

**The Power of the Mind: The Cortex as a Critical Determinant of Muscle Strength/Weakness**

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**ABSTRACT**

We tested the hypothesis that the nervous system, and the cortex in particular, is a critical determinant of muscle strength/weakness and that a high level of corticospinal inhibition is an important neurophysiologic factor regulating force generation. A group of healthy individuals underwent 4-weeks of wrist-hand immobilization to induce weakness. Another group also underwent 4-weeks of immobilization, but they also performed mental imagery of strong muscle contractions five days/wk. Mental imagery has been shown to activate several cortical areas that are involved with actual motor behaviors—including premotor and M1 regions. A control group, who underwent no interventions, also participated in this study. Before, immediately after, and one-week following immobilization, we measured wrist flexor strength, VA, and the cortical silent period (SP; a measure that reflect corticospinal inhibition quantified *via* transcranial magnetic stimulation). Immobilization decreased strength  $45.1 \pm 5.0\%$ , impaired VA  $23.2 \pm 5.8\%$ , and prolonged the SP  $13.5 \pm 2.6\%$ . Mental imagery training, however, attenuated the loss of strength and VA by  $\sim 50\%$  ( $23.8 \pm 5.6\%$  and  $12.9 \pm 3.2\%$  reductions, respectively), and eliminated prolongation of the SP ( $4.8 \pm 2.8\%$  reduction). Significant associations were observed between the changes in muscle strength and VA ( $r=0.56$ ) and SP ( $r=-0.39$ ). These findings suggest neurological mechanisms, most likely at the cortical level, contribute significantly to disuse-induced weakness, and that regular activation of the cortical regions *via* imagery attenuates weakness and VA by maintaining normal levels of inhibition.

**Keywords:** Muscle, Strength, Weakness, Dynapenia, Immobilization, Imagery

## INTRODUCTION

Maximal voluntary force generation, or strength, is controlled by multiple factors. For instance, muscle anatomical and physiological factors are key determinants of strength, or lack thereof (i.e., weakness) (Manini et al., 2012; Mosca et al., 2013). The nervous system has long been suggested to also be a key determinant of strength/weakness (Moritani and deVries, 1979). Indeed, dramatic impairments in voluntary (neural) activation (VA) occur following experimentally-induced weakness (Kawakami et al., 2001; Clark et al., 2008b; Clark et al., 2010). VA reflects the nervous systems ability to fully activate muscle and is assessed by electrically stimulating a peripheral nerve during a maximal voluntary contraction and quantifying the ‘added force’ (Taylor, 2009). While findings of impaired VA indicate the nervous system is a key determinant of strength/weakness, it does not provide insight into the neuroanatomical or neurophysiological factors involved in strength/weakness.

Despite the tonic activity of corticomotoneuronal cells being shown to increase linearly with static force generation in primates more than three decades ago (Cheney and Fetz, 1980; Ashe, 1997), the role of the primary motor cortex (M1) and other high-order cortical regions—and in many instances the entire nervous system— is rarely recognized as being a significant factor in determining muscle strength. Conversely, muscle mass and other muscular mechanisms (e.g., processes involved in excitation-contraction coupling) have received considerably more scientific, as well as popular press, attention (Manini and Clark, 2011; Manini et al., 2012; Russ et al., 2012). For instance, M1 has more historically been considered critical for movement coordination and skill acquisition as opposed to maximal force generation of individual muscles (Jackson, 1873; Remple et al., 2001; Adkins et al., 2006). More recently data from humans has begun to accumulate suggesting that the cortex is a critical determinant of muscle strength. For instance, immobilization-induced weakness results in an increase in intracortical inhibition (Clark et al., 2010), resistance exercise-induced increases in

strength results in a decrease in intracortical inhibition (Weier et al., 2012), and mental imagery of strong muscle contractions increases strength (Ranganathan et al., 2004).

In the present experiment, we sought to test the hypothesis that the cortex is a critical determinant of muscle strength/weakness and VA, and that high levels of intracortical inhibition is an important neurophysiologic factor regulating strength/weakness. To test this hypothesis, healthy individuals underwent 4-weeks of wrist-hand immobilization to induce weakness. Another group of individuals also underwent 4-weeks of immobilization, but they concomitantly performed mental imagery of strong muscle contractions five days/wk. We chose to use a cast immobilization paradigm as it has been shown to dramatically reduce muscle strength and voluntary activation and induce a wide range of neuroplastic effects in the central nervous system (Zanette et al., 1997; Kaneko et al., 2003; Zanette et al., 2004; Crews and Kamen, 2006; Clark et al., 2008b; Lundbye-Jensen and Nielsen, 2008; Clark et al., 2010). Mental imagery has been shown to activate several cortical areas that are involved with actual motor behaviors— including premotor and M1 regions (Hetu et al., 2013). A control group, who underwent no interventions, also participated in this study. Before, immediately after, and one-week following immobilization, we measured changes in wrist flexor strength, VA, and the corticospinal silent period (SP; a measure of corticospinal inhibition quantified *via* transcranial magnetic stimulation (Kobayashi and Pascual-Leone, 2003; Reis et al., 2008)).

## **METHODS**

**Overview of the Study Design.** Twenty-nine healthy adults completed 4-wks of wrist-hand immobilization of the non-dominant limb, and 15 adults served as a control group. A subset of study participants in the immobilization group (n=14) were also assigned to perform mental imagery training five days/week. Descriptive statistics are provided in Table 1. The Ohio University IRB approved this study and subjects provided

written consent. Potential participants were excluded if they were taking *any* medications or supplements, had any major medical issues, or had any known neurological or musculoskeletal limitations of the upper limbs. The non-dominant arm was assessed for isometric muscle strength, VA, and SP duration during a 15% MVC at baseline, 4-weeks later (during which the immobilization groups were immobilized), and 5-weeks after baseline (1-week after cast removal and the restoration of normal activity for participants in the immobilization groups). Subjects abstained from alcohol (24 hours) and caffeine (4-hrs) prior to the sessions. Testing sessions were performed at the same time of day for each subject. Individuals involved in assessments were blinded to experimental group assignment. Subjects were not randomly assigned to treatment group per se, but rather were assigned based on whether they were willing to undergo the immobilization procedures as well as the investigators opinion on whether subjects would comply with the imagery training (e.g., feasibility of their schedule availability for permitting them to report to the facilities five days/week for imagery training).

***Cast Immobilization.*** Subjects in the immobilization groups were fitted with a rigid wrist-hand cast on the non-dominant forearm (Model 1101-1103, Orthomerica, Orlando, Florida) as previously described (Clark et al., 2008a; Clark et al., 2010). In brief, lightweight polyethylene casts were applied, which extend from just below the elbow past the fingers (eliminates wrist flexion/extension movements and finger usage). Casts were removed 3-4 times/week under supervision to wash the arm and inspect for complications. During the recovery period, subjects in the immobilization groups were instructed to return to their normal daily activities, but not begin rehabilitation or a strengthening protocol.

***Mental Imagery Training.*** Mental imagery training was performed 5x/week. For each session, subjects performed 52 imagined maximal contractions of the casted wrist flexor muscles in a quiet room. The duration of each imagined contraction was 5-secs,

154 followed by 5-secs of rest. Training was performed in four blocks of 13 imagined  
155 contractions each with 1-minute of rest between the blocks. During the imagery  
156 sessions, subjects were instructed to relax their arm muscles, and to maximally activate  
157 the brain, but not the muscles. The electromyogram (EMG) was recorded from the flexor  
158 carpi radialis (FCR) muscle to ensure that muscle activation did not occur and real time  
159 feedback was provided. Quantitative analyses of these EMG signals were not  
160 performed, as we did not visually observe any voluntary interference EMG activity  
161 beyond nominal levels that occasionally occurred during the first session. More  
162 specifically, an unblinded scientist supervised these sessions. The imagery script was  
163 digitized such that this person did not have to actually read the script. Rather, they were  
164 charged with monitoring the EMG recordings in real time on a computer monitor and to  
165 provide feedback to the subject if any interference EMG was subjectively noted (i.e.,  
166 activity is observable above baseline noise with the y-axis scale such that very small  
167 increases in activity, were noticeable).

168         On a verbal signal to begin, subjects were instructed to “imagine that you are  
169 maximally contracting the muscles in your left (or right) forearm and imagine that you are  
170 making your wrist flex and push maximally against a hand grip with your hand. We will  
171 ask you to do this for 5-secs at a time followed by a 5-sec rest period for a total time of  
172 around 2-mins. When we tell you to start, we want you to *imagine* that you are pushing  
173 in against a handgrip as hard as you can and continue to do so until we tell you to stop.  
174 After a 5 second rest we will ask you to repeat this. Ready, and begin imagining that you  
175 are pushing in as hard as you can with your left wrist, push, push, push... and stop. (5  
176 seconds of silence) Start imagining that you are pushing in again as hard as you can,  
177 keep pushing, keep pushing... and stop. (5 seconds of silence)...” This verbal cuing and  
178 imagery continued for 2-minutes at which time the study participant was instructed that  
179 they would have a short break (1-min), and then the next blocks would subsequently

begin. It should be noted that this mental exercise was not simply a visualization of oneself performing the task; rather, the performers were instructed to adopt a kinesthetic imagery approach, in which they urged the muscles to contract maximally (Ranganathan et al., 2004).

***Muscle Strength and Voluntary Activation.*** To quantify wrist flexion forces subjects were seated with the elbow at 90°, the hand pronated and the forearm supported and restricted while the head rested on a pad (Figure 1A) (Biodex System 4, Biodex Medical Systems Inc., Shirley, NY). The wrist joint was aligned to the rotational axis of a torque motor to which a constant-length lever arm was attached. The signal was scaled to maximize its resolution (208.7 mV/Nm; Biodex Researchers Tool Kit Software), smoothed over a 10-point running average, and sampled at 625 HZ (MP150 Biopac Systems). Subjects received visual feedback of all exerted forces on a computer monitor located 1-m directly in front of them.

To assess maximal wrist flexion strength, subjects performed a minimum of three maximal voluntary isometric contractions (MVC) with a 1–2-min rest period between each contraction. If subjects continually recorded more force with increasing trials, or if the two highest trials were not within 5% of each other, additional trials were performed until a plateau was reached. Verbal encouragement was provided during testing. The highest value was considered the MVC.

To determine what percentage of the total force generating capacity of the wrist flexors can be produced voluntarily, a combination of voluntary and electrically stimulated contractions was performed (Figure 2A). Electrical stimulation (0.2 msec pulse duration) was delivered to the median nerve in the cubital fossa groove via stimulating electrodes (Ag-AgCl, 35 x 45 mm, No. 2015; Nikomed, Doylestown, Pennsylvania). Stimuli were administered at increasing stimulation intensities until the FCR peak-to-peak (p-p) EMG amplitude reached a plateau ( $M_{max}$ ), and for VA testing the

intensity was subsequently increased 20% above that eliciting  $M_{max}$  (DS7AH; Digitimer, Hertfordshire, UK). To assess VA a supramaximal 100-Hz electrical doublet was delivered while the subject performed a 4–5 s MVC. The increase in force immediately following the stimulation was expressed relative to a potentiated response evoked 1–2 s after the MVC, and VA was calculated as follows:

$$\% VA = [1 - (\text{evoked force during MVC} / \text{evoked force following MVC})] \times 100$$

**Transcranial Magnetic Stimulation (TMS).** EMG was recorded from the non-dominant FCR muscle using bipolar surface electrodes located longitudinally over the muscle on shaved and abraded skin with a reference electrode just distal to the medial epicondyle (Ag/AgCl electrodes with a 25-mm interelectrode distance). The EMG signals were amplified 1000x, band-pass filtered (10-500 Hz), and sampled at 5,000 Hz (MP150, BioPac Systems Inc., Goleta, CA). Single pulse, monophasic waveform magnetic stimuli were delivered using a Magstim 200<sup>2</sup> (The Magstim Co. Ltd., Whitland, England) magnetic stimulator with a 70-mm figure-of-eight focal coil positioned tangential to the scalp with the handle pointing backwards and laterally at 45 degrees from midline. The stimulation location that elicited the largest p-p amplitude of the FCR motor evoked potential (MEP) was identified and marked on a lycra cap for coil placement. This procedure was repeated for each testing session. Next, resting motor threshold (MT) was determined while study participants were seated in the dynamometer by delivering single pulses at gradually increasing stimulation intensities as we previously described (Clark et al., 2008b; Damron et al., 2008). Resting MT was determined and expressed as a percent of the maximal stimulator output. MT was determined by delivering TMS pulses at a low stimulus intensity and gradually increasing the intensity in 2% increments until MEPs were observed. Resting MT was defined as the stimulation intensity that elicited MEPs with a p-p amplitude of  $\geq 50\mu V$  in at least four of eight trials. During this assessment the muscle was completely relaxed as monitored by the EMG signal. We



should note that we have previously reported that the resting MT does not change following immobilization (Clark et al., 2008b), which is consistent with what we observed in the present study. SP duration was quantified during brief 15% contractions (Figure 3A). Here, eight single pulses were delivered at 130% of resting MT, and the SP was quantified and averaged. A single, blinded investigator visually defined the return of the interference EMG signal, and the duration between this TMS pulse and this event was quantified to represent the SP. We have previously reported that this quantification method displays high inter-rater reliability ( $r=0.97$ ) (Damron et al., 2008).

**Sample Size Justification.** Our sample size was calculated based on our observed effect size for imagery training to minimize disuse-induced strength loss ( $\eta^2=0.11$ ) (Clark et al., 2006b). The power calculation was based on the assumption of a mixed model, within-between interaction ANOVA with alpha at 0.05 and power at 0.95. Based on this calculation our estimated sample size to detect significant changes in strength from pre-immobilization to post-immobilization between the immobilization and the immobilization *plus* imagery groups was 15 subjects/group (G\*Power 3.0.3, Universität Kiel, Germany). We chose to set power to 0.95 because the success of this project was vitally dependent upon imagery training maintaining strength.

**Statistical Analyses.** Mixed model ANOVAs (Group [3 Between Subject Factors] x Time [3 Within Subject Factors]) followed by Sidak post hoc tests were utilized to determine changes over time between groups. We should also note that we conducted additional contrast analyses with only the immobilization and immobilization+imagery groups included, and these analyses yielded essentially the same findings as those when the control group was included in the model. Correlation coefficients ( $r$ ) were calculated to examine the relation between 1) the percent change in strength and percent change in VA following immobilization for the immobilization and immobilization+imagery groups, and 2) the percent change in strength and the percent

change in SP duration following immobilization for the immobilization and immobilization+imagery groups. A preset  $\alpha$ -level of significance equal to 0.05 (two-sided) was required for significance. The SPSS statistical package (version 19.0 for Mac, Chicago, IL) was used for data analysis. Data are presented as means $\pm$ SEM. Additionally, to further aid in interpretation, we also report the effect size (ES; partial eta-squared), which represents the proportion of total variation attributable to a given factor when partialing out other factors from the total non-error variation.

## RESULTS

There were no group differences at baseline for strength ( $p=0.94$ ,  $ES<0.01$ ; immobilization group:  $21.8\pm1.8$  N-m, immobilization+imagery group:  $21.4\pm1.6$  N-m, control group:  $22.4\pm3.2$  N-m), VA ( $p=0.16$ ,  $ES=0.08$ ; immobilization group:  $96.2\pm1.8\%$ , immobilization+imagery group:  $98.7\pm0.6\%$ , control group:  $93.8\pm2.2\%$ ), MT ( $p=0.09$ ,  $ES=0.11$ ; immobilization group:  $51.9\pm2.3\%$  of stimulator output (SO), immobilization+imagery group:  $44.4\pm2.2\%$  SO, control group:  $47.1\pm2.1\%$  SO), or SP duration ( $p=0.89$ ,  $ES<0.01$ ; immobilization group:  $107.5\pm4.4$  msec, immobilization+imagery group:  $110.5\pm5.0$  msec, control group:  $108.4\pm4.3$  msec). We observed group x time interactions for the dependent variables of strength ( $p<0.001$ ,  $ES=0.31$ ), VA ( $p=0.004$ ,  $ES=0.16$ ), and SP duration ( $p=0.015$ ,  $ES=0.13$ ). Follow-up analyses indicated that immobilization significantly decreased strength by  $45.1\pm5.0\%$  (Figure 1), impaired VA capacity by  $23.2\pm5.8\%$  (Figure 2), and prolonged the SP by  $13.5\pm2.6\%$  (Figure 3). Mental imagery training, however, attenuated the loss of strength and VA by  $\sim 50\%$  (Figures 1 and 2;  $23.8\pm5.6\%$  and  $12.9\pm3.2\%$  reductions, respectively), and also eliminated prolongation of the SP (Figure 3;  $4.8\pm2.8\%$  reduction). No changes over time were observed in the control group for any of the outcomes (Figures 1-3). We did not observe a group x time interaction for MT ( $p=0.11$ ,  $ES=0.08$ ; immobilization

group:  $51.9 \pm 2.3\%$ ,  $53.1 \pm 2.5\%$ , and  $51.6 \pm 2.5\%$  of stimulator output (SO) at baseline, post, and recovery; immobilization+imagery group:  $44.4 \pm 2.2\%$ ,  $45.5 \pm 2.7\%$ , and  $41.9 \pm 2.5\%$  SO; control group:  $47.1 \pm 2.1\%$ ,  $44.6 \pm 1.7\%$ , and  $45.2 \pm 2.1\%$  SO).

We observed a positive association between the percent change in strength and the percent change in VA following immobilization (Figure 4A;  $r=0.56$ ,  $p<0.01$ ). We observed a negative association between the percent change in strength and the percent change in SP duration following immobilization (Figure 4B;  $r=-0.39$ ,  $p=0.03$ ).

## DISCUSSION

In this study we utilized mental imagery as a manipulation to minimize the immobilization-induced loss of strength and VA to better elucidate the role of the cortex in regulating muscle strength/weakness by examining the association/dissociation between the respective without concomitantly affecting muscle properties. The novel, and most notable, findings of this study are that 1) imagery attenuated the loss of strength and VA by 50%, while also concomitantly eliminating the prolongation of the SP; and 2) we observed significant associations between the percent changes in a) muscle strength and VA, and b) muscle strength and SP duration. Below we discuss the interpretation, significance, and impact of these findings.

The finding that imagery, a neurological-based intervention strategy, attenuated immobilization-induced weakness, coupled with the observation that 32% (obtained by calculating  $R^2$  from the correlation coefficient) of the between-subject variability in the loss of strength was explained by the loss of ability to voluntarily activate the musculature indicates that neurological factors are critical contributors to weakness (at least in the context of a disuse model). 'Neural factors' have long-been considered to be key contributors to muscle performance (Moritani and deVries, 1979), as incomplete motor unit recruitment and/or the inability to mount high motor unit discharge rates are both factors that can result in weakness (Kamen, 2005). As such, this finding is not

surprising per se. In fact, our own previous studies (Clark et al., 2006a; Clark et al., 2006b), and those of others (Kawakami et al., 2001), indicate a moderate-to-strong association between the loss of VA capacity and loss of strength following prolonged disuse. Similarly, the finding that imagery attenuated the loss of strength is also expected as several studies have shown that imagery training (in the absence of disuse) increases muscle strength (Yue and Cole, 1992; Zijdwind et al., 2003; Ranganathan et al., 2004; Fontani et al., 2007); however, to our knowledge, this finding is novel as it is the first report of imagery training significantly attenuating the loss of strength following prolonged disuse. To our knowledge there have been two other studies examining the potential for imagery to attenuate losses of motor function following prolonged disuse (Clark et al., 2006b; Crews and Kamen, 2006). Neither of these observed significant effects. Specifically, Crews and Kamen reported that imagery training (performed 4 times) did not ameliorate the effects of 7-days of cast immobilization on a motor control task changes in a motor control task following 7-days of cast immobilization (Crews and Kamen, 2006). Similarly, our own group did not observe a significant effect on mitigating the loss of strength following prolonged lower limb unweighting (Clark et al., 2006b). It should be noted, however, that the former study employed a short (7-day) immobilization period with only 4-days of imagery training occurring during this time period. While our prior study used a similar duration for the disuse period (4-weeks) and a similar frequency of imagery training (4 days/wk) there were only six subjects in the imagery group and, based on the observed effect sizes, it is likely that it was underpowered. Thus, our findings that imagery attenuated the loss of muscle strength provides proof-of-concept for it as a therapeutic intervention for muscle weakness; however, double-blind placebo controlled studies should be conducted to more fully explore this potential.

Another novel aspect of this work is that our findings, collectively, provide support for our global hypothesis of that the cortex is a critical determinant of muscle strength and VA and that high level of intracortical inhibition is an important neurophysiologic factor regulating force generation of muscle. The cortex, and the motor cortex in particular, has historically been considered critical for movement coordination/control and skill acquisition as opposed to maximal force generation of individual muscles (Jackson, 1873; Remple et al., 2001; Adkins et al., 2006), but growing evidence is now suggesting that it is a critical determinant of muscle strength/weakness. We believe our finding of i) mental imagery (an interventional strategy that activates the motor cortical areas (Hetu et al., 2013)) attenuating the loss of muscle strength while concomitantly eliminating the prolongation of the SP (a neurophysiologic outcome of corticospinal inhibition), coupled with the finding of ii) an association between the changes in strength and the SP, provide strong support for the notion that the cortex is a critical determinant of muscle strength/weakness. If our interpretation is correct, these findings suggest that increases in intracortical inhibition are mechanistically associated with muscle weakness.

Our above mentioned interpretation is based on the predication of imagery and actual movements sharing, at least in part, common cortical substrates, which has been shown in neuroimaging studies (see (Hetu et al., 2013) for a meta-analytical review). For example, a host of brain functional imaging studies indicate that imagery activates several cortical areas, including the primary motor cortex, supplementary and premotor areas, and cingulate gyrus (Rao et al., 1993; Stephan et al., 1995; Porro et al., 1996; Roth et al., 1996; Malouin et al., 2003), all of which are known to contain corticospinal neurons in monkeys (Dum and Strick, 1996). Additionally, TMS studies have shown that MI acutely increases the excitability of the specific representation in the contralateral primary motor cortex (Facchini et al., 2002; Bakker et al., 2008). Furthermore, imagery

training has been shown to increase muscle strength in a variety of muscles (Yue and Cole, 1992; Herbert et al., 1998; Zijdwind et al., 2003; Ranganathan et al., 2004), with the strength gain being accompanied by significant increases in the EEG-derived cortical potential, suggesting imagery training enhances cortical output and increases voluntary activation (Ranganathan et al., 2004). Most recently, Yao and colleagues also demonstrated that kinesthetic imagery (as used herein) increased muscle strength and the movement-related cortical potential on scalp locations over M1 and the supplementary motor cortices, with the authors suggesting that imagery changes the activity level of cortical motor control networks that translates into greater descending command to the target muscle and increase its strength (Yao et al., 2013). So, based on these findings we postulate that in the present study imagery training had a similar effect on the motor cortical areas, providing support for our interpretation. However, it should be noted that there are reports that imagery training slightly increases the H-reflex excitability (Cowley et al., 2008) and has a selective facilitatory effect on the stretch reflex pathways (Aoyama and Kaneko, 2011), and, as such, we can not fully exclude that peripheral nervous system factors could have contributed to the differential results we observed in the imagery group. Similarly, we cannot fully exclude that the silent period is mechanistically indicative of cortical level changes. The duration of the SP is dependent on the intensity of stimulation (Cantello et al., 1992; Inghilleri et al., 1993), and the first 50-msec is widely assumed to be spinally mediated, through mechanisms such as afterhyperpolarization of the motor neurons and recurrent inhibition, with the latter part due to supraspinal inhibition (Fuhr et al., 1991; Cantello et al., 1992; Inghilleri et al., 1993; Wilson et al., 1993; Ziemann et al., 1993). This SP is generally believed to be caused by activation of long-lasting GABA<sub>B</sub> mediated inhibition (Kobayashi and Pascual-Leone, 2003; McDonnell et al., 2006; Reis et al., 2008). With this stated, it should be noted that recent data suggests that the SP can be influenced by spinal-

mediated factors such muscle lengthening (Butler et al., 2012) and that the underlying mechanisms may also be linked to shifts in cortical glutamate + glutamine concentrations (Tremblay et al., 2013). Thus, our interpretation of our current findings must be considered within the context of the somewhat limited understanding of the silent period. However, our mechanistic interpretation of increases in intracortical inhibition being linked to weakness is indeed consistent with findings from other studies (Clark et al., 2010; Weier et al., 2012), although it should be noted that it is inconsistent with others (Plow et al., 2013).

We should note that there are certainly muscular factors that likely contributed to the observed muscle weakness as well. Due to pragmatic reasons (e.g., associated costs), we did not obtain measures pertaining to muscle size, however, it is very likely that muscle atrophy as well as other muscular adaptations contributed to the losses in muscle strength. In fact, based on the observation that MI attenuated ~ 50% of the loss of strength and VA, it seems that one can conclude that around half of the induced weakness was due to muscular adaptations and that the other half was due to reductions in neural drive.

There are several limitations of this study that should be acknowledged. First, our subjects were asked to produce a contraction intensity at their relative strength level at all time points of testing (as opposed to the same absolute force level), and it is possible that selected outcomes in particular (e.g., SP duration) could have been influenced by the absolute amount of force produced. Second, we did not actually record the amount of muscle activity/usage during the immobilization protocol, and as such it is not possible to know whether subtle differences in activity across groups could explain the results. We should note that our casting protocol involves the splint platform extending well beyond the fingers, which minimizes the potential for study participants to engage the wrist flexion musculature, but, nonetheless, we can exclude this as a source of variance

in the present study. Third, we were not able to quantify how successful study participants were in actually performing the mental imagery, and, as such, it is possible, if not probable, that there was a reasonable amount of heterogeneity in the ability of study participants to actually perform MI that we were not able to control for.

In conclusion, the cortex as a determinant of strength/weakness has received limited attention. We used immobilization to induce weakness and impairments in VA, and used mental imagery to activate the cortex during immobilization. We measured the SP duration by stimulating the brain during a contraction to provide an index of GABA<sub>B</sub>-mediated inhibition. Our findings most likely suggest that neurological mechanisms arising at the cortical level are a substantial contributor to disuse-induced muscle weakness, and that regular activation of the motor cortical regions *via* mental imagery attenuates disuse-induced losses in strength and VA by maintaining normal levels of inhibition.

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453 **Table 1.** Descriptive statistics of the study participants (Means±Std. Deviation).

<b>Group</b>	<b>N</b> (% Female)	<b>Age</b> (Years)	<b>Height</b> (cm)	<b>Weight</b> (Kg)	<b>BMI</b> (kg/m <sup>2</sup> )
<b>Immobilization Group</b>	15 (46%)	21.2 ±3.5	170.8 ±10.9	70.1 ±10.8	24.2 ±4.2
<b>Immobilization + MI Group</b>	14 (40%)	20.9 ±3.6	179.4 ±9.1	78.4 ±16.1	24.1 ±3.0
<b>Control Group</b>	15 (47%)	21.5 ±3.4	170.0 ±10.2	67.4 ±13.7	23.3 ±3.8

454 BMI: Body Mass Index; MI: Mental Imagery.  
455 *Note: No significant differences were observed between groups.*  
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**Figure 1. A.** Setup for assessing wrist flexion strength, voluntary activation, and the cortical silent period. **B.** Immobilization (open circles; n=15) resulted in a 45% reduction in strength. Mental imagery training (open triangles; n=14), however, attenuated the loss of muscle strength by ~ 50% (strength loss of 24%). No changes were observed in the control group (closed circles; n=15).

\*<baseline; \*\*<baseline and recovery; §<control group value.

**Figure 2. A.** Example of a force trace assessing voluntary activation (VA). Arrows represent the delivery of a 100-Hz electrical doublet to the peripheral nerve while an individual is maximally contracting (first arrow) and ~2 seconds after the completion of the contraction (second arrow). **B.** Immobilization (open circles; n=15) reduced VA ~25%. Mental imagery training (open triangles; n=14), however, attenuated the impairment in VA by ~ 50%. No changes were observed in the control group (closed circles; n=15).

\*<baseline; §<control group value, †<imagery group value.

**Figure 3. A.** The transcranial magnetic stimulation (TMS) coil induces a magnetic field and a subsequent Eddy current that stimulates neurons within the motor cortex. **B.** Example of an EMG trace illustrating a motor evoked potential (MEP) and silent period (SP). In this study single TMS pulses were delivered to the primary motor cortex during a 15% of maximum contraction to quantify the SP duration as an index of GABA<sub>B</sub>-mediated inhibition. **C.** Immobilization resulted in a 12% prolongation in the SP (n=15). Mental imagery training (n=14), however, eliminated prolongation of the SP. No changes were observed in the control group (n=15).

Data are presented as a %change for clarity, but it should be noted that no baseline differences in groups were observed (Baseline measures for control group:

108.5±4.3 msec, immobilization group was 107.5±4.4 msec, and immobilization+imagery group was 110.5±4.9 msec).

\*>baseline; §<Immobilization group value

**Figure 4. A.** There was a positive association between the percent change in muscle strength and the percent change in voluntary activation following 4-weeks of cast

immobilization (filled symbols: immobilization group; open symbols: immobilization+imagery group). This finding indicates that individuals who experienced the largest immobilization-induced loss of muscle strength also experienced the largest immobilization-induced impairments in voluntary (neural) activation ( $r=0.56$ ,  $p<0.01$ ). **B.** There was a negative association between the percent change in muscle strength and the percent change in the cortical silent period duration following 4-weeks of cast immobilization (filled symbols: immobilization group; open symbols: immobilization+imagery group). This finding indicates that individuals who experienced the largest immobilization-induced loss of muscle strength also experienced the largest immobilization-induced prolongation in the cortical silent period ( $r=-0.39$ ,  $p=0.03$ ).

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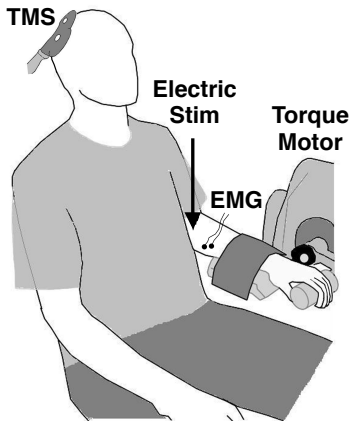
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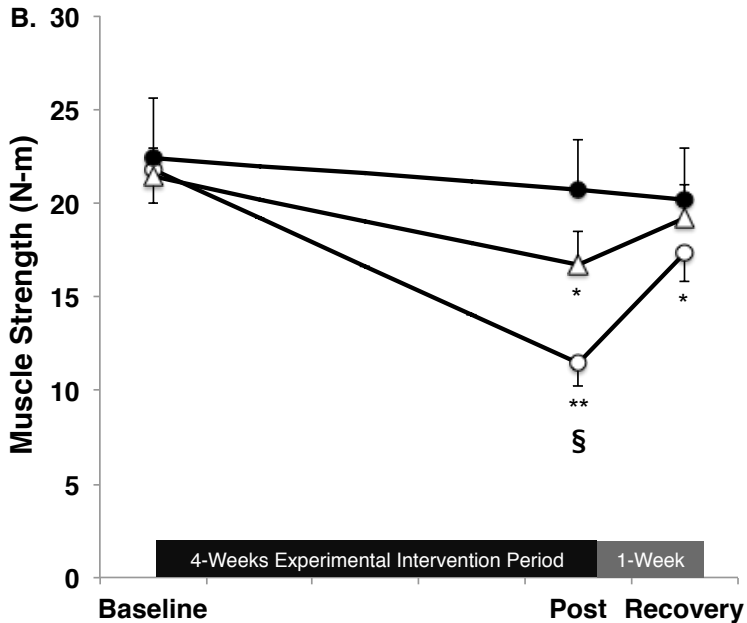
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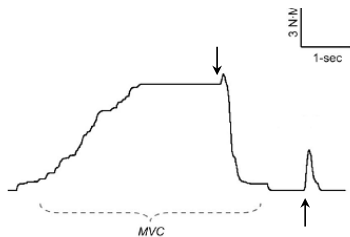
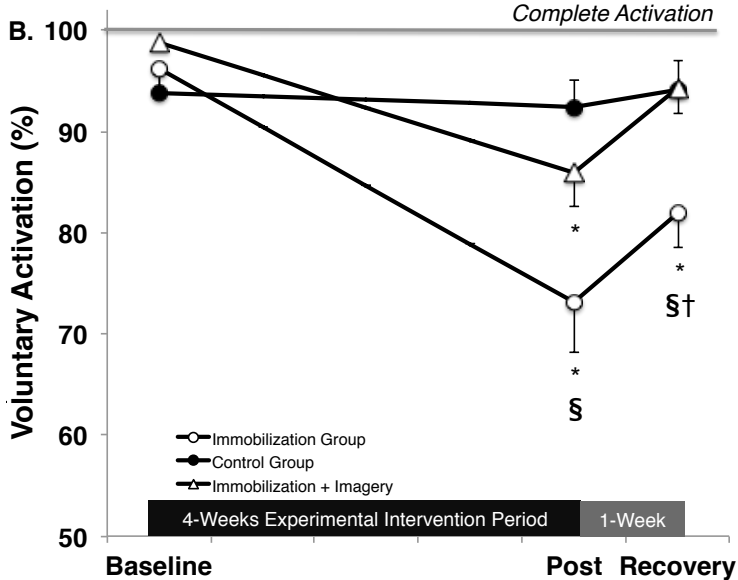
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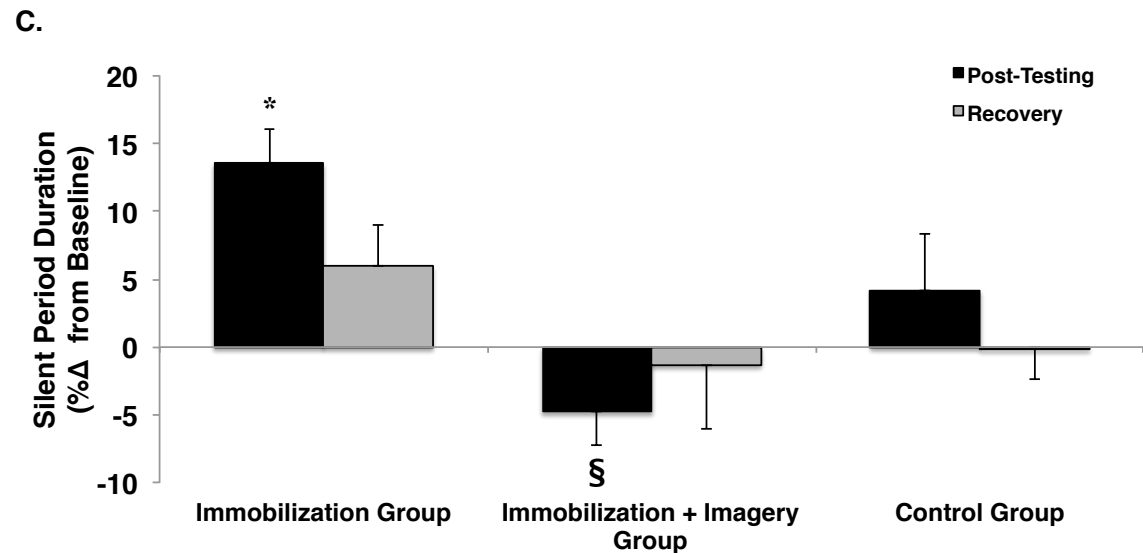
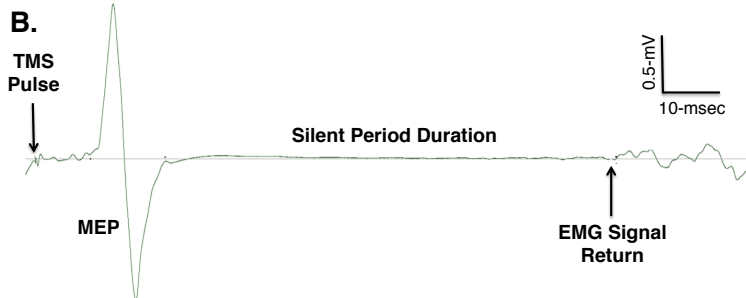
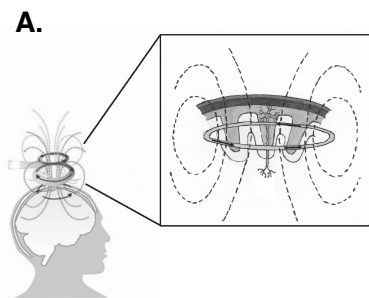


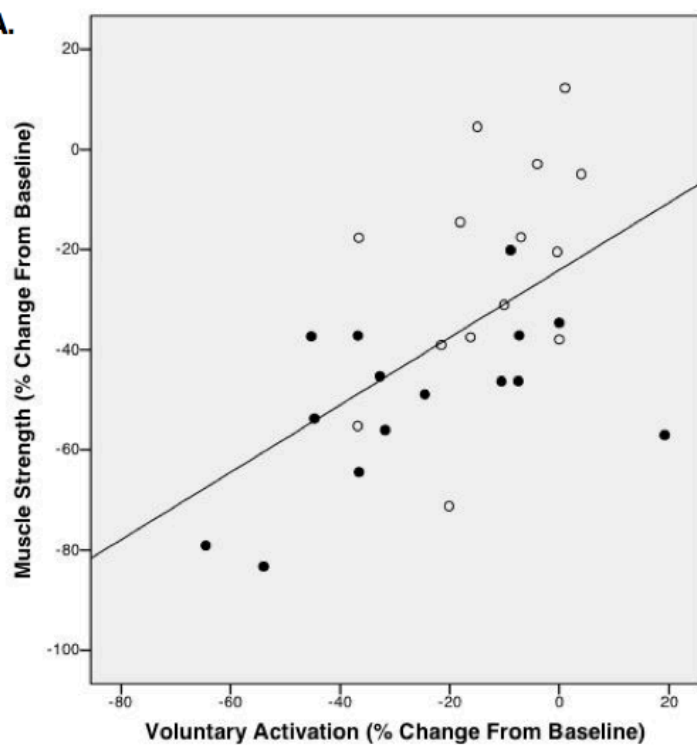
**B.**



**A.****B.**





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