Conditioning Brain Responses to Improve Quadriceps Function in an Individual With Anterior Cruciate Ligament Reconstruction

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Background: Persistent quadriceps weakness and activation failure are common in individuals with anterior cruciate ligament (ACL) reconstruction. A growing body of evidence indicates that this chronic quadriceps dysfunction could be partly mediated due to reduced corticospinal excitability. However, current rehabilitation approaches do not directly target corticospinal deficits, which may be critical for restoring optimal clinical outcomes after the surgery. This case study tested the feasibility of operant conditioning of torque responses evoked by transcranial magnetic stimulation (TMS) to improve quadriceps function after ACL reconstruction.

Hypothesis: Operant conditioning of motor evoked torque responses would improve quadriceps strength, voluntary activation, and corticospinal excitability.

Study Design: Case study and research report.

Level of Evidence: Level 5.

Methods: A 24-year-old male with an ACL reconstruction (6 months postsurgery) trained for 20 sessions (2-3 times per week for 8 weeks) to increase his TMS-induced motor evoked torque response (MEP torque) of the quadriceps muscles using operant conditioning principles. Knee extensor strength, voluntary quadriceps muscle activation, and quadriceps corticospinal excitability were evaluated at 3 time points: preintervention (pre), 4 weeks (mid), and immediately after the intervention (post).

Results: The participant was able to successfully condition (ie, increase) the quadriceps MEP torque after 1 training session, and the conditioned MEP torque gradually increased over the course of 20 training sessions to reach about 500% of the initial value at the end of training. The participant's control MEP torque values and corticospinal excitability, which were measured outside of the conditioning paradigm, also increased with training. These changes were paralleled by improvements in knee extensor strength and voluntary quadriceps muscle activation.

Conclusion: This study shows that operant conditioning of MEP torque is a feasible approach to improving quadriceps corticospinal excitability and quadriceps function after ACL reconstruction and encourages further testing in a larger cohort of ACL-reconstructed individuals.

Clinical Relevance: Operant conditioning may serve as a potential therapeutic adjuvant for ACL rehabilitation.

Keywords: knee injury; quadriceps dysfunction; voluntary activation; arthrogenous muscle inhibition; motor evoked torque; TMS; functional rehabilitation

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Anterior cruciate ligament (ACL) injuries are common in individuals who participate in cutting and pivoting sports, such as football (soccer), basketball, American football, and rugby.⁵ Quadriceps weakness and activation failure (ie, the inability to completely activate the quadriceps muscles due to neural inhibition) rapidly occur after ACL reconstruction and persist for months to years after surgery.^{8,10,23} This persistent quadriceps dysfunction has been linked to abnormal biomechanics, poor self-reported knee function, and reduced work and sports activity levels after surgery.^{19,27,28,40} Furthermore, altered movement patterns and abnormal joint loading due to poor quadriceps strength have been theorized as the underlying cause of early posttraumatic knee osteoarthritis.^{3,7,9} This notion has been supported by prospective and retrospective studies that show a direct association between quadriceps weakness and radiographic evidence of posttraumatic osteoarthritis in individuals with ACL injury and reconstruction.^{11,36} Thus, restoring quadriceps strength and function is critical for long-term knee health of individuals with ACL reconstruction.

A major goal of ACL rehabilitation is to restore the surgically reconstructed knee back to its preinjury status. To achieve this goal, most clinicians strive to restore bilateral knee symmetry, such that the reconstructed knee is able to replicate the non-reconstructed knee in terms of range of motion, stability, strength, and function.¹ However, after the injury and surgery, individuals may experience altered neurophysiological changes due to lost mechanoreceptors of the ACL and compensations in neuromuscular control.³⁷ Furthermore, injury-related pain, effusion, instability, and altered movement patterns may alter the neuronal input to the central nervous system.⁶ Similarly, efferent outputs from the central nervous system are also disrupted, resulting in altered long-latency reflexes and corticospinal excitability.^{21,24} This altered corticospinal excitability may in turn reduce the neural drive to the quadriceps muscle during maximal voluntary contractions and subsequently contribute to the reduction in voluntary activation and persistent quadriceps weakness after ACL reconstruction.^{18,39} Thus, it is important to address the issue of altered neurophysiology and corticospinal dysfunction to optimally restore knee strength and function. However, current rehabilitation interventions typically do not focus on restoring corticospinal function after ACL reconstruction. Furthermore, it is currently unclear if such interventions that directly address corticospinal dysfunction are expected to improve quadriceps strength and function.

In this case study, we attempted to fill this important gap in the literature by testing a behavioral training paradigm aimed at increasing the excitability of the corticospinal pathways. Specifically, we used an operant conditioning paradigm, which is a form of reward-based learning,^{30,35} to increase corticospinal excitability of the quadriceps muscle. Operant conditioning has been effectively used to condition the spinal stretch reflex (or its electrical analog, H-reflex) in rats,² primates,³⁸ and people with and without spinal cord injury.^{32,33} Such reflex operant conditioning has been shown to facilitate neural plasticity and improve locomotor functions (eg, gait symmetry and walking

speed) in individuals with neurological injuries.³³ However, clinical studies of operant conditioning to date have been targeted at improving motor functions in people with central nervous system disorders, and the applicability of operant conditioning to nonneurological injuries has never been investigated. Furthermore, the feasibility of operant conditioning of motor-evoked torque response, which may be more easily translated to the clinic than conditioning an electromyography-evoked potential (e.g., H-reflex), has not been tested. The approach of operant conditioning of motor evoked torque responses to improve quadriceps strength and activation is also unique because by conditioning the motor evoked torque instead of motor evoked potentials, the entire quadriceps muscle group is targeted rather than a particular muscle and the variability in training responses is minimized, as torque responses are less variable than surface electromyography. Hence, based on the current neurophysiological understanding of persistent quadriceps weakness after ACL injury and the availability of the emerging operant conditioning approach, we carried out a case study to evaluate the feasibility of operant conditioning of motor evoked torque responses and its applicability to restore quadriceps function in an individual with ACL reconstruction.

METHODS

Participant Description

The participant involved in this case study identified himself as a white or Caucasian (non-Hispanic ethnicity) adult male (age 22.5 years, body height 188.0 cm, body mass 97.5 kg, body mass index 27.6 kg/m²) who sustained an injury to his left knee (nonpreferred kicking leg) while playing a recreational flag football match at his university. The injury occurred during a seemingly routine evasive sidestep where the participant planted his left leg and attempted to redirect toward the right. During the sidestep, there was no contact made with the opposition or any other object. Subsequent magnetic resonance imaging demonstrated a full-thickness complete tear of the ACL, grade 2 tear of the medial collateral ligament, lateral femoral condyle osteochondral defect, and a vertical longitudinal tear of the posterior horn of the lateral meniscus. The participant was initially treated conservatively with immobilization (nonweightbearing in a long-leg cast in extension for 2 weeks, after which a T Scope Premier Post-Op Knee Brace [Breg, Inc] locked in extension was prescribed) to help reduce swelling and promote healing of the medial collateral ligament prior to surgical intervention. Nineteen weeks after the injury, the participant underwent a successful arthroscopic reconstruction of the torn ligament using bone–patellar tendon–bone autograft and was shortly after released from the hospital. After surgery, the participant underwent standard of care procedures, including rehabilitation to improve activities of daily living. The participant was recruited to participate in the study 6 months after his surgery (~10 months from the injury occurrence). A detailed timeline of the participant's injury status and study involvement can be found in Figure 1A.

Figure 1. Schematic of the (A) participant's injury and general timeline, (B) operant conditioning study timeline, and (C) detailed operant conditioning protocol.

At the time of enrollment, the participant had no known history of significant knee injuries (other than the current ACL reconstruction), lower extremity fracture, diabetes, hypertension, or any other major medical condition that would preclude him from participation. Additionally, we ensured that the participant did not have any known contraindications to transcranial magnetic stimulation (TMS); such as intracranial metallic or magnetic implants, pacemaker or other medical device implants, head injury or fractures, history of seizures or epilepsy, and current epileptogenic medications. Prior to his involvement, the participant was fully informed of all aspects of the research via written and verbal material and provided his full written informed consent on documents approved by the University of Michigan Institutional Review Board. The study was registered on www.clinicaltrials.gov (NCT03209531).

Study Overview

The participant was trained for 20 sessions over an 8-week period (2-3 sessions per week), where he underwent an operant conditioning intervention to increase his motor evoked torque

response (MEP torque) of the quadriceps muscles (Figure 1B).³⁴ An 8-week period was chosen as this is typical for operant conditioning programs.³³ Details of the intervention are described in the subsequent paragraph. There were 3 testing points: pre, mid, and post that occurred at the beginning, middle, and end of the training period, respectively. At the pre testing point, we measured the participant's knee extensor strength and voluntary activation, self-reported knee outcome measures, as well as corticospinal excitability by performing an MEP torque recruitment curve and control TMS trials. Corticospinal excitability measurements were repeated over 2 separate testing sessions. The mid testing point occurred after 4 weeks of training. Here, we remeasured strength and voluntary activation and performed a single bout of corticospinal excitability testing along with additional control TMS stimulations. After 20 sessions of training, we performed post testing, which was a repeat of the mid testing procedures and included self-reported knee outcome measures. Greater details of all of these procedures can be found in the subsequent sections.

Figure 2. A visual depiction of the interpolated triplet technique, including the equation to compute voluntary activation as a percentage; where a = evoked torque when the muscle is at rest, b = peak muscle torque generated by the participant during maximum voluntary isometric contraction (MVIC) and c = peak-evoked torque generated during MVIC. Torque is presented in Newton-meters (N·m) and time in milliseconds (ms).

Intervention: Operant Conditioning of MEP Torque

The goal of this intervention was to train the participant to increase the TMS-induced MEP torque responses of the quadriceps muscles. To achieve this goal, we performed TMS over the participant's primary motor cortex using a mild stimulation (110% of his active motor threshold [AMT] while providing a background contraction at 5% of his knee extensor maximum voluntary isometric contraction [MVIC]) and measured the torque of the resulting muscle twitch using a dynamometer. The participant's AMT and MVIC were established during pretesting. At the beginning of the study, the participant first underwent 2 baseline sessions to establish a stable baseline value for the participant's evoked torque response. During each baseline session, the participant performed 40 *control trials* on the non-reconstructed leg and 225 *control trials* (3 blocks of 75 trials) on the reconstructed leg, where TMS-evoked MEP torque responses were obtained while the participant did not receive feedback or attempt to increase (up-condition) his response. During each training session, we first had the participant perform 20 control trials on the reconstructed leg, which were used to establish an initial criterion value for the session. The participant subsequently performed *conditioning trials* (225 trials split into three 75-trial blocks), which were similar to control trials, except the participant was instructed to increase the amplitude of his evoked torque response to exceed the criterion value (eg, by imagining contracting his quadriceps or performing an exercise/sports action). The participant was provided with immediate visual feedback on whether or not the response exceeded the criterion value (ie, whether or not

the trial was a success). Throughout the training, the criterion value was dynamically determined based on the participant's performance. The criterion for the first block of training was established from the control trials and a new criterion was calculated for each block based on the preceding block.³³ The criterion value was selected such that if evoked responses for the new block were similar to those of the previous block, ~60% of the trials would be successful. For additional incentive, a modest monetary reward was provided if the participant exceeded a success rate of 60% (20 cents for each percentage greater than 60%). We measured the MEP torque of the quadriceps muscle for each trial as the maximum torque within the first 100 ms after the stimulus to remove any volitional response to the stimulation. During each training session, we collected mean amplitude of the initial control trials and conditioning trials. Additionally, we measured the participant's success rate while performing conditioning trials. These procedures were performed using custom software written in LabVIEW 2011 (National Instruments Corp).

Outcome Measures

Knee Strength and Voluntary Activation

The participant was seated on an isokinetic dynamometer (System 4 Pro, Biodex Medical Systems) and secured to the system via chest, waist, and thigh straps. During setup, the dynamometer's axis of rotation was aligned with the axis of rotation of the leg being tested and the distal end of the shank was tightly strapped to the machine's knee extension/flexion attachment. The participant's lower leg was positioned at 60° of knee flexion relative to his full anatomical knee extension (0°). This setup in the dynamometer was used for all measures of knee strength, voluntary activation, and corticospinal excitability, as well as during the training.

Knee extensor strength and voluntary muscle activation were evaluated by collecting the participant's MVIC and performing the interpolated triplet technique on the quadriceps muscle group (Figure 2).¹⁵ These tests were performed bilaterally during the pre, mid, and post testing sessions. The non-reconstructed (right) leg was assessed first followed by the reconstructed (left) leg.^{14,15} Before testing, two 7.0 × 13.0 cm Dura-Stick Plus self-adhesive electrodes (Chattanooga, DJO, LLC) were placed over the participant's proximal and distal quadriceps muscles. As a warmup, the participant then performed 3 submaximal isometric knee extensor contractions at 25%, 50%, and 75% of his perceived maximum effort; after this, he performed a practice isometric knee extension contraction at his maximal effort to potentiate the quadriceps muscles. Electrical stimulation of the quadriceps muscle group was performed using a high-voltage, constant-current electrical stimulator (DS7AH; Digitimer North America, LLC). To determine the maximal current intensity for voluntary activation testing, we stimulated the quadriceps muscles at rest with pulse trains (3 pulses, 100 Hz, 200-μs pulse duration, 400 V) in current steps of 100 mA (beginning at 100 mA) until the electrically evoked torque no longer increased, but decreased.¹⁵ The current was then reduced by 50 mA and a final stimulus was

provided. The current intensity that produced the maximum torque was used for testing.

After a brief rest period, the participant performed three 5-second MVICs that were separated by 2 minutes of rest. During each MVIC, the participant's quadriceps muscles were electrically stimulated using the predetermined current intensity to evaluate the level of voluntary drive to the quadriceps muscles. The stimulator was triggered automatically using a validated automated torque-based triggered approach.¹² Loud verbal encouragement and visual feedback of the participant's torque curve were provided to increase the likelihood of a true maximal effort. The voluntary peak torque prior to the delivery of electrical stimulus was used to evaluate quadriceps strength. Voluntary activation was estimated using the following equation:

$$\% \text{ of Voluntary Activation} = \left[1 - \frac{\text{Evoked Torque During Contraction}}{\text{Evoked Torque at Rest}} \right] \times 100$$

A limb symmetry index was also computed by expressing the peak torque of the reconstructed leg as a percentage of peak torque of the non-reconstructed leg.

Corticospinal Excitability

Corticospinal excitability was evaluated by measuring the participant's recruitment curve (ie, the relationship between stimulus intensity and the MEP torque) and performing control trials. These tests were performed bilaterally during the pre, mid, and post testing sessions. During all TMS procedures (including training), the participant was seated in the dynamometer in order to measure his torque response to stimulation. Motor evoked responses were elicited using a Magstim 200² stimulator (Magstim, Inc) via a 110-mm diameter double-cone coil. The coil was oriented to induce a posterior-to-anterior current flow in the cortex. The quadriceps hotspot location was determined by first measuring 1.0 cm posterior and 2.0 cm lateral from the vertex, such that the hotspot was contralateral to the leg being tested.¹³ From this location, the coil was then systematically moved in order to determine the location that elicited the largest and most consistent knee extensor twitch torque. This location was then marked on a fabric cap to ensure the location did not change within sessions. During the pre session, AMT was established using an adaptive threshold-hunting method based on maximum-likelihood parameter estimation by sequential testing (TMS Motor Threshold Assessment Tool, MTAT 2.0, <http://www.clinicalresearcher.org/software.htm>). For all TMS procedures, the participant performed a small background contraction (5% of MVIC).

Recruitment curves were performed by stimulating over the quadriceps hotspot at intensities ranging from 70% to 140% of AMT (in 10% increments). Five stimuli were provided at each testing intensity and the ensemble average of the 5 traces was

used in the analysis. The peak amplitude was then plotted against the stimulus intensity to construct the recruitment curve. The recruitment curve was fitted with a Boltzmann sigmoidal function.^{4,16} The fit was calculated using the Levenberg-Marquardt algorithm in LabVIEW. The Boltzmann function characterizes the MEP size as a function of stimulus intensity with three parameters as follows:

$$MEP = \frac{MEP_{max}}{1 + e^{\frac{S_{50}-S}{k}}}$$

where MEP amplitude (*MEP*) is the dependent variable and stimulus intensity (*S*) is the independent variable. The parameters relating to maximal MEP torque size (*MEP_{max}*), curve slope (*k*), and stimulus intensity leading to half-maximal MEP torque size (*S₅₀*) were derived from the curve-fitting procedure. The intervention-mediated changes in corticospinal excitability were assessed by examining the changes in these parameters.

Control trials were performed to measure the participant's unconditioned response to TMS. For the pre session, we used the control trials from the baseline sessions of the reconstructed (2 × 225 trials performed over 3 blocks of 75) and the non-reconstructed (2 × 40 trials) legs. During the mid and post testing sessions, the participant performed 40 trials on each leg.

Patient-Reported Outcomes

We also evaluated several self-reported outcomes pertaining to ACL injury to gain a more holistic understanding of the intervention and the participant's experience at the pre and post testing points. These assessments included (1) the Tegner activity level scale, (2) the Marx activity rating scale, (3) the International Knee Documentation Committee Subjective Knee Evaluation Form, (4) the Knee injury and Osteoarthritis Outcome Score, (5) the Lysholm Knee Scoring Scale, and (6) the Patient-Reported Outcomes Measurement Information System Physical Function Questionnaire.

RESULTS

The intervention was both safe and feasible—the participant noted no adverse effects over the course of this study. During the training, the participant successfully increased his TMS-induced quadriceps muscle twitch torque, indicated by a conditioned MEP torque that was larger than the control (Figure 3, A and B). This MEP torque increase occurred in each conditioning session except for the first conditioning session. The feedback and reward adequately incentivized the participant to increase his torque response, as he consistently achieved a success rate of greater than 60th percentile throughout the intervention (Figure 3C). When prompted on his method for increasing his torque response during training, the participant stated that he typically imagined himself performing leg exercises or pitching a baseball.

Figure 3. (A) Average motor evoked torque (MEP torque) during each conditioning session as a percentage of baseline (average of 2 sessions) for the control and conditioned trials. Error bars indicate SD of the 3 blocks of training during each session. (B) Difference between MEP torque responses elicited during the conditioning and control trials as a percentage of baseline (ie, short-term within-session changes in corticospinal excitability). Positive values indicate the participant successfully increased his response during that session. (C) The percentage of conditioning trials that exceeded the criterion value during each session (ie, success rate).

Table 1. Quadriceps peak torque and voluntary activation of the non-reconstructed and reconstructed legs at pre-, mid-, and post-conditioning assessments

Assessment	Leg	PT, N-m	PT, N-m/kg	LSI, %	VA, %
Pre	Reconstructed	254.0	2.6	77.2	79.4
	Non-Reconstructed	328.9	3.4		92.3
Mid	Reconstructed	285.0	2.9	83.5	85.6
	Non-Reconstructed	341.4	3.5		89.4
Post	Reconstructed	286.8	2.9	87.1	90.2
	Non-Reconstructed	329.4	3.4		92.8

LSI, limb symmetry index; Mid, at the 4-week midpoint of conditioning sessions; Post, concluding subsequent to conditioning sessions; Pre, commencing prior to conditioning sessions; PT, peak torque; VA, voluntary activation.

Knee Strength and Voluntary Activation

The quadriceps MVIC of the reconstructed leg improved at the mid and post time points when compared with pre (12% and 13%, respectively). The MVIC of the non-reconstructed leg remained relatively stable at the mid and post time points when compared with pre (4% and 0%, respectively) (Table 1). The limb symmetry index at pre (77%) also improved at mid and post (83% and 87%, respectively). Voluntary activation of the reconstructed leg increased at the mid and post time points when compared with pre (8% and 14%, respectively). Again, the non-reconstructed leg showed small fluctuations at the mid and post time points when compared with pre (−3% and 1%, respectively).

Corticospinal Excitability

In the reconstructed leg, corticospinal excitability appeared to increase throughout the recruitment curve (90% to 140% AMT) due to training (Figure 4, top). When a Boltzmann sigmoidal function was fit to the recruitment curves, we saw that MEP_{max} increased at both mid and post when compared with pre (56% and 85%, respectively). The stimulus intensity leading to half-maximal MEP torque size (S_{50}) slightly reduced at mid and post when compared with pre (−2% and −10%, respectively). Meanwhile, the slope (k) increased at both the mid and post time points when compared with pre (33% and 53%, respectively). In the non-reconstructed leg, corticospinal excitability increased marginally at higher stimulus intensities

Figure 4. Motor evoked torque (MEP torque) recruitment curves during the pre, mid, and post evaluation sessions. Recruitment curves were collected between 70% and 140% of active motor threshold for the reconstructed (top) and non-reconstructed (bottom) legs. Corticospinal excitability parameters gathered by fitting a Boltzmann sigmoidal function to each recruitment curve are located to the right of each of the recruitment curve plots.

(120%, 130%, and 140% AMT) and only during the post assessment (Figure 4, bottom). We found changes in MEP_{max} at the post and mid time points were (−20% and 63%, respectively) when compared with pre. S_{50} appeared to remain unchanged at the post and mid time points when compared with pre (−3% and 5%, respectively). Slope (k) was marginally decreased at mid but appeared to increase at post (−13% and 68%, respectively) when compared with pre.

In the reconstructed leg, the MEP torque values observed during the control trials also increased at both mid and post when compared with pre (81% and 201%, respectively) (Figure 4). In the non-reconstructed leg, the MEP torque was decreased

at mid (−20%) and slightly increased at post (64%) when compared with pre (Figure 5).

Patient-Reported Outcomes

All clinical assessment scores improved between the pre to post time points. These values are provided in Table 2.

DISCUSSION

The purpose of this case study was to investigate whether operant conditioning of motor evoked responses can promote corticospinal excitability and thereafter improve quadriceps

Figure 5. Control motor evoked torque responses (MEP torque) elicited at 110% of active motor threshold during the pre, mid, and post evaluation sessions.

strength and voluntary activation in the ACL reconstructed leg after surgery. The results of this study are very encouraging and indicate that operant conditioning of motor evoked responses can increase corticospinal excitability and improve quadriceps strength and voluntary activation. The participant assessed in this case study underwent operant conditioning sessions where he was trained to systematically increase his MEP torque responses via real-time visual feedback. Through this training, the participant was able to successfully (1) increase his corticospinal excitability; (2) increase his quadriceps strength and voluntary activation of the reconstructed leg, thereby improving his limb symmetry index; and (3) improve his overall clinical assessment scores pertaining to general activity level, knee function, pain level, and quality of life.

There is a growing body of evidence linking deficits in quadriceps strength to reductions in corticospinal excitability after ACL reconstruction surgery.^{17,20,25,39} However, rehabilitation techniques typically focus on directly training strength and do not specifically target the underlying deficits in corticospinal excitability. Hence, this intervention is unique because it was designed to indirectly address quadriceps weakness by training the patient to increase his corticospinal excitability. Indeed, we found that the participant was able to successfully increase his corticospinal excitability, and this was coupled with increases in voluntary activation and quadriceps strength. Although these are exciting results, trainings such as this are unlikely to replace direct high-intensity quadriceps strengthening techniques (eg, eccentric contraction or neuromuscular electrical stimulation). Rather, we feel that this training could be a therapeutic adjuvant to be administered either along with strength training or be used in the acute phase of recovery, where traditional high-intensity interventions could be harmful to the graft or cause patellar fracture.²⁶

Operant conditioning is typically used to downregulate spinal reflexes in patients with neurological injury, such as spinal cord injury.^{22,29,33} This study is the first to use operant conditioning to

Table 2. Comparison of participant's clinical scores measured at the pre and post time points

Clinical Assessment	Pre	Post
Tegner	3	4
Marx	0	3
Lysholm	95	100
KOOS—Symptoms	93	100
KOOS—Pain	89	100
KOOS—ADL	97	99
KOOS—Sports	20	100
KOOS—QOL	63	94
IKDC	60	83
PROMIS	45	52

ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; PROMIS, Patient-Reported Outcomes Measurement Information System; QOL, quality of life.

increase corticospinal excitability using TMS-based motor-evoked responses after ACL reconstruction surgery. Similar to the previous studies, the participant in this study showed corticospinal adaptations to the conditioning protocol; however, the time-course of conditioning differed slightly. The time-course of conditioning has 2 mechanisms, consisting of a short-term component (measured within-session as the difference between conditioning and control trials) and a long-term component (measured over the course of the training through control trials).^{31,33} In this study, the participant successfully increased both components. Notably, he showed short-term adaptations as early as the second training session. This is in contrast to existing studies that conditioned spinal reflexes in neurologically injured patients, where participants typically do not show short-term adaptations until later in the training (approximately 6 sessions).^{33,34} We note that this is an observation from a single participant with an intact nervous system, where conditioning of TMS-evoked motor responses was performed as opposed to H-reflex. It is currently unclear whether the differences in time-course are more related to the methodology used (TMS vs H-reflex) or due to the differences in patient population. Further research is warranted to better understand the time-course of operant conditioning of motor-evoked responses in individuals with ACL injury/surgery.

Study Limitations

There are several limitations to this study. First, this is a case study, and any information has to be confirmed by testing on a

larger number of participants. As with any case study, the main takeaway is the safety and feasibility of the intervention. Second, some of the improvements in quadriceps function may have been due to the normal recovery process. However, we note that the participant was enrolled in this study after completing his traditional rehabilitation, and the contralateral limb showed little improvement over the course of the training. Furthermore, it is unlikely that the magnitude of changes observed in the MEP measures could be attributed to the natural recovery process. Third, many of our training parameters were chosen based on previous literature on neurologically injured patients,³³ but we are unsure how these parameters (eg, stimulation intensity, amount of background contraction, number of visits required, number of conditioning trials) have to be tailored to best treat patients with ACL injuries using TMS. Future studies are required to elucidate the best combination of these parameters. Fourth, the proposed intervention is not immediately translatable to the clinic, as single-pulse TMS has not been approved by the US Food and Drug Administration for this application. However, repetitive TMS, which typically uses a much larger number of TMS pulses, has been approved to treat patients with chronic depression. Thus, there may be a precedence for future use of single-pulse TMS for physical rehabilitation. Last, the benefit-cost ratio of TMS-based interventions are currently unclear because TMS equipment is expensive and third-party payers (ie, health insurance companies) typically do not cover such therapies. Hence, apart from providing strong clinical evidence to support the benefit of operant conditioning, it is critical to develop a robust, easy-to-use, affordable technology to improve the clinical utility of operant conditioning paradigms.

CONCLUSION

This case study supports the safety and feasibility of operant conditioning of motor evoked responses to increase corticospinal excitability and improve quadriceps function after ACL reconstruction. Over the course of the training, the participant was able to increase corticospinal excitability of the quadriceps muscle group, which was coupled with increases in quadriceps strength, voluntary activation, and limb symmetry. These results support the further development of this approach toward testing on a larger cohort of participants in a controlled clinical trial. If successful, therapies such as this could act as an adjuvant for strength training, or as an alternative treatment in the acute phase of recovery, where traditional high-intensity interventions may not be feasible due to safety reasons.

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