EXPLORING THE BRAIN AFTER ACL RECONSTRUCTION: EXAMINATION OF NEUROPHYSIOLOGICAL AND PSYCHOLOGICAL FACTORS DURING THE COURSE OF POST-OPERATIVE REHABILITATION

by

Ryan Zarzycki

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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ABSTRACT

Rupture of the anterior cruciate ligament (ACL) is a devastating injury affecting approximately 250,000 individuals each year in the United States. Upwards of 130,000 anterior cruciate ligament reconstructions (ACLR) are performed each year. While ACLR restores mechanical stability of the knee, many patients continue to experience functional performance deficits, reduced capacity for physical activity and participation, and second injury. Current rehabilitation strategies may not be sufficiently addressing neurophysiologic alterations and psychological factors related to injury. An improved understanding of these factors may result in more effective post-operative rehabilitation protocols, fewer second injuries and safer return to sports.

The overall goals of this work were: 1) to compare corticospinal, intracortical, and spinal-reflexive excitability in athletes after ACLR and controls, and explore the relationship of these neurophysiologic measures to quadriceps strength, 2) to explore the relationship between psychological readiness to return to sport and gait biomechanics, and 3) to determine if a secondary ACL injury prevention program affects psychological readiness to return to sport and if an improvement in psychological readiness is associated with better outcomes.

This work includes data from two distinct studies. For goal #1, athletes after ACLR underwent neurophysiologic testing via transcranial magnetic stimulation and peripheral electrical stimulation when they achieved 3 important rehabilitation milestones: 1) 2 weeks after surgery, 2) achievement of a “quiet knee” defined as full

range of motion and minimal effusion, 3) return to sport (RTS) activities time point defined as achievement of a quadriceps index ≥ 80% and at least 12 weeks post-ACLR. For goals #2 and #3, athletes after ACLR were enrolled after completing impairment resolution defined as: full range of motion, minimal effusion, adequate quadriceps strength and greater than 12 weeks from surgery. Following enrollment, all athletes completed a secondary ACL injury prevention program. Psychological readiness to return to sport and self-reported functional measures were evaluated at enrollment, after the prevention program, and at 1 year after ACLR.

Athletes after ACLR demonstrated alterations in corticospinal, and intracortical excitability early after surgery compared to controls, and these neurophysiologic measures were associated with isometric quadriceps strength during the course of rehabilitation. Changes in these measures did not occur throughout rehabilitation indicating that current rehabilitation may not be addressing cortical alterations associated with chronic quadriceps dysfunction.

For goals #2 and #3 we found that there is a relationship between knee kinematic and kinetic symmetry and psychological readiness to return to sport, prior to return to sport after ACLR. Athletes who scored lower on a psychological readiness to return to sport measure displayed greater asymmetries during gait. Additionally, athletes who demonstrated an improvement in psychological readiness to return to sport had better self-reported function following a secondary injury prevention program and at one year after ACLR.

In conclusion, neurophysiologic pathways from the motor cortex to the quadriceps muscle and psychological factors are related to common impairments and outcomes after ACLR. While research is emerging in these two areas, more research is needed to address the less than optimal outcomes currently related to recovery after ACLR. Addressing cortical excitability and psychological readiness to return to sport during rehabilitation have the potential to improve outcomes after ACLR.

Chapter 1

EXPANDING OUR KNOWLEDGE OF NEUROPHYSIOLOGIC ALTERATIONS AND PSYCHOLOGICAL FACTORS AFTER ACLR

1.1 Outcomes after ACLR are less than optimal

Anterior cruciate ligament (ACL) injuries are common and devastating injuries to athletes. Approximately 250,000 ACL injuries occur each year in the United States.[28] Upwards of 130,000 anterior cruciate ligament reconstructions (ACLR) are performed each year and approximately $3 billion annually are spent on health care costs related to this surgery.[62,64] After ACLR, athletes undergo extensive rehabilitation that can last up to one year. Despite advances in rehabilitation and surgery, outcomes after ACLR are less than optimal. Only 65% of athletes are able to return to their prior levels of sport;[7] functional deficits persist;[54] and second injury rates are high.[95] Current rehabilitation strategies may therefore not be addressing all aspects of an athlete's recovery. Neurophysiological changes in the brain and psychological factors are two aspects that are not well understood in this population. The present work will examine these areas which have the potential to improve clinical care and outcomes following ACLR.

1.2 Neurophysiological Alterations after ACLR

Neuromuscular deficits are persistent following ACL injury and ACLR.[35] Changes within the brain are present following ACLR and likely contribute to the neuromuscular deficits.[30,43,52,74,79] The majority of studies examining brain function in the ACL population have used transcranial magnetic stimulation (TMS) due to its ability to examine neuroplasticity of the motor cortex. TMS allows for assessment of: 1) the excitability of the cortiocospinal tract (connection between the motor cortex and target muscle) and 2) intracortical connections (inhibitory and facilitatory interneurons) using single pulse or paired pulse stimulation protocols respectively (Figure 1).[14,16] Altered corticospinal excitability to the quadriceps (vastus medialis) is evident in subjects after ACLR compared to controls at 6 months and later.[43,52,74] However, research examining neuroplasticity after ACLR is limited especially early after ACLR. This proposal will examine change in cortical excitability throughout rehabilitation at three time points: 1) 2 weeks after ACLR, 2) the time a subject achieves a "quiet knee", and 3) the time when return to sport training is initiated.

The neuromuscular deficits seen after ACLR are most evident in the quadriceps muscle group and can persist for up to 2 years.[67,68,77] The ability to regain quadriceps strength is associated with functional outcomes[24,55] and restoring normal movement patterns.[53,84] Persistent quadriceps weakness and activation deficits lead to gait asymmetries that have been linked to early onset of knee arthritis.[53,92] Recent research using transcranial magnetic stimulation (TMS) indicates that quadriceps activation deficits may be associated with cortical changes in patients at a mean of 48 months after ACLR.[74] Patients with normal activation levels (greater than 95%) had values of corticospinal excitability similar to controls, while patients with activation deficits displayed decreased excitability (i.e. higher thresholds). The relationship between corticospinal excitability and quadriceps muscle function has not previously been investigated during the course of rehabilitation. The current proposal will define this relationship at multiple time points throughout the course of rehabilitation. Defining this relationship is critical for improving strategies to facilitate recovery of normal quadriceps function after ACLR.

1.3 Psychological Factors Affect Outcomes after ACLR

There is a growing body of evidence that psychological factors are also associated with outcomes following ACLR. Factors such as fear of reinjury, lack of confidence, and motivation can affect an athlete's ability to return to their prior level of activity after ACLR.[3,86] Fear of reinjury is one of the most commonly reported factors preventing return to sport in this population.[3,18,44] Despite the growing body of literature regarding psychological factors after ACLR, there are no studies that have examined the association between psychological factors and movement. Previous research has established that athletes after ACLR walk with abnormal strategies. A common finding is that patients walk with a stiffened knee gait pattern exemplified by smaller knee flexion excursion on the surgical limb and lower knee flexion moments compared to controls.[40] While these gait asymmetries are more pronounced early after surgery, patients continue to demonstrate these patterns up to two years.[77] Asymmetrical movement patterns are now linked to second ACL injury and the early development of knee osteoarthritis.[70,92] Current rehabilitation protocols focus on reducing asymmetry and restoring normal movement patterns. In spite of this, many patients continue to demonstrate abnormal gait patterns. It is plausible that fear of reinjury and low confidence are factors contributing to altered movement patterns and these psychological factors are not addressed with current rehabilitation protocols. This work will be the first to examine the relationship between psychological factors and gait after ACLR.

Psychological factors are potentially modifiable with treatment after ACLR.[3] Chmielewski and colleagues found that fear of movement/reinjury changes when measured at 4, 8, and 12 weeks after ACLR.[18] Changes in fear were inversely associated with changes in function (i.e. a decrease in fear was associated with an increase in function). Psychological readiness to return to sport (a construct that includes emotions, fear of reinjury, confidence, and risk appraisal)[8] at 4 months post ACLR was predictive of returning to preinjury activity level at 1 year. The aforementioned studies indicate that a more negative psychological outlook (i.e. more fear and less confidence, etc) may lead to poorer outcomes. Therefore, outcomes might improve if interventions were able to modify a negative psychological outlook. The anterior cruciate ligament-specialized post-operative return-to-sports (ACL SPORTS)[93] program was designed to improve outcomes and allow patients to return to sport more safely. This program bridges the gap between traditional physical therapy and the time when athletes return to sport. During the ACL SPORTS program, patients are gradually exposed to sport specific movements (i.e. plyometrics and agility exercises) which are progressed in complexity and intensity over ten sessions. Recent evidence suggests that graded activity and exposure can be implemented by physical therapists and has the potential to help patients recover from low back pain.[11,26] The ACL SPORTS program has the potential to address fear of reinjury and lack of confidence in a similar manner as graded activity/exposure for patients with low back pain. Findings from this work will answer two important questions, 1) does an extended rehabilitation program improve psychological outlook; and 2) is an improvement in psychological outlook associated with better functional and activity outcomes?

1.4 Innovation of this Work

Studying the brain and neuroplasticity in athletes early after ACLR is innovative for a number of reasons. First, there are very few studies that have specifically examined the brain in the ACLR population. Within these studies, none have explored longitudinal changes to the brain during the course of rehabilitation. Defining neuroplastic changes during the course of rehabilitation is essential to improving clinical care. Addressing these deficits 6 months after ACLR or beyond may be too late as athletes are no longer attending rehabilitation regularly and may have already returned to sports. Chronic neuroplastic changes may represent unresolved impairments putting the athlete at risk for additional injury and/or failure to achieve their desired outcome.

Second, while some studies have examined excitability of the corticospinal tract, few studies have examined intracortical inhibition and facilitation in this population. Neuroplastic changes involving inhibitory/facilitatory circuits may be contributing to the quadriceps strength and activation deficits commonly observed in the clinic. Improved understanding of the influences that inhibitory and/or facilitatory circuits have on quadriceps weakness after ACLR may identify some necessary modifications in rehabilitation protocols. For example, the addition of modalities (such as transcranial direct current stimulation) and new neuromuscular training protocols specifically targeting the nervous system have the potential to address these pathways.

Third, strong evidence exists that biomechanical changes during gait occur after ACLR.[40,41,53,77] Changes in biomechanics have been linked to reinjury[70] and the development of osteoarthritis.[92] Fear and confidence are factors that may affect how someone walks and moves following a major injury and complex surgical procedure. This will be the first work to examine the relationship between these psychological factors and biomechanics. Simply resolving the physical impairments related to ACLR may not be enough if psychological factors affect movement. Findings from this work will set a foundation for future research.

Finally, the ACL SPORTS program[93] provides additional treatment to athletes with the desire of returning to high level activities. It bridges the gap between impairment resolution and return to sport. There is a paucity of research examining a program at this time frame. Most athletes that undergo ACLR have a desire to return to the activity that they were injured in. A graded progression to the demands of the sport could potentially mitigate fear of reinjury and improve confidence which have been shown to affect outcomes. This work will shed light on the proposed theory that psychological factors after ACLR are modifiable with physical therapy interventions. It will also provide evidence in regards to how a change in psychological outlook is associated with outcomes after ACLR.

1.5 Specific Aims

The specific aims of the work are:

Aim 1: Define the corticospinal and spinal-reflexive changes that occur during the course of post-operative physical therapy after ACLR and their relationship with isometric quadriceps strength.

Hypothesis 1.1: ACLR subjects will display less corticospinal excitability in both limbs compared to healthy controls at all three time points.

Hypothesis 1.2: ACLR subjects will display less spinal-reflexive excitability in the surgical limb compared to healthy controls at the 2 weeks after surgery time point.

Hypothesis 1.3: There will be a negative relationship between RMT (higher values equal lower excitability) and quadriceps strength at all time points.

Hypothesis 1.4: There will be a positive relationship between 120% RMT Norm (higher values equal higher excitability) and quadriceps strength at all time points.

Hypothesis 1.5: There will be a positive relationship between spinal-reflexive excitability and quadriceps strength at the 2 weeks after surgery time point.

Aim 2: Define the intracortical changes that occur during the course of post-operative physical therapy after ACLR and their relationship with isometric quadriceps strength.

Hypothesis 2.1: ACLR subjects will display less intracortical facilitation in the surgical limb at all time points.

Hypothesis 2.2: ACLR subjects will display greater intracortical inhibition in the surgical limb at all time points.

Hypothesis 2.3: There will be a positive relationship between facilitation and quadriceps strength at all time points.

Hypothesis 2.4: There will be a positive relationship between inhibition (higher values equal less inhibition) and quadriceps strength at all time points.

Aim 3: Determine the relationship between psychological measures and biomechanics prior to return to sport after ACLR.

Hypothesis 3.1: Following ACLR and post-operative physical therapy, subjects with a negative psychological outlook will display greater kinematic asymmetry during gait then subjects with a neutral or positive outlook.

Hypothesis 3.2: Following ACLR and post-operative physical therapy, subjects with a negative psychological outlook will display greater kinetic asymmetry during gait then subjects with a neutral or positive outlook.

Aim 4: Define changes in psychological factors following an extended rehabilitation program post ACLR and determine if a positive change in psychological outlook is associated with better outcomes.

Hypothesis 4.1: Subjects that undergo the extended rehabilitation program will demonstrate a positive improvement in psychological readiness to return to sport.

Hypothesis 4.2: Subjects that demonstrate a positive improvement in psychological readiness to return to sport as a result of the ACL Sports program will have better self-reported functional and activity outcomes following training, and at 1 and 2 years post ACLR.

Chapter 2

ALTERATIONS IN CORTICOSPINAL EXCITABILITY DO NOT CHANGE DURING THE COURSE OF POST-OPERATIVE REHABILITATION AFTER ACL RECONSTRUCTION

2.1 Abstract

Quadriceps muscle activation deficits and weakness persist after ACL reconstruction and related to poor function, movement asymmetry, and increased risk of reinjury. Changes in the corticospinal and spinal-reflexive pathways may be involved with quadriceps dysfunction. Few studies have examined these pathways during the course of post-operative rehabilitation. The purpose of this prospective longitudinal case control study was twofold: 1) to examine changes in corticospinal and spinal-reflexive excitability after ACLR compared to controls, 2) to determine if measures of corticospinal and spinal-reflexive excitability are associated with quadriceps strength during the course of post-operative rehabilitation.

Eighteen participants in level I/II sports after ACLR between the ages of 18-30 were tested when they achieved 3 important rehabilitation milestones: 1) 2 weeks after surgery, 2) achievement of a “quiet knee” defined as full range of motion and minimal effusion, 3) return to sport (RTS) activities time point defined as achievement of a quadriceps index ≥ 80% and at least 12 weeks post-ACLR. Eighteen sex, age, and activity matched healthy athletes were also tested at 3 time points.

Two measures of corticospinal excitability, spinal-reflexive excitability, and isometric peak quadriceps strength were taken bilaterally at each time point.

Corticospinal excitability measures included resting motor threshold (RMT) and motor evoked potential amplitude at a stimulator intensity 120% RMT (MEP_{120}), while spinal-reflexive excitability was the ratio of the maximal Hoffman reflex to the maximal M-wave (H/M). Isometric quadriceps strength was measured on a Biodex dynamometer; peak quadriceps tourque normalized to body weight was used for analysis.

There was a significant group x limb interaction for RMT and MEP_{120} ($p<.05$). The ACLR group demonstrated higher RMTs and higher MEP_{120} at all three time points. RMT was associated with isometric quadriceps strength at 2 weeks after surgery and quiet knee, while MEP_{120} was associated with quadriceps strength at all three time points.

Alterations in corticospinal excitability are present in athletes after ACLR during the course of post-operative rehabilitation. Corticospinal excitability does not change but is related to quadriceps strength. Additional interventions may be needed to mitigate persistent quadriceps dysfunction after ACLR. No measurements were taken prior to surgery. We are therefore unable to determine if the alterations found were a result of surgery, present before surgery, or present before the initial injury.

2.2 Introduction

Quadriceps femoris muscle weakness and voluntary activation failure persist for years after anterior cruciate ligament reconstruction (ACLR).[27] Deficits in quadriceps function are linked to altered biomechanics[21,39,53], worse self-reported function[24,38,55,72], and increased risk of reinjury.[29] The mechanism underlying quadriceps dysfunction is not completely understood; however, it is theorized that altered afferent information from the injured joint and the lack of afferent information from the native ACL leads to altered efferent drive to the muscle.[68] The spinal-reflexive and corticospinal pathways are associated with quadriceps dysfunction[43,51,52,74], yet there is a paucity of research examining these pathways, especially early following ACLR.

Only one study to our knowledge has examined spinal-reflexive and corticospinal excitability at 2 weeks after ACLR. As part of a longitudinal case-control study, Lepley et al found lower spinal-reflexive excitability in their ACLR cohort compared to controls, and no group differences in corticospinal excitability at 2 weeks after ACLR.[52] At 6 months the ACLR group demonstrated an increase in corticospinal excitability (i.e. active motor thresholds) that was different than controls and an increase in spinal-reflexive excitability that was no longer different than the control group. This study's findings indicate that changes occur in both the corticospinal and spinal-reflexive pathways from 2 weeks to 6 months after ACLR. However, no studies have explored the corticospinal and spinal-reflexive pathways during the course of acute rehabilitation following ACLR. Examination of these pathways during the course of rehabilitation is essential as this is the time when clinicians are regularly working with these athletes. A better understanding of the state of spinal-reflexive and corticospinal pathways is needed to mitigate persistent quadriceps muscle dysfunction post-ACLR.

Cross sectional studies have investigated the relationship between quadriceps strength and corticospinal and spinal-reflexive excitability 6 months after surgery or later. Participants after ACLR demonstrated greater spinal-reflexive excitably bilaterally and less corticospinal excitability to the surgical limb at a mean of 48 month after surgery when compared to a healthy control group.[74] In addition, participants after ACLR with high quadriceps activation (≥95%) demonstrated higher spinal-reflexive excitability while participants with low activation (<95%) demonstrated lower corticospinal excitability. Participants at a mean of 32 months after surgery also demonstrated asymmetries with quadriceps strength and activation, and corticospinal excitability.[43] No studies to date have explored the relationship of quadriceps strength to corticospinal and spinal-reflexive excitability during the course of acute rehabilitation.

Early rehabilitation following ACLR focuses on decreasing pain and effusion, restoring range of motion (ROM), and restoring quadriceps strength. Changes in pain, effusion, ROM, and quadriceps function may affect the corticospinal and spinal-reflexive pathways. Therefore the purpose of this study was twofold: 1) to examine longitudinal changes in spinal-reflexive and corticospinal excitability at three time points during the course of rehabilitation after ACLR and, 2) to determine if a relationship exists between our neurophysiologic measures (spinal-reflexive and corticospinal excitability) and quadriceps strength at three time points during the course of rehabilitation. For purpose #1 we hypothesized that spinal-reflexive alterations would be present early after ACLR based on previous findings.[52] We also hypothesized that corticospinal alterations would only be present at the second and third time points in the ACLR group; specifically, the ACLR group would continue to demonstrate higher RMTs and higher MEP amplitudes compared to controls based on previous findings.[52] For purpose #2 we hypothesized that spinal-reflexive excitability would be associated with quadriceps strength at the first time point given that pain and effusion are present early after surgery, while corticospinal excitability would be associated with quadriceps strength at the second and third time points. For both measures (spinal-reflexive and corticospinal) we hypothesized that greater excitability would be associated with greater quadriceps strength.

2.3 Methods

2.3.1 Participants

Eighteen athletes (10 women, 8 men) after unilateral ACLR and 18 uninjured control athletes, between the ages of 18 and 30, were recruited for this prospective longitudinal case control study (level of evidence: 2). Prior to injury all participants were participating in Level I/II sports (i.e. sports involving cutting, pivoting, jumping) for at least 50 hours per year. Exclusion criteria included: 1) multiple ligament reconstruction, 2) osteo-chondral procedures, 3) any previous lower extremity surgery, and 4) previous ACL injury. Metal or implants in the head or neck, history of neurological disease, seizures, severe migraines, and concussion within the last 6 months were TMS-specific exclusion criteria for both groups. The control group was formed by matching each participant in the ACLR group to a sex and age matched Level I/II athlete without a history of ACL injury or any other major lower extremity injury. In addition, athletes were matched by competitive sport level. Six athletes in each group were Division I athletes, two were club level collegiate athletes, five participated in intramural sports, and five in recreational sports. This study was approved by the University's Institutional Review Board and written informed consent was acquired prior to inclusion.

Neurophysiologic and quadriceps strength testing was performed at three time points after ACLR. The first time point was at 2 weeks after ACLR (2 weeks). The second testing session was performed as soon as the athlete achieved a "quiet knee" defined by full range of motion, minimal or no effusion, and walking with no visible gait deviation. The third testing session was performed when the athlete was greater than 12 weeks from surgery and achieved a quadriceps strength index greater than or equal to 80%. This is the typical time when athletes will begin a running progression and is coined the return to sport (RTS) activities time point. The time between sessions of each athlete in the control group was determined by the time it took their matched athlete in the ACLR group to reach the second and third time points.

2.3.2 Testing

Neurophysiologic testing

Electromyography (EMG) data were collected using a MA-300 system (Motion Lab Systems, Baton Rouge, LA) sampled at 5000Hz. Surface EMG electrodes (bar shaped double differential preamplifiers) were placed over the muscle bellies of the vastus medialis bilaterally based on Seniam placement recommendations.[34] Skin preparation (shaved if hair present, isopropyl alcohol to clean/abrade the skin) preceded electrode placement. Wraps were utilized to stabilize the electrodes and improve electrode to skin contact. All data were acquired through Signal Software (Cambridge Electronic Design Limited, Cambridge, England). This same setup was used for both spinal-reflexive testing and corticospinal excitability testing.

TMS Testing

During testing, subjects were seated in a Biodex dynamometer with hips and knees flexed to 90 degrees. The vertex of the skull was identified as the intersection of a line marking the midpoint between the nasion and inion of the skull and a line marking the midpoint between the tragus of each ear.

Single pulse TMS (Magstim 200 Bistim unit, The Magstim Company Ltd, UK) delivered via a double cone coil was utilized to obtain two measures of corticospinal excitability: 1) resting motor threshold (RMT) and 2) motor evoked potential (MEP) amplitude at an intensity of 120% RMT (MEP_{120}). First, the "hot spot" (the location on the head that elicited the greatest MEP from the contralateral target vastus medialis muscle) was identified with the TMS stimulator set to a supra-threshold intensity. All measurements were performed with the stimulator positioned at this location and markings drawn on the cap ensured consistent coil positioning throughout testing. The RMT was identified through single pulse TMS. The RMT was defined as the lowest stimulator intensity able to elicit a measurable response (MEP $\geq 50\ \mu V$, unamplified) in at least 5 out of 10 pulses delivered with the limb at rest.[42,81] RMT is expressed as a percentage of the maximal stimulator output (%MSO) and reflects membrane excitability of the central core region of a muscles representation within the primary motor cortex.[15] MEP_{120} was calculated as the peak-to-peak amplitude of MEPs produced by single pulses delivered at an intensity of 120% of the RMT. The MEP_{120} recruits a larger pool of neurons in the motor cortex as the intensity is well above threshold intensities and therefore is more reflective of excitability within the entire cortical motorneuronal pool for a muscle.[31] MEP_{120} values were normalized to the maximal M-wave obtained during spinal-reflexive testing. During all TMS testing, pulses were delivered at a rate of <0.2 Hz to prevent conditioning of cortical excitability.

Spinal-reflex excitability

Subjects were positioned in supine with a half bolster under both knees. A bar electrode from a DS7A HV Current Stimulator (Digitimer Ltd, Hertfordshire, UK) was then positioned just lateral to the femoral artery over the femoral nerve. A 1 ms square wave electrical pulse was delivered (at least 10 seconds between pulses) at varying intensities until a Hoffmann's reflex (H-reflex) was produced. The intensity of the stimulator was increased until the maximal H-reflex was produced, as reflected by a decrease in amplitude when testing at higher intensities. The intensity was then increased until a maximal M-wave was produced, as reflected by no further increase in amplitude with increased intensity of the electrical pulse. The average peak-to-peak amplitude of three maximal H-reflexes were normalized to the average peak-to-peak of three maximal M-waves to create the H/M ratio that was used for data analysis.[51,69]

During all reflex testing, stimuli were delivered at a rate of <0.1 Hz to prevent conditioning of the H-reflex.

Quadriceps femoris strength testing

Participants were seated in a Biodex dynamometer with hips flexed at 90 degrees and the knee flexed at 60 degrees. Straps over the thigh and hips were secured tightly to prevent movement. Three warm up trials (50%, 75%, 100% maximal effort) were performed to allow the participant to become familiar with the task. Following warmups, participants performed three maximal voluntary isometric contractions (MVIC) with a one minute rest break between each trial. The peak MVIC from the 3 trials was recorded and normalized to the subject's body weight for analysis.

Self-reported Function

All subjects completed the International Knee Documentation Committee Subjective Knee Form (IKDC).[37] The IKDC measures self-reported function and includes questions about knee symptoms, sports and daily activities, and current knee function. The IKDC is a validated instrument that is used for patients with various knee conditions (originally designed for knee ligament injuries). The ACLR group completed the IKDC at all three time points while the control group only completed the IKDC at the first time point. None of the athletes in the control group experienced an acute or overuse injury during the course of the study. Therefore, the control group's IKDC score at the first time point was compared to the ACLR group's IKDC at each time point.

2.3.3 Statistical Analysis

G*power software v3.9.2 (Universität Düsseldorf, Düsseldorf, Germany) [25] was used to determine sample size for this study. Effect sizes of the primary outcome measure (RMT) were calculated based on pilot data from this study (8 ACLR, 8 control). The power analysis indicated that 16 subjects in each group were needed to achieve a statistical power of .80.

Independent *t*-tests were used to determine group differences in demographics and IKDC. For purpose #1 a mixed-model analyses of variance (ANOVA) were used to compare each neurophysiologic measure with three factors: 1) group (ACLR vs control), 2) limb (surgical vs nonsurgical), and 3) time (2 weeks vs quiet knee vs RTS activities). Limb dominance determined the limb of the control group that was analyzed with the surgical or non-surgical limb of the ACLR group. For example, if a subject underwent ACLR on their dominant limb, the dominant limb of the matched control would be analyzed with the surgical limb and the non-dominant limb with the non-surgical limb. Limb dominance was determined by asking the subject with which leg they preferred to kick a ball with.[76] We used *t*-tests with Bonferroni corrections were performed when significant interactions were found. For purpose #2 linear regression analysis was performed to determine the relationship between quadriceps strength and each neurophysiological measure (H/M, RMT, MEP_{120}) at each time point.

Secondary Reliability Analysis

Ten additional healthy control subjects were recruited to examine test-retest reliability of our corticospinal excitability (RMT and MEP_{120}) measures. RMTs and MEP_{120} were measured by the same examiner during 2 sessions held within 24-48 hours of each other. Sessions were held at the same time of day. Two way random intraclass correlation coefficients for absolute agreement ($ICC_{2,1}$) were calculated.[91] Standard error of the measurement (SEM) was calculated for each measure by the following equation: $SEM=SD(\sqrt{1-ICC})$. Finally, the minimal detectable change (MDC) score was calculated using the following equation: $MDC=SEM \times 1.96 \times \sqrt{2}$.

2.4 Results

Three subjects in the ACLR group demonstrated RMTs greater than 85% MSO in their nonsurgical limb. MEP_{120} could not be collected in these subjects, and they were therefore excluded from the MEP_{120} analysis. H-reflexes were not elicited in one subject after ACLR and four control subjects. These subjects were excluded from the H/M analysis.

Demographics, Function, and Timing

There were no significant group differences in age (ACLR: 21.6 (3.3); control: 22.3 (2.5); p=0.495) or body mass index (ACLR: 24.5 kg/m² (3.0); control: 23.4 (1.9); p=0.188). For the ACLR group, the mean (SD) time from surgery to each time point was: 2 week time point=14.5 (2.2) days, quiet knee=59.2 (19.4) days, and RTS activities=134 (36.5) days. The mean IKDC of the control group (98.9 (1.8)) administered at the first time point was significantly higher (p<0.001 at all time points) than the ACLR group's IKDC at each time point (2 weeks: 31.8 (8.9); quiet knee: 53.4 (12.1); RTS activities: 63.1 (13.0)).

Purpose #1

There was a group by limb interaction for RMT and MEP_{120} (Table 2.1). Athletes after ACLR demonstrated asymmetrical RMTs with the nonsurgical limb having higher RMTs than the surgical ($p=.011$), while the controls were symmetrical ($p=0.398$). The ACLR group's nonsurgical limb demonstrated significantly higher RMTs than the controls matched limb ($p=0.004$), while the ACLR group's surgical limb demonstrated a trend toward higher RMTs (Figure 2.1A and 2.1B). Athletes after ACLR also demonstrated asymmetrical MEP_{120} characterized by higher MEP in the surgical limb compared to the nonsurgical limb ($p=0.012$), while the control group was symmetrical ($p=0.661$). MEP_{120} of both limbs in the ACLR group were significantly higher than the matched limb of the control group (Figures 2.2A and 2.2B). There were no main effects of time ($p\geq0.587$), time x group ($p\geq0.756$), time x limb ($p\geq0.442$), or significant 3-way (group x limb x time) interactions for RMT and MEP_{120} ($p\geq0.345$). There were no significant main effects or interactions in regards to H/M ($p\geq0.172$).

Purpose #2

There was a significant positive association between the surgical limb's quadriceps strength and RMT at 2 weeks ($p=0.035$) (Table 2.2). There were significant negative associations between surgical limb's quadriceps strength and

MEP_{120} at all three time points ($p \leq 0.047$). There were no significant associations between quadriceps strength and H/M at any time points ($p \geq 0.255$).

Differences by Sex

Examining sex differences was not a primary aim of this study. However, after examining group means by sex, it was apparent that sex differences in corticospinal excitability may exist. Based on this observation, we performed a 2 (sex) x 2 (group) x 2 (limb) ANOVA at each time point. At the quiet knee time point, there was a significant 3-way (sex x group x limb) interaction for RMT ($p=0.006$) and MEP_{120} ($p=0.047$) (Table 2.3). The men in the ACLR group demonstrated greater RMTs in both limbs compared to the matched limbs of men in the control group (surgical limb, $p=0.001$; nonsurgical limb, $p=0.045$). RMT for either limb of the women in the ACLR group were not different than controls (surgical limb, $p=0.541$; nonsurgical limb, $p=0.072$). For MEP_{120}, the women in the ACLR group demonstrated higher MEP in the surgical limb compared to the controls matched limb (surgical limb, $p=0.002$; nonsurgical limb, $p=0.861$). No MEP group differences were present in the men (surgical limb, $p=.264$; nonsurgical limb, $p=0.178$). At the 2 weeks after ACLR time point, there was a main effect of sex for both RMT ($p=0.049$) and MEP_{120} ($p=0.048$), but not interaction effects involving sex ($p \geq 0.135$). At the RTS activities time point, there was not a main effect of sex and no interaction effects involving sex ($p \geq 0.119$) (Table 2.4).

Reliability Analyses

ICCs, SEMs and MDCs for RMT and MEP_{120} are presented in Table 2.5. Both

RMT and MEP_{120} displayed excellent reliability ($ICC_{2,1}$: RMT= 0.966; MEP_{120}= 0.897).

2.5 Discussion

The purpose of this study was to explore changes in the spinal-reflexive and corticospinal excitability during the course of rehabilitation and to examine the relationship between these pathways and quadriceps strength. Our findings indicate that alterations in both measures of corticospinal excitability exist early after ACLR and continue to manifest during the course of rehabilitation, without change. Both measures of corticospinal excitability were also associated with quadriceps strength of the surgical limb during the course of rehabilitation. These findings taken together indicate that over the course of acute rehabilitation corticospinal excitability does not change. Given that restoring quadriceps muscle strength and function is imperative after ACLR, additional interventions may be needed to address alterations in corticospinal excitability. Is it important to point out that no measurements were taken prior to ACLR or prior to injury. Therefore, it is unknown if the alterations found between the ACLR group and controls were a result of the surgery, present prior to ACLR, or possibly present before the initial ACL injury.

The ACLR group demonstrated higher RMTs which indicates lower corticospinal excitability while the higher MEP_{120} indicates greater corticospinal excitability at all three time points compared to controls, which at face value seems to be contradictory. However, while both RMT and MEP_{120} are measures of corticospinal excitability, they recruit different pools of neurons within the motor cortex.[31] These findings indicate that initial drive to the quadriceps is lower in athletes after ACLR; yet exaggerated responses are evident when a larger pool of neurons are recruited. This pattern of activation is somewhat analogous to previous studies finding diminished quadriceps control in people that are ACL deficient. During an active short arc quadriceps exercise, subjects that were ACL deficient did not turn off their vastus medialis and vastus lateralis during any part of the movement while control subjects did.[96] In addition, non-copers, which are a sub-group of people after ACL injury that display altered neuromuscular control and movement patterns, display diminished quadriceps control during a force matching tack compared to copers and controls.[98] The diminished quadriceps control was defined by increased vastus lateralis activation during the force matching task in directions where the quadriceps is normally not active. The athletes in the present study show an analogous pattern in their corticospinal excitability alterations. Athletes after ACLR show difficulty reaching threshold to activate the motor cortex (i.e. higher RMT measures), however once activated, their responses in the motor cortex are exaggerated (i.e. higher MEP_{120} measures) compared to healthy athletes. This pattern of activation is likely maladaptive especially for high level athletes returning to sport and could have detrimental influences on long term joint health.

The MEP_{120} measure was related to quadriceps strength at all 3 time points while RMT was related to quadriceps strength at the 2 week time point only. Higher MEP_{120} (i.e. greater excitability) was associated with less quadriceps strength. Lower RMTs (i.e. greater excitability) was associated with less quadriceps strength. This relationship is contrary to our hypotheses in which we anticipated greater excitability would be associated with greater quadriceps strength. This finding may resemble an adaptation by which the central nervous system attempts to compensate for lower quadriceps strength. While this adaptation may provide greater drive to the quadriceps, the lack of change in this relationship throughout the course rehabilitation may indicate a maladaptive alteration in excitability that persists as the athlete progresses back to sport.

Sex by group interactions were present in RMT and MEP_{120} at the quiet knee time point. Interestingly, the men in the ACLR group demonstrated higher RMTs as compared to the men in the control group, but no differences in MEP_{120}, while the women in the ACLR group demonstrated higher MEP_{120} compared to the women in the control group, but no differences in RMT. These findings indicate that women have exaggerated drive to the quadriceps when stimuli are applied well above threshold, yet initial drive (i.e. RMT) is not altered. Cross sectional laboratory studies examining healthy athletes have found greater quadriceps dominant activation patterns in women compared to men, which are hypothesized to contribute to the increased risk of ACL injury by creating greater anterior tibial translation.[28] Greater quadriceps activation, and lower hamstring activation is also present in healthy women athletes compared to men.[10,60,94]   Additionally, Stearns-Reider and Powers found healthy women athletes demonstrated earlier activation of the vastus lateralis and a decrease in rate of torque development with hip extension during a drop-jump task.[87] The authors suggested that women may activate their quadriceps earlier to compensate for deficits hip extension function. It would be interesting to know if the exaggerated responses found in the women of our ACLR group contribute to poor lower extremity control and potentially excessive anterior tibial translation. The higher RMTs found in the men, which indicate reduced initial drive, may actually be protective by limiting the effect of anterior tibial translation caused by activation of the quadriceps. Future studies should prospectively examine corticospinal sex differences in athletes to determine if corticospinal excitability is associated with future ACL injury risk.

Our findings of higher RMTs after ACLR are partly in agreement and partly contradict other research in this area. Lepley et al found increased active motor thresholds at 6 months after surgery which is consistent with our findings at our later two time points (i.e. quiet knee and RTS activities).[52] However they found no differences in active motor thresholds 2 weeks after ACLR. Additionally, Lepley et al measured MEP_{120}, but found no differences compared to healthy controls at 2 weeks or 6 months after surgery. This contradiction between the findings of Lepley et al and the current study could be due to the fact that Lepley et al measured motor threshold during active contraction of the quadriceps (5% of MCIV), rather than at rest. At two weeks after ACLR, pain is common especially during an active contraction. Added pain with the active condition could increase afferent input to the cortex and ultimately influence motor drive to the muscle. Cross sectional studies have found mixed results in terms of active motor thresholds (AMT) in patients after ACLR at time points greater than 6 months. Pietrosimone et al found higher AMTs in the injured limb of athletes after ACLR compared to their uninjured limb and controls.[74] Keunze et al found that athletes after ACLR had greater AMT asymmetry than a control group, but no differences were found between the AMT of the surgical limb and either control limb.[43] The discrepancy in findings from these cross sectional studies likely lie in the variability in time from ACLR to testing within individuals in each study and between studies.

There are limitations to this study. First, as previously mentioned, we did not measure excitability prior to ACLR. We are therefore unable to determine is the group differences found in this study were due to the surgery, or present beforehand. Future research should examine measures of corticospinal excitability prospectively to determine if alterations in excitability are associated with future injury risk. Second, we were unable to measure MEP_{120} in the nonsurgical limb of three athletes within the ACLR group, however group differences were still found. Finally, we could not elicit H-reflexes in one ACLR subject and 4 controls. There were medium effects (cohen's d)[19] between groups in terms of spinal-reflexive excitability in the surgical limb at the 2 weeks after ACLR (d=0.603) and quiet knee (d=0.473) time points. The missing spinal-reflexive values for 5 athletes could have contributed to the lack of statistical differences found between groups. Future research should consider over recruiting subjects when measuring spinal-reflexive excitably in the quadriceps, given that H-reflexes were not isolated in all individuals.

In conclusion, athletes after ACLR demonstrated alterations in corticospinal excitability to the quadriceps throughout the course of rehabilitation and these alterations did not change during the course of rehabilitation. Additionally, both measures of corticospinal excitability were associated with isometric quadriceps strength. Taken together, these findings indicate that current rehabilitation may not be sufficient in promoting long lasting changes in cortical excitability. Interventions incorporating high intensity exercise, which do alter cortical excitability, may be needed to address alterations in corticospinal excitability early after ACLR.

Table 2.1: Measures of corticospinal and spinal-reflexive excitability (Mean (SD)) by group at 2 weeks after ACLR, quiet knee, and RTS activities (**p<.05)

Group	Time Point	Limb	RMT (%MSO)	MEP_{120} (M_{max})	H/M (%)
ACLR	2 weeks	Surgical	61.4 (12.4)	8.3 (5.6)	38.6 (17.5)
		Nonsurgical	67.9 (15.4)	5.7 (5.6)	33.3 (25.5)
	Quiet Knee	Surgical	61.9 (13.0)	7.9 (4.9)	39.6 (21.0)
		Nonsurgical	65.2 (14.5)	5.8 (8.0)	27.8 (19.5)
	RTS Activities	Surgical	61.6 (12.7)	9.0 (5.8)	29.1 (9.6)
		Nonsurgical	66.9 (15.1)	5.9 (4.8)	31.8 (18.0)
Control	2 weeks	Surgical	55.6 (8.2)	3.1 (1.9)	28.2 (15.2)
		Nonsurgical	54.0 (10.1)	3.7 (2.5)	30.0 (14.3))
	Quiet Knee	Surgical	55.7 (9.2)	3.4 (3.1)	30.7 (15.2)
		Nonsurgical	53.9 (9.4)	3.7 (2.9)	31.0 (16.5)
	RTS Activities	Surgical	55.7 (9.1)	3.4 (2.2)	30.0 (13.1)
		Nonsurgical	54.3 (11.5)	3.8 (2.9)	30.8 (12.1)
p-values	Main Effect of Group		0.014**	0.003**	0.480
	Group x Limb Interaction		0.017**	0.031**	0.172
	Group x Limb x Time Interaction		0.542	0.867	0.354

Abbreviations: RMT, resting motor threshold; MSO, maximal stimulator output; MEP_{120}, motor evoked potential amplitude at stimulator intensity of 120% RMT; H/M, Hoffmans reflex normalized to the maximal M-wave; RTS, return to sport.

Table 2.2: Linear regression analyses examining the relationship between quadriceps strength and each neurophysiologic measure by time point for the ACLR Group (**p<.05; *p<.1)

TMS Measure	**2 weeks after ACLR**		
	R^2	**Beta**	**P-value**
RMT	0.249	0.028	0.035**
MEP_{120}	0.422	-8.481	0.004**
H/M	0.096	1.346	0.225
TMS Measure	**Quiet Knee**		
	R^2	**Beta**	**P-value**
RMT	0.229	0.029	0.052*
MEP_{120}	0.345	-9.041	0.013**
H/M	0.000	0.045	0.967
TMS Measure	**RTS activities**		
	R^2	**Beta**	**P-value**
RMT	0.009	0.006	0.711
MEP_{120}	0.311	-7.764	0.016**
H/M	0.024	-1.037	0.556

Abbreviations: RMT, resting motor threshold; MEP_{120}, motor evoked potential amplitude at stimulator intensity of 120% RMT; H/M, Hoffmans reflex normalized to the maximal M-wave; RTS, return to sport.

Table 2.3: Measures of corticospinal and spinal-reflexive excitability (Mean (SD)) by group and sex at the Quiet Knee time point (**p<.05)

Group	Sex	Limb	RMT (%MSO)	MEP_{120} (M_{max})	H/M (%)
ACLR	Men	Surgical	71.1 (9.4)	5.1 (3.3)	43.2 (24.3)
		Nonsurgical	68.6 (12.9)	7.4 (12.6)	32.3 (24.8)
	Women	Surgical	54.5 (10.7)	9.7 (5.0)	32.7 (13.6)
		Nonsurgical	62.5 (15.7)	4.8 (3.6)	25.2 (12.9)
Control	Men	Surgical	53.9 (9.5)	2.8 (2.1)	24.2 (10.8)
		Nonsurgical	55.9 (11.8)	3.0 (1.7)	21.7 (5.4)
	Women	Surgical	57.2 (9.2)	3.9 (3.7)	34.4 (18.4)
		Nonsurgical	52.3 (7.1)	4.3 (3.6)	38.0 (20.0)
P-values	Main Effect of Sex		0.101	0.451	0.718
	Sex x Group Interaction		0.109	0.939	0.065
	Sex x Group x Limb Interaction		0.006**	0.047**	0.744

Abbreviations: RMT, resting motor threshold; MSO, maximal stimulator output; MEP_{120}, motor evoked potential amplitude at stimulator intensity of 120% RMT; H/M, Hoffmans reflex normalized to the maximal M-wave

Table 2.4: Measures of corticospinal and spinal-reflexive excitability (Mean (SD)) by group and sex at the Return to Sport Activities time point

Group	Sex	Limb	RMT (%MSO)	MEP_{120} (M_{max})	H/M (%)
ACLR	Men	Surgical	68.1 (12.2)	8.5 (6.4)	29.7 (15.6)
		Nonsurgical	72.5 (16.6)	3.9 (3.4)	28.5 (15.7)
	Women	Surgical	56.3 (10.9)	9.4 (5.7)	30.1 (8.7)
		Nonsurgical	62.4 (12.9)	7.3 (5.3)	31.5 (20.1)
Control	Men	Surgical	54.5 (8.7)	3.1 (2.8)	23.1 (10.5)
		Nonsurgical	56.8 (15.3)	3.4 (2.5)	31.1 (12.1)
	Women	Surgical	56.6 (9.8)	3.6 (1.7)	37.6 (10.8)
		Nonsurgical	52.4 (7.7)	4.1 (3.3)	28.2 (13.7)
P-values	Main Effect of Sex		0.118	0.257	0.359
	Sex x Group Interaction		0.201	0.521	0.612
	Sex x Group x Limb Interaction		0.142	0.496	0.119

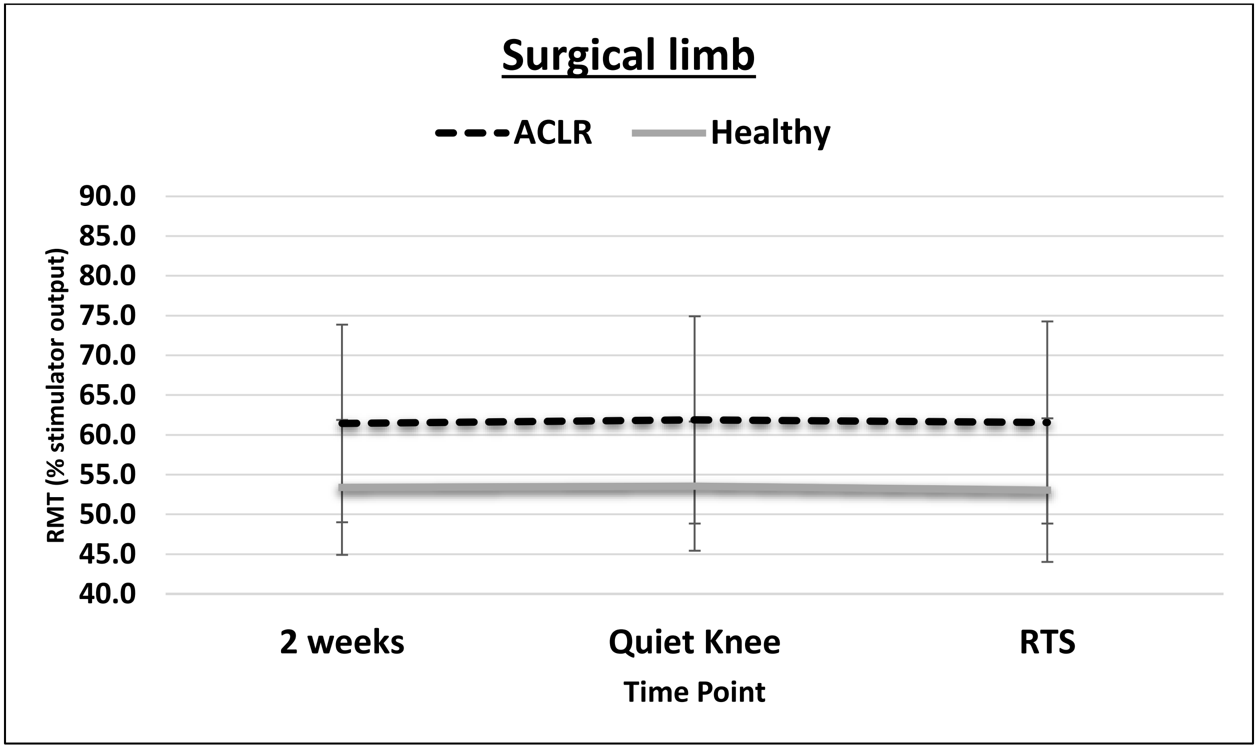
Abbreviations: RMT, resting motor threshold; MSO, maximal stimulator output; MEP_{120}, motor evoked potential amplitude at stimulator intensity of 120% RMT; H/M, Hoffmans reflex normalized to the maximal M-wave

Table 2.5: Test-Retest Reliability Analysis

Measure	ICC	SEM	MDC
RMT	0.966	0.335	.928
MEP_{120}	0.897	0.3	0.9

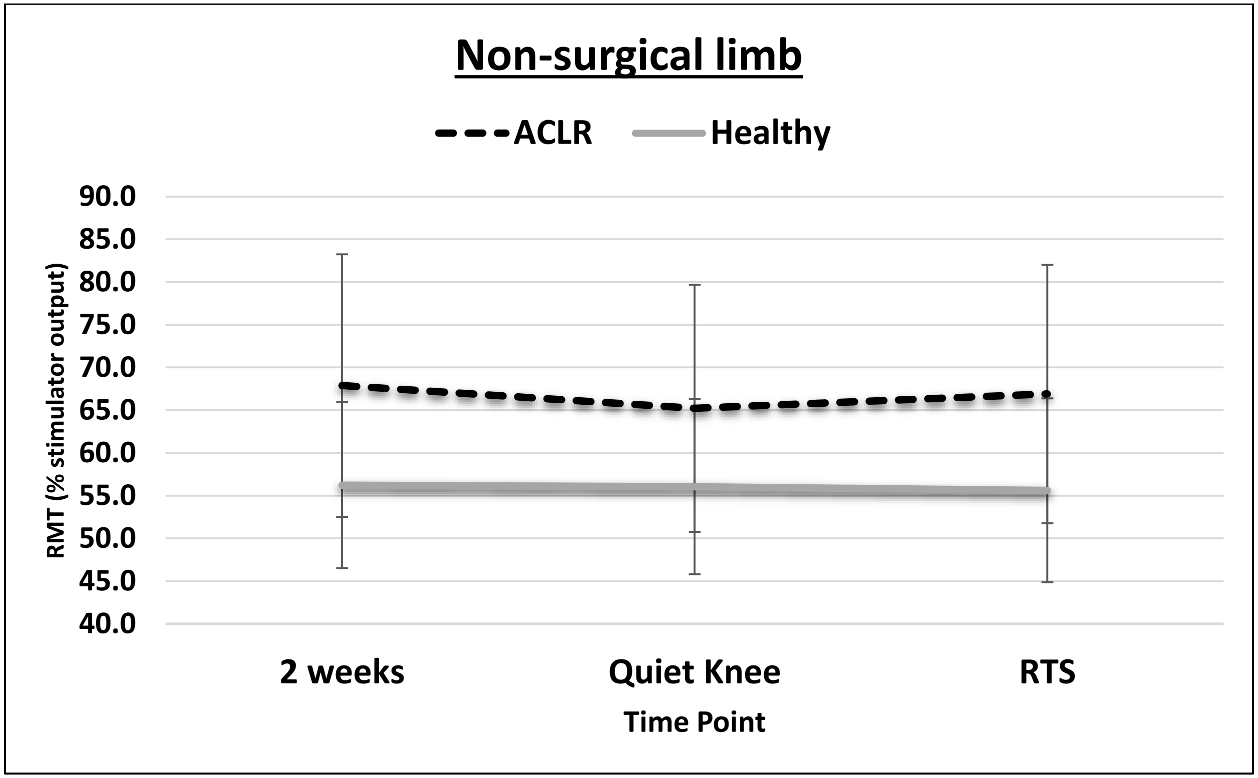
Abbreviations: ICC, intra-class correlation coefficients (2-way random, absolute agreement); SEM, standard error of the measure; MDC, minimal detectable change

Figure 2.1A: Resting motor threshold in the ACLR group's surgical limb compared to the Healthy group's matched control limb.



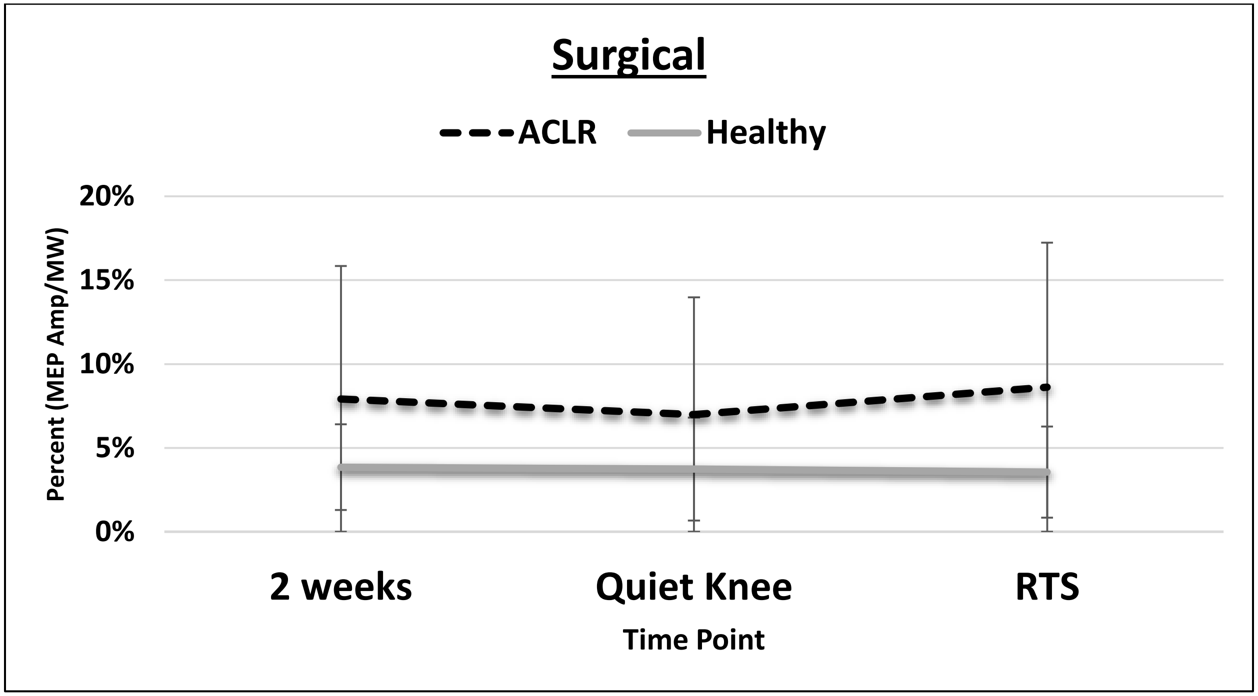
Abbreviations: RTS, return to sport activities time point; RMT, resting motor threshold

Figure 2.1B: Resting motor threshold in the ACLR group's nonsurgical limb compared to the Healthy group's matched control limb.



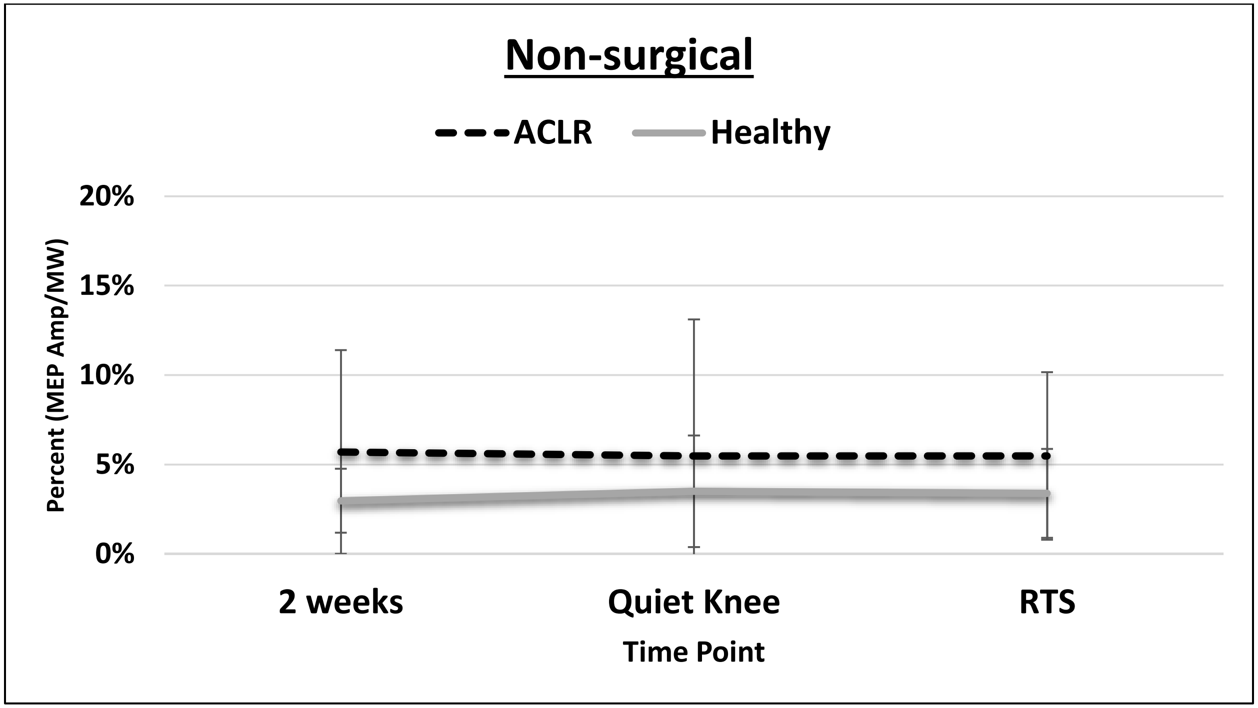
Abbreviations: RTS, return to sport activities time point; RMT, resting motor threshold

Figure 2.2A: MEP_{120} in the ACLR group's surgical limb compared to the Healthy group's matched control limb.



Abbreviations: RTS, return to sport activities time point; MEP_{120}, motor evoked potential at 120% threshold

Figure 2.2B: MEP_{120} in the ACLR group's nonsurgical limb compared to the Healthy group's matched control limb.



Abbreviations: RTS, return to sport activities time point; MEP_{120}, motor evoked potential at 120% threshold

Chapter 3

EXAMINATION OF INTRACORTICAL INHIBITION AND FACILITATION DURING THE COURSE OF POST-OPERATIVE REHABILITATION AFTER ACL RECONSTRUCTION

3.1 Abstract

Quadriceps dysfunction persists after anterior cruciate ligament reconstruction (ACLR), yet the etiology remains elusive. Inhibitory and facilitatory intracortical pathways may be involved in quadriceps dysfunction yet investigation of these pathways early after ACLR does not exist. The purpose of this prospective longitudinal case control study was twofold: 1) examine changes in intracortical excitability after ACLR compared to controls during the course or post-operative rehabilitation, 2) determine if measures of intracortical excitability were associated with isometric quadriceps strength during the course of post-operative rehabilitation.

Eighteen level I/II athletes after ACLR between the ages of 18-30 and eighteen healthy sex and age matched level I/II athletes were tested at three time points: 1) 2 weeks after surgery, 2) achievement of a “quiet knee” defined as full range of motion and minimal effusion, 3) return to sport (RTS) activities time point defined as achievement of a quadriceps index ≥ 80% and at least 12 weeks post-ACLR. Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) measured via transcranial magnetic stimulation, and isometric peak quadriceps strength were

examined at each time point. Isometric quadriceps strength was measured on a Biodex dynamometer; peak quadriceps torque normalized to body weight was used for analysis.

There was a significant group x limb interaction ($p=.017$) for ICF with the athletes after ACLR demonstrating asymmetric facilitation compared to controls. No main effects or 3-way interactions were found for ICF or SICI. There was a significant relationship between SICI and quadriceps strength of the surgical limb at the quiet knee time point. There were significant relationships between ICF and quadriceps strength of the nonsurgical limb at both 2 weeks and quiet knee ($p\leq.050$).

Athletes after ACLR demonstrate asymmetric ICF compared to controls throughout the course of post-operative rehabilitation and measures of intracortical excitability are associated with isometric quadriceps strength of both limbs early after ACLR. Interventions targeting the intracortical pathways have potential to improve outcomes after ACLR by improving quadriceps function. We are unable to determine if the alterations found were a result of surgery or present beforehand due to the fact that pre-operative measurements were not examined.

3.2 Introduction

Quadriceps dysfunction persists for years after ACLR and is associated with altered movement patterns[39,53], lower self-reported function[24,55,72,75], and increased risk or reinjury.[29] While the cause of quadriceps dysfunction is multifactorial, it is hypothesized that alterations in efferent neural pathways to the muscle are involved.[51,68,74] Spinal-reflexive excitability, corticospinal excitability, and intracortical excitability are altered at different time points following ACLR, yet few studies have explored these pathways early after surgery.[43,51,74] Examination of these pathways during the course of post-operative rehabilitation is needed to gain a better understanding of quadriceps dysfunction following ACLR.

We previously reported on corticospinal and spinal-reflexive excitably alterations in this same cohort of athletes (Zarzycki et al., in preparation). Athletes in this study demonstrated alterations in two measures of corticospinal excitability during the course of acute post-operative rehabilitation when compared to the control athletes. Specifically, athletes after ACLR demonstrated higher resting motor thresholds (RMT) and higher motor evoked potential amplitudes (MEP_{120}) in the vastus medialis; no alterations were noted in spinal-reflexive excitability. These findings suggest that athletes after ACLR require more cortical drive to get consistent activity in the quadriceps, but these athletes demonstrate exaggerated responses as more cortical neurons are recruited. This pattern of corticospinal excitability parallels the poor quadriceps activation patterns demonstrated following ACL injury and ACLR.[23,68] To our knowledge, there is only one other study that has examined corticospinal excitability longitudinally following ACLR.[52] Lepley et al found no differences between athletes after ACLR and controls prior to surgery and 2 weeks after ACLR, yet ACLR subjects did display higher active motor thresholds at 6 months after ACLR.

Both of the studies mentioned above used single pulse transcranial magnetic stimulation (TMS) to evaluate corticospinal excitability. The motor evoked potentials

(MEPs) elicited from single pulse TMS targeting the primary motor cortex reflect the strength and excitability of the corticospinal tract, which in turn reflects the balance between intracortical facilitatory and inhibitory pathways.[15] Specific understanding of the excitability in these inhibitory and facilitatory pathways within the motor cortex may help provide a mechanism to explain the alterations in corticospinal excitability. Paired-pulse TMS involves two magnetic stimuli delivered at a given inter-stimulus interval (ISI). When both stimuli are delivered over the same brain region, a subthreshold stimulus applied prior to a suprathreshold stimulus will lead to either inhibition or facilitation of the motor evoked potential (MEP), depending on the length of the ISI.[31] Thus, paired-pulse paradigms allow for individual measurement of the intracortical facilitatory and inhibitory pathways. While these paradigms have been investigated thoroughly[14–16,31,65,71,80,88,99], only a few studies have examined intracortical inhibition and facilitation to the quadriceps in subjects with knee related pathology. Kittleson et al found no differences in intracortical inhibition or facilitation in subjects with knee osteoarthritis and controls.[42] Only one study to our knowledge has used paired-pulse paradigms in subjects after ACLR.[57] Luc-Harkey et al found greater intracortical inhibition of the vastus medialis to be associated with less voluntary quadriceps activation in a cohort of patients at a mean of 44 months after ACLR. There are currently no published studies examining intracortical excitability longitudinally after ACLR and no studies comparing these measures to healthy controls.

The purpose of this study was twofold: 1) to determine if intracortical excitability (inhibition and facilitation) differs in athletes after ACLR compared to healthy matched controls during the course of post-operative rehabilitation, and 2) to determine if a relationship exists between two measures of intracortical excitability and isometric quadriceps strength during the course of post-operative rehabilitation. For purpose #1 we hypothesized that athletes after ACLR would demonstrate greater intracortical inhibition and less facilitation at the first two time points (2 weeks after surgery and quiet knee time point) compared to controls but no differences at our last time point (return to sporting activities time point). For purpose #2 we hypothesized that both measures of intracortical excitability would be positively associated with surgical limb quadriceps strength at all three time points.

3.3 Methods

3.3.1 Participants

Eighteen athletes (10 women, 8 men) after unilateral ACLR and 18 uninjured control athletes, between the ages of 18 and 30, were recruited for this prospective longitudinal case control study (level of evidence: 2). Prior to injury all participants were participating in Level I/II sports (i.e. sports involving cutting, pivoting, jumping) for at least 50 hours per year. Exclusion criteria included: 1) multiple ligament reconstruction, 2) osteo-chondral procedures, 3) any previous lower extremity surgery, and 4) previous ACL injury. Metal or implants in the head or neck, history of neurological disease, seizures, severe migraines, and concussion within the last 6 months were TMS-specific exclusion criteria for both groups. The control group was formed by matching each participant in the ACLR group to a sex and age matched Level I/II athlete without a history of ACL injury or any other major lower extremity injury. In addition, athletes were matched by competitive sport level. Six athletes in each group were Division I athletes, two were club level collegiate athletes, five participated in intramural sports, and five in recreational sports. This study was approved by the University's Institutional Review Board and written informed consent was acquired prior to inclusion.

TMS testing and quadriceps strength testing was performed at three time points after ACLR. The first time point was at 2 weeks after ACLR (2 weeks). The second testing session was performed as soon as the athlete achieved a "quiet knee" defined by full range of motion, minimal or no effusion, and walking with no visible gait deviation. The third testing session was performed when the athlete was greater than 12 weeks from surgery and achieved a quadriceps strength index greater than or equal to 80%. This is the typical time when athletes will begin a running progression and is coined the return to sport (RTS) activities time point. The time between sessions of each athlete in the control group was determined by the time it took their matched athlete in the ACLR group to reach the second and third time points.

3.3.2 Testing

Electromyography

Electromyography (EMG) data were collected using a MA-300 system (Motion Lab Systems, Baton Rouge, LA) sampled at 5000Hz. Surface EMG electrodes (bar shaped double differential preamplifiers) were placed over the muscle bellies of the vastus medialis bilaterally based on Seniam placement recommendations.[34] Skin preparation (shaved if hair present, isopropyl alcohol to clean/abrade the skin) preceded electrode placement. Wraps were utilized to stabilize the electrodes and improve electrode to skin contact. All data were acquired through Signal Software (Cambridge Electronic Design Limited, Cambridge, England).

TMS Testing

During testing, subjects were seated in a Biodex dynamometer with hips and knees flexed to 90 degrees. The vertex of the skull was identified as the intersection of a line marking the midpoint between the nasion and inion of the skull and a line marking the midpoint between the tragus of each ear. Single pulse TMS (Magstim 200 Bistim unit, The Magstim Company Ltd, UK) delivered via a double cone coil was utilized to obtain the resting motor threshold (RMT) defined as the lowest stimulator intensity able to elicit a measurable response (motor evoked potential (MEP) $\geq$ 50 μV, unamplified) in at least 5 out of 10 pulses delivered with the limb at rest.[42,81]

Following measurement of RMT, paired-pulse TMS was used to measure short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). For both of these measures a subthreshold pulse at 80% RMT (the conditioning pulse) was delivered prior to a suprathreshold pulse at 120% (the test pulse). The two pulses were separated by 3 ms for SICI and 15 ms for ICF.[14] SICI leads to a decrease in the peak to peak amplitude of the MEP produced from the test pulse and is mediated by inhibitory cortical interneurons that release the neurotransmitter gamma-aminobutyric

A ($GABA_A$). ICF leads to an increase in peak to peak amplitude of the MEP produced from the test pulse and is mediated by excitatory cortical interneurons that release the neurotransmitter glutamate onto non-N-methyl-D-aspartate (NMDA) receptors.[99] The average peak to peak MEP amplitude of 10 paired-pulse trials each for SICI and ICF were calculated. These average values were then normalized to the average of 10 trials of the test pulse only that were obtained with single pulse TMS at 120% RMT. Thus, SICI and ICF are presented as a percentage of the test pulse only condition. Values on 100% would indicate no changed from the test pulse only condition; i.e., no inhibition or no facilitation and higher values would indicate wither less inhibition (SICI) or greater facilitation (ICF). The order of SICI, ICF, and test pulse only trials were randomized within sessions, between sessions, and between subjects.

Quadriceps femoris strength testing

Peak isometric quadriceps strength was collected with athletes seated on a Biodex (Biodex Medical Systems, Shirley NY) dynamometer with hips flexed to 90 degrees and the knee flexed to 60 degrees. After warm up, three maximal voluntary isometric contractions were collected. Peak torque of the three trials normalized to body weight was used for analysis.

Self-reported Function

All subjects completed the International Knee Documentation Committee Subjective Knee Form (IKDC).[37] The IKDC measures self-reported function and includes questions about knee symptoms, sports and daily activities, and current knee function. The IKDC is a validated instrument that is used for patients with various knee conditions (originally designed for knee ligament injuries). The ACLR group completed the IKDC at all three time points while the control group only completed the IKDC at the first time point. None of the athletes in the control group experienced an acute or overuse injury during the course of the study. Therefore, the control group's IKDC score at the first time point was compared to the ACLR group's IKDC at each time point.

3.3.3 Statistical Analysis

For purpose #1 mixed-model analyses of variance (ANOVA) were used to compare SICI and ICF individually with three factors: 1) group (ACLR vs control), 2) limb (surgical vs nonsurgical), 3) time (2 weeks vs quiet knee vs RTS activities). Limb dominance determined the limb of the control group that was analyzed with the surgical or non-surgical limb of the ACLR group. For example, if a subject underwent ACLR on their dominant limb, the dominant limb of the matched control would be analyzed with the surgical limb and the non-dominant limb with the non-surgical limb. Limb dominance was determined by asking the subject with which leg they preferred to kick a ball with.[76]

For purpose #2 linear regression analysis was performed to determine the association between each neurophysiologic measure (i.e. SICI, ICF) and the quadriceps strength of the surgical limb at each time point.

Secondary Reliability Analysis

Ten additional healthy control subjects were recruited to examine test-retest reliability of our intracortical excitability (SICI and ICF) measures. SICI and ICF were measured by the same examiner during 2 sessions held within 24-48 hours of each other. Sessions were held at the same time of day. Two way random intraclass correlation coefficients for absolute agreement ($ICC_{2,1}$) were calculated.[91] Standard error of the measurement (SEM) was calculated for each measure by the following equation: $SEM=SD(\sqrt{1-ICC})$. Finally, the minimal detectable change (MDC) score was calculated using the following equation: $MDC=SEM \times 1.96 \times \sqrt{2}$.

3.4 Results

SICI and ICF to the nonsurgical limb could not be collected in three subjects after ACLR due to the fact that they demonstrated RMTs greater than 85% MSO in their nonsurgical limb. Their data from both limbs was therefore excluded from the purpose #1 analysis. Demographics, timing, and the IKDC results are presented in Table 3.1.

Purpose #1

There was a significant group x limb interaction for ICF (p=0.017) (Table 3.2). The ACLR group demonstrated less facilitation in the surgical limb compared to the nonsurgical limb regardless of time point (p=0.007) while the control's limbs were not different (p=0.564) (Figure 3.1A and 3.1B). Group differences were not present when comparing the surgical limb of the ACLR group to the controls matched limb (p=0.398) and the nonsurgical limb of the ACLR group to the controls matched limb (p=0.185). There was not a significant main effect of time (p=0.919), time x group (p=0.308), time x limb (p=0.054), or 3-way interaction (p=0.422) for ICF. There was no significant main effects, 2-way, or 3-way interactions for SICI ($p \geq 0.124$) (Figure 3.2A and 3.2B).

Purpose #2

In the ACLR group there was a significant relationship between SICI and isometric quadriceps strength of the surgical limb at the quiet knee time point ($R^2=0.320$, $p=0.018$)(Table 3.3). There were no significant relationships between either SICI or ICF and quadriceps strength at the RTS activities time point ($p \geq 0.212$).

Reliability

Table 3.4 lists the results of our reliability analysis including intraclass correlation coefficients, standard error of the mean, and minimal detectable change scores.

3.5 Discussion

The purpose of this study was to examine measures of intracortical excitability and their relationship to isometric quadriceps strength at three time points during the course of post-operative rehabilitation after ACLR. Our hypotheses were partially supported. For purpose #1 we found athletes after ACLR demonstrate asymmetric ICF, yet ICF did not significantly change throughout the course of rehabilitation. No changes over time or group differences were noted with SICI. For purpose #2 we did find relationships between SICI and surgical limb quadriceps strength in the ACLR group, but no relationships between ICF and quadriceps strength. This is the first study to examine intracortical excitability early after ACLR.

Athletes after ACLR demonstrated interlimb differences in ICF defined by less ICF in the surgical limb compared to their nonsurgical limb. However, post-hoc analyses did not detect differences between groups when comparing the ACLR's surgical limb to the control group's matched limb, and the ACLR's nonsurgical limb to the control group's matched limb. Therefore the interlimb differences found in the ACLR group suggest an abnormality in ICF, but we did not detect a change from the "normal" state. The large amount of ICF variability between patients after ACLR and healthy controls make it difficult to examine changes in this measure over time.

While changes were not observed in ICF and SICI over time, the relationship between intracortical excitability and quadriceps strength was not the same as each time point. At 2 weeks after surgery there was not a significant relationship between intracortical excitability and quadriceps strength. At the quiet knee time point we found a significant relationship between SICI and quadriceps strength. At the RTS activities time point, there were no relationships present. The time from 2 weeks after surgery to 2 months (mean time to the quiet knee time point in this cohort) may therefore be ideal for addressing alterations in intracortical excitability. In addition, the direction of these relationships suggest that less inhibition is associated with greater quadriceps strength. Interventions (e.g. transcranial direct current stimulation[66], EMG biofeedback[73], and neuromuscular electrical stimulation[63]) reducing intracortical inhibition may have potential to improve quadriceps strength and function after ACLR.

To our knowledge, there is only one other published study that has examined intracortical excitability after ACLR. Luc-Harkey et al examined active SICI, ICF, and voluntary quadriceps activation in a cohort at a mean of 44 months after ACLR.[57] Individuals with lesser activation of the surgical limb demonstrated greater intracortical inhibition (SICI) while no relationship was found between intracoritcal facilitation ICF and strength, and no relationships were found in the nonsurgical limb. While this study and our study differ significantly in time from surgery to testing, they both indicate that strong relationships exist between SICI and quadriceps function.

There are limitations to this study. First, similar to our study examining corticospinal excitability, we did not obtain measurements prior to ACLR. This study is therefore unable to determine if the alterations found were a result of surgery or present beforehand. Future research should address this limitation by testing cortical excitability pre-operatively. Second, we were unable to obtain SICI and ICF to the nonsurgical limb in three subjects which could have affected our results. Third, peripheral factors, such as muscle volume and cross sectional area may also related to quadriceps function after ACL injury and ACLR, but were not measured in this study.[68,97] Combining measures of cortical excitability to the quadriceps with imaging techniques would provide a more thorough evaluation of quadriceps muscle recovery during the course of rehabilitation. Finally, our sample size was relatively small and was powered based on resting motor threshold values. Given the variability found in ICF and SICI in the present study, a larger sample size is suggested when investigating intracortical excitability longitudinally.

In conclusion, athletes after ACLR demonstrated interlimb differences in ICF during the course of rehabilitation. Additionally, SICI at the quiet knee time point was related to isometric quadriceps strength of the surgical limb. This is the only study to our knowledge to examine intracortical excitability early after ACLR. More studies with larger cohorts are needed to gain a better understanding of the intracortical pathways in the quadriceps muscle following ACLR.

Table 3.1: Participant Demographics, Timing, and Function (**p<.05)

Group		ACLR	Control	p-value
Demographics	Age (years)	21.6 (3.3)	22.3 (2.5)	0.495
	Body Mass Index (kg/m²)	24.5 (3.0)	23.4 (1.9)	0.188
Days From Surgery to each Time Point	2 weeks after ACLR	14.5 (2.2)	---	---
	Quiet Knee	59.2 (19.4)	---	---
	RTS Activities	134.0 (36.5)	---	---
IKDC	2 weeks after ACLR	31.8 (8.9)	98.9 (1.8)	<0.001**
	Quiet Knee	53.4 (12.1)	---	<0.001**
	RTS Activities	63.1 (13.0)	---	<0.001**

Abbreviations: IKDC, International knee documentation committee subjective knee form; RTS, return to sport. Note: the IKDC score for the ACLR group at each time point was compared to the controls IKDC at their first session.

Table 3.2: Measures of intracortical excitability (Mean (SD)) by group at 2 weeks after ACLR, quiet knee, and RTS activities (**p<.05)

Group	**Time Point**	**Limb**	**ICF (%)**	**SICI (%)**
ACLR	2 weeks	Surgical	183 (68)	53 (29)
		Nonsurgical	316 (222)	64 (42)
	Quiet Knee	Surgical	218 (136)	62 (42)
		Nonsurgical	264 (164)	65 (29)
	RTS Activities	Surgical	209 (110)	50 (22)
		Nonsurgical	240 (104)	55 (30)
Control	2 weeks	Surgical	208 (94)	53 (33)
		Nonsurgical	227 (113)	47 (19)
	Quiet Knee	Surgical	242 (98)	57 (30)
		Nonsurgical	202 (89)	44 (18)
	RTS Activities	Surgical	241 (120)	55 (33)
		Nonsurgical	224 (90)	49 (18)
p-values	Main Effect of Group		0.666	0.231
	Group x Limb Interaction		0.017**	0.124
	Group x Limb x Time Interaction		0.422	0.918

Abbreviations: ICF, intracortical facilitation; SICI, short intracortical inhibition RTS, return to sport.

Table 3.3: Linear regression analyses examining the relationship between quadriceps strength and intracortical excitability (ICF, SICI) by time point for the ACLR Group (**p<.05; *p<.1)

	2 Weeks after ACLR		
TMS Measure	**R^2**	**Beta**	**P-value**
Inhibition	0.065	0.61	0.306
Facilitation	0.216	0.495	0.052*
	Quiet Knee		
TMS Measure	**R^2**	**Beta**	**P-value**
Inhibition	0.320	0.991	0.018**
Facilitation	0.161	0.207	0.110
	RTS Activities		
TMS Measure	**R^2**	**Beta**	**P-value**
Inhibition	0.012	-0.379	0.669
Facilitation	0.096	0.239	0.212

Abbreviations: ICF, intracortical facilitation; SICI, short intracortical inhibition RTS, return to sport.

Table 3.4: Test-Retest Reliability Analysis

Measure	ICC	SEM	MDC
SICI	0.509	13.4	37.3
ICF	0.829	22.0	61.0

Abbreviations: ICC, intra-class correlation coefficients (2-way random, absolute agreement); SEM, standard error of the measure; MDC, minimal detectable change

Figure 3.1A: Intracortical Facilitation (ICF) in the ACLR group’s surgical limb compared to the Healthy group’s matched control limb.

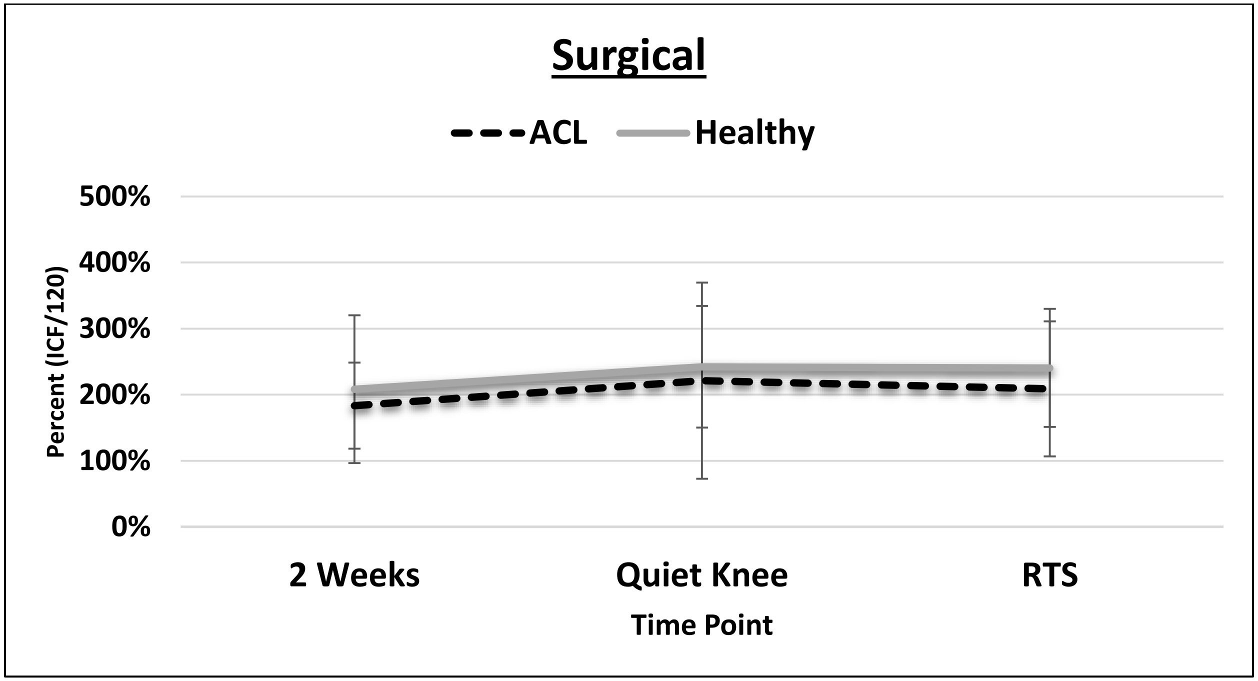


Figure 3.1B: Intracortical Facilitation (ICF) in the ACLR group's nonsurgical limb compared to the Healthy group's matched control limb.

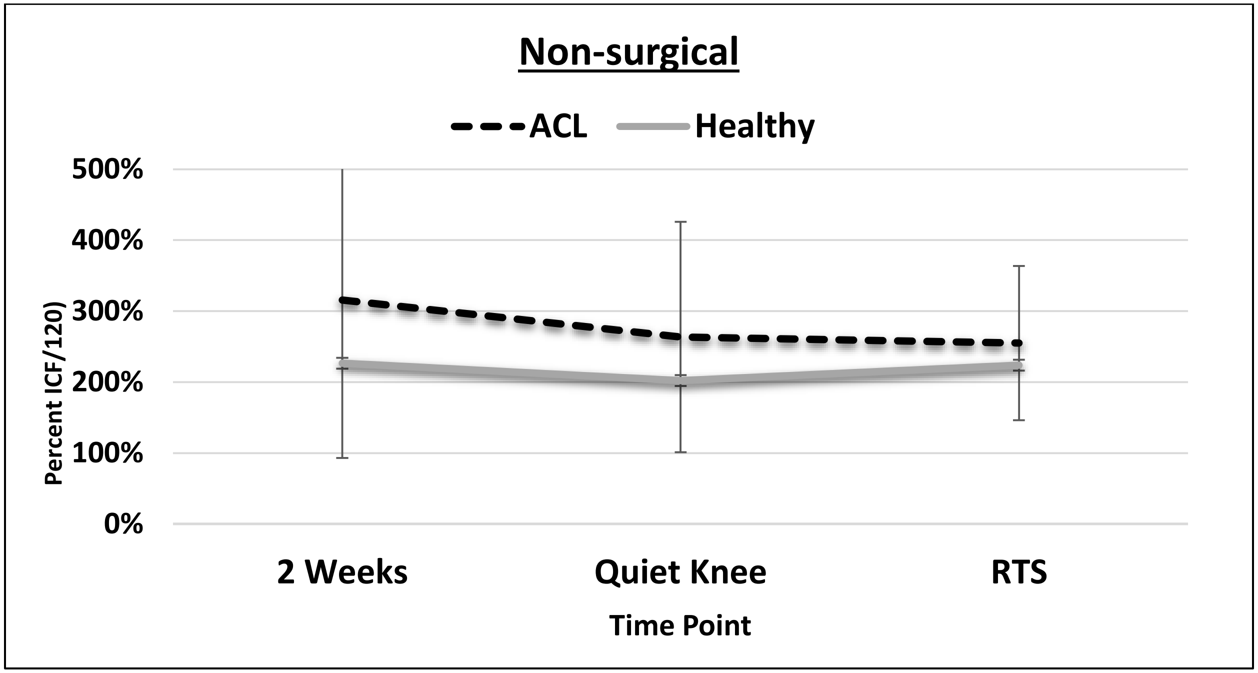


Figure 3.2A: Short Interval Intracortical Inhibition (SICI) in the ACLR group's surgical limb compared to the Healthy group's matched control limb.

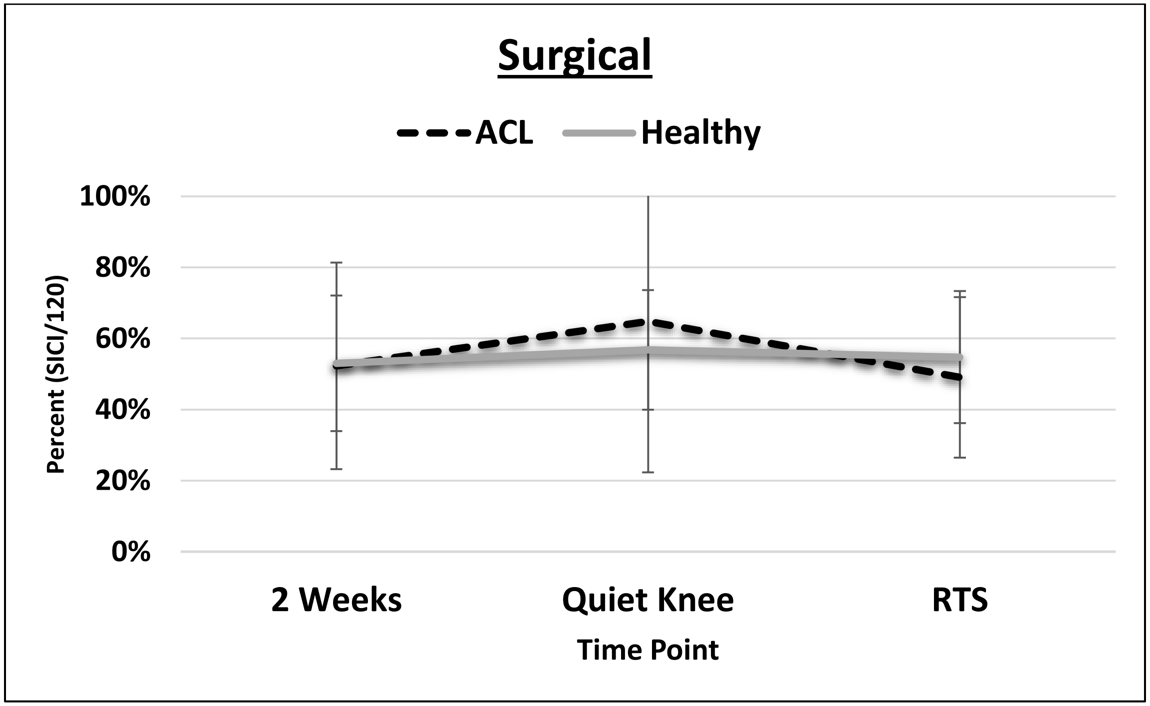
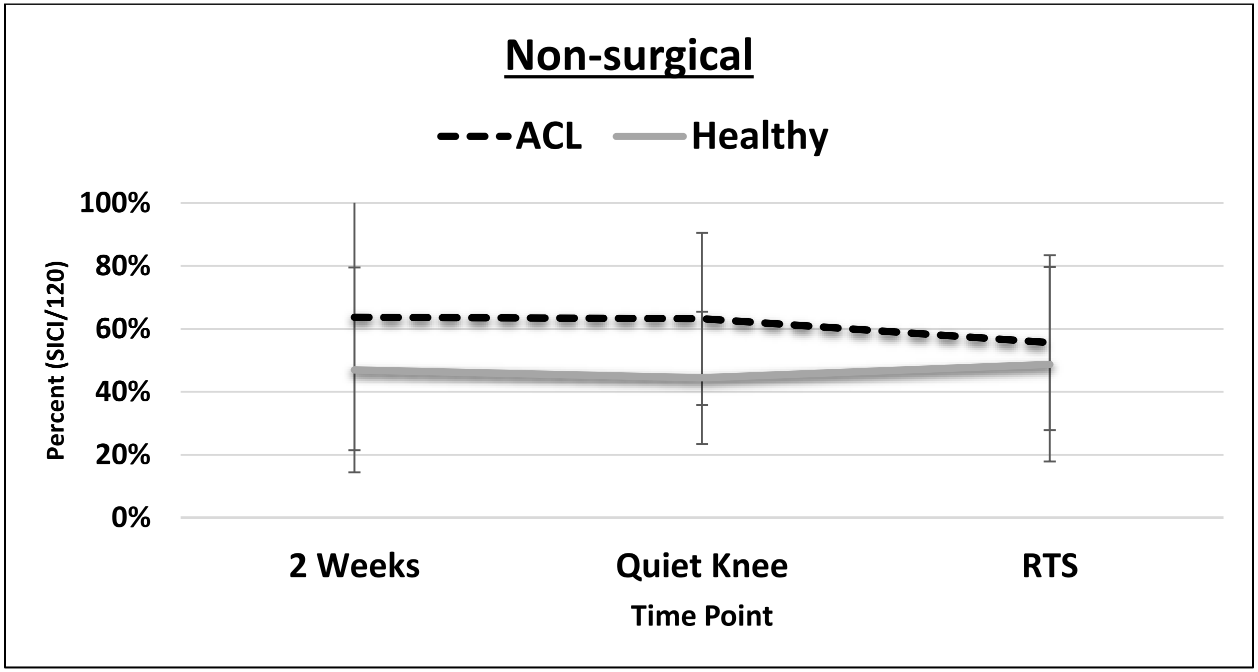


Figure 3.2B: Short Interval Intracortical Inhibition (SICI) in the ACLR group's nonsurgical limb compared to the Healthy group's matched control limb.



Chapter 4

PSYCHOLOGICAL READINESS TO RETURN TO SPORT IS ASSOCIATED WITH KINEMATIC GAIT ASYMMETRY AFTER ACL RECONSTRUCTION

4.1 Abstract

Biomechanical asymmetries occur frequently after anterior cruciate ligament reconstruction (ACLR), and are associated with the early development of osteoarthritis. Psychological factors are associated with functional and activity related outcomes after ACLR. However, the association between biomechanical asymmetry and psychological factors is unknown. The purpose of this secondary analysis of a prospective clinical trial was to determine the relationship between gait symmetry and psychological factors in athletes after ACLR.

Eighty athletes (40 women) underwent gait analysis after impairment resolution (i.e. full range of motion, minimal or no effusion, quadriceps strength index ≥ 80%). Symmetry variables were calculated for knee angles in the sagittal plane at initial contact (IC), peak knee flexion (PKF), and peak knee extension; and peak knee flexion moment (PKFM) and peak knee adduction moment (PKAM). Athletes completed the Anterior Cruciate Ligament-Return to Sport after Injury Scale (ACL-RSI) which measures psychological readiness to return to sport. Pearson correlations were used to examine the association between ACL-RSI and each biomechanical symmetry variable.

Significant correlations were present between ACL-RSI and two kinematic variables: knee flexion angle at IC (r=-.281, p=.012) and PKF (r=-.240, p=.032). Lower scores on the ACL-RSI were associated with greater interlimb kinematic asymmetries.

There is an association between psychological readiness to return to sport and knee kinematics during weight acceptance of gait. The cross-sectional design of this study does not allow us to determine the direction of this relationship. Future research should elucidate the relationship between psychological factors and movement.

4.2 Introduction

Biomechanical gait asymmetries after anterior cruciate ligament reconstruction (ACLR) are evident at 6 months[21] after surgery and can persist for years.[1,13,77] Quadriceps femoris strength deficits can also persist after ACLR and are associated with common gait deviations seen after ACLR.[53,85] Participants after ACLR demonstrate a “stiffened knee” gait pattern characterized by lesser peak knee flexion angles and smaller peak knee flexion moments during stance.[21,40] Participants who are more successful at restoring quadriceps strength demonstrate more normal gait patterns than participants with greater quadriceps deficits.[53,85] However, gait asymmetries exist despite symmetrical quadriceps strength at 6 months after ACLR.[77] Therefore other factors related to neuromuscular control, such as psychological factors, may be contributing to gait asymmetry after ACLR.

Psychological factors are related to functional and activity related outcomes after ACLR.[3,8,48] Studies have examined multiple psychological factors such as fear of reinjury, fear of movement, self-efficacy, confidence, and psychological readiness to return to sport.[8,17,48,50,86,89] Fear of movement and reinjury decrease during the course of post-operative rehabilitation, and are associated with function at a time when athletes return to sport.[17] In addition, changes in fear of movement/reinjury and self-efficacy for rehabilitation tasks predict change in function during the course of post-operative rehabilitation.[18] From an activity related outcomes perspective, fear of reinjury is one of the most commonly cited reasons for not returning to sport.[3,18] Psychological readiness to return to sport (a construct that encompasses emotions, confidence, and risk appraisal) prior to surgery and 4 months after ACLR predict preinjury sport level status 1 year after surgery.[8] Furthermore athletes who return to their pre-injury level of sports 1 year after ACLR have lower levels of fear of reinjury and movement.[49] The aforementioned studies indicate that psychological factors are associated with functional and activity related outcomes after ACLR.

While biomechanical asymmetries persist after ACLR and psychological factors affect outcomes, to our knowledge, no published studies have examined an association between biomechanics and psychological factors. The Anterior Cruciate Ligament – Return to Sport after injury Scale (ACL-RSI) measures psychological readiness to return to sport with questions regarding emotions, confidence, and risk appraisal. The purpose of this study was to determine if a relationship exists between psychological readiness to return to sport and gait biomechanics. We hypothesized that lower scores on the ACL-RSI would be associated with greater kinematic and kinetic asymmetry during over ground walking.

4.3 Methods

4.3.1 Participants

Eighty athletes between the ages of 13-55 who regularly participated (>50 hours per year) in cutting, pivoting, and jumping sports were included in this secondary analysis of a prospective clinical trial. All athletes underwent primary ACLR, completed post-operative rehabilitation, and met the following criteria prior to enrollment: full range of motion, minimal or no effusion, quadriceps strength index ≥ 80%, and initiation of a running progression without increased symptoms. Exclusion criteria included: grade 3 concomitant ligament injury, full-thickness articular cartilage lesions >1 cm^2, prior ACL injury, or significant previous lower extremity injury. At enrollment all participants completed gait analysis and the Anterior Cruciate Ligament – Return to Sport after injury Scale (ACL-RSI). This study was approved by the Institutional Review Board at University of Delaware and written informed consent was acquired prior to inclusion.

4.3.2 Testing

Gait Analysis

Kinematic and kinetic data were collected at enrollment during overground walking. Eight infrared cameras (Vicon, Oxford Metrics LTD, London UK) were used to detect retroreflective markers attached to the base of the 1st and 5th metatarsals, the medial and lateral malleoli, superior and inferior heels, medial and lateral epicondyles of the femurs, greater trochanters, and midline of the iliac crests. Rigid thermoplastic shells with retroreflective markers were attached to each thigh and shank, and the pelvis. This marker set has excellent intersession reliability.[20] Kinetic data were collected using an embedded force plate (Bertec Corporation, Worthington OH). Kinematics and kinetics were sampled at 120 and 1080 Hz respectively.

Participants walked at a self-selected speed maintained to within ±5% along a 6 meter walkway over the force plate. Stance phase joint angles and moments were calculated using rigid body analysis and inverse dynamics respectively (Visual 3D software; C-motion, Germantown MD). Kinematic and kinetic data were low pass filtered (6Hz and 40Hz respectively). Initial contact and toe off were defined by a 50N threshold registered from the force plate. All trials were normalized to 100% of stance. Moments were normalized by mass (kg) and height (m). Variables of interest included knee joint angles in the sagittal plane at initial contact (IC), peak knee flexion (PKF), and peak knee extension (PKE); peak knee adduction moment (PKAM), and peak knee flexion moment (PKFM) were also variables of interest.

Self-Reported Psychological Measure

Participants completed the ACL-RSI.[45,90] This scale includes 12 questions, and measures an athlete's psychological readiness to return to sport, which encompasses emotions (including fear of reinjury), confidence, and risk appraisal. The ACL-RSI is scored on a scale from 0-100 with higher scores indicating a more positive psychological outlook (i.e., less fear of reinjury, more confidence). The ACL-RSI has good face validity, good internal consistency, high construct validity and high test-retest reliability.[45]

4.3.3 Statistical Analysis

Independent *t* tests were used to compare group differences in demographics. Symmetry measures for each kinematic and kinetic variable were calculated by subtracting the involved limbs value from the uninvolved limbs value (symmetry variable = uninvolved limb value – involved limb value). Therefore a positive symmetry value for the kinematic variables indicate lesser knee flexion in the surgical limb, and lesser knee moments in the surgical limb for the kinetic variables. Pearson product correlations were used to test the association between ACL-RSI score and each symmetry variable of interest. When significant correlations were found, a separate analysis was performed to make the findings more clinically relevant. For this separate analysis, participants were split into three groups by their respective ACL-RSI scores. Based on the median ACL-RSI score, the lowest 25% of scores were allocated to the LOW ACL-RSI scores group, the middle 50% to the MIDDLE ACL-RSI scores group, and the highest 25% to the HIGH ACL-RSI scores group. A 2 (limb) by 3 (group) mixed-model analysis of variance was used to compare limb differences between the three groups. When significant interactions were found, post-hoc *t* tests with Bonferroni correction were used to examine limb symmetry in each group. Statistical significance was set at $p \leq .05$.

4.4 Results

Correlation Analyses

Significant associations were found between ACL-RSI and two kinematic symmetry variables: knee flexion angle at IC ($r=-.281$, $p=.012$) and knee flexion angle at PKF (r=-.240, p=.032). There were no associations between ACL-RSI and knee flexion angle at PKE (r=-.096, p=.398), PKFM (r=.114, p=.315), or PKAM (r=.108, p=.340).

Group Analysis

The median ACL-RSI score was 61. Nineteen Participants made up the LOW ACL-RSI group (ACL-RSI score ≤ 47, ACL-RSI mean ± SD: 3.4±1.1), 41 in the MIDDLE ACL-RSI group (ACL-RSI score between ≥ 48 and ≤ 78, 6.2±0.9), and 20 in the HIGH ACL-RSI group (ACL-RSI score ≥ 79, 9.0±0.6). There were no group differences in age (p=.708), sex (p=.481), body mass index (p=.848), or weeks from surgery to enrollment (p=.944)(Table 4.1).

Knee Kinematics

Significant limb by group interactions were found in knee flexion angle at IC (p=.009) and PKF (p=.003)(Table 4.2). At IC the LOW group only displayed significant interlimb asymmetries characterized by less knee flexion in the surgical limb compared to their nonsurgical limb (mean interlimb difference [95% confidence interval], p-value) (LOW: 2.4 [0.7-4.2], p=.008; MIDDLE: -0.7 [-1.9-0.5], p=.278; HIGH: -1.0 [-2.7-0.8], p=.263) (Figure 4.1A-C). None of the group's interlimb differences exceeded the minimal clinically important difference (MCID) of 3 degrees.[22] At PKF the LOW (7.1 [4.9-9.2], p<.001), MIDDLE (2.5 [1.1-3.9], p=.001), and HIGH (3.3 [1.2-5.4], p=.002) groups all displayed interlimb asymmetries characterized by less knee flexion in the surgical limb. Both the LOW and HIGH group's lesser knee flexion in the surgical limb exceeded the MCID.

For knee flexion angle at PKF we performed an additional analysis to determine the proportion of subjects in each group that displayed clinically meaningful reductions (i.e. greater than 3 degrees) in the surgical limb's peak knee flexion angle compared to the nonsurgical limb's peak knee flexion angle. Sixteen of 19 subjects in the LOW group (84%), 16 of 40 in the MIDDLE group (40%), and 9/21 in the HIGH group (43%) demonstrated clinically meaningful reductions in peak knee flexion angle. The LOW group was approximately 8 times more likely to display clinically meaningful reductions in peak knee flexion angle compared to the MIDDLE group (odds ratio=8.331, p=.003) and 6 times more likely to display reduced peak knee flexion compared to the HIGH group (odds ratio=6.517, p=.015).

4.5 Discussion

The purpose of this study was to examine the relationship between psychological readiness to return to sport and gait biomechanics in patients after ACLR. A significant, small to medium[19], relationship was found between ACL-RSI and two of three of the kinematic variables evaluated, while no relationships were found with kinetics. Additionally, the athletes with the lowest ACL-RSI scores (LOW group) psychological outlook demonstrated the greatest sagittal plane kinematic asymmetries when compared to athletes in the MIDDLE and HIGH groups. This is the first study to examine and identify a relationship between psychological factors and knee kinematics after ACLR. The cross-sectional design of this study prevents us from determining the direction of the relationship established. Future research should determine if specific interventions directed at psychological factors lead to improvements in gait asymmetry after ACLR, or vice versa.

The athletes in the LOW group demonstrated more asymmetry in knee flexion angles which was characterized by less knee flexion in the surgical limb at both IC and PKF compared to their nonsurgical limb. At IC the LOW groups surgical limb was in less flexion (i.e. more extended position) compared to the nonsurgical limb, while the MIDDLE and HIGH groups were relatively symmetrical. While the LOW group's limbs were statistically different, their interlimb difference did not exceed the MCID of 3 degrees.[22] This difference may therefore not be clinically significant. However, two previous studies found similar results when analyzing group differences in knee angle at IC. Di Stasi and colleagues compared knee angle at IC between athletes who passed return to sport (RTS) functional testing and athletes that failed RTS testing.[21] The athletes that failed RTS testing at 6 months after ACLR displayed less knee flexion at IC in the surgical limb compared to the nonsurgical limb; the group that passed RTS testing was symmetrical. Rudolph and colleagues compared knee flexion angle at IC between ACL deficient athletes classified as copers with athletes classified as noncopers. Noncopers demonstrated less knee flexion in the surgical limb compared to the nonsurgical limb during walking and jogging. Copers were symmetrical at IC. At PKF the LOW group's interlimb difference (7 degrees less in the surgical limb) in knee flexion angle greatly exceeded the MCID of 3 degrees. The MIDDLE group's mean flexion angle at PKF did not exceed the MCID while the HIGH group's was at the MCID. Reduced peak knee flexion angle was also found in athletes that fail return to sport testing 6 months after ACLR,[22] and non-copers after ACL injury.[82] Therefore the LOW group's sagittal plane knee kinematics during the weight acceptance phase of gait from the present study mirror the gait pattern of athletes that fail return to sport testing and non-copers.

A significant relationship was not found between our kinetic variables and psychological readiness to return to sport. A recent systematic review and meta-analysis found strong evidence that peak knee flexion moments are reduced after ACLR compared to contralateral limb and controls and remain lower for up to 6 years.[40] Moderate to strong evidence was found for reduced peak knee adduction moments in the surgical limb compared to the contralateral limb and controls within the first year after ACLR. Our cohort was tested at a mean of 5.4 months after ACLR. It is plausible that there was not sufficient variability in our cohort's kinetic asymmetry this early after ACLR. Future research should examine the relationship of psychological factors and gait at later time points after ACLR.

The prevalence of knee osteoarthritis (OA) after ACLR is high with a recent systematic review indicating 44% of patients after ACLR develop OA.[59] Altered biomechanics have been implicated as a factor contributing to the increased risk of OA.[2,32] A recent study found that asymmetrical loading (i.e. underloading the surgical limb) during gait early after ACL injury and 6 months after ACLR were associated with radiographic signs of OA five years after surgery.[92] The group with a LOW ACL-RSI scores from our study demonstrated greater asymmetry in knee kinematics.

Future research exploring gait mechanics and OA should consider evaluating psychological factors.

Quadriceps femoris muscle weakness is common after ACLR.[27,68] Studies have examined the relationship between quadriceps strength and biomechanics with mixed findings. Two studies found a relationship between quadriceps strength and gait symmetry indicating better quadriceps strength contributes to better symmetry.[53,85] Conversely, Gokeler et al found no correlation between quadriceps strength and gait analysis parameters. Roewer et al found gait asymmetries were present during weight acceptance despite restoration of quadriceps strength.[77] Our cohort had to demonstrate adequate (≥80% quadriceps index) prior to enrollment. Our findings, therefore, suggest that gait asymmetries are present in athletes with LOW ACL-RSI scores even among athletes with adequate quadriceps strength.

There are limitations to our study. The study design is cross sectional and we are therefore unable to determine cause and effect. A second limitation is that we formed groups based on quartiles of the subject's ACL-RSI scores. Using a different method to divide our cohort into groups could affect the findings. However, the group analysis allowed us to make our findings more clinically relevant.

The results of this study indicate that there is a relationship between psychological readiness to return to sport and sagittal knee kinematics during gait in athletes attempting to return to sport after ACLR. Lower ACL-RSI scores were associated with greater kinematic asymmetries during weight acceptance of gait. The cross sectional design of this study does not allow us to determine the direction of this relationship. Future research should attempt to elucidate the relationship between psychological factors and movement to determine if addressing psychological factors leads to improved symmetry or if addressing gait asymmetries leads to changes in psychological factors.

Table 4.1: Participant Demographics

Variable	Group			p-value model
	Negative† N=19	Neutral† (N=41)	Positive† (N=20)	
Age (years)	22.3 ± 6.5	20.6 ± 7.6	21.0 ± 8.7	0.708
Sex	9 women, 10 men	23 women, 18 men	8 women, 12 men	0.481
BMI (kg/m^2)	25.6 ± 3.8	26.3 ± 3.3	25.9 ± 3.0	0.848
Weeks from Surgery to Enrollment	24.1 ± 8.8	23.6 ± 7.3	23.3 ± 9.2	0.944

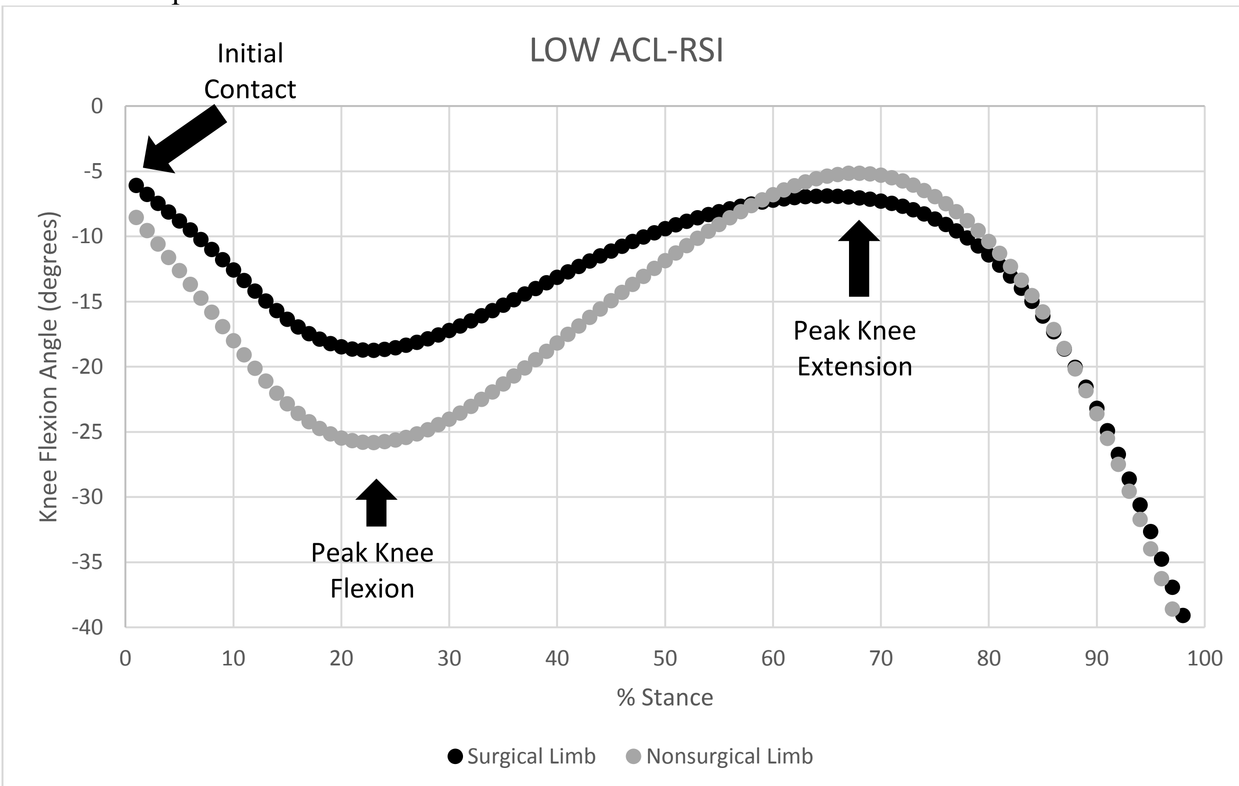
†values are mean ± SD

Table 4.2: Significant limb by group interactions were found for knee flexion angle at IC (p=0.009) and at PKF (p=0.003).

Biomechanical Variable	Group	Surgical Limb†	Nonsurgical Limb†	p-value‡
Knee Flexion Angle @ IC (°)	LOW ACL-RSI N=19	6.1 (3.8)	8.5 (3.9)	0.008
	MIDDLE ACL-RSI N=40	7.2 (3.9)	6.5 (4.2)	0.278
	HIGH ACL-RSI N=21	7.4 (2.3)	6.3 (2.8)	0.263
Knee Flexion Angle @ PKF (°)	LOW ACL-RSI N=19	18.9 (7.0)	26.0 (5.5)	<0.001*
	MIDDLE ACL-RSI N=40	20.4 (5.9)	22.9 (4.8)	0.001
	HIGH ACL-RSI N=21	21.3 (4.2)	24.6 (3.8)	0.002*

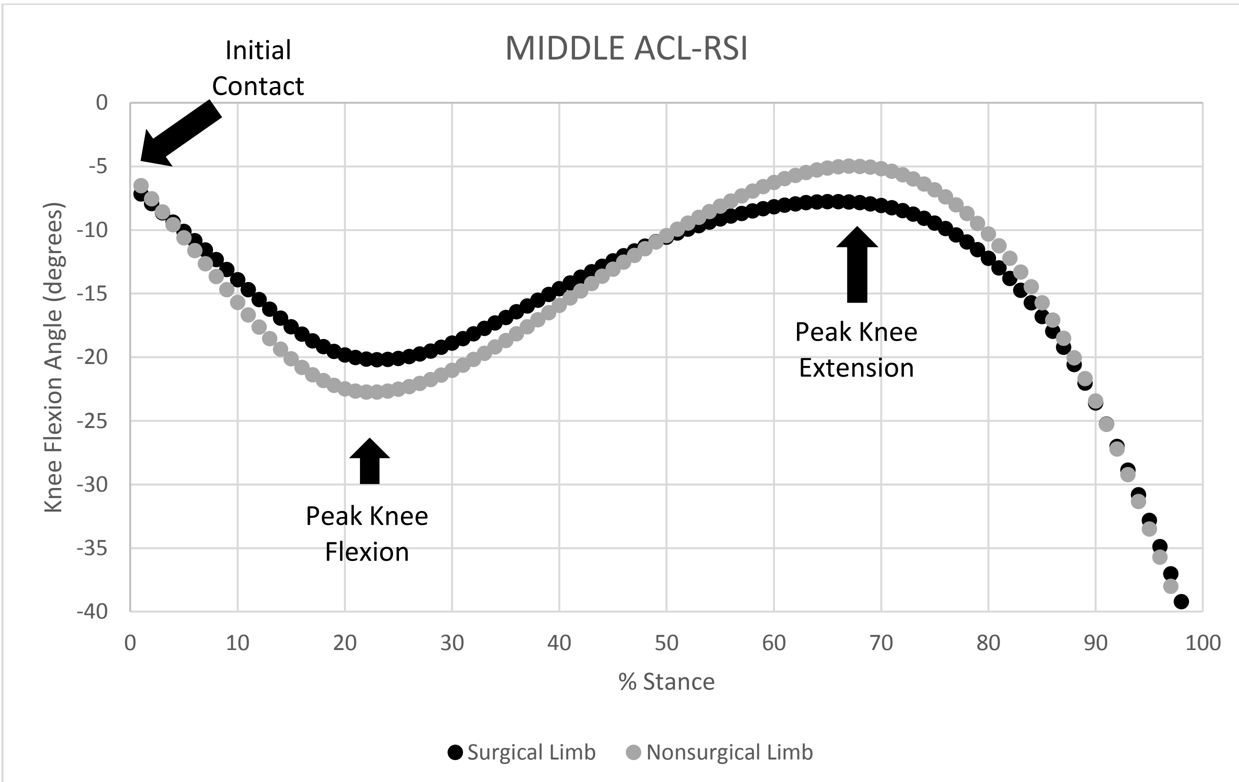
†Values are mean ± (SD).
‡ p-values for post-hoc t tests with Bonferroni correction to examine interlimb differences in each group.
*Interlimb difference exceeded minimal clinically important difference of 3 degrees
Abbreviations: IC, initial contact; PKF, peak knee flexion; ACL-RSI, Anterior Cruciate Ligament-Return to Sport after Injury Scale

Figure 4.1A: Time series curves for sagittal plane knee angles during the stance phase of gait in the LOW ACL-RSI Score's Group.



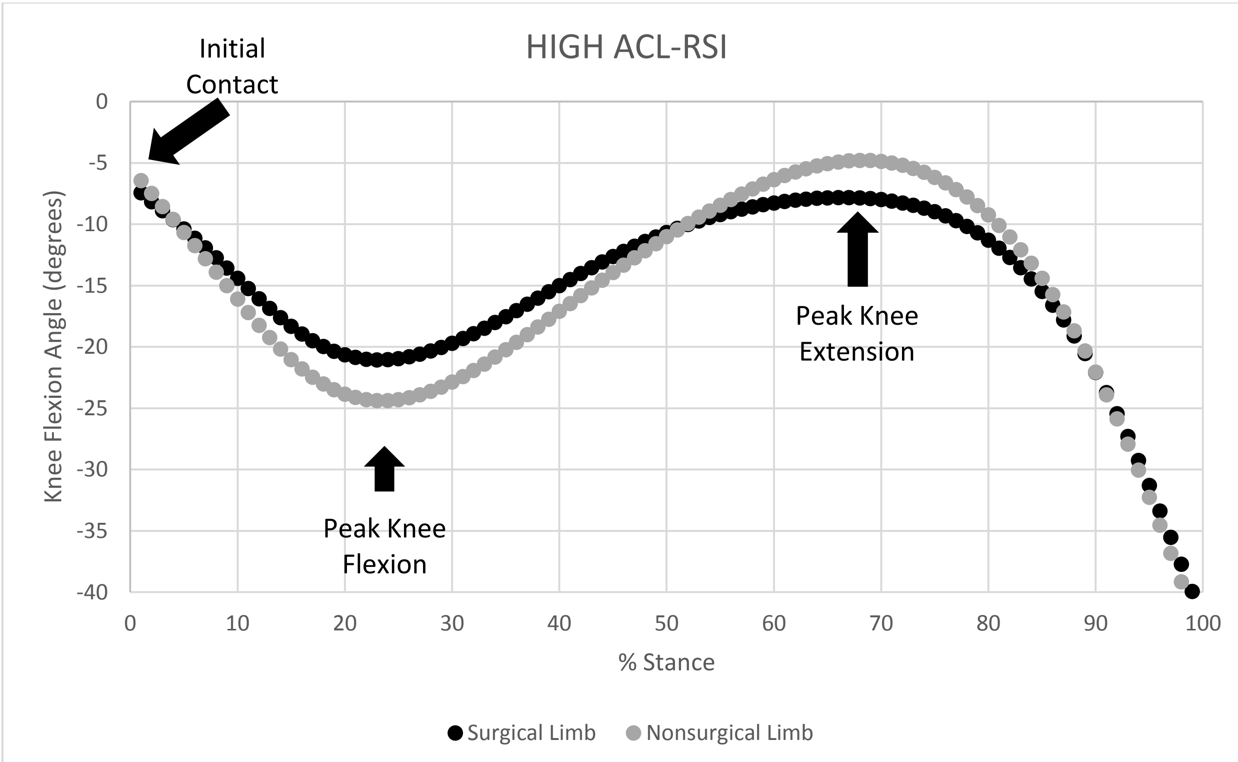
Note: Flexion is negative

Figure 4.1B: Time series curves for sagittal plane knee angles during the stance phase of gait in the MIDDLE ACL-RSI Score's Group.



Note: Flexion is negative

Figure 4.1C: Time series curves for sagittal plane knee angles during the stance phase of gait in the HIGH ACL-RSI Score's Group.



Note: Flexion is negative

Chapter 5

ATHLETES WITH A POSITIVE PSYCHOLOGICAL RESPONSE TO A SECONDARY ACL INJURY PREVENTION PROGRAM HAVE BETTER SELF-REPORTED FUNCTIONAL OUTCOMES

5.1 Abstract

Fear of re-injury and psychological readiness to return to sport have emerged as important factors affecting outcomes following anterior cruciate ligament reconstruction (ACLR). The time when athletes transition from rehabilitation to return to sport can be especially fearful. Psychological factors are potentially modifiable at this time, and improving them may lead to better outcomes. The purpose of this secondary analysis of a prospective clinical trial was to determine: 1) whether a secondary injury prevention program led to improved psychological outlook, 2) whether athletes who showed a positive psychological response to the program had better self-reported function and activity outcomes compared to athletes who did not have a clinically meaningful change in their psychological response.

Following ACLR and completion of formal rehabilitation, 68 level I/II athletes completed the following self-report measures at enrollment (pre-training): Anterior Cruciate Ligament-Return to Sport after Injury scale (ACL-RSI), International Knee Documentation Committee Subjective Knee Form (IKDC), and the five subscales of

the Knee injury and Osteoarthritis Outcome Score (KOOS). Subjects then underwent ten additional sessions, including agility training, plyometric training, and progressive strength training that gradually progressed in quantity and complexity. All self-report measures were repeated after training (post-training). Subjects subsequently completed the IKDC, KOOS, and indicated whether they had returned to their pre-injury level of sport one year after ACLR. Subjects were dichotomized into 2 groups based on their ACL-RSI scores: those who displayed an increase in ACL-RSI score from pre-training to post-training that exceeded the MCID ($\geq$19) were defined as having a positive psychological response (responder) to training while those who did not were defined as nonresponders. A mixed-model analysis of variance was used to determine if group differences existed over the three time points.

The entire cohort displayed an increase in ACL-RSI(mean ± SD) from pre-training (56.9 ± 18.7) to post-training (69.4 ± 20.7)($p<.001$). Fifty-seven percent of the cohort qualified as responders. A significant group x time interaction was found for the IKDC, KOOS-Sport, and KOOS-QOL ($p\leq.031$). The responders had higher IKDC scores at post-training and higher KOOS-Sport scores at post-training and 1 year. There was not a significant group difference in the number of athletes that returned to their pre-injury level of sport at 1 year ($p=.113$).

Fifty-seven percent of the athletes in this study displayed a meaningful improvement in psychological outlook. Responders demonstrated better self-reported function at post-training and one year after ACLR. Treatment programs incorporating progressive agility, plyometric, and strength training have the potential to positively influence psychological readiness to return to sport in a sub-group of athletes.

5.2 Introduction

Upwards of 200,000 anterior cruciate ligament (ACL) ruptures occur each year in the United States.[61] Anterior cruciate ligament reconstruction (ACLR) is the gold standard treatment for athletes involved in cutting, jumping, and pivoting sports with the goal of returning the athlete to their prior level of sport. However, recent data suggests that less than two-thirds of athletes that undergo ACLR return to their prior level of sport despite good knee function.[7,9] Psychological factors, such as fear of reinjury, confidence, self-efficacy, and psychological readiness to return to sport have emerged as potential barriers for athletes attempting to return to sport.[5,6,8,36,44,49,50] Webster et al developed the the ACL-Return to Sport after Injury Scale (ACL-RSI) which measures psychological readiness to return to sport.[90] Psychological readiness to return to sport encompasses three psychological responses (emotions, confidence, and risk appraisal) specifically related to returning to sport. Cross sectional studies have found that athletes who were able to return to sport had higher ACL-RSI scores.[5,45] Prospective studies also indicate that higher ACL-RSI scores, indicating a more positive psychological outlook, are predictive of returning to sport and return to competition.[8,47]

Transitioning back to sport can be especially fearful for athletes after ACLR.[3] This also happens to be the time when athletes are weaned from consistent rehabilitation and focus is placed on an independent program. The ACL Specialized Post-Operative Return to Sport (ACL-SPORTS) secondary injury prevention program was designed to bridge the gap between the time when formal physical therapy traditionally ends and the time an athlete returns to sport.[93] While this program was not specifically designed to address psychological factors, such as fear of reinjury and confidence, it does apply the concepts of graded activity and graded exposure that have been investigated with other patient populations. For example, graded exposure is effective in reducing disability, pain, and catastrophizing in patients with chronic low back pain.[56] The ACL-SPORTS secondary injury prevention program therefore has the potential to improve psychological readiness to return to sport.

No published studies to our knowledge have investigated the effects of a secondary injury prevention program on psychological factors. Furthermore, it is unknown whether a change in psychological outlook during the time an athlete is transitioning back to sport leads to better functional and activity related outcomes. Therefore, the purpose of this study was threefold: 1) to determine if this secondary injury prevention program leads to a more positive psychological outlook (i.e. reduced fear, improved confidence), 2) to determine if athletes who demonstrate an improvement in psychological readiness to return to sport have better function after the program, and at 1 year after ACLR, 3) to determine if athletes who demonstrate an improvement in psychological readiness to return to sport have better activity related outcomes at 1 year after ACLR. We hypothesized that the cohort as a whole would demonstrate an improvement in psychological readiness to return to sport after the secondary injury program. We also hypothesized that athletes with an improvement in psychological readiness to return to sport would demonstrate better outcomes immediately after the program and at 1 year after ACLR compared to athletes that did not demonstrate a meaningful positive response.

5.3 Methods

5.3.1 Participants

Sixty-eight level I/II athletes between the ages of 13 and 55 (participated in cutting, pivoting, jumping sports for at least 50 hours per year)[33] after primary ACLR were included in this secondary analysis of a prospective clinical trial. All athletes were part of a randomized controlled trial (NCT01773317) investigating the effect of a secondary injury prevention program with or without the addition of a specialized neuromuscular training program.[93] This clinical trial was approved by the institutional review board at the University of Delaware and all subjects completed informed consent.

Following ACLR, all subjects received post-operative rehabilitation and had to meet the following criteria prior to enrollment: between 3 and 10 months after ACLR, at least 80% quadriceps strength index, full range of motion, minimal effusion present, ability to hop on one leg without pain, and had started a running progression. Subjects were excluded from enrollment in this trial if they presented with a previous ACL injury or other significant lower extremity injury, concomitant grade III ligament injury, or an osteochondral defect $\geq 1\text{cm}^2$.

5.3.2 Testing

Training Program

Full details of the secondary injury prevention protocol have been published.[93] All subjects in the trial underwent 10 sessions of progressive strengthening, plyometric training, and agility training. Proper form (encouraging greater knee flexion and reducing lower extremity valgus) was encouraged throughout the sessions during the plyometric and agility exercises. Plyometric and agility exercises were gradually progressed in quantity and complexity over the course of the 10 sessions. For example, single legged plyometric exercises were performed over ground during the first 3 sessions. Sessions 4-10 incorporated a hurdle that increased in height over the sessions. For agilities, linear movements were introduced first and then progressed to multidirectional movements with the athlete completing movements related specifically to their individual sport and utilizing a ball/equipment specific to their sport.

Self-Reported Measures

All subjects completed the ACL-RSI at enrollment (pre-training) and also after the training program (post-training).[90] This scale includes 12 questions, and measures an athlete's psychological readiness to return to sport, which encompasses emotions (including fear of reinjury), confidence, and risk appraisal. The ACL-RSI is scored on a scale from 0-100 with higher scores indicating a more positive psychological outlook in terms of returning to sport (i.e., less fear of reinjury, more confidence). Subjects in the present study were dichotomized into 2 groups based on their ACL-RSI score. Subjects who displayed an increase in ACL-RSI score from pre-training to post-training that equaled or exceeded 10 points were defined as having a positive psychological response (responder) to training while those who did not were defined as non-responders. An increase of 10 or greater was chosen to define the groups based on face validity and known group validity due to the fact that there are no established minimal detectable change (MDC) or minimal clinically important difference (MCID) scores for the ACL-RSI. Face validity was based on expert consensus from our research group who has extensive clinical and research experience in the ACL population. We believe that an increase of 10 reflects a significant improvement as it indicates at least a 1 point increase on each of the twelve questions on the ACL-RSI. Langford et al examined ACL-RSI scores at 3 and 6 months after ACLR, which is within the same time frame as our cohort. At 3 months the group of athletes that returned to competition at one year scored 9 points higher on the ACL-RSI and eleven points higher at 6 months.

In addition to the ACL-RSI, all subjects completed the International Knee Documentation Committee Subjective Knee Form (IKDC)[33], and the 5 subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS)[78] at pre-training, post-training, and one year after ACLR. The IKDC is a validated instrument that is used for patients with various knee conditions and includes questions about symptoms, sports and daily activities, as well as current knee function.[37] The KOOS was designed to evaluate short-term and long-term outcomes in subjects after knee injury and knee osteoarthritis. It is reliable and valid for competitive athletes and includes 5 subscales: 1) KOOS pain, 2) KOOS symptoms, 3) KOOS activities of daily living (KOOS-ADL), 4) KOOS Sport and Recreation, 5) KOOS quality of life (KOOS-QOL).[83] Finally, subjects were asked at one year after ACLR if they have returned to their previous level of sport activity.

5.3.3 Statistical Analysis

All statistical analyses were performed using SPSS Version 24.0 (IBM Corp, Armonk, NY). A paired t-test was used to determine differences in ACL-RSI scores of the entire study population from pre-training to post-training. A mixed model analysis of variance was performed for the IKDC and each subscale of the KOOS to determine group (responder vs. nonresponder) differences over the three time points (pre-training, post-training, 1 year). Independent t-tests and chi-square were used to determine differences between groups in timing and demographics. Chi-square tests were used to determine if group differences existed in the number of athletes that returned to their previous level of sport at 1 year. A p-value $\leq .05$ was determined a priori to denote statistically significant differences between groups.

5.4 Results

Pre-training to Post Training ACL-RSI

There was a significant increase in ACL-RSI score from pre-training to post-training when analyzing all sixty-eight athletes as a whole (pre-training: 56.9 ± 18.7, post-training: 69.4 ± 20.7, $p<.001$).

Responder vs. Nonresponder Analyses

Thirty-nine athletes (57%) demonstrated an increase in ACL-RSI ≥ 10 to form the responder group (pretraining score= 56.4 ± 19.4; post-training score=79.2 ± 15.5), while twenty-nine athletes had a change < 10 and formed the nonresponder group (pretraining score= 58.4 ± 18.1; post-training score=56.8 ± 17.8). There were no significant group differences in sex (p=.220), age (p=.230), body mass index (p=.498), weeks from surgery to pre-training (p=.430), or weeks from surgery to post-training (p=.445)(Table 1).

There was a significant main effect of group, main effect of time, and group x time interaction for IKDC, and KOOS-Sport (Table 2). Both group's IKDC scores improved from pre-training to post-training (p≤.014), while only the nonresponders improved from post-training to 1 year (p<.001). The responders displayed significantly higher IKDC scores than the nonresponders only at post-training (p<.001). For KOOS-Sport only the responders improved significantly from pre to post-training (p<.001) and only the nonresponders improved from post-training to 1 year (p=.007). The responders displayed higher KOOS-Sport scores at post-training (p=.002) and 1 year (p=.022). There was a significant main effect of time and group x time interaction for KOOS-QOL. The responders improved from pre to post-training and post-training to 1 year (p<.001), while the nonresponders only improved from post-training to 1 year (p<.001). There were main effects of time for KOOS-

Symptoms, KOOS-Pain, and KOOS-ADLs ($p \leq .001$), but not group x time interactions ($p \geq .517$).

At 1 year there was not a significant group difference in the percentage of athletes that returned to their previous level of sport (responder: 31/39, 79%; nonresponder: 18/29, 62%; $p = .113$)

5.5 Discussion

The purpose of this study was to determine if a secondary ACL injury prevention program led to an improved psychological outlook and to determine if athletes who demonstrated a positive psychological response to this program had better self-reported function and activity related outcomes. Our first hypothesis was confirmed as the entire cohort demonstrated a significant improvement in psychological outlook after completing the program. Our second hypothesis was also confirmed. The responder group demonstrated better self-reported function at post-training and at one year when compared to the nonresponders. Our third hypothesis was not supported as there was not a significant difference among the groups in the number of athletes who returned to their previous level of sport at 1 year. Findings from this study offer important considerations for clinicians and future research. A supervised secondary injury prevention program, with no direct focus on altering psychological factors, has the potential to positively influence psychological readiness to return to sport and lead to improved self-reported function.

There were group by time interactions for the IKDC, KOOS-Sport, and KOOS-QOL scales. These three scales encompass questions regarding sport, higher level activities, and overall knee related quality of life. They are therefore appropriate to use with athletes at this point in rehabilitation process. All groups improved over the course of the study (i.e. pre-training to 1 year) in all three measures. However, the responder group displayed significant improvements in all three scales from pre-training to post-training while the nonresponders only improved in IKDC. On the other hand, the nonresponders improved in self-reported function on all 3 scales from post-training to 1 year while the responders only improved on the KOOS-QOL. This indicates that there is a timing aspect to improvements in self-reported function between the groups with the responders reporting better function earlier. This has both positive and potentially negative implications for the responder group. From a positive perspective, a 90% or better score on a self-reported functional measures is often used as one criteria needed to allow an athlete to return to sport. The responders approached 90% on the IKDC and exceeded 90% on the KOOS-Sport at post-training. Better self-reported function may allow these athletes to return to sport earlier than the nonresponder group. From a negative perspective, early return to sport after ACLR is associated with increased risk of sustaining a reinjury or second ACL injury.[12,29,46] Having better self-reported function and a better psychological outlook may allow an athlete to return to sport before they are physically ready. Future research should explore the relationship between psychological readiness, functional impairment measures (e.g. strength testing and single-legged hop testing), and second ACL injury.

The athletes in our cohort displayed similar ACL-RSI scores to other studies around this time frame. Langford et al examined psychological readiness to return to sports at 6 months post-ACLR.[47] Athletes that returned to competitive sport at 12 months had mean ACL-RSI scores of 63, while athletes that did not return to competition had a mean of 52. Ardern et al examined ACL-RSI scores at 4 months after ACLR finding that athletes who returned to sport at 1 year had a mean of 57, while athletes who did not return to sport had a mean of 40.[8] Using a receiver operation curve analysis, the authors found a cutoff score of 56 at 4 months after ACLR was best at discriminating the athletes that are able to return to sport versus those that are not able. In the present study, the responders displayed very similar scores (mean of 56) to the nonresponders (mean of 58) and both group's scores were at or very close to the cut off score determined by Ardern et al. Our entire cohort therefore displayed psychological readiness scores that could potentially benefit from improvement.

To our knowledge, this is the first study to examine if changes in psychological outlook after completing a secondary injury prevention program led to improved self-reported function after ACLR. However, the relationship between functional outcomes and psychological factors have been investigated.[17,18] A recent clinical review indicates that self-reported function and fear of reinjury are associated during the late stages of rehabilitation.[36] Inconsistent findings have been found during the earlier stages of rehabilitation, when physical impairments may contribute more to functional deficits.[50] Future research should continue to evaluate how specific interventions affect psychological outlook given the association between psychological factors and outcomes after ACLR.

There are limitations to this study. First, there are currently no known minimal detectable change (MDC) or minimally clinically important difference (MCID) scores established for the ACL-RSI on the original 0-100 scale. Only one study examined test-retest reliability and calculated minimal detectable change scores.[45] This study used a 1-10 scale as opposed to more recent studies[4–6] using a 0-100 scale and is therefore inappropriate to use. We therefore dichotomized our groups based on known groups validity and face validity. Future research should attempt to calculate MDC and MCID scores for the ACL-RSI. Second, based on the studies design we are not able to ascertain whether having an improvement in psychological readiness led to better self-reported function or if an improvement in function led to psychological readiness scores. Future research should examine interventions directly related to improving psychological readiness to return to sport.

In conclusion, 57% of the athletes in this study demonstrated a positive psychological response by our definition to the secondary ACL injury prevention program. These athletes (responders) demonstrated better self-reported function immediately following the program and at 1 year after ACLR when compared to the nonresponders. Our findings suggest that graded interventions commonly used in secondary injury prevention programs (i.e. plyometrics, agilities, strengthening) may modify psychological outlook in a sub-group of athletes returning to sport after ACLR. Future research should examine whether interventions directly addressing psychological outlook (e.g. cognitive behavioral therapy) improve functional and activity related outcomes after ACLR.

Table 5.1: Demographics and Timing between Responders and Nonresponders

	Responder (N=39)	Nonresponder (N=29)	p-value
Sex	23 women, 16 men	12 women, 17 men	0.220
Age (years)	20.6 ± 7.6	23.0 ± 8.5	0.230
BMI (kg/m²)	25.9 ± 3.6	26.4 ± 2.9	0.498
Weeks from surgery to pre-training	24.4 ± 7.8	22.9 ± 7.7	0.430
Weeks from surgery to post-training	31.7 ± 9.2	31.1 ± 7.4	0.445

Abbreviations: BMI, body mass index

Table 5.2: Self-Reported Functional measures at pre-training, post-training, and 1 year between Responders and Nonresponders. (Values are means ± standard deviations. * indicates p<.05)

Measure	Group	Pre	Post	1 Year	ME Time	ME Group	Group x Time
IKDC	**Responder**	**76.9 ± 9.9**	**88.7 ± 8.1**	**92.6 ± 10.3**	**<.001***	**0.010***	**0.003***
	Nonresponder	**75.0 ± 8.4**	**79.7 ± 9.4**	**89.8 ± 9.7**			
KOOS-Sport	**Responder**	**78.1 ± 15.4**	**91.7 ± 10.7**	**95.0 ± 8.4**	**<.001***	**0.026***	**0.031***
	Nonresponder	**76.9 ± 13.9**	**82.4 ± 13.0**	**89.5 ± 11.0**			
KOOS-QOL	**Responder**	**54.8 ± 15.7**	**69.5 ± 21.2**	**82.7 ± 15.3**	**<.001***	**0.183**	**0.030***
	Nonresponder	**56.9 ± 12.9**	**61.9 ± 13.9**	**75.4 ± 15.1**			
KOOS-Sxs	**Responder**	**86.4 ± 9.7**	**88.5 ± 10.9**	**91.7 ± 8.7**	**0.001***	**0.007***	**0.637**
	Nonresponder	**81.3 ± 9.8**	**81.5 ± 10.9**	**87.0 ±11.2**			
KOOS-Pain	**Responder**	**91.5 ± 6.3**	**94.6 ± 5.4**	**97.0 ± 3.9**	**<.001***	**0.062**	**0.854**
	Nonresponder	**89.8 ± 8.2**	**92.1 ± 7.4**	**94.4 ± 5.2**			
KOOS-ADLs	**Responder**	**98.0 ± 3.2**	**99.4 ± 1.5**	**99.6 ± 1.4**	**0.001***	**0.002***	**0.517**
	Nonresponder	**96.4 ± 4.0**	**97.2 ± 3.5**	**98.4 ± 3.2**			

Abbreviations: IKDC**,** International Knee Documentation Committee Subjective Knee Form; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QOL, quality of life; ME, main effect; Int, interaction

Chapter 6

IMPROVING OUTCOMES AFTER ACL RECONSTRUCTION

6.1 Purpose

The purpose of this work was to expand our knowledge of psychological factors and neurophysiologic factors after ACLR. The goals of this body of work were to: 1) compare corticospinal, intracortical, and spinal-reflexive excitability between athletes after ACLR and controls, 2) examine the relationship between psychological readiness to return to sport and movement after ACLR, and 3) examine whether a positive change in psychological readiness to return to sport is related to better outcomes after ACLR. The central hypotheses were: 1) differences in corticospinal, intracortical, and spinal-reflexive excitability would exist between athletes after ACLR and controls during the course of post-operative rehabilitation, 2) psychological readiness would be related to movement after ACLR, and 3) athletes with a positive psychological change would demonstrate better outcomes after a secondary injury prevention program.

6.2 Corticospinal and Spinal-reflexive Alterations after ACLR

Aim 1: Define the corticospinal and spinal-reflexive changes that occur during the course of post-operative physical therapy after ACLR and their relationship with isometric quadriceps strength.

Hypothesis 1.1: ACLR subjects will display less corticospinal excitability in both limbs compared to healthy controls at all three time points.

Hypothesis 1.2: ACLR subjects will display less spinal-reflexive excitability in the surgical limb compared to healthy controls at the 2 weeks after surgery time point.

Hypothesis 1.3: There will be a negative relationship between RMT (higher values equal lower excitability) and quadriceps strength at all time points.

Hypothesis 1.4: There will be a positive relationship between 120% RMT Norm (higher values equal higher excitability) and quadriceps strength at all time points.

Hypothesis 1.5: There will be a positive relationship between spinal-reflexive excitability and quadriceps strength at the 2 weeks after surgery time point.

Quadriceps muscle dysfunction persists after ACL injury and ACLR despite the development of post-operative protocols, extensive research, and improvements in surgical techniques. Quadriceps weakness is related to poor movement patterns, poor self-reported function, and high reinjury rates. Improving quadriceps strength is therefore critical to outcomes after ACLR. Findings from this aim indicate that corticospinal excitability is altered in athletes after ACLR reconstruction and corticospinal excitability is related to quadriceps strength during the course of post-operative rehabilitation. We also found that these alterations do not change. While other cross sectional studies have found group corticospinal differences in athletes after ACLR compared to controls, this is the first study to identify alterations early after surgery. These findings offer important considerations for clinical care and future research. Interventions directly targeting the corticospinal pathway may be needed to address fully restore quadriceps function after ACLR. We were unable to determine if the alterations found were a result of the surgery or present beforehand. Future research is needed to determine if alterations in corticospinal excitability exist prior to surgery. Future research should also examine the effect of targeted interventions on corticospinal excitability after ACLR.

6.3 Intracortical Alterations after ACLR

Aim 2: Define the intracortical changes that occur during the course of post-operative physical therapy after ACLR and their relationship with isometric quadriceps strength.

Hypothesis 2.1: ACLR subjects will display less intracortical facilitation in the surgical limb at all time points.

Hypothesis 2.2: ACLR subjects will display greater intracortical inhibition in the surgical limb at all time points.

Hypothesis 2.3: There will be a positive relationship between facilitation and quadriceps strength at all time points.

Hypothesis 2.4: There will be a positive relationship between inhibition (higher values equal less inhibition) and quadriceps strength at all time points.

Findings from Aim 1 established that alterations in corticospinal excitability exist early after ACLR using single pulse TMS. The measures of corticospinal excitability provide global measurements of excitability that are dependent on the balance of inhibitory and facilitatory intracortical neurons projecting onto the corticospinal tract. Paired-pulse TMS can provide individual measurements of intracortical inhibition and facilitation. A better understanding of these pathways are required to develop appropriate rehabilitation strategies. Results from this aim suggest that intracortical facilitation is asymmetric after ACLR with reduced facilitation present in the surgical limb. However, intracortical inhibition demonstrated the greatest relationship to quadriceps strength. Therefore, interventions aimed at intracortical inhibitory and facilitatory pathways may be needed to mitigate chronic quadriceps dysfunction. It is important to note that both intracortical measures (especially facilitation) displayed large variability. Future research should examine if intracortical excitability can be modified with specific treatments after ACLR; however, future research should consider the large variability in these measures.

6.4 Psychological Readiness to Return to Sport is related to Asymmetry

Aim 3: Determine the relationship between psychological measures and biomechanics after ACLR.

Hypothesis 3.1: Following ACLR and post-operative physical therapy, subjects with a negative psychological outlook will display greater kinematic asymmetry during gait then subjects with a neutral or positive outlook.

Hypothesis 3.2: Following ACLR and post-operative physical therapy, subjects with a negative psychological outlook will display greater kinetic asymmetry during gait then subjects with a neutral or positive outlook.

Fear of reinjury, lack of confidence and negative emotions have emerged as important factors affecting outcomes after ACLR. Additionally, gait asymmetries are common after ACLR and are associated with early development of osteoarthritis. However, no studies to date have explored the relationship between psychological factors and gait biomechanics. Findings from this aim, suggest that psychological readiness to return to sport, a construct that encompasses emotions, confidence, and risk appraisal, is related to asymmetrical sagittal plane knee kinematics and kinetics after ACLR. While the cross-sectional design of this study does not allow us to determine cause and effect, it does provide a foundation for future research. Future research should examine the effects of interventions specifically targeting psychological readiness to return to sport on movement after ACLR.

6.5 Psychological Readiness is Modifiable and Related to Outcomes

Aim 4: Define changes in psychological factors following an extended rehabilitation program post ACLR and determine if a positive change in psychological outlook is associated with better outcomes.

Hypothesis 4.1: Subjects that undergo the extended rehabilitation program will demonstrate a positive improvement in psychological readiness to return to sport.

Hypothesis 4.2: Subjects that demonstrate a positive improvement in psychological readiness to return to sport as a result of the ACL Sports program will have better self-reported functional and activity outcomes following training, and at 1 and 2 years post ACLR.

As previously mentioned psychological factors are related to outcomes after ACLR. Psychological factors do change during the course of acute rehabilitation. Many authors have speculated that psychological factors are modifiable but few studies have investigated the effect of specific rehabilitation programs on psychological factors. Findings from this study, indicate that the ACL-SPORTS secondary injury prevention program does lead to a more positive outlook in terms of psychological readiness to return to sport for a subgroup of athletes attempting to return to sport. In addition, athletes who demonstrated a positive response, based on our definition, had better self-reported outcomes immediately after the program and one year after surgery. These findings suggest that psychological factors are modifiable prior to return to sport. However, many athletes did not demonstrate an improvement in psychological readiness to return to sport. Future research should continue to explore the effect of specific interventions on psychological factors.

6.6 Clinical Relevance

These dissertation work set out to explore neurophysiologic and psychological factor after ACLR. Research has just started to scratch the surface in these two areas. The work from this dissertation adds to the growing body of literature indicating that central nervous system alterations exist after ACLR and psychological factors affect outcomes. From a neurophysiologic perspective, quadriceps dysfunction persists despite our best efforts as clinicians to rehabilitate this impairment. This works indicates that current rehabilitation strategies may not be completely addressing all factors related to quadriceps dysfunction. Additional interventions may be needed to mitigate weakness and activation deficits. Potential interventions include transcranial direct current stimulation, EMG biofeedback, neuromuscular electrical stimulation, power training, and pharmacological interventions. My future research will investigate the effect of such interventions. From a psychological perspective, this work indicates that interventions including graded exercise and graded exposure have the potential to improve psychological factors related to fear, negative emotion, and lack of confidence. Emerging evidence suggest that cognitive behavioral strategies, such as motivation interviewing, are beneficial in patients with chronic pain. These strategies have the potential to improve outcomes in athletes after ACLR as well.

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APPENDIX A

IRB APPROVAL LETTER AIMS 1 & 2

UNIVERSITY OF DELAWARE

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	June 24, 2015
TO:	Ryan Zarzycki, DPT
FROM:	University of Delaware IRB
STUDY TITLE:	[765899-1] Changes in Corticospinal Excitability After ACL Reconstruction
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	June 24, 2015
EXPIRATION DATE:	June 16, 2016
REVIEW TYPE:	Full Committee Review

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

APPENDIX B

IRB APPROVAL LETTER AIMS 3 & 4

UNIVERSITY OF DELAWARE

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	March 7, 2014
TO:	Lynn Snyder-Mackler, PT, ScD, FAPTA
FROM:	University of Delaware IRB
STUDY TITLE:	[225014-11] Can Neuromuscular Training Alter Movement Patterns(Renewal Period)
SUBMISSION TYPE:	Continuing Review
ACTION:	APPROVED
APPROVAL DATE:	March 7, 2014
EXPIRATION DATE:	March 14, 2015
REVIEW TYPE:	Full Committee Review

Thank you for your submission of Other materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

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All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

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