Operant Conditioning of Corticospinal Pathways Following Anterior Cruciate Ligament Reconstruction and Total Knee Arthroplasty

by

Kazandra Rodriguez

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Doctoral Committee:

Associate Professor Chandramouli Krishnan, Co-Chair
Professor Riann Palmieri-Smith, Co-Chair
Clinical Associate Professor Adam Lepley
Professor Brian Umberger
Professor Edward Wojtys

Kazandra Rodriguez

kazandra@umich.edu

ORCID iD: 0000-0002-4947-8510

Dedication

To my family and husband, whose unwavering support and encouragement have been instrumental in the pursuit of my academic and personal goals.

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Abstract

Reduced corticospinal excitability has been theorized to contribute to quadriceps dysfunction after knee injury and surgery. Current rehabilitation methods do not directly target corticospinal pathways, which may limit recovery. Operant conditioning is an emerging approach that can address this issue; however, whether it can improve quadriceps function is unclear. Further, dosage parameters used during operant conditioning (i.e., stimulus intensity and number of trials) appear to be selected arbitrarily and lack empirical support. Given the importance of appropriate dosage for intervention efficacy, sub-optimal dosage parameters may limit therapeutic benefits. Therefore, this dissertation aimed to: 1) determine the feasibility and effect of dosage parameters (intensity, number of trials) on the ability to increase corticospinal excitability following anterior cruciate ligament (ACL) reconstruction and total knee arthroplasty (TKA) and 2) evaluate the effect of operant conditioning on quadriceps function following ACL reconstruction.

This dissertation consists of four studies. In Study 1, we evaluated the reliability of the motor evoked responses elicited by transcranial magnetic stimulation in ACL reconstructed individuals. We found that raw motor evoked torque (MEP_{TORQUE}) and motor evoked potentials (MEP_{EMG}) demonstrated good reliability. However, MEP_{TORQUE} generally demonstrated higher reliability than MEP_{EMG}, regardless of the normalization method. Findings from Study 1 support the use of MEP_{TORQUE} as a suitable target variable for upregulating quadriceps corticospinal excitability after knee surgery.

In Study 2, we tested: 1) the ability of individuals with ACL reconstruction to up-condition quadriceps corticospinal excitability in a single session and 2) the influence of stimulus intensity on changes in corticospinal excitability following ACL reconstruction. We found that ACL reconstructed individuals improved their corticospinal excitability within a single session, which were paralleled by acute neural adaptations. However, the ability to up-condition and the associated neural adaptations were not influenced by stimulus intensity. Findings from Study 2 indicate that operant conditioning is a feasible intervention for improving corticospinal excitability after ACL reconstruction, and any of the stimulus intensities (100/120/140% of active motor threshold) tested are suitable for future interventions.

In Study 3, we tested the effect of multiple training sessions on 1) the ability to increase corticospinal excitability and 2) quadriceps strength and voluntary activation following ACL reconstruction. We found that the conditioning group significantly improved their corticospinal excitability during training whereas the sham-conditioning group did not. Both groups also improved quadriceps strength and voluntary activation in the reconstructed leg. Findings from Study 3 suggest that ACL reconstructed individuals can improve their corticospinal excitability and that operant conditioning has the potential to improve quadriceps function after ACL reconstruction.

In Study 4, we tested: 1) the ability of individuals with TKA to up-condition quadriceps corticospinal excitability within a single session and 2) the influence of stimulus intensity and number of trials on changes in corticospinal excitability after TKA. We found that individuals with TKA were able to improve their corticospinal excitability, which was paralleled by acute neural adaptations in the corticospinal pathway. However, the ability to up-condition and the associated neural adaptations were not influenced by stimulus intensity. In addition, individuals

with TKA did not improve their corticospinal excitability after 75 trials, but succeeded following 150 and 225 trials, indicating that 150 trials is sufficient for acute neural adaptations.

Collectively, this dissertation establishes the feasibility and optimal dosage of operant up-conditioning and its ability to successfully improve corticospinal excitability following ACL reconstruction and TKA.

Chapter 1 Literature Review and Introduction to the Dissertation

The purpose of this literature review is to thoroughly describe 1) anterior cruciate ligament (ACL) injury and reconstruction, as well as knee osteoarthritis (OA); 2) the prevalence of quadriceps weakness and its functional implications in the anterior cruciate ligament and knee osteoarthritis population; 3) mechanisms contributing to quadriceps weakness; 4) peripheral and central sources of quadriceps voluntary activation deficits; 5) assessments of quadriceps dysfunction; 6) and interventions used to target quadriceps voluntary activation deficits

1.1 Background on Anterior Cruciate Ligament Injury and Knee Osteoarthritis

1.1.1 Anterior Cruciate Ligament Injury

1.1.1.1 Overview and Relevant Anatomy

The anterior cruciate ligament (ACL) is one of the four major ligaments found at the knee joint complex that is critical for tibiofemoral joint stabilization.[1, 2] The ACL is comprised of three bundles: the anteromedial bundle, the intermediate bundle, and the posterolateral bundle.[3-7] The anteromedial bundle inserts at the anterior and proximal region of the femur and attaches to the anteromedial region of the tibia.[3] The posterolateral bundle inserts at the posterodistal region of the femur and attaches to the posterolateral region of the tibia.[3] During knee flexion the anteromedial bundle tightens to limit anterior tibial translation and the posterolateral bundle loosens.[3, 8] During internal rotation the anteromedial bundle and the posterolateral bundle both lengthen.[3, 8] The primary mechanical function of the ACL is to resist anterior translation of the

tibia during knee flexion and extension,[9, 10] while also proving stability in the transverse plane limiting internal and external rotation.[4]

Functionally, the ACL contributes not only to mechanical stability, but also provides somatosensation about the knee. The ACL contributes to somatosensory function as it is densely populated with mechanoreceptors and sensory receptors that play a role in joint proprioception and pain.[11-16] The ACL is composed of approximately 1.0-2.5% of neural tissue including Ruffini corpuscles, Pacinian corpuscles, and Golgi tendon organ receptors.[17] The Ruffini receptors are located on the surface of the ligament, which are concentrated in the femoral region and respond to changes in joint angle, velocity, and pressure.[18, 19] The Pacinian corpuscles are also located in the ACL and respond to sudden changes in accelerations or decelerations that may occur during vibration or low pressure.[19] In contrast, the GTO receptors detect high levels of mechanical pressure and compression with the ability to communicate signals for extended periods of time.[19] When the mechanoreceptors detect changes, neural signals are communicated to the dorsal horn of the spinal cord and ultimately transmit to regions of the brain such as the motor cortex, basal ganglia, and cerebellum.[20] Following ACL tear, the mechanoreceptors can be damaged with individuals experiencing poor joint sense due to altered sensory feedback.[20, 21]

1.1.1.2 Epidemiology of ACL Injury and Reconstruction

ACL injury is a common injury, particularly in young, athletic populations[22, 23]with recent epidemiological data reporting an overall annual incidence of 68.6 per 100,000 person-years after adjusting for age and sex.[24] Epidemiological data from the NCAA Injury Surveillance System also points to a growing number of ACL injuries each year with a 1.3% annual increase observed from 1988 to 2004.[24, 25] Following ACL injury, ACL reconstruction is commonly recommended to restore mechanical stability and knee function. Thus, the increase in number of

ACL injuries and recommendations of surgical reconstruction have led to a rise in the incidence of ACL reconstruction cases in the United States across all age groups[24, 26] In fact, epidemiological research reports a 22% increase in ACL reconstructions from 2002 to 2014 with a substantial increase in surgical rate for adolescents aged 13 to 17 years.[27]

In addition to the initial injury, additional complications may arise. For example, the incidence of second ACL injury on the ipsilateral limb occurs in approximately 6% of individuals within 5 years.[28, 29] The contralateral limb may also suffer an ACL injury with 11.8% of individuals experiencing a contralateral ACL tear after 5 years[29] with higher rates reported in adolescents.[30] Notably, ACL injury and reconstruction are both associated with an increased risk of early onset knee osteoarthritis within 10 to 15 years after injury.[31] Following ACL injury, the incidence of knee osteoarthritis has been reported to occur in 5 – 90% of individuals between 5 to 20 years after the initial ACL injury[32-37] with an estimated average of 50% [38]. Thus, the initial ACL injury and subsequent ACL reconstruction present a critical public health problem over the lifespan.

1.1.1.3 Risk Factors of ACL Injury

ACL injury is a common injury in individuals between the ages of 18 and 45 years, particularly those who participate in sport and exercise involving cutting and pivoting movements. ACL injury is most common among younger individuals with an incidence rate that peaks between the age of 19 and 25 years in males and 14 and 18 years in females.[24] The influence of sex on ACL injury risk has been extensively studied with the majority of evidence revealing a higher incidence in females.[23, 39-43] while some research reports higher incidence in males.[24] Limited research has also linked the risk of ACL injury to race. For example, Caucasian female athletes were 6.55 higher odds of sustaining an ACL injury than non-white female

athletes in the Women's National Basketball Association.[44] However, it is unclear whether the increased risk for ACL injury in Caucasians is consistent among males and non-professional athletes due to lack of investigation. Thus, factors such as age, sex, and race may play a role in the risk for ACL injury.

1.1.2 Knee Osteoarthritis

1.1.2.1 Overview and Relevant Anatomy

Tibiofemoral osteoarthritis is a pathology characterized by degradation of the extracellular matrix and cell stress following micro- and macro-trauma that initiates a dysfunctional repair process.[45] The activation of pro-inflammatory pathways results in atypical joint metabolism that ultimately manifests in cartilage degradation of the tibiofemoral region, bony structural changes of the tibiofemoral region, the presence of osteophytes in the tibiofemoral region, joint inflammation, and poor joint function.[45] Tibiofemoral osteoarthritis can be categorized into two groups, those with radiographic evidence of osteoarthritis and patient symptoms (e.g. symptomatic osteoarthritis) and those with radiographic evidence of osteoarthritis but without patient symptoms (e.g. asymptomatic osteoarthritis). Radiographic signs of osteoarthritis are identified using radiographic markers such as joint space narrowing and the presence of osteophytes.[46, 47] The radiographic markers are also used to assess the severity and progression of joint disease. In addition to structural changes, symptoms may develop such as joint pain, joint stiffness, or functional limitations and are indicative of symptomatic osteoarthritis.

Knee osteoarthritis is a leading cause of persistent disability[48] resulting in significant global burden. The combination of radiographic and inflammatory changes ultimately contributes to significant functional limitations that have long-term implications for mobility and

quality of life. Currently there is no cure for tibiofemoral osteoarthritis, but treatments focus on minimizing joint pain, preserving joint function, and undergoing surgery if needed.[49] Thus, the development of treatments that can restore joint function and eliminate pain are imperative to preventing disability in individuals with tibiofemoral osteoarthritis.

1.1.2.2 Epidemiology of Knee Osteoarthritis

The incidence rate of knee osteoarthritis is known to vary with age with the disease estimated to affect 40% of individuals over the age of 60.[50] Among adults, radiographic knee osteoarthritis has an overall age-standardized prevalence rate of 27.8% in individuals over the age of 45 with age-standardized prevalence rates for symptomatic knee osteoarthritis ranging from 6.7 to 12.6%.[51] A retrospective analysis also indicates post-traumatic osteoarthritis accounts for 10% of all knee osteoarthritis cases,[52] which is not surprising given injury history is a risk factor for knee osteoarthritis.[53] Following ACL injury and reconstruction, post-traumatic knee osteoarthritis is incredibly common with a prevalence rate of 44% in individuals with ACL reconstruction and 37% in ACL-deficient individuals.[54] The prevalence rate is also further increased by concomitant meniscal injury, which rises to 52%.[54] Hence, knee osteoarthritis presents a significant public health problem, particularly in individuals who suffer an ACL injury and concomitant meniscal injury.

1.1.2.3 Risk Factors of Knee Osteoarthritis

A higher prevalence of knee osteoarthritis in women has been consistently reported in the literature[55-58] with women also experiencing more severe osteoarthritis.[55, 59, 60] Other factors associated with a higher prevalence of knee osteoarthritis include obesity and history of previous injury also increases the risk for developing knee osteoarthritis.[53, 60] Individuals with previous knee injury have nearly a 6-fold increase in developing knee osteoarthritis compared to

individuals without a previous knee injury.[53] A recent meta-analysis also indicates individuals with a history of ACL injury and meniscal injury had 4.2 and 6.2 greater odds of developing knee osteoarthritis than individuals without a history of injury, respectively.[61] Thus, demographics such as sex, age, BMI, and history of injury may influence risk for developing knee osteoarthritis.

1.1.2.4 Knee Osteoarthritis Severity

Knee osteoarthritis (OA) is a disease that develops gradually over time with progression to higher stages indicating greater knee joint degeneration. Radiographic osteoarthritis is considered the gold standard for identifying individuals with knee osteoarthritis. The Kellgren-Lawrence (K-L) grading scale is a common method for defining radiographic evidence of osteoarthritis and the severity of joint disease. The K-L scoring system categorizes osteoarthritis into 5 levels from a level of 0 to 4 with higher levels corresponding to greater osteoarthritis severity. osteoarthritis grading on the K-L scale is defined by the following stages:[62-64]

- **grade 0 (none)**: definite absence of x-ray changes of osteoarthritis
- **grade 1 (doubtful)**: doubtful joint space narrowing and possible osteophytic lipping
- **grade 2 (minimal)**: definite osteophytes and possible joint space narrowing
- **grade 3 (moderate)**: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
- **grade 4 (severe)**: large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

Radiographic osteoarthritis is diagnosed when radiographic changes demonstrate a grade 2 or higher. Notably, the presence of radiographic osteoarthritis does not necessarily correspond to the presence of symptomatic osteoarthritis.[65] As such, other forms of non-radiographic

assessments are used to determine symptomatic osteoarthritis severity. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a widely used questionnaire that assesses self-reported factors such as pain, stiffness, and functional limitations.[66] Hence, radiographic and self-reported functional scores are used in conjunction to determine disease severity and its impact on disability in individuals with knee osteoarthritis.

1.1.2.5 Total Knee Arthroplasty

Total knee arthroplasty (TKA), also known as total knee replacement, is one of the most frequently performed surgical procedures in the United States[67] with over 300,000 procedures performed in 2022.[68] TKA is used to treat end-stage knee osteoarthritis when conservative treatment fails to manage pain and restore knee function. During the procedure, diseased regions of the knee joint are replaced with artificial components. Specifically, the arthritic knee cartilage and bone are removed and replaced with a metal implant and spacer, which can mimic normal knee joint function. The goal of TKA is restore normal knee alignment, improve joint function, and alleviate OA-related symptoms. Positive outcomes are well-documented after TKA with increased mobility, improved joint function, and diminished pain commonly reported after surgery.[69-73] Importantly, individuals generally experience increased quality of life, satisfaction with the surgery, and minimal complications after TKA.[72, 74-78] Hence, TKA appears to be a valuable option when non-surgical interventions are no longer viable.

1.2 Prevalence of Quadriceps Weakness

1.2.1 Prevalence of Quadriceps Weakness in the ACL Injured and Reconstructed Population

Following ACL injury and reconstruction, quadriceps strength deficits are ubiquitous. Quadriceps strength is important as clinicians commonly use it as a metric for determining return to activity after knee surgery. The golden standard for assessing strength are isokinetic and isometric methods using a dynamometer. A common measure used to identify the presence of quadriceps weakness is the quadriceps strength limb symmetry index, defined as the strength of the injured limb divided by the strength of the uninjured limb and is expressed as a percentage typically. A high limb symmetry index indicates quadriceps strength symmetry while a low limb symmetry index indicates quadricep strength deficits in the involved limb relative to the uninvolved limb. A value of 90% quadriceps strength limb symmetry index is typically used as a threshold for identifying individuals with quadriceps weakness after ACL injury with values lower than 90% indicative of quadriceps weakness.[79-82] Alternatively, normalized quadriceps strength can be used to identify quadriceps weakness, as bilateral strength deficits may lead to underestimations of the extent of muscle weakness. In the ACL reconstructed individual, quadriceps strength values greater than 3.0 Nm/kg are indicative of adequate quadriceps strength with values similar to the quadriceps strength of healthy controls.[83]

Despite significant quadriceps strength deficits commonly reported after ACL injury and reconstruction, the prevalence of quadriceps weakness has yet to be reported in large-scale epidemiological studies. Cross-sectional studies at return to activity report quadriceps weakness in the involved limb relative to the uninvolved limb for the majority of subjects with 52-81.8% of ACL reconstructed individuals affected.[84, 85] Long-term quadriceps weakness after ACL reconstruction are also observed in 55% of participants with quadriceps weakness in the involved limb relative to the uninvolved limb an average of 4 years after ACL reconstruction.[86] Quadriceps weakness is also confirmed with longitudinal work which reports 88%, 50%, and

25% of ACL reconstructed individuals fail to achieve 90% quadriceps strength symmetry at 6 months, 9 months, and 12 months post-reconstruction, respectively.[80]

Collectively, the literature indicates ACL reconstructed individuals demonstrate significant quadriceps weakness in the reconstructed leg compared to both the non-reconstructed leg and healthy control leg (Appendix A, Appendix B, Appendix C). Furthermore, quadriceps deficits are observed during both isokinetic and isometric testing. Although the extent of quadriceps weakness varies, quadriceps strength of the reconstructed leg can be as low as 33.1% of the non-reconstructed leg with both acute and chronic deficits observed (Appendix A, Appendix B, Appendix C). Thus, the presence of quadriceps weakness in the ACL population is substantial in magnitude and duration, highlighting the importance of improving quadriceps strength following ACL injury and reconstruction.

1.2.2 Prevalence of Quadriceps Weakness in the Knee Osteoarthritis Population

The presence of quadriceps weakness is ubiquitous among individuals with knee osteoarthritis. In fact, quadriceps weakness is an early clinical sign of knee osteoarthritis observed before the onset of self-reported symptoms and poor mobility[87, 88] and is believed to contribute to the development of knee osteoarthritis.[88] Although epidemiological studies have yet to examine the prevalence of quadriceps weakness among the knee osteoarthritis population, longitudinal research may lend insight. In cross-sectional studies the magnitude of quadriceps deficits is reported to be between 7-56%[87, 89-97] in individuals with knee osteoarthritis compared to healthy controls. Among the ACL-Delaware cohort, 54% of ACL-injured or reconstructed individuals diagnosed with clinical knee osteoarthritis exhibit quadriceps deficits greater than 10% after 5 years.[98] The extent of quadriceps weakness in the osteoarthritis population also

appears to be related to disease severity with greater strength deficits observed in individuals with higher severity grades.[97, 99]

The presence of quadriceps weakness in individuals with knee osteoarthritis is consistently reported; however, it is debated whether quadriceps weakness is a consequence of joint disease or if it is a risk factor for the development of knee osteoarthritis. The literature points to quadriceps weakness as a risk factor for knee osteoarthritis with meta-analysis research including more than 5,700 individuals reporting baseline quadriceps weakness as a risk factor for knee osteoarthritis.[100] In addition, quadriceps weakness increased the odds of radiographic tibiofemoral osteoarthritis in the lateral compartment by double,[101] indicative of quadriceps weakness as a risk factor for lateral compartment osteoarthritis. However, another study found no relationship between quadriceps strength and incident radiographic tibiofemoral osteoarthritis in men or in women in the Multicenter Osteoarthritis Study cohort of 1,617 adults between the ages of 50 and 79 years.[102] Collectively, the literature points to quadriceps weakness preceding the development of knee osteoarthritis, but quadriceps weakness can develop or worsen after knee osteoarthritis and may be region-dependent. Given that muscle weakness is considered a risk factor for disease progression in knee osteoarthritis,[103] identifying individuals with quadriceps weakness and the mechanisms that contribute to weakness in joint disease is critical to restoring joint function in the osteoarthritis population.

1.2.3 Prevalence of Quadriceps Weakness in the Total Knee Arthroplasty Population

Quadriceps weakness is well-documented prior to and following total knee arthroplasty.[104-107] Although the prevalence of quadriceps weakness among individuals with TKA is currently unknown, it is clear that individuals suffer substantial quadriceps weakness after surgery. Shortly after surgical discharge, quadriceps strength declines rapidly with deficits

up to 88% of the pre-operative levels.[104, 108] Despite gradual increases in quadriceps strength within the first few months after surgery[109-111] improvements in quadriceps strength appear to stagnate around six to twelve months after surgery.[112] Further, while some individuals may recover to preoperative strength values, individuals with TKA often fail to achieve quadriceps strength that is similar to the contralateral leg or healthy control leg.[104, 110, 111, 113] In fact, deficits up to 29% have been reported in individuals six months after TKA.[104, 110] Moreover, individuals with TKA demonstrate similar or slightly less deficits in quadriceps strength compared with the contralateral leg and healthy control leg even years after surgery.[106, 112-114] Further, these quadriceps deficits persist years after surgery compared with the contralateral leg and the healthy control leg.[106, 112-115] Long-term impairments in quadriceps strength are particularly concerning as quadriceps strength is considered a key predictor of functional recovery after TKA.[116-118] Thus, addressing quadriceps weakness is critical for promoting long-term outcomes following TKA.

1.2.4 Functional Implications of Quadriceps Weakness

1.2.4.1 ACL Injured and Reconstructed Individuals

Quadriceps weakness after ACL injury and reconstruction can have both acute and long-term consequences. Acute consequences of quadriceps weakness include increased pain, decreased functional performance,[119] and psychological factors such as learned helplessness.[120] Long-term consequences of quadriceps weakness may include biomechanical changes due to the importance of adequate quadriceps strength to support shock absorption and propulsion during gait.[121] For example, women with weaker quadriceps exhibit higher loading rates.[122] ACL reconstructed individuals with quadriceps weakness demonstrate lower peak knee flexion and peak knee flexion moments during walking compared to ACL reconstructed individuals without

quadriceps weakness.[123] Further, quadriceps strength symmetry explained 26% of the variance in knee joint angle at peak knee flexion,[123] suggesting quadriceps weakness as a contributing factor to aberrant biomechanics after ACL reconstruction.

However, other research suggests biomechanical changes may not necessarily be related to poor quadriceps strength symmetry. In a cohort of 76 ACL reconstructed individuals, quadriceps strength symmetry was not related to biomechanical variables including peak knee flexion angle, peak knee extension moment, knee excursion during weight acceptance and midstance.[124] The lack of relationship between quadriceps strength symmetry and biomechanical variables persisted when groups were dichotomized into a symmetrical and an asymmetrical group,[124] implying quadriceps weakness may not necessarily correspond to biomechanical changes.

Quadriceps weakness is also believed to be implicated in poor functional outcomes following ACL injury and surgery. Lower quadriceps strength symmetry is associated with worse performance during hop tests, shuttle run tests, and side step tests.[119, 125, 126] In addition, lower quadriceps strength at return to activity is correlated with lower self-reported knee function, as measured by scores on the International Knee Documentation committee Subjective Knee Evaluation Form (IKDC).[127] In fact, quadriceps strength predicts 74% of the variance in IKDC scores.[128] Quadriceps strength also appears to be important to psychological function as it explains 36% of the variance in readiness to return to sport and 59% of the variance in emotional response after injury.[128]

Quadriceps weakness of the involved limb also appears to have consequences for joint health. For example, quadriceps weakness is linked to risk for re-injury of the affected knee [127] and injury of the contralateral knee.[129] The increased risk for re-injury and contralateral injury

indicate quadriceps weakness can compound the negative consequences of the initial injury and is not isolated to the injured limb. In fact, quadriceps weakness can also develop in the non-injured limb,[129] yet the most troubling consequence of quadriceps weakness is its link to the early onset of post-traumatic knee osteoarthritis.[129, 130] Thus, addressing quadriceps weakness prior to the biological and radiographic signs of degradation is critical in the ACL population.

1.2.4.2 Individuals with Knee Osteoarthritis and Total Knee Arthroplasty

Quadriceps weakness is pervasive among individuals with knee osteoarthritis and total knee arthroplasty, which can have serious long-lasting effects. A long-term consequence of quadriceps weakness is decreased mobility as individuals with knee osteoarthritis and poor quadriceps strength report lower levels of physical activity levels.[131, 132] Although the role of quadriceps strength on physical activity levels after TKA has yet to be investigated, it is plausible that the findings in knee osteoarthritis may extend to after TKA as poor quadriceps strength and physical activity levels continue to be reported despite undergoing TKA.[104, 112, 115, 133] Quadriceps weakness is also associated with poor self-reported physical function in individuals with knee osteoarthritis[97, 134, 135] and total knee arthroplasty,[136] with lower quadriceps strength predictive of functional disability in individuals with knee OA.[92, 137] Notably, individuals with knee osteoarthritis and high quadriceps strength self-report less pain and fewer functional limitations on the WOMAC compared to those in the low quadriceps strength tercile,[132] indicating the importance of strength to symptomatic osteoarthritis and mobility. These findings are consistent with research in TKA individuals as preoperative quadriceps exercise led to lower self-reported pain and improved self-reported function on the WOMAC within the first 3 months after TKA when compared with the control group.[138] Quadriceps strength deficits also appear to have implications on functional performance. The role of quadriceps strength on

physical function tests is supported by evidence reporting quadriceps strength as a predictor for functional performance during sit to stand tests[139] and the timed walking test[140] in individuals with knee osteoarthritis[139, 140] and total knee arthroplasty.[118, 136] Hence, quadriceps strength appears to play a significant role in the functional capacity of individuals with knee osteoarthritis and total knee arthroplasty.

In addition to its effect on function, quadriceps weakness may have biomechanical implications in individuals with knee osteoarthritis. During walking, longer support and step times and shorter swing times are linked to quadriceps weakness in women with knee osteoarthritis.[141] Notably, slower walking speeds are also linked with poor quadriceps strength in both individuals with knee osteoarthritis and total knee arthroplasty.[141, 142] Higher quadriceps strength is also reportedly linked to greater peak knee flexion[143-145] and peak knee extension angles [145] during the stance phase of walking in individuals with knee OA. In individuals with TKA, asymmetrical quadriceps strength (i.e., poor quadriceps strength in the TKA leg) is associated with asymmetrical knee biomechanics during walking[146] and sit-to-stand tasks.[147] Quadriceps weakness in the TKA leg is also associated with lower knee extension excursions, knee extension moments, and peak vertical ground reaction forces during walking.[148] Thus, quadriceps weakness appears to influence both performance measures and the biomechanical adaptations observed in both individuals with knee osteoarthritis and TKA, which may contribute to poor functional outcomes in these populations.

The key consequence of quadriceps weakness is its implications in worsening joint health. Quadriceps weakness is related to higher odds of developing tibiofemoral osteoarthritis, patellofemoral osteoarthritis, and mixed osteoarthritis.[149] Although it is currently unclear whether quadriceps weakness directly leads to cartilage loss, individuals with knee osteoarthritis and

lower quadriceps strength are at a greater risk for cartilage loss in the lateral patellofemoral joint compared to those with higher strength.[132] Furthermore, greater quadriceps strength appears to be protective of joint health as individuals with knee malalignment did not demonstrate greater cartilage loss in the presence of high quadriceps strength.[132] Given that muscle weakness is a risk factor for the development and progression of knee osteoarthritis,[103] eliminating quadriceps weakness is critical to preserving joint health and restoring function of the joint. Importantly, addressing quadriceps impairments may help prevent or delay the need for total knee arthroplasty.

1.3 Mechanisms of Quadriceps Weakness

The development of quadriceps weakness is commonly attributed to two factors, changes in muscle morphology and alterations in neural signaling to the muscle. Given the link between quadriceps weakness and the risk of knee osteoarthritis,[100] it is critical to understand the mechanisms that lead to the development of quadriceps weakness. Hence, the following sections will discuss the factors that lead to quadriceps weakness.

1.3.1 Muscle Atrophy as a Mechanism for Quadriceps Weakness

A source theorized to contribute to quadriceps weakness is atrophy of the quadriceps muscle.[129] Skeletal muscle atrophy is defined by a reduction in size of the muscle fibers (i.e. cross-sectional area).[150] Atrophy occurs when the balance of muscle protein synthesis relative to muscle protein breakdown is altered.[151-153] Following joint injury or disease, the knee joint may be immobilized or unloaded to avoid pain, leading to quadriceps disuse atrophy. In cases of disuse atrophy, anabolic resistance can develop[154] due to diminished protein synthesis rates[155] and/or reduced responsiveness of the muscle to dietary protein intake.[154-156] While the underlying

mechanisms contributing to reduced muscle protein synthesis with muscle disuse are currently unclear, it is theorized that lower translational capacity (i.e., reduced number of ribosomes[157] and efficiency of the mRNA responsible for protein synthesis may contribute to lower protein synthesis rates.[158] This may involve one or more pathways such as the Akt-mTORC1 pathway and the IGF-1-Akt-mTOR pathway. One way this may occur is due to the insulin resistance that develops due to disuse,[159, 160] which attenuates activation of the Akt-mTORC1 pathway,[161] leading to decreased protein synthesis. Regardless of the mechanisms, the diminished muscle protein synthesis due to anabolic resistance is important as it is believed to be the primary mechanism for muscle atrophy.[151, 162] When atrophy occurs, the reduction in size and/or force of the skeletal muscle fibers results in a diminished capacity to produce force at the whole muscle level. Hence, quadriceps atrophy is believed to contribute to quadriceps weakness.[163, 164]

However, acute disuse does not explain the protracted muscle atrophy observed when ACL-injured individuals are engaging in rehabilitation and exercise.[165, 166] Injury-related atrophy results in cellular level changes that result in a diminished ability to maintain or hypertrophy the muscle.[167-169] In addition, maladaptive changes to the nervous system occur at the cortical[170-172] and spinal levels,[171, 173] which influence excitability of the alpha motor neuron.[174] Changes in the excitability of the spinal-reflex and corticospinal pathway affect the alpha motor neuron excitability, which may diminish signaling from the alpha motor neuron to the muscle and limit the ability to volitionally contract the muscle.[174] If the loss of neural signaling persists, it may ultimately contribute to atrophy acutely after ACL reconstruction.[175, 176]

Quadriceps atrophy has been reported in both individuals with ACL reconstruction and knee osteoarthritis,[177, 178] which is theorized to lead to quadriceps weakness.[179] Quadriceps atrophy in the reconstructed leg is observed early after surgery[180, 181] and lingers during

rehabilitation.[177, 182] Concerningly, muscle atrophy persists long after ACL reconstruction. Despite participation in rehabilitation programs designed to restore muscle size and engagement in exercise, atrophy in the reconstructed leg is observed years after surgery.[183, 184] Quadriceps strength declines are also related to atrophy following ACL reconstruction with quadriceps cross-sectional area explaining 30.7% of the variance in quadriceps strength 6 months after surgery.[177] These findings were confirmed by other research in ACL reconstructed individuals an average of approximately 3 years after surgery, with quadriceps cross-sectional area strongly correlated with quadriceps strength.[165] Vastus intermedius and vastus medialis cross-sectional area predicted 72.5% and 75.6% of the variance in quadriceps strength with lower cross-sectional area (e.g. atrophy) corresponding to lower quadriceps strength.[165] However, vastus lateralis CSA was weakly, but significantly, associated with quadriceps strength while rectus femoris CSA was not associated with quadriceps strength.[165] Hence, quadriceps atrophy is long-lasting and an important factor to quadriceps weakness after ACL reconstruction.

In individuals with knee osteoarthritis, bilateral quadriceps atrophy is observed compared with individuals without knee osteoarthritis. One study utilizing CT imaging reported decreased total quadriceps volume in women with knee osteoarthritis compared to women without knee osteoarthritis.[178] Notably, the reduction of total quadriceps volume was also associated with incident knee osteoarthritis,[178] suggesting quadriceps atrophy as a factor to the development of knee osteoarthritis. When looking at the quadriceps muscle individuals, it appears several of the quadriceps muscles exhibit notable atrophy. Individuals with patellofemoral knee osteoarthritis demonstrate lower normalized muscle volumes for vastus lateralis, rectus femoris, and vastus medialis but not vastus intermedius for the involved leg compared to individuals without knee osteoarthritis.[185] Importantly, quadriceps atrophy is associated with quadriceps weakness in

individuals with knee osteoarthritis. Lean mass cross-sectional area explained 27% of the variance in quadriceps strength of the involved limb with lower cross-sectional area corresponding to lower quadriceps strength in individuals with grade IV knee osteoarthritis.[186] In addition, the study reported lean mass cross-sectional area explained 41% of the variance in quadriceps strength of the uninvolved limb in individuals with grade IV knee osteoarthritis.[186] Thus, quadriceps atrophy appears to be an important factor to quadriceps weakness in both the involved and uninvolved legs in individuals with knee osteoarthritis.

Despite limited evidence, individuals with total knee arthroplasty appear to suffer quadriceps atrophy. Prior to surgery, individuals with TKA demonstrate significantly smaller quadriceps cross-sectional areas in the involved leg compared to the contralateral leg, including the vastus medialis.[187, 188] Following TKA, individuals with TKA demonstrate significant reductions in cross-sectional area of the quadriceps muscle following surgery compared with preoperative values shortly after and several weeks after surgery.[104, 188] However, recent evidence suggests that quadriceps cross-sectional area improves within the first few months after TKA compared with pre-operative levels.[189] In fact, individuals with TKA demonstrate similar muscle thickness in the vastus medialis, vastus intermedius, and rectus femoris muscles in the TKA leg and the contralateral leg, suggesting muscle size may be similar between limbs.[190] However, individuals with TKA still demonstrate significantly lower muscle thickness bilaterally in the vastus medialis, vastus intermedius, and rectus femoris compared with healthy individuals, suggesting individuals with TKA are unable to regain normative muscle size in either leg.[190] This inability to regain normative quadriceps muscle size is concerning as quadriceps atrophy and low muscle thickness are predictive of poor quadriceps strength in individuals with TKA.[104] Thus,

addressing quadriceps atrophy is critical to restoring normative quadriceps muscle size and function.

1.3.2 Changes in the Muscle Fiber

Muscle atrophy can be accompanied by adaptations in the muscle fibers such as changes in fiber cross-sectional area, fiber pennation angle, and fascicle length.[191, 192] The muscle fibers are characterized by both their biochemical and functional properties and include: type I slow-twitch fibers and type II fast-twitch fibers with type I fibers contributing to prolonged, lower force contractions and muscle endurance, while type II fibers contribute to shorter, high force contractions.[193]Muscle fibers can also exhibit intermediate phenotypes such as type I/IIa, type IIa/x and are referred to as hybrid fibers. A hybrid fiber co-expresses fiber phenotypes and demonstrates functional and metabolic properties intermediate to the fibers expressed.[193] For example, a type IIa/x hybrid fiber would demonstrate a lower force output than a pure IIx fiber, but higher than a pure IIa fiber. In response to the initial injury and the subsequent disuse and immobilization due to injury, the muscle fibers may shift in fiber type and/or atrophy, with fiber atrophy resulting in whole muscle atrophy and thereby, muscle weakness.[129]

Loss of fiber cross-sectional area is observed in populations with knee injury, surgery, and joint disease. For example, lower vastus lateralis cross-sectional area of the type IIa fibers of the involved leg compared with the uninvolved leg is observed after ACL injury.[169] Decreased cross-sectional area of the type IIA fibers in the vastus lateralis also persists after ACL reconstruction at return to activity.[169] Type II fiber atrophy of the vastus medialis in the involved leg[194], but not the vastus lateralis[195] are also reported in the literature for individuals with knee osteoarthritis. Although only evaluated in the vastus lateralis, diminished muscle fiber cross-sectional areas and diameters were observed in type I, type IIA, and type IIA/X fibers five weeks

after surgery compared with pre-operative values, indicating atrophy across all muscle fibers after TKA.[188] In contrast, no differences in type I fiber cross-sectional area of the vastus lateralis are observed between-legs in ACL-injured,[169] ACL reconstructed,[169] or knee osteoarthritis individuals[195] while limited evidence supports type I fiber atrophy for the vastus medialis in individuals with knee osteoarthritis.[194] Given concurrent reductions in quadriceps strength were observed in all four populations,[169, 188, 195] it is plausible atrophy of muscle fibers may contribute to whole muscle quadriceps weakness. Hence, quadriceps muscle fiber atrophy, particularly atrophy of the type IIa fibers, may have negative implications for quadriceps function.

Pennation angle can also change as a result of muscle atrophy. Changes in pennation angle are believed to occur to accommodate changes in muscle size as pennation angle increases with hypertrophy[196] and decreases with atrophy.[197] Pennation angle influences the amount of force the muscle can produce during voluntary contraction with lower pennation angles corresponding to reductions in force output.[198] Hence, pennation angle may be a relevant factor to quadriceps weakness in individuals with a knee injury or joint disease.

Currently, there is limited evidence for pennation angle changes in ACL-injured, ACL reconstructed, and knee osteoarthritis individuals. Research to date suggests pennation angles are unchanged in the vastus lateralis of individuals with knee osteoarthritis.[199, 200] Pennation angle is also unlikely to contribute to quadriceps weakness in individuals with knee osteoarthritis as strength deficits are still present when pennation angles are unchanged.[200] However, it unknown what role pennation angle may play in quadriceps weakness after TKA as it has yet to be investigated. In contrast, lower pennation angles are observed in the vastus lateralis of the involved leg compared with the uninvolved leg after an ACL injury.[169] However, results are mixed after ACL reconstruction with lower[169] or unchanged pennation angles reported in the

vastus lateralis.[201] Differences in time since surgery (e.g. return to activity vs 2 years post-reconstruction) and measurement techniques (e.g. immunohistochemical techniques from biopsies vs ultrasonography) likely explain the mixed results. Together, these findings suggest that pennation angle may become lower after ACL injury possibly contributing to quadriceps weakness. Given that pennation angles can be increased by strength training[196] and decreased due to detraining,[202] early rehabilitation and intervention may be valuable to restoring pennation angle changes and mitigating quadriceps weakness after surgery.

In addition to changes in individual muscle fibers, the muscle fascicle may also undergo structural changes. The muscle fascicle is a bundle of skeletal muscle fibers surrounded by the connective tissue.[203] Fascicle length is shown to be affected after injury,[204] disease,[205] or disuse.[206] Reductions in fascicle length are theorized to occur due to a loss or shortening of sarcomeres in series.[64] Importantly, fascicle length changes of sufficient magnitude can result in decreased force production,[207] which may have implications for whole muscle strength. Shorter fascicle length may also negatively influence the fascicle force-velocity curve as elderly individuals demonstrate a positive shift in the force-velocity curve after resistance training.[208] Specifically, shorter fascicle length in the vastus lateralis corresponded with lower force output for a given fascicle velocity prior to resistance training compared with post-training in elderly individuals.[208] Given individuals also demonstrated lower isometric and isokinetic quadriceps strength with lower vastus lateralis fascicle length,[208] shorter fascicle length may be maladaptive for strength and contribute to quadriceps strength deficits after knee injury or joint disease.

Thigh muscle fascicle length have been investigated in individuals with knee joint injury and disease due to its potential influence on force production. For example, ACL reconstructed individuals with a semitendinosus and gracilis graft demonstrate shorter fascicle length in the

biceps femoris.[209] However, despite changes in fascicle length, hamstrings strength did not differ between-legs and compared with controls.[209] It is possible changes in fascicle length, but not hamstrings strength, may be due to the similar muscle thickness between-legs and groups,[209] suggesting a lack of atrophy. Shorter fascicle length are also observed in the vastus lateralis for individuals with knee osteoarthritis compared with healthy controls.[200] Notably, NMES and strength training interventions are capable of increasing fascicle length in individuals with knee osteoarthritis and are accompanied by improvements in quadriceps strength.[199, 200] Hence, targeting fascicle length may be helpful in restoring quadriceps strength. However, additional research is needed to delineate whether strength changes were due to changes in fascicle length or due to other factors since increases in muscle thickness were also observed.[199, 200] It is also unclear if fascicle length changes occur in the quadriceps after ACL injury and reconstruction due to the lack of investigation to date. Further research on the role of fascicle length in quadriceps strength would inform whether it is a relevant target to improving quadriceps strength after knee surgery and joint disease.

1.3.3 Modulation of Muscle Fiber Phenotype

Transitions or shifts in muscle fiber phenotype may result from injury, disease, or inactivity. Fiber type transitions occur when the metabolic environment of the fiber is altered, which activates cell signaling[210] and transcriptional mechanisms responsible for fiber type. In physiological fiber shifts, the firing pattern of neurons to the muscle fiber is a key factor for the type of muscle fiber expressed.[211] When changes in the neurons' firing frequency and temporal patterns occur, the membrane potential can be altered and lead to changes in the intracellular calcium ion levels.[211] Adaptations in the calcium levels are sensed by a messenger (i.e.

calcineurin) and activate pathways that modulate gene expression responsible for the muscle fiber type expressed.[212]

Fiber type transitions can manifest in several ways such as type I fibers shifting to type II fibers, type II fibers shifting to type I fibers, or a shift from a pure fiber to a hybrid fiber. Identifying fiber type transitions is critical after knee injury and joint disease, as fiber type distributions inform muscle function. For example, a large shift from predominantly type I fibers to predominately type II fibers may change the force capability and fatigue-resistance of the muscle due to the differences in fiber type properties, which may result in suboptimal functioning of the muscle. Thus, identification of maladaptive fiber type changes is an important first step to understanding the sources of neuromuscular dysfunction after knee injury and joint disease.

Fiber type transitions have been shown to occur following knee injury and joint disease and have the potential to impact quadriceps strength and voluntary activation. Individuals exhibit a shift in fiber type from predominantly type I fibers prior to reconstruction to predominantly type II fibers after ACL reconstruction in the involved vastus lateralis.[169] The fiber shifts are characterized by a decrease in type IIa fibers but a two-fold increase in type IIa/x hybrid fibers.[169] Given the proportion of type I, type IIa, and type IIa/x hybrid fibers were similar between the involved leg and the uninvolved leg prior to reconstruction, but differed after reconstruction,[169] it is likely that the fiber shifts occurred due to surgery or the disuse after surgery. Similar to ACL reconstructed individuals, a shift to a greater proportion of hybrid IIa/x fibers is observed in the vastus lateralis of individuals with knee osteoarthritis compared with healthy controls.[195] Unlike the ACL reconstructed population, individuals with knee osteoarthritis demonstrate a lower proportion of type I fibers[195] and no change in the proportion

of type II fibers in the vastus lateralis relative to healthy controls,[195, 213] which may be due to other factors such as aging and obesity. Regardless, a shift to hybrid IIa/x fibers in the vastus lateralis appears to be consistent in both the ACL reconstructed and knee osteoarthritis populations.

Although fiber type shifts can be beneficial in some scenarios such as after exercise, the fiber type shifts observed after knee injury and joint disease may be maladaptive. The shift from slow-to-fast fiber types and the high proportion of hybrid fibers demonstrated in individuals after knee injury and joint disease is indicative of the loss of neural signals and mechanical loading of the muscle.[214] An increase in the proportion of fast-twitch fibers, particularly hybrid type IIa/x, can drive the muscle to function more optimally for brief, high power contractions,[193] which can have negative implications for quadriceps function during sustained or low intensity contractions. Further, hybrid IIa/x fibers are activated by high motor threshold motor units,[193] which are inhibited after knee injury and joint disease due to voluntary activation deficits. Hence, it is plausible the fiber type adaptations after knee injury and disease are maladaptive for quadriceps strength.

Evidence in individuals with knee injury also link muscle fiber type and quadriceps size and function. For example, the presence of hybrid IIa/x fibers in the involved leg is associated with quadriceps atrophy after ACL reconstruction.[169] In addition, increases of hybrid IIa/x fibers in the involved leg is associated with lower quadriceps strength in individuals with knee osteoarthritis[195] and individuals with ACL reconstruction.[169] These links suggest that changes in muscle fiber phenotype may have negative consequences on quadriceps size and function. Hence, preventing or reversing the shift to hybrid IIa/x fibers through interventions promoting voluntary activation may be valuable to mitigating quadriceps weakness after knee injury and

joint disease. However, additional investigation is needed to delineate the contribution of atrophy and fiber type transitions to determine whether fiber type transitions play an important role in quadriceps weakness or if it is simply due to atrophy.

1.3.4 Myostatin

Myostatin is a growth factor responsible for regulating the size of muscle by inhibiting muscle growth. Increased myostatin expression negatively modulates the protein kinase B signaling pathway, resulting in inhibition of protein synthesis[215] and the activation of the ubiquitin-proteasome pathway.[216] Given the inhibition of protein synthesis, the rate of protein synthesis to protein degradation may be downregulated, resulting in muscle atrophy. In addition, myostatin overexpression downregulates the differentiation of myoblasts, which may further diminish the capability for tissue formation.[217, 218] Hence, ensuring optimal levels of myostatin may be relevant to mitigating muscle atrophy.

Given that an increased production of myostatin can result in muscle atrophy and myostatin production can change with ACL injury, it is plausible that myostatin may contribute to quadriceps weakness and atrophy in persons with ACL injury. After ACL injury, the expression of myostatin mRNA levels are higher in the vastus lateralis of the injured leg compared with the uninjured leg.[219] Circulating myostatin levels also appear to increase after ACL reconstruction and remain elevated up to 4 weeks after surgery compared with levels prior to surgery.[168] Furthermore, elevated circulating myostatin levels within one week of ACL reconstruction are paralleled by reductions in thickness of the vastus medialis, rectus femoris, and vastus intermedius muscles in the involved leg.[220] Unfortunately, it is difficult to determine whether the loss of muscle thickness is due to the elevated myostatin or if changes in muscle thickness and myostatin are both a secondary consequence of factors such as unloading.

However, benchtop work provides direct evidence that inhibition of myostatin mRNA levels may be protective against muscle fiber atrophy after ACL transection.[216] ACL-transected rats treated with anti-myostatin antibody treatment demonstrate similar vastus lateralis fiber area 21 days after transection compared to uninjured rats.[216] In contrast, untreated rats demonstrated lower vastus lateralis fiber area than ACL-transected rats with antibody treatment and uninjured rats.[216] Thus, there is direct evidence that inhibiting myostatin levels can mitigate fiber atrophy.

Elevated myostatin levels may also play a role in quadriceps atrophy and weakness in individuals with knee osteoarthritis. Similar to individuals with ACL injury, higher serum and synovial myostatin levels are reported in individuals with knee osteoarthritis compared to healthy controls.[221] Unfortunately, it is less clear whether myostatin levels play a role in individuals with knee osteoarthritis as quadriceps size and strength were not assessed. However, research in individuals with hip osteoarthritis supports the role of myostatin in disuse atrophy as greater myostatin mRNA levels were associated with decreased type II fiber area of the vastus lateralis.[222] In benchtop research, ACL-transected rats with osteoarthritis demonstrate greater myostatin expression and a 10% reduction in gastrocnemius cross-sectional area compared to rats without ACL-transection and osteoarthritis.[221] Hence, it appears elevated myostatin levels in rats with osteoarthritis can have negative implications for muscle and fiber size. However, direct evidence is needed to link elevated myostatin levels with quadriceps atrophy and weakness to confirm this theory for persons with knee osteoarthritis.

Given the negative outcomes associated with elevated myostatin, reestablishing normal myostatin levels may be a relevant target to restoring quadriceps size and function after knee injury and joint disease. For example, quadriceps strength improved when myostatin levels returned to levels similar to baseline in ACL reconstructed individuals.[168] Benchtop work also

supports the value of inhibiting myostatin through therapeutic intervention as NMES application in ACL-injured rats was shown to lower myostatin mRNA levels and prevent atrophy of the quadriceps muscles up to 15 days after intervention compared with ACL-injured rats without NMES.[223] Hence, lowering elevated myostatin levels or preventing excessive increases in myostatin may be valuable to mitigating quadriceps atrophy and weakness after ACL injury and reconstruction. However, direct evidence linking myostatin levels to quadriceps atrophy after knee joint trauma is needed to confirm this theory, which could inform potential therapeutic interventions for the treatment of quadriceps atrophy and weakness.

1.3.5 Diminished neural signals

The final factor theorized to contribute to atrophy after knee injury or joint disease is the diminished transmission of neural signals to the quadriceps.[129] The ability to fully activate the muscle depends on the muscle being able to completely recruit all available motor units at the maximal firing rate.[224] Diminished ability to fully activate the muscle is known as muscle inhibition (e.g. voluntary activation failure) and signals a failure in recruiting all motor units and/or a decrease in firing rate. [225] In large muscles, one motor neuron can activate many muscle fibers.[226] Hence, diminished neural signaling from one or more motor neurons may influence the function of numerous muscle fibers, affecting the quadriceps substantially.

A negative implication of diminished voluntary activation of the muscle fibers is its potential role in the loss of muscle size. When one or more motor neurons fail to be recruited, the number of muscle fibers activated during a contraction is decreased.[225] When the muscle fibers are unable to be activated due to chronic voluntary activation deficits, muscle fiber and whole muscle atrophy may develop. The importance of quadriceps voluntary activation to maintaining quadriceps size is well-documented in exercise research. For example, individuals who perform

knee extension exercises maintain quadriceps physiological cross-sectional area and voluntary activation, while individuals who did not perform exercises demonstrate loss of voluntary activation and physiological cross-sectional area.[227] Evoked muscle contractions via NMES intervention are also protective against muscle atrophy during leg immobilization,[228] further supporting the connection between muscle activation and atrophy. Thus, maintaining neural signaling to the muscle through muscle activation, whether voluntarily or involuntarily, could play a role in maintaining quadriceps muscle size.

Although voluntary activation deficits are theorized to contribute to atrophy, its role remains debated. Atrophy attributed to the loss of neural signals and mechanical loading can occur due to conditions such as disuse, denervation, and injury.[214] The atrophy of both type I and type II fibers and grouping by fiber type is characteristic of neurogenic atrophy,[229] while the selective atrophy of type II fibers, regardless of fiber type grouping, is characteristic of disuse atrophy.[230] In the involved leg of the vastus medialis, approximately 32% and 68% of individuals with knee osteoarthritis demonstrate neurogenic atrophy and disuse atrophy, respectively.[194] Individuals with TKA appear to demonstrate neurogenic atrophy as both type I and type II fibers atrophy after surgery.[213] After ACL injury and reconstruction, atrophy occurs in the involved limb as a slow-to-fast fiber type transition[169] and the loss of type II fibers is observed,[169, 231] with some data also reporting type I fiber atrophy.[231] Notably, changes in the muscle fibers occurred despite participation in rehabilitation and returning to previous activity levels.[169] Thus, it is plausible chronic voluntary activation deficits impair neural signaling to the muscle and explain the atrophic changes observed after joint disease and knee surgery. However, it is difficult to isolate whether atrophic changes are due to loss of neural signals, diminished mechanical loading, or both. Further, atrophy may be a secondary consequence of the quadriceps weakness

that occurs due to voluntary activation deficits. These limitations may explain why quadriceps voluntary activation is poorly correlated with quadriceps volume and cross-sectional area, while quadriceps strength was positively correlated with quadriceps size after ACL reconstruction.[165] Given the weak relationship was observed when notable voluntary activation deficits were present,[165] it is unlikely voluntary activation deficits play a significant role in quadriceps atrophy. Regardless, direct research is needed to evaluate whether voluntary activation deficits could contribute to quadriceps atrophy or if it is solely a secondary consequence of quadriceps weakness.

1.4 Contributions to Voluntary Activation Deficits after Knee Injury and Joint Disease

1.4.1 Peripheral Factors and Other Sources of Voluntary Activation Deficits

In individuals with knee injury or joint disease, peripheral factors and other various sources can change the extent of joint afferent discharge or efferent signaling. Factors that may influence joint afferent discharge include pain, swelling, and damage to mechanoreceptors, which are believed to contribute to voluntary activation deficits. Other mechanisms can alter the efferent signaling from the alpha motor neuron to the muscle and are believed to contribute to voluntary activation deficits. These mechanisms include pre-synaptic inhibition, reciprocal inhibition, recurrent inhibition, non-reciprocal inhibition, flexion reflex, and gamma loop dysfunction. The following section will summarize the role of each factor to quadriceps voluntary activation deficits after joint disease and knee surgery

1.4.1.1 Contribution of Pain to Voluntary Activation

One potential peripheral source of quadriceps voluntary activation deficits is the presence of pain. Quadriceps voluntary activation deficits due to pain are believed to occur due to

increases in afferent discharge to the central nervous system, which subsequently reduces signaling to the muscle.[232] For example, when inflammation is present in the joint it can sensitize nociceptive afferent fibers in the peripheral nerve and increase afferent signaling[233] which may contribute to voluntary activation deficits after knee injury and joint disease. Some evidence points to a link between pain and quadriceps voluntary activation deficits[234, 235], while other data suggests no relationship.[163, 236, 237] Reductions in pain due to intra-articular injections of local anesthetics results in improvements of quadriceps voluntary activation[238] and isokinetic quadriceps strength[239] which supports the role of pain as a source to quadriceps voluntary activation deficits and weakness. Similarly, experimental anterior knee pain models, where hypertonic saline is injected into the infrapatellar fat pad, result in immediate declines in quadriceps strength and voluntary activation.[240] In contrast, experimental knee effusion models indicate quadriceps voluntary activation deficits can occur without the presence of pain, suggesting other peripheral and central sources can also lead to substantial quadriceps activation deficits after ACL injury. While evidence points to pain as a contributing factor to quadriceps voluntary activation deficits, particularly in the acute phase after reconstruction, pain is unlikely to play a significant role in chronic deficits when pain is typically absent.

1.4.1.2 Contribution of Joint Effusion to Voluntary Activation

Joint effusion, or swelling within the joint, is ubiquitous following ACL injury and reconstructive surgery and can persist after joint injury or disease.[241, 242] Joint effusion is considered as a potential source of quadriceps activation deficits, even when inflammation (i.e. inflammation not mediated by pressure}, pain, or structural damage are not present. Knee effusion increases the intra-articular pressure, which stimulates group II afferent sensory receptors that are sensitive to changes in pressure and stretch.[243-247] This increased stimulation of

the group II sensory fibers increases afferent signaling and is communicated to the spinal cord and brain. The group II firing excites group Ib inhibitory interneurons located in the spinal cord[248] which communicate inhibitory signals to the alpha motor neuron and inhibit the quadriceps muscle.[249] Knee effusion is linked to changes indicative of neural dysfunction such as diminished electromyographic activity, lower H-reflex amplitudes, and reductions in force output for the quadriceps.[250-253] Thus, knee effusion due to injury or joint disease may be a relevant factor contributing to the presence of voluntary activation deficits.

Despite notable knee effusion observed up to 3 months after ACL injury and up to 12 months after ACL reconstruction[241] the link between knee effusion and voluntary activation deficits is less clear. For example, research in ACL-injured individuals report quadriceps voluntary activation did not differ across the four effusion grades (e.g., zero, trace, 1+, and 2+/3+)[254] suggesting effusion does not contribute to quadriceps activation deficits. However, when ACL-injured individuals were dichotomized into small and large effusion levels, individuals with large effusions (i.e. grades 2+ and 3+) exhibited lower voluntary activation compared with individuals with small effusions (e.g. grades 1+ or less).[254] While it is possible the presence of substantial effusion may influence quadriceps voluntary activation, effusion grade was a poor surrogate measure for quadriceps voluntary activation.[254] The inability of effusion grade to predict quadriceps voluntary activation may be due to evaluating effusion grade using the stroke test. During the stroke test, the examiner moves their finger from the medial tibiofemoral joint line to the suprapatellar pouch several times with the aim to move the joint swelling to the suprapatellar pouch. Next, a downward finger movement is performed from the distal lateral thigh toward the lateral joint line. The stroke test grades effusion of the knee joint using a 5-point scale, whereby a zero grade indicates no visible effusion and a 3+ grade indicates

that significant fluid is present and cannot be moved out of the medial aspect of the knee.[255] Hence, the imprecise nature of the stroke test may explain the inability to link effusion grade to quadriceps voluntary activation. Knee model research demonstrates that when known volumes of hypertonic saline are injected into the intra-articular space, there is a linear relationship with greater volumes corresponding to lower H-reflex amplitudes.[252] Given the thresholds for lower H-reflex amplitudes of the vastus medialis were between 20 to 30 ml and between 50 to 60 ml for the rectus femoris and vastus lateralis[252] it is likely effusion plays a role in acute activation deficits when notable effusion is present but plays a lesser role in chronic activation deficits when effusion is lower or negligible.[241]

Similarly, the role of knee effusion in voluntary activation deficits remains unknown in individuals with knee osteoarthritis and total knee arthroplasty. In individuals with knee osteoarthritis, quadriceps voluntary activation deficits are observed in the absence of knee effusion suggesting effusion can't be the sole contributor to the activation deficits observed in this population.[256] However, this does not necessarily preclude knee effusion from contributing to voluntary activation deficits in individuals with knee osteoarthritis. In contrast, knee effusion is associated with lower quadriceps strength in individuals with TKA, suggesting knee effusion may contribute to the voluntary activation deficits that lead to quadriceps weakness. However, voluntary activation was not evaluated in this cohort, thus we cannot confirm whether knee effusion is related to voluntary activation. Regardless, addressing knee effusion appears to be important to restore quadriceps function after joint disease and TKA.

1.4.1.3 Contribution of Mechanoreceptor Damage to Voluntary Activation

Mechanoreceptors are responsible for communicating changes in pressure, touch, or vibration, and can be found in the skin, muscles, tendon, ligaments, and joints. Following

damage to the joint, the sensory mechanoreceptors responsible for innervating the ACL can become damaged. The damage to mechanoreceptors is believed to result in the alteration or loss of sensory information from the ACL to the muscle, which may lead to quadriceps voluntary activation deficits.[236] In fact, reduced mechanoreceptor function is linked to quadriceps activation deficits due to impaired afferent transmission to the muscle.[238] Thus, restoring the function of mechanoreceptors may be an important factor in preventing chronic quadriceps voluntary activation deficits.

One potential mechanism to restore mechanoreceptor function is the regeneration of the mechanoreceptor. However, research indicates the ability of mechanoreceptors from the ACL remnant to regenerate is either limited[257] or does not occur.[258] Furthermore, regenerated mechanoreceptors may not necessarily function in a manner consistent with the behavior exhibited prior to injury in the original mechanoreceptors. Given impaired somatosensory function is believed to occur after injury,[259, 260] further investigation is needed to understand whether restoring mechanoreceptor function contributes to improvements in quadriceps voluntary activation in individuals with knee injury or joint disease.

1.4.1.4 Other Factors Contributing to Voluntary Activation Deficits

Several additional mechanisms believed to contribute to voluntary activation deficits include pre-synaptic inhibition, reciprocal inhibition, recurrent inhibition, non-reciprocal inhibition, flexion reflex, and gamma loop dysfunction. These mechanisms contribute to diminished efferent signaling from the alpha motor neuron to the muscle, which is believed to impair quadriceps voluntary activation. However, no investigations have been able to directly link these mechanisms to voluntary activation deficits after knee injury or joint disease. Instead, theories linking the factors to voluntary activation have been based on knee effusion models,

research in other injured populations, or on indirect research in individuals with ACL injury or knee osteoarthritis.[249, 261-266] While it is plausible these mechanisms may contribute to voluntary activation deficits, their role is not supported by strong evidence in individuals with knee surgery or joint disease. Thus, well-designed studies that can directly establish the link between each of the mechanisms with voluntary activation are needed.

1.4.2 Spinal-Reflex Contributions to Voluntary Activation

Alterations in the excitability of the spinal-reflex pathway are believed to contribute to voluntary activation deficits after knee injury and joint disease. Changes at the spinal level can contribute to voluntary activation deficits by changing the excitability of the quadriceps alpha motor neuron pool.[249] Spinal-reflex excitability is assessed using the quadriceps Hoffmann reflex (H-reflex), which can be quantified using the H-max to M-max (H:M) ratio. The H:M ratio is considered an estimate of the proportion of the motor neuron pool that can be reflexively activated, with lower ratios indicating a diminished ability to reflexively activate the motor neuron pool.[265, 267] Changes in quadriceps H:M ratios are commonly attributed to altered afferent information relayed from the involved joint to the alpha motor neuron, which is believed to contribute to quadriceps voluntary activation deficits.[251] Thus, adaptations in spinal-reflex excitability may be an important factor in addressing quadriceps voluntary activation deficits after knee injury and joint disease.

Following ACL injury and reconstruction, spinal-reflex changes are commonly reported (Table 1.1). A small amount of evidence shows unilateral decreases[171] and bilateral increases[171, 232, 268, 269] in quadriceps H:M ratios have been reported. These conflicting findings likely result from the various time periods after ACL injury and reconstruction where measurements are recorded. However, a recent meta-analysis strongly supports bilateral increases in H:M ratios

after ACL reconstruction.[268] Changes in spinal-reflex excitability also appear to be time-dependent with decreased spinal-reflex excitability arising shortly after injury and increased spinal-reflex excitability eventually developing after ACL reconstruction.[171] Diminished H:M ratios shortly after ACL injury and reconstruction may occur due to peripheral factors such as effusion, which is known to decrease spinal-reflex excitability.[265, 267] However, as knee effusion resolves and corticospinal excitability declines, increased spinal-reflex excitability may manifest to compensate for the loss of descending drive after ACL reconstruction.[171, 269] Thus, early reductions in spinal-reflex excitability may have negative consequences for quadriceps strength and voluntary activation, while increases in spinal-reflex excitability may help to preserve quadriceps function after ACL reconstruction.[269] However, direct evidence is needed to assess longitudinal changes in spinal-reflex excitability and how this may influence quadriceps dysfunction after ACL injury and reconstruction.

Table 1.1 Review of the literature for spinal-reflex changes after ACL reconstruction.

Author	**>3 years (0 = no; 1= yes)**	**H/M Ratio, Hoffmann's reflex/M-wave**		
		Healthy Control Leg Mean ± SD	**ACL Reconstructed Leg Mean ± SD**	**ACL Non-Reconstructed Leg Mean ± SD**
Kuenze et al. 2013	1	NE	NE	NE
Lepley et al. 2014	1	0.196 ± 0.102	0.265 ± 0.154	0.274 ± 0.165
Kuenze et al. 2015	0	0.26 ± 0.18	0.29 ± 0.2	0.31 ± 0.22
Pietrosimone et al. 2015	1	0.19 ± 0.10	0.27 ± 0.12	0.28 ± 0.16
Lepley et al. 2015 (2 weeks)	0	0.31 ± 0.12	0.11 ± 0.08	0.17 ± 0.11
Lepley et al. 2015 (6 months)	0	0.28 ± 0.11	0.24 ± 0.09	0.26 ± 0.12
Harkey et al. 2016	1	0.27 ± 0.16	0.29 ± 0.17	0.28 ± 0.17
Luc-Harkey et al. 2017	1	NA	NE	NE
Zarzycki et al. 2018	0	0.273 ± 0.15	0.368 ± 0.165	0.322 ± 0.243
Norte et al. 2018	1	0.14 ± 0.12	0.21 ± 0.19	0.18 ± 0.17
Ward et al. 2018	1	NA	0.30 ± 0.20	0.20 ± 0.20
Lepley et al. 2019a	1	0.304 ± 0.204	0.310 ± 0.172	0.256 ± 0.155
Bodkin et al. 2019	0	NA	0.20 ± 0.17	0.17 ± 0.15
Lepley et al. 2019b	1	NA	0.31 ± 0.172	0.256 ± 0.155
Burland et al. 2019a	0	NA	0.14 ± 0.09	0.16 ± 0.16
Burland et al. 2019b	0	NA	0.26 ± 0.22	0.22 ± 0.12
Burland et al. 2020a	0	NA	0.20 ± 0.21	0.19 ± 0.13
Burland et al. 2020b	1	NA	0.28 ± 0.18	0.22 ± 0.15
Scheurer et al. 2020	0	NE	NE	NE

SD standard deviation, *NE* not evaluated, *NA* not applicable, *ACL* anterior cruciate ligament

In contrast, no studies to date evaluated spinal-reflex changes after total knee arthroplasty. Instead, interpretations are based on the limited evidence in individuals with knee osteoarthritis. Based on current research evaluating spinal-reflex changes in the soleus, H:M ratios in the involved leg during standing do not appear to be changed in individuals with knee osteoarthritis.[270] Unfortunately, no studies have examined quadriceps H:M ratios in individuals with knee osteoarthritis so it remains unclear whether spinal-reflexive changes may contribute to quadriceps voluntary activation deficits in this population. Thus, there is a critical need to evaluate spinal-reflex excitability in individuals with knee osteoarthritis and total knee arthroplasty to determine whether spinal-reflex changes contribute to quadriceps voluntary activation deficits, which may inform how activation deficits are addressed in this population.

1.4.3 Corticospinal Contributions to Voluntary Activation

In individuals with knee surgery or osteoarthritis, diminished corticospinal excitability can develop and is believed to contribute to voluntary activation deficits. Descending pathways such as the corticospinal tract link upper motor neurons in the cerebral cortex to lower motor neurons in the spinal cord responsible for controlling movement. It is theorized that changes in the signaling of action potentials along the corticospinal pathway contributes to voluntary activation deficits.[174] Specifically, diminished corticospinal excitability is believed to depress alpha motor neuron excitability, leading to quadriceps voluntary activation deficits. Hence, addressing decreased corticospinal excitability is a growing area of interest for improving voluntary activation and quadriceps strength.

A common non-invasive technique used to quantify corticospinal excitability is transcranial magnetic stimulation (TMS).[271] Single-pulse and paired-pulse TMS protocols are suitable for assessing neural drive to the quadriceps as the magnetic pulse has lower subject

discomfort compared to electrical stimulus paradigms. In addition, the techniques provide direct measures of neural drive along the corticospinal pathways to the muscle that cannot be determined with voluntary activation assessments. Hence, investigation using both voluntary activation and TMS assessments can provide further insight into whether corticospinal changes contribute to quadriceps voluntary activation deficits.

Commonly reported measures of corticospinal excitability include the motor threshold and the motor evoked potential (MEP). The application of a TMS pulse produces a muscle contraction via a magnetic field, which depolarizes cortical neurons to create action potentials that produce a muscle contraction.[272] During the muscle contraction, a neural signal is measured via EMG known as the motor evoked potential (MEP). The MEP amplitude provides an estimate for the amount of action potential transmission along the corticospinal tract to the muscle[273] with lower MEPs indicating reduced transmission. The minimum stimulus intensity needed to elicit the motor response (e.g., MEP) is the motor threshold, which can be determined during a small contraction (i.e. active motor threshold, AMT) or when resting (i.e. resting motor threshold, RMT).[274] Motor threshold represents the relative excitability of the pyramidal cell membrane[273] with a higher motor threshold indicating a greater amount of stimulation is required to evoke a motor response and diminished corticospinal excitability. In pathological populations, measures of corticospinal excitability are typically recorded bilaterally as differences may exist between legs. However, the uninvolved leg can also undergo corticospinal changes and may lead to incorrect interpretations when making between-limb comparisons. Accordingly, measurements are also typically compared to healthy controls to help determine the effect of pathology on corticospinal excitability.

Motor threshold and MEP changes are the most commonly investigated measures of corticospinal excitability in individuals with ACL injury, reconstruction, and knee osteoarthritis.[171, 275, 276] Increased corticospinal excitability is also linked to voluntary activation[269] with increasing corticospinal excitability appearing to be a promising intervention target for improving muscle function in pathological populations, including ACL reconstructed individuals.[277-279] Therefore, the following section will be focused on the motor threshold and MEP amplitude changes reported in individuals with ACL injury or knee osteoarthritis, which will be key variables in this dissertation work.

1.4.3.1 ACL-Deficient Individuals

Following ACL injury, adaptations in the corticospinal pathway are believed to occur and contribute to voluntary activation deficits. Investigations of corticospinal excitability in ACL-deficient individuals are reported in Table 1.2.

Table 1.2 Review of the literature for corticospinal changes in ACL-deficient individuals.

Author, Year	Time since injury > 1 year (0 = no; 1 = yes)	Motor Threshold, %MSO		Motor Evoked Potential	
		ACL Reconstructed Leg	ACL Non-Reconstructed Leg	ACL Reconstructed Leg	ACL Non-Reconstructed Leg
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Heroux & Tremblay 2006	1	55 ± 12.2565*	59.5 ± 14.4703*	NR	NR
Lepley et al. 2015	0	37.3 ± 9.1	37.4 ± 8.4	0.03 ± 0.03	0.04 ± 0.06
Ward et al. 2016	0	51.8 ± 9.9	50.1 ± 9.2	0.56 ± 0.23	0.58 ± 0.23
Burland et al. 2020	0	46.2222 ± 12.9497*	NR	NR	NR

SD standard deviation, *NE* not evaluated, *NA* not applicable, *MSO* maximum stimulator output, *ACL* anterior cruciate ligament, * extracted from figures

Acutely after ACL injury, corticospinal excitability is not altered in the vastus medialis or the rectus femoris of the injured leg.[171, 280] However, chronic adaptations in corticospinal excitability reportedly develop in ACL-deficient individuals (median - 22 months post-injury} with lower resting motor thresholds, but similar motor evoked potentials in the rectus femoris of

the injured leg compared to the uninjured leg.[275] The lower motor thresholds with similar MEP amplitudes in the injured leg indicate both increased and unchanged corticospinal excitability, which may appear to be a conflicting and unexpected finding. However, motor threshold and MEP amplitudes measure different aspects of corticospinal excitability with the findings indicating a diminished ability to activate pyramidal neurons, but an unchanged motor output when activated.[273] It is possible the corticospinal changes may be an adaptation to increase neural drive to the quadriceps to maintain voluntary activation.[275] However, additional research would be needed to confirm the magnitude, direction, and timing of corticospinal changes and its relationship with voluntary activation and the spinal-reflex pathways in ACL-deficient individuals as voluntary activation was not assessed. Regardless, ACL injury appears to cause neuroplastic changes in the injured leg that may have implications for quadriceps function.

1.4.3.2 ACL Reconstructed Individuals

In ACL reconstructed individuals, changes in the corticospinal pathway are observed after surgery and may influence voluntary activation of the quadriceps. Corticospinal adaptations following ACL reconstruction are reported in Table 1.3. ACL reconstruction appears to affect the corticospinal pathways as bilateral decreases in active motor thresholds of the vastus medialis are reported two weeks after surgery compared to presurgery.[171] However, changes in MEP amplitudes were not observed.[171] These findings suggest ACL reconstructed individuals have a greater ability to excite the pyramidal neurons shortly after surgery with no change in the amount of information transmitted to the quadriceps and motor output. (i.e., MEP) compared to prior to surgery. Importantly, these results also suggest that ACL reconstruction has widespread effects that affect not only the reconstructed leg, but the contralateral leg as well.

When comparing to healthy individuals, evidence is mixed with some research reporting bilaterally increased motor threshold and MEP amplitudes (at 120% RMT)[281] while other research reports no changes bilaterally[171] two weeks after reconstruction. However, the latter study followed the same ACL reconstructed individuals 6 months after surgery and reported bilateral increases in the active motor threshold of the vastus medialis with no changes in MEP amplitudes compared to healthy controls.[171] In addition, no between-limb differences were observed at two weeks or 6 months after reconstruction.[171, 281] Collectively, evidence early after surgery points to the development of bilateral increases in motor threshold and possible increases in MEP amplitudes of the vastus medialis that develop between 2 weeks and 6 months after surgery. These findings suggest ACL reconstructed individuals have a diminished ability to excite the pyramidal neurons that affects not only the reconstructed leg, but the contralateral leg as well. While investigation of corticospinal excitability between 2 weeks and 6 months after reconstruction is needed to clarify the timing of corticospinal adaptations, it is clear decreased corticospinal excitability occurs in the recovery phase after ACL reconstruction.

Corticospinal adaptations appear to be persistent as changes in motor thresholds and MEP amplitudes are commonly reported years after ACL reconstruction. While evidence is mixed, increased motor threshold for the reconstructed leg[269, 282-284] and non-reconstructed leg[282, 283] are noted in the majority of studies. Similarly, higher motor thresholds are reported in the reconstructed leg compared with the non-reconstructed leg.[86, 170, 269] Our recent meta-analysis addresses the conflicting findings and confirms the bilateral increases in motor threshold compared to healthy controls with higher motor thresholds in the reconstructed leg compared with the non-reconstructed leg.[268] These findings indicate lower corticospinal excitability occurs

bilaterally and persists long after ACL reconstruction, which may have negative implications for quadriceps function.

Table 1.3 Review of the literature for corticospinal changes in ACL reconstructed individuals.

Author	>3 years (0 = no; 1= yes)	Motor Threshold, %MSO			Motor Evoked Potential		
		Healthy Control Leg Mean ± SD	ACL Reconstructed Leg Mean ± SD	ACL Non-Reconstructed Leg Mean ± SD	Healthy Control Leg Mean ± SD	ACL Reconstructed Leg Mean ± SD	ACL Non-Reconstructed Leg Mean ± SD
Kuenze et al. 2013	1	NE	NE	NE	NE	NE	NE
Lepley et al. 2014	1	37.5 ± 12.7	43.9 ± 16.3	37.3 ± 15.0	NE	NE	NE
Kuenze et al. 2015	0	63.05 ± 10.33	61.81 ± 11.98	56 ± 14.47	NE	NE	NE
Lepley et al. 2015 (2 weeks)	0	36.3 ± 7.7	31.0 ± 6.9	34.8 ± 11.9	0.02 ± 0.01	0.02 ± 0.02	0.03 ± 0.03
Lepley et al. 2015 (6 months)	0	36.8 ± 8.6	46.1 ± 8.7	47.4 ± 6.5	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.02
Pietrosimone et al. 2015	1	37.5 ± 12.7	45.14 ± 15.22	38.35 ± 14.39	NE	NE	NE
Luc-Harkey et al. 2017	1	NA	48.17 ± 13.05	46 ± 12.58	NA	0.34 ± 0.27	0.29 ± 0.16
Norte et al. 2018	1	39 ± 4.1	45.2 ± 8.6	44.3 ± 8.4	NE	NE	NE
Ward et al. 2018	1	NA	46.40 ± 9.90	43.90 ± 8.60	NA	NE	NE
Zarzycki et al. 2018	0	55.6 ± 8.2	61.4 ± 12.4	67.9 ± 15.4	0.032 ± 0.019	0.084 ± 0.056	0.057 ± 0.057
Bodkin et al. 2019	0	NA	46.1 ± 7.46	45.04 ± 6.97	NA	0.13 ± 0.12	0.095 ± 0.072
Burland et al. 2019a	0	NA	41.83 ± 5.3	37.25 ± 18.07	NA	0.05 ± 0.02	0.10 ± 0.19
Burland et al. 2019b	0	NA	47.88 ± 11.65	45.25 ± 14.31	NA	0.028 ± 0.01	0.04 ± 0.03
Lepley et al. 2019a	1	37.60 ± 5.30	49.80 ± 9.60	45.10 ± 9.40	0.0225 ± 0.0121	0.0134 ± 0.0077	0.0374 ± 0.0513
Lepley et al. 2019b	1	NA	51.0 ± 9.3	45.9 ± 9.5	NA	0.013 ± 0.007	0.028 ± 0.010
Burland et al. 2020a	0	NA	41.17 ± 11.95	41.92 ± 13.03	NA	0.07 ± 0.08	0.08 ± 0.15
Burland et al. 2020b	1	NA	48.31 ± 10.91	44.38 ± 9.6	NA	0.03 ± 0.04	0.03 ± 0.02
Scheurer et al. 2020	0	30.1 ± 8.2	44.9 ± 8.4	NE	NE	NE	NE

SD standard deviation, *NE* not evaluated, *NA* not applicable, *MSO* maximum stimulator output, *ACL* anterior cruciate ligament

For MEP amplitudes in the reconstructed leg, lower or unchanged MEP amplitudes are reported when compared with the non-reconstructed leg[171, 285] and higher or unchanged MEP amplitudes are reported when compared to healthy controls[171, 281]. However, no differences in MEP amplitudes between the non-reconstructed leg and the control leg are consistently

reported.[171, 281, 283] Our meta-analysis confirms no change in MEP amplitudes in either leg following ACL reconstruction[268] which indicates no changes in the transmission of action potentials along the corticospinal pathway occurs. The variability in findings is likely due to variance in participant characteristics (e.g., time since surgery, graft type, sex, etc.), a limited number of studies primarily cross-sectional in nature, and differences in methodology. Examples of methodological differences include the level of background contraction during testing (resting, 5% MVIC, etc.) and the muscle tested (rectus femoris vs vastus lateralis), which are known to influence measurement of corticospinal excitability[274, 286] and make comparisons across studies difficult. Thus, a measure that can evaluate the net effect of the quadriceps muscle, rather than an individual muscle, may help eliminate the variability in findings and provide consensus as to whether MEP amplitudes are altered after ACL reconstruction. The motor evoked torque response is a promising alternative to the EMG-evoked MEP (MEP_{EMG}) commonly used as the motor evoked torque is stable, reliable between-sessions, and can measure the net effect of TMS-evoked responses on the quadriceps.[287] While motor evoked torque responses have been utilized in a case-study of an individual with ACL reconstruction, further research is needed to support it as a reliable measure in a larger sample to determine whether it would be a valuable alternative to MEP_{EMG}.

1.4.3.3 Individuals with Knee Osteoarthritis and Total Knee Arthroplasty

Currently, the literature on corticospinal changes in individuals with TKA remain to be investigated. Accordingly, interpretations for TKA are limited to evidence in individuals with knee osteoarthritis, which is unclear due to conflicting findings. A case-report of an individual with knee osteoarthritis observed lower MEP amplitudes in the rectus femoris of the involved leg compared to the uninvolved leg, across all examined stimulus intensities.[276] This suggests there

is diminished corticospinal excitability on the involved leg with lower action potential transmission to the quadriceps compared to the contralateral leg.[276] However, motor thresholds are known to influence MEP amplitudes[288] and any differences in motor threshold between-limbs may have contributed to the differences in MEP amplitude. Unfortunately, motor thresholds were not reported making it difficult to determine whether motor threshold played a role. A study also reported higher active motor thresholds of the vastus medialis in both legs and no between-limb differences for ACL reconstructed individuals with knee osteoarthritis compared to healthy individuals.[282] These findings indicate lower corticospinal excitability occurs bilaterally due to diminished ability to activate the pyramidal neurons. However, it is difficult to determine whether corticospinal changes occurred due to ACL injury and reconstruction or are due to the presence of knee osteoarthritis. It is possible changes are due to ACL injury and reconstruction as research in individuals with knee osteoarthritis reports no significant differences in resting motor threshold of the vastus lateralis in the involved leg compared to the healthy control leg.[289] However, differences in the muscle (i.e. vastus medialis, vastus lateralis, rectus femoris) and variables (i.e. RMT, AMT, MEP) assessed may contribute to conflicting findings and make comparisons across studies difficult. Thus, investigation of both active motor threshold and MEP amplitudes are critically needed to determine whether the corticospinal pathway is affected in individuals with knee osteoarthritis. Further, investigation of a measure such as torque may be valuable when assessing MEP amplitudes which can determine the net effect of corticospinal changes in the quadriceps, rather than being limited to the study of a single quadriceps muscle. Assessment of motor evoked torque and motor thresholds would also provide insight into the role of corticospinal changes to quadriceps in individuals with knee osteoarthritis and TKA

would inform next steps for possible interventions to restore quadriceps strength and voluntary activation.

1.4.3.4 Relationship between corticospinal excitability and quadriceps function

The decreased corticospinal excitability noted after ACL reconstruction may contribute to the deficits in quadriceps activation also apparent in this patient population.[86, 269, 290, 291] For example, ACL reconstructed individuals with low quadriceps voluntary activation (<95%) demonstrate significantly higher vastus medialis active motor thresholds than healthy controls.[269] However, ACL reconstructed individuals with high quadriceps voluntary activation (≥95%) demonstrate similar vastus medialis active motor thresholds than healthy controls.[269] These findings suggest lower corticospinal excitability due to the diminished ability to activate the pyramidal neurons may be a relevant factor to the voluntary activation deficits observed and highlights the importance of maintaining corticospinal function after ACL reconstruction. Other research supports this as lower active motor thresholds are associated with greater quadriceps voluntary activation in the reconstructed leg.[86, 290] Thus, maintaining normative active motor thresholds through intervention may be key to maintaining voluntary activation after ACL reconstruction. However, the relationship between corticospinal excitability and voluntary activation has only been examined in the vastus medialis meaning these results may not necessarily extend to the other quadriceps muscles. Thus, assessing the net effect of the quadriceps muscles using measures like the motor evoked torque, may better represent corticospinal changes and strengthen the relationship with voluntary activation. Longitudinal investigation of motor evoked torque, motor threshold, and voluntary activation would also inform whether increased corticospinal excitability corresponds to improvements in voluntary activation after ACL reconstruction and potential avenues for future interventions.

While corticospinal changes appear to contribute to voluntary activation deficits after ACL reconstruction, it is less established in individuals with knee osteoarthritis and remains to be investigated after TKA. As such, interpretations are based on the limited studies in individuals with knee osteoarthritis. Unlike ACL reconstructed individuals, higher resting motor thresholds in the vastus lateralis are not associated with voluntary activation deficits in individuals with knee osteoarthritis.[289] While voluntary activation deficits are commonly reported[92, 113, 256] differences in quadriceps voluntary activation were not observed in the participants with knee osteoarthritis compared to healthy controls and may explain the lack of relationship with corticospinal excitability.[289] Thus, it is plausible the relationship with corticospinal excitability may strengthen when voluntary activation deficits are greater. Corticospinal excitability does still appear to play a role in quadriceps function as higher resting motor thresholds are associated with greater quadriceps strength in individuals with knee osteoarthritis.[289] The link between decreased corticospinal excitability and improved quadriceps strength in individuals with knee osteoarthritis is an unexpected finding and differs from individuals with ACL reconstruction.[86] It is plausible voluntary activation is an important covariate with lower corticospinal excitability acting as a compensatory mechanism for maintaining quadriceps strength when voluntary activation deficits are present, but may be maladaptive when voluntary activation is adequate. However, concurrent evaluation of corticospinal excitability, voluntary activation, and quadriceps strength is needed to confirm this theory and whether corticospinal excitability contributes to voluntary activation deficits in individuals with knee osteoarthritis and total knee arthroplasty.

1.4.3.5 Targeting the Corticospinal Pathway to Improve Quadriceps Function

Based on the current literature, it is clear corticospinal adaptations develop after ACL reconstruction and total knee arthroplasty. Given the link between decreased corticospinal excitability and quadriceps voluntary activation deficits[86, 290] improving corticospinal excitability may be a key factor to improving quadriceps function in individuals with knee surgery. As corticospinal changes can develop within 6 months after ACL reconstruction and persist for years[171, 269, 285] targeting the neural pathways early appears critical to mitigating quadriceps weakness and voluntary activation deficits. Hence, interventions that can be safely implemented early after surgery and directly target the corticospinal pathways are desirable and may translate to improvements in quadriceps function.

While several therapeutic interventions exist that are able to improve quadriceps function, most are unable to directly target the corticospinal pathway. For example, interventions such as neuromuscular electrical stimulation and eccentric exercise are able to improve quadriceps strength and voluntary activation in individuals with knee osteoarthritis and knee surgery.[200, 292-296] However, recovery of quadriceps strength and voluntary activation are often not achieved,[200, 292-294, 297] which may be due to the inability to directly target the neural pathways that result in these deficits. Interventions that target the corticospinal pathway such as transcranial direct current stimulation and repetitive TMS protocols may be useful to restore quadriceps function.[298] Unfortunately, effects due to transcranial direct current are not reliable and demonstrate variable effects for improving corticospinal excitability, while repetitive TMS can induce seizures and thus is not safe.[299, 300]

Operant up-conditioning of the corticospinal pathway via TMS is a powerful technique that can directly target corticospinal excitability and may have therapeutic benefit in individuals

knee surgery and joint disease.[277, 278] Operant conditioning uses a form of motor learning reinforced by rewards to provoke a desired behavior. [301] Operant conditioning of the spinal-reflex and corticospinal pathways have provided promising evidence that the neural pathways can be up- or down-regulated in healthy and pathological populations.[277, 302, 303] Thus, operant up-conditioning of the corticospinal pathway may improve corticospinal excitability and restore quadriceps voluntary activation after knee surgery.

Recently, a case study of an ACL reconstructed participant supports the feasibility of operant up-conditioning of motor evoked torque response to improve corticospinal excitability.[277] Acute and long-term improvements in motor evoked torque of the reconstructed leg were observed in the participant following an 8-week intervention.[277] In addition, the operant up-conditioning paradigm was able to elicit improvements in voluntary activation and quadriceps strength, providing preliminary evidence that improving corticospinal excitability may correspond to improved quadriceps function.[277] Previous operant conditioning protocols have provided similar evidence with successful conditioning corresponding to improved muscle strength, walking speed, and gait biomechanics.[278, 279, 303] Given that individuals with ACL reconstruction and total knee arthroplasty suffer quadriceps dysfunction and abnormal gait biomechanics[104, 110, 111, 146, 148, 304-307] operant conditioning may be a valuable supplement to standard of care for improving joint function and preventing the development and/or progression of joint disease in either leg. Unfortunately, little is known whether operant up-conditioning can successfully improve corticospinal excitability in individuals with total knee arthroplasty Therefore, implementation of operant up-conditioning in both individuals with ACL reconstruction and total knee arthroplasty is critical to determining its potential to improve corticospinal excitability and quadriceps function.

Despite the potential therapeutic benefits associated with operant conditioning, it is possible increasing corticospinal excitability may not translate to improvements in quadriceps function. In the case that operant up-conditioning of the motor evoked torque (i.e., increasing excitability} is unable to improve voluntary activation and quadriceps strength, valuable information can still be determined. If increased corticospinal excitability does not correspond to improvements in voluntary activation and quadriceps strength, it can be concluded corticospinal adaptations do not significantly contribute to quadriceps dysfunction. Regardless of the results, investigation on the effects of operant up-conditioning will inform whether direct intervention of the corticospinal pathway is effective or whether alternative strategies are needed to restore quadriceps voluntary activation and strength.

In order to better understand operant conditioning and its ability to increase corticospinal excitability, it is important to establish the appropriate dosage at which it should be delivered. It is well established that appropriate dosage is central to developing an effective intervention. If the dosage of operant up-conditioning is sub-optimal, the intervention may fail to elicit meaningful improvements in the corticospinal pathway. Given that operant up-conditioning is not able to successfully improve corticospinal excitability in some participants,[278, 302] it is plausible inadequate dosage may contribute to the inability to increase corticospinal excitability. However, it is unclear how the dosage of operant conditioning may affect the ability to increase corticospinal excitability of the quadriceps.

One key dosage parameter is the TMS stimulus intensity applied during operant conditioning. When using lower stimulus intensities, variability of the motor evoked response increases, which can increase signal noise and may lead to inconsistent effects of operant up-conditioning. Yet, use of higher stimulus intensities may be uncomfortable for the participant.[308,

[309] Thus, identifying the stimulus intensity that can safely provide consistent improvements in corticospinal excitability during operant conditioning is essential. However, it is unclear whether the current stimulus intensity used in operant conditioning protocols provides superior effects over other stimulus intensities. Therefore, investigation on the effect of stimulus intensity on the ability to up-condition corticospinal excitability is warranted.

Another aspect of dosage during operant conditioning is the number of training trials performed during a training session. Based on motor learning research, an individual's performance is influenced by the amount of practice.[310, 311] Accordingly, the effects of operant up-conditioning of motor evoked torque responses are likely to be impacted by the number of training trials. However, the amount of training trials typically used (3 blocks of 75 trials) in current operant conditioning protocols is based on studies originally designed to decrease spinal-reflex excitability of the triceps surae.[312] Consequently, the adapted protocols intended to up-regulate corticospinal excitability and applied for muscles other than those originally studied may not be designed effectively. In addition, the high number of training trials currently used (3 blocks of 75 trials) in operant conditioning paradigms may present a barrier to its feasibility in a clinical setting.[277, 302, 312] Thus, determining the effect of the total number of training trials on the ability to up-condition is crucial to designing a feasible and effective operant conditioning intervention.

1.5 Summary of the Literature Review

In summary, quadriceps weakness and voluntary activation deficits are ubiquitous following joint disease and knee surgery. Quadriceps strength and voluntary activation are common targets for restoring quality of life and functional ability, yet quadriceps dysfunction persists despite rehabilitative intervention. Adaptations of quadriceps corticospinal excitability

point to the corticospinal pathway as a relevant source of the chronic voluntary activation deficits individuals suffer after knee injury, knee surgery, and joint disease. The inability of standard therapeutic interventions to completely restore quadriceps strength and voluntary activation underscores the need for alternative approaches. Novel interventions that are capable of directly targeting the corticospinal pathway, such as operant up-conditioning, may offer a promising means to addressing quadriceps voluntary activation deficits and improving quadriceps strength in individuals following knee injury, knee surgery, or joint disease.

1.6 Introduction to the Dissertation

Diminished excitability of the corticospinal pathways has been theorized to contribute to poor quadriceps strength and voluntary activation after knee injury and surgery. Current interventions are unable to directly target the corticospinal pathway, which may be a key barrier to restoring quadriceps function. Operant conditioning is an emerging approach with the ability to directly target the corticospinal pathway. However, it is unclear whether operant conditioning is feasible after TKA and ACL reconstruction and whether operant up-conditioning can improve quadriceps function in ACL reconstructed individuals. Further, it is well-established that appropriate dosage is needed to ensure the efficacy of an intervention as sub-optimal dosage parameters may limit therapeutic benefits. However, the dosage parameters used during operant conditioning (i.e., stimulus intensity and number of training trials) appear to be chosen arbitrarily and lack evidence supporting their superiority. Therefore, the overarching aims of this dissertation were to determine the optimal stimulus intensity and number of trials on the ability to improve corticospinal excitability following ACL reconstruction and TKA and whether operant conditioning of the corticospinal pathway is capable of improving quadriceps function following ACL reconstruction. We addressed these research questions through four experiments

that were collected between 2020-2023. The specific aims and hypotheses for each of these experiments are detailed below.

Aim 1A: To determine the test-retest reliability of the quadriceps motor evoked torque (MEP_{TORQUE}) and motor evoked potential (MEP_{EMG}) responses in individuals with ACL reconstruction.

Hypothesis 1A: We hypothesized that the MEP_{TORQUE} would demonstrate higher reliability coefficients, indicating better reliability, when compared with the MEP_{EMG}.

Aim 1B: To compare various normalization methods and the influence of normalization method on the reliability of MEP_{TORQUE} and MEP_{EMG} measurements.

Hypothesis 1B: We hypothesized that the normalized method used would influence the reliability of MEP_{TORQUE} and MEP_{EMG} measurements.

Significance of Aim 1: Quadriceps corticospinal excitability is commonly evaluated using the motor evoked responses, which can be monitored via surface electromyography (MEP_{EMG}) or using joint torque (MEP_{TORQUE}). However, it is unknown whether MEP responses can be obtained reliably after ACL reconstruction and whether MEP_{TORQUE} offers superior reliability over MEP_{EMG} in this population. Further, MEP responses can be normalized using various procedures and may influence the reliability of MEP data. The results of this experiment will establish whether quadriceps MEP_{TORQUE} is a reliable measure for evaluating corticospinal excitability after ACL reconstruction. Knowledge from this study will also inform the design of interventions that evaluate corticospinal excitability by determining suitable target variables.

Aim 2A: To evaluate the ability of individuals with ACL reconstruction to improve quadriceps corticospinal excitability within a single session of operant up-conditioning and whether upregulating corticospinal excitability would elicit acute neural adaptations.

Hypothesis 2A: We hypothesized that ACL reconstructed individuals would be able to increase their MEP_{TORQUE} in a single training session due to operant up-conditioning, which would be paralleled by acute neural adaptations (i.e., aftereffects).

Aim 2B: To determine the effect of the stimulus intensity used during operant conditioning on the ability to improve corticospinal excitability and its associated neural adaptations in ACL reconstructed individuals.

Hypothesis 2B: We hypothesized that the ability to improve quadriceps corticospinal excitability and the associated neural adaptations would increase with higher stimulus intensities.

Significance of Aim 2: Operant conditioning of the quadriceps motor evoked torque is an emerging approach that can directly target the corticospinal pathway and has the potential to improve quadriceps function after ACL reconstruction. The ability to successfully upregulate the corticospinal pathway is critical in harnessing the full benefits of operant conditioning. One possible factor that may influence the ability to upregulate corticospinal excitability may be the stimulus intensity used during training as it is a parameter that contributes to the dosage during the intervention. However, the optimal stimulus intensity used during training has yet to be established. Findings from this experiment will determine whether operant conditioning is a suitable approach to targeting quadriceps corticospinal excitability following ACL

reconstruction. Knowledge gained from this study will also determine the optimal stimulus intensity during training, which will have important implications for the design and implementation of operant conditioning interventions following ACL reconstruction.

Aim 3A: To determine the effect of multiple operant up-conditioning training sessions on the ability to improve corticospinal excitability in ACL reconstructed individuals who received training compared with those who did not receive training.

Hypothesis 3A: We hypothesized that individuals in the conditioning group would successfully increase their MEP_{TORQUE} responses due to operant up-conditioning and would increase to a greater extent than individuals in the sham-conditioning group.

Aim 3B: To determine the effect of multiple operant up-conditioning training sessions on quadriceps strength and voluntary activation.

Hypothesis 3B: We hypothesized that individuals in the conditioning group would demonstrate significant increases in voluntary activation and quadriceps strength following the intervention, while individuals in the sham-conditioning group would remain unchanged.

Significance of Aim 3: Following ACL reconstruction, individuals suffer substantial deficits in quadriceps strength and voluntary activation. A case study from our laboratory suggests that operant up-conditioning of the corticospinal pathway can improve quadriceps strength and voluntary activation. With a larger sample size, our investigation will establish whether operant conditioning is a feasible intervention to improve quadriceps function after ACL reconstruction. The inclusion of a control group will also help determine whether improvements in quadriceps

function following multiple training sessions are attributable to the operant conditioning paradigm.

Aim 4A: To evaluate the ability of individuals with TKA to increase their quadriceps corticospinal excitability within a single session of operant conditioning and elicit acute neural adaptations.

Hypothesis 4A: We hypothesized that individuals with TKA would increase their quadriceps MEP_{TORQUE} responses within a single session due to operant up-conditioning, which would be paralleled by acute neural adaptations.

Aim 4B: To determine the effect of stimulus intensity and number of training trials used during operant conditioning on the ability to upregulate MEP_{TORQUE} and the associated acute neural adaptations.

Hypothesis 4B: We hypothesized that stimulus intensity would not influence the ability to up-condition or the associated neural adaptations. We also hypothesized that quadriceps MEP_{TORQUE} would increase as the number of trials increased, such that the final block would show the largest MEP_{TORQUE} and the first block would show the smallest MEP_{TORQUE}.

Significance of Aim 4: Despite undergoing formal rehabilitation, quadriceps dysfunction persists well after TKA. Operant conditioning of the corticospinal pathway may be a valuable technique for improving quadriceps function following TKA. Findings from this study would reveal whether operant conditioning is a feasible intervention following TKA and provide preliminary data that may merit longitudinal investigation. Findings from this study will also

inform the optimal stimulus intensity and number of training trials needed to maximize the effects of operant conditioning, which will inform the design of future interventions in individuals with TKA.

1.7 Organization of the Dissertation

The chapters that follow represent the primary work of this dissertation and investigate the four aims outlined in the previous section.

In Chapter 2, we evaluated the reliability of raw and normalized quadriceps motor evoked responses in ACL reconstructed individuals. This work was previously published in the Journal of Electromyography and Kinesiology.[313] This work established the motor evoked torque response as a suitable target variable for upregulating corticospinal excitability in the experiments that followed.

In Chapter 3, we evaluated the ability of ACL reconstructed individuals to improve their quadriceps corticospinal excitability within a single session of operant conditioning and induce neural adaptations, as well as the influence of stimulus intensity on these outcomes. This work has been submitted to the Journal of Sport and Health Science and is currently in review.

In Chapter 4, we tested the effect of multiple operant conditioning training sessions on the ability to improve quadriceps corticospinal excitability in individuals with ACL reconstruction. We also evaluated the effect of multiple operant conditioning training sessions on quadriceps function following ACL reconstruction.

In Chapter 5, we evaluated the ability of individuals to improve quadriceps corticospinal excitability and induce acute neural adaptations within a single session of operant conditioning following TKA. In addition, we tested the influence of stimulus intensity and the number of trials

on the ability to upregulate corticospinal excitability and its associated neural adaptations. This work is currently in preparation for submission.

In Chapter 8, we summarize the key findings from this dissertation and propose future investigations that could advance our understanding of operant conditioning.

1.8 Bibliography

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Chapter 2 Quadriceps Motor Evoked Torque is a Reliable Measure of Corticospinal Excitability in Individuals with Anterior Cruciate Ligament Reconstruction

Abstract:

Background: Quadriceps motor evoked responses elicited via transcranial magnetic stimulation (TMS) can be recorded using knee joint torque (MEP_{TORQUE}) or surface electromyography (MEP_{EMG}). MEP responses are typically normalized to reduce variability of the MEP data. However, it is unknown whether quadriceps MEP responses can be reliably obtained after anterior cruciate ligament (ACL) reconstruction and whether the normalization approach influences the reliability of MEP data. *Objective:* This study comprehensively evaluated the test-retest reliability of raw and normalized quadriceps motor evoked responses elicited by TMS in individuals with ACL reconstruction. *Methods:* Fifteen participants were tested on three different days that were separated at least by 24 hours. Motor evoked responses were collected during a small background contraction on the reconstructed leg across a range of TMS intensities using MEP_{TORQUE} and MEP_{EMG} responses. MEP_{TORQUE} and MEP_{EMG} were evaluated using different normalization procedures (raw, normalized to maximum voluntary isometric contraction, peak MEP, and background contraction). MEP_{TORQUE} was also normalized to the magnetically-evoked peripheral resting twitch torque. The area under the recruitment curve was computed for both raw and normalized MEPs. Intraclass correlation coefficients (ICCs) were determined to assess test-retest reliability. *Results*: We found that MEP_{TORQUE} generally showed greater reliability than MEP_{EMG} for all normalization procedures. Vastus medialis MEP_{EMG} generally showed greater reliability than rectus femoris MEP_{EMG}. Finally, both MEP_{TORQUE} and MEP_{EMG} exhibited good

reliability, even when not normalized. *Conclusions*: These findings indicate that MEP_{TORQUE} and MEP_{EMG} offer reliable measures of corticospinal function and suggest that MEP_{TORQUE} is a suitable alternative to MEP_{EMG} for measuring quadriceps corticospinal excitability in individuals with ACL reconstruction.

2.1 Introduction

Deficits in quadriceps strength and voluntary activation (i.e., the ability to completely contract the muscle during a maximal contraction) are commonly observed following anterior cruciate ligament (ACL) reconstruction.[1, 2] Emerging evidence suggests that corticospinal transmission and excitability are significantly altered following ACL reconstruction[3, 4] and these alterations have been associated with reduced quadriceps strength and voluntary activation in individuals with ACL reconstruction.[5, 6] The association between corticospinal excitability and quadriceps strength and voluntary activation has led to the theory that improving corticospinal function could restore quadriceps function. Accordingly, there is a growing interest in evaluating longitudinal changes in corticospinal excitability in individuals with ACL reconstruction. However, in order to confidently attribute the changes in corticospinal function that occur over time (e.g., after an intervention) to changes in quadriceps function, it is imperative to be able to obtain reliable measurements of corticospinal excitability.

Transcranial magnetic stimulation (TMS) is a commonly used non-invasive technique for assessing changes in corticospinal excitability after injury or disease.[7, 8] When applied to the primary motor cortex (M1), a single TMS pulse with sufficient intensity can elicit efferent volleys along the corticospinal pathways known as motor evoked responses.[9] The size of the motor evoked response is believed to represent the integrity and overall excitability of the corticospinal pathway,[10] with higher amplitudes corresponding to greater excitability.[11]

Quadriceps motor evoked responses can be monitored either via surface electromyography (EMG) or through knee joint torque, with EMG-based motor evoked potential (MEP) being the most commonly used.[12-15] An advantage of using MEP data measured via torque (MEP_{TORQUE}) is that torque measurements are inherently stable, unlike EMG, which may eliminate the need for the MEP normalization procedures typically used for MEP data.[16] On the other hand, MEP data measured via EMG (MEP_{EMG}) are advantageous as they can determine the contribution of an individual quadriceps muscle to corticospinal changes, while MEP_{TORQUE} can only provide the net-effect of the entire quadriceps muscle group.[15] While both methods have advantages and disadvantages, prior research in healthy individuals suggests measurements of raw and normalized MEP_{TORQUE} demonstrate greater reliability compared with MEP_{EMG} for the quadriceps.[16] However, no studies to date have investigated the reliability of TMS-induced MEPs in individuals with ACL reconstruction. Thus, it remains unclear whether reliable quadriceps MEP responses are obtainable in this population. Moreover, it is unclear if MEP_{TORQUE} offers superior reliability over MEP_{EMG} in individuals with ACL reconstruction.

Another issue that needs consideration when considering the reliability of MEPs is the normalization process used in MEP evaluation. Normalization procedures (e.g., maximum voluntary isometric contraction [MVIC], M-max, etc.) are commonly used to reduce the variability of quadriceps MEP signals[16-18] because the raw MEP data could be influenced by factors that affect the torque or EMG signal such as sensor placement, sensor orientation, contact quality of sensors, posture, and joint position.[19-21] Prior research on healthy individuals indicates that the normalization process used in MEP evaluation affects the reliability of the MEP data. Specifically, measurements of MEP_{EMG} demonstrated improved reliability when normalized by MVIC compared to raw MEP_{EMG}.[16] In contrast, MEP_{TORQUE} showed good reliability for both raw

and normalized measures.[16] However, the effects of such normalization processes on MEP reliability is not clear in individuals with ACL reconstruction.

Therefore, the primary purpose of this study was to determine the test-retest reliability of TMS-induced MEP_{EMG} and MEP_{TORQUE} responses in the quadriceps muscles of individuals with ACL reconstruction. A secondary purpose of this study was to compare various normalization procedures and the influence of these procedures on test-rest reliability of MEP_{EMG} and MEP_{TORQUE}. We hypothesized that the reliability coefficients of MEP_{TORQUE} would demonstrate higher repeatability when compared with the MEP_{EMG}. We also hypothesized that normalization methods would influence the reliability of MEP_{EMG} and MEP_{TORQUE} measurements.

2.2 Methods

2.2.1 Participants

Fifteen individuals with ACL reconstruction (5 males, 10 females, 20.9 ± 4.1 years, 1.74 ± 0.06 m, 70.2 ± 11.9 kg, 7.13 ± 3.01 months post-operative, 14 right footed, 1 left footed) participated in this study. Inclusion criteria were: 1) aged 14-40 years 2) suffered a complete ACL rupture and 3) received an ACL reconstruction with an autograft at least 6 weeks prior to the testing. Exclusion criteria included: 1) medications that may influence corticospinal excitability (e.g. tricyclic antidepressants, antipsychotics, etc.); 2) having ear or metal implants in the skull; 3) having a cardiac pacemaker; 4) a history of unexplained recurrent headaches, seizures, recent head injury, medical or heart condition that could influence study outcomes or significant adverse reaction to TMS; 5) currently pregnant; 6) previous ACL injury; 7) previous major injury to either knee; or 8) other recent significant knee injury or lower-extremity fracture. All participants read and signed a written informed consent/assent document approved by the

University of Michigan Institutional Review Board. Parental consent was obtained if the participant was a minor child.

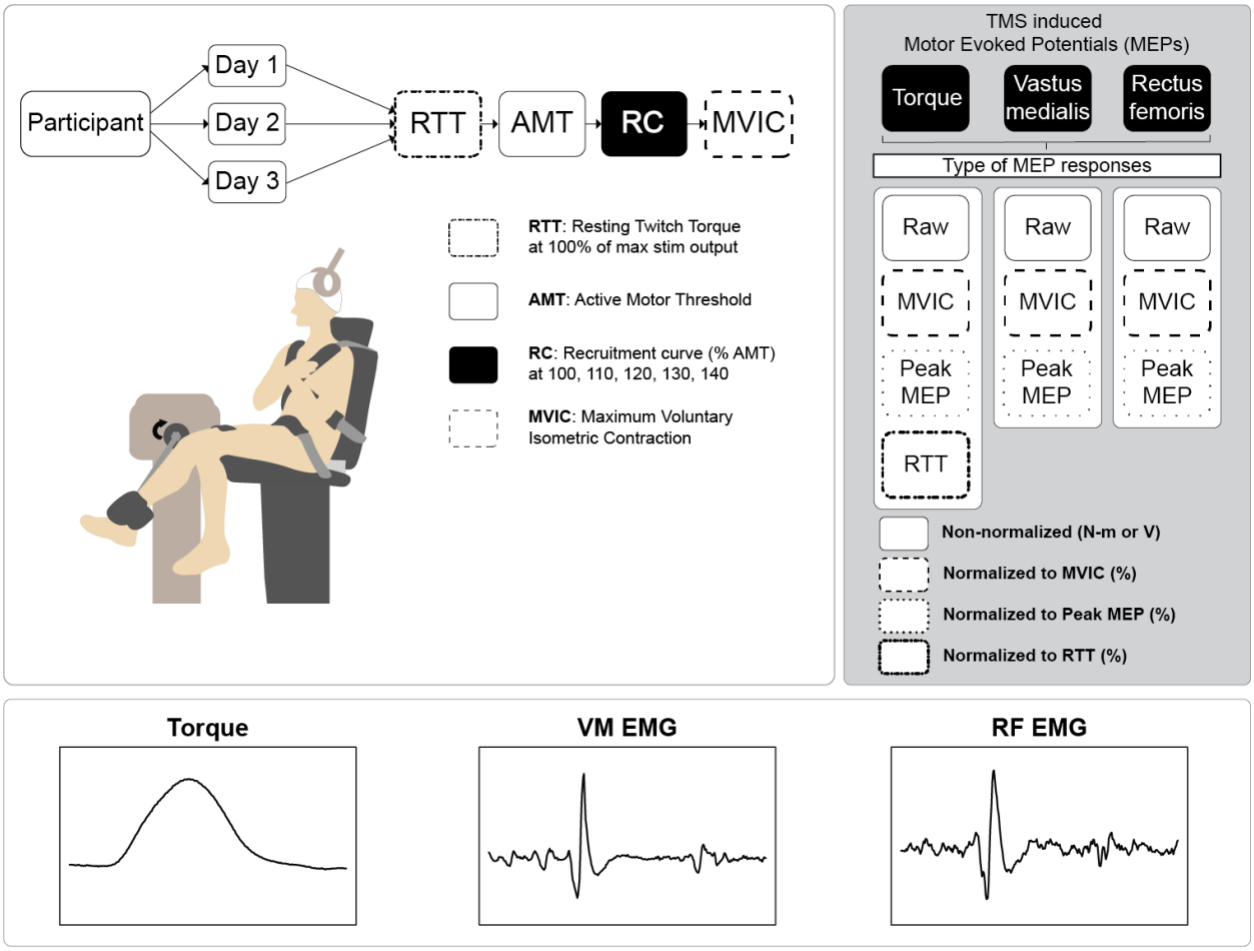

Figure 2.1 Schematic of the participant set-up, experimental protocol, and normalization methods used for evaluating reliability across three sessions. Torque, vastus medialis EMG, and rectus femoris EMG traces from a representative subject are also shown. *Abbreviations*: AMT, active motor threshold; EMG, electromyography; MEP, motor evoked response/potential; MVIC, maximal voluntary isometric contraction; N-m, Newton-meters; RC, recruitment curve; RF, rectus femoris; RTT, magnetically-evoked peripheral resting twitch torque; V, volts; VM, vastus medialis; %, percentage.

2.2.2 Experimental Approach

The reliability of MEP_{TORQUE} and MEP_{EMG} of the quadriceps muscles was assessed on the ACL reconstructed leg on three separate testing sessions that were separated by at least one day (5.77 ± 5.26 days). The MEP_{TORQUE} data were collected in all fifteen participants, while MEP_{EMG} data were collected in eight participants. The second and third visits were scheduled at

the end of each previous session with the described procedures repeated for subsequent sessions. A schematic of the experimental protocol is shown in Figure 2.1.

2.2.3 Transcranial Magnetic Stimulation Protocol

Participants were seated on an isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY, USA) with the trunk and knee of the reconstructed leg set to 85° and 60° of flexion, respectively. The trunk and knee positions and the dynamometer chair settings for the participant were held constant across sessions to ensure lower limb position was consistent. A Magstim 200^2 stimulator (Magstim Company Ltd, Whitland, UK) and a standard double cone coil (110 mm diameter) were used to assess the participant's magnetically-evoked peripheral resting twitch torque (RTT) at the beginning of each session. The coil was placed directly over the quadriceps (20 cm above the patella) and five stimulations at 100% of maximum stimulator output were given to record the RTT. The largest RTT value was then determined and used as the target for the background contraction performed during the TMS protocol. The magnitude of RTT was used instead of a set percentage of MVIC to minimize the effects of maximal contractions on MEP amplitudes due to alterations in excitability of the corticospinal pathways.[22-24]

After obtaining the RTT, participants were then taken out of the dynamometer chair to place surface EMG electrodes. The skin over the anterior surface of the thigh was first cleaned using alcohol pads. Wireless surface EMG electrodes (Ag, rectangular sensors; case dimension: 27 mm length x 37mm width x 15mm height) with a bi-polar parallel bar electrode configuration (Trigno, Delsys, Inc., Natick, MA, USA) were then placed on the muscle bellies of the vastus medialis (VM) and rectus femoris (RF) according to the SENIAM guidelines (www.seniam.org). The electrodes were secured tightly with self-adhesive tapes and elastic bandages. The participants were then seated back and secured to the dynamometer as before to collect TMS-

induced motor evoked responses. TMS pulses were delivered at random intervals over the primary motor cortex (M1) during a small background contraction of the quadriceps muscle (i.e., maximum RTT value). To perform the small background contraction, participants received visual feedback that showed a torque target corresponding to the individual's maximum RTT value. A cloth cap was tightly secured to the participant's skull to enable hotspot localization of the quadriceps during TMS. The vertex was identified by the intersection of the lines connecting the two auditory tragi and the nasion and inion. An offset to account for the TMS coil dimensions was used and an initial stimulation location 2 cm lateral and 2 cm posterior to the vertex was marked on the cap. The TMS coil was oriented to induce a posterior-anterior current flow in M1 and was systematically shifted to identify the location that elicited the largest and most consistent knee extension twitch torque at the lowest TMS intensity.[15, 25, 26]

The active motor threshold (AMT) was determined by identifying the minimum TMS intensity necessary to evoke a MEP in ≥ 50% of the attempted trials (≥ 10 trials) during a small background contraction of the quadriceps muscle.[27] The 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.html).[28] After determining the AMT, MEP_{EMG} and MEP_{TORQUE} were collected at eight different intensities (70–140% AMT) with five trials at each intensity.

2.2.4 Maximal Voluntary Isometric Strength

Strength testing was performed immediately after TMS procedures while participants were seated in the dynamometer. Submaximal isometric contractions (2 at 50%, 2 at 75%) were used as a warm-up prior to the participant performing two maximal voluntary isometric

contractions (MVIC). Verbal encouragement from the researchers and visual feedback of the torque curves were provided during MVIC trials to ensure maximal performance.

2.2.5 Data Analysis

The EMG sensors had an internal Butterworth high-pass (20 ± 5 Hz cut-off, >40 dB/dec) and low-pass filter (450 ± 50 Hz cut-off, >80 dB/dec) and an internal amplifier (Common Mode Rejection Ratio >80 dB; input impedance $>10^{15}$ Ω; gain = 909). A custom written program in LabView (version 11.0, National Instruments Corp., Austin, TX, USA) was used to collect and process the TMS data. The raw EMG, torque, and synchronized TMS pulses were low pass filtered at 500 Hz using an 8th order analog Butterworth filter (SCXI 1143, National Instruments) and sampled at 1000 Hz using an 18-bit M-series data acquisition module (USB 6281, National Instruments).

The magnitude of the MEP_{TORQUE} was calculated using the average peak torque elicited by the TMS at each testing intensity after accounting for the torque associated with background contraction (i.e., after subtracting the background torque from the TMS-evoked torque). The magnitude of the MEP_{EMG} was determined using the average peak-to-peak MEP amplitude elicited by the TMS at each testing intensity. The MEP_{TORQUE} and MEP_{EMG} were then evaluated using the following normalization methods: (1) raw data (i.e., without any normalization), (2) normalized to peak MEP amplitude (Equation 2.1), (3) normalized to the magnitude of the background contraction (i.e., magnitude of torque or EMG observed during TMS at RTT level background contraction, depending on the variable used in the analysis) (Equation 2.2), and (4) normalized to MVIC (Equation 2.3). The MEP_{TORQUE} was also normalized to the peripheral RTT elicited by the TMS at 100 % of maximum stimulator output (Equation 2.4).

$$\text{Peak MEP Normalization} = \frac{\text{MEP}}{\text{Peak MEP}} \times 100$$

Equation 2.1

$$\text{Background Contraction Normalization} = \frac{\text{MEP}}{\text{Background Contraction}} \times 100$$

Equation 2.2

$$\text{MVIC Normalization} = \frac{\text{MEP}}{\text{MVIC}} \times 100$$

Equation 2.3

$$\text{Resting Twitch Torque Normalization} = \frac{\text{MEP}_{\text{Torque}}}{\text{Resting Twitch Torque}} \times 100$$

Equation 2.4

The total area under the recruitment curve (AUC) was also computed for the raw and normalized variables for both MEP_{TORQUE} and MEP_{EMG} using the trapezoidal integration method to provide a summary measure of motor cortical excitability across all stimulation intensities (i.e., 70%-140% AMT).[29-31]

2.2.6 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Version 26. Descriptive statistics were calculated for MEP_{TORQUE} and MEP_{EMG} obtained at each intensity across the three testing sessions. Intraclass correlation coefficients (ICCs) were determined to assess the test-retest reliability of MEP_{TORQUE} and MEP_{EMG} amplitudes across the three sessions. A two-way mixed-effects model for single measurement and absolute agreement were used to conduct ICC analyses at each TMS intensity for raw motor evoked responses, normalized motor evoked responses, and area under the curve of the raw and normalized MEP_{TORQUE} and MEP_{EMG}. Established guidelines by Cicchetti were used to interpret ICC values: Poor (<0.40), Fair (0.40-0.59), Good (0.60-0.74), and Excellent (0.75–1.00).[32]

2.3 Results

Participant data for raw MEP_{TORQUE}, torque during background contraction, torque during maximum voluntary isometric contraction and resting twitch torque are reported in Appendix D. In addition, participant data for raw MEP_{EMG}, EMG during background contractions, and EMG during maximum voluntary isometric contractions are reported for vastus medialis and rectus femoris in Appendix E.

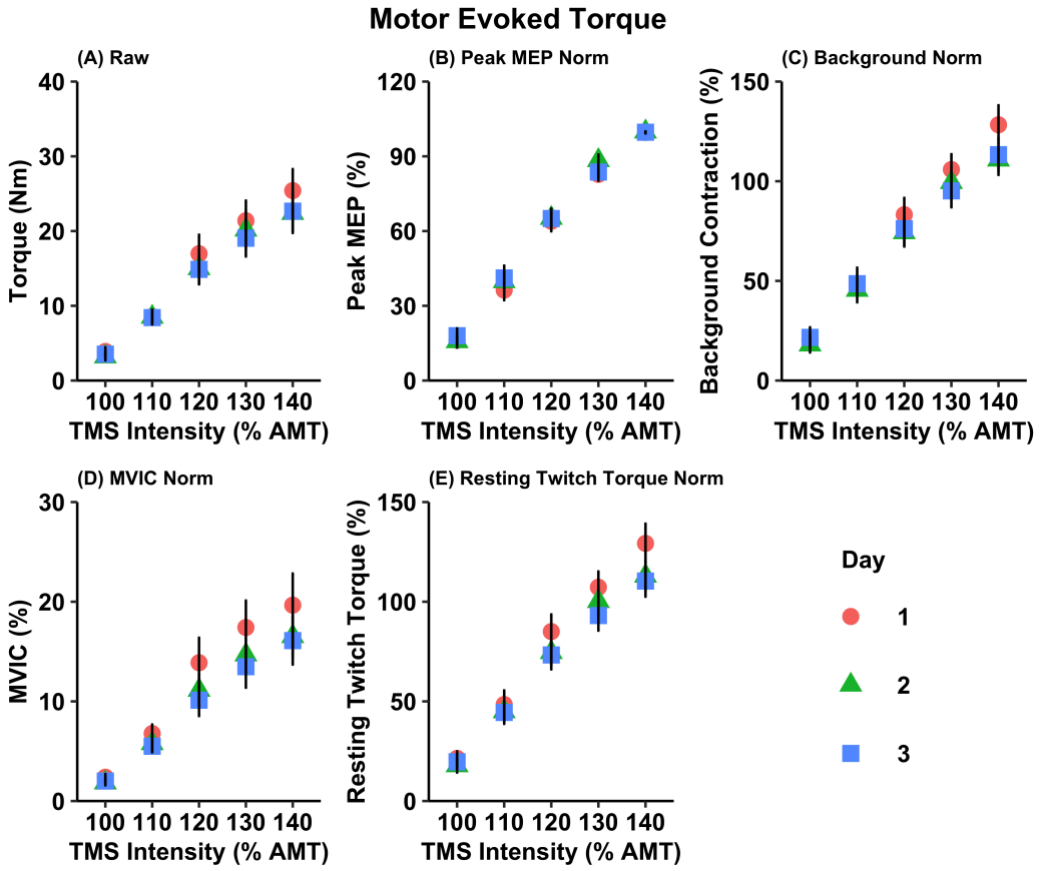

Figure 2.2 Plots showing the mean MEP_{TORQUE} at each TMS intensity for the five different normalization techniques across the three testing sessions: (A) raw MEP_{TORQUE} with no normalization, (B) MEP_{TORQUE} normalized to the peak MEP_{TORQUE} amplitude elicited between 100 %–140 % of AMT, (C) MEP_{TORQUE} normalized to the background contraction, (D) MEP_{TORQUE} normalized to the peak torque values obtained during MVIC, and (E) MEP_{TORQUE} normalized to the magnetically-evoked peripheral RTT elicited at 100 % of maximum stimulator output with the TMS coil placed directly over the quadriceps muscle. Error bars represent standard error of the mean. *Abbreviations*: AMT, active motor threshold; MEP, motor evoked response; MEP_{TORQUE}, motor evoked torque; MVIC, maximum voluntary isometric contraction; Norm, normalization; RTT, resting twitch torque; TMS, transcranial magnetic stimulation.

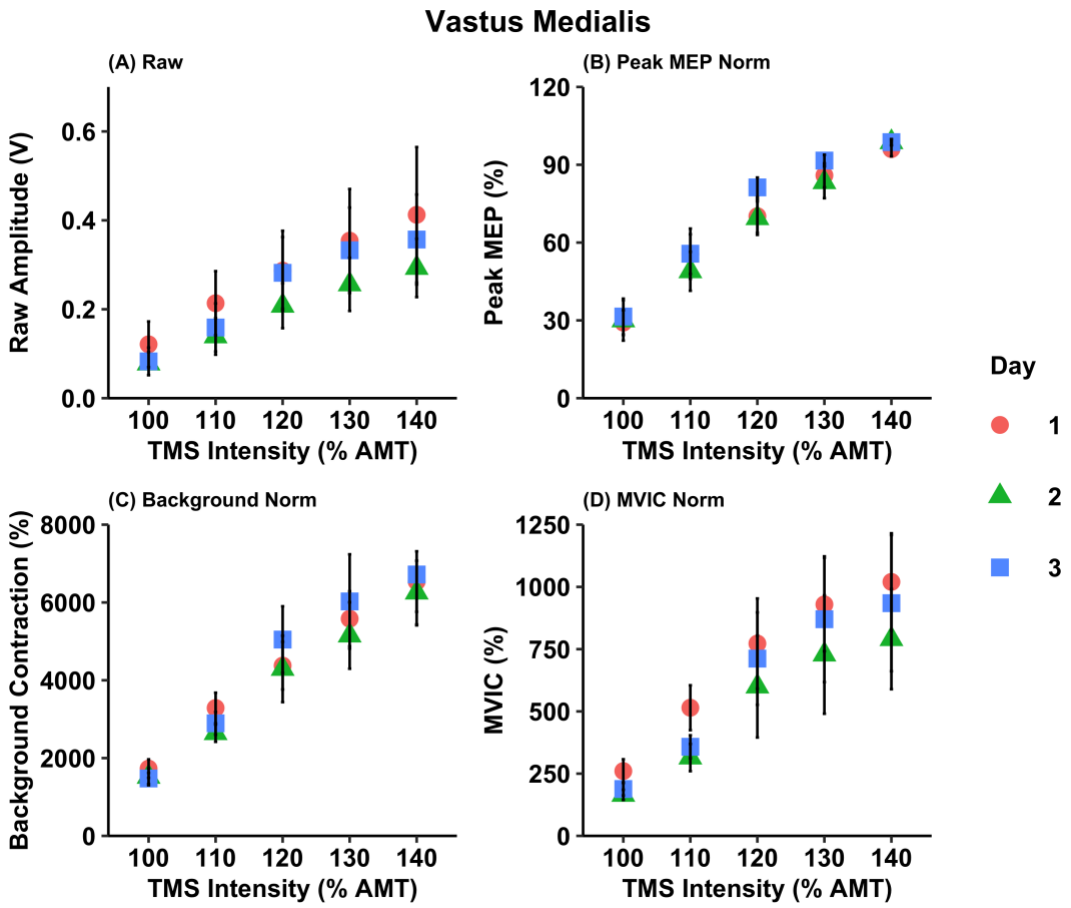

Figure 2.3 Plots showing the mean motor evoked potential (MEP_{EMG}) of the vastus medialis muscle at each TMS intensity for the four different normalization techniques across the three testing sessions: (A) raw vastus medialis MEP_{EMG} with no normalization, (B) vastus medialis MEP_{EMG} normalized to the peak MEP_{EMG} amplitude elicited between 100 %–140 % of AMT, (C) vastus medialis MEP_{EMG} normalized to the background contraction, (D) vastus medialis MEP_{EMG} normalized to the peak values obtained during MVIC. Error bars represent standard error of the mean. *Abbreviations*: AMT, active motor threshold; MEP, motor evoked potential/response; MEP_{EMG}, motor evoked potential; MVIC, maximum voluntary isometric contraction; Norm, normalization; TMS, transcranial magnetic stimulation; VM, vastus medialis.

The TMS-induced MEP_{TORQUE} and MEP_{EMGs} (vastus medialis and rectus femoris) for all intensities across the three test days are shown in Figure 2.2, Figure 2.3, and Figure 2.4 respectively. The ICC values for both the raw and normalized MEP_{TORQUE} and MEP_{EMG} data across various TMS intensities are provided in Table 2.1. In addition, ICC values for the area under the curve of raw and normalized MEP_{TORQUE} and MEP_{EMG} are reported in Table 2.2.

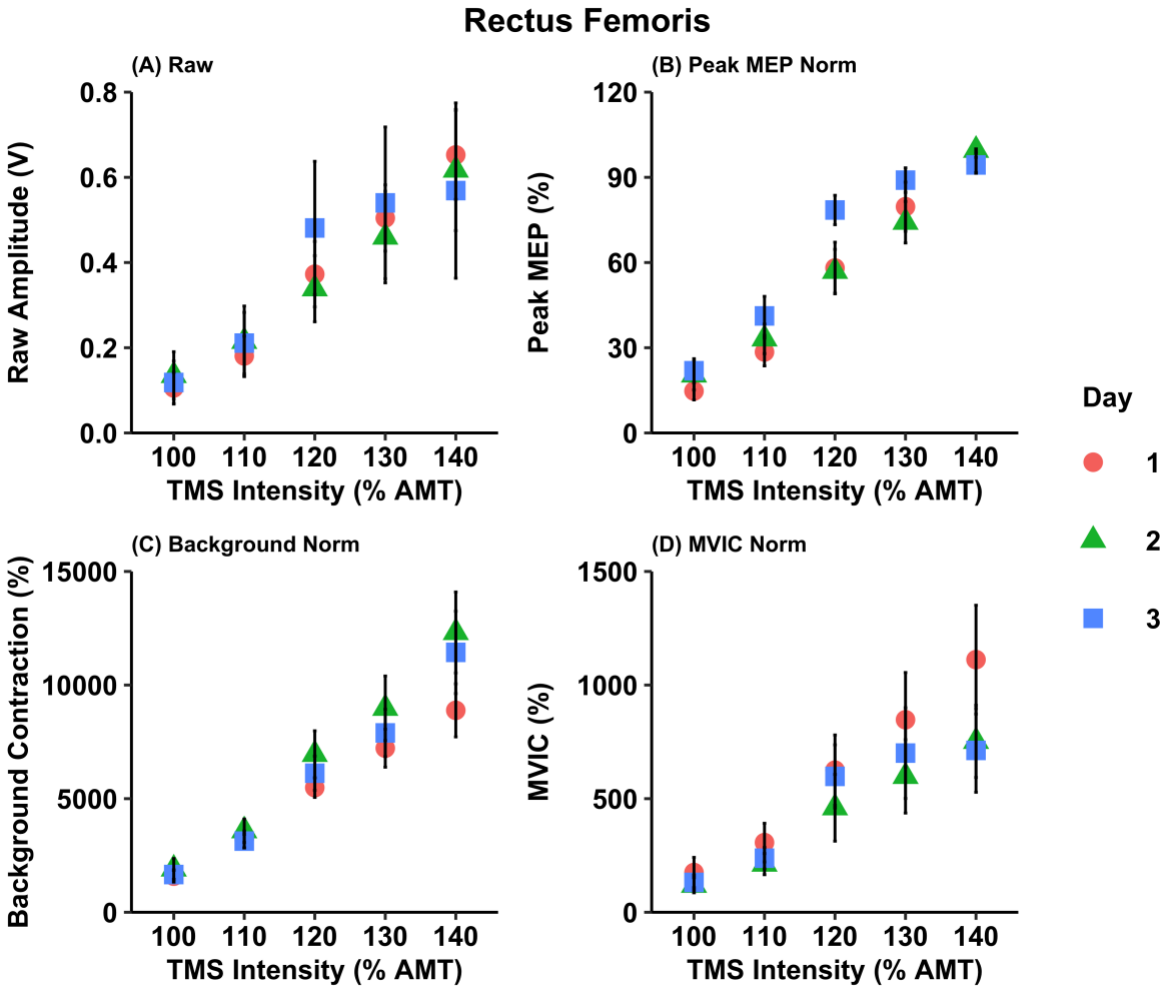

Figure 2.4 Plots showing the mean MEP_{EMG} of the rectus femoris muscle at each TMS intensity for the four different normalization techniques across the three testing sessions: (A) raw rectus femoris MEP_{EMG} with no normalization, (B) rectus femoris MEP_{EMG} normalized to the peak MEP_{EMG} amplitude elicited between 100 %–140 % of AMT, (C) rectus femoris MEP_{EMG} normalized to the background contraction, (D) rectus femoris MEP_{EMG} normalized to the peak values obtained during MVIC. Error bars represent standard error of the mean. *Abbreviations*: AMT, active motor threshold; MEP, motor evoked potential/response; MEP_{EMG}, motor evoked potential; MVIC, maximum voluntary isometric contraction; Norm, normalization; RF, rectus femoris; TMS, transcranial magnetic stimulation.

The raw MEP_{TORQUE} displayed good to excellent reliability (0.654, 0.947) at TMS intensities at or greater than 100% AMT. In general, MEP_{TORQUE} showed good to excellent reliability (0.654, 0.947) for all normalization procedures with two key exceptions: 1) the peak MEP_{TORQUE} normalization procedure, where reliability was poor (-0.035, 0.308) at 130% and 140% AMT and 2) the MVIC normalization procedure, where reliability was fair (0.410, 0.592)

at 100% and 110% AMT. In addition, the area under the curve for raw and normalized MEP_{TORQUE} demonstrated good to excellent reliability (0.708, 0.923).

Table 2.1 Between-session reliability scores [ICC (3, 1)] for raw and normalized TMS motor evoked torque and EMG (MEP_{EMG}) responses across various TMS intensities.

Normalization	Variable	100% AMT	110% AMT	120% AMT	130% AMT	140% AMT
Raw	**Torque**	0.660	0.685	0.929	0.931	0.947
	VM	0.838	0.880	0.742	0.743	0.739
	RF	0.853	0.796	0.611	0.557	0.807
Peak MEP	**Torque**	0.761	0.795	0.718	0.308	-0.035
	VM	0.799	0.615	0.252	0.006	-0.152
	RF	0.478	0.372	0.282	0.292	0.003
Background Contraction	**Torque**	0.833	0.860	0.866	0.834	0.822
	VM	0.631	0.634	0.745	0.731	0.717
	RF	0.475	0.517	0.389	0.051	-0.101
MVIC	**Torque**	0.415	0.585	0.829	0.874	0.876
	VM	0.358	0.454	0.893	0.834	0.899
	RF	0.390	0.357	0.480	0.314	0.610
RTT	**Torque**	0.882	0.840	0.843	0.744	0.691

Abbreviations: AMT, active motor threshold; EMG, electromyography; ICC, intraclass correlation coefficients; MEP, motor evoked potential; MVIC, maximum voluntary isometric contraction; RF, rectus femoris; RTT, magnetically-evoked peripheral resting twitch torque; TMS, transcranial magnetic stimulation; VM, vastus medialis. Shaded numbers indicate ICC scores that are ≥ 0.60 (i.e., indicating good reliability).

The raw vastus medialis MEP_{EMG} and background normalized MEP_{EMG} demonstrated good to excellent repeatability (0.631, 0.880). However, peak vastus medialis MEP_{EMG} normalization demonstrated good to excellent reliability at 100 and 110% AMT (0.615, 0.799), but poor reliability at higher intensities (-0.152, 0.252). In contrast, the MVIC normalized vastus medialis MEP_{EMG} was reliable at stimulus intensities of 120% AMT and higher (0.834, 0.899) but demonstrated poor reliability at lower intensities (0.358, 0.454). In addition, the area under

the curve of raw and normalized vastus medialis MEP_{EMG} showed good to excellent reliability (0.745, 0.849), with the exception of peak MEP_{EMG} normalization, which demonstrated fair reliability (0.481).

Table 2.2 Between-session reliability scores [ICC (3, 1)] for area under the curve (AUC) of the raw and normalized TMS motor evoked torque (MEP_{TORQUE})and EMG (MEP_{EMG}) responses.

Normalization	Variable	Area Under the Curve (AUC)
Raw	**Torque**	0.923
	VM	0.810
	RF	0.762
Peak MEP	**Torque**	0.710
	VM	0.481
	RF	0.033
Background Contraction	**Torque**	0.884
	VM	0.745
	RF	0.058
MVIC	**Torque**	0.830
	VM	0.849
	RF	0.430
RTT	**Torque**	0.851

*Abbreviations***:** AUC, area under the curve; EMG, electromyography; ICC, intraclass correlation coefficients; MEP, motor evoked potential; MVIC, maximum voluntary isometric contraction; RF, rectus femoris; RTT, magnetically-evoked peripheral resting twitch torque; TMS, transcranial magnetic stimulation; VM, vastus medialis. Shaded numbers indicate ICC scores that are ≥ 0.60 (i.e., indicating good reliability).

Finally, the raw rectus femoris MEP_{EMG} responses demonstrated fair to excellent repeatability (0.557-0.853) across testing sessions. However, normalized rectus femoris MEP_{EMG} demonstrated poor reliability for all methods (-0.101, 0.480), with the exception of good reliability for MVIC normalized rectus femoris MEP_{EMG} at 140% AMT. For the area under the curve, only raw rectus femoris MEP_{EMG} showed excellent reliability, (0.762) while normalized rectus femoris MEP_{EMG} showed poor reliability (0.033, 0.430).

2.4 Discussion

The purpose of this study was to determine the test-retest reliability of TMS-induced MEP_{EMG} and MEP_{TORQUE} responses in the quadriceps muscles of individuals with ACL reconstruction and to evaluate the effect of various normalization approaches on the test-retest reliability. Based on the ICC values, we found MEP_{TORQUE} responses generally exhibit higher reliability than MEP_{EMG}. Comparing the muscles, vastus medialis MEP_{EMG} generally demonstrated higher reliability when compared with rectus femoris MEP_{EMG}. Finally, MEP_{TORQUE} and MEP_{EMG} demonstrated good to excellent reliability even when using raw values without normalization. These findings establish MEP_{TORQUE} and MEP_{EMG} are reliable measures of corticospinal function and suggest MEP_{TORQUE} could serve as a reliable alternative to MEP_{EMG} in individuals with ACL reconstruction.

A notable finding from this study was that both raw and normalized MEP_{TORQUE} responses demonstrated good to excellent reliability for the quadriceps of individuals with ACL reconstruction. These findings suggest MEP_{TORQUE} responses are a reliable measure for assessing quadriceps corticospinal excitability after ACL reconstruction. These findings are consistent with previous research in healthy individuals, which also report good to excellent reliability for raw and normalized MEP_{TORQUE}.[16] Evidence supporting MEP_{TORQUE} reliability is valuable for studies interested in evaluating the net effect of multi-headed muscles like the quadriceps rather than being limited to a single muscle.[12, 14, 33] Unlike MEP_{EMG} responses, MEP_{TORQUE} is also not influenced by peripheral factors (e.g., electrode placement, fat tissue, cross talk), which is ideal for reliability across testing sessions. Further, MEP_{EMG} represents the electrical activity of a single muscle whereas MEP_{TORQUE} is generated by the activity of several agonistic and antagonistic muscles. Thus, TMS may be activating the entire leg muscles, and hence their total

output (torque) may be more reliable than an output of a single muscle. The high reliability demonstrated with MEP_{TORQUE} may also enhance the confidence in attributing corticospinal changes to factors such as injury and surgical status or the effects of an intervention after ACL reconstruction. However, a disadvantage of MEP_{TORQUE} is that the contribution of individual muscles to the overall changes cannot be determined if only torque data are collected. Therefore, for researchers and clinicians with access to both EMG and a dynamometer, we recommend evaluating MEP_{EMG} responses along with MEP_{TORQUE} to determine the contribution of each quadriceps muscle (or the antagonistic hamstring muscles) to net corticospinal adaptations following ACL reconstruction.

In general, we found MEP_{EMG} responses were reliable with vastus medialis demonstrating higher reliability compared with rectus femoris. Surprisingly, raw MEP_{EMG} responses demonstrated high ICC values supporting good to excellent reliability. This finding is partially consistent with recent work in healthy individuals,[16] which found raw MEP_{EMG} to be reliable only at higher intensities. It is not clear why raw MEP_{EMG} was reliable across stimulation intensities in individuals with ACL reconstruction, but not in healthy uninjured individuals. It is possible the higher number of sessions (i.e., three vs two sessions) may have contributed to the differences between studies. However, when evaluating our data with two sessions, we did not find that the number of sessions affected the reliability of raw MEP_{EMG} responses. Lower sample size for the MEP_{EMG} could have also contributed to this phenomenon and would benefit from investigation with a larger sample size to confirm our findings in individuals with ACL reconstruction.

Regarding normalization, our results indicate reliability of MEP_{EMG} responses generally worsen when normalized, particularly for the rectus femoris. The diminished reliability when

normalizing is unexpected as normalization procedures are commonly recommended and used.[34, 35] However, recent research in healthy individuals also suggests normalizing to peak MEP corresponds to lower reliability,[16] which was consistent with our findings in individuals with ACL reconstruction. We recognize a key issue for peak MEP normalization is that the peak MEP value on a given day can vary whether it occurs at 130% AMT or 140% AMT, which can impact the reliability across days. Another issue with peak MEP normalization is that this approach limits the ability to compare across sessions because normalizing the MEP values to the peak MEP will artificially mask any changes that might occur due to an injury or intervention – for example, if the MEP values increased or decreased throughout the recruitment curve after an intervention, peak MEP normalization will mask these changes by making them look similar. Finally, changes in MVIC values over time due to injury or surgery may also cause these normalization approaches to be unsuitable for individuals with ACL reconstruction, particularly early after surgery. Based on the lower reliability for the normalization approaches, use of raw MEP_{EMG} responses for the vastus lateralis and rectus femoris may be worth considering for individuals with ACL reconstruction.

2.5 Limitations

There are several limitations to the current study. First, this study evaluated individuals that were several months after ACL reconstruction surgery. Thus, this study may not generalize broadly to all individuals after ACL reconstruction, particularly early after the surgery. In addition, the vastus lateralis was not evaluated in this study and we cannot confirm whether raw and normalized MEP_{EMG} would be reliable for this muscle after ACL reconstruction. Previous research on healthy individuals indicates that the reliability of vastus lateralis is lower than the vastus medialis and rectus femoris muscles.[16] Hence, it is likely that the reliability of the vastus

lateralis muscle would also be lower in the ACL reconstructed population, although this needs to be verified. Furthermore, the number of participants included in the analyses for the MEP_{TORQUE} and MEP_{EMG} differed, which could have contributed to the differences in the reliability between the two measures. However, our results were consistent with previous studies on healthy participants and were not notably affected when we performed a secondary analysis evaluating the reliability of MEP_{TORQUE} obtained using only the individuals with EMG data. Hence, we believe that the results were not confounded by the differences in sample size between the MEP_{TORQUE} and MEP_{EMG} data. Finally, this study did not evaluate the M-wave in order to minimize participant discomfort. As such, we cannot compare the reliability of MEP_{TORQUE} to the conventional MEP_{EMG} normalized to M-wave. Concurrent evaluation of MEP_{TORQUE}, MEP_{EMG}, and the M-wave would be needed to comment on whether MEP_{TORQUE} is more reliable in this population. However, MEP_{TORQUE} was very reliable in this study and is supported by previous research.[16] Thus, MEP_{TORQUE} has the added benefit of minimizing participant discomfort from electrical stimulation during M-wave procedures, while also being a reliable measure of corticospinal excitability.

2.6 Conclusion

In summary, this study found that the MEP_{TORQUE} obtained during an active contraction of the quadriceps muscle offered a reliable measure of corticospinal excitability in individuals with ACL reconstruction. Normalization of MEP_{TORQUE} and MEP_{EMG} using peak MEP is not recommended due to lower reliability compared with other normalization approaches. Normalization of MEP_{TORQUE} and MEP_{EMG} with MVIC values may also pose an issue in this population, especially if the MVIC values are changing due to the recovery process. Future studies evaluating the reliability of motor evoked torque with comparisons to the conventional

M-wave normalized MEP_{EMG} are needed to confirm whether motor evoked torque offers better reliability than M-wave normalization for measuring corticospinal excitability in individuals with ACL reconstruction.

2.7 Acknowledgement

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Chapter 3 Conditioning of Motor Evoked Responses following Anterior Cruciate Ligament Reconstruction: Effects of Stimulus Intensity

Background: Operant conditioning of the motor evoked torque (MEP_{TORQUE}) is an emerging approach that can directly target the corticospinal pathway in individuals with anterior cruciate ligament (ACL) reconstruction. However, it remains unclear whether operant conditioning can elicit acute improvements in corticospinal excitability and whether these improvements are influenced by the stimulus intensity. *Hypothesis:* Quadriceps MEP_{TORQUE} responses can be up-conditioned within a single session and will elicit acute adaptations in corticospinal excitability, with higher stimulus intensities eliciting greater effects. *Methods:* Thirty-six participants were assessed during a single session of an operant conditioning protocol. Participants were randomized into one of three groups for the stimulus intensity used during operant conditioning based on the participant's active motor threshold (AMT) (100%, 120%, and 140%). Two recruitment curves (PRE and POST training), one baseline control (CTRL) block, and three conditioning (COND) blocks were performed. Linear mixed models with group as between-subjects factor and block (CTRL, COND1, COND2, COND3) or time (PRE, POST) as within-subjects factor were used to evaluate the 1) feasibility of up-conditioning, 2) acute corticospinal adaptations, and 3) effect of stimulus intensity. *Results:* Individuals with ACL reconstruction were able to up-condition their MEP_{TORQUE} in a single session ($p < 0.001$; CTRL: 17.27 ± 1.28, COND: 21.35 ± 1.28 [mean ± standard error (SE)]), but this ability was not influenced by the stimulus intensity used during training ($p = 0.841$). Furthermore, significant improvements in neural excitability were observed ($p = 0.047$; PRE: 687.91 ± 50.15, POST: 761.08 ± 50.15 [mean

± SE]), but stimulus intensity did not influence neural adaptations (p = 0.669). *Conclusions:* Operant conditioning can elicit acute neural adaptations in ACL reconstructed individuals. While future operant conditioning paradigms in ACL reconstructed individuals may effectively use any of the three stimulus intensities studied herein, further research may be warranted when applying this finding to long-term operant conditioning interventions. *Clinical Relevance:* Operant conditioning may be a feasible approach to improve corticospinal excitability after ACL reconstruction.

3.1 Introduction

Substantial loss of quadriceps strength and voluntary activation (i.e., the ability to fully contract the muscle during a maximal contraction) are well established following anterior cruciate ligament (ACL) reconstruction.[1, 2] A growing body of evidence suggests that corticospinal excitability is significantly altered in ACL reconstructed individuals[3, 4] and have been linked to poor quadriceps strength and voluntary activation after surgery.[5, 6] Scientists have theorized that diminished corticospinal excitability would reduce neural drive to the muscle and may subsequently contribute to quadriceps dysfunction after ACL reconstruction[7-9]. Accordingly, there is a growing interest in novel interventions that target restoring corticospinal excitability with the goal to improve quadriceps function after ACL reconstruction.[10]

In order to improve quadriceps strength and voluntary activation, a number of interventions have been utilized in individuals with ACL reconstruction. Interventions such as neuromuscular electrical stimulation and eccentric exercise are commonly used and are shown to improve quadriceps strength and voluntary activation.[11-13] However, these techniques are unable to directly target the corticospinal pathway and may present a key barrier to improving quadriceps function. In contrast, noninvasive brain stimulation modalities, such as transcranial

direct current stimulation (tDCS) and high-frequency repetitive transcranial magnetic stimulation (TMS), are able to directly modulate corticospinal excitability.[14] However, although tDCS is simple, safe, and low-cost, the effects are not consistent across studies.[15] Recent studies also show that tDCS is not effective in improving motor cortex excitability of the quadriceps muscles.[15] High-frequency repetitive TMS, on the other hand, is expensive and carries a small risk of inducing seizure, especially when participants are taking medications that reduce the seizure threshold.[16] Therefore, new approaches to safely modulate corticospinal excitability are critically needed for improving quadriceps strength and voluntary activation.

Operant conditioning of motor evoked potentials is an emerging approach that appears capable of directly targeting corticospinal excitability without negative side effects. Operant conditioning utilizes a form of reward-based learning[17] to reinforce a desired behavior. Evidence from animal and human experiments supports the use of operant conditioning paradigms to modulate the excitability of the spinal-reflex and corticospinal pathways.[18-20] Operant up-conditioning of the corticospinal pathway is shown to be feasible and effective in evoking improvements in corticospinal excitability of healthy and pathological populations, including ACL reconstruction.[10, 21, 22] Operant conditioning paradigms have been applied with the aim of increasing corticospinal excitability to improve motor function, which is supported by concurrent improvements in muscle strength, muscle activation, and gait.[10, 21, 22] Therefore, operant conditioning appears to be an intervention capable of targeting the corticospinal pathway and could prove valuable in improving strength and activation in ACL reconstructed individuals.

While operant conditioning protocols have demonstrated overall success in upregulating corticospinal excitability, there are many aspects of its application that we need to better understand. One such factor requiring additional study is related to why some persons appear

capable of modulating corticospinal excitability while others do not. For example, in individuals without neurological conditions, only 63% of individuals are able to successfully increase corticospinal excitability during operant conditioning.[21] It is well known that appropriate dosage is critical for effective intervention. Hence, it is plausible that a sub-optimal dosage of operant conditioning may explain why only some individuals are able to up-condition corticospinal excitability. However, it remains to be determined what role the dosage of operant conditioning plays in the ability to increase corticospinal excitability of the quadriceps.

One aspect of dosage is the stimulus intensity used during the operant conditioning paradigm. At lower stimulus intensities, variability of the motor evoked response increases,[23] which may introduce noise and reduce the ability of operant up-conditioning after ACL reconstruction. On the other hand, while higher stimulus intensity may elicit greater improvements, it may not be comfortable for all participants. Hence, it is important to determine the stimulus intensity that can enable consistent operant up-conditioning effects with minimal discomfort to the participant. However, the stimulus intensity used in current operant conditioning protocols[10, 21] appears to be arbitrary, as its superiority over other stimulus intensities has yet to be determined. Thus, determining the impact that stimulus intensity may have on the ability to up-condition the corticospinal pathway is critically needed.

Therefore, the purpose of this study was to determine 1) if corticospinal excitability can be improved via operant conditioning in a single session and whether up-conditioning can result in acute improvements in neural excitability and 2) does stimulus intensity used during operant conditioning affect these outcomes in individuals with ACL reconstruction. We hypothesized that ACL reconstructed individuals would be able to up-condition their motor evoked torque (MEP_{TORQUE}) responses within a single session and that a single training session would result in

significant acute improvements in corticospinal excitability, as measured by changes in the MEP_{TORQUE} recruitment curve before and after the intervention (i.e., aftereffects). In addition, we hypothesized that the ability to up-condition the quadriceps MEP_{TORQUE} and the associated aftereffects would increase with increasing stimulus intensity, such that 140% AMT would show the most improvement and 100% AMT would show the least improvement in MEP_{TORQUE} of the quadriceps muscle.

3.2 Methods

3.2.1 Participants

Power analysis in General Linear Mixed Model Power and Sample Size (GLIMMPSE 3.0) software[24] indicated that a total sample size of N=36 (12 per group) provided a power (1- β) > 84% to detect a significant group-by-block interaction effect. The following assumptions were made for this analysis: (1) a 20% to 50% increase in MEP_{TORQUE} from baseline with a 30% difference between groups and a standard deviation of mean differences of 50%, (2) a conservative correlation in repeated measures of r = 0.75, (3) homogenous variances and covariances, and (4) an adjusted p-value of 0.0056 to account for 9 post-hoc simple effects comparisons (3 at each of the 3 conditioning blocks) for group-by-block interaction.

A total of 36 individuals with ACL reconstruction (21 males, 15 females, 22.9 ± 6.1 years, 24.6 ± 3.7 m^2/kg, 12.4 ± 7.7 months post-operative, 11 right-injured, 25 left-injured, 33 right-footed, 3 left-footed) participated in this study. Inclusion criteria were: 1) aged 14-45 years; 2) suffered a complete ACL rupture; and 3) received an ACL reconstruction at least 3 months prior to testing. Exclusion criteria included: 1) having ear or metal implants in the skull; 2) having a cardiac pacemaker; 3) a history of unexplained recurrent headaches, seizures, recent head injury, medical or heart condition that could influence study outcomes or significant

adverse reaction to TMS; 4) currently pregnant; 5) other recent significant knee injury or lower-extremity fracture; and/or 6) body mass index greater than 40 kg/m^2. Prior to participation, participants reviewed and signed a written informed assent/consent document approved by the University of Michigan Institutional Review Board. Parental consent was also obtained if the participant was a minor child.

3.2.2 Study Overview

The ability to up-condition and the effects of stimulus intensity on operant up-conditioning of the quadriceps MEP_{TORQUE} were evaluated on the ACL reconstructed leg during a single session. Participants were block randomized to one of three groups for the stimulus intensity used during operant conditioning based on the individual's active motor threshold (AMT) (i.e., corticospinal excitability). The groups were the following: 1) 100% AMT; 2) 120% AMT; or 3) 140% AMT and participants performed the operant up-conditioning procedures for a total of 225 training trials (3 blocks of 75 trials). A schematic of study procedures is depicted in Figure 3.1.

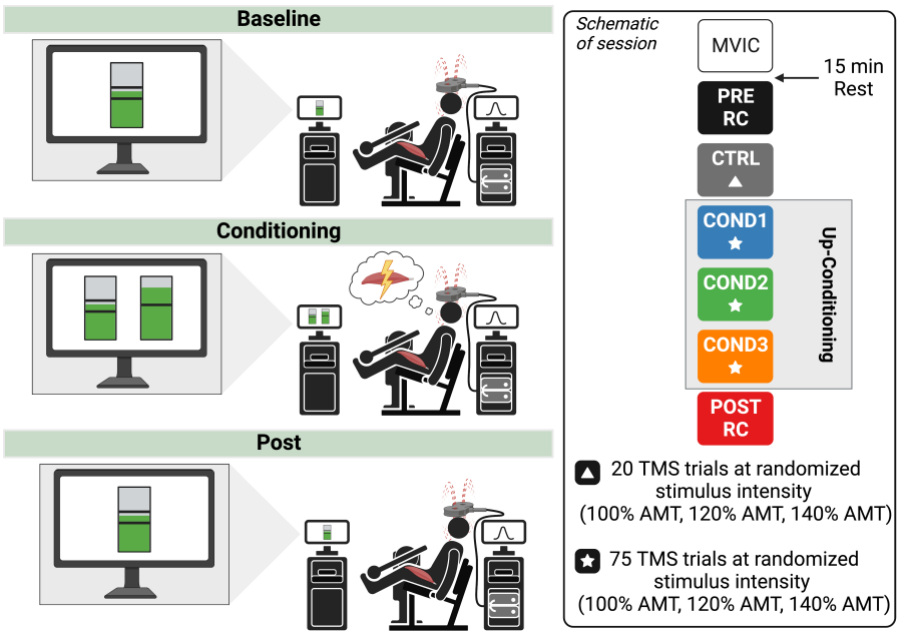

Figure 3.1 A schematic of the experimental protocol. *Abbreviations:* MVIC, maximum voluntary isometric contraction; RC, recruitment curve; CTRL, baseline control block; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; TMS, transcranial magnetic stimulation; AMT, active motor threshold.

3.2.3 Experimental Protocol

A schematic of the experimental set-up is provided in Figure 3.1. The aim of the operant conditioning intervention was to train the participant to increase the MEP_{TORQUE} of the quadriceps muscle on the ACL reconstructed leg within a single session. Participants were seated and fastened into an isokinetic dynamometer (Humac Norm, CSMi, Stoughton, USA) with the trunk and knee set to 85 and 60 degrees of flexion, respectively. Participants warmed-up with a series of submaximal knee extension contractions, two each at 50% 75%, and 100% of their perceived maximum. Participants rested, briefly, before performing two maximal voluntary isometric contractions (MVICs) of their knee extensors. During MVIC, visual display of the torque curves and strong verbal encouragement were provided to ensure maximal effort. Participants received 120 seconds of rest between MVIC trials. Peak MVIC knee extensor torque

values were used to calculate the 10% MVIC background contraction performed during corticospinal excitability procedures. Participants rested for 15 minutes prior to TMS procedures.

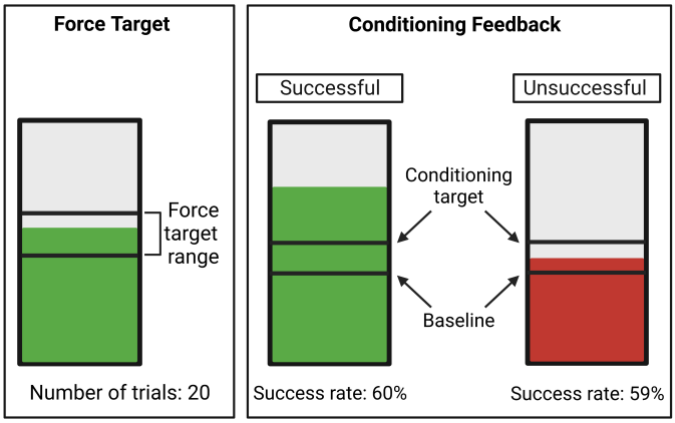

Figure 3.2 On the left is a schematic indicating visual feedback for a 10% MVIC background contraction, which was shown for both the control and conditioning blocks. The participant's torque output is indicated by the green bar, which must stay within the force target range to maintain a 10% MVIC background contraction. Below the force target, participants can see the number of completed trials. On the right is a schematic illustrating visual feedback of a successful or unsuccessful trial provided to participants during the conditioning blocks. The conditioning bar will turn green when the most recent training trial successfully increased the MEP_{TORQUE} (i.e., MEP_{TORQUE} greater than the conditioning target). The conditioning bar will turn red when the most recent training trial was unsuccessful in increasing the MEP_{TORQUE}. Below the feedback bar, participants can see their current success rate, which updates after each conditioning trial and resets at the start of each conditioning block.

While seated on the dynamometer, MEP_{TORQUE} responses were elicited using a Magstim 200^2 stimulator (Magstim Co Ltd, Whitland, UK). A 110-mm diameter double-cone coil was used to apply TMS to the primary motor cortex on the hemisphere contralateral to the tested leg. The coil was oriented to induce a posterior to anterior current flow in the cortex. A temporary quadriceps hotspot location was determined and marked on a fabric cap by identifying a point that is located 2.0 cm posterior and 2.0 cm lateral to the vertex of the skull.[25] The coil was systematically moved from this location to find the hotspot (i.e., the location over the skull that results in the largest and most consistent MEP_{TORQUE} during a 10% MVIC background contraction). Participants received visual feedback to maintain a consistent background contraction (Figure 3.2). The location of the hotspot was marked on a fabric cap to ensure consistent coil location during the session. The active motor threshold (AMT) was determined as

the minimum TMS intensity needed to evoke a MEP_{TORQUE} response in ≥ 50% of attempted trials (≥10 trials).[26] The AMT was used to determine stimulus intensity during the control (CTRL) and conditioning (COND) blocks.

Once the hotspot location and AMT were determined, the baseline TMS input-output recruitment curve (PRE) was recorded at 8 different intensities (70%-140% AMT). Following which, a baseline control block of 20 TMS trials was collected as has been done previously.[10, 27] The control block (CTRL) was used to establish the participant's baseline excitability and to determine the initial criterion value (i.e., the 50th percentile value of the MEP_{TORQUE} from the 20 control trials) for the operant conditioning training. During the control block, participants were instructed to focus on maintaining a consistent background contraction (10% of MVIC) as described above and received a TMS pulse to the contralateral hemisphere at the assigned stimulus intensity (100% AMT, 120% AMT, or 140% AMT) when the contraction was maintained. No feedback was provided to participants during the control block.

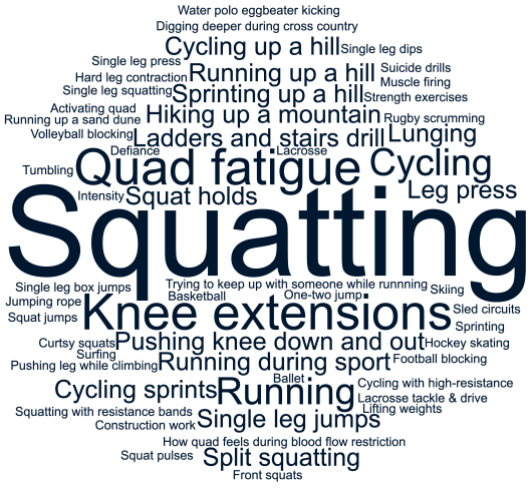

Figure 3.3 Wordcloud depicting the motor imagery visualizations used by participants during up-conditioning procedures. Words with a larger font size correspond to visualizations that were more frequently used by participants, while words with a smaller font size correspond to less commonly used visualizations.

Following the 20 control trials, three blocks of 75 conditioning trials were performed. The conditioning block was similar to the control trials, except the participant was instructed to

use motor imagery to try and train the corticospinal pathways to increase the MEP_{TORQUE} responses above the criterion value. Examples were provided, such as imagining contracting their quadriceps or the quadriceps feeling a "burn" when doing exercises (e.g., squats, leg presses, etc.) or performing an exercise/sports action (e.g., hopping during a lay-up or kicking a ball). Motor imagery visualizations used by participants are depicted in Figure 3.3. The initial criterion value for the first conditioning training block (COND1) was set to the 50th percentile value of the participant's MEP_{TORQUE} in the control block. The criterion value for the subsequent training blocks was dynamically determined based on the participant's performance on the preceding block. The criterion value was determined such that if MEP_{TORQUE} amplitudes for the new block were similar to the MEP_{TORQUE} amplitudes of the previous training block, ~50% of the trials would be successful.[10, 28] Participants received visual feedback about their performance on each trial, indicating whether participants were successful at up-regulating the motor evoked torque responses (i.e., increased above the criterion value). The feedback bar increased and turned green if successful or decreased and turned red if unsuccessful (Figure 3.2). During each conditioning block, participants also received feedback on the percentage of successful trials during the current conditioning block. The participant's goal during the conditioning blocks was to achieve a trial success rate ≥ 60% and a small monetary incentive was provided to achieve this target (20 cents for each percentage greater than 60%). During conditioning trials, researchers also provided verbal encouragement and positive verbal feedback. Following the third conditioning block, a second TMS input-output recruitment curve (POST) was collected to evaluate the acute changes in corticospinal excitability due to the operant conditioning training.

3.2.4 Data Management

All data collection and analysis were performed using custom programs written in LabVIEW. Torque data along with the TMS synchronization pulses were sampled at 1000 Hz. Torque signals were low-pass filtered (10 Hz, 4th order) using a zero-lag digital Butterworth filter.[29] Torque data were segmented from 200 ms prior to the stimulation over a window of 500 ms for each of the stimulations. The segmented torque data were ensemble averaged to construct an average torque curve for each block. The size of the MEP_{TORQUE} amplitude was calculated as the peak twitch torque, offset by the background contraction. In addition, the area under the curve (AUC) of the MEP_{TORQUE} was evaluated for both the PRE and POST TMS input-output recruitment curves from 100% AMT to 140% AMT.

3.2.5 Statistical Analysis

The distribution and variation of the outcome variable (i.e., within-session change in MEP_{TORQUE}) was assessed using descriptive statistics. Data were visually inspected using graphical methods such as histograms, residual plots, and Q-Q plots. The Shapiro-Wilks test was used to confirm the assumptions of normality for the outcome variable. A linear mixed model with group (100%, 120%, and 140% AMT), block (CTRL, COND1, COND2, COND3), and group × block as fixed effects and subject as a random effect was used to evaluate if ACL reconstructed individuals were able to up-condition the MEP_{TORQUE} in a single session and if stimulus intensity influenced the ability to up-condition. The MEP_{TORQUE} during the baseline control and the conditioning blocks were used as the dependent variable and the MEP_{TORQUE} during the baseline control block was used as a covariate in the model. A second linear mixed model with group (100%, 120%, and 140% AMT), time (PRE, POST), and group × time as fixed effects and subject as a random effect was used to evaluate if operant up-conditioning resulted in significant improvements in acute corticospinal excitability and if stimulus intensity influenced the neural adaptations in a single session. The AUC of the MEP_{TORQUE} was used as a dependent variable for this analysis. A significant main or interaction effect was followed by appropriate post-hoc analyses with a Šidák correction. A significance level of alpha = 0.05 was used for all analyses.

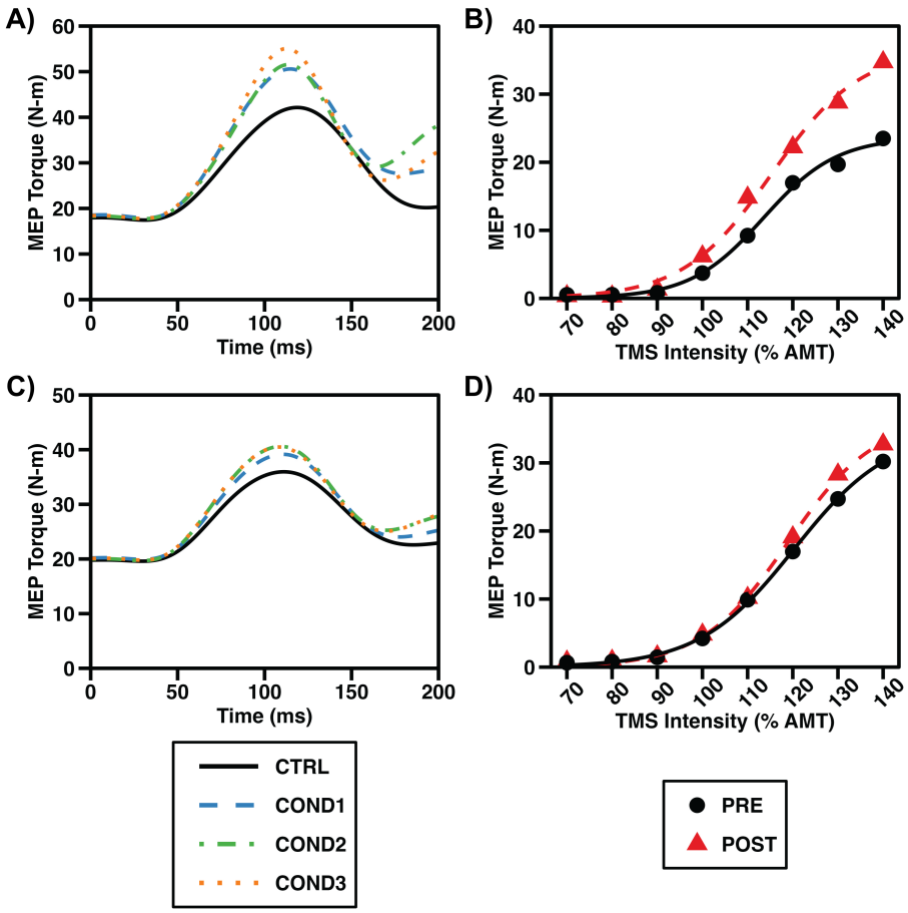

Figure 3.4 Ensemble averaged motor evoked torque (MEP_{TORQUE}) plots for a single subject (A & B) and for all participants (C & D). Data from a representative participant for a) ensemble averaged MEP_{TORQUE} for the baseline control block (CTRL) and all three conditioning blocks (COND); b) MEP_{TORQUE} recruitment curves prior to operant conditioning (PRE) and following operant conditioning (POST). Ensemble averaged group data are shown in panels c and d. *Abbreviations:* MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; ms, milliseconds; TMS, transcranial magnetic stimulation; AMT, active motor threshold; CTRL, baseline control block; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; PRE, prior to operant conditioning; POST, following operant conditioning.

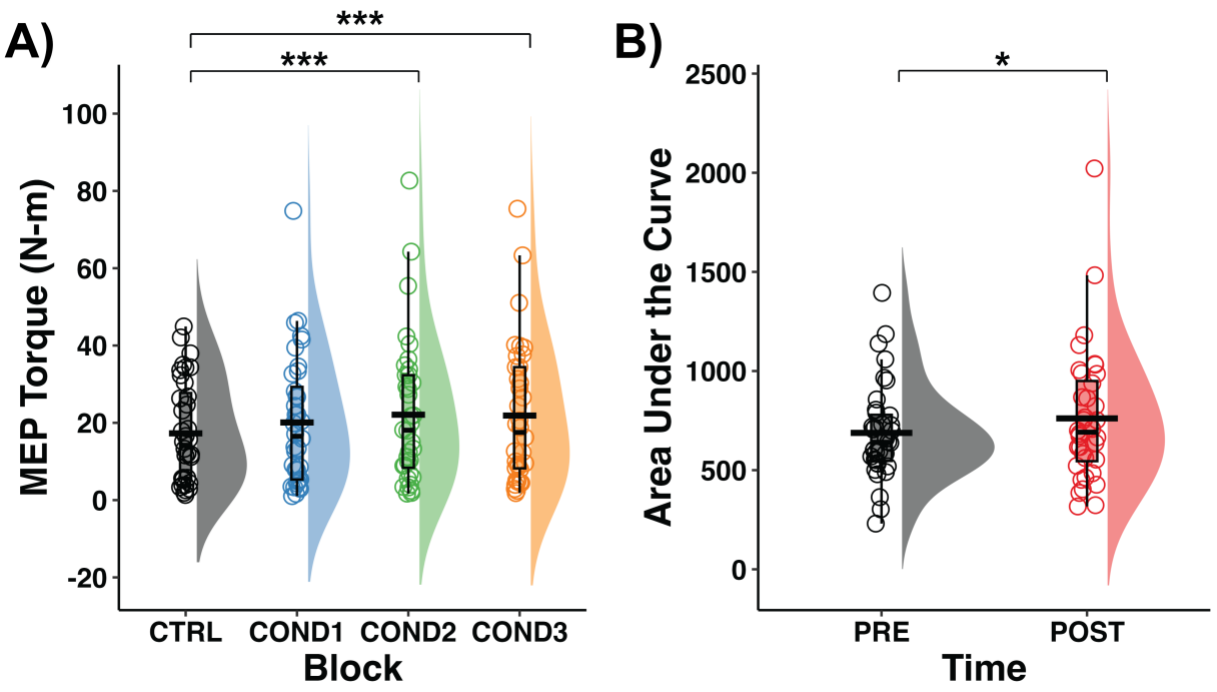

Figure 3.5 Raincloud plot depicting A) the distribution of MEP_{TORQUE} during the baseline control block immediately before operant conditioning (CTRL) and all three conditioning blocks (COND) and B) the distribution of area under the curve of MEP_{TORQUE} prior to up-conditioning procedures (PRE) and immediately after up-conditioning procedures (POST). Open circles represent data points from each individual participant. Black horizontal lines represent the mean across all participants for each block/timepoint. *Abbreviations:* MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; CTRL, baseline control block; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; PRE, prior to operant conditioning; POST, following operant conditioning; *, $p < 0.05$; ***, $p < 0.001$.

3.3 Results

3.3.1 Ability to Up-Condition the MEP_{TORQUE} and the Effect of Stimulus Intensity

Ensemble averaged data from a representative participant and group data on the ability to up-condition the quadriceps MEP_{TORQUE} is shown in Figure 3.4. During the operant conditioning paradigm, there was a significant main effect of block ($F_{3,99} = 7.358$, $p < 0.001$) on the MEP_{TORQUE} amplitude (Figure 3.5). Post-hoc analysis revealed that MEP_{TORQUE} amplitude during COND2 and COND3 were significantly higher than CTRL (p <0.001, CTRL[†]: 17.272 ±

[†] Reported as mean ± pooled standard error of the mean

1.275, COND2[†]: 22.095 ± 1.275, COND3[†]: 21.877 ± 1.275) while COND1 was not (p = 0.051, COND1[†]: 20.089 ± 1.275). During the operant up-conditioning paradigm, there was no significant effect of group (i.e., stimulus intensity) ($F_{2,32}$ = 0.174, p = 0.841) or the interaction between group and block ($F_{6,99}$ = 0.896, p = 0.501) (Figure 3.6).

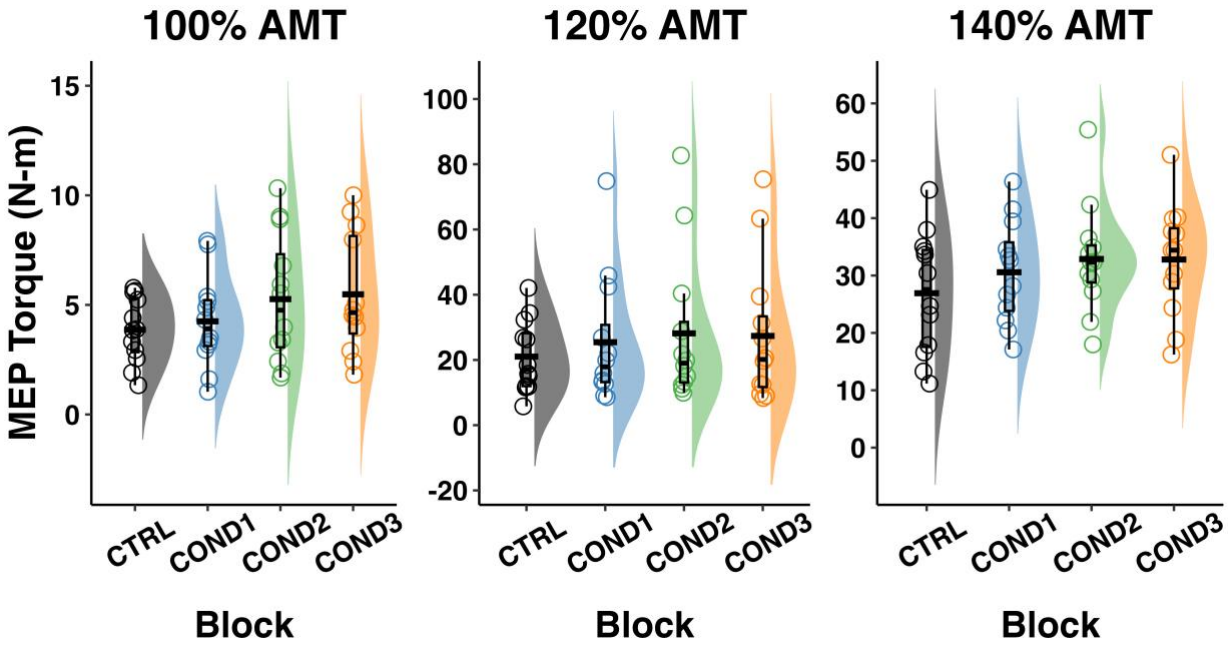

Figure 3.6 Raincloud plots depicting the distribution of MEP_{TORQUE} (shaded waveforms) during the baseline control (CTRL) block and all three conditioning blocks (COND) for each stimulus intensity group (100% AMT, 120% AMT, 140% AMT). Open circles represent data points from each individual participant. Black horizontal lines represent the mean across all participants for each block. *Abbreviations:* MEP_{TORQUE}, motor evoked torque; AMT, active motor threshold; N-m, newton-meters; CTRL, baseline control block; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3.

3.3.2 Acute Adaptations in Corticospinal Excitability and the Influence of Stimulus Intensity

Data from a representative participant and averaged group data for the PRE and POST MEP_{TORQUE} recruitment curves are shown in Figure 3.4. A significant main effect of time on the MEP_{TORQUE} AUC was observed ($F_{1,33}$ = 4.277, p = 0.047). Post-hoc analysis indicated that

[†] Reported as mean ± pooled standard error of the mean

MEP_{TORQUE} AUC was greater following the intervention compared to prior to the intervention (p = 0.047; PRE†: 687.911 ± 50.148, POST†: 761.1 ± 50.148), indicating acute neural adaptations occurred in individuals with ACL reconstruction (Figure 3.5). However, there was no significant effect of group (i.e., stimulus intensity) ($F_{2,33}$ = 0.407, p = 0.669) or the interaction between group and time ($F_{2,33}$ = 0.174, p = 0.501).

3.4 Discussion

The purpose of this study was to determine 1) if corticospinal excitability can be improved via operant conditioning in a single session and whether up-conditioning can result in acute improvements in neural excitability and 2) does stimulus intensity used during operant conditioning affect these outcomes in individuals with ACL reconstruction. As hypothesized, we found that individuals with ACL reconstruction were able to up-condition the quadriceps MEP_{TORQUE} in a single session. However, contrary to our hypothesis, the stimulus intensity used during training did not significantly impact the ability to up-condition the MEP_{TORQUE}. In addition, acute improvements in neural excitability were observed following a single session of operant conditioning, but the changes were not influenced by the stimulus intensity used during training. Together, these results support operant conditioning of the MEP_{TORQUE} as a feasible approach to improving corticospinal excitability in individuals with ACL reconstruction, regardless of the stimulus intensity used.

A significant finding from the current study was that quadriceps MEP_{TORQUE} during the conditioning blocks were higher compared with the first baseline control block. This finding indicates that individuals with ACL reconstruction are able to successfully up-condition the

† Reported as mean ± pooled standard error of the mean

quadriceps MEP_{TORQUE} in a single session of operant conditioning. While previous studies have not focused on a single-session of operant conditioning, a recent case study found that MEP_{TORQUE} did not increase after the first session of an 8-week operant conditioning intervention in an individual with ACL reconstruction.[10] However, the ACL reconstructed individual was able to up-condition the MEP_{TORQUE} during the second session and all subsequent sessions in the 8-week intervention.[10] It is not surprising that the participant in the case study was unable to up-condition within the first session, as there were some participants in the current study (28%) who were not able to successfully up-condition their MEP_{TORQUE} in a single session. It is likely that some participants may need additional training sessions to learn how to successfully up-condition their MEP_{TORQUE}. Therefore, multiple training sessions or additional conditioning blocks may be needed to ensure participants are able to adequately up-condition the MEP_{TORQUE} during operant conditioning paradigms.

When considering the influence of stimulus intensity, our findings demonstrate TMS stimulus intensity does not significantly impact the ability to up-condition the quadriceps MEP_{TORQUE} in a single session. While it appears on average, stimulus intensities of 100% AMT and 140% AMT had slightly higher increases in the MEP_{TORQUE}, this was not statistically significant. The lack of group differences for stimulus intensity is surprising, given that MEP responses are typically more variable at intensities closer to the motor threshold. However, it is likely that the use of MEP_{TORQUE} (which is less variable and more reliable) instead of MEP_{EMG} may have contributed to this observation. Moreover, it is plausible that other dosage parameters such as the number of training trials in a session and the total number of training sessions may have a greater effect on the ability to up-condition the MEP_{TORQUE}. Factors that impact an individual's aptitude for motor skill learning/mental imagery may also be of greater importance

than the stimulus intensity used.[30] For example, individuals with lower imagery ability may have greater difficulty during the mental practice used during operant conditioning protocols, which may result in slower progress compared to those with greater imagery ability.[31, 32] Thus, investigation into the impact of other dosage parameters and individual differences would be valuable to improving operant conditioning protocols for individuals with ACL reconstruction.

Another notable finding from this study was that up-conditioning of the MEP resulted in significant improvements in corticospinal excitability (i.e., aftereffects) within a single session in ACL reconstructed individuals. This study is the first to date to report acute neural adaptations in the reconstructed leg following a single session of operant conditioning. Our findings are consistent with previous research reporting increased area under the recruitment curve after healthy individuals completed six sessions of H-reflex up-conditioning.[33] Given that ACL reconstructed individuals are reported to exhibit decreased corticospinal excitability compared to healthy individuals,[3, 4] operant conditioning may be a valuable approach to restoring corticospinal excitability after ACL reconstruction, particularly at a timepoint when other high-intensity training methods are contraindicated (e.g., early after the surgery). Long-term operant conditioning interventions in other populations have also shown widespread benefits including improved muscle strength and gait biomechanics,[10, 22, 34] which are known to be altered in ACL reconstructed individuals.[2, 35] Thus, long-term operant conditioning of the motor evoked torque may be a promising intervention with the potential to improve motor function following ACL reconstruction.

As was the case with MEP_{TORQUE} up-conditioning, we found that TMS stimulus intensity did not significantly impact the acute adaptations (i.e., aftereffects) in corticospinal excitability from pre-intervention to post-intervention. Given that stimulus intensity did not impact the

ability to up-condition, it is not surprising that stimulus intensity did not also impact the magnitude of acute neural adaptations in a single session. This is because our exploratory analysis evaluating the relationship between the changes in MEP_{TORQUE} from CTRL to COND and changes in MEP_{TORQUE} AUC from PRE to POST, we found that a greater ability to up-condition the MEP_{TORQUE} was moderately associated with larger aftereffects ($r = 0.501$, $p = 0.001$). This association underscores the importance of a participant's ability to up-condition in order to harness the potential benefits of operant conditioning. Future research investigating individual differences (i.e., why certain individuals are able to up-condition to a greater extent) would improve the design and implementation of future interventions. Regardless, it appears any of the three stimulus intensities studied herein could be effectively used in operant conditioning paradigms following ACL reconstruction.

3.5 Limitations

There are some limitations to this study that should be considered. First, this study evaluated the effect of stimulus intensity on the ability to up-condition the MEP_{TORQUE} during a single session. While we did not find stimulus intensity to influence the ability to up-condition or its associated effects, it is plausible that stimulus intensity may have a greater influence when there are additional training sessions due to cumulative effects. In addition, this study only tested three stimulus intensities (100%, 120%, and 140% of AMT) and we cannot confirm whether other stimulus intensities that were not tested (e.g., >140% AMT) may impact the ability to up-condition the quadriceps MEP_{TORQUE}. Also, it is possible that quadriceps fatigue may have contributed to the higher MEP_{TORQUE} observed during the conditioning blocks compared to the baseline control block. However, when comparing the MEP_{TORQUE} between PRE and POST (after matching for the stimulus intensity used during training) and COND3, we found that POST

was higher than PRE but much lower than the third conditioning block (PRE: 17.05 ± 1.18, COND3: 21.88 ± 1.18, POST: 18.67 ± 1.18 [mean ± SE]). In contrast, if fatigue was the sole explanation for the increase in corticospinal excitability, one would expect the quadriceps MEP_{TORQUE} during POST to be similar to or higher than that of the third conditioning block. Therefore, the increase in quadriceps corticospinal excitability during and following operant conditioning is most likely to be explained by the motor imagery used during operant conditioning. Although we observed significant increases in corticospinal excitability and acute neural adaptations due to a single session of operant up-conditioning, it is unknown whether these changes in corticospinal excitability would be sufficient to induce clinically meaningful improvements for relevant clinical outcomes such as quadriceps strength or self-reported knee function. Finally, this study evaluated the effect of stimulus intensity in a relatively small sample size of ACL reconstructed individuals. While the number of participants per group was similar to other studies evaluating corticospinal excitability after ACL reconstruction,[35-37] it is possible with a larger sample size a significant effect for stimulus intensity could be identified.

3.6 Conclusion

In conclusion, we found that individuals with ACL reconstruction are able to successfully up-condition the quadriceps MEP_{TORQUE} during a single session of operant conditioning training. This up-conditioning was paralleled by an increase in corticospinal excitability of the quadriceps muscles. However, the TMS stimulus intensity used during operant conditioning does not appear to affect the ability to up-condition the quadriceps MEP_{TORQUE} or acute neural adaptations. These findings indicate that operant conditioning of MEP_{TORQUE} may serve as valuable adjunct to ACL reconstruction rehabilitation protocols and that any of the stimulus intensities evaluated in the current study could be appropriate when used in operant conditioning interventions. Future

studies investigating the influence of stimulus intensity over a greater number of sessions are needed to confirm whether stimulus intensity does not appear to affect the ability to up-condition the quadriceps MEP_{TORQUE} in individuals with ACL reconstruction.

3.7 Acknowledgement

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Chapter 4 Operant Up-Conditioning of the Quadriceps Motor Evoked Torque as a Means to Improve Quadriceps Function after Anterior Cruciate Ligament Reconstruction

Abstract

Background: Diminished corticospinal excitability is theorized to contribute to poor quadriceps function following anterior cruciate ligament (ACL) reconstruction. However, recovery of quadriceps function may be limited as current rehabilitation methods do not directly target changes in corticospinal excitability. Operant conditioning of the motor evoked torque (MEP_{TORQUE}) is a promising approach capable of improving corticospinal excitability. However, it is unknown whether increasing corticospinal excitability can improve quadriceps function following a short-term operant conditioning intervention in ACL reconstructed individuals. *Objective:* The aim of this study was to evaluate whether individuals with ACL reconstruction can increase the quadriceps MEP_{TORQUE} response with training and whether these up-conditioning effects result in improvements in quadriceps function following a two-week intervention. *Methods:* Twenty-two ACL reconstructed individuals were randomized into one of two groups for a two-week operant conditioning intervention. Quadriceps MEP_{TORQUE} elicited via transcranial magnetic stimulation (TMS) was evaluated on the reconstructed leg in both groups, but one group received training to improve their MEP_{TORQUE} responses and received TMS (COND) and the other only received TMS (SHAM-COND). Quadriceps strength and voluntary activation on the reconstructed leg was evaluated prior to and following the intervention. Corticospinal excitability was evaluated during training sessions using quadriceps MEP_{TORQUE}. *Results:* The COND group demonstrated a significantly higher percent increase in

quadriceps MEP_{TORQUE} during training compared with the SHAM-COND group. In addition, quadriceps strength and voluntary activation improved on the reconstructed leg, regardless of group. *Conclusion:* Operant conditioning training can elicit within-session improvements in corticospinal excitability after ACL reconstruction. Given that quadriceps strength and voluntary activation increased in both groups, the improvements in quadriceps strength and voluntary activation do not appear to be solely attributed to the operant up-conditioning training.

4.1 Introduction

Anterior cruciate ligament (ACL) injury is one of the most common musculoskeletal injuries, particularly in young, athletic populations.[1]Reconstructive surgery is the gold standard of care after ACL injury and is intended to restore knee joint function and promote long-term joint health. Despite undergoing surgical and rehabilitation interventions, ACL reconstructed individuals suffer substantial deficits in quadriceps strength and voluntary activation that persist long after surgery.[2, 3] Addressing quadriceps weakness is critical as it is linked to poor self-reported knee function, aberrant walking biomechanics, and decreased activity levels after ACL reconstruction.[4-7] Further, quadriceps weakness has been linked prospectively and retrospectively to the development of early onset post-traumatic knee osteoarthritis.[8, 9] Thus, restoring quadriceps strength is an important rehabilitation goal to recover pre-injury joint function and ensure long-term joint health following ACL reconstruction.

Following ACL injury and reconstruction, the inability to fully activate the quadriceps can develop and may contribute to the difficulty of improving quadriceps strength during rehabilitation. Peripheral factors such as pain, joint effusion, and damage to the mechanoreceptors typically develop after injury and surgery, which can influence afferent signaling to the central nervous system.[10] In addition, central factors such as adaptations in the

spinal-reflex and corticospinal pathways can develop following ACL reconstruction.[11-13] Diminished excitability of the corticospinal pathway can reduce efferent drive to the quadriceps muscle during contraction, which may contribute to the deficits in quadriceps strength and voluntary activation after ACL reconstruction.[12, 13]Accordingly, restoring optimal functioning of the corticospinal pathways may be key to regaining quadriceps strength and voluntary activation. Unfortunately, current rehabilitation paradigms are unable to directly target the neural pathways, which make it difficult to address the changes in corticospinal excitability following ACL reconstruction. Interventions such as transcranial direct current stimulation and high-frequency repetitive transcranial magnetic stimulation (TMS) can be used to alter corticospinal excitability. However, the effects from transcranial direct current stimulation are not reliable and high-frequency repetitive TMS protocols may have small seizure risks.[14, 15] Thus, a novel paradigm that can directly target the corticospinal pathways would provide insight into whether improving corticospinal excitability corresponds to improvements in quadriceps strength and voluntary activation.

Operant conditioning of the spinal-reflex and corticospinal pathways harnesses a form of reward-based learning,[16] and may be a promising supplement to standard rehabilitation. Operant conditioning can be used to up-condition (i.e., increase the response through training) or down-condition to modify behavior. Operant conditioning interventions in animal models have been shown to effectively down-condition measurements of spinal-reflex excitability such as the H-reflex.[17, 18] More recently, operant conditioning paradigms have been applied in pathological populations (e.g. spinal cord injury, multiple sclerosis) to up- or down-condition the spinal-reflex and corticospinal pathways.[19, 20] Notably, operant conditioning can lead to changes not only in neural excitability, but can also improve strength of the targeted muscle.[20] In addition, improved

gait symmetry, increased muscle activation during walking, and faster walking speeds have been observed after operant conditioning in individuals with neurological conditions.[20, 21] Thus, applying operant conditioning paradigms appears to be a promising approach to target the corticospinal pathway and may translate to improvements in muscle and physical function.

Despite the potential of operant conditioning to improve corticospinal excitability, little is known about its benefits for ACL reconstructed individuals. A case study from our lab provides preliminary support for operant up-conditioning of quadriceps motor evoked torque (MEP_{TORQUE}) responses in the ACL reconstructed leg.[22] Importantly, improved quadriceps strength and voluntary activation of the reconstructed leg were also observed following the eight-week operant conditioning intervention.[22] Thus, there is encouraging evidence to support operant up-conditioning of the MEP_{TORQUE} as a feasible intervention to improve quadriceps strength and voluntary activation after ACL reconstruction. However, a larger sample of ACL reconstructed individuals is needed to confirm the ability of operant conditioning to improve quadriceps strength and voluntary activation. Further, it is difficult to determine whether improvements in quadriceps strength and voluntary activation occurred due to the subject's participation in general exercise activities or if changes were due to the intervention. Hence, there is a critical need for a controlled randomized clinical trial of operant up-conditioning in a larger sample of ACL reconstructed individuals. Therefore, the purpose of this study was to 1) evaluate the ability of operant up-conditioning to increase the quadriceps MEP_{TORQUE} after ACL reconstruction and 2) quantify the effects of operant up-conditioning on quadriceps strength and voluntary activation after a two-week intervention.

4.2 Methods

4.2.1 Participants

Sample size was determined *a priori* assuming an effect size with the partial $\eta^2 = 0.34$ and an α level of 0.05. A power analysis in G*Power[23] indicated that a total sample size of N=22 (11 per group) provided a power (1- β) > 85% to detect a significant main effect for group and time.

A total of 22 individuals with ACL reconstruction (12 females, 11 males, 23.9 ± 7.5 years, 25.1 ± 5.2 kg/m^2, 14.0 ± 5.4 months post-operative, 12 right-injured, 10 left-injured, 21 right-footed, 1 left-footed) participated in this study. Inclusion criteria were: 1) aged 14-45 years; 2) suffered a complete ACL rupture; and 3) received an ACL reconstruction at least 4 months prior to testing. Exclusion criteria included: 1) contralateral ACL tear 2) having ear or metal implants in the skull; 3) having a cardiac pacemaker; 4) a history of unexplained recurrent headaches, seizures, recent head injury, medical or heart condition that could influence study outcomes or significant adverse reaction to TMS; 5) currently pregnant; 6) other recent significant knee injury or lower-extremity fracture; and/or 7) body mass index greater than 40 kg/m^2. Participants provided written informed consent and parental consent was also obtained if the participant was a minor child. All study protocols were approved by the University of Michigan Institutional Review Board (IRBMED: HUM00166442).

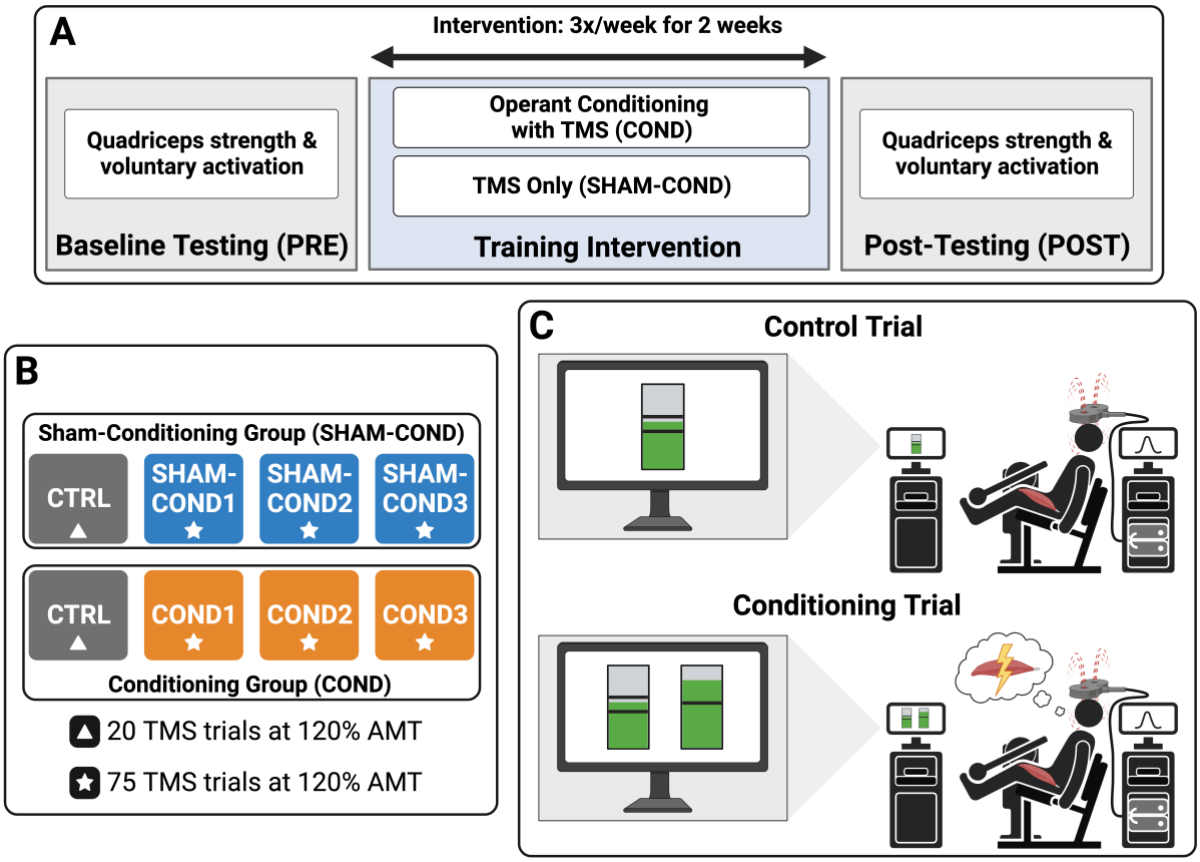

Figure 4.1 In **Panel A** is a schematic of the study design. In **Panel B** is a schematic of a single training session for the sham-conditioning group (SHAM-COND) and the conditioning (COND) group. The SHAM-COND blocks were completed with the same procedures as the control block. In **Panel C** is a schematic of the experimental procedures during a control/sham-conditioning trial **(top)** and a conditioning trial **(bottom)**. *Abbreviations:* CTRL, control block; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; SHAM-COND1, sham-conditioning block 1; SHAM-COND2, sham-conditioning block 2; SHAM-COND3, sham-conditioning block 3; TMS, transcranial magnetic stimulation; AMT, active motor threshold.

4.2.2 Study Overview

This was a randomized, controlled clinical trial (NCT05519345) designed to test the feasibility of a two-week operant conditioning intervention to increase the quadriceps MEP_{TORQUE} and its ability to improve quadriceps function after ACL reconstruction. Participants were randomly assigned to one of two groups: 1) TMS with training to improve the quadriceps MEP_{TORQUE} of the reconstructed leg (i.e., conditioning group, COND) or 2) TMS without up-conditioning training (i.e., sham-conditioning group, SHAM-COND). Regardless of group

assignment, all subjects completed a two-week intervention (three training sessions per weeks) on the reconstructed leg. Two testing sessions were collected, one baseline session completed prior to training (PRE) and one session following completion of the intervention (POST). During both testing sessions, quadriceps strength and voluntary activation were evaluated on the reconstructed leg. Study design is outlined in Figure 4.1.

4.2.3 Training Sessions

A schematic of the experimental set-up and the training session protocol is depicted in Figure 4.1. The aim of the operant conditioning training sessions was to train participants in the conditioning group to increase quadriceps MEP_{TORQUE} on the reconstructed leg during each training session. Participants were seated and fastened into an isokinetic dynamometer (Humac Norm, CSMi, Stoughton, USA) with the trunk and knee set to 85 and 60 degrees of flexion, respectively. While seated on the dynamometer, MEP_{TORQUE} responses were elicited using a Magstim 200^2 stimulator (Magstim Co Ltd, Whitland, UK). A 110-mm diameter double-cone coil was used to apply TMS to the primary motor cortex on the hemisphere contralateral to the reconstructed leg. The coil was oriented to induce a posterior to anterior current flow in the cortex. A temporary quadriceps hotspot location was determined and marked on a fabric cap by identifying a point that was located 2.0 cm posterior and 2.0 cm lateral to the vertex of the skull.[24] The coil was systematically moved from this location to find the hotspot (i.e., the location over the skull that resulted in the largest and most consistent MEP_{TORQUE} during a 10% MVIC background contraction). Participants received visual feedback to maintain a consistent background contraction (Figure 4.2). The location of the hotspot was marked on a fabric cap to ensure consistent coil location during the session. The active motor threshold (AMT) for the session was determined as the minimum TMS intensity needed to evoke a MEP_{TORQUE} response

in ≥ 50% of attempted trials (≥10 trials) using the relative-frequency method.[25, 26] The AMT was used to determine stimulus intensity during the control (CTRL) and conditioning (COND) blocks.

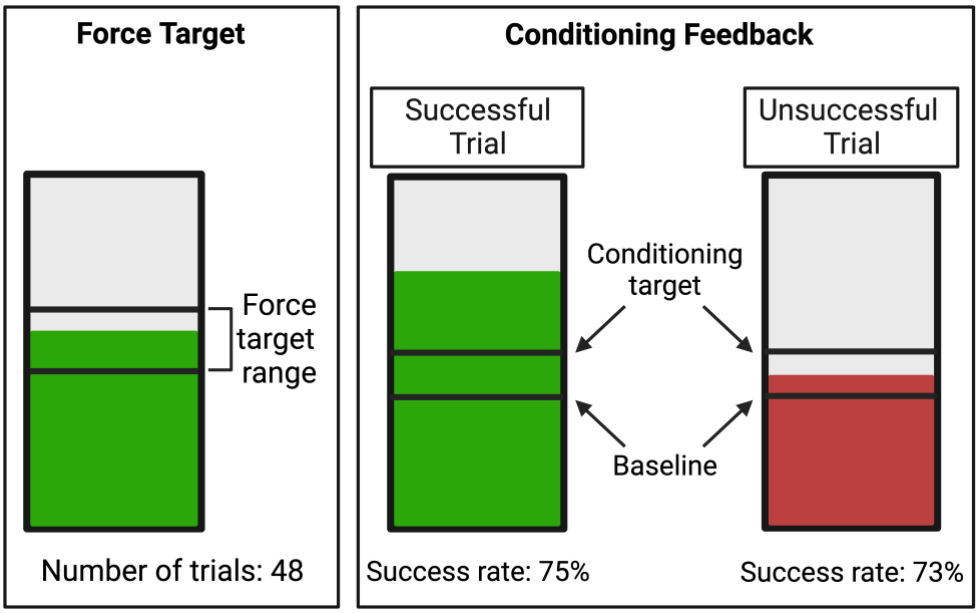

Figure 4.2 On the left is a schematic depicting the visual feedback provided for a small background contraction (10% of MVIC), which was shown for both the control and conditioning blocks. The participant's torque output is indicated by the green bar, which must stay within the force target range to maintain a 10% MVIC background contraction. Below the force target, participants can see the number of completed trials. On the right is a schematic illustrating visual feedback of a successful or unsuccessful trial provided to participants during the conditioning blocks. The conditioning bar will turn green when the most recent training trial successfully increased the MEP_{TORQUE} (i.e., MEP_{TORQUE} greater than the conditioning target). The conditioning bar will turn red when the most recent training trial was unsuccessful in increasing the MEP_{TORQUE}. Below the feedback bar, participants can see their current success rate, which updates dynamically after each conditioning trial and resets at the start of each block. *Abbreviations*: MVIC, maximum voluntary isometric contraction; MEP_{TORQUE}, motor evoked torque.

Once the hotspot location and AMT were determined, the baseline control block of 20 TMS trials was collected as has been done previously.[22, 27] The control block (CTRL) was used to establish the participant's baseline excitability and to determine the initial criterion value (i.e., the 50th percentile value of the MEP_{TORQUE} from the 20 control trials) for the operant conditioning training. During the control block, participants were instructed to focus on maintaining a consistent background contraction (10% of MVIC) as described above and received a TMS pulse to the contralateral hemisphere at 120% of the participant's AMT when

the contraction was maintained. Regardless of group assignment, participants did not attempt to increase (i.e., up-condition) their MEP_{TORQUE} or receive feedback about their performance during the control block.

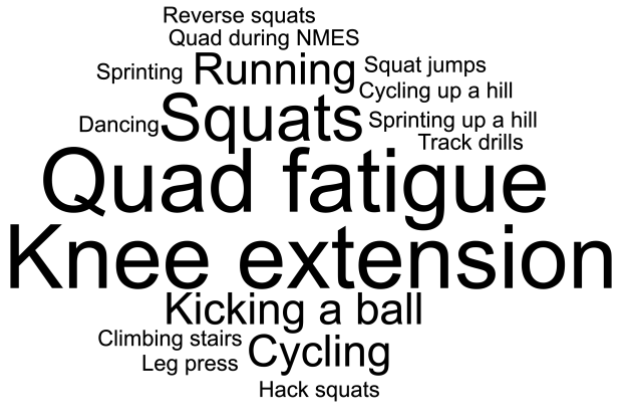

Figure 4.3 Wordcloud depicting the motor imagery visualizations used by participants during up-conditioning procedures. Words with a larger font size correspond to visualizations that were more frequently used by participants, while words with a smaller font size were less frequently used.

Following the 20 control trials, both groups performed 3 blocks of 75 trials. Individuals randomized to the sham-conditioning group performed three blocks of 75 control trials (i.e., sham-conditioning blocks) with the same procedures as the control trials. In contrast, individuals randomized to the conditioning group performed three blocks of 75 conditioning trials. The conditioning block was similar to the control trials, except the participant was instructed to use motor imagery to try and train the corticospinal pathways to increase the MEP_{TORQUE} responses above the criterion value. Examples were provided, such as imagining contracting their quadriceps or the quadriceps feeling a "burn" when doing exercises (e.g., squats, leg presses, etc.) or performing an exercise/sports action (e.g., hopping during a lay-up or kicking a ball). Motor imagery visualizations used by participants are depicted in Figure 4.3. The initial criterion value for the first conditioning training block (COND1) was set to the 50th percentile value of the participant's MEP_{TORQUE} in the control block. The criterion value was determined such that if

MEP_{TORQUE} amplitudes for the new block were similar to the MEP_{TORQUE} amplitudes of the previous training block, ~50% of the trials would be successful.[22, 27] Participants received visual feedback about their performance on each trial, indicating whether participants were successful at up-regulating the motor evoked torque responses (i.e., increased above the criterion value). The feedback bar increased and turned green if successful or decreased and turned red if unsuccessful (Figure 4.2). During each conditioning block, participants also received feedback on the percentage of successful trials during the current conditioning block. The participant's goal during the conditioning blocks was to achieve a trial success rate ≥ 60% and a small monetary incentive was provided to achieve this target (20 cents for each trial greater than 60%). During conditioning trials, researchers also provided verbal encouragement and positive verbal feedback.

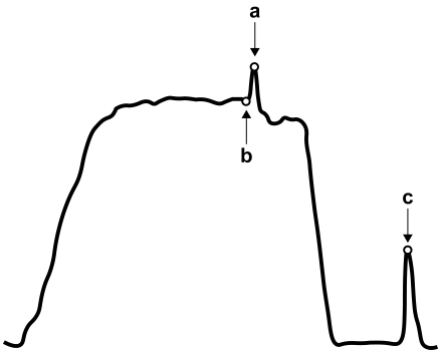

Figure 4.4 Schematic depicting voluntary activation calculation using the interpolated twitch technique using the superimposed torque ("a"), maximal torque at stimulation ("b") and evoked torque at rest ("c").

4.2.4 Outcome Measures

4.2.4.1 Knee Strength and Voluntary Activation

Participants were seated on an isokinetic dynamometer (Humac Norm, CSMi, Stoughton, USA) and secured to the device with the trunk and knee set to 85 and 60 degrees of flexion, respectively. This dynamometer setup was used for all testing procedures including knee strength, voluntary activation, and for training sessions. Quadriceps strength and voluntary

activation were determined by conducting maximal voluntary isometric contractions (MVICs) and using the interpolated triplet technique (ITT) (Figure 4.4).[28] The procedures were collected on the reconstructed leg during the PRE and POST testing sessions. Two 7.0 × 13.0 cm Dura-Stick Plus self-adhesive electrodes (Chattanooga, DJO, LLC) were placed on the proximal and distal quadriceps muscles prior to testing. A high-voltage, constant-current electrical stimulator (DS7AH; Digitimer North America, LLC) connected to the electrodes was used to electrically stimulate the quadriceps. At rest, the quadriceps muscle was stimulated with pulse trains (3 pulses, 100 Hz, 200-μs pulse duration, 400 V) at several intensities (100 mA, 200 mA, 300 mA, 250 mA). The current intensity that produced the maximum torque was used for testing.

Participants warmed-up with a series of submaximal knee extension contractions, two each at 25%, 50%, 75%, and 100% of their perceived maximum. Participants rested, briefly, before performing two 5-second MVICs of their knee extensors. During each MVIC, visual display of the torque curves and strong verbal encouragement were provided to ensure maximal effort. In addition, the quadriceps was electrically stimulated using the established current intensity to determine the level of voluntary drive to the quadriceps muscles. A validated automated torque-based triggered approach was used to automatically trigger the stimulator.[29] Quadriceps strength was determined as the voluntary peak torque prior to the electrical stimulus. Quadriceps strength was then normalized to body mass. Voluntary activation was calculated using the following equation:

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

Equation 4.1

Participants received 120 seconds of rest between MVIC trials. Peak MVIC knee extensor torque values were also used to calculate the 10% MVIC background contraction performed during the training sessions.

4.2.5 Data Management

Data collection and analysis was performed using custom programs written in LabVIEW. Torque and sync data were sampled at 1000 Hz. Torque signals were low-pass filtered (10 Hz, 4th order) using a zero-lag digital Butterworth filter.[30] Stimulation onset was determined from sync data and used to identify the maximum amplitude occurring prior to stimulation for quadriceps strength. The same software was also used to identify the maximum amplitudes of the evoked torque occurring after stimulation. The torque value identified at stimulation was subtracted from the maximum amplitude. This calculation was repeated for each trial and averaged to determine quadriceps voluntary activation.

For the corticospinal excitability data, torque data was segmented from 200 ms prior to the stimulation over a window of 500 ms for each of the stimulations. The segmented torque data was ensemble averaged to construct an average torque curve for each block. The size of the MEP_{TORQUE} was calculated as the peak twitch torque, offset by the amplitude of the background contraction. The percent change in MEP_{TORQUE} was calculated for each training session using the following equation:

$$\%\,\Delta \text{ in } \mathrm{MEP_{TORQUE}} = \left(\frac{\mathrm{MEP_{TORQUE}} \text{ during } \mathrm{COND3}}{\mathrm{MEP_{TORQUE}} \text{ during } \mathrm{CTRL}}\right) \times 100$$

Equation 4.2

4.2.6 Statistical Analysis

Descriptive statistics were used to evaluate the distribution and variation of each outcome variable. In addition, graphical methods such as histograms, residual plots, and Q-Q plots were used to visually inspect the data. Assumptions of normality were verified using the Shapiro-Wilks test. A linear mixed model with group (COND, SHAM-COND), session (1-6), and group × session as fixed effects and subject as a random effect were used to evaluate the ability of ACL reconstructed individuals to improve the MEP_{TORQUE} during training and whether the changes in MEP_{TORQUE} were influenced by the group and session. The percent change in quadriceps MEP_{TORQUE} was used as the dependent variable.

In addition, two separate linear mixed-models with group (COND, SHAM-COND), time (PRE, POST), and group × time as fixed effects and subject as a random effect were used to evaluate if quadriceps strength and voluntary activation improved on the reconstructed leg following the intervention and if the intervention group influenced the changes in quadriceps strength and voluntary activation. Normalized quadriceps strength and voluntary activation of the reconstructed leg during the PRE and POST testing sessions were used as the dependent variables and normalized quadriceps strength and voluntary activation at PRE were used as the covariate in each model. Any identified significant main effects or interaction effects were followed by appropriate post hoc analyses using a Šidák correction. A significance level of alpha = 0.05 was used for all analyses.

4.3 Results

4.3.1 Ability to Up-Condition Quadriceps MEP_{TORQUE}

Ensemble averaged group data on the ability to up-condition the quadriceps MEP_{TORQUE} is shown in Figure 4.5. During training, there was a significant main effect of group ($F_{1,20}$ = 7.347, p = 0.013). Post-hoc analysis revealed that individuals in the COND group demonstrated a significantly higher percent increase in MEP_{TORQUE} (i.e., percent change from the control block to the third conditioning block) during the training sessions compared to the SHAM-COND group (COND[†]: 155.585 ± 10.804, SHAM-COND[†]: 114.171 ± 10.804, p = 0.013). Hence, ACL reconstructed individuals in the COND group were able to successfully up-condition the $MEP_{TORQUE,}$ while those in the SHAM-COND demonstrated marginal increases in MEP_{TORQUE}. However, there was no significant main effect of session ($F_{5,100}$ = 1.763, p = 0.127) or the interaction between group and session ($F_{5,100}$ = 0.714, p = 0.614).

4.3.2 Change in Quadriceps Function Due to Operant Conditioning

During the operant conditioning intervention, there was a significant main effect of time ($F_{1,20}$ = 6.893, p = 0.016). Post-hoc analysis revealed that normalized quadriceps strength was significantly higher at POST compared with PRE (p = 0.016, PRE[†]: 2.397 ± 0.031, POST:[†]: 2.516 ± 0.031). However, there was no significant main effect of group ($F_{1,19}$ = 0.029, p = 0.867) or the interaction between group and time ($F_{1,20}$ = 0.047, p = 0.830) (Figure 4.6). Regarding quadriceps voluntary activation, there was a significant main effect of time ($F_{1,20}$ = 5.059, p = 0.036). Post-hoc analysis revealed that quadriceps voluntary activation was significantly higher

[†] Reported as mean ± pooled standard error of the mean

at POST compared with PRE (p = 0.036, PRE†: 85.523 ± 1.611, POST: 91.126 ± 1.611). However, there was no significant main effect of group ($F_{1,19}$ = 0.038, p = 0.848) or the interaction between group and time ($F_{1,20}$ = 0.110, p = 0.744) (Figure 4.6).

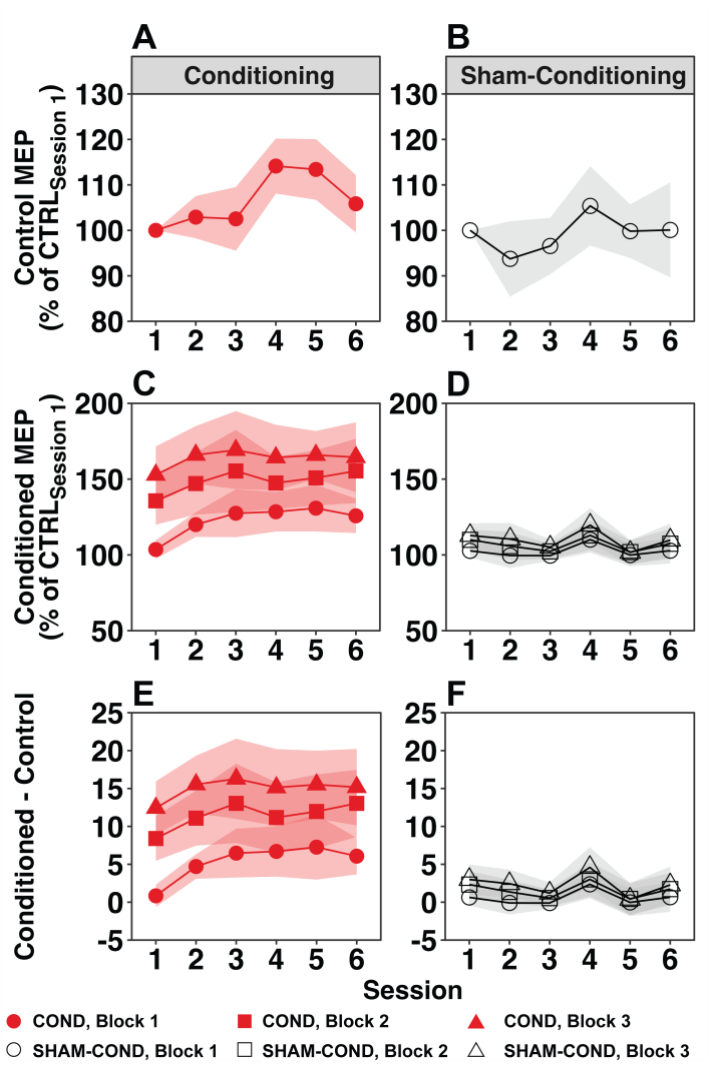

Figure 4.5 Time course of changes in MEP_{TORQUE} during the operant conditioning intervention in individuals with ACL reconstruction. Data for the conditioning group (A) and sham-conditioning group (B) for the changes in the control (CTRL) MEP_{TORQUE} as a percentage of the CTRL value from training session 1 across each training session. Data for each block is shown for the change in the conditioned MEP_{TORQUE} as a percentage of the CTRL value from training session for the conditioning group (C) and sham-conditioning group (D). Data for each block is depicted for the conditioning group (E) and sham-conditioning group (F) for the difference between each conditioning block and the CTRL value from training session 1 across each training session. *Abbreviations:* MEP_{TORQUE}, motor evoked torque; ms, milliseconds; CTRL, baseline control block; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; SHAM-COND1, sham-conditioning block 1; SHAM-COND2, sham-conditioning block 2; SHAM-COND3, sham-conditioning block 3.

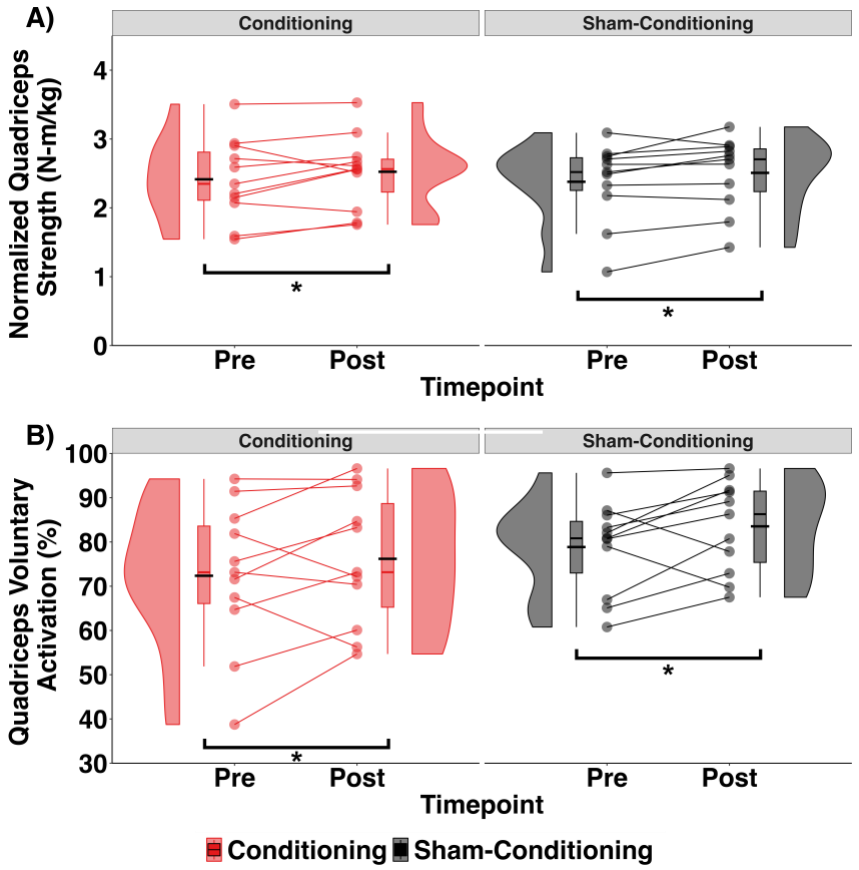

Figure 4.6 Raincloud plots depicting the distribution of the distribution of normalized quadriceps strength prior to the operant conditioning intervention (PRE) and following the operant conditioning intervention (POST) for the conditioning group and sham-conditioning group. *Abbreviations*: kg, kilograms; MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; PRE, prior to operant conditioning intervention; POST, following operant conditioning intervention; %, percentage.

4.4 Discussion

The purpose of this study was to 1) determine whether individuals with ACL reconstruction who received training were able to successfully increase the quadriceps MEP_{TORQUE} and 2) evaluate the effect of operant up-conditioning on quadriceps strength and voluntary activation following a two-week intervention. As hypothesized, we found that ACL reconstructed individuals in the conditioning group were able to successfully improve their quadriceps MEP_{TORQUE} during training sessions, while individuals in the sham-conditioning group did not. In addition, improvements in normalized quadriceps strength and voluntary activation of the reconstructed leg were observed in both groups. Our findings support operant

conditioning of the MEP_{TORQUE} as a feasible approach to improving corticospinal excitability in individuals with ACL reconstruction. While improvements in quadriceps function were not specific to the operant conditioning intervention, it is still possible that a longer-term intervention could reveal differential effects.

A significant finding of this study was that ACL reconstructed individuals in the conditioning group demonstrated a significantly higher percent increase in MEP_{TORQUE} (i.e., percent change from the control block to conditioning block 3) compared with the sham-conditioning group. This finding indicates that ACL reconstructed individuals are able to consistently improve their corticospinal excitability during multiple operant up-conditioning sessions. It is not surprising that ACL reconstructed individuals were able to successfully improve their corticospinal excitability as our previous work demonstrated that ACL reconstructed individuals were able to improve their corticospinal excitability within a single session (Chapter 3). This finding is particularly encouraging, given that corticospinal excitability may be altered following ACL reconstruction. [31, 32] Thus, operant conditioning appears to be a valuable approach for improving corticospinal excitability after ACL reconstruction, especially during periods when other high-intensity training methods are contraindicated (e.g., shortly after the surgery).

Regarding voluntary activation, we found that quadriceps voluntary activation of the reconstructed leg improved in both groups following the operant conditioning intervention. We observed a modest increase (~5%) in quadriceps voluntary activation from PRE to POST, which appears to be a reasonable improvement as a case study from our lab reported 8% and 14% increases in voluntary activation of the reconstructed leg following four and eight weeks of training, respectively.[22] Surprisingly, we did not find that improvements in voluntary activation

differed between the conditioning and sham-conditioning groups. Hence, we believe the similar improvements in voluntary activation for both groups was likely due to some other factor such as the repeated TMS stimulations or the repeated quadriceps contractions performed during the training sessions, rather than solely the operant conditioning intervention. One explanation may be that repeated volitional quadriceps contractions and/or repeated magnetically-evoked quadriceps contractions due to TMS stimulations may improve quadriceps strength by activating the mechanism of post-activation potentiation.[33] When post-activation potentiation occurs, the myosin regulatory light chains phosphorylate, which increases calcium sensitivity of the myofilaments.[34, 35] The increased calcium sensitivity results in increased myosin cross-bridge activity and can ultimately contribute to increases in torque output.[34] Hence, the cumulative effects of post-activation potentiation over multiple training sessions may contribute to the improvements in quadriceps voluntary activation we observed in both groups. Another possible explanation is that the repeated volitional quadriceps contractions performed during training sessions may have resulted in muscle fiber fatigue, requiring participants to increase their neural drive by engaging additional motor units and/or increasing the firing rate of activated motor units.[36-38] Higher-threshold motor units may have also been recruited at the same level of contraction due to reductions in the recruitment thresholds of these motor units due to the repeated magnetically-evoked contractions.[39] Similarly, the cumulative effects of recruiting additional motor units and/or increasing motor unit firing rate during the training sessions may have induced adaptations that lead to greater quadriceps voluntary activation.

As was the case with voluntary activation, we found that the operant conditioning intervention resulted in significant improvements in normalized quadriceps strength of the reconstructed leg for both groups. However, the conditioning and sham-conditioning groups

exhibited similar improvements in normalized quadriceps strength. The improvements in quadriceps strength for both groups are unexpected, as there were a limited number of training sessions. Following an eight-week operant conditioning intervention, previous studies report conflicting findings. For example, one study reported improvements in muscle strength for individuals with and without neurological conditions,[20] while another reported no changes in muscle strength.[19] However, a case study conducted in our laboratory found that an ACL reconstructed individual demonstrated improved quadriceps strength following four weeks and eight weeks of operant conditioning training.[22] Due to a lack of a control/sham-conditioning group, we cannot comment whether the improvements in quadriceps strength reported in the case study were due to the operant up-conditioning or some other factor such as the repeated quadriceps contractions or repeated TMS stimulations performed during the paradigm. One possible explanation for the improvements in quadriceps strength we observed in the current study is that participation in standard rehabilitation may have contributed to the changes we observed. However, participation in rehabilitation is unlikely to fully explain these changes as the majority of individuals had completed rehabilitation prior to enrollment and were at least 12 months post-operative. Hence, we believe the improvements in quadriceps strength were also likely due to the repeated quadriceps contractions or repeated TMS stimulations during the operant conditioning intervention. Although improvements in quadriceps strength cannot be solely attributed to operant conditioning, it is plausible that supplementing the motor imagery with techniques such as action observation or sensory priming may improve motor imagery ability and contribute to greater effects of the operant conditioning intervention. For example, providing participants with videos of an individual contracting their quadriceps muscle (i.e., action observation) prior to the conditioning blocks or providing sensory stimulation such as

vibration of the quadriceps muscles during the conditioning blocks both involve priming techniques commonly used in neurorehabilitation.[40] This video-guided motor imagery technique may be especially valuable in individuals with ACL reconstruction as researchers have theorized that increased activation of the lingual gyrus may be indicative of an increased reliance on a visual-motor strategy during knee extension/flexion.[41] Further, longer-term intervention may be needed as previous operant conditioning interventions required several weeks (≥ 4 weeks) of training to induce long-term adaptations in corticospinal excitability,[19, 22] which likely precede the improvements in muscle strength associated with operant conditioning. Thus, ACL reconstructed individuals may require supplementing the current protocol tested with techniques that improve an individual's motor imagery ability and/or with additional training sessions in order to elicit the chronic neural adaptations necessary to improve quadriceps strength beyond the effect of repeated volitional and/or magnetically-evoked contractions.

4.5 Limitations

There are some limitations to this study that should be considered. First, this study evaluated whether a two-week operant conditioning intervention would result in improvements in quadriceps function. While we did not observe greater improvements in quadriceps function for the conditioning group compared with the sham-conditioning group, it is plausible that additional training sessions would result in greater cumulative effects in the COND group and thereby, greater improvements in quadriceps function. However, this would likely require a four to eight week intervention, which was not feasible within our time frame. Future studies investigating longer-term operant conditioning interventions would lend insight into whether additional training sessions could elicit greater improvements in quadriceps function. In addition, we did not include a third control group that did not receive TMS. Thus, we cannot determine the

extent of improvements in quadriceps strength that were due to operant conditioning and the extent that were due to the role of repeated quadriceps contraction and/or repeated TMS trials. Research evaluating a third group that does not receive TMS would provide valuable insight into what additional role operant conditioning may contribute to improvements in quadriceps function and whether it generates meaningful improvements that support its use in a clinical setting. Finally, this study evaluated the ability of a two-week operant conditioning intervention to improve quadriceps function and corticospinal excitability in a relatively small sample size of ACL reconstructed individuals. Although our study had a greater number of participants per group compared with previous operant conditioning interventions,[19, 27] it is possible a larger sample size could reveal a significant effect for group.

4.6 Conclusion

In conclusion, we found that ACL reconstructed individuals were able to successfully improve their corticospinal excitability during the training sessions of two-week operant conditioning intervention. In addition, quadriceps strength and voluntary activation of the reconstructed leg improved in both groups following the intervention. Together, these findings indicate that operant conditioning of the MEP_{TORQUE} may be a feasible intervention to addressing the changes in corticospinal excitability observed after ACL reconstruction, but a two-week intervention does not appear to be sufficient to elicit clinically meaningful improvements in quadriceps function.

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Chapter 5 Conditioning following Total Knee Arthroplasty: Effects of Stimulus Intensity and Number of Conditioning Trials

Abstract

Background: Following total knee arthroplasty (TKA), individuals suffer chronic deficits in quadriceps strength and voluntary activation. Operant conditioning of the motor evoked torque (MEP_{TORQUE}) responses is an emerging approach capable of targeting the corticospinal pathway, which may help improve quadriceps function after TKA. However, using appropriate dosage parameters (i.e., stimulus intensity and number of training trials) is critical to ensuring effective intervention in individuals with TKA. *Objective:* To determine whether individuals with TKA can 1) improve their quadriceps MEP_{TORQUE} responses within a single session, 2) induce acute changes in corticospinal excitability, and 3) the effect of stimulus intensity and number of training trials. *Methods:* Thirty participants were assessed during a single session of an operant conditioning intervention. Participants were randomly allocated to one of three groups based on the participant's active motor threshold (AMT) (100% AMT, 120% AMT, 140% AMT) to evaluate the effect of stimulus intensity on the ability to improve MEP_{TORQUE} and its associated acute neural adaptations. Participants received 3 blocks of conditioning trials (COND), where they trained to up-condition their quadriceps MEP_{TORQUE} using principles of operant conditioning. MEP_{TORQUE} recruitment curves were collected before (PRE) and after the training (POST) to evaluate the effect of operant up-conditioning on acute corticospinal adaptations. Control (CTRL). TMS pulses were provided before and after each block of COND trials to set targets for COND trials and also to evaluate the effect of number of training trials on operant up-

conditioning of MEP_{TORQUE} responses. *Results:* Individuals with TKA were able to successfully up-condition their MEP_{TORQUE} in a single session ($p<0.001$; CTRL1: 16.826 ± 0.627, COND1: 16.307 ± 0.627, COND2: 18.524 ± 0.627, COND3: 19.656 ± 0.627 [mean ± standard error (SE)]). Similarly, short-neural neural adaptations were observed ($p<0.001$, PRE: 685.888 ± 51.076, POST: 827.387 ± 51.076 [mean ± SE]). While the stimulus intensity used during training did not affect the ability to up-condition MEP_{TORQUE} ($p=0.979$) or its associated acute neural adaptations ($p=0.405$), the number of training trials significantly influenced these outcomes ($p < 0.001$, $p = 0.007$, respectively). *Conclusion:* Operant conditioning with at least 150 conditioning trials can induce acute corticospinal adaptations in individuals with TKA. The three stimulus intensities examined in this study may be used in future operant conditioning interventions.

5.1 Introduction

Following total knee arthroplasty (TKA), impairments in quadriceps strength and voluntary activation (i.e., the inability to fully contract the muscle during a maximal contraction) are commonly reported.[1-7] Researchers have theorized that a reduction in corticospinal excitability would diminish neural drive to the muscle and thereby, contribute to poor quadriceps function.[8] Although unexplored in individuals with TKA, research suggests corticospinal excitability is diminished following anterior cruciate ligament reconstruction[9, 10] and is linked to the deficits in quadriceps strength and voluntary activation after surgery.[11, 12] Given that both populations undergo knee surgery and suffer quadriceps dysfunction, it is plausible that decreased corticospinal excitability may contribute to poor quadriceps strength and voluntary activation following TKA. Thus, novel interventions that can target the corticospinal pathway may be valuable to restoring quadriceps function following TKA.

Various interventions have been considered in individuals with knee osteoarthritis with the goal to improve quadriceps strength and voluntary activation. For example, neuromuscular electrical stimulation and eccentric exercise have been used after TKA and may improve quadriceps strength and voluntary activation.[3, 13-15] Unfortunately, these interventions are unable to directly target the corticospinal pathway, which may limit improvements in quadriceps function. Techniques such as transcranial direct current stimulation (tDCS) and high-frequency repetitive transcranial magnetic stimulation (TMS) are also used in various populations and can directly alter corticospinal excitability through non-invasive brain stimulation.[16] While tDCS is safe, cost-effective, and easy to use, inconsistent tDCS-induced effects are reported in the literature.[17] Further, recent research reports that tDCS is unable to effectively increase corticospinal excitability of the quadriceps muscles.[17] In contrast, high-frequency repetitive TMS is costly and involves a small risk of triggering seizures, particularly in individuals using medications that lower the seizure threshold.[18] Thus, identifying novel techniques that can safely and effectively improve corticospinal excitability is a critical step to improving quadriceps function.

Recently, operant conditioning of motor evoked potentials has generated interest as a technique to safely and directly modulate corticospinal excitability. Operant conditioning is a behavioral intervention that uses rewards to incentivize an individual to learn and perform a desired motor skill.[19] Both animal and human subject research have demonstrated the ability to modulate spinal-reflex and corticospinal excitability during operant conditioning interventions.[20-23] Although operant conditioning has yet to be used in individuals with TKA, up-conditioning of the corticospinal pathway has been shown to be feasible and effective in eliciting improvements in corticospinal excitability for individuals with and without various pathologies.[23-25] Previous

operant conditioning studies have modulated corticospinal excitability as a strategy to enhance motor function, which is substantiated by concurrent improvements in muscle activation, muscle strength, and gait.[23-25] Therefore, operant conditioning of the corticospinal pathway appears to be a powerful technique to improve corticospinal excitability and may have clinical benefits for restoring quadriceps function after total knee arthroplasty.

Despite promising evidence supporting the use of operant conditioning to improve corticospinal excitability, it is unknown what factors may influence its implementation and the associated effects. While the majority of participants are able to successfully modulate their corticospinal excitability during operant conditioning protocols, about one-third of the individuals are typically unable to successfully condition their responses.[23, 26] Unfortunately, it remains unclear why some individuals can condition their responses whereas others cannot. Recent research has revealed that individual factors such as baseline excitability and hormonal levels in females may play a role in the ability to up-condition their responses.[26] However, it is unknown whether factors related to the conditioning protocol contribute to this phenomenon. For example, it is well established that adequate dosage is integral to the efficacy of an intervention. If a sub-optimal dosage of operant conditioning is used, diminished intervention effects would be expected and may explain why some individuals are unable to improve their corticospinal excitability.

An important component of the dosage during operant conditioning is the stimulus intensity used to up-condition the motor evoked response. When lower stimulus intensities are used, increased variability of the motor evoked response[27] may contribute noise and diminish the ability to up-condition the motor evoked response. However, when higher stimulus intensities are used, it may elicit greater improvements but may not be well-tolerated by all participants.

Accordingly, it is critical to identify the stimulus intensity that can elicit consistent improvements during operant conditioning with minimal participant discomfort. Current operant conditioning protocols appear to arbitrarily select the stimulus intensity used[23, 24] as the superiority of the stimulus intensity used over other intensities has yet to be established. Hence, establishing the influence of stimulus intensity on the ability to improve corticospinal excitability is imperative for developing an effective operant conditioning protocol after TKA.

Another factor relevant to the dosage during operant conditioning is the number of conditioning trials performed. With fewer conditioning trials, participants may have inadequate practice with the motor imagery performed during conditioning, which may diminish the ability to successfully up-condition. On the other hand, while a greater number of conditioning trials may generate larger effects, some participants may struggle to maintain these improvements throughout the duration of the session due to mental fatigue or boredom.[28-31] Current operant conditioning protocols use a high number of training trials (3 blocks of 75 trials), which may not be feasible in a rehabilitation setting. Thus, determining whether the ability to up-condition the corticospinal pathway is possible with fewer training trials is important to developing a clinically-feasible protocol for operant conditioning.

Therefore, the primary purpose of this study was to establish if a single session of operant up-conditioning of the corticospinal pathways in individuals with TKA can improve corticospinal excitability and induce acute neural adaptations in the corticospinal pathways. A secondary purpose of this study was to evaluate if the stimulus intensity and number of training trials used during operant up-conditioning influenced these improvements. We hypothesized that individuals with TKA would successfully increase their motor evoked torque (MEP_{TORQUE}) responses within a single session, which would be paralleled by acute neural adaptations, as

measured by changes in the MEP_{TORQUE} recruitment curve before and after the intervention (i.e., aftereffects). Based on our prior work in individuals with anterior cruciate ligament (ACL) reconstruction, we also hypothesized that improvements in quadriceps MEP_{TORQUE} during operant up-conditioning and the associated aftereffects would not be influenced by the stimulus intensity used during training. In addition, we hypothesized that quadriceps MEP_{TORQUE} would increase as the number of training trials increased, such that the final conditioning block would demonstrate the highest MEP_{TORQUE} and first conditioning block would demonstrate the lowest MEP_{TORQUE}, regardless of the stimulus intensity used.

5.2 Methods

5.2.1 Participants

Table 5.1 Group means for quadriceps MEP_{TORQUE} derived from unpublished data evaluating the effect of block and stimulus intensity on improvements in MEP_{TORQUE} during operant conditioning in ACL reconstructed individuals. A standard deviation $\sigma = 10.4$ for the outcome variable (quadriceps MEP_{TORQUE}) was derived from the unpublished data and used for the variability across outcomes. In addition, a standard ratio = 1 was assumed for all blocks.

Group	**Block 1** Mean	**Block 2** Mean	**Block 3** Mean	**Block 4** Mean
100 % AMT	3.9	4.3	5.3	5.5
120 % AMT	21.0	25.4	28.1	27.4
140 % AMT	26.9	30.6	32.9	32.8

Abbreviations: ACL, anterior cruciate ligament; AMT, active motor threshold; MEP_{TORQUE}, motor evoked torque.

Sample size was determined *a priori* using the group means and standard deviations (Table 6.1) for quadriceps MEP_{TORQUE} derived from unpublished data evaluating the effect of block and stimulus intensity on improvements in MEP_{TORQUE} during operant conditioning in ACL reconstructed individuals (Chapter 4). Based on this data, a power analysis in General Linear Mixed Model Power and Sample Size (GLIMMPSE 3.0) software[32] indicated that a total

sample size of N=27 (9 per group) provided a power (1- β) > 90% to detect a significant main effect for conditioning block. The following assumptions were made for this analysis: (1) mean and standard deviation values were equal to those observed in the data for ACL reconstruction (2) repeated measure correlation coefficients were equal to those observed in the data for ACL reconstruction (Table 6.2), (3) homogenous variances and covariances, and (4) an adjusted p-value of 0.0167 to account for 3 post-hoc simple effects comparisons (1 at each of the 3 conditioning blocks) for the main effect of group.

Table 5.2 The unstructured correlation matrix for block derived from unpublished data evaluating the effect of block and stimulus intensity on improvements in MEP_{TORQUE} during operant conditioning in ACL reconstructed individuals.

Block 1	Block 2	Block 3	Block 4
1	0.92	0.86	0.86
0.92	1	0.97	0.96
0.86	0.97	1	0.99
0.86	0.96	0.99	1

Abbreviations: ACL, anterior cruciate ligament; MEP_{TORQUE}, motor evoked torque.

A total of 30 individuals with TKR (18 females, 12 males, 60.37 ± 4.57 years, 31.20 ± 4.71 kg/m^2, 4.14 ± 2.17 years post-operative, 12 right-replaced, 18 left-replaced, 27 right-footed, 3 left-footed) participated in this study. Inclusion criteria included: 1) aged 45-70 years and 2) underwent total knee replacement at least 12 months prior to testing. Exclusion criteria included: 1) having a cardiac pacemaker; 2) having ear or metal implants in the skull; 3) other recent lower-extremity injury or lower-extremity fracture; 4) body mass index greater than 40 kg/m^2; 5) history of uncontrolled diabetes or hypertension; and/or 6) a history of unexplained recurrent headaches, seizures, recent head injury, medical or heart condition that could influence study outcomes or significant adverse reaction to TMS. Participants reviewed and signed a written

informed consent document approved by the University of Michigan Institutional Review Board prior to enrollment.

5.2.2 Study Overview

A schematic of the study overview is illustrated in Figure 5.1. This is a cross-sectional study designed to test the feasibility of a single-session of operant up-conditioning of the quadriceps motor evoked torque response to improve the motor evoked torque in individuals with total knee arthroplasty. Participants were randomized to one of three groups based on the TMS intensity (% active motor threshold [AMT) used during training: 1) 100% AMT; 2) 120% AMT; or 3) 140% AMT. All procedures were performed on the reconstructed leg. All study procedures for testing and training were identical between groups, except that the stimulus intensity used during training was manipulated across groups.

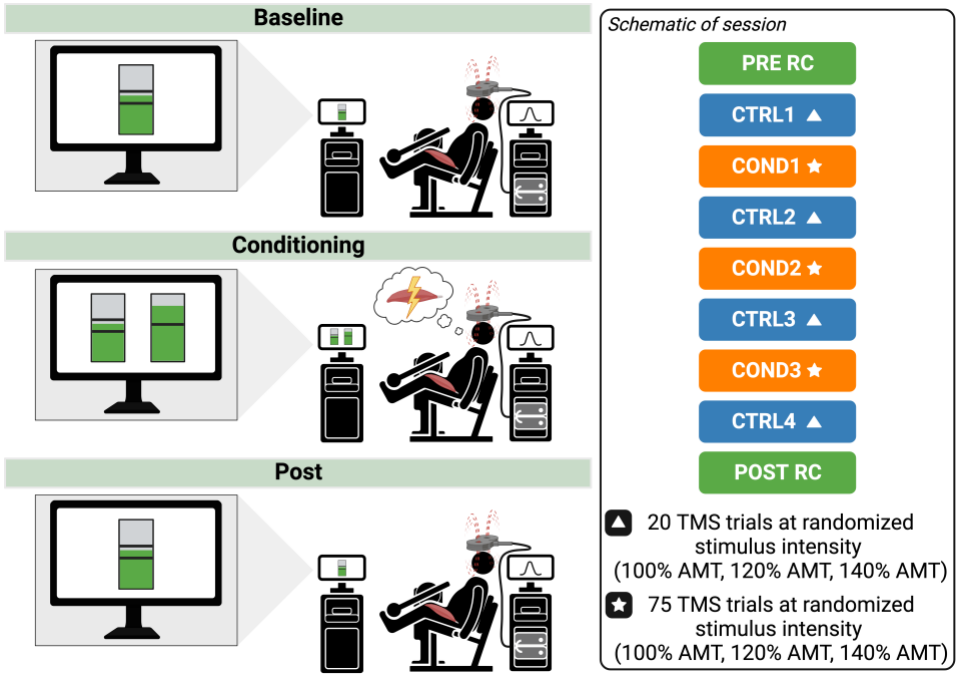

Figure 5.1 A schematic of the experimental protocol. *Abbreviations:* MVIC, maximum voluntary isometric contraction; RC, recruitment curve; CTRL1, control block 1; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; TMS, transcranial magnetic stimulation; AMT, active motor threshold.

5.2.3 Experimental Protocol

During the operant conditioning intervention, participants were trained to increase the MEP_{TORQUE} of the quadriceps muscle on the reconstructed leg during a single session. Participants were seated and secured into an isokinetic dynamometer (Humac Norm, CSMi, Stoughton, USA) with the trunk and knee set to 85 and 60 degrees of flexion, respectively. While secured into the dynamometer, a 110-mm diameter double-cone coil connected to a Magstim 200^2 stimulator (Magstim Co Ltd, Whitland, UK) was used to elicit motor evoked torque (MEP_{TORQUE}) responses. The coil was positioned over the primary motor cortex on the hemisphere contralateral to the tested leg and oriented to induce a posterior to anterior current flow in the cortex. The point located 2.0 cm posterior and 2.0 cm lateral to the vertex of the skull was determined as the temporary quadriceps hotspot location and marked on a fabric cap.[33] The coil was systematically moved from this temporary location to identify the hotspot (i.e., the location over the skull that resulted in the largest and most consistent motor evoked torque response during a small background contraction (12 N-m for females, 16 N-m for males)). Visual feedback was provided to participants to maintain a consistent background contraction (Figure 5.2). The hotspot location was marked on the fabric cap to ensure consistent coil placement during the session. The active motor threshold (AMT) was established as the minimum stimulus intensity needed to induce a motor evoked torque response in ≥ 50% of attempted trials (≥10 trials) using the relative-frequency method.[34, 35] The AMT was used to establish the stimulus intensity during the control (CTRL) and conditioning (COND) blocks.

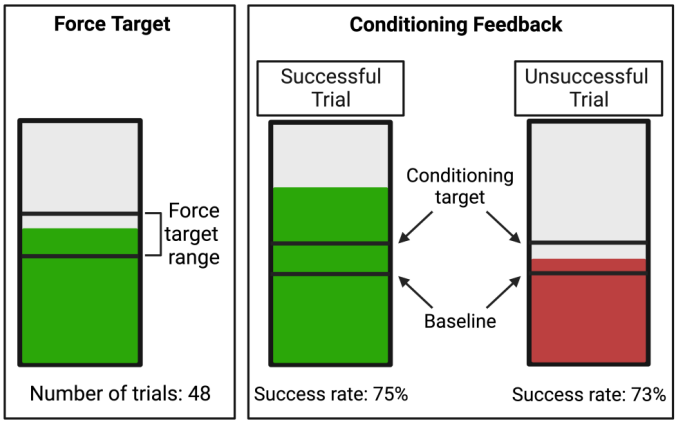

Figure 5.2 On the left is a schematic indicating visual feedback for a small background contraction (12 N-m for females, 16 N-m for males), which was shown for both the control and conditioning blocks. The participant's torque output is indicated by the green bar, which must stay within the force target range. Below the force target, participants can see the number of completed trials. On the right is a schematic illustrating visual feedback of a successful or unsuccessful trial provided to participants during the conditioning blocks. The conditioning bar will turn green when the most recent training trial successfully increased the MEP_{TORQUE} (i.e., MEP_{TORQUE} greater than the conditioning target). The conditioning bar will turn red when the most recent training trial was unsuccessful in increasing the MEP_{TORQUE}. Below the feedback bar, participants can see their current success rate, which updates after each conditioning trial and resets at the start of each conditioning block. *Abbreviations*: MEP_{TORQUE}, motor evoked torque; N-m, Newton-meters.

Once the hotspot location and AMT were established, we performed a baseline TMS recruitment curve (PRE) that was recorded at 8 different intensities (70%-140% AMT). Immediately after, we collected a baseline control block of 20 TMS trials as has been done previously.[24, 36] The baseline control block (CTRL1) was used to determine the participant's baseline corticospinal excitability and to calculate the initial criterion value (i.e., the 50th percentile value of the motor evoked torque responses from the 20 control trials) for the subsequent conditioning block. During the control block, participants were instructed to focus on sustaining a consistent background contraction as previously described and received a TMS pulse to the contralateral at the assigned stimulus intensity (100% AMT, 120% AMT, or 140% AMT) when the contraction was sustained. No feedback regarding performance was provided to participants during the control blocks.

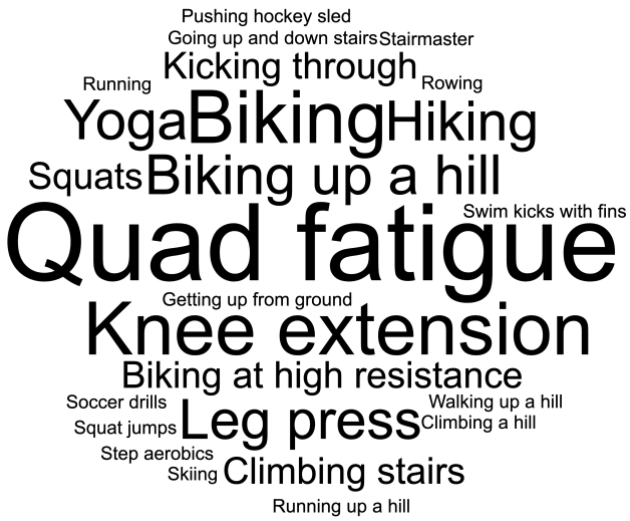

Figure 5.3 Wordcloud depicting the motor imagery visualizations used by participants during up-conditioning procedures. Words with a larger font size correspond to visualizations that were more frequently used by participants, while words with a smaller font size were less frequently used.

Following the baseline control block, a block of 75 conditioning trials was collected. The conditioning block was similar to the control block, except the participant was instructed to use motor imagery to try and train the corticospinal pathways to increase the motor evoked torque responses above the criterion value. Examples were given such as the quadriceps feeling a "burn" or imagining the contraction of the quadriceps when doing exercises (e.g., leg presses, squatting, etc.) or performing an exercise action (e.g., walking up a hill or cycling with high resistance). Motor imagery visualizations utilized by participants are represented in Figure 5.3. The initial criterion value for the first conditioning training block (COND1) was established as the 50th percentile value of the participant's MEP$_{TORQUE}$ during the control block. The participant's performance during the preceding block was used to dynamically establish the criterion value for the subsequent training blocks. The criterion value was established such that if MEP$_{TORQUE}$ amplitudes during the current block were similar to the MEP$_{TORQUE}$ amplitudes during the preceding training block, ~50% of the trials would be successful (i.e., above the criterion value).[24, 37] Participants received visual feedback regarding their performance on each

trial, indicating whether participants were successful at increasing the motor evoked torque responses above the criterion value. The feedback bar increased and turned green if successful or decreased and turned red if unsuccessful (Figure 5.2). Participants also received dynamic feedback on the percentage of successful trials during the current conditioning block. The participant's goal during each conditioning block was to obtain a trial success rate ≥ 60% and earned a small monetary incentive to achieve this target (20 cents for each percentage greater than 60%). Researchers also provided verbal encouragement and positive verbal feedback during conditioning blocks.

A total of three conditioning blocks were performed (COND1, COND2, COND3) with the previously described procedures. Following each conditioning block, a control block was also collected to evaluate the effect of number of conditioning trials (CTRL2, CTRL3, CTRL4). After the final control block, a second TMS recruitment curve (POST) was performed to determine the acute adaptations in corticospinal excitability due to the operant conditioning intervention.

5.2.4 Data Management

Custom-written LabVIEW (National Instruments Corp., Austin, TX USA) programs were used to perform all data collection and analysis. Torque data and TMS synchronization pulses were sampled at 1000 Hz. Torque signals were low-pass filtered (10 Hz, 4th order) using a zero-lag digital Butterworth filter.[38] Torque data were segmented from 200 ms prior to the stimulation over a window of 500 ms for each of the stimulations. For each block, ensemble averages of the segmented torque data were used to construct an average torque curve. The magnitude of the MEP_{TORQUE} amplitude was computed as the peak twitch torque after accounting (i.e., subtracting) for the background contraction torque. The PRE and POST TMS recruitment curves

from 100% AMT to 140% AMT were also used to determine the area under the curve (AUC) of the MEP_{TORQUE} .

5.2.5 Statistical Analysis

Descriptive statistics were used to evaluate the distribution and variation of the outcome variable (i.e., within-session change in MEP_{TORQUE}). Graphical methods such as histograms, residual plots, and Q-Q plots were used to visually inspect the data. The assumption of normality for the outcome variable was confirmed using the Shapiro-Wilks test. A linear mixed model with block (CTRL1, COND1, COND2, COND3), group (100%, 120%, and 140% AMT), and block × group as fixed effects and subject as a random effect was used to determine if TKA individuals were able to successfully improve the MEP_{TORQUE} in a single session and if stimulus intensity affected the improvements in MEP_{TORQUE}. The MEP_{TORQUE} during the baseline control (CTRL1) and the conditioning blocks were used as the dependent variable and the MEP_{TORQUE} during the baseline control block (CTRL1) was used as a covariate in the model. A second linear mixed model with time (PRE, POST), group (100%, 120%, and 140% AMT), and time × group as fixed effects and subject as a random effect was used to determine if operant up-conditioning elicited significant increases in acute corticospinal excitability and whether stimulus intensity affected the corticospinal adaptations during a single session. For this model, the AUC of the MEP_{TORQUE} was used as the dependent variable. Finally, a separate linear mixed model with block (CTRL1, CTRL2, CTRL3, CTRL4), group (100%, 120%, and 140% AMT), and block × group as fixed effects and subject as a random effect was used to determine the effect of number of conditioning trials and stimulus intensity on the change in MEP_{TORQUE} during the session. The MEP_{TORQUE} during the control blocks were used as the dependent variable and the MEP_{TORQUE} during the baseline control block (CTRL1) was used as a covariate in the model. Post-hoc tests using a

Šidák correction were used when a significant main or interaction effect were observed. A significance level of alpha = 0.05 was used for all analyses.

5.3 Results

5.3.1 Changes in MEP_{TORQUE} During Conditioning and the Effect of Stimulus Intensity

Ensemble averaged data from a representative participant and group data on the ability to up-condition the quadriceps MEP_{TORQUE} is shown in Figure 5.4.

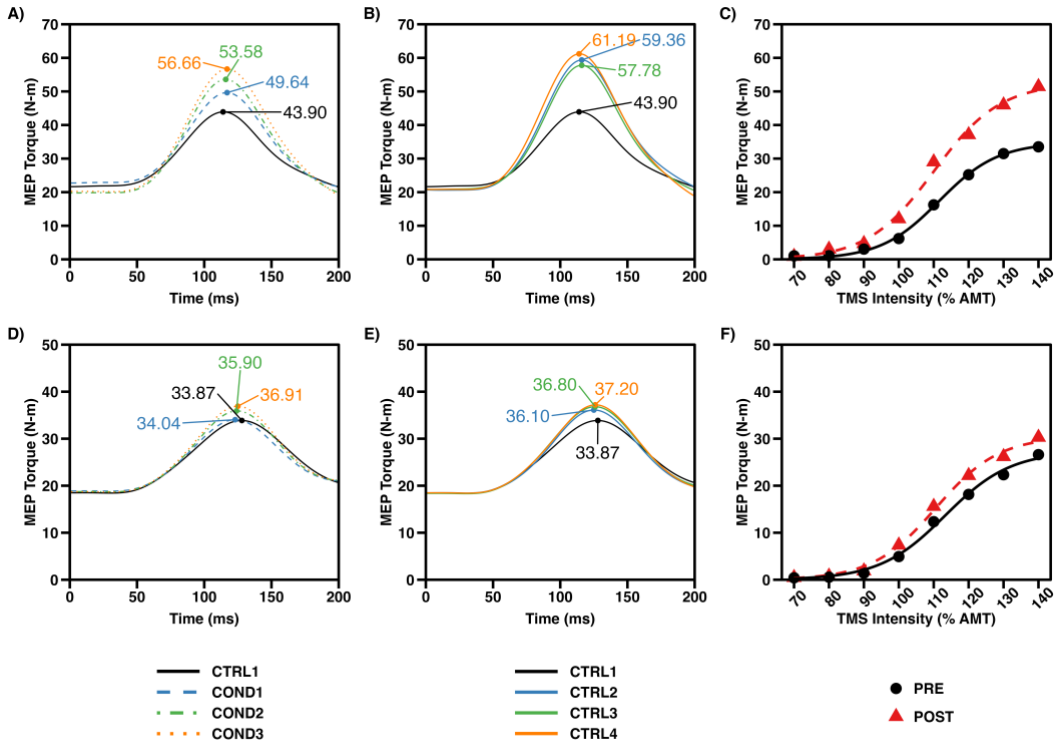

Figure 5.4 Ensemble averaged motor evoked torque (MEP_{TORQUE}) plots for a single subject (a-c) and for all participants (d-f). Data from a representative participant for a) ensemble averaged MEP_{TORQUE} for the baseline control block (CTRL1) and all three conditioning blocks (COND); b) ensemble averaged MEP_{TORQUE} for all four control blocks (CTRL); c) MEP_{TORQUE} recruitment curves prior to operant conditioning (PRE) and following operant conditioning (POST). Ensemble averaged group data are shown in panels d, e and f. *Abbreviations:* AMT, active motor threshold; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; CTRL1, baseline control block 1; CTRL2, control block 2; CTRL3, control block 3; CTRL4, MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; ms, milliseconds; PRE, prior to operant conditioning; POST, following operant conditioning; TMS, transcranial magnetic stimulation.

During conditioning, we detected a significant main effect of block ($F_{3,81} = 10.719$, $p < 0.001$) on the MEP_{TORQUE} amplitude (Figure 5.5). Post-hoc analysis demonstrated that MEP_{TORQUE} amplitude during COND2 and COND3 were significantly higher than CTRL1 ($p = 0.038$, $p = <0.001$, respectively, CTRL1[†]: 16.826 ± 0.627, COND2[†]: 18.524 ± 0.627, COND3[†]: 19.656 ± 0.627) while COND1 was not ($p = 0.823$, COND1[†]: 16.307 ± 0.627), indicating that the participants were able to successfully up-condition their corticospinal excitability and that the number of training trials affected this ability. During conditioning, we did not detect a significant effect of group (i.e., stimulus intensity) ($F_{2,26} = 0.021$, $p = 0.979$) or the interaction between block and group ($F_{6,81} = 0.710$, $p = 0.643$) (Figure 5.5).

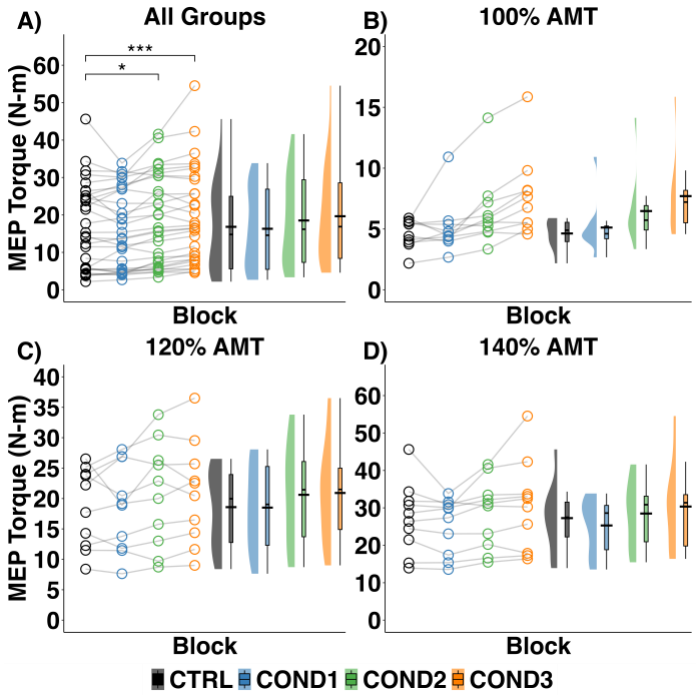

Figure 5.5 Raincloud plots depicting the distribution of the distribution of MEP_{TORQUE} during the baseline control block immediately before operant conditioning (CTRL1) and all three conditioning blocks (COND) for (a) all groups, (b) stimulus intensity group 100% AMT only, (c) stimulus intensity group 120% AMT only and (d) stimulus intensity group 140% AMT only. Open circles represent data points from each individual participant. Black horizontal lines represent the mean across all participants for each timepoint. *Abbreviations*: AMT, active motor threshold; COND1, conditioning block 1; COND2, conditioning block 2; COND3, conditioning block 3; CTRL1, control block 1; MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; *, $p < 0.05$, ***, $p < 0.001$.

[†] Reported as mean ± pooled standard error of the mean

5.3.2 Acute Changes in Corticospinal Excitability and the Effect of Stimulus Intensity and Number of Training Trials

We detected a significant main effect of time on the MEP_{TORQUE} AUC ($F_{1,27} = 20.029$, $p<0.001$). Post-hoc analysis revealed that MEP_{TORQUE} AUC increased following the intervention compared to prior to the intervention ($p <0.001$; PRE[†]: 685.888 ± 51.076, POST[†]: 827.387 ± 51.076), indicating that operant up-conditioning of MEP_{TORQUE} resulted in acute corticospinal adaptions in individuals with TKA (Figure 5.6). However, we did not detect a significant effect of group (i.e., stimulus intensity) ($F_{2,27} = 0.935$, $p = 0.405$) or the interaction between group and time ($F_{2,27} = 1.769$, $p = 0.190$) (Figure 5.6).

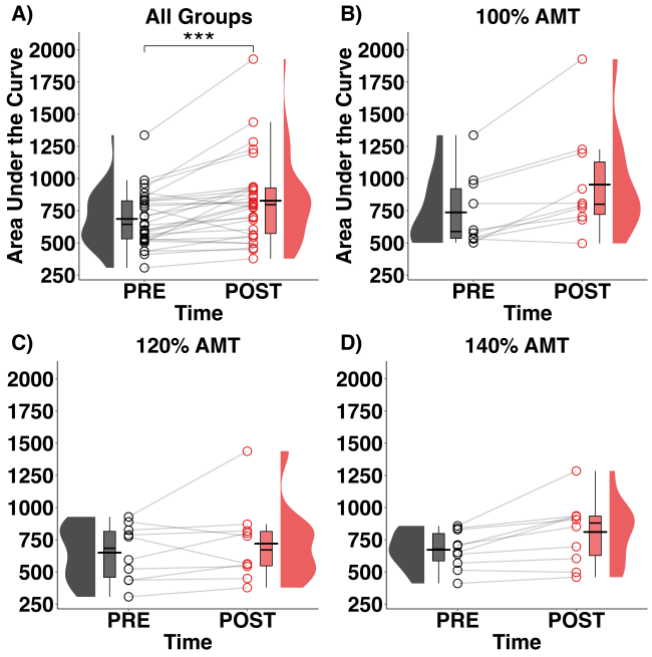

Figure 5.6 Raincloud plots depicting the distribution of area under the curve of MEP_{TORQUE} prior to up-conditioning procedures (PRE) and immediately after up-conditioning procedures (POST) for (a) all groups, (b) stimulus intensity group 100% AMT only, (c) stimulus intensity group 120% AMT only and (d) stimulus intensity group 140% AMT only. Open circles represent data points from each individual participant. Black horizontal lines represent the mean across all participants for each timepoint. *Abbreviations*: AMT, active motor threshold; MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; PRE, prior to operant conditioning; POST, following operant conditioning; ***, $p <$ 0.001.

[†] Reported as mean ± pooled standard error of the mean

During the control blocks, we detected a significant main effect of block ($F_{3,81} = 4.379$, $p = 0.007$) on the MEP_{TORQUE} amplitude (Figure 5.7). Post-hoc analysis revealed that MEP_{TORQUE} amplitude during CTRL3 and CTRL4 were significantly higher than CTRL1 ($p = 0.008$, $p = 0.006$, respectively, CTRL1[†]: 16.826 ± 0.865, CTRL3[†]: 20.194 ± 0.865, CTRL4[†]: 20.270 ± 0.865) while CTRL2 was not ($p = 0.112$, CTRL2[†]: 19.104 ± 0.865), indicating that the acute neural adaptations due to operant conditioning were dependent on the number of training trials used in the training. In addition, we did not detect a significant effect of group (i.e., stimulus intensity) ($F_{2,26} = 0.084$, $p = 0.920$) or the interaction between block and group ($F_{6,81} = 0.607$, $p = 0.724$) (Figure 5.7).

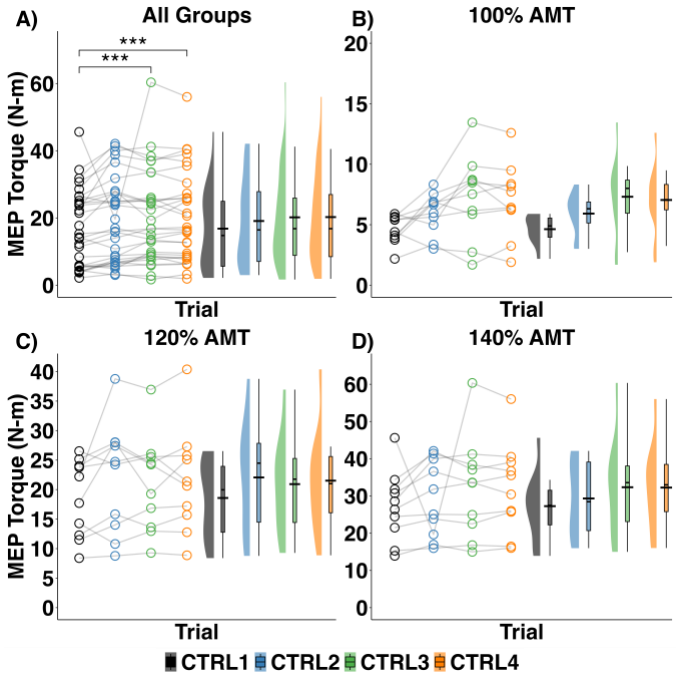

Figure 5.7 Raincloud plots depicting the distribution of the distribution of MEP_{TORQUE} during the baseline control block immediately before operant conditioning (CTRL1) and after each conditioning block (CTRL2, CTRL3, CTRL4) for (a) all groups, (b) stimulus intensity group 100% AMT only, (c) stimulus intensity group 120% AMT only and (d) stimulus intensity group 140% AMT only. Open circles represent data points from each individual participant. Black horizontal lines represent the mean across all participants for each timepoint. *Abbreviations*: AMT, active motor threshold; CTRL1, control block 1; CTRL1, control block 1; CTRL2, control block 2; CTRL3, control block 3; CTRL4, control block 4; MEP_{TORQUE}, motor evoked torque; N-m, newton-meters; *, $p < 0.05$; ***, $p < 0.001$.

[†] Reported as mean ± pooled standard error of the mean

5.4 Discussion

The purpose of this study was to determine 1) if a single session of operant up-conditioning of the corticospinal pathway in individuals with TKA could elicit improvements in corticospinal excitability and induce acute adaptations in corticospinal pathways and 2) whether the number of training trials and the stimulus intensity used during up-conditioning influenced these changes in individuals with total knee arthroplasty. In agreement with our hypothesis, we found that individuals with TKA were able to improve their quadriceps corticospinal excitability within a single session of operant up-conditioning, which were paralleled by acute neural adaptations of the corticospinal pathway. In addition, as hypothesized, these changes were influenced by the number of training trials but not by the stimulus intensity used during training. Collectively, these findings suggest that operant conditioning of the quadriceps MEP_{TORQUE} is a feasible approach to improve corticospinal excitability in individuals with total knee arthroplasty, regardless of the stimulus intensity used. However, at least 150 training trials are need to induce acute neural adaptations.

An important finding of this study was that quadriceps MEP_{TORQUE} increased during the conditioning blocks compared to the control block. This finding indicates that individuals with TKA can successfully up-condition their corticospinal responses within a single session of operant conditioning. This finding is particularly encouraging, considering that individuals with TKA are typically older than other patient populations with quadriceps dysfunction (e.g., ACL injury or surgery, meniscus injury, etc.), and that older adults typically have difficulty in learning a cognitively demanding tasks such as operant conditioning of motor evoked responses. Although the majority of participants in our study were able to successfully up-condition in a single session, there were some participants who were unable to up-condition (~37%). In fact, it

is not uncommon for a subset of participants to not successfully improve their neural responses in a single session[24, 26] or after multiple conditioning sessions.[23, 36, 37] Given the consistent reports that some participants are unable to up-condition, it is important to better understand the underlying reasons for this issue to improve the efficacy of operant conditioning paradigms.

Another key finding from this study was that individuals with TKA demonstrated acute improvements in corticospinal excitability (i.e., aftereffects) following a single session of operant conditioning. This is the first study to demonstrate acute corticospinal adaptations in individuals with TKA following up-conditioning. Our findings are consistent with recent evidence reporting healthy females were able to successfully increase their H-reflex responses within a single session of operant conditioning.[26] A growing body of evidence demonstrates that operant conditioning interventions have the potential to improve muscle strength and gait biomechanics,[24, 25, 39] which are known to be affected following total knee arthroplasty.[40-42] Notably, these alterations in quadriceps strength and gait biomechanics may persist well after surgery,[41-43] suggesting current standard of care is inadequate to fully restore motor function after surgery. Therefore, long-term operant conditioning interventions that target the motor evoked torque may be a promising supplement to rehabilitation following total knee arthroplasty.

When evaluating whether the ability to up-condition the corticospinal pathways is dependent on the stimulus intensity used during training, we found that TMS stimulus intensity did not influence the ability to improve the quadriceps MEP_{TORQUE} in a single session. This finding is consistent with a previous study from our lab where we found that stimulus intensity had no effect on the ability to up-condition the quadriceps MEP_{TORQUE} in individuals with ACL reconstruction (Chapter 3). Together, these findings suggest that other factors are more likely to influence the ability to up-condition the quadriceps MEP_{TORQUE}. Recent research suggests

baseline levels of excitability appear to be a significant predictor of how successful an individual is at up-conditioning, with higher baseline values corresponding to greater up-conditioning.[26] An exploratory analysis of our data also found that baseline excitability (i.e., AUC of the MEP_{TORQUE} at PRE) was a significant predictor of the percent change in MEP_{TORQUE} during conditioning in our data ($R^2 = 0.172$, $p = 0.023$), but to a lesser extent than previously reported findings ($R^2 = 0.605$, $p < 0.001$).[26] The greater number of training trials performed in our data (225 trials) may explain the diminished contribution of baseline excitability on the ability to up-condition in our data as the previous study had participants perform 100 to 150 trials.[26] It is plausible that baseline excitability plays a greater role on the ability to up-condition initially, but has a diminished role when a greater number of training trials are performed due to additional motor imagery practice. In addition, differences in our participants (healthy female vs TKA) and the outcome variable studied (soleus H-reflex vs quadriceps MEP_{TORQUE}) may explain the diminished contribution of baseline excitability on the ability to up-condition in our data. However, it cannot be established what role individual differences may play in the ability to up-condition after TKA. Future work examining the influence of other factors such as individual differences (e.g., age, activity level, motor imagery ability) or other dosage parameters would inform the development of effective operant conditioning paradigms following TKA.

When considering the role of stimulus intensity, we found that TMS stimulus intensity did not influence the acute adaptations (i.e., aftereffects) in corticospinal excitability prior to and following the intervention. It is not surprising that stimulus intensity did not influence the acute changes in corticospinal excitability during a single session as this is consistent with our finding that stimulus intensity did not influence the ability to up-condition, as well as our research with ACL reconstructed individuals (Chapter 3). Taken together with our up-conditioning findings, it

is clear that a participant's ability to up-condition is critical in order to maximize the potential benefits of operant conditioning. Future investigation of the factors that influence a participant's ability to up-condition would provide valuable insight for developing effective operant conditioning protocols. Nevertheless, this study establishes that operant conditioning protocols for individuals with TKA may effectively use any of the three stimulus intensities studied, although 120% AMT appears to be a good compromise between variability (i.e., signal-to-noise) and participant discomfort.

When evaluating whether acute neural adaptations were influenced by the number of training trials used during the session, we found that acute improvements were observed following 150 conditioning trials, but there were no further increases for the remainder of the session. This finding is surprising as one would expect that the additional increase in MEP_{TORQUE} observed during the final conditioning block would correspond to a greater increase in the neural adaptations after the final block (i.e., during CTRL4 and POST AUC). The diminishing returns for acute neural adaptations suggests there may be a "ceiling effect", after which additional conditioning trials may not elicit further acute adaptations within a single session. In addition, it is plausible that other parameters for the number of conditioning trials that were not studied herein (e.g., 100 or 200 trials) may induce even greater acute neural adaptations than those observed in the current study. Regardless, the clinical implication of this finding suggests that 150 and 225 conditioning trials both appear to be sufficient to elicit acute neural adaptations in individuals with TKA. However, using 150 conditioning trials would increase the feasibility of operant conditioning in a clinical setting. Future investigations are needed to establish whether 150 conditioning trials are sufficient to elicit consistent up-conditioning effects across a greater number of training sessions and induce long-term neural adaptations following TKA.

5.5 Limitations

There are some potential limitations to the current study that warrant consideration. First, we examined the influence of stimulus intensity on the ability to improve the quadriceps MEP_{TORQUE} during a single session. Although we found that stimulus intensity does not appear to influence the ability to up-condition or its aftereffects, it is possible that cumulative effects due to multiple training sessions could reveal stimulus intensity as an influential factor in the ability to up-condition. In addition, we cannot comment whether stimulus intensities that were not tested in the current study (e.g., > 140% AMT) may influence the ability to improve the MEP_{TORQUE} after total knee arthroplasty as we only tested three intensities (100%, 120%, and 140% of AMT). Lastly, muscle fatigue may have influenced the increase in quadriceps MEP_{TORQUE} demonstrated during the conditioning blocks compared to the control block. However, we believe that fatigue did not confound our analysis as our previous work in individuals with knee surgery indicate that mild fatigue does not result in an increase in MEP_{TORQUE}. Hence, the improvements in corticospinal excitability during the session were more likely due to the motor imagery practice during operant conditioning.

5.6 Conclusion

In summary, we found that individuals with TKA were able to successfully up-condition the quadriceps MEP_{TORQUE} within a single training session of operant conditioning, which were paralleled by acute neural adaptations in the corticospinal pathway. However, the stimulus intensity used during training did not influence the capacity to improve the quadriceps MEP_{TORQUE} or the acute changes in corticospinal excitability observed. In addition, the number of trials performed influenced the ability to up-condition and the associated neural adaptations. Together, these findings reveal that operant conditioning of the MEP_{TORQUE} may be a feasible

approach for improving corticospinal excitability after TKA. While any of the three stimulus intensities tested could be used, we recommend using a low or moderate stimulus intensity (i.e., 100 to 120% AMT) and 150 training trials during operant conditioning paradigms in individuals with TKA.

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Chapter 6 Summary and Future Directions

6.1 Summary

This dissertation presents a body of work investigating the feasibility and effect of the dosage parameters used during operant conditioning on the ability to improve corticospinal excitability following knee surgery, as well as the effect of operant conditioning on quadriceps function after ACL reconstruction.

In Chapter 2, we evaluated the reliability of raw and normalized quadriceps motor evoked responses using torque (MEP_{TORQUE}) and electromyography (MEP_{EMG}) following ACL reconstruction. We found that raw and normalized MEP_{TORQUE} and MEP_{EMG} demonstrated good reliability in individuals with ACL reconstruction. Notably, MEP_{TORQUE} generally demonstrated greater reliability than MEP_{EMG}, regardless of the normalization method. Thus, we established MEP_{TORQUE} as a suitable alternative to MEP_{EMG} for evaluating quadriceps corticospinal excitability following knee surgery. Accordingly, we used MEP_{TORQUE} as the target variable for upregulating quadriceps corticospinal excitability in Chapters 3, 4, and 5.

In Chapter 3, we tested the ability of ACL reconstructed individuals to improve their corticospinal excitability and whether stimulus intensity influenced this ability and its associated neural adaptations during a single session of operant conditioning. We found that individuals with ACL reconstruction were able to successfully upregulate their corticospinal excitability during a single session and induced short-term neural adaptations. However, the ability to improve corticospinal excitability and the associated neural adaptations were not influenced by

the stimulus intensity used during training. Thus, we established the feasibility of operant conditioning to improve corticospinal excitability after ACL reconstruction and provided preliminary support for the short-term intervention studied in Chapter 4. This study also provided insight into training dosage parameters (i.e., the stimulus intensity used during training) as any of the three stimulus intensities studied were found to be sufficient to be used in future interventions.

In Chapter 4, we tested the effect of multiple operant up-conditioning training sessions on the ability to increase corticospinal excitability and its effect on quadriceps strength and voluntary activation in individuals with ACL reconstruction. We found that individuals in the conditioning group were able to successfully upregulate quadriceps corticospinal excitability, while those in the sham-conditioning group did not improve. We also found that quadriceps strength and voluntary activation increased in the reconstructed leg for both groups. While this may indicate that operant conditioning training was not solely responsible for the improvements in quadriceps function, a long-term intervention with additional training sessions may increase the cumulative effects of operant conditioning.

In Chapter 5, we tested the ability of individuals with TKA to improve their corticospinal excitability within a single session of operant conditioning and the effect of stimulus intensity and number of trials on the changes in corticospinal excitability. We found that individuals with TKA were able to successfully improve their corticospinal excitability and induce short-term neural adaptations. However, stimulus intensity did not influence the ability to improve corticospinal excitability or its associated neural adaptations in individuals with TKA. We also found that the number of training trials affected the ability to up-condition and induce neural adaptations as 150 and 225 training trials were adequate to elicit changes in these outcomes

while 75 trials were not. Thus, our findings support operant conditioning as a feasible intervention capable of improving quadriceps corticospinal excitability after TKA. This study also provided additional evidence that any of the three stimulus intensities studied can be effectively used in future interventions. Notably, our findings also suggest that a fewer number of trials can be performed with similar effects, which may improve the feasibility of operant conditioning after TKA in a clinical setting.

In summary, we have investigated whether individuals can successfully improve their corticospinal excitability following ACL reconstruction and TKA, the optimal dosage for operant conditioning of quadriceps MEP_{TORQUE}, and the effects of operant conditioning on quadriceps function. Although our findings provide preliminary support for operant conditioning after ACL reconstruction and TKA, there are several areas of research that warrant further investigation to expand upon this dissertation.

6.2 Future Directions

First, our work in Chapters 3 and 5 evaluated the effect of dosage parameters (i.e., stimulus intensity and number of training trials) on the ability to up-condition and its associated short-term neural adaptations in a single-session. One limitation with this approach is that our findings may differ when a greater number of training session are completed due to cumulative effects. It is plausible that these cumulative effects may lead to stimulus intensity having a greater influence on the ability to up-condition and its associated acute neural adaptations. In addition, greater cumulative effects with additional training sessions may reveal that even fewer training trials are needed to up-condition than our findings suggest. Future work should investigate whether the optimal dosage parameters determined for a single session of operant conditioning would be the most effective parameters when completing a longer-term

intervention. This work would inform the design and implementation of future interventions to ensure operant conditioning interventions are effective and clinically feasible.

Second, we tested the ability of individuals to improve corticospinal excitability, but not all participants that received training were successful. For example, 28% of the individuals with ACL reconstruction and 37% of the individuals with TKA were unable to improve their corticospinal excitability during a single session of operant conditioning. Although this observation is consistent with previous operant conditioning interventions, it is unknown why some individuals were unable to successfully improve their corticospinal excitability. While we believe additional training sessions would improve the success rate, this must be corroborated by long-term investigation. In addition, incorporating other techniques that can improve an individual's motor imagery ability may result in greater success rates and larger changes in corticospinal excitability during operant conditioning. For example, providing tactile sensations such as vibration over the quadriceps muscle (i.e., sensory priming) or showing video examples of people contracting their quadriceps (i.e., action observation) involve techniques frequently used in neurorehabilitation interventions and may improve corticospinal excitability.[1-3] Future work investigating whether these techniques can enhance an individual's ability to improve their corticospinal excitability would reveal strategies that could be used to improve operant conditioning interventions.

Third, we tested the effect of operant conditioning on corticospinal excitability and quadriceps function while participants were seated in a dynamometer, which may not translate to dynamic tasks such as walking. However, research suggests seated operant conditioning protocols can improve lower-extremity kinematics and muscle activity during walking in individuals with spinal cord injury.[4] Hence, it is plausible that operant conditioning of the

corticospinal pathways could improve knee biomechanics during walking in ACL reconstructed individuals. However, clinical interventions are necessary to establish whether operant conditioning could be a valuable approach to restoring gait biomechanics after ACL reconstruction.

Lastly, this dissertation investigated the effects of operant conditioning with a limited number of sessions and thus we cannot confirm if our findings would be similar after a longer-term intervention. For example, we established that a single session of operant conditioning can induce short-term neural adaptations. However, it is unknown whether a longer-term operant conditioning training intervention can induce long-term neural adaptations. While our findings in Chapter 4 suggest that quadriceps contractions improved quadriceps function and not the operant conditioning training itself, this may differ following a long-term intervention. Therefore, future research examining longer-term operant conditioning interventions should also explore whether additional training sessions could generate improvements in quadriceps function.

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Appendices

Appendix A: Literature Review For Isometric Strength Following ACL Reconstruction

Table A.1 Review of the literature for isometric strength following ACL reconstruction. *Abbreviations*: *NE* not evaluated, *NA* not applicable, *NR* not report, *HT* hamstrings graft, *PT* patellar tendon graft, *IKDC* International Knee Documentation Committee Questionnaire, *ACL* anterior cruciate ligament, *LSI* Limb Symmetry Index.

PMID	Participant Population	Angle of Testing, degrees	n	Sex, M/F	Age, years	Graft Type	Physical Activity Levels	Time Since surgery	MVC Isometric (Nm/kg)			MVIC Isometric LSI (%)	
									Involved	Uninvolved	Control	ACL LSI	Control LSI
26633588	General population, HT reconstruction	60	24	24/0	28.1	HT	NR	1 mo	1.47 ± 0.62	2.6 ± 0.63;	NA	NR	NA
26633588	General population, HT reconstruction	60	24	24/0	28.1	HT	NR	2 mo	2.18 ± 0.65	2.88 ± 0.73;	NA	NR	NA
26633588	General population, HT reconstruction	60	24	24/0	28.1	HT	NR	3 mo	2.61 ± 0.67	3.14 ± 0.64	NA	NR	NA
25112209	Competitive athletes	45	20	20/0	24.2	PT	NA	4 mo	NA	NA	NA	66 ± 13	NA
25112209	Competitive athletes	45	20	20/0	24.2	PT	NA	6 mo	NA	NA	NA	74 ± 13	NA
25693627	Healthy university/ high school	90	20	9/11	20.9	PT/HT	Tegner (pre-surgery): 6.2	6 mo	2.58 ± 0.69	2.79 ± 0.82	3.53 ± 0.93	NR	NR

							Tegner (6 months): NR						
25683732	Orthopaedic clinic	90	20	7M/13 F	20.65	PT	Tegner: 5.90	7.0 mo	2.03 ± 0.51	2.89 ± 0.81	NA	NR	NA
25315083	Orthopaedic clinic	90	54	23/31	19.9	PT	Tegner: 6.0, IKDC: IKDC=80.4	7.24 mo	2.2 ± 0.6	3.2 ± 5.8	NA	72.2±18.5	NA
26471854	Orthopaedic clinic	90	52	32/20	20.7	PT	IKDC: 80.9	7.4 mo	1.55±0.56	NR	NA	72.77 ± 16.78	NA
28290752	Healthy	90	4	2/2	27.4	HT	Tegner: 5.0	7.4 mo	1.95 ± 0.43	2.92 ± 0.8	NA	66.8	NA
29652169	Orthopaedic clinic	60	67	43/24	21.34	PT	Tegner: 6.38	7.52 mo	2.34 ± 0.68	3.24 ± 0.72	3.14 ± 0.93	71.97 ± 16.47	95.44 ± 6.91
26471851	Recreationally active	90	17	10/7	21.41	PT/HT	Tegner: 7.0	7-10 mo	2.03 ± 0.57	2.88 ± 0.73	2.63 ± 0.92	NA	NA
26183172	Returning to preinjury participation in pivoting or cutting	60	139	49/90	16.7	HT/PT/ Allograft	NR	8.2 mo	2.3 ± 0.5	2.6 ± 0.5	NA	88.7 ± 17.5	NA
29893603	Orthopaedic clinic, university, community	90	34	20/14	22.5	HT/PT/ Allograft	6.1	9.0 mo	1.9 ± 0.6	2.6 ± 0.7	2.7 ± 0.6	NR	NR

27257127	Orthopaedic clinic	60	15	0/15	18.2	NR	50 h of pivoting/ cutting sports per week	9.2 mo	1.55 ± 0.50	1.88 ± 0.27	1.88 ± 0.46	81.5 ± 17.6	NR
23034645	Participated in sports with high level of joint loading	65	10	NR	28	HT	NE	12 mo	2.32 ± 0.56	2.75 ± 0.57	NA	NR	NA
24824771	Elite athletes	70	8	3/5	F: 24.2 M: 28.3	HT/Allograft	NE	25 mo	3.44 ± 0.63	4.43 ± 0.98	4.09 ± 0.52	NA	NA
23835518	Orthopaedic department, patient	90	23	23/0	27.2	HT	MET Score: 37.7	26.5 mo	2.54 ± 0.65	2.76 ± 0.56	2.92 ± 0.55	91.84 ± 15.9	NA
29667429	Orthopaedic clinic	90	20	9/11	20.9	PT/HT	IKDC: 77.1 ± 17.9	28.3 mo	2.55 ± 0.66	2.77 ± 0.81	NA	81.1 ± 14.2	NA
21246615	Recreationally active	90	15	0/15	24.73	NR	Tegner: 5.73	2-14 yr	3.67 ± 0.66	3.94 ± 0.73	4.09 ± 1.02	NA	NA
25203517	Recreationally active	90	22	12/10	22.5	HT/BTB	Tegner: 6.4	31.5 mo	2.46 ± 0.83	NR	2.72 ± 0.49	0.85 ± 0.21	0.97 ± 0.14
25978101	Recreationally active	90	22	12/10	22.5	HT, PT	Tegner: 6.3	31.5 mo	2.50 ± 0.84	2.92 ± 0.65	2.84 ± 0.54	NR	NA
25622244	University, recreationally active	90	22	12/10	22.5	HT/PT	Tegner: 6.4	31.5 mo	3.07 ± 1.03	3.59 ± 0.80	3.56 ± 0.73	0.85 ± 0.21	0.97 ± 0.14

31897518	General population	90	16	8/8	20.4	PT/HT/Allograft/Repair	Tegner (pre): 9.3 Tegner (current): 7.5	33.9 mo	2.37 ± 0.52	2.80 ± 0.59	2.58 ± 0.47	NA	NA
26720104	Recreationally active	90	53	27/26	23.4	NR	Exercise 3-5x/week, Tegner: 6.8	44.1 mo	2.23 ± 0.76	NE	2.57 ± 0.76	NE	NE
23307572	Recreationally active	60	26	13/13	24.2	PT/HT/Allograft	Exercise at least 3x/week for 30 mins	44.7 mo	2.59 ± 0.68	NA	3.35 ± 0.84	NA	NA
25994515	Recreationally active	60	32	18M/14F	24.1	NR	NR	45.1 mo	2.23 ± 0.76	NA	2.6 ± 0.8	NA	NA
25844855	University community	90	28	9/19	21.28	HT/PT/Allograft	Tegner: 5.92	48.1 mo	2.68 ± 0.78	NE	3.13 ± 1.07	NE	NE
24618459	University community	90	29	9/20	21.2	PT/HT/Allograft	Tegner: 5.9	48.2 mo	2.67 ± 0.76	2.79 ± 0.78	3.13 ± 1.06	NA	NA

27128669	Physically active 30 min 3 times per week	90	39	11/28	22	PT/HT/ Allograft	IKDC: 86.5	49 mo	2.72 ± 0.62	2.94 ± 0.59	NA	NR	NA
28511105	Recreationally active	90	39	12/27	21.84	PT/HT	Tegner: 7.15	49.43 mo	2.83 ± 0.61	3.05 ± 0.62	NA	NR	NA
31951147	Recreationally active	45	42	22/20	21.8	PT/HT/ Allograft	Tegner: 7.0	50.5 mo	2.31	2.34	2.59	NA	NA
28388231	Recreationally active	90	20	6/14	21.1	HT/PT/ Allograft	Tegner: 7.1	50.7 mo	1.86 ± 0.74	2.50 (SD not reported)	2.56 ± 0.37	NR	NR
29350554	General population	90	28	7/21	22.4	NA	Tegner: 7.3	52 mo	2.9 ± 0.6	3.1 ± 0.6	NA	NA	NA
30852644	Orthopaedic clinic and university community	90	11	5/6	22.6	PT/HT	Tegner: 7.9	69.4 mo	2.95 ± 0.56	3.27 ± 0.7	3.52 ± 0.61	NA	NA
29893603	Orthopaedic clinic, university, community	90	30	10/20	24.9	HT/PT/ Allograft	6.9	70.5 mo	2.2 ± 0.6	2.3 ± 0.6	2.7 ± 0.6	NR	NR
24145725	Physically active (150 min of moderate exercise or 60 min of vigorous exercise per week)	90	8	7/1	24.8	NR	Tegner: 7.1	NR	2.85 ± 0.33	3.05 ± 0.48	4.18 ± 0.32	NR	NR

NE not evaluated, *NA* not applicable, *NR* not report, *HT* hamstrings graft, *PT* patellar tendon graft, *IKDC* International Knee Documentation Committee Questionnaire, *ACL* anterior cruciate ligament, *LSI* Limb Symmetry Index

Appendix B: Literature Review for Isokinetic Strength Less Than One Year After ACL Reconstruction

Table B.1 Review of the literature for isokinetic strength less than one year after ACL reconstruction. *Abbreviations*: *NE* not evaluated, *NA* not applicable, *NR* not report, *HT* hamstrings graft, *PT* patellar tendon graft, *IKDC* International Knee Documentation Committee Questionnaire, *ACL* anterior cruciate ligament, *LSI* Limb Symmetry Index.

ID	Participant Population	n	Sex, M/F	Age, years	Graft Type	Physical Activity Levels	Time since surgery	Velocity of Testing, deg/s	MVC Isokinetic (Nm/kg)			MVIC Isokinetic LSI (%)	
									Involved	Uninvolved	Control	ACL LSI	Control LSI
12942198	General population	36	11/25	23.5	PT	NA	1 mo	60	NR	NR	NA	33.1	NA
DOI: 10.3233/IES-2004-0169	Orthopaedic clinic	67	NA	27.0	PT	NA	2 mo	180	NR	NR	NA	66	NA
							2 mo	240	NR	NR	NA	72	NA
26460100	General community	75	65/11	27.9	HT	Tegner (preinjury): 6.4	3 mo	60	1.79 ± 0.51	2.66 ± 0.44	2.91± 0.40	NR	NR
							3 mo	180	1.36 ± 0.36	1.86 ± 0.30	1.95 ± 0.33	NR	NR
30001937	Competitive athletes	24	NR	15.5	NR	NA	3 mo	60	1.1 ± 0.5	2.0 ± 0.6	2.0 ± 0.5	NR	NR

11914763	Athletes playing in competitive sports at regional or national levels or in active sports at least 3 times per week	80	52/28	28	HT	Tegner post-op: 6.5	3 mo	60	NR	NR	NA	77.2	NA
							3 mo	180	NR	NR	NA	84.8	NA
							3 mo	300	NR	NR	NA	87.9	NA
25026933	Orthopaedic clinic	28	14/14	19.6	PT/HT/All ograft	IKDC: 66.5	3 mo	60	1.4 ± 0.5	2.2 ± 0.4	2.2 ± 0.4	63.0 ± 19.3	86.6 ± 9.6
15098637	General population	76	66/10	24.9	HT	IKDC: A – 16 B – 22 C – 30 D – 8	3 mo	60	NR	NR	NA	66.1	NA
							3 mo	240	NR	NR	NA	77.9	NA

DOI: 10.3233/IES-2004-0169	Orthopaedic clinic	67	NR	27.0	PT	NA	4 mo	60	NR	NR	NA	67	NA
							4 mo	180	NR	NR	NA	76	NA
							4 mo	240	NR	NR	NA	80	NA
12860546	Orthopaedic clinic	62	PT: 23/8 HT: 24/10	PT: 25.8 HT: 26.3	PT/HT	Median IKDC PT: 80 Median IKDC HT: 75	4 mo	60	NR	NR	NA	PT: 63.7 ± 16.4 HT: 72.8 ± 20.1	NA
							4 mo	240	NR	NR	NA	PT: 66.9 ± 16.8 HT: 78.4 ± 23.2	NA

25112209	Competitive athletes	20	20/0	24.2	PT	Tegner: 5.2	4 mo	60	NR	NR	NA	57 ± 13	NA
							4 mo	180	NR	NR	NA	67 ± 13	NA
30276020	Competitive athletes and recreationally active	7	7/0	23.0	HT	NE	5 mo	60	2.80	NA	3.43	NA	NA
							5 mo	120	2.31	NA	2.94	NA	NA
							5 mo	300	1.22	NA	1.27	NA	NA
16226644	General population	9	5/4	28	HT	No more than recreational athletes and none involved in competitive sports	6 mo	60	NR	NR	NA	68	NA
							6 mo	180	NR	NR	NA	87	NA
DOI: 10.3233/IES-2004-0169	Orthopaedic clinic	67	NR	27.0	PT	NE	6 mo	60	NR	NR	NA	75	NA
							6 mo	180	NR	NR	NA	83	NA

							6 mo	240	NR	NR	NA	88	NA
26460100	General community	75	65/11	27.9	HT	Tegner (preinjury): 6.4	6 mo	60	2.24 ± 0.59	2.66 ± 0.44	2.91± 0.40	NR	NR
							6 mo	180	1.60 ± 0.37	1.91 ± 0.31	1.95 ± 0.33	NR	NR
11914763/	Athletes playing in competitive sports at regional or national levels or in active sports at least 3 times per week	80	52/28	28	HT	Tegner post-op: 6.5	6 mo	60	NR	NR	NA	84.4	NA
							6 mo	180	NR	NR	NA	85.3	NA
							6 mo	300	NR	NR	NA	94.7	NA
10810475	General population	31	22/9	27	PT	NA	6 mo	60	NR	NR	NA	71.4	NA
							6 mo	120	NR	NR	NA	77.4	NA

11706731	General population	31	22/9	27	HT	NA	6 mo	60	NR	NR	NA	88.0	NA
							6 mo	120	NR	NR	NA	89.7	NA
25112209	Competitive athletes	20	20/0	24.2	PT	Tegner: 6.5	6 mo	60	NR	NR	NA	77 ± 17	NA
							6 mo	180	NR	NR	NA	77 ± 17	NA
12942198	General population	36	11/25	23.5	PT	NA	6 mo	60	NR	NR	NA	63.2	NA
							6 mo	180	NR	NR	NA	69.3	NA
15483539	General population	40	NA	28	PT	Final follow-up: Lysholm: 90	6 mo	60	NR	NR	NA	64 ± 15	NA
							6 mo	180	NR	NR	NA	74 ± 20	NA
15098637	General population	76	66/10	24.9	HT	IKDC: A – 29 B – 42 C – 5 D – 0	6 mo	60	NR	NR	NA	91.8	NA
							6 mo	240	NR	NR	NA	96.9	NA
11794266	General population	Total: 49	Total: 27/22	PT: 24.3	PT/HT	Tegner: PT: 3.6	6 mo	60	NR	NR	NA	PT: 59.5	NA

		PT: 17 HT: 32	PT: 10/7 HT: 17/15	HT: 24.6		HT: 4.0						± 19.6 HT: 62.4 ± 11.1 PT: 67.4 ±	
							6 mo	240	NR	NR	NA	18.6 HT: 74.8 ± 16.7	NA
10843124	Orthopaedic clinic	25	16/9	23.8	PT	NA	6 mo	60	NR	NR	NA	76	NA
							6 mo	240	NR	NR	NA	92	NA
21576712	General population	20	NA	29.3	HT	NA	6 mo	60	NR	NR	NA	79.9 ± 11.6	NA
							6 mo	180	NR	NR	NA	77.4 ± 15.5	NA

14530853	Collegiate or recreational athletes	14	7/7	24	PT	NE	6.5 mo	60	NR	NR	NA	74.9± 17.8	NA
30109947	Competitive athletes	118	118/0	23.6	PT	IKDC: 68.3	6.6 mo	60	2.00 ± 0.45	2.61 ± 0.45	2.61 ± 0.37	77.3 ± 13.6	103.6 ± 9.1
25899211	Community area	66	20/46	17.6	PT/HT/Allograft	IKDC: 85.8	6.7 mo	180	1.57 ± 0.30	NE	1.73 ± 0.29	NA	NA
23322072	Orthopaedic clinic	22	22/0	28.8	PT	Tegner (preinjury): 7.5 Tegner (at testing): 5.0	7.0 mo	120	1.87 ± 0.47	2.52 ± 0.42	2.47 ± 0.48	74.01	98.83
							7.0 mo	180	1.62 ± 0.40	2.10 ± 0.40	2.02 ± 0.39	74.13	98.95
							7.0 mo	300	1.28 ± 0.26	1.61 ± 0.29	1.56 ± 0.28	74.57	99.08
24067150	General population	15	8/7	20.2	PT	NE	7.1 mo	60	1.47	2.17	1.76	65.4	NR
30672626	Orthopaedic clinic	29	18/11	23.7	PT/HT	Tegner: 5.7	7.2 4 mo	90	1.6 ± 0.46	2.2 ± 0.46	NA	71.0 ± 16.0	NA
26471854	Orthopaedic clinic	52	32/20	20.7	PT	IKDC: 80.9	7.4 mo	60	1.55 ± 0.56	NR	NA	73.6 ± 23.5	NA

29652169	Orthopaedic clinic	67	43/24	21.34	PT	Tegner: 6.38	7.5 2 m o	60	1.43 ± 0.50	2.05 ± 0.57	2.28 ± 0.55	70.93 ± 22.54	100.92 ± 15.86
12860546	Orthopaedic clinic	57	PT: 23/8 HT: 24/10	PT: 25.8 HT: 26.3	PT/HT	Median IKDC PT: 80 Median IKDC HT: 75	8 mo	60	NR	NR	NA	PT: 74.5 ± 11.3 HT: 87.9 ± 13.7	NA
							8 mo	240	NR	NR	NA	PT: 75 ± 21.3 HT: 90.7 ± 28.2	NA
16377968	Orthopaedic clinic	153	99/54	PT: 33.7 QSGT: 31.3	HT/PT	Involved in only recreational activity	11 mo	180	NR	NR	NA	PT: 85.1 ± 9.2 HT: 88.2 ± 6.4	NA

						PT: 86.8 ± 7.7 HT: 87.5 ± 5.2	
	11 mo	300	NR	NR	NA		NA

NE not evaluated, *NA* not applicable, *NR* not report, *HT* hamstrings graft, *PT* patellar tendon graft, *IKDC* International Knee Documentation Committee Questionnaire, *ACL* anterior cruciate ligament, *LSI* Limb Symmetry Index

Appendix C: Literature Review for Isokinetic Strength At Least One Year After ACL Reconstruction

Table C.1 Review of the literature for isokinetic strength at least one year after ACL reconstruction. *Abbreviations*: *NE* not evaluated, *NA* not applicable, *NR* not report, *HT* hamstrings graft, *PT* patellar tendon graft, *IKDC* International Knee Documentation Committee Questionnaire, *ACL* anterior cruciate ligament, *LSI* Limb Symmetry Index.

PMID	Participant Population	n	Sex, M/F	Age, years	Graft Type	Physical Activity Levels	Time since surgery	Velocity of Testing, deg/s	MVC Isokinetic (Nm/kg)			MVIC Isokinetic LSI (%)	
									Involved	Uninvolved	Control	ACL LSI	Control LSI
12208905	Orthopaedic clinic	56	31/25	29.2	HT/PT	Median: 6 (PT) 5 (HT)	1 yr	60	NR	NR	NA	PT: 83.5 HT: 84.8	NA
							1 yr	180	NR	NR	NA	PT: 87.7 HT: 86.2	NA
							1 yr	240	NR	NR	NA	PT: 88.3 HT: 87.2	NA
16226644	General population	9	5/4	28	HT	No more than recreational athletes and none involved in competitive sports	1 yr	60	NR	NR	NA	91	NA
							1 yr	180	NR	NR	NA	91	NA
26460100	General community	75	65/11	27.9	HT	Tegner (preinjury): 6.4	1 yr	60	2.35 ± 0.57	2.77 ± 0.45	2.91± 0.40	NA	NA
							1 yr	180	1.72 ± 0.38	1.94 ± 0.33	1.95 ± 0.33	NA	NA
12860546	Orthopaedic clinic	39	PT: 23/8 HT: 24/10	PT: 25.8 HT: 26.3	PT/HT	Median IKDC PT: 85 Median IKDC HT: 80	1 yr	60	NR	NR	NA	PT: 77.3 ± 26.9 HT: 88.9 ± 16.5	NA
							1 yr	240	NR	NR	NA	PT: 85.2 ± 25.1 HT: 91 ± 20.8	NA
11914763	Athletes playing in competitive sports at regional or national levels or in active sports at least 3 times per week	80	52/28	28	HT	Tegner post-op: 6.5	1 yr	60	NR	NR	NA	92.5	NA
							1 yr	180	NR	NR	NA	86.1	NA
							1 yr	300	NR	NR	NA	96.9	NA

12531751	General population	89	NA	NA	PT/HT	NE	1 yr	60	NR	NR	NA	PT: 85 HT: 79	NA
12942198	General population	36	11/25	23.5	PT	NE	1 yr	60	NR	NR	NA	72.9	NA
							1 yr	180	NR	NR	NA	81.8	NA
15483539	General population	11	NA	28	PT	Final follow-up: Lysholm: 90	1 yr	60	NR	NR	NA	82 ± 13	NA
							1 yr	180	NR	NR	NA	82 ± 13	NA
11794266	General population	Total: 49 PT: 17 HT: 32	Total: 27/22 PT: 10/7 HT: 17/15	PT: 24.3 HT: 24.6	PT/HT	Tegner: PT: 4.8 HT: 4.3	1 yr	60	NR	NR	NA	PT: 76.8 ± 15.3 HT: 83.5 ± 16.7	NA
							1 yr	240	NR	NR	NA	PT: 79.9 ± 17.2 HT: 85.4 ± 15.7	NA
10843124	Orthopaedic clinic	25	16/9	23.8	PT	NE	1 yr	60	NR	NR	NA	86	NA
							1 yr	240	NR	NR	NA	97	NA
21576712	General population	20	NA	29.3	HT	NE	1 yr	60	NR	NR	NA	91.5 ± 15.6	NA
							1 yr	180	NR	NR	NA	91.7 ± 15.1	NA
10843124	Orthopaedic clinic	25	16/9	23.8	PT	NE	1.5 yr (18 mo)	60	NR	NR	NA	90	NA
							1.5 yr (18 mo)	240	NR	NR	NA	96	NA
26460100	General community	75	65/11	27.9	HT	Tegner (preinjury): 6.4	2 yrs	60	2.43 ± 0.56	2.77 ± 0.43	2.91± 0.40	NA	NA
							2 yrs	180	1.76 ± 0.39	1.93 ± 0.34	1.95 ± 0.33	NA	NA
12942198	General population	36	11/25	23.5	PT	NE	2 yrs	60	NR	NR	NA	89.1	NA
							2 yrs	180	NR	NR	NA	90.6	NA
15483539	General population	14	NA	28	PT	Final follow-up: Lysholm: 90	2 yrs	60	NR	NR	NA	82 ± 15	NA
							2 yrs	180	NR	NR	NA	89 ± 8	NA
12208905	Orthopaedic clinic	56	31/25	29.2	HT/PT	Median: 6 (PT) 5 (HT)	3 yrs	60	NR	NR	NA	PT: 94.7 HT: 88.1	NA
							3 yrs	180	NR	NR	NA	PT: 95.9 HT: 92.1	NA
							3 yrs	240	NR	NR	NA	PT: 96.6 HT: 93.5	NA

16399466	Orthopaedic clinic	85	40/45	23.4	HT	Tegner (pre): 8.3 Tegner (follow-up) 7.1	3.7 yrs (44.4 mo)	60	NR	NR	NA	96.6 ± 16.0	NA
							3.7 yrs (44.4 mo)	300	NR	NR	NA	102.4 ± 20.6	NA
17322130	Orthopaedic clinic	62	44/18	27	PT/HT	Tegner: 8	6 yrs	60	NR	NR	NR	PT: 86 HT: 91	102
							6 yrs	120	NR	NR	NR	PT: 89 HT: 91	104
16377968	Hospital	48	39/9	32	PT/HT	PT Tegner: 5 HT Tegner: 6	6 yrs	60	NR	NR	NA	PT: 90.0 ± 11 HT: 93 ± 15	NA
							6 yrs	180	NR	NR	NA	PT: 95 ± 12 HT: 98 ± 15	NA
29997727	Recreationally active	11	7/4	23.1	NR	NE	6.01 yrs	180	NR	NR	NA	76.4 ± 17.2	NA

NE not evaluated, *NA* not applicable, *NR* not report, *HT* hamstrings graft, *PT* patellar tendon graft, *IKDC* International Knee Documentation Committee Questionnaire, *ACL* anterior cruciate ligament, *LSI* Limb Symmetry Index

Appendix D: Subject Motor Evoked Torque Data Across Days for Chapter 2

Table D.1 Subject data across days for raw MEP torque, background torque, resting twitch torque, and maximum voluntary isometric contraction. *Abbreviations*: AMT, active motor threshold; ID, participant ID; MEP, motor evoked potential; MVIC, maximum voluntary isometric contraction; RTT, resting twitch torque; **bolded** MEP values indicate MEP maximum, † indicates a single value was used for normalizing data across stimulus intensities.

ID	% AMT	MEP Torque			Back Torque			RTT†			MVIC†		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1													
	70	0.177	0.311	0.283	28.688	28.728	28.226	27.616	25.273	20.775	218.838	194.315	198.725
	80	0.408	0.361	0.822	28.763	28.756	28.529						
	90	1.431	0.999	1.673	28.560	28.577	28.538						
	100	3.844	2.834	3.231	28.832	28.485	28.569						
	110	5.338	5.396	6.036	28.795	28.742	28.578						
	120	8.461	8.317	7.397	28.523	28.519	28.242						
	130	12.425	13.143	10.977	28.439	28.526	28.474						
	140	**16.665**	**16.529**	**14.577**	28.812	28.338	28.517						
2													
	70	0.324	0.306	0.422	9.846	10.213	10.089	10.148	10.912	14.309	NAN	NAN	NAN
	80	0.486	0.354	0.982	10.231	10.055	9.748						
	90	0.807	1.003	2.085	10.074	10.113	9.990						
	100	3.383	1.992	5.224	10.264	10.128	10.115						
	110	7.110	6.539	9.929	10.202	10.116	10.012						

	120	13.450	9.412	12.997	10.170	10.109	9.953						
	130	13.852	11.840	13.887	10.130	10.093	10.272						
	140	**17.941**	**14.806**	**18.228**	10.214	9.947	9.892						
3													
	70	1.158	0.358	0.568	33.032	34.102	34.300	31.874	29.132	27.402	118.744	145.624	176.324
	80	0.757	1.110	0.362	34.037	33.788	34.712						
	90	1.308	0.996	0.996	33.572	34.075	34.437						
	100	5.352	3.446	2.105	34.079	34.058	34.693						
	110	12.939	11.054	7.263	34.232	33.234	33.213						
	120	40.690	33.149	35.639	34.027	32.781	33.044						
	130	44.600	41.793	45.868	34.227	32.754	32.808						
	140	**51.992**	**44.693**	**49.442**	33.111	33.534	32.892						
4													
	70	0.415	0.378	0.247	20.309	19.703	20.406	19.864	20.082	15.020	114.594	127.751	136.240
	80	0.294	0.255	0.385	19.982	19.623	20.977						
	90	0.239	0.340	0.185	20.126	19.756	20.141						
	100	3.098	5.233	3.375	20.780	20.370	20.023						
	110	8.543	13.802	8.775	20.735	19.766	20.274						
	120	17.071	17.727	12.096	20.477	19.681	20.655						
	130	24.097	22.257	17.705	20.501	20.242	19.910						
	140	**26.333**	**24.084**	**22.691**	20.540	20.561	20.157						
5													
	70	0.171	0.194	0.215	15.019	15.746	15.381	15.014	14.207	15.157	NAN	NAN	NAN
	80	0.620	0.197	0.506	15.495	15.321	15.680						
	90	1.502	1.099	1.047	15.228	15.104	16.110						
	100	3.633	3.467	3.053	16.084	15.508	16.087						
	110	6.779	6.906	5.694	15.158	15.172	15.945						

	120	9.820	10.327	9.116	15.768	15.229	15.500						
	130	12.205	12.587	11.413	14.950	15.357	15.425						
	140	**16.142**	**14.775**	**14.248**	14.995	15.490	15.443						
6													
	70	0.728	0.329	0.544	21.436	20.956	21.825	21.315	21.925	23.249	NAN	NAN	NAN
	80	0.901	0.275	0.548	22.017	21.233	21.250						
	90	1.541	0.878	1.161	21.582	21.088	21.005						
	100	5.772	5.727	4.154	21.899	20.867	21.342						
	110	12.326	11.842	13.806	21.583	21.183	21.606						
	120	24.851	19.741	21.731	21.690	21.681	21.513						
	130	24.137	**23.514**	22.425	21.323	21.560	21.819						
	140	**29.356**	22.126	**25.586**	21.243	21.849	21.647						
7													
	70	0.476	0.156	0.676	21.019	20.720	21.592	21.259	20.346	19.327	83.564	100.117	73.072
	80	0.328	0.510	0.540	21.521	21.152	20.921						
	90	1.050	0.932	0.732	20.982	21.678	21.088						
	100	2.004	1.869	1.875	21.425	21.130	21.377						
	110	6.509	5.165	5.826	20.689	21.496	20.534						
	120	14.475	15.575	14.641	21.202	20.809	20.957						
	130	17.921	22.540	20.112	20.994	20.813	20.775						
	140	**23.586**	**24.963**	**24.291**	21.018	20.745	20.510						
8													
	70	0.112	0.122	0.011	10.180	10.163	10.211	10.291	12.411	13.949	180.875	173.306	193.655
	80	0.107	0.176	0.050	10.188	10.119	10.287						
	90	1.273	1.404	1.699	10.222	10.124	10.262						
	100	2.662	2.757	3.451	10.362	10.191	10.491						

	110	6.258	7.576	8.218	10.252	10.060	10.299						
	120	8.078	7.931	8.700	10.317	10.243	10.133						
	130	10.775	9.532	**11.767**	10.327	10.048	10.255						
	140	**11.190**	**10.221**	11.354	10.220	10.091	10.283						
9													
	70	0.218	0.545	0.248	20.338	20.131	20.632	20.200	16.680	17.566	NAN	NAN	NAN
	80	0.387	0.395	0.327	20.536	20.405	20.493						
	90	0.598	0.366	0.514	20.110	19.886	20.608						
	100	0.801	0.986	0.620	20.531	20.150	20.647						
	110	1.509	1.421	1.498	20.738	20.561	20.445						
	120	3.446	3.462	5.892	20.362	19.909	20.247						
	130	10.569	9.246	10.993	20.261	20.105	20.468						
	140	**15.321**	**11.287**	**13.083**	20.205	20.545	20.365						
10													
	70	0.296	0.077	0.440	11.838	12.122	12.415	11.637	13.056	14.552	NAN	NAN	NAN
	80	0.483	0.302	1.770	11.578	12.091	12.205						
	90	1.970	2.775	4.189	12.009	12.189	11.669						
	100	7.073	7.726	8.997	11.645	12.128	11.640						
	110	13.762	11.643	13.996	11.804	12.004	11.850						
	120	15.016	15.639	17.875	11.857	12.304	12.075						
	130	17.152	**20.412**	**19.138**	11.512	11.745	11.973						
	140	**22.954**	20.361	18.845	11.530	12.196	11.921						
11													
	70	0.779	0.314	0.377	22.290	22.217	22.997	21.969	21.760	21.322	114.429	104.078	119.782
	80	1.105	0.729	0.532	22.027	22.571	22.428						
	90	2.263	1.131	1.271	22.489	22.528	22.647						

	100	4.138	2.060	4.672	22.834	22.947	22.421						
	110	13.928	8.519	11.865	22.108	22.532	22.496						
	120	17.278	15.849	13.823	22.248	22.489	23.041						
	130	**23.133**	17.764	18.330	22.168	21.829	22.721						
	140	21.877	**22.145**	**22.499**	21.924	22.028	22.920						
12													
	70	0.140	0.071	0.156	16.496	16.753	16.207	15.774	19.098	22.984	173.495	171.113	159.960
	80	0.177	0.152	0.368	16.340	16.275	16.265						
	90	0.915	0.541	1.544	16.664	16.295	15.940						
	100	2.855	1.716	2.696	16.551	16.344	16.479						
	110	10.574	6.712	10.230	16.265	16.326	16.023						
	120	13.088	11.459	9.851	16.671	15.690	16.635						
	130	17.580	14.639	14.192	16.342	15.910	16.908						
	140	**21.148**	**17.292**	**17.340**	16.070	16.203	16.001						
13													
	70	1.384	1.070	1.485	33.268	34.012	34.120	32.565	37.142	35.305	231.216	230.933	268.801
	80	2.015	1.309	1.127	32.948	32.934	33.236						
	90	1.568	1.557	0.914	33.166	33.672	33.449						
	100	2.336	2.737	2.004	33.464	33.945	33.060						
	110	8.926	13.869	9.730	33.040	34.514	33.526						
	120	31.398	27.517	22.730	32.542	33.388	33.658						
	130	**40.007**	**39.136**	28.662	32.658	33.683	33.941						
	140	39.616	38.302	**36.010**	32.589	32.616	32.907						
14													
	70	0.938	0.200	0.360	15.038	14.981	14.519	14.323	11.268	14.049	NAN	144.351	143.974
	80	0.666	0.335	0.407	15.112	14.522	14.458						
	90	0.625	0.250	1.487	14.881	14.656	14.499						

	100	2.384	1.375	2.984	14.844	14.585	14.263						
	110	8.039	4.565	5.412	15.139	14.974	14.109						
	120	12.031	7.570	10.916	14.759	14.695	14.139						
	130	19.895	12.459	12.052	14.857	14.641	13.965						
	140	**25.751**	**17.054**	**15.432**	14.667	14.365	14.090						
15													
	70	4.111	2.276	0.973	30.883	30.393	30.983	31.005	26.610	30.599	NAN	NAN	NAN
	80	4.530	2.350	2.204	30.554	31.191	30.630						
	90	9.561	3.407	2.805	31.033	30.986	30.596						
	100	8.997	3.835	4.514	30.262	31.166	31.323						
	110	5.964	12.344	8.040	20.101	31.025	30.777						
	120	25.340	21.159	19.706	30.769	31.331	31.236						
	130	32.331	31.544	28.113	30.626	30.872	32.004						
	140	**41.264**	**37.043**	**36.271**	30.522	30.980	31.725						

Appendix E: Subject Motor Evoked Potential Data Across Days for Chapter 2

Table E.1 Subject data across days for raw MEP torque, background torque, resting twitch torque, and maximum voluntary isometric contraction. Abbreviations: AMT, active motor threshold; ID, participant ID; MEP, motor evoked potential; MVIC, maximum voluntary isometric contraction; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; **bolded** MEP values indicate MEP maximum**;** † indicates a single value was used for normalizing data across stimulus intensities.

ID	% AMT	MEP VM			MEP RF			Background VM			Background RF			MVIC VM†			MVIC RF†		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	70	0.1828	0.0532	0.0915	0.1611	0.1372	0.1636	0.0207	0.0166	0.0191	0.0179	0.0245	0.0247	0.2108	0.1207	0.1124	0.1317	0.1674	0.1950
	80	0.2013	0.1052	0.1835	0.1540	0.1950	0.3984	0.0216	0.0158	0.0194	0.0186	0.0247	0.0289						
	90	0.2611	0.1652	0.2251	0.1823	0.4650	0.4515	0.0211	0.0149	0.0175	0.0181	0.0261	0.0247						
	100	0.5119	0.2757	0.3192	0.3668	0.5481	0.5061	0.0195	0.0128	0.0183	0.0165	0.0224	0.0211						
	110	0.7113	0.4302	0.5408	0.5032	0.8498	0.7362	0.0192	0.0135	0.0167	0.0173	0.0221	0.0222						
	120	0.8339	0.3068	0.7864	0.5950	0.7141	1.5125	0.0179	0.0126	0.0173	0.0161	0.0162	0.0226						
	130	1.1028	0.4435	0.9391	0.7894	0.8706	1.7331	0.0176	0.0135	0.0180	0.0166	0.0178	0.0211						
	140	**1.5368**	**0.6362**	**0.9839**	**1.2832**	**1.5458**	**2.0814**	0.0191	0.0119	0.0153	0.0166	0.0177	0.0153						
3	70	0.0149	0.0106	0.0110	0.0165	0.0118	0.0094	0.0050	0.0045	0.0045	0.0067	0.0049	0.0044	0.0161	0.0187	0.0202	0.0183	0.0207	0.0247
	80	0.0125	0.0086	0.0112	0.0143	0.0109	0.0137	0.0046	0.0040	0.0044	0.0058	0.0045	0.0046						
	90	0.0251	0.0251	0.0222	0.0208	0.0207	0.0300	0.0043	0.0049	0.0048	0.0047	0.0054	0.0048						
	100	0.0959	0.0417	0.0446	0.0541	0.0203	0.0175	0.0045	0.0042	0.0044	0.0054	0.0049	0.0045						
	110	0.1817	0.1261	0.0989	0.1244	0.0712	0.0370	0.0045	0.0037	0.0042	0.0055	0.0044	0.0044						

	120	0.3160	0.3785	0.3840	0.2499	0.2992	0.2502	0.0047	0.0039	0.0042	0.0055	0.0043	0.0046						
	130	0.3256	**0.4289**	0.4706	0.2880	0.3037	**0.2947**	0.0039	0.0043	0.0039	0.0049	0.0052	0.0039						
	140	**0.3298**	0.3819	**0.4798**	**0.3269**	**0.3050**	0.2935	0.0035	0.0039	0.0041	0.0048	0.0049	0.0039						
4	70	0.0093	0.0120	0.0085	0.0041	0.0055	0.0061	0.0046	0.0042	0.0035	0.0015	0.0021	0.0021	0.0271	0.0295	0.0197	0.0481	0.0489	0.0602
	80	0.0092	0.0122	0.0081	0.0041	0.0068	0.0169	0.0047	0.0041	0.0034	0.0015	0.0022	0.0048						
	90	0.0120	0.0109	0.0143	0.0081	0.0060	0.0539	0.0046	0.0040	0.0033	0.0015	0.0020	0.0074						
	100	0.0585	0.0547	0.0497	0.0111	0.0198	0.1590	0.0045	0.0038	0.0033	0.0016	0.0021	0.0079						
	110	0.1105	0.0892	0.0732	0.1985	0.0908	0.2693	0.0041	0.0038	0.0037	0.0046	0.0019	0.0080						
	120	0.1662	0.1288	0.0961	0.3441	0.1244	0.3556	0.0043	0.0041	0.0037	0.0060	0.0020	0.0070						
	130	0.2030	0.1322	**0.1204**	0.4204	0.2031	**0.4087**	0.0042	0.0037	0.0031	0.0065	0.0024	0.0047						
	140	**0.2193**	**0.1983**	0.1181	**0.4683**	**0.3318**	0.3816	0.0038	0.0044	0.0032	0.0052	0.0032	0.0016						
7	70	0.0087	0.0117	0.0079	0.0076	0.0130	0.0221	0.0034	0.0037	0.0031	0.0033	0.0042	0.0046	0.0202	0.0223	0.0186	0.0473	0.0576	0.0401
	80	0.0194	0.0166	0.0086	0.0116	0.0153	0.0245	0.0037	0.0038	0.0029	0.0030	0.0044	0.0065						
	90	0.0362	0.0451	0.0330	0.0205	0.0555	0.0595	0.0034	0.0038	0.0028	0.0032	0.0049	0.0048						
	100	0.0454	0.0564	0.0416	0.0342	0.0603	0.0891	0.0040	0.0036	0.0029	0.0030	0.0040	0.0052						
	110	0.0878	0.0887	0.0793	0.0418	0.0916	0.1434	0.0034	0.0034	0.0027	0.0029	0.0042	0.0049						
	120	0.1810	0.2409	0.2442	0.1051	0.4954	0.5425	0.0033	0.0037	0.0026	0.0024	0.0042	0.0055						
	130	0.2160	0.3280	0.3633	0.1787	0.7386	**0.7911**	0.0033	0.0042	0.0031	0.0030	0.0046	0.0057						
	140	**0.3622**	**0.3320**	**0.4244**	**0.8322**	**0.8502**	0.7258	0.0039	0.0033	0.0030	0.0284	0.0037	0.0054						
8	70	0.0081	0.0136	0.0076	0.0094	0.0103	0.0110	0.0033	0.0032	0.0025	0.0027	0.0028	0.0024	0.0376	0.0533	0.0478	0.1530	0.2147	0.2543
	80	0.0140	0.0191	0.0138	0.0177	0.0129	0.0155	0.0035	0.0027	0.0026	0.0030	0.0028	0.0024						
	90	0.0224	0.0324	0.0360	0.0240	0.0250	0.0191	0.0032	0.0031	0.0025	0.0030	0.0027	0.0025						
	100	0.0644	0.0715	0.0535	0.0619	0.1743	0.0504	0.0029	0.0025	0.0026	0.0028	0.0034	0.0024						
	110	0.1044	0.0820	0.0594	0.1192	0.1781	0.0941	0.0037	0.0029	0.0021	0.0029	0.0027	0.0024						

	120	0.0549	0.0769	0.0630	0.1607	0.1767	0.0845	0.0030	0.0028	0.0024	0.0032	0.0025	0.0024						
	130	0.0885	0.0797	0.0590	**0.2872**	0.2042	0.1475	0.0031	0.0027	0.0027	0.0029	0.0027	0.0027						
	140	**0.1116**	**0.0814**	**0.0753**	0.1952	**0.3664**	**0.1591**	0.0029	0.0030	0.0028	0.0030	0.0025	0.0024						
11	70	0.0299	0.0408	0.0190	0.0301	0.0163	0.0111	0.0094	0.0083	0.0076	0.0084	0.0041	0.0034	0.0563	0.0671	0.0702	0.1067	0.1096	0.1010
	80	0.0778	0.0503	0.0388	0.0848	0.0210	0.0217	0.0094	0.0082	0.0069	0.0092	0.0034	0.0030						
	90	0.1220	0.0804	0.0630	0.0472	0.0337	0.0294	0.0095	0.0077	0.0071	0.0084	0.0037	0.0029						
	100	0.1862	0.1026	0.1243	0.0970	0.0433	0.0413	0.0105	0.0076	0.0074	0.0093	0.0035	0.0030						
	110	0.4249	0.2444	0.3047	0.2497	0.0932	0.1054	0.0088	0.0074	0.0073	0.0070	0.0034	0.0030						
	120	0.6359	0.4786	0.4441	0.5763	0.3847	0.4096	0.0096	0.0082	0.0084	0.0078	0.0062	0.0068						
	130	**0.7770**	0.5287	0.4419	**0.7307**	0.5132	0.3078	0.0089	0.0074	0.0073	0.0070	0.0036	0.0035						
	140	0.6816	**0.5473**	**0.4671**	0.6961	**0.5456**	**0.3153**	0.0095	0.0072	0.0067	0.0058	0.0031	0.0026						
12	70	0.0082	0.0060	0.0082	0.0095	0.0085	0.0048	0.0028	0.0028	0.0028	0.0032	0.0029	0.0014	0.0403	0.0489	0.0340	0.1027	0.1083	0.0426
	80	0.0233	0.0087	0.0142	0.0207	0.0132	0.0102	0.0030	0.0028	0.0025	0.0028	0.0026	0.0015						
	90	0.0297	0.0229	0.0339	0.0418	0.0232	0.0224	0.0026	0.0026	0.0027	0.0047	0.0032	0.0016						
	100	0.0644	0.0352	0.0422	0.0749	0.0458	0.0299	0.0029	0.0024	0.0026	0.0027	0.0031	0.0014						
	110	0.1480	0.0700	0.1052	0.1363	0.0974	0.0567	0.0030	0.0025	0.0027	0.0028	0.0030	0.0016						
	120	0.1558	0.1149	0.0961	0.1679	0.1345	0.0621	0.0030	0.0028	0.0025	0.0027	0.0030	0.0016						
	130	0.1355	0.1134	**0.0955**	0.4410	0.1401	0.0794	0.0024	0.0027	0.0025	0.0040	0.0029	0.0015						
	140	**0.1619**	**0.1468**	0.0951	**0.6597**	**0.1899**	**0.0927**	0.0024	0.0025	0.0025	0.0047	0.0027	0.0015						
13	70	0.0174	0.0130	0.0217	0.0415	0.0328	0.0345	0.0079	0.0053	0.0080	0.0136	0.0094	0.0113	0.0176	0.0372	0.0826	0.1021	0.1308	0.1354
	80	0.0173	0.0130	0.0175	0.0421	0.0242	0.0311	0.0071	0.0052	0.0082	0.0117	0.0079	0.0102						
	90	0.0185	0.0269	0.0251	0.0424	0.0980	0.0579	0.0071	0.0053	0.0080	0.0084	0.0129	0.0092						
	100	0.0200	0.0376	0.0416	0.0659	0.1251	0.0889	0.0066	0.0053	0.0069	0.0071	0.0079	0.0083						
	110	0.0970	0.0764	0.1194	0.0464	0.2951	0.3047	0.0069	0.0055	0.0082	0.0020	0.0064	0.0094						

	120	0.1598	0.1016	0.3654	0.7721	0.6319	0.9271	0.0070	0.0048	0.0072	0.0105	0.0052	0.0097					
	130	**0.2123**	0.1999	0.4449	**0.7825**	**0.9666**	**0.9365**	0.0069	0.0047	0.0072	0.0130	0.0076	0.0093					
	140	0.1626	**0.2103**	**0.5037**	0.7146	0.9265	0.8199	0.0070	0.0047	0.0070	0.0088	0.0087	0.0069					
14	70	0.0066	0.0082	0.0064	0.0187	0.0252	0.0165	0.0022	0.0024	0.0019	0.0074	0.0067	0.0070	0.0152	0.0190	0.0114	0.0291	0.0736	0.0488
	80	0.0078	0.0058	0.0066	0.0326	0.0126	0.0525	0.0021	0.0020	0.0021	0.0074	0.0029	0.0068						
	90	0.0195	0.0133	0.0166	0.0751	0.0584	0.0551	0.0023	0.0022	0.0017	0.0067	0.0071	0.0065						
	100	0.0437	0.0252	0.0284	0.1854	0.1778	0.0833	0.0024	0.0023	0.0018	0.0082	0.0077	0.0047						
	110	0.0565	0.0442	0.0501	0.2065	0.1682	0.1512	0.0022	0.0024	0.0017	0.0068	0.0062	0.0045						
	120	0.0776	0.0442	0.0585	0.3824	0.0855	0.1860	0.0029	0.0021	0.0019	0.0075	0.0027	0.0039						
	130	0.1279	0.0497	0.0596	0.6223	0.1985	0.1612	0.0033	0.0017	0.0020	0.0139	0.0032	0.0053						
	140	**0.1464**	**0.1029**	**0.0639**	**0.6976**	**0.4930**	**0.2508**	0.0023	0.0017	0.0017	0.0054	0.0039	0.0031						