# Transcranial Magnetic Stimulation and Volitional Quadriceps Activation

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**Context:** Quadriceps-activation deficits have been reported after meniscectomy. Transcranial magnetic stimulation (TMS) in conjunction with maximal contractions affects quadriceps activation in patients after meniscectomy.

**Objective:** To determine the effect of single-pulsed TMS on quadriceps central activation ratio (CAR) in patients after meniscectomy.

Design: Randomized controlled clinical trial.

Setting: University laboratory.

**Patients or Other Participants:** Twenty participants who had partial meniscectomy and who had a CAR less than 85% were assigned randomly to the TMS group (7 men, 4 women; age =  $38.1 \pm 16.2$  years, height =  $176.8 \pm 11.5$  cm, mass =  $91.8 \pm 27.5$  kg, postoperative time =  $36.7 \pm 34.9$  weeks) or the control group (7 men, 2 women; age =  $38.2 \pm 17.5$  years, height =  $176.5 \pm 7.9$  cm, mass =  $86.2 \pm 15.3$  kg, postoperative time =  $36.6 \pm 37.4$  weeks).

*Intervention(s):* Participants in the experimental group received TMS over the motor cortex that was contralateral to the involved leg and performed 3 maximal quadriceps contractions with the involved leg. The control group performed 3 maximal quadriceps contractions without the TMS.

*Main Outcome Measure(s):* Quadriceps activation was assessed using the CAR, which was measured in  $70^{\circ}$  of knee flexion at baseline and at 0, 10, 30, and 60 minutes posttest. The CAR was expressed as a percentage of full activation.

**Results:** Differences in CAR were detected over time ( $F_{4,72} = 3.025$ , P = .02). No interaction ( $F_{4,72} = 1.457$ , P = .22) or between-groups differences ( $F_{1,18} = 0.096$ , P = .76) were found for CAR. Moderate CAR effect sizes were found at 10 (Cohen d = 0.54, 95% confidence interval [CI] = -0.33, 1.37) and 60 (Cohen d = 0.50, 95% CI = -0.37, 1.33) minutes in the TMS group compared with CAR at baseline. Strong effect sizes were found for CAR at 10 (Cohen d = 0.82, 95% CI = -0.13, 1.7) and 60 (Cohen d = 1.06, 95% CI = 0.08, 1.95) minutes in the TMS group when comparing percentage change scores between groups.

**Conclusions:** No differences in CAR were found between groups at selected points within a 60-minute time frame, yet moderate to strong effect sizes for CAR were found at 10 and 60 minutes in the TMS group, indicating increased activation after TMS.

Key Words: central activation ratio, arthrogenic muscle inhibition, knee, meniscus

## **Key Points**

- Quadriceps central activation ratios and maximal voluntary isometric contractions were not statistically different between the transcranial magnetic stimulation and control groups at any of the time points.
- Moderate effect sizes for central activation ratio were found at 10 and 60 minutes after transcranial magnetic stimulation compared with baseline scores, whereas strong effect sizes in the transcranial magnetic stimulation group were found for both central activation ratio and maximal voluntary isometric contraction at 10 and 60 minutes after transcranial magnetic stimulation when comparing percentage change between groups.

rthrogenic muscle inhibition is an ongoing reflex inhibition of the uninjured musculature surrounding a distended or damaged joint<sup>1,2</sup> that affects the ability to activate motor neurons for recruitment during a contraction.<sup>3</sup> This reflex inhibition is mediated presynaptically by  $\gamma$ -aminobutyric acid inhibitory interneurons and postsynaptically by Renshaw cells, both of which are influenced by supraspinal centers.<sup>2,4</sup> This reflex inhibition decreases neural drive to the muscle, which prevents activation of motor neurons and consequently decreases the capacity for muscle contraction. Although arthrogenic muscle inhibition might be initiated as a protection mechanism to diminish excess forces on a joint after

injury,<sup>4</sup> this inhibition becomes problematic when muscleactivation deficits persist long after the initial injury<sup>5</sup> and might limit the ability to regain optimal muscle function.<sup>6</sup>

Quadriceps muscle inhibition has been reported with various knee conditions, including anterior cruciate ligament injury,<sup>7–9</sup> osteoarthritis,<sup>6,10–13</sup> total knee arthroplasty,<sup>6,14–16</sup> and meniscectomy.<sup>17,18</sup> Quadriceps inhibition not only decreases the ability to perform maximal tasks but also can alter gait<sup>19</sup> and shock-attenuation strategies during tasks such as landing.<sup>20</sup> Arthrogenic muscle inhibition affecting the quadriceps is a serious clinical impairment that might need to be targeted with specialized therapeutic interventions before muscle strengthening.<sup>13,21,22</sup>

						Lower Extremity	International Knee Documentation Committee
					Postoperative	Functional	Subjective Knee
Group	Sex	Age, y	Height, cm	Mass, kg	Time, wk	Scale <sup>38</sup>	Scale <sup>39</sup>
Transcranial magnetic							
stimulation ( $n = 11$ )	7 men, 4 women	$38.1\pm16.2$	$176.8 \pm 11.5$	$91.8\pm27.5$	$36.7\pm34.9$	$61.2\pm12.3$	$65.2\pm18.1$
Control (n = 9)	7 men, 2 women	$38.2\pm17.5$	$176.5\pm7.9$	$86.2\pm15.3$	$36.6\pm37.4$	$68.1\pm10.5$	$68.1\pm15.4$

<sup>a</sup> No differences were found between groups.

Conventional rehabilitation programs focusing solely on muscle strengthening might not provide adequate stimuli to effectively treat arthrogenic muscle inhibition<sup>5</sup> and might contribute to the perpetuation of muscle dysfunction even when traditional therapeutic exercise is used.<sup>23</sup> Researchers have theorized that specialized interventions might be necessary to overcome underlying muscle inhibition modulated by the central nervous system so patients can achieve a greater level of neuromuscular function and, thus, optimal therapeutic outcomes.<sup>22,23</sup> Muscle function plays a vital role in shock attenuation at the joint,<sup>6</sup> and decreased muscle activation might impair the ability of the neuromuscular system to protect the joint, which might lead to early joint degeneration.<sup>20,24</sup> Therefore, an intervention that increases muscle activation during rehabilitation might increase neuromuscular control and improve function.23 Different therapeutic agents, such as transcutaneous electric nerve stimulation<sup>22</sup> and focal knee joint cooling,<sup>25</sup> have been reported to effectively increase quadriceps muscle activation. Pietrosimone et al<sup>23</sup> suggested that improvements in muscle activation using a disinhibitory agent might allow patients to access previously inhibited motor neurons during therapeutic exercise and, hence, develop optimal motor patterns.

Recently, transcranial magnetic stimulation (TMS) used with maximal voluntary isometric contractions (MVICs) has been reported to increase quadriceps activation within an hour in healthy participants<sup>26,27</sup> and participants with quadriceps weakness.<sup>28</sup> Transcranial magnetic stimulation is a safe, relatively pain-free method of stimulating neural tissue.<sup>29,30</sup> The magnetic stimulation is directed onto the region of the motor cortex that generates volitional movement in the periphery and subsequently excites corresponding descending corticospinal tracts that directly project on motor neurons within the targeted muscle.<sup>30</sup> Interestingly, TMS has been reported to decrease presynaptic inhibition by affecting interneurons,<sup>31</sup> which is a mechanism reported to modulate arthrogenic muscle inhibition.1,32 If this inhibition could be decreased before performing therapeutic exercise using a technique such as TMS, patients might have more motor neurons available to optimize neuromuscular function. Regaining optimal muscular function before developing severe joint degeneration might delay joint breakdown. Yet it remains unknown if TMS would effectively address quadriceps-activation deficits in patients who have inhibition and are at risk for hastened progression of osteoarthritis in the knee.

Patients who have had meniscectomy are good models for studying arthrogenic muscle inhibition because they have relatively standard postoperative joint damage and they tend to acquire quadriceps inhibition after these procedures.<sup>33</sup> Consequently, this population also is at heightened risk of developing knee osteoarthritis,<sup>34</sup> which might have links to altered muscle function.<sup>35</sup> Researchers<sup>22,25,28,36,37</sup> have assessed the ability of various disinhibitory agents to immediately activate a chosen muscle group in a time frame that closely mimics that of a clinical therapeutic exercise session. One motive for determining the immediate effects of these modalities is to demonstrate that these agents would be used in conjunction with conventional therapeutic exercise. Therefore, the purpose of our study was to determine the effect of receiving single-pulse TMS over the motor cortex and performing quadriceps MVICs on volitional quadriceps activation in participants after meniscectomy. We hypothesized that quadriceps activation would be greater in patients receiving TMS and performing MVICs than in a control group only performing MVICs.

## METHODS

Thirty-one people volunteered for the study, but 11 volunteers were excluded before baseline testing because their quadriceps central activation ratios (CARs) were more than 85%. Twenty participants were assigned randomly to the TMS or the control group (Table 1). Participants were included if they had undergone partial meniscectomy via arthroscopy a minimum of 10 days before and a maximum of 3 years before the study (postoperative time =  $36.62 \pm 35.06$  weeks) and had quadriceps activation less than 85% when measured by the CAR with the burst-superimposition technique. Exclusion criteria included neurologic disorders, history of depression, history of seizures or migraines, and diagnosed heart conditions that precluded participants from exercising. Both investigators (C.E.G. and B.G.P.) performing the intervention before group assignment were blinded to the randomization, and the investigator (C.E.G.) collecting the muscle-activation data was blinded to group assignment throughout testing. The main outcome measure was volitional quadriceps muscle activation assessed by CAR, whereas the secondary outcome measures included quadriceps MVIC and knee pain during the contraction. All outcome measures were collected at baseline and at 0, 10, 30, and 60 minutes posttest. These time points were chosen (1) to provide a general sense of the muscle activation during a time interval that was similar to the length of a traditional therapeutic exercise session and (2) to resemble those used in previous studies<sup>22,25,26,28,37</sup> in which disinhibitory agents were evaluated. Self-reported function was collected using the Lower Extremity Functional Scale<sup>38</sup> and International Knee Documentation Committee Subjective Knee Scale.39 All participants provided written informed consent, and our study was approved by the Institutional Review Board (HRS 13399) at the University of Virginia.

## Instruments

The Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY) was used to measure maximal voluntary force during the muscle-activation testing.<sup>22,25</sup> A square-wave stimulator (model S88; GRASS Technologies, West Warwick, RI) and a stimulation isolation unit (model SIU8T; GRASS Technologies) produced a 100-millisecond train of 10 stimuli at 100 pulses per second with a pulse duration of 0.6 milliseconds and a 0.01-millisecond pulse delay.<sup>22,25</sup> The stimulation isolation unit with an estimated 3000- $\Omega$  load produced an estimated 125 V.<sup>22</sup> Two 7 × 13-cm Dura Stick II (Chattanooga Group, Hixson, TN) self-adhesive electrodes were used to deliver the stimulus to the quadriceps muscles.

The Magstim 200 (Magstim Company Ltd, Carmarthenshire, United Kingdom) was used to deliver a single magnetic pulse. A figure-8 coil was used and positioned so that the current had a posterior-anterior direction. Surface electromyographic (EMG) signal at the quadriceps was collected to determine the optimal placement for the TMS coil over the motor cortex. Disposable, 10-mm, pregelled Ag/AgCl electrodes (BIOPAC Systems Inc, Goleta, CA) were applied, and the signal was amplified (model EMG100C; BIOPAC Systems Inc) with a gain of 1000 before being converted digitally with a 16-bit data acquisition system (model MP150; BIOPAC Systems Inc). The EMG signal was collected at 2 kHz with a common mode rejection ratio of 110 dB, a noise voltage of 0.2  $\mu$ V, and an input impedance of 1 M $\Omega$ . AcqKnowledge software (version 3.7.3; BIOPAC Systems Inc) was used to visualize the EMG and force signals.

A 100-mm visual analog scale (VAS) was used to determine subjective knee pain during a knee-extension MVIC. This 100-mm line was bordered by boxes stating *Absolutely No Pain* on 1 end and *Worst Pain Imaginable* on the other end.

## **Experimental Procedures**

Participants were positioned in the dynamometer with their hips flexed to 85° and their knees flexed to 70°.<sup>22,25</sup> The tibia of the involved leg was secured to the arm of the dynamometer with a padded hook-and-loop strap that was positioned proximal to the ankle. The anterior thigh was shaved, debrided, and cleaned with alcohol before application of the EMG and burst superimposition electrodes. The 2 burst-superimposition stimulating electrodes were applied to the proximal vastus lateralis and the distal vastus medialis. Two EMG electrodes were adhered 1.75 cm apart on the greatest bulk of the vastus lateralis, which was identified during a submaximal isometric contraction at 70° of knee flexion. The ground reference electrode was positioned on the contralateral medial malleolus.

## **Burst Superimposition**

Three submaximal electric stimuli (30, 70, and 100 V) were administered in conjunction with 3 submaximal isometric contractions (25%, 50%, and 75%) before testing to familiarize the participant with the burst-superimposition procedures. In addition to submaximal trials, participants performed 3 to 5 practice MVICs until the investigator was confident that each participant could exert a consistent maximal effort.<sup>22,25</sup>

The supermaximal exogenous stimulus was applied to the quadriceps when the test administrator observed that a maximal force plateau had been reached (Figure 1). Two trials separated by a 60-second rest were averaged at each time interval (baseline and 0, 10, 30, and 60 minutes posttest) for data analysis.

At the beginning of each time interval, an MVIC without an augmented electric stimulation was performed. Each participant was instructed to rate the pain felt in the knee during the MVIC on the 100-mm VAS line.<sup>22</sup>

## **TMS Protocol**

Before group allocation, participants were instructed to wear swim caps (Water Gear, Inc, Pismo Beach, CA) so we could locate optimal positioning of the motor cortex and to insert earplugs (Aearo Co, Indianapolis, IN) to muffle the sound of the TMS. Two landmark lines were drawn on the swim cap: 1 sagittally separating the hemispheres and 1 intersecting the sagittal line coronally at the external auditory meatus. During all contractions, participants were instructed to cross their arms over their chests and to close their eyes.

Before the TMS treatment, participants were instructed to extend their knees at 25% of their perceived MVICs while a submaximal magnetic stimulus was delivered to the motor cortex contralateral to the involved leg. The first 2 submaximal stimuli were performed at 40% and 60% of 2 T to familiarize the participants with the stimulus. The remaining submaximal stimuli were performed at 80% of 2 T, which induced a motor evoked potential but did not expose the participant to unnecessary maximal stimuli. Submaximal stimuli (average = 5) were performed until the optimal positioning of the coil over the corresponding section of the motor cortex was located. We used the largest peak-to-peak motor evoked potential of the vastus lateralis (visualized on EMG) to determine the optimal placement for the magnetic coil. When located, the site was marked on the participant's swim cap.

The coil was secured in a holder (Magic Arm; Manfrotto Camera Lighting Supports, Bassano Del Grappa, Italy) and positioned over the previously located section of the motor cortex. Participants performed a contraction at 50% of their perceived MVICs while a stimulus of 90% of 2 T was administered to the motor cortex to ensure that the previously identified stimulation point could be accessed appropriately with the coil secured in the holder. After the submaximal trials, 3 quadriceps MVICs were performed 30 seconds apart, and 1 maximal magnetic stimulus (2 T) was administered when the participant reached a plateau in his or her MVIC (Figure 2). Before administering the magnetic stimulation, the investigator used both hands to guide the head of the participant directly under the coil, then removed his hands.

## **Control Protocol**

Participants in the control group wore swim caps and earplugs while performing all contractions with their eyes closed and arms placed across their chests. They performed 4 submaximal contractions at 25% of their perceived MVICs, 1 at 50% of their perceived MVICs, and 3 MVICs 30 seconds apart. Participants in the control group did not receive magnetic stimulation.



Figure 1. Representative force tracing during the superimposed-burst testing. Point A represents the force during a maximal voluntary isometric contraction. Point B represents the force increase after the train of electric stimuli. Point C indicates on vastus lateralis electromyography when the train of electric stimulation was delivered to the quadriceps muscle. No magnetic stimulation was delivered during voluntary activation testing (baseline and 0, 10, 30, and 60 minutes posttest) in the control or transcranial magnetic stimulation groups.

#### **Data Analysis**

The CAR was calculated by dividing the force measurements of the MVIC ( $F_{MVIC}$ ) by the peak force (sum of the force produced by the burst superimposition [ $F_{SIB}$ ] and  $F_{MVIC}$ ) as previously performed:

 $CAR = (F_{MVC})/(F_{SIB} + F_{MVIC})$ 

The peak force value and the MVIC value were calculated from the mean of the 2 best separate trials at each time in the series when the supermaximal stimulus was applied. The  $F_{MVIC}$  was calculated from a 0.1-second period immediately before the administration of the exogenous supermaximal stimulus.<sup>22</sup> All MVICs were normalized to body mass. Pain scores were calculated by measuring the distance between the mark made by the

participant and the end marked *Absolutely No Pain*. Pain scores were presented in millimeters, with higher scores representing higher levels of pain.

#### **Statistical Analysis**

An a priori sample-size calculation was performed using data from a previous study<sup>25</sup> in which investigators reported moderate effect sizes for CAR after focal joint cooling. Therefore, we estimated that we would find a 10% difference between groups and an SD of 10% for both groups, which is similar to what has been published with this measure.<sup>22,40,41</sup> Using an  $\alpha$  level of .05 and power of 0.80, we calculated that we would need 9 people per group to find statistical significance. Before the primary analysis, 3 separate, 2-tailed, independent-samples *t* tests were used to determine if CAR, normalized MVIC, and VAS scores



Figure 2. Representative force tracing during a transcranial magnetic stimulation (TMS) treatment. Point A represents the force during a maximal voluntary isometric contraction. Point B represents the force increase after the magnetic stimulation. Point C indicates when the magnetic stimulation was delivered to the motor cortex. Abbreviation: TMS, transcranial magnetic stimulation.

were different at baseline. Three  $2 \times 5$  analyses of variance with repeated measures on time were used to determine differences in CAR, MVIC, and VAS between treatment groups over time. The  $\alpha$  level was set a priori at .05. All statistical analyses were performed with SPSS (version 16.0 for Windows; SPSS Inc, Chicago, IL).

Standardized effect sizes were used to individually calculate the magnitude of both the TMS and the control intervention at each posttest, as well as the effect between groups using percentage change scores from baseline for both CAR and MVIC. Within-groups effect sizes were calculated by subtracting the posttest mean from the baseline mean and dividing that value by the pooled SD of the scores. The between-groups effect sizes were calculated by subtracting the percentage change in the TMS group from that of the control group and dividing it by the pooled SD of the percentage change scores for each group at each posttest. A 95% confidence interval (CI) was constructed around each effect size.

## RESULTS

The CAR, MVIC, and VAS scores (means ± SDs) are reported in Table 2. We found no difference in CAR ( $t_{18} =$ -0.878, P = .39), normalized MVIC ( $t_{18} = -0.936$ , P =.36), or VAS ( $t_{18} = -0.803$ , P = .43) between the TMS and control groups at baseline (Table 2). A difference in CAR was seen over time ( $F_{4,72} = 3.025$ , P = .02) but no interaction ( $F_{4,72} = 1.457$ , P = .22,  $1 - \beta = .431$ ) or difference between groups ( $F_{1,18} = 0.096$ , P = .76,  $1 - \beta =$ .06; Figure 3). We noted no main effects over time for MVIC ( $F_{4,72} = 0.79$ , P = .53,  $1 - \beta = .24$ ) or VAS ( $F_{4,72} =$ 0.64, P = .64,  $1 - \beta = .2$ ) and no main effects between groups for MVIC ( $F_{1,18} = 0.32$ , P = .58,  $1 - \beta = .08$ ) or

			Group			
	Tr	anscranial Magnetic Stimula	ation		Control	
Time	Central Activation Ratio, %	Maximal Voluntary Isometric Contraction, Nm	Visual Analog Scale, mm	Central Activation Ratio, %	Maximal Voluntary Isometric Contraction, Nm	Visual Analog Scale, mm
Baseline	$70.1\pm11.6$	194.1 ± 92.3	13.8 ± 17.1	$74.5\pm10.5$	$216.5 \pm 54.1$	$8.2\pm13.1$
0 min	$74.0 \pm 12.4$	211.6 ± 112.0	15.7 ± 20.2	$75.2 \pm 7.8$	$212.5 \pm 48.5$	7.7 ± 15.2
10 min	$76.0 \pm 10.3^{a}$	213.6 ± 87.7	$15.7 \pm 20.3$	$75.3 \pm 9.4$	214.6 ± 46.1	$9.8\pm13.8$
30 min	$75.1~\pm~10.7$	$203.3 \pm 72.0$	$16.3\pm26.6$	$78.0\pm9.3$	224.6 ± 49.1	$11.4 \pm 15.7$
60 min	$75.8 \pm 11.3^{\mathrm{a}}$	211.1 ± 79.2	13.2 ± 17.3	75.0 ± 11.0	$213.0\pm59.0$	8.7 ± 14.0

<sup>a</sup> No differences were found in primary or secondary outcome measures between groups.

VAS ( $F_{1.18} = 0.564$ , P = .46,  $1 - \beta = .11$ ). In addition, no interactions were demonstrated for MVIC ( $F_{4,72} = 1.49$ ,  $P = .21, 1 - \beta = .44$ ) or VAS ( $F_{4,72} = 0.184, P = .95, 1 - \beta$ = .09). Moderate effect sizes were found at 10 (Cohen d =0.54, 95% CI = -0.33, 1.37) and 60 (Cohen d = 0.50, 95%CI = -0.37, 1.33) minutes for CAR in the TMS group compared with baseline values, whereas the control group had small or weak effects at all time points compared with baseline (Table 3). Weak effect sizes were calculated for MVIC at all time levels when compared with baseline in the TMS and control groups (Table 3). When using percentage change scores to calculate effect sizes between groups at posttest, we calculated strong effect sizes for CAR at 10 (Cohen d = 0.82, 95% CI = -0.13, 1.7) and 60 (Cohen d = 1.06, 95% CI = 0.08, 1.95) minutes and for MVICs at 10 (Cohen d = 0.84, 95% CI = -0.11, 1.72) and 60 (Cohen d = 1.22, 95% CI = 0.21, 2.12) minutes in the TMS group (Table 3). Nine of 11 patients (82%) receiving TMS had an increase of 5 CAR percentage points, but only 5 of 9 patients (56%) in the control group had an increase of at least 5 CAR percentage points (Figures 4 and 5).

## DISCUSSION

We are the first to investigate the effects of TMS on muscle activation in patients with quadriceps inhibition after partial meniscectomy. We did not find an increase in CAR or MVIC after TMS when comparing groups (Figure 3). Authors have reported increases in quadriceps





Figure 3. Central activation ratio means and SDs over time. Means for the transcranial magnetic stimulation group were not different from the control group at any of the time points.

activation in healthy participants<sup>26,27</sup> and increased quadriceps-contraction forces in patients with total knee arthroplasties after TMS interventions.<sup>28</sup> The immediate effect of the TMS intervention in our participants might not have been as robust as that in the healthy<sup>26,27</sup> and total knee joint arthroplasty populations<sup>28</sup> of the previous studies. In addition, the dosage and nature of the intervention might not have been sufficient to have produced definitive effects in CAR. Only 3 stimuli were administered to the motor cortex in conjunction with MVICs, and this might not have been enough exposure to allow for disinhibition of an inhibited motor-neuron pool.

The objective of our study was to determine the effect of a single-pulsed TMS on CAR. Because other disinhibitory modalities, such as transcutaneous electric nerve stimulation<sup>22</sup> and focal joint cooling,<sup>22,25</sup> have been reported to elicit strong immediate effects on CAR, we hypothesized that TMS would have strong immediate effects on CAR. However, the sample size for our study might have been too small to reveal differences between groups using an intervention that might not elicit strong immediate effects. Our inability to identify differences between groups might have been due to relatively low power in detecting interactions  $(1 - \beta = .43)$  and between-groups effects  $(1 - \beta = .06)$ . In addition, TMS might require successive interventions to reveal effects on CAR that are similar to those found immediately after focal joint cooling<sup>22,25</sup> and transcutaneous electric nerve stimulation.<sup>22</sup> Progressive repeated voluntary contractions in addition to a disinhibitory intervention also might be necessary to encourage the motor system to use previously inhibited motor neurons.

Although the level to which quadriceps CAR must increase to alter function has not been defined clearly, 4 of the 11 participants (36%) receiving the TMS had at least 1 posttest data point exceeding 10 CAR percentage points from their baseline scores, whereas an additional 5 of the 11 participants (45%) exceeded 5 CAR percentage points after TMS (Figure 4). Therefore, 9 of the 11 participants (82%) had an increase of 5 CAR percentage points (Figure 4). Conversely, only 5 of the 9 participants (56%) in the control group had at least a 5-CAR percentage-point increase, and only 1 (11%) had an increase of more than 10 CAR percentage points (Figure 5). Some participants in the control group had immediate increases in CAR, which might have been caused by the repetitive MVICs performed during the control intervention and might have been a product of the activation testing, but the TMS group had CAR increases that seemed to be greater and to occur in a larger portion of the population (Figures 4 and

				Within-Groups	s Effect Size	Sa						
		Transcranial Ma	gnetic Stimul	ation		Cor	itrol			Between-Group	os Effect Size	þ
Posttest	Central	Activation Ratio	Maximal Vc Co	oluntary Isometric	Central /	Activation Ratio	Maximal V C	oluntary Isometric ontraction	Central A	ctivation Ratio	Maximal Vo Coi	untary Isometric itraction
Time, min	Cohen d	95% Confidence Interval	Cohen d	95% Confidence Interval	Cohen d	95% Confidence Interval	Cohen d	95% Confidence Interval	Cohen d	95% Confidence Interval	cohen d	5% Confidence Interval
0	0.32	-0.53, 1.15	0.17	-0.67, 1.00	0.08	-0.85, 1.00	-0.07	-0.99, 0.85	0.45	-0.46, 1.32	0.65c	-0.28, 1.53
10	0.54c	-0.33, 1.37	0.22	-0.63, 1.05	0.08	-0.85, 1.00	-0.04	-0.96, 0.89	0.82 <sup>d</sup>	-0.13, 1.7	0.84 <sup>d</sup>	-0.11, 1.72
30	0.45	-0.41, 1.28	0.11	-0.73, 0.94	0.35	-0.59, 1.27	0.16	-0.77, 1.08	0.32	-0.58, 1.19	0.29	-0.6, 1.17
60	0.50°	-0.37, 1.33	0.20	-0.65, 1.03	0.05	-0.88, 0.97	-0.07	-0.99, 0.86	1.06 <sup>d</sup>	0.08, 1.95	1.22 <sup>d</sup>	0.21, 2.12
<sup>a</sup> Indicat	es (posttest es (transcrai	<ul> <li>baseline)/pooled</li> <li>nial magnetic stimu</li> </ul>	SD. lation group -	- control aroun)/poc	oled SD.							

5). Although our study was designed to assess discrete time points within a 60-minute interval, CAR might fluctuate differently among individuals after TMS. Furthermore, this informal qualitative data analysis might suggest that some individuals respond and others do not respond to TMS. Researchers of disinhibition should focus on determining if there is a systematic means of identifying participants who are likely to respond beneficially to a TMS intervention.

Although conventional interferential statistics did not reveal that CAR was different, moderate effect sizes at 10 and 60 minutes for CAR were found after TMS compared with baseline values, and strong effect sizes for TMS were calculated at both 10 and 30 minutes when comparing percentage change scores between groups at all posttests (Table 3). Although moderate to strong effect sizes were found for CAR at 10 and 60 minutes when comparing the TMS posttests with the baseline scores and when comparing TMS percentage change scores with those of the control group, 95% CIs for 3 of these point measures (not the 60minute between-groups effect size) crossed zero, making it impossible to definitively suggest CAR increased after TMS (Table 3). Small effect sizes were noted for MVIC compared with baseline values in both the TMS and control groups (Table 3). Moderate effect sizes were found between groups at 0 minutes, whereas strong effect sizes were seen at 10 and 60 minutes in the TMS group (Table 3).

Quadriceps inhibition is a serious impairment that has been demonstrated in patients with acute7-9,17,18,42 and chronic joint injuries.<sup>12,13,22</sup> The CAR has been reported to be affected by alterations in both motor-unit recruitment and firing frequency,43 which decrease the torque-generating capabilities of the muscle. The inability to optimally activate the muscles might lead to altered neuromuscular control, including altered kinematics during gait and dynamic activities (eg, landing) that might lead to or hasten the progression of joint degeneration. Conventionally, clinicians treat muscle-strength deficits without targeting the underlying arthrogenic muscle inhibition, which has been considered a limiting factor in joint rehabilitation and might require specialized therapy for regaining inhibited muscle.<sup>2</sup> Therefore, identifying a disinhibitory agent that can adequately excite the neural system to improve the performance of therapeutic exercise is important in combating arthrogenic muscle inhibition. Moderate to strong effects for CAR immediately after an initial TMS treatment in this small population might be enough evidence to justify future studies in which the effects of TMS on CAR in patients with inhibited musculature are evaluated. In addition, researchers should evaluate potential pathways and neural mechanisms that can be influenced by TMS in patients with neuromuscular deficits after joint injury.

Magnetic stimulation of the motor cortex causes excitation of the neural tissue, which is transmitted through descending pathways to the muscle.<sup>44</sup> At this point, the neural mechanisms that contribute to muscle activation in inhibited quadriceps after TMS are unknown. Iles<sup>31</sup> reported that presynaptic inhibition from  $\gamma$ -aminobutyric acid interneurons is decreased after magnetic stimulation. A decrease in presynaptic inhibition, which ultimately down-regulates motor-neuron pool excitability, might increase the number of motor neurons available during

Indicates moderate effect sizes

Indicates strong effect sizes

Effect Sizes (Cohen d) and 95% Confidence Intervals Within and Between Groups

ė

Table



Figure 4. Central activation ratio (CAR) means for individuals in the transcranial magnetic stimulation group over time. Squares represent individuals who increased in CAR at least 10 CAR percentage points from baseline. Triangles represent individuals who increased in CAR at least 5 CAR percentage points from baseline. Circles represent individuals who did not increase in CAR or whose increase was less than 5 CAR percentage points.

an MVIC, increasing volitional activation. Authors have suggested that posttetanic potentiation or increased amplitude of postsynaptic potentials might play a role in the increased activation of muscle after TMS.<sup>27,28</sup> Posttetanic potentiation is caused by a transient saturation of calciumbuffering systems, leading to excess calcium availability for each action potential.<sup>45</sup> Increased calcium can produce increased neurotransmitter release from the presynaptic cell, which has the potential to increase synaptic transmission to corresponding postsynaptic cells. Increased postsynaptic transmission to previously inhibited alpha motor neurons might allow for increased activation of the muscle. Possible consequences of repeated TMS during MVICs might be long-term potentiation, which is thought to be associated closely with the effects described by previous authors.<sup>27,28</sup> Long-term potentiation is the enhancement of synaptic transmission after exposure to certain stimuli that can last from hours to weeks. It is based on the Hebb rule,



Figure 5. Central activation ratio (CAR) means for individuals in the control group over time. Squares represent individuals who increased in CAR at least 10 CAR percentage points from baseline. Triangles represent individuals who increased in CAR at least 5 CAR percentage points from baseline. Circles represent individuals who did not increase in CAR or whose increase was less than 5 CAR percentage points.

suggesting that "synapses that fire together will wire together."<sup>46</sup> Multiple treatments of TMS in conjunction with MVICs might be needed to cause long-term potentiation.

We noted methodologic differences between our study and previous studies of TMS.<sup>26–28</sup> Past research<sup>28</sup> on the effects of TMS in a population with quadriceps inhibition involved patients who had total knee arthroplasties and a mean age of 62 years. We studied patients after partial meniscectomy who had a mean age of 38.1 years. The variability in the mean weeks after surgery was large for both groups tested, yet means and SDs for both groups were similar (Table 1). For this initial investigation into the effects of TMS in the meniscectomy population, we were interested in studying patients who had marked clinical quadriceps inhibition (CAR  $\leq 0.85$ ) due to meniscectomy, regardless of the time since surgery. In future studies, researchers might consider whether an optimal postoperative time frame exists for administering a TMS intervention.

In addition, we used the burst-superimposition technique, whereas other researchers have used the interpolated-twitch technique.<sup>26–28</sup> A similar figure-8–shaped coil was used in our study and in previous research, but our positioning was individualized for each participant. We located the area of the motor cortex that gave us the largest peak-to-peak motor evoked potential of the vastus lateralis. In past research, the coil was placed at a predetermined area for each participant (over the vertex 2 cm contralateral to the quadriceps being investigated between Cz and C3 tangentially to the midline).<sup>26–28</sup> The number of treatment stimuli that we gave was the same as in past research.<sup>26–28</sup> We performed an additional 5 submaximal stimuli before the treatment session during the location of the motor cortex.

#### CONCLUSIONS

Quadriceps CAR and MVIC were not increased after TMS compared with the control group. Moderate CAR effect sizes were found at 10 and 60 minutes after TMS compared with baseline scores, whereas strong effect sizes for TMS were noted for both CAR and MVIC at 10 and 60 minutes when comparing percentage change TMS scores with those of the control group.

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