each of the four conditions. To maintain similar levels of motoneuron excitability during TMS trials, subjects held a background contraction of 5 % maximal SOL EMG output using visual feedback of SOL EMG low-pass filtered at 3 Hz. SOL EMG output was standardized for each of the four sessions for every participant. Two measures of CS excitability were evaluated: (1) TMS intensity at active MEP threshold (AMT) for SOL and (2) SOL MEP amplitude at 1.2 × AMT. AMT was determined by manually adjusting stimulator output in 1 % intervals of TMS output to find the lowest intensity at which clearly discernible MEP responses (>50 μV) were evoked in at least four out of eight responses. The average time after each condition that data were collected for this measure of CS excitability was 43 ± 17 min (mean ± SD; range 13–80) for the right leg

and 53 ± 14 min (range 22–78) for the left leg (averaged across the four conditions and all subjects).

Measures of spinal excitability

M versus H (M/H) SOL recruitment curves were constructed from responses to 60 stimuli delivered to the tibial nerve at the popliteal fossa. The stimulation was delivered randomly every 3–5 s at intensities ranging from below M-wave and H-reflex threshold to 2–3 times the minimum current required to evoke M_{max}. Subjects held a background SOL contraction as described above for the TMS trials when collecting M/H recruitment curves. Three measures of spinal excitability were evaluated.

1. *H-reflex recruitmentt gain*. A linear regression using the least sum of squares method was fitted to the middle portion of the ascending limb of the M/H recruitment curve when H-reflexes were 25–75 % of the maximal H-reflex (H_{max}). The slope of this regression was used as an indication of H-reflex recruitment gain (Lagerquist et al. 2006b).
2. *H-reflex recruitment relative to M-wave recruitment.* The size of the H-reflex on the ascending limb of the M/H recruitment curve (H_A) was calculated using responses evoked with an M-wave of approximately 5 ± 2 percent of M_{max}. Between 9 to 18 H-reflexes fell within this range for a given subject and were included in the average. This method allows the facilitation or inhibition of the H-reflex to be measured while using the M-wave as a measure of stimulus consistency.
3. *H_{max}:M_{max} ratio.* The H_{max}:M_{max} ratio was calculated using the average of the three largest H-reflexes (H_{max}) and the single largest M-wave (M_{max}) from each M/H recruitment curve.

Statistics

All data were tested for normality using the Kolmogorov–Smirnov–Lilliefors test. To test for significant effects of Time or Condition, separate 2 × 4 repeated-measures ANOVA tests were used to analyze 5 of our 6 dependent variables (MVC, MEPs at 1.2 × AMT; H_{max}:M_{max} ratio, M/H recruitment curve slope, and H_A values). Similar ANOVAs were used to test for significant differences in the background SOL EMG during MEP and H-reflex acquisition and for torque and EMG recorded during the MVICs over time and between the four conditions. These variables were evaluated using 2 levels of "Time" (before and after each 40-min condition) and 4 levels of "Condition" (tnNMES, VOL, V + tnNMES, and CON). In the event of a significant main effect or interaction, post hoc analysis was performed using the Tukey honestly significant differences test. There were, however, no significant main effects of Time or Condition for any variable; thus, only results from interactions are described in detail in the results section. Friedman tests were used to evaluate the AMT data because it was not normally distributed. All data are presented as means ± standard errors. The alpha level for all tests was set at $p < 0.05$.

Results

There was no change in AMT or MEP amplitude at 1.2 × AMT for rSOL or lSOL following any of the conditions. In contrast, the slope of the M/H recruitment curve increased approximately twofold and H-reflexes collected when the M-wave was ~5 % of M_{max} (H_A) increased by ~1.5-fold for rSOL following V + tnNMES only. There were no changes in spinal measures of excitability for lSOL following any condition.

SOL M_{max} did not change during our experiments. M_{max} data showed no Time × Condition interaction for rSOL [$F_{(3,27)} = 1.4$; $p = 0.3$] or lSOL [$F_{(3,27)} = 0.4$; $p = 0.7$]. Averaged M_{max} values for rSOL were 8.5 ± 4.1 and 8.1 ± 3.8 mV before and after all four conditions, respectively. Equivalent values for lSOL were 8.3 ± 4.9 and 8.9 ± 5.4 mV, respectively.

Plantar-flexor MVCs

The amount of torque generated during plantar-flexion MVCs was unaffected by any of the four conditions in the present study. There was no significant Time × Condition interaction (right leg: [$F_{(3,27)} = 0.41$; $p = 0.75$]; left leg: [$F_{(3,27)} = 1.1$; $p = 0.4$]) for MVC torque. For the group, MVC torque averaged across the four conditions and both legs was 275 ± 114 Nm at the beginning of the experiment and was 279 ± 116 Nm after the intervention. Similarly, there was no significant Time × Condition interaction (right leg: [$F_{(3,27)} = 0.29$; $p = 0.83$]; left leg: [$F_{(3,27)} = 0.40$; $p = 0.75$]) for EMG recorded during the MVCs. For the group, the EMG recorded during the MVCs averaged across the four conditions and both legs was 314 ± 163 μV at the beginning of the experiment and was 304 ± 167 μV after the intervention.

Background EMG

The magnitude of the EMG activity generated during the voluntary contractions that subjects held during MEP and H-reflex acquisition was not different between conditions or across time. There was no Time × Condition interaction for rSOL or lSOL background EMG during MEP (rSOL: [$F_{(3,27)} = 1.2$; $p = 0.3$]; lSOL: [$F_{(3,27)} = 1.1$; $p = 0.4$]) or

H-reflex acquisition (rSOL: [$F_{(3,27)} = 1.6$; $p = 0.2$]; lSOL: [$F_{(3,27)} = 0.6$; $p = 0.6$]). During collection of the MEPs, the EMG values measured before and after all conditions were 5.1 ± 0.9 and 4.9 ± 0.8 % maximal EMG for rSOL, respectively, and 4.9 ± 0.8 and 4.8 ± 0.6 % for lSOL, respectively. Equivalent values obtained during H-reflex acquisition were 5.0 ± 0.8 and 5.1 ± 0.7 % maximal EMG for rSOL and 4.8 ± 0.8 and 4.8 ± 0.7 % for lSOL.

CS excitability

There were no changes in the excitability of CS circuits following any of the four conditions in the present study. The 2 two-way repeated-measures ANOVAs and 2 Friedman tests used to analyze the SOL MEP data showed that all interaction effects had *p*-values equal to or greater than 0.2. Averaged across participants, AMT before and after all conditions was 61 ± 12 and 60 ± 11 % for rSOL and 60 ± 11 and 60 ± 12 % for lSOL, expressed as a percentage of maximal TMS output. The amplitude of MEPs evoked at 1.2 × AMT for rSOL and lSOL did not change following any condition and is shown in Fig. 2.

Spinal excitability

Spinal excitability for rSOL changed following the V + tnNMES condition only. M/H recruitment curves recorded from a single subject before and after 40 min of V + tnNMES are shown in Fig. 3. Panel A shows the entire range of the recruitment curve (from 0 to 100 % M_{max}), and panel B shows the portion between 1 % and 8 % M-wave on an expanded scale. The slope of the ascending limb of the recruitment curve (when H-reflexes were between 25 and 75 % H_{max}) was ~3× greater after V + tnNMES compared to before (pre = 13; post = 40), and H_A values (H-reflex amplitude when the M-wave was ~5 % M_{max}) increased 1.6× (from 50 % to 80 % M_{max}; panel C). The H_{max}:M_{max} ratio for this subject was ~80 % M_{max} before and after the V + tnNMES condition.

Analysis of the slopes from the rSOL M/H recruitment curves across the group showed a significant Time × Condition interaction [$F_{(3,27)} = 3.5$; $p = 0.03$]. Post hoc analysis revealed that only the V + tnNMES condition resulted in a significant slope increase for rSOL (approximately twofold increase; $p = 0.03$, see Fig. 4a) from 7.9 ± 0.6 before to 16.2 ± 1.8 after the V + tnNMES.

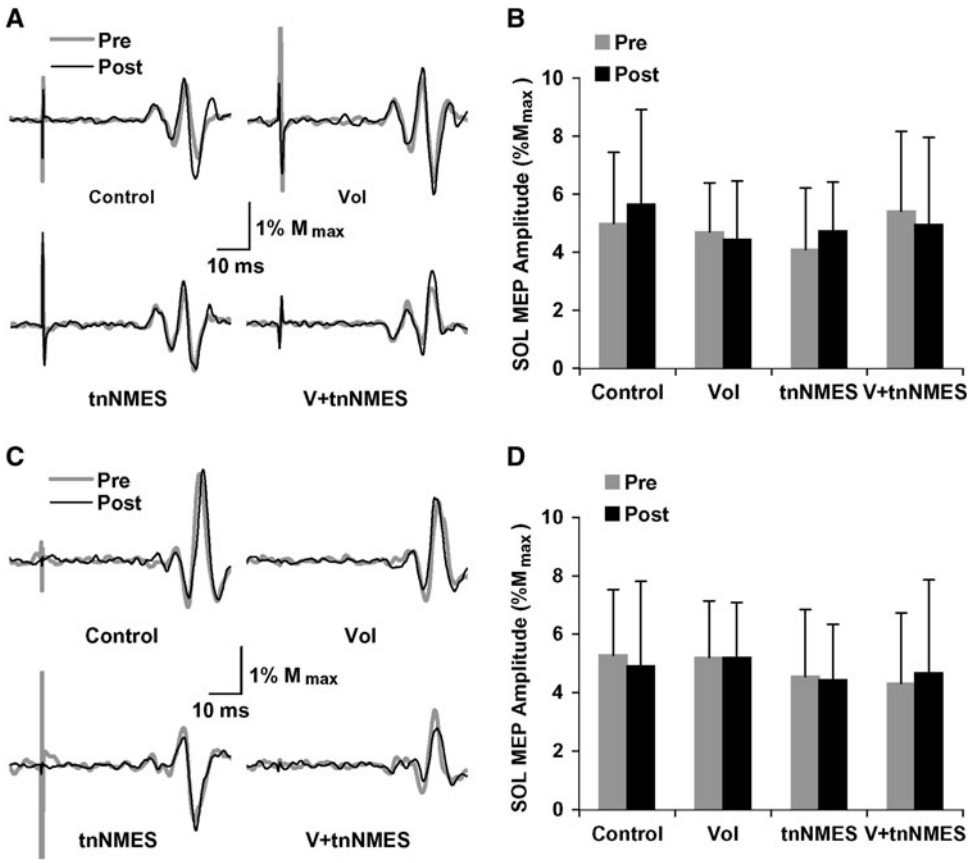

Fig. 2 Individual (**a**, **c**) and group SOL MEP data (**b**, **d**) recorded from the *right* (**a**, **b**) and *left* leg (**c**, **d**). Data collected before and after conditioning trials are shown in *gray* and *black*, respectively. Values have been normalized to each person's respective SOL M_{max}. *Error bars* represent one standard error

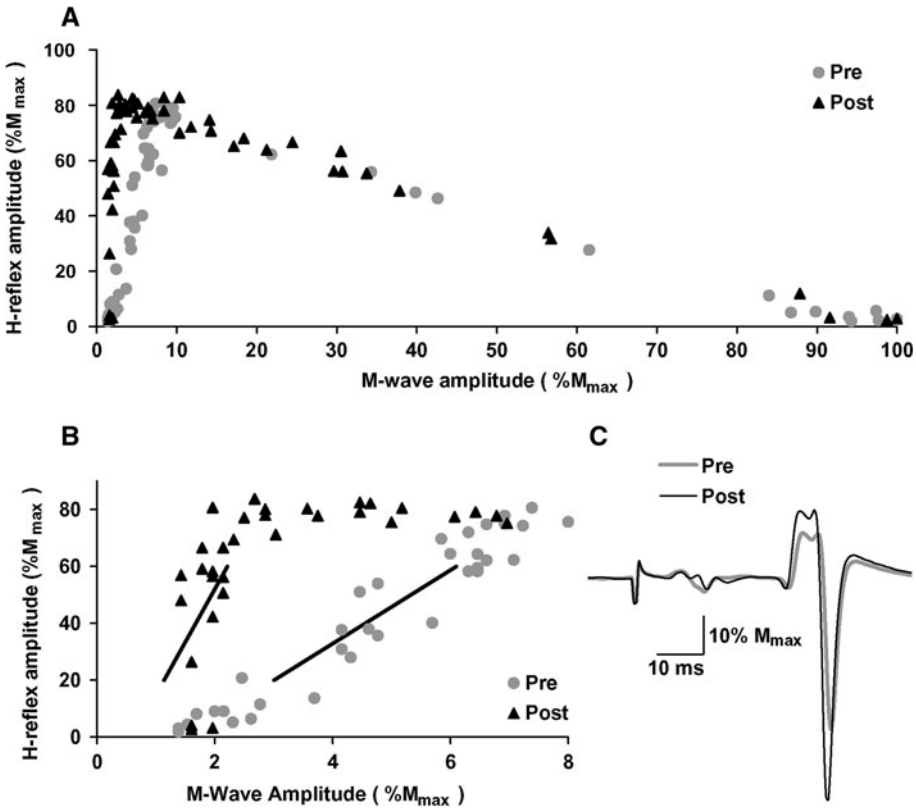

Fig. 3 H versus M SOL recruitment curves collected from a single subject before (*gray*) and after (*black*) 40 min of tibial nerve stimulation and concurrent isometric voluntary activation of the plantar-flexors. **a** Data collected over the full range of stimulus intensities. **b** Data selected from the ascending limb of the same recruitment curves shown in **a** when the H-reflex was between 1 and 8 % M_{max}. The linear regressions of pre- and post-data are indicated by *gray* and *black lines*, respectively in **b**. **c** The mean M-wave and H-reflex wave forms for a single subject when the M-wave was ~5 % M_{max}

There was no significant Time × Condition interaction for the slope of the recruitment curve collected from lSOL [$F_{(3,27)} = 0.5$; $p = 0.7$].

There was a significant increase in the size of the rSOL H-reflex when the M-wave was ~5 % M_{max} (H_A) after the V + tnNMES condition only (see Fig. 5a). H_A data from rSOL showed a significant Time × Condition interaction [$F_{(3,27)} = 6.1$; $p = 0.02$]. Post hoc analysis revealed that only the V + tnNMES condition resulted in a significant increase in ~1.5-fold in H_A ($p = 0.02$) for rSOL from 19 % M_{max} before to 29 % M_{max} after V + tnNMES. There was no change in H_A for lSOL after any condition (Time × Condition interaction: [$F_{(3,27)} = 0.6$; $p = 0.7$]).

H_{max}:M_{max} ratios from rSOL and lSOL were unaffected by any of the four conditions. There was no Time × Condition interaction for rSOL [$F_{(3,27)} = 1.3$; $p = 0.3$] or lSOL [$F_{(3,27)} = 1.2$; $p = 0.3$]. When group values were averaged, H_{max}:M_{max} ratios before and after all four conditions were 51 ± 19 and 50 ± 17 for rSOL, respectively, and 55 ± 21 and 53 ± 20 for lSOL, respectively.

Discussion

The present experiments were designed to determine whether a single 40-min session of VOL, tnNMES, or V + tnNMES of the right plantar-flexors increased the excitability of CS or spinal circuits that control rSOL and lSOL. Two main findings are reported: (1) CS excitability was not affected by any of the conditions; (2) spinal excitability increased only on the stimulated side (rSOL) and only following the condition which paired voluntary contractions with electrical stimulation (V + tnNMES). These findings suggest that the mechanisms responsible for activity-dependent plasticity in the CNS are different for SOL compared to other muscle groups previously studied in this manner. This has implications for understanding activity-dependent plasticity in the CNS and for the development of rehabilitation strategies for the plantar-flexors following CNS injury.

Lack of change in CS excitability for rSOL

In previous studies, CS excitability increased for the active muscles following 12 min of intermittent index finger abduction (Lee et al. 2010) and 30 min of intermittent isometric dorsi-flexion of the ankle (Khaslavskaia and Sinkjaer 2005). Similar to repeated voluntary movement training, repeated muscle contractions evoked by a single session of NMES increased CS excitability for muscles of the throat (Hamdy et al. 1998), hand (Ridding et al. 2000; Charlton et al. 2003; Barsi et al. 2008), and leg (Khaslavskaia et al. 2002; Knash et al. 2003; Khaslavskaia and Sinkjaer 2005; Mang et al. 2010, 2011). Furthermore,

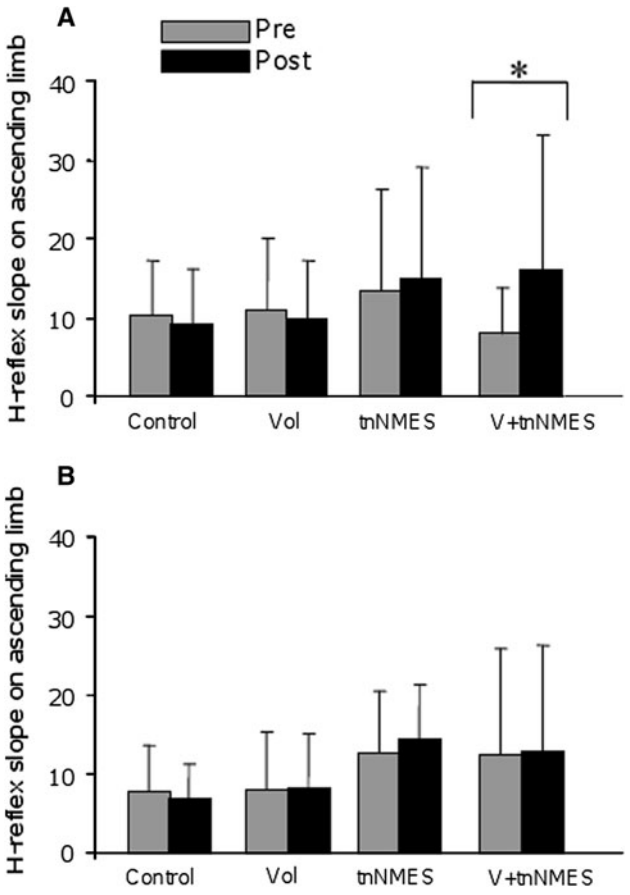

Fig. 4 Group SOL H-reflex slope data from the *right* (**a**) and *left* leg (**b**). Data collected before and after conditioning trials are shown in *gray* and *black*, respectively. Values have been normalized to each person's respective SOL M_{max}. *Asterisks* indicate significant differences ($p < 0.05$) between pre- and post-values. *Error bars* represent one standard error

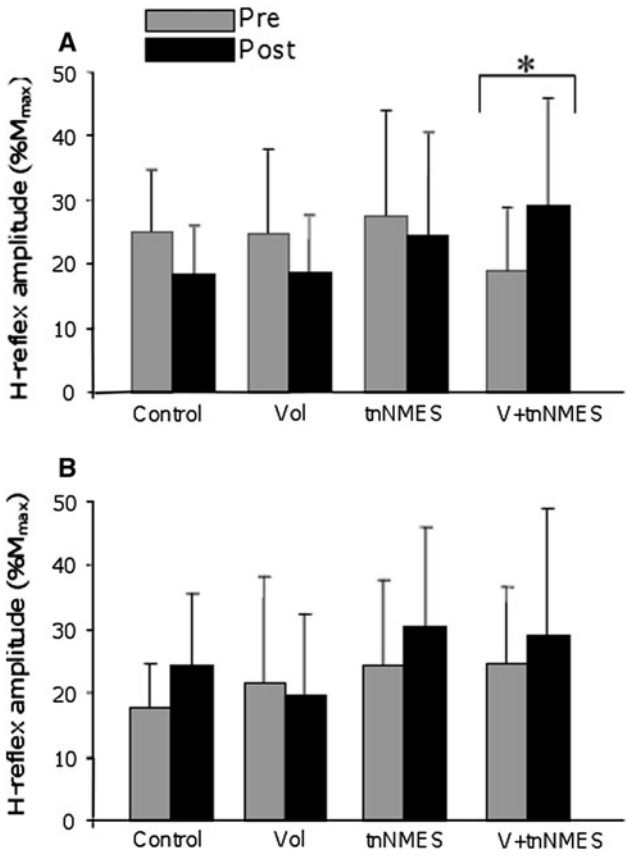

Fig. 5 Group SOL H_A data from the *right* (**a**) and *left* leg (**b**). Data collected before and after conditioning trials are shown in *gray* and *black*, respectively. Values have been normalized to each person's respective SOL M_{max}. *Asterisks* indicate significant differences ($p < 0.05$) between pre- and post-values. *Error bars* represent one standard error

combining voluntary contractions with NMES to activate the finger flexors/extensors (Barsi et al. 2008) and TA (Kido-Thompson and Stein 2004; Khaslavskaia and Sinkjaer 2005) enhanced CS excitability more than voluntary contractions or NMES alone. Contrary to our hypotheses, none of the conditions in the present study (VOL, NMES, or V + tnNMES) increased the excitability of CS pathways controlling the active muscle, rSOL. Thus, not only did neither the VOL nor the tnNMES conditions increase CS excitability for SOL when applied separately, even their combination, which increases CS excitability more than either VOL or NMES alone for other muscles, did not increase CS excitability. These results, combined with the wealth of evidence showing activity-dependent changes in CS excitability for every other muscle tested thus far, suggest that mechanisms regulating activity-dependent CNS plasticity are different for SOL than other muscles.

The lack of an increase in CS excitability for SOL following voluntary contractions and tnNMES may reflect the fact that SOL is under less cortical control than other muscles studied previously. Compared to TA, SOL has relatively smaller MEPs in stationary subjects (Maertens de Noordhout et al. 1999; Bawa et al. 2002) and during walking (Capaday et al. 1999), and reflexes in TA have a stronger transcortical component than in SOL (Christensen et al. 2000). Further, voluntary isometric dorsi-flexion contractions of the ankle are associated with the activation of a significantly larger cortical area than similar plantar-flexion contractions (Trinastic et al. 2010). Interestingly, NMES of the common peroneal nerve, which innervates TA (the antagonist to the muscle presently studied), enhanced CS excitability for both TA and SOL (Kido-Thompson and Stein 2004; Mang et al. 2011). Taken together with the results of the present study, this suggests that afferent drive from a heteronymous nerve, but not the homonymous tibial nerve, enhances CS excitability for SOL. Multiple cortical regions are activated during

electrical stimulation of the common peroneal (Francis et al. 2009) and tibial nerves (Ferretti et al. 2004; Arienzo et al. 2006), and stimulation of both nerves activates the motor cortex at latencies consistent with direct pathways from the thalamus (Hauck et al. 2006). Thus, it is presently not clear why stimulation of the antagonist nerve (Kido-Thompson and Stein 2004; Mang et al. 2011), but not the homonymous nerve (present study), increases CS excitability for SOL, and these putative differences require confirmation by stimulating both nerves in the same group of participants.

Alternatively, the lack of a significant increase in CS excitability for SOL and the increased CS excitability for other muscles in similar studies might reflect differences in protocols between studies. However, the intensity, duration, and patterns used in the present study fall within the range of parameters that have previously enhanced CS excitability for other muscles. For example, other studies that have shown NMES-induced increases in CS excitability have used intensities ranging from below motor threshold (Hoffman and Field-Fote 2007) to 50 % M_{max} (Kido-Thompson and Stein 2004) and contraction patterns ranging from 500 ms on, 500 ms off (Ridding et al. 2000) to 20 s on, 20 s off (Mang et al. 2010, 2011). Moreover, the intensity of NMES (2–3 % MVC), level of contraction (20 % MVC), and duration of stimulation (40 min) in the present study are very similar to the parameters used by Khaslavskaia and Sinkjaer (2005) when they demonstrated that CP nerve stimulation delivered at twice motor threshold, combined with voluntary dorsi-flexion of 30 % MVC in a 1-s on, 2-s off pattern for 30-min enhanced CS excitability for TA. Thus, we believe that the lack of change in CS excitability for SOL in the present study is due to differences in neural circuits that control SOL compared to other muscles previously studied, rather than a difference in protocols between studies.

Change in spinal excitability for rSOL following V + tnNMES

Presently, spinal excitability increased when voluntary contractions were paired with NMES, but not when either condition was applied alone. This "combined" protocol has been shown previously to be the most effective for increasing CS excitability, and it is thought that the combination of voluntary drive and sensory feedback has an additive effect on CNS excitability (Khaslavskaia and Sinkjaer 2005; Barsi et al. 2008). While SOL may have relatively weak cortical control, it has uniquely strong spinal reflex connections, particularly from Ia afferents. Compared to TA, for which Ia connections to the TA motoneuron pool are relatively weak and H-reflexes are typically small and difficult to evaluate (Jusic et al. 1995; Brooke et al. 1997), H-reflexes in SOL are 50 % M_{max} on average, suggestive of relatively strong afferent projections to the SOL motoneuron pool (Taborikova and Sax 1968). Potentially, relatively stronger cortical connectivity (Capaday et al. 1999; Maertens de Noordhout et al. 1999; Bawa et al. 2002) and weaker spinal connectivity to the TA (Taborikova and Sax 1968) compared to SOL may account for the fact that common peroneal nerve stimulation increased CS excitability with no change in spinal excitability for TA (Knash et al. 2003; Mang et al. 2010), while we presently showed enhanced spinal, but not CS, excitability for rSOL following the V + tnNMES condition. Contrary to our findings, voluntary training alone enhanced SOL H-reflexes in the trained limb in a previous study (Lagerquist et al. 2006a), but this was after 5 weeks of training rather than after just 40 min as in the present study.

The enhanced H-reflexes for rSOL following V + tnNMES, with no change in MEPs, may provide a clue about the mechanism responsible for the increased spinal excitability. MEPs are influenced by the excitability of cortical neurons and the motoneuron pool (Rothwell et al. 1991). No change in MEP amplitude is strong evidence that excitability did not change at either location, at least for those neurons recruited by the stimulation. Had the excitability of the whole motor pool increased, the amplitude of both H-reflexes and MEPs would have been expected to increase accordingly. Hence, our data suggest that if the mechanism responsible for the increased H-reflexes was distributed evenly across the motor pool, its effect must be pre-synaptic to the SOL motor pool. Post-tetanic potentiation of neurotransmitter release (Hagbarth 1962) and reduced pre-synaptic inhibition (PSI) of afferent terminals are two potential candidates. However, it is important to note that while both CS (Bawa and Lemon 1993) and afferent (Henneman et al. 1965) inputs recruit motoneurons according to Hennemann's size principle, there is evidence from the upper limb for subtle differences in the population of motoneurons that are recruited by these different inputs (Morita et al. 1999). Thus, caution should be exercised when making mechanistic conclusions based on different responses in H-reflexes and MEPs (Nielsen et al. 1999). If, in the present study, markedly different motor units were recruited by the H-reflexes and MEPs, the mechanism responsible for the increased H-reflexes may have involved increased motoneuronal excitability rather than a pre-synaptic mechanism. Differentiating between a pre- and post-synaptic mechanism was not part of the present study, and additional experiments will be required to identify the mechanism responsible for the presently observed increased spinal excitability.

Lack of crossed effects

The cross-education response to chronic training is well documented to influence both the upper and lower body musculature. However, acute experiments examining more immediate crossed effects for CS excitability have been completed in the upper body, but not in the lower body. Chronic unilateral voluntary training increases the strength and motor performance of homologous muscles on the opposite side of the body for upper and lower limb muscles (for review, see Carroll et al. 2006). The mechanism underlying this phenomenon is not fully understood, but is likely neural, rather than muscular, in nature (Carroll et al. 2006). For example, CS excitability is enhanced for the homologous muscles of the contralateral limb during unilateral rhythmic movements (Carson et al. 2004) and following unilateral ballistic movements (Lee et al. 2010) of the upper limb. It has been shown that chronic unilateral strength training of the plantar-flexors does not affect spinal excitability for the contralateral limb (Lagerquist et al. 2006a; Dragert and Zehr 2011) and that chronic unilateral leg strengthening decreases corticospinal inhibition associated with both the trained and untrained leg (Latella et al. 2011). However, to our knowledge, acute crossed effects on CS excitability for leg muscles have not been investigated. Interestingly, contractions produced by NMES appear to induce greater cross-education effects than voluntary contractions. NMES-evoked contractions increased muscle strength by 40 % in the contralateral limb (Cabric and Appell 1987) compared to the 10–20 % increase usually observed with voluntary contractions (Enoka 1988). In the one study that investigated acute crossed effects of voluntary and electrically evoked contractions on the CNS, Hortobagyi et al. (2003) found that 5 s of voluntary wrist flexion enhanced MEPs and depressed H-reflexes in the contralateral wrist flexors for up to 1 min and that similar electrically evoked contractions facilitated both MEPs and H-reflexes. The combination of voluntary drive and NMES enhanced MEPs but depressed H-reflexes. These data suggest that in the arm, unilateral muscular contractions generated by voluntary drive, NMES, or both together, have acute crossed effects at both cortical and spinal levels.

Presently, we found no evidence of a crossed effect at a cortical or spinal level for SOL following 40 min of repeated unilateral muscle contractions generated voluntarily, electrically, or by a combination of both. However, there are key differences in the methodology of the present work and the study by Hortobagyi et al. (2003), which may explain the contrasting results of the two studies. We tested the SOL muscle in the leg, while Hortobagyi et al. (2003) tested the wrist flexors. We also tested for more enduring acute crossed effects (up to 1 h post) compared to measurements taken immediately ($\leq$1 min post) following muscular contractions (Hortobagyi et al. 2003). In addition, the contractions generated in the present study during VOL and V + tnNMES were approximately 20–23 % MVC compared to contractions of $\sim$75 % MVC (Hortobagyi et al. 2003). Furthermore, Hortobagyi et al. (2003) found that unlike high-intensity NMES (50 % MVC), NMES delivered at a low intensity to produce only a radiating paresthesia did not have crossed effects on H-reflexes or MEPs. Thus, NMES delivered at a higher intensity than the present study (2–3 % MVC) may have induced crossed effects. Also in contrast to our findings, unilateral tnNMES was recently reported to increase bilateral MEPs in both the upper and lower body (Hayashi et al. 2008). However, Hayashi et al. (2008) tested patients undergoing spinal surgery under anesthetic and delivered 5 s of tnNMES at the lateral malleolus. The present experiments used healthy, awake subjects and applied 40 min of intermittent tnNMES at the popliteal fossa.

Technical considerations

A limitation of the present study is that the relatively long time course of data collection after each intervention ($\sim$60 min) may have reduced our ability to detect changes in CS excitability. Specifically, the CS excitability measures were taken on average 43 min post-intervention for the right leg and 53 min post-intervention for the left leg. Previous work investigating the persistence of increased CS excitability following a single session of electrical stimulation alone or in combination with voluntary movement has demonstrated that increased CS excitability persists for at least 30 min and as long as 150 min (Fraser et al. 2002; Khaslavskaia et al. 2002; Charlton et al. 2003; Knash et al. 2003; Kido-Thompson and Stein 2004; Khaslavskaia and Sinkjaer 2005). Low-intensity NMES applied to activate muscles of the hand for 120 min enhanced CS excitability for 120 min following the stimulation (Charlton et al. 2003). Likewise, similar studies that used motor cortical mapping procedures to evaluate CS excitability, which typically require $\sim$60 min, detected significant increases in CS excitability for muscles of the hand (Ridding et al. 2000, 2001), and 30 min of CP nerve stimulation increased CS excitability for TA for $\sim$30–60 min following the NMES (Khaslavskaia et al. 2002; Khaslavskaia and Sinkjaer 2005; Knash et al. 2003; Kido-Thompson and Stein 2004). In addition, Fraser et al. (2002) found that just 10 min of pharyngeal nerve stimulation enhanced CS excitability of swallowing musculature for 150 min and that maximum enhancement of CS excitability did not occur until 60–90 min following the stimulation, suggesting that CS excitability increased over time following the stimulation before returning to baseline excitability levels.

Thus, while we cannot determine from our data whether CS excitability increased immediately after the interventions, our data do indicate that CS excitability is not increased after a single session of NMES in the same way as it is for other muscles that have been tested previously.

In the present study, MEPs were collected while subjects maintained a background voluntary contraction within a narrow range. Although past work suggested that CS plasticity cannot be measured during voluntary activity (Ridding and Rothwell 1995), more recent studies suggest that changes in CS excitability are still evident during voluntary activity (Khaslavskaia et al. 2002; Knash et al. 2003; Kido-Thompson and Stein 2004); thus, we do not believe that the background contraction negated our ability to measure changes in CS excitability. Finally, the number of subjects in the present study is comparable to similar experiments (Ridding et al. 2000; Charlton et al. 2003; Khaslavskaia and Sinkjaer 2005; Mang et al. 2010, 2011), and the NMES protocol used was similar to that used in previous experiments in our laboratory that resulted in enhanced CS excitability for leg muscles (Mang et al. 2010, 2011). Therefore, we believe that our results demonstrate a true difference in activity-dependent plasticity between the plantar-flexors and other muscle groups.

Conclusions

To our knowledge, this is the first study to demonstrate that a single session of voluntary effort in conjunction with NMES increases spinal excitability in the absence of cortical changes, suggesting that the mechanisms affecting CNS plasticity are different for SOL compared to other muscle groups that have been studied in this manner. We found no evidence of crossed effects on CNS excitability. These results suggest that while voluntary training and NMES of the plantar-flexors can be beneficial for producing movement and reducing atrophy, a single session may not be effective for strengthening CS pathways for the SOL muscle.

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