OPTIMIZING HEALTHCARE DECISION MAKING FOLLOWING ACL-RECONSTRUCTION

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Doctor of Philosophy

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by
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ABSTRACT

Reinjury rates are high among individuals following anterior cruciate ligament reconstruction (ACLR). To improve outcomes following ACLR, functional assessments are administered to identify deficits prior to the patient's return to activity (RTA). Through the Lower Extremity Assessment Protocol (LEAP) program, these assessments are administered at 4- and 6-months following surgery. This battery of assessments consists of patient reported outcomes, quadriceps and hamstring strength and symmetry, and single leg hopping performance and symmetry. Manuscript I used data from the 6-month assessment, manuscript II assessed the progression from the 4- and 6-month assessments, and manuscript III utilized 4- and 6-month measures to determine the effectiveness of a rehabilitation intervention. The focus of manuscript I was to assess the utility of commonly administered functional assessments to predict the ability to RTA and subsequent ACL injury. We found that greater measures of quadriceps symmetry and subjective knee function increased the odds of RTA and also increased the odds of subsequent ACL injury. In individuals that returned to activity after 8-month, the odds of subsequent ACL injury decreased with every month RTA was delayed. Current practice of accelerating patients back to high levels of activity may increase their probability for subsequent reinjury. The focus of manuscript II was to identify components of a 4-month functional assessments that can predict patients that demonstrate persistent muscle weakness. We found that higher age, lower levels of activity, and higher measures of quadriceps symmetry at the 4-month assessment were indicative of patients with persistent muscle weakness. Serial assessments administered throughout the post-ACLR progression could inform clinicians on the patient's progression and their response to current treatments. The focus of manuscript III was to assess the ability of visuomotor therapy to modulate corticospinal excitability inpatients following ACLR. We found that a single session of visuomotor therapy increased quadriceps corticospinal excitability compared to a sham intervention of passive motion. Submaximal, force matching tasks may address underlying neuromuscular impairments developed following ACLR. Objective measures of patient function can be used to guide clinicians in their decisions of post-operative treatments, progressions, or that of returning to high levels of activity.

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Approval of the Dissertation

This dissertation, *Optimizing Healthcare Decision Making Following ACL-Reconstruction* has been approved by the Graduate Faculty of the Curry School of Education and Human Development in partial fulfillment for the degree of Doctor of Philosophy

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SECTION II: MANUSCRIPT I

Predicting ACL Reinjury from Return to Activity Assessments at 6-months Post-Surgery: A Prospective Cohort Study

Abstract

Background: Return to activity (RTA) assessments are commonly administered following ACL-Reconstruction (ACLR) to manage post-operative progressions back to activity. To date, there is little knowledge on the clinical utility of these assessments to predict patient outcomes such as subsequent ACL injury once returned to activity.
Hypothesis/Purpose: To identify what measures of patient function at 6-months post-ACLR best predict return to activity and subsequent ACL injury at a minimum of 2-years following ACLR.
Study Design: Prospective Cohort
Methods: A total of 234 consecutive patients with primary, unilateral ACLR completed a battery of functional assessments approximately 6-months following index surgery. Performance tests consisted of patient reported outcomes, isokinetic knee flexor and extensor strength, and single leg hopping tasks. A total of 193 (82%) completed follow-up through medical record reviews, phone interviews and questionnaires at a minimum of two-years following ACLR to identify current level of activity and status and timing of RTA and ACL reinjury. Logistic regression and Cox proportional hazard models were used to assess the ability of measures of patient function at 6-months to predict RTA and ACL reinjury, controlling for patient sex, age, and activity level. Analyses were also performed on a stratified sample based on Early RTA (<8-months) and Delayed RTA (>8-months), sex, and graft type (patellar tendon, hamstring).
Results: A total of 46 individuals had a subsequent graft (14%) or contralateral ACL injury (10%). A greater proportion of females reinjured their contralateral ACL (15/24, 63%) whereas a greater proportion of males reinjured their ipsilateral ACL graft (15/20, 75%, *P*=.017) Greater knee extension symmetry at 6-months increased the probability of reinjury (B=.016, *P*=.048). In patients who returned to sports before 8 months post ACLR, every 1% increase in quadriceps strength symmetry at 6-months increased the risk of reinjury by 2.1%(B=.021, *P*=.05). In patients who returned to sports after 8 months post ACLR, every month that RTA was delayed reduced the risk of reinjury by 28.4% (B=-.284, *P*=.042).
Conclusions: Patients with more symmetric quadriceps strength at 6 months post ACLR were more likely to experience another ACL rupture, especially in those who returned to sport earlier than 8-months after the index surgery. Patients that delayed their return to activity after 8-months had lower probability of reinjury. Clinicians should be cognizant that returning patients to activity earlier than 8-months post-ACLR may place them at an increased risk for reinjury.

Introduction

Reinjury rates after primary ACL reconstruction (ACLR) have been reported up to 28% for individuals who to return to high levels of physical activity and sports.[29,36] In addition to high reinjury rates, decreased physical activity,[37] lower subjective function,[27] and early onset post-traumatic osteoarthritis[5,11] have challenged contemporary management strategies for patients rehabilitating after ACLR. To effectively manage healthcare decisions following ACL injury, measures of patient function that best identify patients at risk for subsequent ACL injury are needed. Currently, patients are commonly referred to complete performance assessments that guide the progression to unrestricted activities at approximately 6-months following ACLR.[8] Conventional practice is to use post-operative strength and jumping symmetry tests to inform the timing of return to activity and sport with the ultimate goal of promoting greater strength and symmetry as benchmarks for successful progress through rehabilitation.

The goal of safely returning patients to high levels of physical activity challenges clinicians and researchers alike to identify appropriate timepoints throughout the recovery process to identify and treat functional impairments. Functional assessments used to guide RTA are commonly administered around 6-months.[9,22,23] These assessments do not often cause immediate activity clearance, but provide objective measures to better inform clinicians on deficits that may need to be addressed throughout the RTA progression.[4,10,28] Laboratory measurement techniques administered throughout these assessments allow precise and objective data of muscle and patient function to be collected. The clinical challenge is to compile a battery of assessments that are clinically feasible, time-sensitive, and best describe measures of patient function that predict outcomes. The most commonly used assessments used for managing return to sport decision making are the time since surgery, subjective function quantified through

patient questionnaires, quadriceps and hamstring strength assessed through isometric and isokinetic tests, and single-leg hopping.[9,21,24] To date, there is limited information about the ability of these assessments at 6-months to predict an effective return to sport without a subsequent ACL injury.

The use of objective measures to manage activity clearance has risen dramatically in the past decades.[9] Time since surgery is the most commonly used metric when managing clearance for sport activity, with many clinicians using it as the only measure.[9] In assessing quadriceps strength, the most common target for patients and clinicians is a limb symmetry index (LSI) of 90%, using the contralateral limb as an objective comparison.[19] Low rates of passing return to activity assessments (>90% LSI) are commonly reported following ACLR.[4] The ability to predict subsequent outcomes, such as reinjury, prior to release for unrestricted activity could empower clinicians with the knowledge to how to treat ACLR patients while they are still under the supervision of healthcare providers.

The ability to identify common components of return to activity assessments, such as quadriceps strength and single leg hop distance, that predict patients who sustain subsequent ACL injury can allow clinicians to more efficiently manage rehabilitation progressions and return to activity decision making following ACLR. Therefore, the purposes of this study were to identify what measures of patient function at 6-months post-ACLR best predict return to activity and subsequent ACL injury at a minimum of 2-years following ACLR and describe the demographic characteristics of patients that had a reinjury. We hypothesize lower measures of quadriceps strength and symmetry at 6-months post ACLR will increase the probability of subsequent ACL injury.

Methods

This was a prospective cohort study with minimum of 2-years follow up. The dependent (outcome) variables for the study was return to activity (RTA) (Yes/No), months following ACLR to RTA, and ACL Reinjury (Yes/No). ACL Reinjury was defined as a subsequent injury to the ACLR graft or the contralateral ACL. Independent (predictor) variables were measures of patient function collected during the patient's functional assessment: patient reported outcomes (PROs), knee extensor and flexor strength, and single-leg hopping distance.

Participants

All patients were referred from a multi-surgeon academic orthopaedic subspecialty practice to complete a battery of functional assessments in a controlled laboratory setting approximately 6-months post-ACLR. Data used in this study were collected as a part of an ongoing program where patients routinely complete post-operative assessments following a lower extremity surgery.[4,24] Patients and their clinicians were provided a detailed report including the data from the assessment to guide rehabilitation progressions and return to activity decision making. Patients were included in the analyses if they had a history of primary, isolated, unilateral ACLR confirmed through their medical records. Patients were excluded from analyses if they had a history of other lower extremity surgery, concomitant ligament reconstructions, surgical complications, or any neurological disorders. Participants followed the same post-operative rehabilitation guidelines distributed by their surgeon. This study was approved by our university's institutional review board and all patients voluntarily provided written, informed consent.

Patient Reported Outcomes

Following enrollment and consent, all participants completed the Knee Osteoarthritis Outcome Score (KOOS) and the International Knee Documentation Committee (IKDC) subjective form to evaluate subjective knee function. These measures have been shown to be valid and reliable within patients following ACLR.[12] Pre-injury level of physical activity was quantified through the Tegner Activity Scale.[7] Kinesiophobia was assessed through the Tampa Scale for Kinesiophobia and global function through the Veterans Rand-12.

Knee Extensor and Flexor Strength

Isokinetic, concentric knee flexion and extension strength was measured bilaterally using a Biodex Systems IV dynamometer (Biodex Medical Systems, Inc. Shirley, NY) at a speed of 90 deg/sec. All testing was performed on the uninvolved limb, followed by testing of the involved limb. Participants completed practice trials on each limb for familiarization before testing. The participants were verbally encouraged to provide maximal effort through their full range of motion for 8 test contraction repetitions.

Single-Leg Hopping

Single-leg hopping performance was measured bilaterally using a battery of three hopping tasks: the single hop for distance, the triple hop for distance, and the 6-meter timed hop. The participant was given as many practice trials until they were comfortable completing the task. All testing was performed on the uninvolved limb, followed by testing of the involved limb for a total of three trials on each limb. All hopping tasks required the participant to maintain single-limb stability at the conclusion of each hop. All tasks for distance were measured from the toe at start to the heel at landing. The 6-meter timed hop was instrumented with timing gates

(Fitlight Corp. Aurora, ON, Canada) that were placed 1-meter of the ground at the start and finish.

Two-Year Follow-Up

Follow-up assessment for all patients occurred at minimum of 2-years post-ACLR. Patient follow-up data were obtained via phone interview, email, or subsequent clinic visit identified through medical records review. Patients were assessed on the 1) the ability to return to their pre-injury level of activity (RTA) and 2) incidence of subsequent ACL injury on the primary involved or contralateral knee. The date of RTA and ACL Reinjury were collected if applicable.

Data Processing

Unilateral measures of peak torque were normalized to the participant's body weight (Nm/kg). Strength and hopping symmetry measures were calculated using the following equation: $Limb\ Symmetry = \left(\frac{involved\ limb}{uninvolved\ limb}\right) * 100.$

Statistical Analysis

Analyses with RTA (Yes/No) as the dependent variable were performed on all patients. Analyses with ACL Reinjury (Yes/No) as the dependent variable were performed on patients that successfully returned to prior levels of activity.

Descriptive statistics were collected for time to RTA, time from ACLR to subsequent injury, and time from RTA to subsequent injury. Cox proportional survival curves were performed controlling for age, sex, and activity level for 1) RTA (Yes/No) as the dependent variable and time from ACLR to RTA (months) as the measure of time, 2) Reinjury (Yes/No) as the dependent variable and time from ACLR to Reinjury (months) as the measures of time and 3)

Reinjury (Yes/No) as the dependent variable and time from RTA to Reinjury (months) as the measures of time. Chi-square tests were performed to assess the distribution of sex, graft type, and activity level on patients that did and did not have a subsequent ACL injury. In those that did have a subsequent ACL injury, chi-square tests were performed to assess the distribution of sex and graft type on the side of ACL injury (ACLR graft or Contralateral ACL).

Pearson's *r* correlations were performed between measures of quadriceps strength and symmetry to time to RTA, IKDC, KOOS Sport, Tampa Scale for Kinesiophobia, and the Veterans Rand-12 questionnaire.

Regression models were all adjusted to control for the potential covariates: sex, age, and pre-injury activity level. A logistic regression model was performed with RTA (Yes/No) as the outcome variable and measures of patient function as the predictor variables. Predictor variables of patient function consisted of the IKDC, KOOS Sport, knee extensor strength and symmetry, knee flexor strength and symmetry, single hope distance and symmetry, triple hope distance and symmetry, and the 6-meter timed hop and symmetry.

Another logistic regression analysis was performed with Reinjury (Yes/No) as the dependent variable and measures of patient function as the independent variable (IKDC, KOOS Sport, knee extensor strength and symmetry, knee flexor strength and symmetry, single hope distance and symmetry, triple hope distance and symmetry, and the 6-meter timed hop and symmetry). The study cohort was then stratified by the median time of RTA (8-months). Patients with RTA < 8-months were operationally defined as "Early RTA" and those with RTA $\geq$ 8-months as "Delayed RTA". The same logistic regression models were performed within the Early RTA and Delayed RTA sub-groups. An *a priori* alpha was set $\leq .05$ for all analyses. All statistical analyses were conducted through SPSS (Version 26; IBM Inc., Chicago, IL).

Results

A total of 357 consecutive ACLR patients were enrolled and evaluated between November, 2013 and April, 2018, 122 patients were excluded from analyses due to prior history of lower extremity surgery, concomitant ligament reconstructions, surgical complications, or a neurological disorder (Figure 1). The remaining 235 patients were included in the analyses (Figure 1). Confirmation of an ACL graft or contralateral ACL injury at a minimum of 2-years post-ACLR were collected for 193 patients (82%) (104 Female, Age=21.2±9.2 years, 73.7±17.8 kg, 172.0±17.8 cm, 6.73±1.4 months post ACLR). Of the 193 patients, 155 returned to prior levels of physical activity (80%). Study descriptives can be found in Figure 2. There were no significant differences in the overall proportion of reinjury between males and females (chi = 0.13, *P*=.86). In patients that had a subsequent ACL injury, a greater proportion of females reinjured their contralateral ACL and a greater proportion of males reinjured their ipsilateral ACL graft ($\chi^2 = 6.18$, *P*=.017, Table 1). Of the 155 patients that returned to activity, graft type distribution was Patellar Tendon: n=95 (61.3%), Hamstring: n=58 (37.4%), and Quadriceps Tendon: n=2 (1.3%). For all analyses of graft type, those with Quadriceps Tendon Graft were removed due to low sample. There were no differences between patellar tendon and hamstring grafts in the proportion of reinjury (χ^2= 0.24, *P*=.71) or the side of reinjury (χ^2= 1.81, *P*=.23, Table 2).

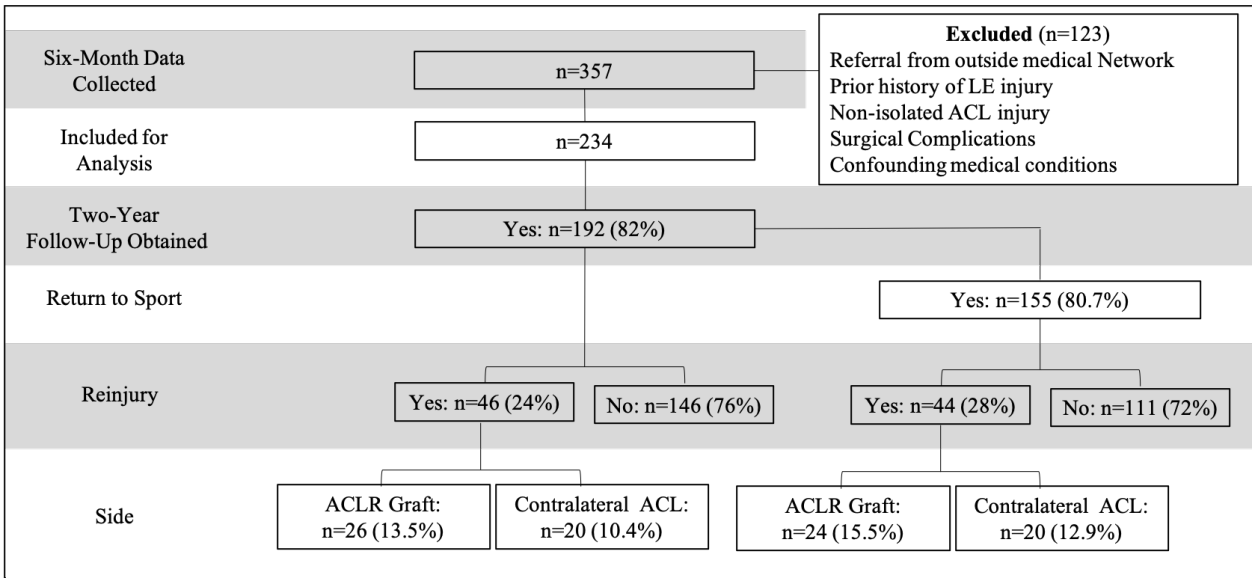
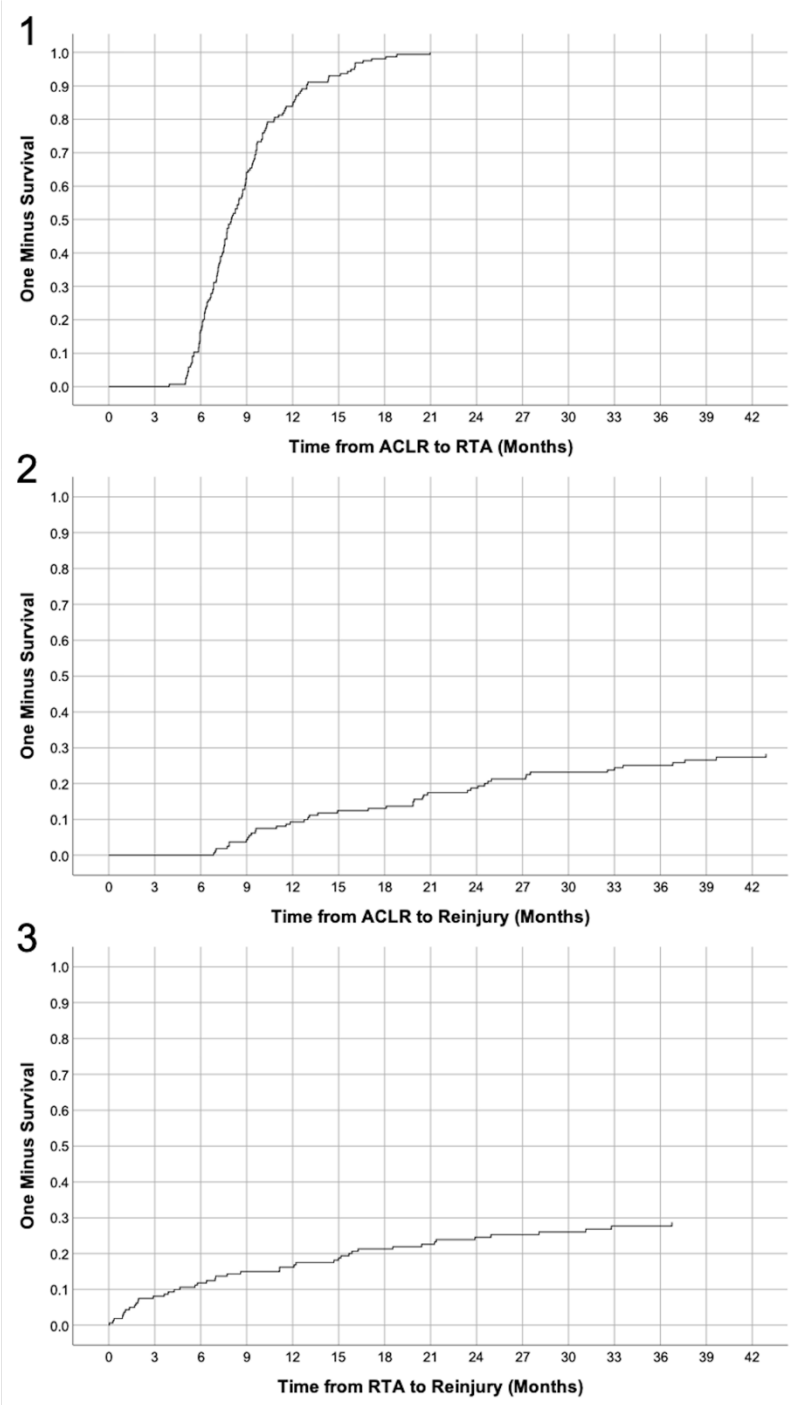


Figure 1: Flow chart of study participants.



		Mean ± SD	Median (IQR)
1	ACLR to RTA (months)	8.81 ±3.16	7.99 (6.40, 9.36)
2	ACLR to Reinjury (months)	19.13 ± 10.10	18.99 (9.58, 24.93)
3	RTA to Reinjury (months)	10.89 ± 9.90	7.35(1.91,16.78)

Figure 2: Survival Curves of study participants following ACLR.
RTA: Return to Activity

Table 1: Proportion of reinjury side for patient sex and graft type

All Patients with Subsequent ACL Injury						
	Sex*			Graft Type†		
	Female	Male	Total	PT	HS	Total
ACLR Graft	9	15	24	12	12	24
Contralateral ACL	15	5	20	14	6	20
Total	24	20	44	26	18	44

*χ^2= 6.18, *P*=.017
†χ^2= 1.81, *P*=.23
Abbreviations: PT: Patellar Tendon, HS: Hamstring

There were weak, positive, statistically significant relationships between measures of quadriceps strength at 6-months to all KOOS subscales, Tampa Scale for Kinesiophobia, and the Veterans Rand-12 questionnaire (Table 2). There were weak, positive, statistically significant relationships between measures of quadriceps symmetry at 6-months to the KOOS subscales of Pain, Sport, Activities of Daily Living, and Quality of Life (Table 2).

Table 2: Relationships between measures of quadriceps strength and symmetry at 6-months post-ACLR to time to RTA and measures of subjective function. Significant *r* values are **bolded**.

Correlations

		Time from ACLR to RTA	KOOS Symptoms	KOOS Pain	KOOS ADL	KOOS Sport	KOO QoL	Tampa	VR12
Quadriceps Strength	*r*	-0.061	**0.206**	**0.249**	**0.275**	**0.359**	**0.223**	**0.192**	**0.277**
	P	0.452	0.011*	0.002*	0.001*	0.001*	0.006*	0.022*	0.001*
Quadriceps Symmetry	*r*	-0.133	0.129	**0.197**	**0.161**	**0.31**	**0.181**	0.021	0.069
	P	0.099	0.114	0.015*	0.048*	<.001*	0.026*	0.804	0.412

Logistic regression statistics for RTA can be found in Table 3. Factors that significantly increased the probability of RTA were higher measures of IKDC, KOOS-Sport, quadriceps symmetry, and single hop symmetry (Table 3).

Table 3: Logistic Regression to Identify Factors Associated with return to activity controlled for age, sex, and pre-injury activity level. (n=193) Odds ratios should be interpreted as every 1-unit increase in [independent variable], increases a patient's probability of returning to activity by [Beta].

Independent Variables	Beta	Odds Ratio [95% CI]	*P*-Value
IKDC	.039	1.04 [1.01, 1.07]*	.005
KOOS-Sport	.028	1.03 [1.01, 1.05]*	.009
Knee Extensor Strength (Nm/kg)	.823	2.28 [0.88, 5.86]	.088
Knee Extensor Symmetry (%)	.034	1.04 [1.01, 1.06]*	.004
Knee Flexor Strength (Nm/kg)	.231	1.26 [0.27, 5.85]	.768
Knee Flexor Symmetry (%)	.008	1.01 [0.99, 1.03]	.443
Normalized Single Hop (m/m)	2.19	8.95[.80, 100.5]	.076
Single Hop Symmetry (%)	.047	1.05 [1.02, 1.08]*	.002
Normalized Triple Hop (m/m)	.51	1.67[0.76, 3.64]	.200
Triple Hop Symmetry (%)	.018	1.02 [.987, 1.05]	.249
6-m Timed Hop (seconds)	-.22	0.80[0.52, 1.24]	.317
6-m Timed Hop Symmetry (%)	-.013	.987 [.964, 1.01]	.268

Abbreviations. IKDC: International Knee Documentation Committee, KOOS: Knee Osteoarthritis Outcome Score

Logistic regression statistics for reinjury can be found in Table 4. Factors that significantly increased the probability for reinjury were higher measures of KOOS-Sport, knee extensor symmetry, and triple-hop symmetry (Table 4).

Table 4: Logistic Regression to Identify Factors Associated with Reinjury controlled for Age, Sex, and Pre-Injury Activity Level In participants that returned to sport. (n=155) Odds ratios should be interpreted as every 1-unit increase in [independent variable], increases a patient's probability of reinjury by [Beta].

Independent Variables	Beta	Odds Ratio [95% CI]	*P*-Value
Time from ACLR to RTA	-.093	.912 [0.81, 1.03]	.143
IKDC	.016	1.02 [0.99, 1.05]	.314
KOOS-Sport	.038	1.04 [1.01, 1.07]*	.023
Knee Extensor Strength (Nm/kg)	.825	1.58 [0.70, 3.56]	.065
Knee Extensor Symmetry (%)	.022	1.02 [1.01, 1.04]*	.045
Knee Flexor Strength (Nm/kg)	.761	2.14 [0.54, 8.43]	.276
Knee Flexor Symmetry (%)	.009	1.01 [0.99, 1.03]	.284
Normalized Single Hop (m/m)	2.31	10.12[.96, 106.1]	.054
Single Hop Symmetry (%)	.027	1.03 [.99, 1.06]	.149
Normalized Triple Hop (m/m)	.592	1.81[0.81, 4.05]	.150
Triple Hop Symmetry (%)	.046	1.05 [1.01, 1.10]*	.046
6-m Timed Hop (seconds)	-.437	0.65[0.31, 1.36]	.252
6-m Timed Hop Symmetry (%)	-.032	0.97 [0.93, 1.01]	.116

Abbreviations. IKDC: International Knee Documentation Committee, KOOS: Knee Osteoarthritis Outcome Score

A total of 78 patients (50.3%) returned to activity prior 8-months post-ACLR. In patients with Early RTA (<8 months) neither quadriceps strength (B=.80, *P*=.20, OR=2.22[0.67, 3.74]) nor time to RTA (B=.495, *P*=.10, OR=1.64[.92, 2.94]) predicted reinjury. However, in patients with Early RTA, quadriceps strength symmetry predicted subsequent ACL injury (B=.021, *P*=.05, OR=1.02[1.00, 1.04]). Every 1% increase in quadriceps strength symmetry at 6-months increased the risk of reinjury by 2.1%.

A total of 77 patients (49.7%) retuned to activity later than 8-months post-ACLR. In patients with Delayed RTA (>8-months), quadriceps strength (B=.817, *P*=.22, OR=2.26[0.62, 8.30]) and symmetry (B=.014, *P*=.41, OR=1.01[0.98, 1.05]) at 6-months did not predict reinjury.

In those with Delayed RTA, the time to RTA did predict subsequent ACL injury (B=-.284, *P*=.042, OR=0.75[0.58,0.98]). In patients that RTA after 8-months, every month that RTA was delayed resulted in reduced risk of reinjury by 28.4%.

Discussion

Physical performance assessments administered throughout the post-operative recovery can yield insight into functional deficits that may persist prior to release to unrestricted activity. The purpose of this study was to identify what measures of patient function at 6-months post-ACLR best predict return to activity and subsequent ACL injury at a minimum of 2-years following ACLR. Of the total cohort included in final analyses, there was a reinjury rate of 24%, with 14% of patients reinjuring their ACLR graft and 10% injuring their contralateral ACLR. In patients that returned to activity, greater quadriceps symmetry at 6-months post-surgery increased the probability of subsequent ACL injury. In individuals that returned to activity prior to 8-months, greater quadriceps symmetry remained a predictor for reinjury. In patients that returned to activity after 8-months, quadriceps strength and symmetry at 6-months did not predict reinjury; however, every month that RTA was delayed decreased the probability of subsequent injury.

In the current cohort, the average time of return to activity was 8.8-months post-ACLR, with 65% of the patients returning to unrestricted physical activity prior to 9-months, and 84% prior to 12-months (Figure 2). In the current study, younger patients and those with a greater quadriceps' symmetry at 6-month testing had a greater probability of returning to prior levels of physical activity. A lower age has been previously reported to predict return to activity status,[29] and is thought to be due to an increased exposure of activity and sport.[39] Quadriceps strength

symmetry was also found to increase probability of returning to pre-injury levels of activity within this cohort. This supports current practice of health care providers, including the attending surgeons involved with this study, that use quadriceps strength symmetry as primary measures to manage return to activity decisions.[1,9]

In the patients that returned to previous levels of physical activity (n=155), the reinjury rate increased from 24% to 28% (n=44/155). This injury rate is consistent with prior reported reinjury rates (Graft or Contralateral ACL) following primary ACLR between 10% and 28%.[14,23,29,36] In the current cohort, the average time from ACLR to reinjury was 19.3 months (Range: 6.84, 42.9 months) with 68% (n=30/44) sustaining the reinjury in less than 24-months post-ACLR. Further, the average time from return to activity to reinjury was 10.9-months (Range: 0.03, 36.8 months) and the median being 7.35-months, indicating that 50% of reinjuries occurred within 7.35 months from RTA. This is in agreement with prior literature reporting individuals following ACLR are at a high reinjury risk within the first 2-years from surgery and returning to sport.[20,35,39] Sport and activity clearance from health care professionals may be perceived by patients as an unrestricted release to pre-injury functional status. However, with biological and functional adaptations observed up to 2- to 5-years following ACLR,[16,31,38] patients should be aware of the predictors of re-injury and counseled appropriately up to and beyond the return to activity progression.

Compared to prior studies that found a difference in reinjury rates depending on the type of graft type used,[2] the current study found no differences in the proportions of reinjury between patellar tendon and hamstring grafts. Graft type decisions are commonly based on patient and surgeon preference and often based on the age and activity levels of the patients, thus biasing observational studies such as this. In randomized controlled trials with two-year outcomes, there

has been found to be no influence from graft type on ACLR graft or contralateral ACL reinjury rates.[25] In regards to patient sex, no difference in reinjury were observed within the overall proportions of between males and females; however, when looking at the side of reinjury, females had a significantly greater proportion of contralateral ACL injuries where males had a greater proportion of ACLR graft reinjuries. Studies have observed similar findings, with males demonstrating greater proportions of ACL graft injuries while females demonstrate greater proportions of contralateral ACL injuries.[6,30,34] It is unknown if a greater incidence of contralateral ACL injuries are observed in females due to biomechanical adaptations that occur following the initial ACLR or due to pre-existing conditions disposing them to ACL injury. This is an area for future research.

When assessing the ability of clinical assessments to predict returning to activity, this study's findings supports how clinicians currently use these assessments to guide return to activity decisions.[9] Higher measures of patient subjective function, quadriceps strength, and single leg hopping performance were found to significantly predict those that successfully returned to activity (Table 3). However, when we look at the ability of these tests to predict subsequent ACL injury, we see that the results challenge the way in which the data from these assessments performed at 6-months should be used (Table 4). In the current study, patients that demonstrate greater subjective function (KOOS Sport), higher measures of quadriceps symmetry, and more symmetrical single-leg hopping (Triple hop) at 6-month testing were found to have a greater probability for reinjury. In the current study, data collected at the 6-month assessment were available to surgeons and other members of the healthcare team to provide feedback to the patients regarding rehabilitation progress. Patients receiving objective feedback may influence decisions for RTA progression and clearance. In the current study, patients with

greater measures of quadriceps symmetry and subjective function were more likely to RTA (Table 3). It is possible that individuals with high functional outcomes from RTA assessments experienced increased exposure for subsequent injury. Prior literature has reported lower reinjury rates with later timepoints of RTA.[15] Traditionally, clinicians will base return to activity timing on the ability for patients to achieve optimal strength and symmetry (over 90% LSI).[19] However, findings from the current study may suggest that the "reward" of early RTA may increase the "risk" of subsequent injury. Clinicians should discuss this risk-reward paradox with their patients when counselling them about RTA.

To further analyze the clinical utility of these assessments similarly to prior research,[15] the study cohort was stratified between those that retuned to prior levels of activity before and after 8-months as this is a previously reported time to release to sports,[17] as well as providing an equal number of patients within each cohort (Early RTA: n=78, Delayed RTA: n=77). In patients with Early RTA, these results held true. Greater measures of quadriceps limb symmetry at 6-months increased the odds of reinjury. In patients with Delayed RTA, quadriceps strength and symmetry measured at 6-months did not predict reinjury. However, based on the findings of this study, every month that return to activity was delayed after 8-months reduced the probability by 28%. In patients with Early RTA, these findings contradict current thought around the use of commonly administered return to activity testing.[22] The common clinical goal is to maximize quadriceps strength and symmetry to reduce the likelihood of reinjury. Qualitative studies have identified patient perceptions of achieving high measures of strength and symmetry in order to receive clearance for returning to sport,[33] and perceived pressures from parents and coaches to do so.[13] These notions for 6-month assessments are not supported with the current study; rather the opposite, with greater quadriceps symmetry at 6-months actually increasing the probability of

subsequent ACL injury. In the patients with Delayed RTA, 6-month quadriceps strength and symmetry measures did not predict reinjury. This may be expected because 6-month performance assessments may not accurately represent how the patient in functioning at the time they return to activity over two-months later. However, prior literature assessing quadriceps strength following the release to prior levels of activity by their treating surgeon and rehabilitation clinicians failed to identify quadriceps strength as an important predictor for reinjury, questioning the utility of this measure to effectively do so.[29]

Findings of reducing injury probability from delaying return to activity after 8-months differ from a previous study[14] of 69 athletes that demonstrated delayed time to unrestricted sport did not reduce the probability of knee reinjury after 9-months. The prior study classified knee reinjury as any subsequent injury to either knee, such as meniscal injuries, patellar subluxations, and subsequent ACL graft ruptures which may differ when comparing predictors for isolated secondary ACL injuries. The finding of delaying RTA to reduce ACL reinjury in those after 8-months may support the importance of time following ACLR for proper recovery. Even in patients who score high on subjective and objective measures of function, there may be a healing processes occurring throughout this time. Recent proposals of delaying RTA to 2-years following ACLR have been made due to biological healing processes of the ACLR graft.[26] Ultimately, the decision regarding the safest time for return to unrestricted physical activity following ACLR should take into consideration many factors including subjective readiness, objective function, time from surgery and exposure to high risk environments.[18,40] These factors should also be serially measured so patients and clinicians both are aware of potential deteriorating function in advance of reinjury.[4]

The use of objective data to track outcomes over the course of post-operative rehabilitation through return to activity is an important aspect of patient care. However, the traditional approach of using strength and hopping data at a 6-month time point after ACLR for RTA decisions, especially earlier than 8 months after surgery, should be approached with caution based on the findings of this current study. Quadriceps strength and symmetry data still hold clinical value because relationships exist with measures of knee function, global function, and patient fear of movement (Table 2). These relationships between strength and function to subjective outcomes have been previously reported.[3,32] With the optimal goal of increasing patient function, commonly assessed through PROs, 6-month assessments may still guide clinicians to identify functional deficits to achieve this. Serial assessments following 6-months may hold greater clinical value to assess patient progression and capture a more accurate description of patient function prior to returning to activity. Functional assessments administered at 6-months should be used to guide post-operative treatments and dictate the RTA progression but should be utilized with caution if used to release patients to unrestricted activity prior to 8-months post-ACLR

The assessments administered in the current study provides objective measures of function to the patient and clinician to inform decisions which may influence patient outcomes. This is a point of care research design that is representative of actual clinical use of return to activity testing and resulting patient outcomes. Patient outcomes of RTA and reinjury were also self-reported. Neither post-operative, physical activity nor exposure were tightly controlled and objectively quantified within the current study and should be an area for future research.

In conclusion, patients with higher levels of subjective function and quadriceps symmetry had a greater probability of returning to activity. However, in patients that returned to activity

earlier than 8-months, higher measures of quadriceps symmetry at 6-months increased the probability of reinjury. In patients that returned to activity later then 8-months, every month return to activity was delayed reduced the probability of reinjury by 28%. Functional assessments administered with the intention to release to activity prior to 8-months should be used with caution. Clinicians should discuss this risk-reward paradox with high functioning patients seeking early return to activity.

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SECTION II: MANUSCRIPT II

Quadriceps and Patient Function in Serial Assessments Throughout the Post-ACL Reconstruction Progression

Abstract

Background: Quadriceps strength deficits are commonly observed at the time of return to play (RTP) assessments in patients following ACL-Reconstruction (ACLR). Individuals commonly demonstrate patterns of persistent muscle weakness, defined as the inability to regain quadriceps strength of the ACLR limb despite undergoing traditional strengthening rehabilitation. The ability to identify patients that may not respond to traditional therapy from interim assessments throughout the recovery process may help individualize treatment plans and optimize outcomes.
Purpose: To assess the changes in patient strength and function from 4- to 6-month assessments following ACLR, determine relationships between changes in strength to changes in subjective function, and identify factors that predict patients that fail to increase in strength.
Study Design: Prospective, laboratory study
Methods: A total of 47 patients (27 female, 24.3±11.1 years, 75.4±19.3kg, 175.4±24.7 cm) completed a battery of performance assessments at approximately 4- and 6-months following primary ACLR (4.03±.49and 6.46±.68 months). These tests consisted of the International Knee Documentation Committee (IKDC) and the Knee Osteoarthritis Outcomes Score subjective outcome scores, Tegner activity scale, and isokinetic knee flexor and extensor strength. The independent variables were the 4- and 6-month assessments and the dependent variables were measures of muscle function. Paired t-tests were performed to compare differences between the two assessments. Patients were categorized per their ability to increase in strength beyond a previously defined threshold (0.22 Nm/kg) between the two sessions. Binary logistic regression was used to determine predictors of patients that failed to meet strength changes. The dependent variable was the ability to increase strength (yes/no) and the independent variables were age, pre-injury activity level, and quadriceps symmetry at the 4-month assessment.
Results: Patients demonstrated improvements in patient-reported outcomes and measures of quadriceps and hamstring strength between visits (all *P*'s < .05). An increase in quadriceps strength (*r*=.417, *P*=.005) and symmetry (*r*=.356, *P*=.014) were related to improvements in subjective function (IKDC). There was no relationship between changes in quadriceps strength to changes in the ACL-Return to Sport Index (*r*=.153, *P*=.712). For every year increased in age, the likelihood of achieving improvements in quadriceps strength decreased by 7 % (B=-.073, *P*=.039). For every level increase in physical activity (defined through Tegner), the likelihood of achieving improvements in quadriceps strength increased by 61% (B=.61, *P*=.022). For every percent increase in quadriceps strength symmetry, the likelihood of achieving improvements in quadriceps strength decreased by 4.4% (B=-.044, *P*=.05). **Conclusions**: From 4- to 6-months post-ACLR, significant increases in subjective function, quadriceps and hamstring strength and symmetry, and RTP confidence were observed. Higher age, lower pre-injury activity levels, and higher limb symmetry indexes at 4-months were predictors of patients that did not achieve thresholds of improvements in quadriceps strength between the 4- and 6-month assessments. These findings can provide clinical timelines to achieve strength goals and identify potential risk factors to lower strength gains at the terminal stages of ACLR rehabilitation.

Introduction

Return to activity (RTA) assessments are administered following ACL-Reconstruction (ACLR) with the goal of determining physical and mental readiness to safely and effectively return to unrestricted activity.[1] Quadriceps strength and decreased knee function are not only reported at the timepoint of these RTA assessments,[2,3] but have been observed through longitudinal studies up to three years after returning to activitiy.[4-6] Administering a single functional assessment at the time of returning to activity can provide insightful information to guide this process; however, may not describe how the patient is progressing and responding to post-operative rehabilitation. Serial assessments throughout the post-operative rehabilitation may allow for greater insight to patient response to clinical care and guide treatment progressions and clinical decision making.

Persistent muscle weakness is a common sign in individuals following ACL-Reconstruction (ACLR).[7] Quadriceps strength deficits are among the most commonly reported sign following ACLR and overcoming acute atrophy and strength loss being among the main rehabilitation goals throughout recovery.[8] These deficits have been found to relate to patient outcomes; such as subjective function, physical activity, and risk of reinjury.[9,10] Patients and clinicians alike are frustrated with marginal strength gains that present throughout the post-operative recovery.[15] Differences in recovery within patients is multifactorial, consisting of and not limited to differences in rehabilitation protocols (volume, intensity, etc.), psychological barriers, and muscular inhibition.[16,17] A study documenting serial return to activity assessments found that a large proportion of ACLR patients (45%) were not able to exceed thresholds of strength gains indicative of subjective improvements though completing additional rehabilitation.[2] This study utilized subsequent assessments in patients that demonstrated low

strength at initial 6-month RTS testing. Administering functional assessments earlier in the rehabilitation process may provide insight into patients' responses to current therapies while still under supervision of healthcare providers. Resistance to quadriceps strengthening has been proposed to be influenced by underlying neurophysiological adaptations, described as arthrogenic muscle inhibition (AMI).[11] Neuromuscular adaptations have been shown to relate to patient strength and function at the time of and after RTS.[12-14] Laboratory instrumentation and methodology is needed to identify individuals with muscular impairments from AMI. The clinical manifestations of AMI are best defined retrospectively as persistent muscle weakness, thereby identifying patients that failed to meet or exceed strength goals over the course of rehabilitation. Clinical factors that can identify patients that will go on to demonstrate signs of persistent muscle weakness throughout the post-operative recovery may allow individualization of treatments to address these underlying impairments.

The implementation of serial assessments throughout the post-operative recovery following ACLR would allow greater insight to clinical functional targets and provide characteristics of patients that fail to increase in strength despite undergoing rehabilitation. The ability to identify patients that may not progress with traditional strength training may empower clinicians to seek and administer alternative treatments to optimize patient function. Therefore, the purpose of this study is to assess the changes in patient strength and function from 4- to 6-month assessments following ACLR, determine relationships between changes in strength to changes in subjective function, and identify factors that predict patients that fail to increase in strength. We hypothesize that lower levels of physical activity and lower measures of quadriceps strength at 4-months will predict individuals that fail to increase strength between assessments.

Methods

This was a prospective cohort study in patients following ACLR performed in a controlled laboratory setting. The dependent variables for the study were measures of patient function. Independent variables were the study visits at approximately 4- to 6-month assessments.

Table 1: Patient Demographics

	Mean±SD
Patients, n	47
Age, years	24.3±11.1
Sex (Female:Male)	27:20
Mass, kg	75.4±19.3
Height, cm	175.4±24.7
Time Since Surgery Visit 1, Months	4.03±.49
Time Since Surgery Visit 2, Months	6.46±.68
Pre-Injury Activity Level (Tegner)	8.04±1.4

All Demographic variables are presented from the 4-month assessment

Participants

All patients were referred from a multi-surgeon academic orthopaedic subspecialty practice to complete a battery of functional assessments in a controlled laboratory setting at 4- and 6-months post-ACLR. Data used in this study were collected as a part of an ongoing program where patients complete post-operative assessments following a lower extremity surgery.[4,24] A total of 66 consecutive patients were assessed between March, 2019 and December, 2019 at approximately 4-months following ACLR. Of which, 47 patients completed subsequent functional assessments at approximately 6-month following ACLR. All patients had a history of primary, isolated, unilateral ACLR with no surgical complications. Participants followed the same post-operative rehabilitation guidelines. Patients were excluded from the

study if they had a lower extremity joint surgery prior to ACLR, a concomitant ligament reconstruction, graft failure, surgical complication, any lower extremity injury within 6-months. This study was approved by our university's institutional review board and all patients provided voluntary, informed consent.

Patient Reported Outcomes

Following enrollment, all participants completed the International Knee Documentation Committee (IKDC) subjective questionnaire and the Knee Osteoarthritis Outcome Score (KOOS) to evaluate subjective knee function. These measures have been shown to be valid and reliable within patients following ACLR.[19,20] Physical activity was quantified through the Tegner Activity Scale.[21] The ACL-Return to Sport Index (ACL-RSI) was administered to quantify the phycological readiness of returning to sport or prior levels of activity. The IKDC, KOOS, and ACL-RSI were all administered again at the 6-month visit. All patients at the 6-month visit were asked "Following your last visit with us, did you complete additional physical therapy or rehabilitation visits targeted towards strengthening your knee?" and "If yes, how many total visits/sessions did you complete?"

Knee Extension and Flexion Strength

Isokinetic, concentric knee extension and flexion strength was measured bilaterally using a Biodex Systems IV dynamometer (Biodex Medical Systems, Inc. Shirley, NY) at a speed of 90 deg/sec. All testing was performed on the uninvolved limb, followed by testing of the involved limb. The participants completed practice trials on each limb for practice and familiarization prior to testing. The participants provided maximal effort through their full range of motion for 8 repetitions. Measures of peak torque for knee extension and flexion were exported from the

multimode dynamometer (Biodex, System IV. Shirley, NY). All strength assessments were identical between the 4- and 6-month assessments.

Data Processing

Involved Limb and Symmetry Calculations

Unilateral measures of peak torque were normalized to the participant's body weight (Nm/kg). Symmetry measures were calculated using the equation: $Limb\ Symmetry = \left(\frac{involved\ limb}{uninvolved\ limb}\right) * 100$. Change scores were calculated as the difference in measures from the 6-month and 4-month tests. An increase in strength was operationally defined as an increase in peak knee isokinetic torque (90 deg/sec) of ≥0.22 Nm/kg. Patients were dichotomously labeled as those that increased strength (≥0.22 Nm/kg) and those that did not (<0.22 Nm/kg). This threshold has been previously identified as an amount of strength indicative of subjective improvements in knee function.[2]

Statistical Analysis

Paired sample t-tests were used to assess differences in strength and patient-reported outcomes between the 4- and 6-month visits. Pearson *r* correlations were run to compare the relationships between the number of additional rehabilitation visits to patient demographics and changes in patient-reported outcomes and strength. A chi-square test was preformed to compare the proportion of individuals that received additional rehabilitation to those that achieved meaningful strength gains indicative of subjective improvement.[2]

All further analyses were performed for patients that sought additional rehabilitation between the 4- and 6-month tests (n=40, Table 4), as strength increases were not expected in

patients that discontinued rehabilitation. Pearson's *r* correlations were run to assess the relationship between changes of knee extensor and flexor strength and symmetry to changes in patients-reported outcomes (IKDC, KOOS subscales) and return to sport confidence (ACL-RSI).

To identify characteristics that may predict those that do not increase strength between visits, independent sample t-tests were used to compare measures of demographics, patient-reported outcomes, and strength symmetry between groups of patients that did and did not increase strength between visits (≥.22 Nm/kg). Variables that were significantly different between groups were entered into separate binary logistic regression models as the independent variable and group (increase in strength: Yes/No) as the dependent variable. All statistical analyses were conducted through SPSS (Version 26; IBM Inc., Chicago, IL). An *a priori* alpha was set at ≤.05.

Results

A greater number of rehabilitation visits between the 4- and 6-month assessments were related to a higher pre-injury level of activity (r=.48, P=.002). No other relationships were found between measures of rehabilitation visits and changes in strength or patient-reported outcomes (all P's > .05). The proportion of patients that completed additional rehabilitation and met thresholds of strength changes can be found in Table 3. In individuals that sought additional rehabilitation between the 4- and 6-month tests, 14/40 (35%) did not demonstrate increases in quadriceps strength indicative of subjective improvements. Patients that achieved substantial quadriceps strength gains (≥.22 Nm/kg) were significantly younger (21.2±6.1), had higher pre-injury levels of physical activity (Tegner = 8.5±1.3), and had lower quadriceps strength

symmetry (57.4±14.6%) than patients that did not increase their quadriceps strength between visits (Age: 28.8±15.0, *P*=.017; Activity: 7.4±1.3, *P*=.014; LSI: 66.3±12.5, *P*=.038).

For every year increased in age, the probability of achieving improvements in quadriceps strength decreased by 7% (B=-.073, *P*=.039, OR=.93[0.87, 1.00]). For every level increase in physical activity (defined through Tegner), the probability of achieving improvements in quadriceps strength increased by 61% (B=.61, *P*=.022, OR=1.85[1.14, 2.99]). For every percentage point increase in quadriceps strength symmetry, the likelihood of achieving improvements in quadriceps strength decreased by 4.6% (B=-.044, *P*=.05, OR=.96[.92, 1.00). In individuals that sought additional rehabilitation between the 4- and 6-month tests, relationships between change scores of subjective measures of function and knee extensor and flexor function can be found in Table 4.

Table 2: Change scores between 4- and 6-month assessments. n=47

	4-month Visit	6-month Visit	Change	*P*-value
IKDC	71.0±13.8	83.47±11.4	12.5±10.7	<.001
KOOS Symptom	81.2±15.5	85.9±15.3	4.7±11.4	.008
KOOS Pain	87.6±11.6	91.7±10.0	4.1±10.4	.009
KOOS Sport	67.1±26.1	85.9±15.3	18.8±22.5	<.001
KOOS QoL	57.5±20.6	71.0±20.8	13.5±17.7	<.001
KOOS ADL	95.9±6.9	98.2±4.0	2.3±3.2	<.001
ACL-RSI	59.2±24.8	75.0±20.4	15.8±17.8	<.001
Involved Knee Extensor Peak Torque (Nm/kg)	1.40±.44	1.72±.46	0.32±0.31	<.001
Uninvolved Knee Extensor Peak Torque (Nm/kg)	2.30±.44	2.41±.41	0.11±.22	.002
Knee Extensor Symmetry (%)	61.0±15.0	71.4±14.2	10.4±13.0	<.001
Involved Knee Flexor Peak Torque (Nm/kg)	.88±.29	1.02±.25	0.14±.25	<.001
Uninvolved Knee Flexor Peak Torque (Nm/kg)	1.02±.32	1.08±.23	0.06±.27	.130
Knee Flexor Symmetry (%)	87.4±15.8	95.4±15.35	8.0±4.3	.001

Table 3: Proportion of patients that increased strength and completed rehabilitation between 4- and 6-month visits. Chi-square=3.48, *P*=.097

		Strength Changes Between 4- and 6-months		
		<.22 Nm/kg	≥ .22 Nm/kg	Total
Completed additional rehabilitation between study visits	Yes	14	26	40
	No	5	2	7
	Total	19	28	47

Table 4: Relationships between change scores of patient reported outcomes and measures of knee extensor and flexor flexion in patients that completed rehabilitation between visits (n=40). **Bolded** values represent statistical significance (*P*<.05).

Change Scores Between 4- and 6-months		Time between Visits	IKDC	KOOS Symptom	KOOS Pain	KOOS Sport	KOOS QoL	KOOS ADL	ACL-RSI	VR-12
Knee Extensor Peak Torque (Nm/kg)	*r*	**.582**	**.417**	.277	**.331**	**.304**	.230	-.055	.153	**.461**
	P	<.001*	.005*	.059	.023*	.038*	.120	.712	.304	.001*
Knee Flexor Peak Torque (Nm/kg)	*r*	**.279**	.180	.162	.217	.068	-.012	-.033	.067	.190
	P	.058	.266	.278	.144	.651	.937	.827	.657	.201
Knee Extensor Symmetry (%)	*r*	**.457**	**.356**	.246	**.299**	.279	.221	-.123	.174	**.363**
	P	<.001*	.014*	.095	.041*	.058	.135*	.409	.241	.012*
Knee Flexor Symmetry (%)	*r*	-.025	.214	.144	.201	.115	.126	-.033	.074	.267
	P	.869	.150	.244	.175	.443	.399	.828	.621	.069

Discussion

Strength deficits are commonly observed in individuals following ACLR at the time point of returning to activity. The ability for clinicians to identify patients that may demonstrate resistance to strengthening would provide opportunities to alter treatment perspectives. The purpose of the current study was to evaluate patient strength and function from 4- to 6-month assessments following ACLR, determine relationships between changes in strength to changes in subjective function, and identify factors that predict patients that fail to increase strength. From 4- to 6-months post-ACLR, significant increases in subjective function, quadriceps and hamstring strength and symmetry, and RTP confidence were observed. Higher age, lower pre-injury activity levels, and higher limb symmetry indexes at 4-months were predictors of patients that did not achieve thresholds of improvements in quadriceps strength between visits. These findings can assist clinicians in providing timelines to achieve strength goals and identifying potential risk factors to lower strength gains at the terminal stages of ACLR progression.

Post-operative rehabilitation progressions following ACLR commonly start transitioning to functional tasks at approximately 4-months post-surgery.[22] This study aimed to capture patient strength and function at this timepoint as well at 6-months post-ACLR as this has been reported as a timepoint to start the RTS progression. At 4-months post-ACLR, patients reported low unilateral strength measures (1.40±.44 Nm/kg) compared to clinical targets of 3.0 Nm/kg[23] and to the contralateral limb (61.0±15.0%). Strength deficits have been associated with poor functional biomechanics during functional movements that may predispose an individual to injury.[24-26] Without assessing muscular function at this time period, patients may be integrated into functional tasks with strength deficits, thus placing them at risk for aberrant movement patterns. Administering interim strength assessments at 4-months post-ACLR may better inform

clinicians on strength deficits that may need to be addressed prior to engagement and progression into more functional tasks.

As a study cohort, patients demonstrate increases in quadriceps and hamstring strength, patients-reported outcomes, and RTS confidence (ACL-RSI) between the 4- and 6-month assessments. A previous quadriceps strength threshold of 0.22 Nm/kg was used to determine clinical improvements in quadriceps strength, as it has been found to be indicative of subjective improvement.[2] Of the 40 patients that completed additional rehabilitation between study visits, 14 (35%) did not achieve this threshold. This study aimed to explore what potential factors may influence low strength gains throughout this time. Individuals with a higher age, lower levels of pre-injury levels of activity, and greater measures of quadriceps strength symmetry at 4-months were found to predict those that did not increase strength. Both younger age and higher pre-injury levels of activity have been found to be predictors of higher patient function following ACLR.[27] Additionally, adolescent athletes have demonstrated greater motivation throughout the rehabilitation process when returning to sport.[16] A heightened motivation in young individuals wanting to return to higher levels of activity may influence rehabilitation compliance and drive resulting in greater strength improvements.

Higher quadriceps limb symmetry at 4-months was also observed as a risk factor for low quadriceps strength gains. Quadriceps strength symmetry is the most commonly sought objective measure of muscle function in patients following ACLR,[28] with a common goal of reaching 90% LSI prior to release to unrestricted activity.[25] It is important to note that quadriceps symmetry is not a true measure of muscular strength, as contralateral limb weakness can inflate the symmetry measure. Interpreting high values of quadriceps limb symmetry without consideration of the magnitude of strength values could overestimate recovery of quadriceps function in the involved

limb. In this study, high limb symmetry measures during interim testing at 4-months was found to increase the probability of not increasing unilateral strength. High limb symmetry measures throughout this time could be interpreted as reaching a clinical target (90% LSI) and may possibly deter patient motivation and rehabilitation decisions to continue the rehabilitation progression. As seen in Figure 1, higher values of quadriceps symmetry can be achieved with low measures of quadriceps strength in the involved limb. The three labeled patients have a quadriceps limb symmetry of 84%, 89%, and 95%; all of which are close to, or achieve, the target of 90% LSI. However, when evaluating the magnitude of strength on their contralateral (comparison) limb, they lie within the lower 15th percentile of the study cohort. High measures of quadriceps symmetry throughout the post-operative recovery should encourage clinicians and patients to continue with current practices and not viewed as reaching terminal targets to progress from strengthening.

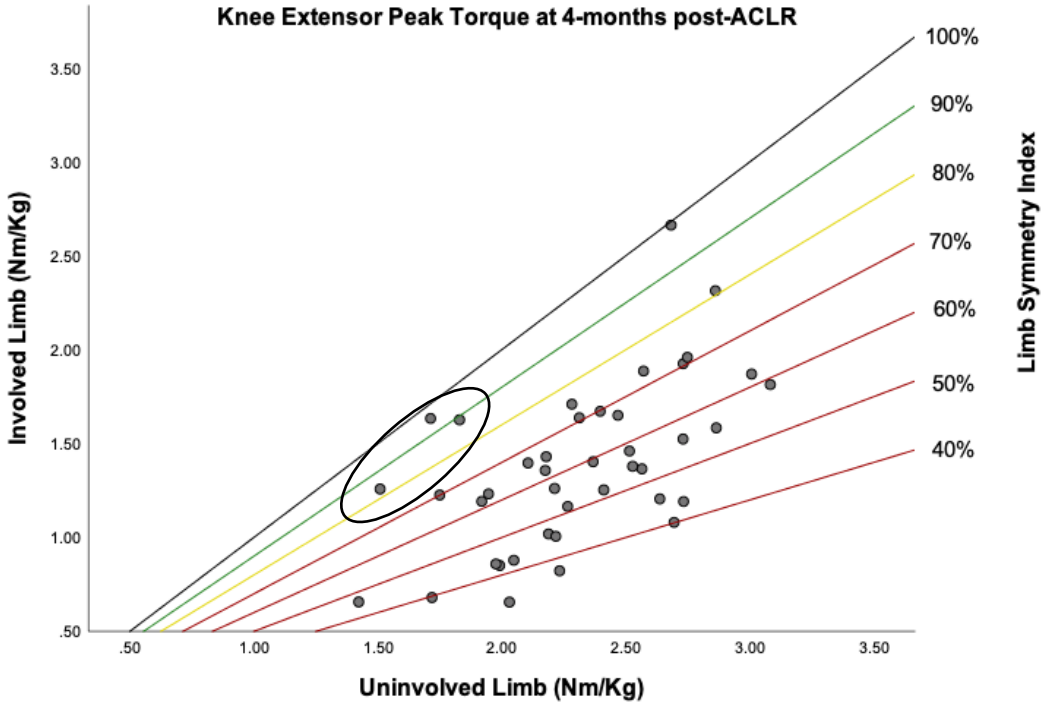

Figure 1: Quadriceps strength of the involved (ACLR) and uninvolved (contralateral) limb during the 4-month assessment. Lines are indicative of the Limb Symmetry Index ((Involved/uninvolved)*100) as labeled on the right axis. As seen, high limb symmetry measures are able to be achieved with low strength of the uninvolved limb (x-axis).

Assessing the relationships between change scores between the 4- and 6-month assessments revealed that increases in quadriceps strength were associated with increases of subjective knee function. Prior literature has found these relationships present both at the time point of return to sport and up to 5-years post-operative, further emphasizing the utility of these functional assessments to describe subjective function following ACLR.[10,29] The current study did not observe any significant correlations between changes in quadriceps strength or symmetry and changes in the ACL-RSI. The ACL-RSI is administered to observe psychological readiness of returning to sport and has been found to relate to subsequent ACL injuries.[30-32] Prior studies have found a relationship between quadriceps symmetry and ACL-RSI at 12-months following ACLR.[33] This finding may illustrate that patient confidence corresponds to quadriceps function at the time of returning to sport however, increasing quadriceps strength or symmetry does not relate an increase in patient confidence throughout the recovery process as seen in the current study. In addition to targeting strength and functional deficits that present following ACLR, psychological aspects of returning to sport should be considered throughout the rehabilitation progression.

Study visits were administered at 4- and 6-months following ACLR from common rehabilitation protocols and knowledge of the time needed to achieve meaningful strength gains.[2,22] Though the study collected subjective reported information about the number of rehabilitation visits the patients engaged in between visits, objective data on exact rehabilitation exercises, compliance, and volume were not collected and should be an area for future research.

Interim assessments administered throughout the post-ACLR recovery may provide insight to functional improvements and timelines needed to achieve clinical goals. Greater age, lower levels of physical activity, and higher measures of quadriceps limb symmetry at 4-months

post-ACLR were found to predict patients that fail to increase strength above clinical thresholds at 6-months. An increase in quadriceps strength and symmetry between 4- and 6-months post-ACLR were found to relate to increases in subjective function, but no relationship was found with increases in patient confidence of returning to sport. Serial assessments throughout the post-operative progression may provide clinical utility for treatments and referrals to optimize patient outcomes.

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SECTION II: MANUSCRIPT III

Visuomotor Therapy Modulates Corticospinal Excitability in Patients following ACL-Reconstruction

Abstract

Background: Corticospinal adaptations have been observed in patients following ACL-Reconstruction (ACLR) around the time of returning to activity. In addition, these measures have been related to quadriceps strength deficits, a commonly observed sign in these patients. Visuomotor therapy, a combination motor control task with visual biofeedback, has been shown to increase corticospinal excitability. Implementation of visuomotor therapy to modulate corticospinal excitability in patients following ACLR may enhance quadriceps function and patient outcomes.
Purpose: To assess the immediate changes of corticospinal excitability following a single session of visuomotor therapy in patients following ACLR near the time of return to activity.
Hypothesis: That a single session of visuomotor therapy will increase motor evoked potentials of the quadriceps in patients following ACLR
Study Design: Single blinded, sham-controlled crossover study
Methods: Assessments of quadriceps strength were administered at approximately 4- and 6-months following ACLR. Quadriceps motor evoked potentials (MEP) were assessed at 80, 90%, 100%, 110%, 120%, 130%, 140%, and 150% of the patient's active motor threshold (AMT). Patients were randomized to receive a single session of visuomotor therapy(active) or passive motion(sham). Quadriceps MEPs were then reassessed for treatment effect. Following a one-week washout period, all patients received the crossover intervention. Wilcoxon sign ranked tests were performed to assess the changes in MEPs before and after the passive motion and visuomotor therapy interventions. Non-parametric effect sizes (r) were interpreted as small: 0.10-0.29; moderate: 0.30-0.49; and large: ≥ 0.50. Spearman rank correlations were performed between MEP change scores for the visuomotor therapy intervention for all stimulus intensities to strength changes between the 4- and 6-month assessments and to the patient's AMT.
Results: Moderate to large increases in motor response following visuomotor therapy 90% (P=.008, r=0.60), 110% (P=.038, r=0.46), 120% (P=.021, r=0.52), 130% (P=.021, r=0.52), 140% (P=.008, r=0.60) and 150% (P=.021, r=0.52) AMT were found. Moderate increases in motor response was observed following the passive motion at 80% AMT (P=.028, r=0.49). A strong, negative relationship was found between the MEP change for visuomotor therapy at intensity of 120% AMT to AMT (ρ=-.92, P<.001). A moderate, negative relationship was found between MEP response at 120% AMT to quadriceps strength changes between 4- and 6-months (ρ=-.66, P<.038).
Conclusions: A single session of visuomotor therapy was found to increase quadriceps corticospinal motor response greater than the response to sham therapy. Lower corticospinal excitability was related to a lower change in motor response following visuomotor therapy. Lower quadriceps strength change from 4-6 months was related to a higher change in motor response following visuomotor therapy. Visuomotor therapy is a potential supplement to quadriceps rehabilitation programs when upregulation of corticospinal excitability is indicated.

Introduction

Persistent muscle weakness is a common sign following Anterior Cruciate Ligament Reconstruction (ACLR).[1] Strength deficits following this injury have been attributed to the inability to fully activate the quadriceps, presenting barriers to progress during post-operative rehabilitation.[2] Underlying neurophysiologic mechanisms, such as spinal and corticospinal excitability, have been found to be reduced following ACLR.[3] Further, lower corticospinal excitability is related to quadriceps muscle function at the time of returning to activity.[4] Interventions to overcome these underlying neurophysiological barriers to rehabilitation progress may optimize patient outcomes after ACLR.

Patients with ACLR experience an acute "shut-down" of the quadriceps muscle group following surgery known as arthrogenic muscle inhibition (AMI).[5] Central manifestations of AMI have been observed at both spinal and cortical levels.[6-8] Depression of reflex spinal excitability has been observed 2-weeks following ACLR and following immediate knee effusion in healthy individuals,[9] but are not observed to differ from that of healthy individuals or the contralateral limb at 6-months after surgery.[3] However, lower measures of corticospinal excitability have been observed around 6 months after surgery.[3,4] Depressed corticospinal excitability results in a greater number of neural signals needed to elicit activation of a muscle.[2] Depressed corticospinal excitability has been observed at 3-months following ACLR,[10] however the only longitudinal data to date suggested that corticospinal impairments develop between 2 weeks and 6-months following ACLR.[3] Lower corticospinal excitability is related to poor quadriceps strength at the time of returning to sport, suggesting a potential physiologic mediator between functional outcomes in patients with ACLR.[4]

Current treatments proposed to combat neural adaptations following ACLR are cryotherapy, exercise, neuromuscular electrical stimulation (NMES), and vibration.[11-14] A review of these treatments concluded that low-quality evidence exists for the efficiency of intervening on muscle activation or quadriceps inhibition.[12,15] A majority of these treatments are aimed to address the spinal inhibition observed immediately following ACLR.[11,16] Currently, there are limited treatment options aimed at corticospinal depression that have been shown to positively impact muscle function following ACLR.[4,17] This might be due to the challenges in accurately diagnosing an underlying cause of persistent muscle weakness. Prescribing interventions that address measurable neuromuscular deficits continues to be the hallmark of individualized patient care following ACLR.

The use of visual feedback informing internal physiological processes, such as muscle activation, torque, and joint position, has been termed "visuomotor therapy".[18,19] Visuomotor therapy has been used within pathologic populations such as stroke, TBI, and even chronic immobilization with the goal of providing neuroplasticity within the motor cortex and spinal motor neurons.[20,21] Visuomotor therapy encompasses completion of sub-maximal motor control tasks accompanying real-time visual biofeedback.[22,23] Visuomotor therapy is hypothesized to modulate corticospinal excitability through stimulation of visual processing centers which then activate cortical areas responsible for movement execution.[24] Compared to passive movement tasks, submaximal, precision-oriented tasks has been found to increase motor evoked potentials and cortical motor representation of lower limb musculature in healthy individuals.[22] In addition, a single session of electromyography biofeedback during a knee maximal voluntary isometric contraction was found to increase quadriceps strength and corticospinal excitability within

healthy individuals.[25] The ability to investigate such therapies in patients following ACLR may provide treatment options in patients with neuromuscular deficits.

A decrease in corticospinal excitability may not observed in all patients following ACLR; however, it has been found to discriminate patients with and without quadriceps strength values indicative of satisfied outcomes.[4] To date, there are no established interventions to address corticospinal changes that impede muscular function. The ability to prevent or reverse detrimental corticospinal adaptations seen within this population may address underlying impairments that contribute to persistent quadriceps weakness. Therefore, the purpose of this study was to assess the ability of visuomotor therapy to modulate corticospinal excitability measured with quadriceps motor evoked potentials in patients following ACLR. We hypothesize that a single session of visuomotor therapy will increase quadriceps motor evoked potentials more so than a sham intervention in patients following ACLR.

Methods

This was a single blinded, sham controlled, crossover randomized trial performed in a controlled, laboratory setting. The dependent variable was motor evoked potential (MEP) at stimulus intensities of 80, 90%, 100%, 110%, 120%, 130%, 140%, and 150% of the active motor threshold (AMT). The independent variable was the intervention performed, visuomotor therapy or passive motion.

Participants

A total of 11 patients following ACLR participated in the study. One participant withdrew during the visuomotor therapy session due to subjective fatigue, leaving a total of 10 participants for analyses. All participants had history of isolated ACLR with no surgical

complications at a single center. Patients referred for routine post-ACLR testing completed a battery of muscle strength assessments at approximately 4- and 6-months following ACLR. Following the completion of both the 4- and 6-month assessments, patients were enrolled to complete two treatment sessions in random order with a minimum of a one week wash-out period between sessions (Figure 1). Patients were excluded from the study if they had any surgical complication, any other lower extremity injury within 6-months, or any TMS exclusion criteria such as: current neuropathy, known muscular abnormalities, history of skull fracture, history of neurological disorders, currently taking medication that may lower seizure threshold, history of subdural or epidural hematoma, implanted biomedical devices above the clavicle, pregnancy, and consumption of caffeine or alcohol 12-hours prior to testing.[26] This study was approved by our university's institutional review board and all patients provided voluntary, written, informed consent.

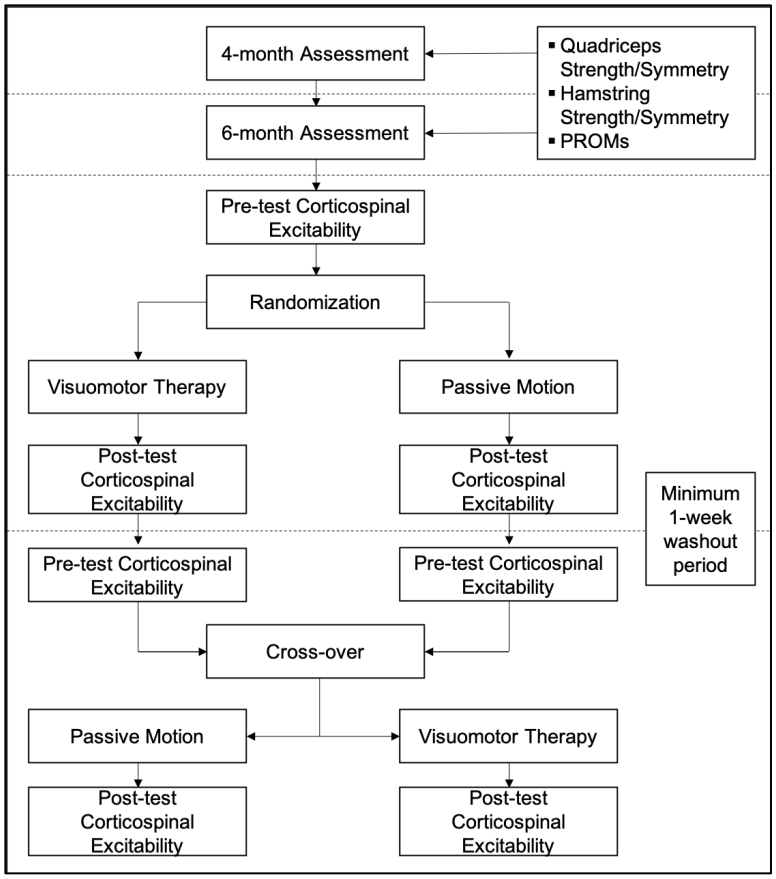

Figure 1: Study procedural flowchart.

Isokinetic, concentric knee extension was measured using a Biodex Systems IV dynamometer (Biodex Medical Systems, Inc. Shirley, NY) at a speed of 90 deg/sec. The participants completed practice trials for practice and familiarization. The participants provided maximal effort through their full range of motion for 8 repetitions. Measures of peak torque for knee extension and flexion were exported from the multimode dynamometer (Biodex, System IV. Shirley, NY).

Active motor threshold (AMT) was assessed using Transcranial Magnetic Stimulation (TMS) (MagStim Rapid, MagStim Comp. Ltd., Wales, UK) as previously described.[27] AMT is quantified as a percentage of maximum unit stimulation (%2-Tesla). Patients were seated in an

isokinetic dynamometer with the trunk flexed to 85º and their flexed to 90º. Patients sat in front of a screen providing real-time biofeedback of their knee extension torque. For all trials, patients were instructed to match their torque to 5% of their maximum voluntary isometric contraction. AMT was collected using a TMS with a 110-mm double cone coil. Stimulation location was marked on a lycra swim cap (TYR Sport, Inc, Seal Beach, CA) that the patient wore throughout the duration of testing. Pre-gelled Al/AgCl electrodes were used to collect surface EMG from the VM (EL503, Biopac, Goleta, CA). All data were digitized and synchronized with a 16-bit data acquisition system (MP150, Biopac, Goleta, CA) and processed through Acqknowledge Software (Version 4.2.0, Biopac, Goleta, CA). AMT was defined as the minimum intensity needed to produce an MEP response greater than contraction noise, an observable torque response, or a minimum of 5/10 trials. MEPs were then collected at 80%, 90%, 100%, 110%, 120%, 130%, 140%, and 150% of the determined AMT to construct the recruitment curve.[28] Five trials were collected at each stimulus intensity. The MEP recruitment curve was collected prior to and following the administered treatment. Patients remained in the same seated position and wore the swim cap marked with the stimulation location during all intervention trials. The TMS coil was placed in the same location for all post-treatment MEP measures.

Patients were randomized to receive one of two treatments, visuomotor therapy or passive motion. Patients crossed-over to receive the other intervention at the subsequent study visit. A minimum one-week washout period was provided between treatment sessions. A randomization sequence was generated *a priori* by a study coordinator and order assignments were placed in a sealed, opaque envelopes. Following the pre-assessment measure of the MEPs, the blinded assessor left the room and the unblinded researcher opened the envelope to determine order allocation.

Visuomotor Therapy

The active intervention in this study was visuomotor therapy. Patients were seated in the isokinetic dynamometer with their hips flexed to 85º. A target sine wave with a maximum amplitude of 30% MVIC and a minimum amplitude of 5% MVIC and a frequency of 0.128 Hz was visually presented to the patient. The patient was instructed to match their torque to the presented target throughout the duration of testing (Figure 2). Each visuomotor therapy trial was 60-seconds, followed by 30-seconds of rest for 10 repetitions, totaling 15 minutes.

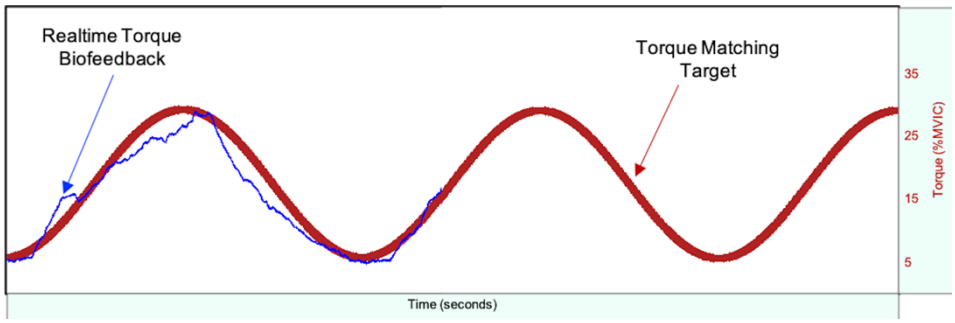

Figure 2: Representative trial of live biofeedback from visuomotor therapy trial. The blue line is real-time knee extensor torque. The red line the torque target instructed to match.

Passive Motion

The sham therapy in this study was passive knee motion which has been previously used as a comparison for modulating corticospinal excitability.[22] Patients were seated in the isokinetic dynamometer with their hips flexed to 85º. The dynamometer then passively moved the patient from 80º to 120º of knee flexion for 60-seconds, followed by 30-seconds of rest for 10 repetitions, totaling 15 minutes. The patient was provided visual feedback of their knee position throughout the trials. The patient was instructed to relax their knee throughout the intervention.

Data Processing

Unilateral measures of peak torque for the 4- and 6-month assessments were normalized to the participant's body weight (Nm/kg). Symmetry measures were calculated using the equation: $Limb\ Symmetry = \left(\frac{involved\ limb}{uninvolved\ limb}\right) * 100$. Change scores of strength between visits were calculated by the difference in measures from the 6- and 4-month assessments tests. MEP amplitude was measured by peak to peak EMG response elicited from the TMS. Any single trial with a MEP amplitude three standard deviations away from the mean were removed from analyses. Changes in MEP for all stimuli were calculated by the difference of the post- and pre-intervention MEPs. Descriptive measures of MEPs were normalized to M-wave. The maximum MEP response for any stimulus intensity (80-150% AMT) was operationally defined as the "Max MEP change".

Statistical Analysis

The assumption of normality was assessed with the Shapiro-Wilk test. Levene's test was used to assess homogeneity of the data. Wilcoxon sign ranked tests were performed to assess the changes in MEPs before and after the passive motion and visuomotor therapy interventions. Effect sizes were calculated from the Wilcoxon ranked sum tests for all comparisons yielding a *P*-value < 0.05 through the following equation: $r = \frac{Z}{\sqrt{n}}$. Effect sizes were interpreted as small: 0.10-0.29; medium: 0.30-0.49; and large: ≥ 0.50.

Spearman rank correlations were calculated between MEP change scores for the visuomotor therapy intervention for all stimulus intensities to strength changes between the 4-

and 6-month assessments and to the patient's AMT. All statistical analyses were conducted through SPSS (Version 26; IBM Inc., Chicago, IL).

Results

Descriptive statistics can be found in Table 1. The assumption of normality was violated for dependent measures of MEPs (*P*'s <.001); therefore, nonparametric statistics were performed.

Table 1: Patient Demographics

	Mean±SD
Patients, n	10
Age, years	26.1±6.2
Sex (Female:Male)	8:2
Graft Type (PT:HS)	7:3
Mass, kg	70.95±13.12
Height, cm	169.67±12.66
Time Since Surgery Visit 1, Months	4.32±.50
Time Since Surgery Visit 2, Months	6.77±.80
Pre-Injury Activity Level (Tegner)	7.50±1.65

Higher changes in motor response were observed following visuomotor therapy at 90% (*Z*=2.67, *P*=.008, r=0.60), 110% (*Z*=2.07, *P*=.038, r=0.46), 120% (*Z*=2.31, *P*=.021, r=0.52), 130% (*Z*=2.31, *P*=.021, r=0.52), 140% (*Z*=2.67, *P*=.008, r=0.60) and 150% (*Z*=2.31, *P*=.021, r=0.52) AMT (Figure 3). A significant increase in motor response was observed following the passive motion at 80% AMT (*Z*=2.19, *P*=.028, r=0.49) (Figure 3). No other significant changes were observed following the sham therapy. Quadriceps MEP changes following visuomotor therapy can be found in Table 2.

Table 2: Changes ([Post]-[Pre]) in Quadriceps MEP following single session of therapy. Median [IQR]

		80% AMT	90% AMT	100% AMT	110% AMT	120% AMT	130% AMT	140% AMT	150% AMT
MEP Changes (% of M-max)	Visuomotor Therapy	0.11 [-.01,.17]	.21* [.08,1.1]	0.58 [-.18,1.3]	2.25* [1.1,5.2]	2.84* [1.17,5.4]	4.29* [.92,5.4]	2.77* [1.1,7.3]	4.77* [3.1,6.4]
	Passive Motion	.002* [.00, .01]	-.0003 [.00, .002]	.001 [.00, .002]	.003 [.00, .011]	.003 [-.03, .02]	-.008 [-.01, .01]	-.002 [-.03, .02]	-.004 [.-.02, .01]

*Represent a significant increase in Quadriceps MEP. Positive values represent an increase in MEP. Abbreviations; MEP: Motor evoked potential

A strong, negative relationship was found between the MEP change for visuomotor therapy at intensity of 120% AMT to AMT (ρ=-.92, P<.001) indicating that participants with higher AMT (lower corticospinal excitability) tended to exhibit less change in motor response following visuomotor therapy. A moderate, negative relationship was found between MEP response at 120% AMT to quadriceps strength changes between 4- and 6-months indicating that participants with less quadriceps strength change from 4- to 6-months post ACLR tended to exhibit a higher change in motor response following visuomotor therapy (ρ=-.66, P<.038). No other significant relationships were observed with other stimulus intensities to AMT or change in quadriceps strength (all P's > .05).

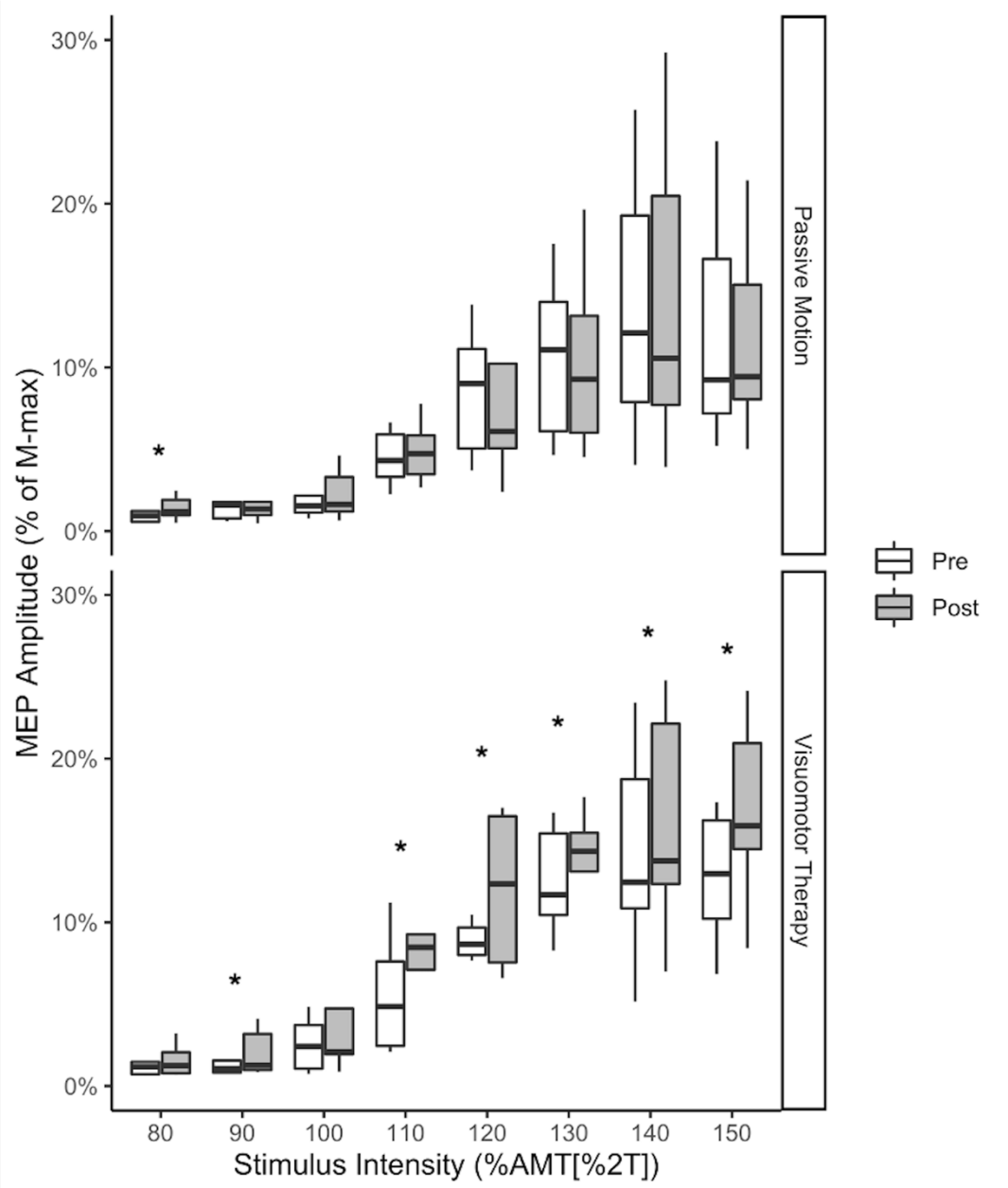

Figure 3: Motor response curve for passive motion and visuomotor therapy trials. Abbreviations- AMT: Active Motor Threshold. *P <.05.

Discussion

Corticospinal adaptations accompanying deficits in muscular function have been observed in patients following ACLR.[27] The ability to modulate corticospinal excitability in patients following ACLR may provide potential treatments to quadriceps rehabilitation programs

when upregulation of corticospinal excitability is indicated. The current study observed that compared to a sham therapy, a single session of visuomotor therapy increased corticospinal excitability of the quadriceps in patients following ACLR. Visuomotor therapy may be a viable option as a supplement to post-operative rehabilitation to address corticospinal adaptations in patients with ACLR.

A single session of visuomotor therapy was found to increase corticospinal excitability whereas sham therapy did not. Visuomotor therapy consists of providing visual guided feedback to describe internal motor commands and has been shown to stimulate visual processing centers to activate cortical areas responsible for movement execution. [19,29-31] Compared to tasks of maximal voluntary contractions, visual biofeedback during submaximal force tasks have been observed to increase MEPs of the tibialis anterior muscle in healthy individuals, with greatest improvements observed after 2-weeks of training.[23] The results from a single session of visuomotor therapy in the current study suggest this may be a possible intervention implemented throughout ACLR recovery to combat supraspinal adaptations.

Many approaches to incorporate disinhibitory modalities have been made in patients following ACLR.[15] Initial rehabilitation goals following ACLR are to regain quadriceps activation through NMES and early strengthening exercises. Cross-sectional studies have observed deficits in quadriceps activation long after the post-operative recovery,[32] suggesting that proper neuromuscular activation may not be fully restored in all individuals. This early impact of muscular inhibition acutely following ACLR has been hypothesized to promote corticospinal changes, also referred to as neuroplasticity. Neuroplasticity, describing changes in neural activation patterns, have been observed in individuals following ACLR in many brain processing centers.[33,34] Corticospinal excitability, as assessed in the current study, quantified the

excitability of the descending corticospinal tract originating in the primary motor cortex. It is theorized that the lasting effects of acute inhibition may result in negative neuroplastic changes within the primary motor cortex, leading to deficits of neuromuscular function, including persistent muscle weakness, and thereby influencing patient outcomes. The current study found that a visually guided submaximal force production task (5-30% of MVIC) increased motor response following a single session. Where maximal activation or force generating exercises may be limited by patient pain and graft healing following ACLR, introducing novel motor control tasks requiring submaximal contractions may be a potential intervention to combat negative neuroplastic changes throughout any portion of post-surgical recovery.

The current study found a negative relationship between the changes in quadriceps motor response following visuomotor therapy with the patients baseline active motor threshold. Patients with lower corticospinal excitability (higher AMT) demonstrated lower changes in quadriceps MEP following visuomotor therapy. A higher AMT indicates a greater amount of energy needed to elicit a motor response. Lower changes in MEP responses following visuomotor therapy in patients with lower corticospinal excitability may suggest that a greater duration of therapy is needed. A previously published 4-week intervention of visuomotor therapy in healthy individuals resulted in the greatest improvements being seen after 2-weeks.[23] Our current study provided a single session of visuomotor therapy to ACLR participants. Impairment-based rehabilitation suggests individualization of treatment exercises and volumes should be based on measurable deficits to optimize patient outcomes.[35] Although it is expected that not all patients following ACLR will demonstrate evidence of altered corticospinal excitability,[36] individuals with high measures of AMT indicating impaired corticospinal excitability, were reported to have weaker

quadriceps.[4] A single session administered in current study may not be sufficient to elicit changes in motor response within these individuals.

Supraspinal adaptations following ACLR have been observed in individuals with low quadriceps strength and been hypothesized to influence muscle recovery in patients presenting with persistent muscle weakness.[2,4,37] Quadriceps strength was assessed longitudinally in the current study at approximately 4- and 6-months following ACLR. An inverse relationship was observed between quadriceps strength change between 4- and 6 months post ACLR and the magnitude of change in motor responses following visuomotor therapy. This relationship suggests that individuals with lower quadriceps strength changes over the 2 month period demonstrated greater motor response changes following visuomotor therapy. Exact mechanisms involved in MEP changes following visuomotor therapy are unclear, however modulation of intracortical inhibition has been found to contribute to plasticity of the primary motor cortex.[38,39] Measures of intracortical inhibition have not only been observed in patients following ACLR but have been demonstrated relationships to quadriceps voluntary activation, indicating that individuals with greater intracortical inhibition have lower voluntary activation of the quadriceps.[8] Lower changes in quadriceps MEP following visuomotor therapy may be indicative of individuals that have impaired quadriceps activation due to AMI leading to less improvement in quadriceps strength. Though commonly assessed through measures of neuromuscular function, there is clinical evidence of persistent quadriceps weakness in patients that may be preventing progression of strength throughout ACLR rehabilitation.[40] Greater changes in quadriceps MEP amplitude in patients with low changes in muscular strength may suggest that patients who are resistant to strength gains may benefit the most from visuomotor therapy.

Incorporation of visuomotor therapy into personalized post-operative ACLR rehabilitation plans is an important area of future research.

Limitations:

This study used a sample size similar to prior research assessing corticospinal excitability modulation of the quadriceps.[25] Findings of an increase in quadriceps motor response was observed following a single session of visuomotor therapy. This single-session design was administered to assess immediate effects of visuomotor therapy in individuals following ACLR. Longer-term clinical trials implementing visuomotor therapy throughout the post-operative recovery is needed to assess plastic changes in neuromuscular function. The current study had an unbalanced proportion of males and females. With known sex differences in neuromuscular movement patterns following ACLR,[41] the effect of patient sex on modulating corticospinal excitability should be an area for future research. It is not possible from the current study to determine the underlying physiological changes of these findings, as changes from the spinal motoneurons to the intracortical interneurons may be involved. However, with deficits observed at supraspinal levels in patients following ACLR, visuomotor exercises implemented throughout the recovery process may provide a novel approach to improve neuromuscular function.

In conclusion, a single session of visuomotor therapy was found to increase corticospinal excitability in patients following ACLR near the time point of returning to activity. Greater changes in quadriceps MEP after visuomotor therapy occurred in patients with lower AMT and in patients exhibiting less improvement in quadriceps strength between 4- and 6-months after ACLR. Visuomotor therapy utilizing submaximal force tasks should be explored as an intervention throughout the post-ACLR recovery to prevent or treat corticospinal adaptations.

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APPENDIX A

The Problem

Problem Statement/Significance

This project addresses the problem of managing ACLR patients in three ways: 1) Using objective data effectively to make healthcare decisions, 2) Identifying reasons why patients aren't able to regain strength during ACLR rehabilitation, and 3) Developing a new approach to overcome neuromuscular causes of persistent muscle weakness.

Manuscript I

Musculoskeletal injury is a leading cause for a decrease in physical activity.[1,2] Decreased physical activity is among one of the top factors increasing the risk of chronic diseases, such as cardiovascular disease, diabetes, obesity, and cancer.[2] Detrimental health outcomes as a result of musculoskeletal injury challenges current practice of injury prevention, treatment and re-engagement in a healthy and physically active lifestyle following injury.

To prevent common detrimental outcomes following ACLR, functional deficits need to be identified and treated prior to returning patients to physical activity. Current traditional thresholds of limb symmetry are used for sport and activity clearance; however, there is a lack of knowledge on the long-term health outcomes, such as re-injury, that these proposed thresholds provide. Evidence-based measures of patient function that can discriminate between individuals that do and do not have successful outcomes would have large clinical implications for post-operative rehabilitation and the return to play (RTA) progression. Objective measures of muscular function that predict patient outcomes of returning to activity and subsequent ACL injury provide the ability challenge current RTA progression and improve patient outcomes.

Manuscript II

The common stigma associated with ACL-Reconstructions is to return to activity as soon as possible. Individuals around this time, on average, demonstrate quadriceps strength symmetry deficits of 40% compared to their uninjured limb.[3] Following ACLR, patients and clinicians, alike, are frustrated with the marginal strength gains that occur late within the rehabilitation process and the inability to confidently return to activity as a result.[4,5] Resistance to quadriceps strengthening resulting in persistent muscle weakness is a common presentation in individuals following ACLR,[3] impeding proper recovery of muscle function.[6] Individuals presenting with persistent muscle weakness likely will not respond to traditional strengthening treatments, thus wasting resources, time and money. The ability to identify patients that may not progress with traditional strength training may empower clinicians to seek and administer alternative treatments to optimize patient function.

Manuscript III

Underlying neurological adaptations that occur following ACL-injury and reconstruction have been found to mediate muscular force production.[7] Arthrogenic muscle inhibition (AMI), defined as a neural reflex limiting the ability to fully activate the muscle, limits strength gains and leads to limitations of physical activity.[8] This inhibition of quadriceps activation and strengthening is thought to occur as a protective mechanism of the knee following the traumatic injury or surgical intervention. Originally thought to only influence muscle function acutely following ACLR through spinal reflexes, supraspinal adaptations observed within the motor cortex have been found to relate to muscle strength and patient function at the time of returning to activity.[9]

A decreased corticospinal excitability is indicative of a greater number of neural signals needed to cause activation of the muscle.[10] These corticospinal adaptations have been observed at 6-months post-ACLR and are thought to be a neuroplastic consequence of the AMI originating from spinal mechanisms acutely following ACLR.[7] A decrease in corticospinal excitability is not observed in all patients following ACLR. However, it has been found to discriminate patients with and without quadriceps strength indicative of satisfied outcomes.[9] To date, there are no established interventions to address these neuroplastic changes that occur and impede muscular function. The ability to prevent or reverse detrimental adaptations seen within this population may address underlying impairments that cause persistent muscle weakness and provide treatment directions to patients that present with it. Current impairment-based treatments are prescribed following ACLR aimed to reverse clinical signs of AMI; however, signs of rehabilitation-resistant muscle weakness are still observed, indicating that current practice may not be targeting the correct impairments. Providing impairment-based treatments dependent on observed corticospinal deficits will allow for an individualized approach for patients to progress to activity, reducing secondary health burdens that many individuals following ACLR experience.

Research Question(s) and Experimental Hypotheses

Manuscript I: Predicting ACL Reinjury from Return to Activity Assessments at 6-months Post-Surgery: A Prospective Cohort Study

Research Question

To identify what measures of patient function at 6-months post-ACLR best predict return to activity and subsequent ACL injury at a minimum of 2-years following ACLR.

Research Hypothesis

We hypothesize that lower quadriceps strength and symmetry will decreases the probability of returning to prior levels of activity and increase the probability of a subsequent ACL injury.

Manuscript II: Quadriceps and Patient Function in Serial Assessments Throughout the Post-ACL Reconstruction Progression

Research Question

To assess the changes in patient strength and function from 4- to 6-month assessments following ACLR, determine relationships between changes in strength to changes in subjective function, and identify factors that predict patients that fail to increase in strength.

Research Hypothesis

We hypothesize that lower levels of physical activity and lower measures of quadriceps strength and symmetry at 4-months will predict individuals that fail to increase strength between assessments.

Manuscript III: Visuomotor Therapy Modulates Corticospinal Excitability in Patients following ACL-Reconstruction

Research Question

To assess the immediate changes of corticospinal excitability following a single session of visuomotor therapy in patients following ACLR near the time of return to activity.

Research Hypothesis

We hypothesize That a single session of visuomotor therapy will increase motor evoked potentials of the quadriceps in patients following ACLR

Project and Designs

I. Manuscript I

Profile of ACLR Individuals that Predict Successful Outcomes

a. Research Question

What measures of muscle function at a 6-months post-ACLR best predict return to activity and subsequent ACL injuries at a minimum of 2-years following ACLR?

b. Experimental Design

- Prospective Cohort Study

Independent Variables

- International Knee Documentation Committee (IKDC) Subjective Questionnaire
- Knee Osteoarthritis Outcome Score (KOOS) – Sport Subscale
- Knee Extensor Strength (Nm/kg)
- Knee Extensor Symmetry (%)
- Knee Flexor Strength (Nm/kg)
- Knee Flexor Symmetry (%)
- Normalized Single Hop (m/m)
- Single Hop Symmetry (%)
- Normalized Triple Hop (m/m)
- Triple Hop Symmetry (%)
- 6-m Timed Hop (seconds)
- 6-m Timed Hop Symmetry (%)

Dependent Variables

- Return to Activity (Yes/No)
- Secondary ACL Injury (Yes/No)

c. Inclusion

- 12- 65 years of age
- History of unilateral, uncomplicated ACL injury and ACL Reconstruction
- Initial LEAP visit between 5-7 months following their initial ACL-Reconstruction
- Patient underwent ACL reconstruction and attended LEAP visit with the intent to return to previous levels of activity

d. Exclusion

- Prior history of lower extremity surgery or lower extremity injury within the past 6-months
- Multiple ligament reconstruction or a prior history of graft failure prior to the time of the initial LEAP
- Surgical complication following ACL Reconstruction
- Referral from outside medical network

II. Manuscript II

Persistent Muscle Weakness: Identification of individuals with the inability to regain strength

a. Research Question

1. How do individuals following ACLR progress from 4- to 6-months post-surgery?
2. What are the differences in patient function at 4-months that discriminate individuals that do and do not demonstrate improvements of quadriceps strength?

b. Experimental Design

Independent Variables usefulness

- Groups: 1) Increase in Quadriceps Strength 2) Persistent muscle weakness

Dependent Variables

- Subjective Function: IKDC, KOOS Sport (%)
- Return to Sport Confidence: ACL-RSI (%)
- Knee extensor peak torque (Nm/kg)
- Knee extensor peak torque symmetry (%)
- Knee flexor peak torque (Nm/kg)
- Knee flexor peak torque symmetry (%)

c. Inclusion

- 12- 65 years of age
- History of unilateral, uncomplicated ACL injury and ACL Reconstruction
- Patients attended the Exercise and Sports Injury Lab (EASIL) at approximately 4-months post-ACLR for their Strength and Endurance Protocol (STEP) test.
- Patient underwent ACL reconstruction and attended STEP/LEAP visits with the intent to return to previous levels of activity

d. Exclusion

- Multiple ligament reconstruction or a prior history of graft failure prior to the time of the initial LEAP
- Prior history of lower extremity surgery or lower extremity injury within the past 6-months
- Any injury event that occurred between the STEP and LEAP visits
- Referral from outside medical network

III. Manuscript III

The effect of Visuomotor Therapy on Cortical Excitability in Individuals following ACLR.

a. Research Question

- Does the administration of visuomotor therapy influence quadriceps motor evoked potentials (MEP) in patients following ACLR.

b. Experimental Design

Independent Variable

- Groups: 1) Visuomotor Therapy (Active) 2) Passive Motion (Sham)

Dependent Variable

- Change in Quadriceps MEP from 80 to 150% of the patient's active motor threshold (AMT)

c. Inclusion

- 18- 45 years of age
- History of uncomplicated ACL injury and ACL Reconstruction
- Patient underwent ACL reconstruction and attended LEAP visit with the intent to return to previous levels of activity
- Patient completed prior STEP and LEAP assessments

d. Exclusion

- Prior history of lower extremity surgery or lower extremity injury within the past 6-months
- Referral from outside medical network
- History or immediate family history of seizures or epilepsy
- Multiple ligament reconstruction or a history of graft failure

- Serious surgical complication following ACL reconstruction
- Chondral resurfacing procedure (microfracture or OATS procedure)
- History of cardiopulmonary disorder
- Current symptoms of meniscal injury or failed meniscal repair
- Current neuropathy (numbness and tingling)
- Known muscular abnormality
- History of skull fracture
- History of neurological disorders including poorly controlled migraine headaches, seizure disorder, history or immediate family history of seizures and/or epilepsy
- Taking medications that lower seizure threshold
- History of subdural hematoma or epidural hematoma
- History of neurological disorders
- Implanted biomedical device (active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators)
- Conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes
- Pregnant women
- Significant activity change 48 hours prior to enrollment

Study Assumptions

- Participants will provide accurate information regarding lower-extremity injury and surgical history
- Participants will provide maximal effort and attention during all exercises
- Obtained measures of corticospinal excitability are valid and reliable
- Knee extension tasks were representative of peak quadriceps function
- The quadriceps central activation ratio (CAR) represents the force generated by activated motor units recruited volitionally when compared to the maximal capacity of the muscle
- The transcutaneous electrical stimulation administered during the supra-imposed burst activated all quadriceps muscle tissue not active during the maximal voluntary isometric contraction
- Participants were not on any medication (not-screened for) that could alter spinal or corticospinal excitability

Delimitations

- Performed at a single-site academic institution
- Physically active individuals between the ages of 18-45 years
- Primary, unilateral and uncomplicated ACL reconstruction
- Timing of STEP (4-month) and LEAP (6-months) tests may vary (±1 month) due to patient referral patterns

Limitations

- Patient exposure to reinjury following ACLR was not objectively measured
- Patient feedback through their LEAP report may have modified their activity levels or exposure to reinjury

- Outcomes for returning to activity and reinjury were self-reported for some patients
- Rehabilitation that the patients completed prior to the 6-month functional assessment and between the 4- and 6-month functional assessments were not tightly controlled for
- A single session of therapy may not represent how patients engage with post-operative therapy following ACLR
- There was not an equal distribution of males/females that completed the visuomotor therapy

Operational Definitions & Equations

1. ACL Re-injury – A subsequent tear of any ACL following the initial ACL-Reconstruction. The subsequent injury may be an injury of the reconstructed ipsilateral graft or the contralateral ACL. All injuries were verified by chart review from follow-up clinic visits or verbal confirmation through phone calls.
2. Active motor threshold – An intensity of TMS that produces a motor evoked potential (MEP) at a target muscle in at least 5 out of 10 trials during a contraction producing 5% of the participants MVIC[11,12]
3. Arthrogenic muscle inhibition- A presynaptic, reflex inhibition of a muscle surrounding a joint after distension or damage to structures of a joint[13,14]
4. Biofeedback – a modality to provide real-time information regarding a physiological event or series of events that would typically not be perceived by the user[15]
5. Cortical plasticity – The adaptive capacity of the nervous system. For each new learning event, there is some necessary and sufficient change in the nervous system that supports learning.[16]

6. Corticospinal excitability – The excitable properties of the corticospinal neurons in response to input from sensory areas of the cortex, subcortical inputs from the spinal cord, basal ganglia, and cerebellum.[17] The discharge from muscle, cutaneous, and joint receptors cause modification of cortically generated motor commands.[18]
7. Early intervention – The application of a treatment acutely following injury or surgery aimed to prevent or reverse detrimental outcomes that may occur otherwise.
8. Isokinetic strength - The peak torque during a task where the velocity of movement is set at a certain speed.
9. Isometric force control - A measure of the ability of a participant to match and sustain a target isometric knee extension contraction at a percentage of their maximal contraction. This measure is quantified using the coefficient of variation and the root mean square error relative to the target force.
10. Limb symmetry – The comparison of the involved limb (ACL-Reconstructed limb) to the uninvolved (Healthy) limb. The limb symmetry index
    (LSI) is calculated as: (Injured Limb/ Uninjured Limb)*100
11. Maximal Voluntary Isometric Contraction (MVIC) – The peak force that can be generated voluntarily with the joint in a stationary position.
12. Motor evoked potential (MEP) - depolarization of cortical neurons via electromagnetic stimulation over the motor cortex eliciting a efferent motor response of a muscle of interest.[19]
13. Muscular activation failure – The inability to contract all motor units of the muscle. The ability to volitionally activate 95% has been defined as fully activated.[8,20]

14. Neurologic Adaptation – a change in peripheral, spinal, or cortical reflex and/or measure of motor output in response to a structural change in anatomy (musculoskeletal injury)
15. Neuromuscular Control – as the unconscious activation of dynamic restraints occurring in preparation for and in response to joint motion and loading for the purpose of maintaining and restoring functional joint stability.[21]
16. Patient Reported Outcome (PRO) - subjective evaluations that measure the impact of injury or illness on the individual's function, lifestyle, and well-being
17. Persistent Muscle Weakness – strength deficits that report following injury or surgery and that do not improve following prescribed treatments and rehabilitation.[22]
18. Post-traumatic osteoarthritis (PTOA) – the arise of osteoarthritic process of cartilage degeneration secondary to joint trauma.[23]
19. Proprioception- the afferent information arising from ‘‘proprioceptors’’ located in the ‘‘proprioceptive field.’’ The ‘‘proprioceptive field’’ is specifically defined as that area of the body ‘‘screened from the environment’’ by the surface cells, which contained receptors specially adapted for the changes occurring inside the organism independent of the ‘‘interoceptive field’’.[21,24]
20. Quadriceps activation (QA) The proportion of motor neuron pool that can be volitionally activated.[8]
21. Quadriceps central activation ratio (CAR) – A ratio of the maximal voluntary isometric force (FMVIC) to the total force generated when an additional supramaximal percutaneous electrical stimulus is administered during a MVIC.[8,25] Expressed as CAR = [FMVIC/ (FMVIC + FSIB)]. A CAR of less than .95 indicates central activation failure or inhibition.[13,20]

22. Quadriceps inhibition (QI) – Failure of central motor drive which results in less than maximal voluntary activation of the muscle.[25]
23. Return to Activity – The ability to the patient to return to prior levels of physical activity or sport following ACLR. This was captured through patients follow-up visits, chart review, and/or questionnaires administered via phone.
24. Sensorimotor Control – The interaction between sensation of sensory information, the integrating of information in the central nervous system and motor output to perform motor outputs.[21,24]
25. Sensorimotor System - The sensory, motor, and central integration and processing components involved in maintaining joint homeostasis during functional movements.[24]
26. Transcranial magnetic stimulation – A method for studying the relationship between brain activity and motor tracts through the use of electromagnetic stimulation of the motor cortex. Motor response cam be measured over the targeted muscle via electromyography.[26,27]
27. Visuomotor therapy - utilization of visual patient feedback describing an internal physiological process[28,29]
28. Voluntary activation failure- The inability to produce all available force of a muscle despite maximal conscious effort.[8]

Innovation

Manuscript I

Injury to ACL is among the highest time loss orthopaedic injuries among competitive athletes with approximately one out of two individuals returning to competitive levels of sport following ACLR.[30,31] Of individuals that do return to sport, up to 20% obtain a secondary ACL injury indicating current return to play assessments and guidelines are not safely returning patients to active lifestyles.[32]

The proposed study would provide evidence-based measures of muscle function to clinicians to provide safe recommendations to individuals recovering from ACLR. Determined predictors would change the way clinicians and researchers advise RTA progression in individuals following ACLR to reduce the incidence of subsequent detrimental outcome. Current return to activity decisions are traditionally based on the time-since surgery, providing no individualized variability for treatment recommendations. The knowledge of functional measures that predict patient outcomes would shift patient care towards treatments dependent on an individualized profile to provide optimal short- and long-term outcomes.

Manuscript II

Persistent muscle weakness is a common sign in individuals following ACLR. Clinical factors that can identify patients that will go on to demonstrate signs of persistent muscle weakness throughout the post-operative recovery may allow individualization of treatments to address these underlying impairments. Furthermore, a single assessment at the time of RTA can provide insightful information to guide patient progression; however, may not describe how the patient is responding to current rehabilitation. Serial assessments throughout the post-operative

rehabilitation may allow for greater insight to patient response to clinical care and guide treatment progressions and clinical decision making.

A multi-visit design of this study would provide evidence-based recommendations on the profile of a patient that is resistant to traditional quadriceps strengthening. Clinical signs to identify individuals that demonstrate persistent quadriceps weakness would eliminate unnecessary time and referrals of treatments that would not better the individual. The frequency of persistent muscle weakness places a large economic and health burden on individuals following ACLR.[33] The proposed study would provide clinical measures that would be able to identify patients with persistent muscle weakness which would reap greater benefits through alternative treatment strategies.

Manuscript III

Individuals that demonstrate muscle weakness at the time of return to sport have been shown to have neurophysiological adaptations of the corticospinal pathways when compared to individuals with greater muscular strength.[9] Interventions within this population should be aimed to address physiological deficits. If individuals fail to demonstrate strength gains in response to traditional rehabilitation, underlying neurological adaptions shown to influence muscle function should be targeted. The following study will investigate the effect of visuomotor therapy on cortical excitability and quadriceps function. Visuomotor therapy encompasses completion of sub-maximal motor control tasks with real-time visual biofeedback to create use-dependent changes of the cortical neurons. Visuomotor therapy targets these changes through stimulation of visual processing centers which then activate cortical areas responsible for movement execution. Further exploration of interventions to address physiologic impairments would change treatment perspectives for individuals that present with rehabilitation resistant quadriceps weakness.

Individuals following ACLR that present with muscle weakness are currently prescribed additional strengthening rehabilitation. This creates a cyclical pattern of treatment referral and lack of patient response, causing chronic quadriceps weakness and placing individuals at greater risk of harmful outcomes. To break this cycle, treatments should be administered to address observed physiological impairments. The proposed study provides a framework to clinically define individuals with persistent muscle weakness and intervene on observed physiologic impairments, changing the way clinicians treat individuals following ACLR.

APPENDIX B

Literature Review

Injuries to the anterior cruciate ligament (ACL) are common among the young, active population.[34] These individuals commonly present with muscle dysfunction at the time of returning back to physical activity. Evidence suggests the causal relationship of quadriceps weakness to reduced physical activity, an increased risk for subsequent ACL injuries, and degenerative joint diseases such as osteoarthritis.[35,36] Neurophysiological adaptations have been demonstrated within individuals following ACLR with greater impairments being observed in individuals with low quadriceps strength.[9] This suggests that underlying neurological changes may mediate muscle function and contribute to the physiological origins of persistent muscle weakness. To date, there is limited knowledge on how to clinically detect individuals that may present with persistent muscle weakness and treatments to effectively address it. The purpose of this literature review is to describe and interpret the current state of literature in the areas of RTA decision making, strength progression throughout the post-operative recovery, and neurophysiological impairments that are observed following ACLR.

A. Neuroanatomy of the Anterior Cruciate Ligament

The growing research on the topic of ACL injury, reconstructive surgery, and post-operative treatments requires the extensive knowledge of the functional anatomy; comprised neural structures, and surrounding joint musculature that an isolated ACL injury may compound. The following will serve as a review for the neuroanatomy of the ACL and the surrounding structures.

The anterior cruciate ligament (ACL) is one of the two cruciate ligaments that are found within the synovial joint of the knee and is comprised of type I collagen.[37] The ACL itself is comprised of two bundles or bands, the anteromedial and posterolateral bundles.[38] The collagenous fibers of each band are bundled into fascicular units around 3 mm in diameter and spiral along the axis of the ligament from the proximal attachment on the posteromedial aspect of the lateral femoral condyle to the distal insertion on the anteromedial aspect of the medial condyle of the tibia.[39] The ACL limits anterior translation and rotational actions of the tibia; however, the separate bundles limit these motions in different knee-joint positions. Biomechanical studies have found the greatest force transmitted through the AM bundles at 60 and 90 degrees of knee flexion and the greatest force for the PL bundle was at full extension.[40] The forces of the PL bundles have been found to be more representative the forces attenuated by the entire ACL,[40] stressing the importance of modeling a reconstruction of the ACL to the PL bundle. Majority of ACL injuries also occur with the knee near full extension, stressing the importance of the biomechanical stability of the PL bundle.[41]

Neural Structures of the ACL

Several mechanoreceptors are also found within the type I collagen of the ACL. In addition to the mechanical properties that the ACL has on the knee joint, such as preventing anterior translation and rotational forces to the knee, the sensory receptors provide proprioceptive information joint position as well as initiating reflexes of the surrounding muscular structures.[42-46] The presence of numerous mechanoreceptors within the ACL suggests that thought ACLR may restore mechanical instability of the knee, neural mechanisms of reflex and afference may not be restored.

Mechanoreceptors within the ACL function as transducers, converting physical energy detected into a nervous signal. The intraligamentous mechanoreceptors are stimulated by tension, providing afference of joint acceleration, direction, and exact position during motion. Different types of mechanoreceptors convey different information of the joint due to the receptor's adaptability. Histological studies of the ACL have found multiple mechanoreceptors present, such as free nerve endings, Ruffini end organs, pacinian corpuscles, and Golgi-tendon like organs.[42,43] Ruffini corpuscles, commonly found within the knee joint capsule, are slowly adapting mechanoreceptors.[47] These receptors have a low threshold to pressure changes within a joint, and play a role in signaling the limits of rotation of the knee in extension. [47] Pacinian corpuscles are rapidly adapting mechanoreceptors known for informing the acceleration of the joint through space. [48,49] These receptors within the ACL are thought to signal at a response proportionate to the acceleration of the joint regardless of position. [50] The most abundant, free nerve endings, serve as the nociceptive system of the joint, which are inactive during normal circumstances and become more active when the joint is subject to change from chemical or mechanical deformation.[51] These receptors neighbor blood vessels and assist in function in vasomotor control. The synovial sheaths covering the ACL are also contain numerous free nerve endings.[52] Golgi-like endings, most commonly found in large joints, are responsible for detecting extreme ranges of joint movement. The cruciate ligaments contain more Golgi-like endings compared to all other internal structures of the knee.

Majority of the mechanoreceptors are found in the interfascicular region of the ACL, followed by the sub-synovial layer, and very few in the border zone between the ligament and the synovium.[53] In the sagittal plane, majority of the mechanoreceptors are located within the ligament insertion points, with greater numbers in the femoral third than the tibial third.[53]

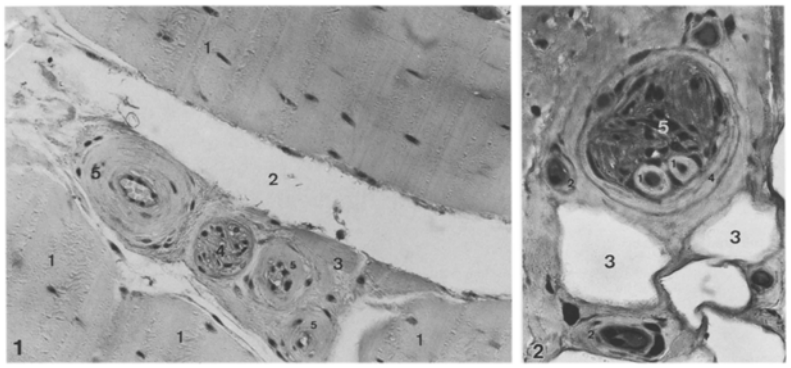


Figure 1: Interfascicular bundle of the ACL with blood vessels and nerves. 1) Collogenous fascicles 2) Interfascicular space, 3) interfascicular connective tissue, 4) nerve, and 5) blood vessels. Figure from Haus et. al., 1990

Activation or depolarization of the mechanoreceptors within the ACL cause an excitation of afferent pathways. There are four types of peripheral nerves carrying afferent information: small nerves with unmyelinated fibers, mixed nerves with myelinated and unmyelinated nerve fibers, mixed nerves with 1-3 blood vessels are their margins, and mixed nerves with blood vessels at their margins and an additional perineural sheath.[53] Intra-operative electrophysiological studies have found that excitation of these nerves carry signals to the posterior articular branches.[54] These branches run alongside the synovial and periligamentous vessels that then penetrates the posterior joint capsule to the tibial nerve.[55,56] Proximally, the tibial nerve merges with the common peroneal nerve to form the sciatic which enters the spinal cords at levels L4 to S3.

All sensory afference convey information from the corresponding proprioceptors in the dorsal root ganglion and enters the central nervous system at the posterior horn of the spinal cord. The central end of the bifurcated axon terminates in the grey matter of the dorsal horn of the spinal cord providing somatosensory information from the dorsal root ganglion. These

branches may activate reflexes originated in the spinal circuitry or provide ascending input to the brain where it then portrays into the sub-modalities of perception; joint position, force, pain, or touch.[57] These sub-modalities are carried to the brain via different neural pathways. All sensory information from the lower extremity is carried via the gracile fascicle and terminate in the gracile nucleus. Circuits within the spinal cord also drastically influence the responding motor output.

The central end of the sensory axon terminates on many axons including but not limited to spinal interneurons, ascending sensory neurons, and directly to alpha motor neurons. These neural connections, often influenced by descending signals, help conduct human movement.[58] To better understand the post-traumatic muscular neurophysiology following ACLR, human reflex loops should be studied. The following are the different efferent motor responses that occur through spinal cord circuitry and may influence motor output following excitation of neural structures within the ACL.

The flexion-withdrawal reflex is a common spinal reflex caused by afferent sensory information. A stimulus initiates the flexion withdrawal reflex through cutaneous afferent receptors. The reflex utilizes divergent polysynaptic pathways to excite corresponding neural pathways responsible for activating flexor muscles of the stimulated limb simultaneously inhibiting extensors of the stimulated limb.[59] The facilitation and inhibition of the reflex motor response occurs through interneurons within the spinal cord which mediates the descending motor commend through alpha-motor neurons. During stance, the opposite response would occur to the contralateral limb – excitation of the limbs extensors while inhibiting the flexor muscles- to support the body's weight.

The excitation of one muscle group while simultaneously inhibiting the antagonist muscle is called reciprocal inhibition.[60] This inhibition prevents muscle contractions that have the capability to resist the desired movement.

The stretch reflex is monosynaptic reflex caused from afferent signals from muscle spindles that are located with the muscle. Muscle spindles are sensory receptors that have a fusiform shape and lie within the muscle fibers and provide sensory information on the length of the muscle in which they reside. These sensory receptors primary inform the CNS on the relative position of the corresponding body segment. The muscle spindle is composed of intrafusal muscle fibers innervated by gamma-motor neurons, as opposed to the muscle extrafusal muscle fibers which are innervated by alpha-motor neurons. Activation of the gamma-motor neurons shorten the end regions of the intrafusal muscle fibers, making the sensory receptor more sensitive or increasing the firing rate of the Ia afferent nerves. Activation of the gamma motor neurons adjust the sensitivity of the muscle spindles. Within the spinal cord, excitement of the these Ia afferent pathways cause excitatory connections on the alpha motor neurons that innervate the homonymous muscle and those that innervate synergist muscles (muscles that perform the same action). An inhibitory signal will be conveyed to the antagonist muscle via inhibitory interneurons, an example of reciprocal inhibition.

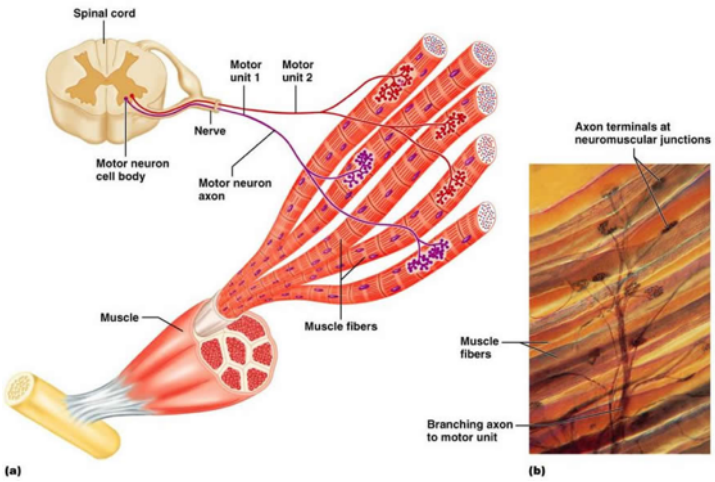


Figure 2: Motor unit illustration (alpha motor neurons innervating extrafusal muscle fibers)

The gamma motor neurons, innervating the intrafusal muscle fibers, can adjust the sensitivity of the muscle fibers. If the gamma and alpha motor neurons activate at the same time, the muscle spindle is kept under tension maintaining the firing rate of the Ia afferent neurons. This is called alpha-gamma co-activation and stabilizes the sensitivity of the muscle spindles that are needed during voluntary movements.

The same inhibitory interneurons that are involved within the stretch reflex help coordinate functional motor output.[60] Regulation of these interneurons control reciprocal inhibition but also co-contraction of agonist and antagonist muscles. Another spinal motor interneuron are Renshaw cells. Renshaw cells make inhibitory connections with several motoneurons, including the alpha-motor neuron that excites them and corresponding Ia inhibitory interneurons.[61,62] The connection to the corresponding alpha-motor neuron helps regulate the firing of the neuron and the synaptic connection to the inhibitory interneuron regulates the strength of inhibition of the antagonist motor neuron.[62]

Golgi-tendon organs are slender sensory receptors that are located in the collagen fibers within a tendon of a muscle.[59] Each tendon is innervated by a single Ib afferent neuron. Shortening of the muscle causing tension of the tendon elicits activation of the GTO and therefore the excitement of type Ib neurons. The Ib neuron synapses to an Ib inhibitory interneuron causing inhibition of the alpha-motor neuron for the agonist muscle.[63] The GTO and Ib neurons do not only prevent damage by inhibiting muscular torque production that may cause strain to capsular joint structures but allow for precise motor output for fine motor control.

The strength and sign of synaptic transmission varies on the task performed. For example, Ib neuron have an inhibitory effect on homologous muscle during rest but provide an excitatory effect on the same alpha-motor neurons during walking.[59] The change of synaptic transmission with different tasks is called state-dependent reflex reversal. This is not the only place where the strength of the reflex can be modified. Three location where reflex pathways can be modified are at the 1) alpha motor neuron, 2) interneurons (except Ia monosynaptic pathways), and 3) the presynaptic terminal of the afferent fibers. All three locations can be modulated through descending neural signals from the brain stem, cerebral cortex and other areas of the spinal cord.

Hoffmann's Reflex

Characteristics of the monosynaptic connections of the Ia afferent fibers to alpha-motor neuron can be studied through the Hoffmann's Reflex. This reflex is measured by stimulating a mixed nerve (afferent and efferent fibers present) and measuring the motor output that occurs due to the spinal reflex and the efferent motor response.[64] At a low stimulus, only the H-reflex is evoked due to thresholds of Ia afferents being lower than that on alpha motor neurons. The H-wave, or motor output due to spinal reflex, occurs later due to the signal having to travel to the spinal cord, synapse to

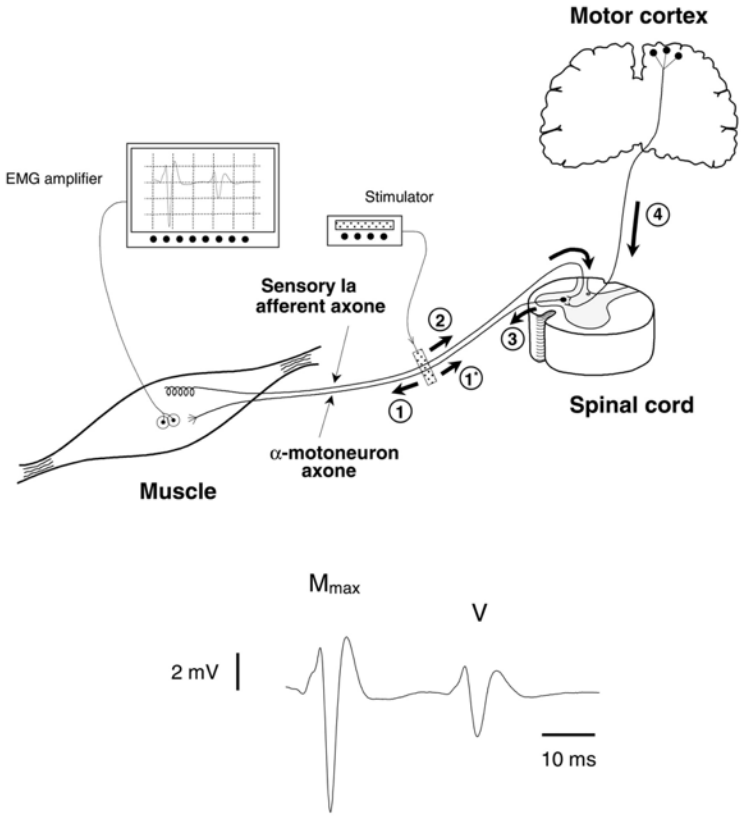


Figure 3: Measurement of the Hoffmann's Reflex. Signal 1 would elicit the M-wave. Signal 2 would elicit the spinal reflex and corresponding motor output (Signal 3). Signal 2* would be the antidromic response of the stimulation. Signal 4 would be the descending motor drive. Palmieri et. al., 2004

the alpha motor neuron, and ascend back to the contractile motor fibers. The maximal h-wave is called h-max represents the hypothetical total motor neuron pool present for that muscle. The M-wave is the motor response and represents the direct stimulation of the motor axon innervating the muscle. As stimulus strength increases, the H-wave will decrease as the M-wave increases. This represents the antidromic conduction of the alpha motor neuron being larger than the orthodromic response from the spinal reflex. Once the h-max and m-max are recorded, a H:M ratio is often portrayed to interpret the total motor neuron pool that can be activated.[64]

Surrounding Musculature

The ACL is described as a primary passive stabilizer of the tibio-femoral joint, in contract to the dynamic muscular stabilizers that surround the joint. Muscles provide active stabilization of the joint during functional movements. The quadriceps muscle group, composed of four muscles: the rectus femoris, vastus lateralis, vastus medialis, and vastus intermedius, all cross the knee joint anteriorly via the quad tendon, patella, and patellar tendon. The primary action at the knee is extension of the tibia in an open chain position causing anterior translation of the tibia on the femur. The hamstring muscle group, composed of the biceps femoris, semitendinosus and semimembranosus muscles, cross the knee posteriorly and cause flexion of the knee. The hamstrings actively prevent anterior translation of the tibia, a commonality to the passive ACL.[65]

Innervation of the quadriceps muscle group is through the femoral nerve. Injury and reconstruction of the ACL has demonstrated inhibition of the femoral alpha-motor neurons innervating the extrafusal muscle fibers of the quadriceps.[13] Through the femoral nerve is a mixed nerve providing efferent motor input to the quadriceps muscles, the direct sensory

afference of the ACL that transcends to the CNS is not through the femoral pathways rather through pathways of the tibial nerve.[65] The tibial nerve provides motor efference to the hamstring muscle group, however, the motor inhibition that is observed within the quadriceps muscle group is not seen post-operatively within the hamstring muscle group. This proposes the questions of direct mechanisms and causes for quadriceps inhibition observed following ACLR. Hilton's law, established in 1863, is defined as "The same trunks of nerves whose branches supply the groups of muscle moving a joint furnish also a distribution of nerves to the skin over the insertions of the same muscle; and -what at the moment more especially merits our attention – the interior of the joint receives it's nerves from the same source."[66] According to Hilton's Law, the femoral nerve plays a significant role in the innervation of the knee joint capsule and other internal structures. Following ACLR, an inflammatory response occurs locally that effects more than the ligamentous structure itself, such as the synovial layer and epi-ligamentous tissue.[67] Though unknown, it may be this global response that greatly inhibits the quadriceps muscle compared to other muscles that cross the same joint.

B. Epidemiology of ACL Injuries

A broad range of injury rates of the ACL have been demonstrated throughout the literature and have been found to be strongly influences by age, sex, and level of activity. A common rate reported is over 250,000 ACL injuries within the US per year. This commonly cited number is from a prior estimation and has not been established by peer-review literature.[68] The true incidence of ACL injuries ranges from .01% to .05% of the general population, equating to 32,000 to 160,000 injuries per year. However, this rate increasing drastically in active individuals, rising to .002% to 1.62% in amateur athletes and 0.15% to 7.32% in professional

athletes.[69] Obtaining national estimates of injuries is difficult with injury and healthcare data not being reported to a common source. Best representation of the epidemiology of ACL injuries are best captured through incidence rates established from single clinics, national sport injury databases, and insurance databases – all of which present with limitations in estimating the total incidence of a single injury.

The total incidence of ACL injuries has been reported higher in males,[34] however, females have been found to be at a greater risk for ACL injuries from non-contact mechanisms.[70-72] A non-contact mechanism is defined as an injury occurring movement where no external force is applied to the patient. The most common non-contact mechanism of ACL injuries occur though a cutting motion, rapidly changing acceleration during movement.[73] The higher injury rates in males may be to the inclusion of contact sports such as football. Non-modifiable factors such as hormonal differences and bony alignment may increase the risk of injury for females.[74-76] Though differences have been seen in these measures, focus lies on risk factors that can be modifiable to the patient, such as neuromuscular control, movement patterns, and skill acquisition.[70] Common kinematic patterns for non-contact ACL injury are hip internal rotation and adduction, knee valgus, and tibial external rotation on a pronated, externally rotated foot.[70] Injury prevention studies aim to prevent this motion during functional tasks to decrease the risk exposure within athletes.[41,77]

A study a national collegiate sport database (NCAA-Surveillance Injury System) looking at ACL injury rates between males and females during a 5-year period observed non-contact soccer injury rates (per 1000 Athlete-Exposures [AE]) of 0.31 for females and 0.13 for males.[78] Females similarly reported higher non-contact injury rates (0.29) compared to males (0.07) participating in basketball.[78] These trends of higher non-contact injury rates are seen among

many sports.[72,79,80] When looking at the overall incidence of ACL injuries however, males consistently have higher rates.[34]

ACL injuries and reconstruction are most commonly seen within individuals between 18 and 22 years of age.[81] When looking at sex differences, the peak incidence rate differ among age at the time of injury. For males, the highest rates were found between 19 and 25 years of life; for females, the highest rates were between 14 and 18 years.[81] Incidence rates among males significantly declined from this stage in life but remained relatively stable for females indicating that females may be at a higher injury risk for a greater duration of time. A cross sectional study looking at the trends of ACLR between 1997 and 2004 found that this trend does not change, individuals around 20 years of age are among the highest patient population seeking this medical treatment, with rates up to 18 per 100,000 people.[34] The trends of ACLR within individuals in the 40s; however, has drastically changed.[34] Reports have suggested that the greater numbers of individuals seeking ACLR are due to greater sport participation,[82] and that patients are performing high-level

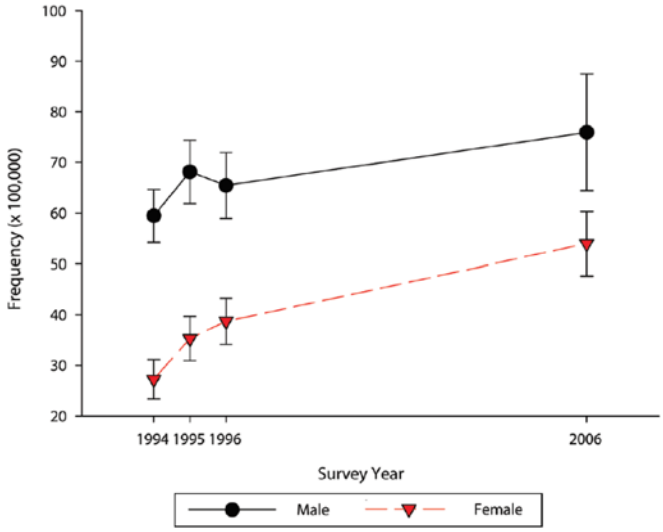


Figure 4 – Incidence of ACLR by sex. Mall et. al.,2014[28]

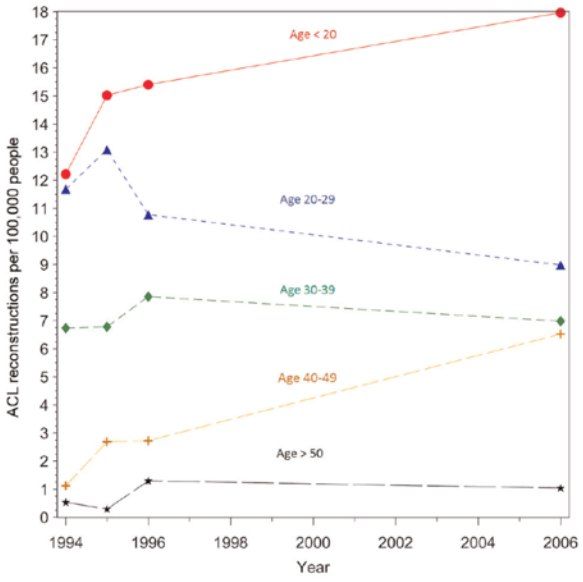


Figure 5 – Frequency of ACLR by age. Mall et. al., 2014[28]

of physical activity later into life.[83,84] Individuals around the age of 40 may be electing ACLR in order to maintain physical lifestyles though outside the time frame of competitive sport. High levels of physical activity are among the greatest risk factors for ACL injury.[85] In regards to sport differences, the highest rates are reported within soccer and basketball.[80] The common mechanism of ACL injury is tibial external rotation, thus making sense of the highest rates of injury being reported in activities requiring sudden change of movements.

C. Outcomes following ACL-Reconstruction

a. Returning to Activity

The primary role for ACLR is to restore joint stability to return the patient back to high levels of activity. The ACL, demonstrating greatest loads during rotational forces, may not need to be reconstructed following injury in patients that are not returning to high levels of activity demanding non-linear movements. Studies have shown positive outcomes in patients remaining ACL-deficient (ACLD) and do not return to high levels of activity.[86] ACLD patient that do return to sport report high bouts of instability, pointing to the treatment of ACLR.[87]

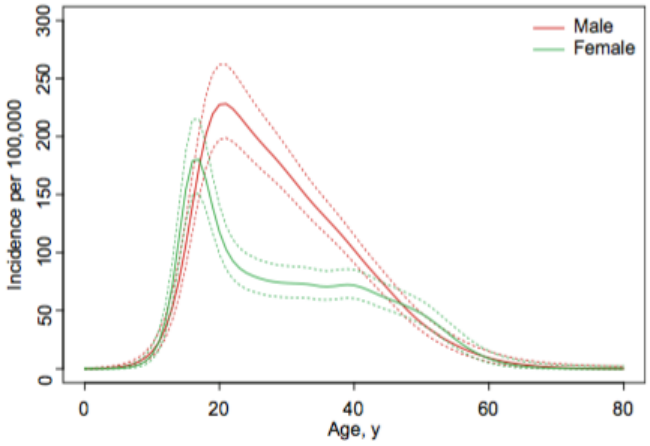


Figure 6: Incidence of ACL injury by age and gender. Sanders et.al., 2016[40]

ACLR is primary observed within the young, active athlete, with the average patient receiving surgery at the age of 22.[81] Individuals following ACLR demonstrate that majority of these patients are highly active, presenting a mean Tegner activity

score of 8.4, indicating that high levels of competitive sport.[3] A systematic review of 48 studies and 5,570 individuals following ACLR found that 81% of individuals returned to some level of physical activity following ACLR; however, only 65% of individuals returned to their pre-injury level of activity.[31] The percentage of return to pre-injury levels decreased more with competitive athletes, with only 55% returning back to their pre-injury competitive sport.[31,88]

Majority of research in the ACLR population assess physical components of muscle function to improve patient outcomes and safely return the individual to sport. Non-modifiable factors that influence the ability to return to sport have been reported as graft type, age and sex.[88] Individuals that receive a bone-patellar tendon bone (BPTB) graft have been shown to have greater odds in returning to pre-injury levels of activity,[88] individuals over the age of 25 are half as likely to return to pre-injury levels when compared to individuals younger than 25,[89] and males are 1.5 times more likely to return to pre-injury levels of sport and competitive sport compared to females.[31,88]

Though research suggests that the majority of patients do return to activity following ACLR, there has been substantial evidence indicating a decline in performance once returned to competitive sport. Athletes that were found to return to sport still demonstrated large limb symmetry deficits during single-leg hopping tasks.[90] The ACLR limb did not only

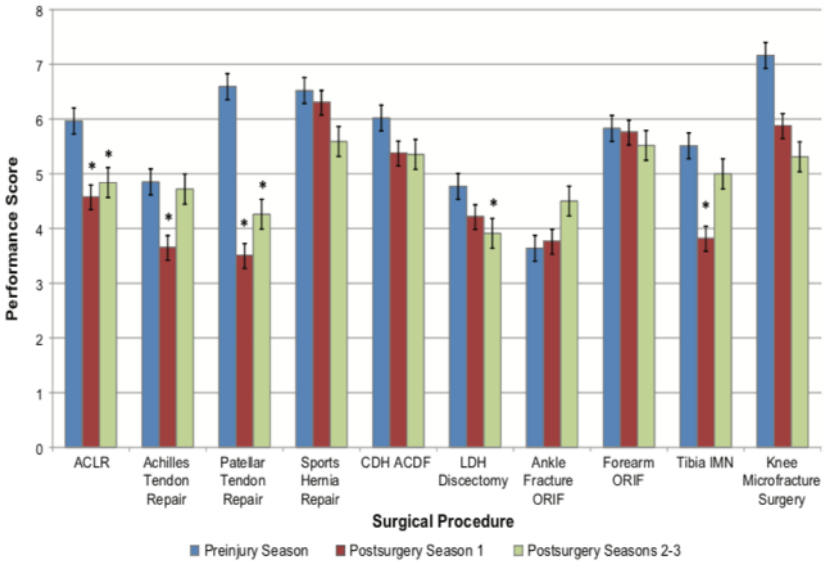


Figure 7: Comparison of a statistical athlete performance metric 3 seasons following common orthopaedic procures in NFL athletes. Mai et. al.,2016[52]

demonstrate weakness in comparison to the uninvolved limb, but demonstrated less torque production and hopping performance compared to healthy-matched controls.[90,91] In professional football athletes, injury and reconstruction of the ACL has shown a shorter career length (1.6 years), which is significantly less than all other orthopaedic procedures in NFL athletes.[30] In addition to ACLR resulting in a shorter professional career, the athletes that did return to playing in the NFL were found to have lower performance (a metric comprised of a standardized scoring system of based on metric important to that player's position) 3-years following the injury.[30,92] This research suggests that though athletes may report returning to previous levels of activity, the duration in which they remain at that level may be considerably less than their healthy counterparts.

Return to sport assessments have been increasingly administered to improve outcomes in individuals following ACLR. It is important to note that physical capabilities alone may not be enough to ensure this. The highest reported reason for reduced physical activity levels was the fear of re-injury, stressing the importance of physiological factors when returning patients to sport.[88] Higher responses of motivation, confidence, optimism, and lower reports of fear are all associated to a greater likelihood of returning to pre-injury levels of activity.[93,94]

Current assessments evaluating patient function at the time of return to sport following ACLR have been compared between individuals that do and do not return to sport. Individuals that did not return to sport demonstrated lower symmetry measures of single-leg hopping tasks.[95] Patients that were able to successfully return to previous levels of activity also demonstrate higher mass-normalized extensor peak torque compared to individuals that did not return to previous levels of activity.[96] Individuals at the time of return to play were almost 15-times more likely to return to their previous activity level if they demonstrated no joint effusion, no episodes

of joint instability, and demonstrated an international knee documentation committee (IKDC) subjective questionnaire score above 95%.[96] To date, no current thresholds have been established to determine the likelihood of a successful return to sport. Anecdotal thresholds of limb symmetry are currently used to progress patient care and make return to sport decisions. Assessments may also weigh objective measures of muscle function without taking into consideration the phycological "readiness" of the patient.

b. Subjective Function

Patient reported outcomes (PRO) are commonly collected within patients following a musculoskeletal injury to assess subjective reports of patient function. Within the ACL literature, the most commonly reported PROs are the IKDC and the Knee Osteoarthritis Outcome Score (KOOS). These measures have been shown to be valid to report subjective function within this population.[97-99] The IDKC consist of 10 questions aimed to evaluate symptoms such as pain, stiffness, swelling and giving way.[100] The KOOS is stratified into five subscales: symptoms, pain, activities of daily living, sport, and quality of life, and is aimed to capture the short-term and long-term symptoms and function of the patient[101] and was developed as a supplement to the KOOS in order to assess specific functional domains. These questionnaires are often expressed as a percentage of the total score, 100 indicating the highest possible subjective function.

The KOOS and IKDC alike have been shown to be sensitive to detect change in knee function following ACLR.[101] Patients that report a score greater than 89.9% on the IKDC have been found to be 3 times more likely to achieve a knee extensor limb symmetry over 90%.[102] In comparison to time-since surgery measures, which have been shown not to correlate with "passing" return to play criteria,[103] subjective function may be a better indicator of whether an athlete is likely to demonstrate "passing" outcomes.

With the difficulties of collecting longitudinal data on reinjury and/or return to sport outcomes, many studies will assess relationships of muscle function to subjective function quantified through these PROs. Following ACLR, patients demonstrate lower levels of subjective function compared to healthy individuals, and these measures often hold relationships to measures of muscle function.[104,105] Compared to limb symmetry measures commonly collected on knee extensor strength, anthropometric normalized unilateral extensor strength was found to hold a stronger relationship to subjective function.[104,105] A threshold of 3.0 Nm/kg was found to predict those that demonstrate patient reported outcomes of a healthy individuals.[104] Limitations within these studies are that the time since surgery was not controlled for with the samples collected and that thresholds were established based on subjective scores reported from healthy individuals and not longitudinal measures of "successful outcomes." Unpublished data from the Exercise and Sports Injury Lab and a sample of 424 individuals 6-months post-ACLR, only 6 (1.4%) individuals demonstrated strength measures above the 3.0 Nm/kg threshold, indicating that this may not accurately represent patients following ACLR at the time of return to play. The relationship between objective measures of muscle function and subjective function have also been demonstrated to be dependent on the time since surgery.[106] Patients under 2-years from ACLR demonstrate stronger relationships with unilateral normalized measures of muscle function where patients over 5-years from ACLR demonstrated stronger relationships to measures of limb-symmetry, with single-leg hopping tasks demonstrating the strongest correlations.[106] Another limitation to these studies are the cross-sectional design, not allowing results to directly show the progression of the subjective function following ACLR.

Longitudinal studies following patients following ACLR have established thresholds of PROs have been established to best indicate subjective patient satisfaction.[107] Individuals under

5-years from ACLR were contacted and asked a dichotomous question of "Do you report successful outcomes following your ACL-Reconstruction?" An IKDC of 75.9% was found to strongly discriminate patients that did and did not report "success" following their injury and reconstruction.[107] This threshold is comparatively lower than the arbitrary 90% that is commonly reported.[105] However, the outcome of "success" may require a much lower level compared to returning to high levels of activity and may allow subjective reporting to vary for each individual.

When assessing an individual during the ACL surgical and rehabilitation phase, the question persists of what variables best predict long-term outcomes within this population. Surgical variables have been explored in a large cohort of individuals following ACLR with a follow-up of 2- and 6-years.[108] The use of an allograft predicted worse outcomes on the IDKC and KOOS both 2- and 6-years following ACLR. An additional lateral meniscal procedure accompanying the ACLR, smoking status, and a higher BMI were also related to worse KOOS scores 2-years following ACLR. An important finding in the current study was that outcomes at 2-years strongly predicted patient function at 6, emphasizing the importance of patient care acutely following ACLR.[108] Additionally, variables of muscle function pre-operatively have been explored on their relationship of outcomes post-ACLR.[109] Individuals reporting higher quadriceps strength demonstrated greater subjective function on the Cincinnati Knee Score 2-years following ACLR.[109] An arbitrary limb symmetry index deficit of 20% was compared within this study and found that individuals receiving ACLR with an LSI deficit greater than 20% demonstrated significantly less knee function compared to patients presenting for surgery with lower than a 20% deficit.[109]

Another milestone in the post-ACL progression is the time of return to sport clearance. As return to sport assessments increase within clinical practice, functional measures of muscle function have been used to identify what predicts long-term outcomes of subjective function. Symmetry measures of single-leg hopping performance at the time of return to sport was shown to be the strongest predictors of PROs 2-years following ACLR.[110,111] Supporting these findings, a one-leg maximal jump for distance in addition to quadriceps strength was found to predict 53% of the variance of KOOS scores in individuals following ACLR.[112]

c. Reinjury

Injury to the ACL is a burdening injury, not only causing pain and disfunction due to changes in knee anatomy but leaves the often young, active individual with Kinesiophobia and other psychosocial concerns from the removal of team sports or regular activity regimens.[94,113] A main objective of ACLR and post-operative rehabilitation is decrease the likelihood that the individuals suffers a subsequent injury of the same toll. However, individuals following ACLR are at a 15 times greater risk for injury to the reconstructed graft or the contralateral ACL compared to an individual that has not sustained an ACL injury.[114] This high risk of reinjury places an importance on return to sport research to identify factors or thresholds that best predict individuals that do and do not obtain a secondary injury.

Subsequent injury to the reconstructed ACL has demonstrated further decline in patient function. In comparison to primary ACLR, secondary revisions have resulted in a greater decline in physical activity and patient reported outcomes.[115] In addition, patients following a subsequent ACLR have shown greater chondral injuries in the medial compartment,[115] which may demonstrate greater progression of PTOA following ACLR.[116] Subsequent injuries and surgeries following the primary ACLR have been hypothesized to accelerate the physiological processes

of post-traumatic osteoarthritis, which has been shown to be a factor associated with subsequent surgeries.[117]

Quantifying the incidence of secondary ACL injury poses difficult challenges of long-term patient follow-up or review of national insurance databases. Incidence rates of subsequent injury are inconclusive. A 2-year follow up reports a 6% incidence rate of an injury to the ipsilateral graft or contralateral ACL;[118] however, these rates have been shown to increase with greater follow-up time. A common cohort of patients across three studies found that 5, 10, and 15-year incidence rates increased to 12%, 27%, and 31%.[32,119,120] Within 5-years following ACLR, there were significantly greater reinjuries through non-contact mechanisms and in individuals in higher activity levels.[119] No differences within sex or graft type have been observed. Within 12-months from the primary ACLR, greater rates of injury were observed to the graft; however, over 2-years from the primary surgery, a greater number of contralateral ACL injuries were reported.[121] Following this same cohort to 10-years post ACLR found that this trend only held up within individuals who received a BPTB graft.[32] The cumulative incidence of graft rupture within individuals that received a BPTB remained relative stable after 24 months compared to the contralateral ACL that had a cumulative incidence rise to 20% around 9-years following the primary ACLR.[32] Individuals that a received a HS graft in this study had similar cumulative incidence[32] rates of reinjury between the graft and contralateral ACLR around 10% around 7-years following the initial ACLR. These trends were similar when assessing these individuals 15-years following ACLR.[120] Graft rupture were higher in those with a HS graft at 15-years post-ACLR, with the cumulative incidence climbing to 15% compared to 8% within those who received a BPTB graft. Contralateral graft injuries were found to significantly higher within the BPTB group (cumulative incidence: 24%) at 15-years post-ACLR compared to those

that received a HS graft (cumulative incidence: 11%).[120] In conclusion, about 1 out of 3 individuals in this cohort were found to have a subsequent injury 15-years following their primary ACLR.[120]

The high variability of secondary injury within the ACLR population may be due to samples varying in age, sex, and activity level. In an attempt to control for these factors, Paterno et. al. collected a cohort of young (18-25) that returned to cutting sports following ACLR.[114,122] These studies found a 15-times greater risk of a subsequent injury within the first 12-months with this risk decreasing to 5 times more likely to obtain a subsequent ACL injury from 12 to 24 months compared to healthy athletes.[114] This data highlights the high risk of subsequent injury within the first year following ACLR. The current system of surgery, rehabilitation, and return to sport progression may not be identifying deficits that may contribute to these subsequent injuries.

Subsequent ACL injuries are commonly defined as an injury to the ACLR graft or the contralateral ACL. Reinjury rates do not differ between side following ACLR.[122,123] However, the proportion of patients that re-injure their ACLR graft compared to their contralateral ACL has differed between patients' sex. Males have demonstrated greater proportions of ACL graft injuries while females demonstrate greater proportions of contralateral ACL injuries.[36,114,124] Recent systematic review assessing the ability of RTA assessments to protect against subsequent ACL injury found that achieving 90% limb symmetry on measures of strength and hopping performance decreased the probability of subsequent ACLR graft injury but increased the probability of contralateral ACL injury.[125] No current research has investigated what components of these assessments influence the probability of reinjury dependent on side.

d. Post-Traumatic Osteoarthritis

In addition to the decrease in physical activity and higher risks of subsequent injury, individuals following ACLR demonstrate an alarming risk of osteoarthritis (OA). OA is defined as a chronic disorder that affects function of moveable joint, affecting the articular cartilage, subchondral bone, and surrounding soft tissue. The incidence of OA following ACL injury is often referred to as post-traumatic osteoarthritis (PTOA), relating to the following an acute traumatic joint injury compared to osteoarthritis.[126-128] OA is thought to have the greatest effect in the aging population; however, over one-half of adults with symptomatic knee OA are below the age of 65 and the peak prevalence being reported at the age of 50 years.[129,130] The onset of OA within adults has negatively impacted work and quality of life.[131][9] This raises a greater concern when discussing PTOA following ACLR, with a peak incidence occurring within individuals under the age of 25.[81]

Aging within the healthy knee does not necessarily cause OA but other age related cellular changes might initiate degenerative processes.[132] The purpose of articular cartilage is to absorb and distribute forces and load during joint movement. The cartilage extracellular matrix (ECM) is made up of molecules that allow for elastic and compressive properties, as well as providing lubrication for the joint. Within the aging knee the ECM composition changes resulting in increased stiffness and fatigue failure.[132-134] These changes are most often seen in the patella, medial condyle, and lateral femoral condyle.[135] Changes in cartilage are also seen by the deposition of calcium crystals, which is an effect of aging and not OA. This development of calcium crystals stimulate chondrocyte production of inflammatory mediators and ECM degrading enzymes, further causing the development of OA.[136] Individuals with obesity, joint

injury, or joint malalignment are at a higher risk of developing OA at an earlier age and with an increased severity.[132]

Prospective studies have indicated that individuals following a traumatic joint injury are 3 to 6 times more likely to be diagnosed with knee OA.[137] The question still exists of what mediating factors demonstrate between ACLR and the development of PTOA. Currently, there is no cure for OA, emphasizing the importance of researching possible interventions following traumatic joint injuries. Recent population-based studies have found age, obesity, tobacco use, and concomitant meniscal repair to be risk factors for PTOA diagnosis following ACLR.[138] Modifiable risk factors of obesity and tobacco use may be of importance to patient education following ACLR. Knee biomechanics following ACLR has also been a proposed mediator for the onset of PTOA.[139-141] Compressive and shear behaviors are altered within osteoarthritic cartilage, presenting with decreased cartilage stiffness and increases the propensity to swill compared to healthy knee cartilage.[141] A combination of molecular changes and kinematic adaptations have been proposed to predispose an individual to PTOA.[139] Though no treatment currently exists to prevent molecular changes of the knee cartilage, interventions may occur through assuring proper knee kinematic and kinetics during walking and running tasks.

Kinematic alterations in individuals following ACLR have been linked to strength deficits observed following ACLR.[142] Individuals that exceed 90% knee extensor knee symmetry have been found to demonstrate symmetrical force absorption during walking tasks.[142] Knee extensor strength has also been associated with sagittal plane knee angle and moment symmetry.[143] From these results, biomechanical influences of cartilage degeneration following ACLR may be largely impacted by assuring adequate knee strength to prevent gait adaptations.

PTOA following ACLR is concerning with majority of ACL injuries occurring within individuals under the age of 25,[81] predisposing young individuals with old knees. Currently, there is no cure for osteoarthritis. The most common treatment to subside treatments are anti-inflammatory prescriptions, corticosteroid injections, and total or partial knee replacements. Early onset of PTOA within this young population of individuals following ACLR may place them at greater risk of activity modifying treatments, such as partial and total knee replacements, at a young age.

Individuals under the age of 30 were found to develop signs of degenerative joint disease around 10-years following ACLR, where individuals over the age of 30 demonstrated signs of OA around 5-years following their surgery.[144] In a sample of 11 individuals, there was a strong relationship between years following surgery and OA progression.[144] Similar methodology with a 10- to 15-year follow-up demonstrate similar results with over 60% of individuals demonstrating radiographic signs of osteaoarthirits.[145] Incidence of OA was also observed at a much higher rate in the involved knee compared bilaterally.[145] Most PTOA following ACLR is observed in the tibiofemoral joint, however rates of patellofemoral OA is also shown to increase with time post-surgery.[146] Signs of PTOA are shown to present before symptomatic reporting of joint pain. At 15-years post-ACLR, 42% of patients demonstrate radiographic signs of PTOA; however, only 25% were symptomatically diagnosed with OA.[146] On a Kellgren-Lawrence (KL)

Scale used to diagnose joint OA, symptomatic PROs have been shown not to differ until an individual is scored a KL grade of 4, the highest possible score demonstrating large joint osteophytes, narrow joint space, and sever deformity of the bone.[147] At this time, it may be too late to pursue the limited options available for pain reduction.

Table 1: Kellgren-Lawrence grading scale for knee osteoarthritis.

Grade	Radiologic Findings
0	No radiological findings of osteoarthritis
I	Doubtful narrowing of joint space and possible osteophytic lipping
II	Definite osteophytes and possible narrowing of joint space
III	Moderate multiple osteophytes, definite narrowing of joint space, small pseudocystic areas with sclerotic walls and possible deformity of bone contour
IV	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

PTOA following ACLR has been hypothesized to occur due to adaptations in joint kinetics, changing the wear patterns of the joint cartilage.[148] ACLR is sought to restore normal mechanics by reconstructing a passive structure limiting motion within the knee. However, ACLR should not been seen as a treatment to prevent PTOA following ACL injury. In a cohort of 219 soccer players, there was no difference is OA diagnosis in athletes that underwent ACLR or conservative treatment.[149] A systematic review comparing ACLR vs conservative treatment, the percentages of patients with knee OA was slightly increased in those following ACLR (44%) compared to ACLD (37%) but did not demonstrate substantial evidence that either treatment should be elected to reduce the risk of PTOA.[150] A recent systematic review on the development of radiographic OA following ACLR reported rates of 20% of ACL-injured knees had moderate to severe radiographic changes compared to 5% of the contralateral limb.[151] Non-operative treatment of ACL injuries had a significantly less risk of developing any sign of OA compared to

those treated with ACLR.[151] This trend was reversed when looking at the progression to moderate to severe OA (KL grade ≥3) 10-years following ACL injury.[151]

D. Evidence Based Criteria for Return to Sport

Return to sport guidelines that predict safe and successful outcomes continue to be the "holy grail" regarding research following ACLR. To date, most thresholds continue to be arbitrary scores and values not entirely based on evidence.[152] Due to the ease of collecting subjective questionnaires, many studies analyze the relationships of muscular function needed to obtain a certain score. The more difficult, and arguably more important, outcomes require longitudinal follow-up from the patient, collecting long-term outcomes such as returning to activity, subsequent injury, and diagnosis of osteoarthritis.

A recent study sought to see what tools and variables clinicians utilized to determine return to activity status and found that over 32% of clinicians use the sole variable of time since surgery.[153] This is a concerning result with individuals reporting large strength and functional deficits around the time of return to sport.[154,155] Time from surgery has also found no association with functional assessments like the single-limb vertical jump.[103] Though not everything, time since surgery should be considered as a factor prior to release to sport, as individuals released before 7-months found higher rates of re-injury (15.3%) compared to individuals returning after 7-months post ACLR (5.2%).[156] Also, every month that return to sport was delayed was found to result in a decrease in reinjury risk by 51%.[157] Behind time since surgery, the most commonly reported assessments utilized among clinicians were subjective questionnaires (15% of studies), SL hopping tests (4%), and isokinetic and isometric strength testing (9%).[153] Since the release of the this review in 2011, the proportion of clinicians who use objective number of strength and hopping performance have likely increased with the increased focus of research in this area and

the availability of testing equipment. Still, evidence-based thresholds that are able to predict long-term outcomes within this population are still absent.

Mixed findings have been reported regarding the relationship to subjective questionnaires to successful outcomes. Majority of studies that associate variables to PROs are conducted in a cross-sectional manner, not able to draw conclusions to patient progression or long-term follow-up outcomes.[106,158] The IKDC was unable to predict ACLR patients' ability to return to previous levels of sport 1- or 2-years following their surgery.[88,159] However, the same questionnaire at the time of return to play was able to predict individuals who returned to competitive an recreational levels of activity 5-years from ACLR.[96,160] This data suggests that subjective knee reports of function may not be the best measure to predict returning to activity, placing greater importance on objective assessments of muscle function.

Compared to subjective questionnaires of knee function, such as the IKDC and the KOOS, psychological questionnaires have been found to hold strong relationships on the ability to return to play. Measures such as the ACL-Return to Sport Index (ACL-RSI) and the Tampa Scale for Kinesiophobia have been administered within this patient population to quantify psychological properties of the patient.[161,162] Both of these questionnaires have been found to successfully predict individuals who successfully return to previous levels of activity.[4,159,162,163]

Current evidence guiding post-operative rehabilitation is often dependent on the time since surgery (Table 1).[164] The most common rehabilitation goal following ACLR is the regaining of quadriceps strength and function. Following the time from surgery, these measures is the most commonly used to determine sport clearence.[153]The thresholds of strength or symmetry that an individual needs to surpass in order to achieve safe outcomes, however is still unknown. The most commonly used thresholds are 85% or 90% symmetry, comparing the strength in the surgical limb to the strength in the non-surgical limb.[105,165] Though no study has used regression-based analyses to determine a set threshold, it is common to see study cohorts stratified by these thresholds and to compare dependent measures of interest.[165,166]

Table 2: Common Rehabilitation progression post-ACLR. Bousquet et. al.,2018[123]

Phase	Time Post-ACLR (weeks)	Goals
1	0-6	Protection, RoM, Muscle Initiation
2	7-14	Periodized Strength Development-Muscular Endurance
3	15-21	Periodized Strength Development-Muscular Strength
4	22+	Periodized Strength Development-Muscular Power/Speed/Agility Phase

Individuals with quadriceps strength equal to 85% or higher than the contralateral limb have reported higher rates of return to sport compared to those below.[88] However, the utilization of limb symmetry has been found to overestimate knee function that the time of return to play.[167] The concern of bilateral weakness following ACL injury and reconstruction may over inflate administered limb symmetry assessments. Another way to quantify quadriceps function is analyzing anthropometric measures of strength, normalizing the torque exerted by the patient's body weight. These measures have been found to hold greater relationships to patient reported outcomes acutely following ACLR.[105,106] Looking at these normalized thresholds, individuals that were able to return to previous levels of activity report significantly greater knee extensor

torque (81.5% of body weight [ft*lb./lb.]) at the time of return to play compared to patients that did not (73.9% of body weight).[96,168] However to date, these measures have been found to range from 1.2 Nm/kg to 3.0 Nm/kg.[105,169]

The difficultly of tracking longitudinal outcomes are also confounded with the ability of the research findings (RTP assessments) to influence patient care. Individuals that were found to fail RTP testing (<90% quadriceps strength index), had a 84% higher reinjury rate compared to those who passed the assessment.[157] Each month delayed for sport clearance also reduced the risk for reinjury by 51%.[157] Though thresholds of quadriceps strength and symmetry are not established, these findings suggest the importance of quadriceps function as a measure that should be utilized before return to sport assessment.

In addition to strength assessments administered following ACLR, functional testing also commonly administered at the time of return to sport.[110,170] A common battery of hopping tests consist of the single-hop, triple-hop, cross-over hop, and the 6-meter timed hop.[171] The single hop test has been found to have the greatest relationship to subjective function and landing mechanics indicative to ACL injury mechanisms.[106,110,111,172] Knee landing biomechanics have also been studied in attempt to quantify the knee kinematics and kinetics during a task that may simulate ACL injury mechanisms.[173] Studies utilizing functional movements such as the drop landing and single-leg drop have found that asymmetries at the time of return to play predict decreased knee function 2-years post-ACLR.[166,174] These findings show that currently, no athlete or patient profile has been created that can predict safe and successful outcomes. A combination of subjective function, quadriceps strength and symmetry, and functional hoping and landing tasks should be administered to determine progressions regarding return to sport.

E. Neurophysiological Deficits Following ACLR

Following ACL injury and reconstruction, individuals experience arthrogenic muscle inhibition resulting in the inability to fully activate their quadriceps.[8,22] This has been theorized to originate from aberrant sensory afference from joint swelling, [175,176] inflammation,[177] pain,[178] and structural changes. Neuromuscular adaptations can be observed regarding voluntary muscle activation,[8] torque production,[179] EMG activity, and spinal and cortical excitability.[10,180]

The hypothesized altered sensory input that causes these overserved adaptations following ACLR draws attention to the influence of aberrant afferent signals. Sensory nerves that terminate within the knee joint capsule or intracapsular ligaments are thought to have a primary role in causing this muscular inhibition.[181] Clinical modalities have been sought to reduce AMI by targeting these peripheral sensory receptors.[175] The reduction of aberrant sensory afference through cryotherapy and the use of transcutaneous electrical stimulation (TENS) to substitute sensory feedback has been hypothesized to treat acute affects from AMI.[175] To observe the neural effects of ACLR and the effectiveness of peripheral interventions, studies commonly assess the ability to volitionally activate a muscle of interest.

AMI is defined as an ongoing, reflex response after joint injury that inhibits the ability to completely contract a muscle despite no structural damage to the muscle or innervating nerve.[8] This inability to completely activate a muscle is often a consequence of injury, resulting from the inability of the CNS to provide maximal descending input to the muscle.[25] This is commonly been observed in the quadriceps in patients following knee injury.[8,180] Not only do these adaptations have short-term consequences on rehabilitation, but have been found to be a predictor of long-term degenerative diseases such as PTOA.[145,182] The short- and long-term

implications of AMI emphasizes the importance of research delving into the exploration of physiologic mechanisms of activation failure and interventions to overcome them.

Many studies have observed quadriceps activation failure following ACLR. Table B1 shows the average CAR collected within 16 studies with the average time since surgery.[6,7,10,104,158,183-194] Defining activation failure as a CAR below 95%,[20] it can be seen that majority of individuals following ACLR demonstrate activation failure, regardless on the amount of time since surgery.

Table 3: Quadriceps activation failure in ACL-Reconstructed knees.

Author, Journal	Year	n	Time since surgery (mo)		CAR Results	
			mean	sd	mean	sd
Lepley, SJMSS[7]	2015	20	6.39	0.65	91.20	6.20
Lepley, KSSTA[193]	2015	24	7.10	1.10	83.90	10.40
Lepley, KSSTA[187]	2016	54	7.24	1.10	88.80	9.10
Thomas, JAT[191]	2015	17	8.50	1.50	82.00	11.00
Norte, JAT[158]	2018	34	9.00	4.30	85.50	11.40
Kuenze, JAT[195]	2017	10	27.90	16.60	86.51	5.03
Otzel, PTS[192]	2015	24	30.00	18.00	91.00	7.00
Kuenze, JSR[104]	2015	22	31.50	23.50	84.60	10.20
Harkey, MSSE[189]	2016	74	39.60	38.70	90.00	9.00
Goetschus, JAT[188]	2016	53	44.10	29.60	84.40	11.90
Luc-Harkey, EBR[185]	2017	27	44.47	36.58	88.59	7.67
Norte, JSR[6]	2017	72	46.50	58.00	88.40	10.10
Pietrosimone, JAT[10]	2015	20	48.10	36.20	88.00	12.00
Pamukoff, JAT[184]	2017	20	50.70	21.30	83.30	11.10
Ward, JAT[196]	2018	28	52.00	42.00	90.00	6.00
Norte, JAT[158]	2018	30	70.50	41.60	90.50	8.40

Spinal circuitry has been found to contribute to AMI.[14,197] Spinal inhibition is assessed through the Hoffmann's Reflex (H-Reflex) to quantify motor neuron pool excitability through monosynaptic reflex activity of the spinal cord.[64,198] The H-Reflex is obtained through the stimulation of a mixed nerve which sends potentials along the afferent and efferent pathways.

The motor neuron pool is an estimate alpha motor neurons available for use (H-reflex) normalized by the total amount present (M-wave) leaving the H:M Ratio.[64] This measure is commonly used within the sports medicine literature to assess the impact of injury or interventions on spinal reflexes.[175,189,199-201] A lower motor neuron pool excitability reflects greater spinal inhibition. Due to simulating the consequences of ACLR through joint effusions,[202] spinal adaptations have been the most commonly examined measure of AMI.

Studies performing the H-reflex on individuals following ACLR have demonstrated varied findings.[6,7,10,158,189,203,204] Table B2 shows the following studies that report the H:M ratio in individuals following ACLR. H:M values for healthy individuals range from 0.14 to 0.18.[6] As seen from the table, the only study to report significant differences from healthy individuals is one that tightly controlled for time since surgery, collecting patients 2-weeks following ACLR. These findings suggest that studies collecting measures on spinal excitability should tightly control for the time since surgery and that spinal adaptations may only occur acutely following surgery.

Table 4: Spinal excitability adaptations in ACL-Reconstructed knees.

			Time since surgery (mo)		H:M	
Author, Journal	Year	n	mean	sd	mean	sd
Lepley, SJSSM[7]	2015	20	0.51	0.08	0.11	0.08
Lepley, SJSSM[7]	2015	20	6.39	0.65	0.24	0.09
Norte, JAT[158]	2018	34	9.00	4.30	0.19	0.19
Kuenze, JAT[205]	2015	22	31.50	23.50	0.29	0.20
Harkey, MSSE[189]	2016	73	39.60	38.70	0.29	0.17
Hart, JAT[204]	2014	30	44.00	59.00	0.21	0.19
Norte, JSR[6]	2017	72	46.50	58.00	0.21	0.19
Pietrosimone, JAT[10]	2015	28	48.10	36.20	0.27	0.12
Norte, JAT[158]	2018	30	70.50	41.60	0.21	0.19

Cortical excitability

Emerging research suggests that the sensory changes following ACLR influences more than spinal neurons, but alters somatosensory afference to the cerebral cortex as well.[206,207] Cortical influence on motor output has been most commonly researched in hand and wrist movements due to the large cortical representation in the primary motor cortex.[208] However, the last decade has delved into the lower extremity and the supraspinal consequences of injury.[209,210] Descending neural drive has been found to have a drastic influence on spinal reflexes and motor output which may potentially be able to effect AMI.[211,212] The use of transcranial magnetic stimulation (TMS) allow the opportunity to study the corticospinal tract by stimulating the primary motor cortex. This allows a non-invasive method to measure neural conduction, excitability, facilitation, and inhibition of the primary motor cortex.[12,213,214] The excitability of these descending neural projections defines integrity of the corticospinal tract and the excitability of the corticospinal system and approximate the maximum percentage of the total motor neuron pool activated by a single cortical stimulus.[213]

The collection of measures assessing cortical excitability has increased over the past decade to better define neurological adaptations that may occur following ACLR.[6,7,10,158,180,205,215] Table C3 shows the AMT demonstrated in individuals following ACLR. Healthy values for quadriceps AMT range from 36 to 39. The only study that does not show a significant difference to healthy control values include patients collected at 2-weeks post-ACLR.[7] This may suggest neuroplastic patterns influencing the descending motor commands occur during the rehabilitation process, prior to return to play. Majority of the studies included had a broad range of time since surgery.

Table 5: Cortical excitability adaptations in ACL-Reconstructed knees.

Author, Journal	Year	n	Time since surgery (mo)		AMT (%2T)	
			mean	sd	mean	sd
Lepley, SJSSM[7]	2015	20	0.51	0.08	31.00	6.90
Lepley, SJSSM[7]	2015	20	6.39	0.65	46.10	8.70
Norte, JAT[216]	2018	34	9.00	4.30	45.80	7.90
Kuenze, JAT[205]	2015	22	31.50	23.50	61.80	11.98
Norte, JSR[154]	2017	72	46.50	58.00	45.20	8.60
Pietrosimone, JAT[10]	2015	28	48.10	36.20	45.14	15.22
Ward, JAT[196]	2018	28	52.00	42.00	46.40	9.90
Pietrosimone, JSR[180]	2013	15	54.40	40.90	33.20	12.05
Norte, JAT[158]	2018	30	70.50	41.60	42.80	9.10

F. Interventions for Muscle Inhibition and Neurophysiological Deficits

Arthrogenic muscle inhibition (AMI) is thought to contribute to the persistent muscle weakness that is demonstrated in individuals following ACLR.[14] AMI has been connected to articular joint swelling, inflammation, pain, and joint laxity.[181,217-219] Of these, only joint laxity is addressed with reconstruction of the ACL. Post-operative patients present with joint swelling, inflammation, and pain; hypothesized to create changes in joint afference to spinal and supraspinal systems leading to a limitation of the activation of the quadriceps.

Cryotherapy has been shown to decrease nerve conduction velocity, muscle spasms, pain, and block transmission of signals through sensory nerve fibers. The treatment of cryotherapy is thought to decrease the aberrant afferent signals that may in turn influence descending motor drive. A recent systematic review found that cryotherapy had a moderate effect in increasing voluntary activation of the quadriceps following injury.[220-222] In addition to strength, measured

by MVIC, cryotherapy also was found to increase the quadriceps motor neuron pool recruitment (H-reflex).[175]

Limited studies have described the application of transcutaneous electrical stimulation (TENS) on individuals following ACLR. However, treatment effects have been collected within individuals diagnosed with knee osteoarthritis and healthy individuals following a knee joint effusion.[175,223,224] With individuals diagnosed with knee OA, TENS was found to have a moderate effect on subjective function and had a greater long-term effect 4 weeks following the treatment compared to individuals that did not receive the TENS treatment.[223]

The application of TENS in ACL deficient individuals did not influence strength or central activation ratio.[225] Within laboratory studies describing the effect of TENS within individuals following a knee joint effusion found that the application of TENS successfully increased knee extensor strength and motor neuron pool excitability.[175,226,227] However, changes in the H-Reflex were lost 30 minutes following the treatment.

Neuromuscular electrical stimulation (NMES) is a common treatment following ACLR to promote neural re-education of muscle activation.[164] Low quality evidence has been supported to the isolated use of NMES to improve knee extensor strength or activation.[169,228] However, NMES in isolation is rarely used within clinical practice, commonly performed in conjunction with active exercise. However, isolated exercise therapy in individuals following ACLR has been found to be effective in increasing knee extensor strength and activation.[204,229]

Interventions such as cryotherapy and TENS have shown to influence spinal excitability and strength in individuals following knee joint effusion.[175] This methodology is aimed to simulate the spinal adaptations that occur acutely following ACLR.[7] However, these spinal adaptations are not demonstrated at the time of return to sport, proposing questions on other

neurophysiological contributors to muscle function at this time. Cortical excitability has been found to correlation to muscle strength in individuals following ACLR at the time or return to sport, indicating the importance of the underlying neurophysiology that may influence motor function.[9]

Corticospinal adaptations observed within individuals following ACLR are assessed through the measurement of motor threshold (MT). A muscle motor threshold is the minimum amount of electricity needed to elicit a motor response of the targeted muscle. Often termed "cortical excitability", the motor threshold is assessing the excitability of the entire corticomotor neuron tract, from the pyramidal cells of the primary motor cortex to the motor unit within the muscle.[230] Adaptations assessed by motor thresholds are unable to say if deficits are due to changes within the primary motor cortex or at another location through the motor tract. The changes observed within individuals 6-12 months post-ACLR, have been seen within measures of MT and not H-reflex; indicating that adaptations are supraspinal.[7,9]

Interventions aimed to combat neurological deficits seen following ACLR have been studied to address inhibitory mechanisms hypothesized to originate from spinal reflexes observed through the Hofmann's Reflex.[175,204,220,231,232] To date, there is no intervention to address corticospinal adaptations observed within individuals following ACLR. Though these adaptations are not observed within all individuals following ACLR, those that do present with low levels of corticospinal excitability have been observed to demonstrates strength levels indicative of unsatisfied outcomes.[9] Individuals that present with persistent quadriceps weakness may possess underlying neurological impairments that may limit muscular function. These findings stress the importance of shifting current treatment practices to address neurological mediators to patient function.

Investigations of corticospinal excitability following sports medicine injuries are relatively new to literature, with the current literature primarily consisting of descriptive laboratory studies identifying differences between healthy controls or longitudinal studies assessing measures over time.[7,199] The only study to assess corticospinal excitability of the quadriceps within a treatment repeated measures design utilized healthy participants as the study sample.[15] The authors found that a single session of electromyography (EMG) biofeedback during a maximal voluntary isometric contraction (MVIC) was found to increase patient strength and corticospinal excitability.[15] It is important to note that significant changes were observed in healthy participants, with no joint or cortical pathology. The visual feedback was administered with the aim of providing an external focus of attention. Such tasks have been shown to improve motor skill acquisition and retention compared to task demanding internal focus.[233-240] Participants shifted their direction of attention to an aspect of the environment (EMG Biofeedback) rather than manipulate the physiologic event (increase knee torque). Similar utilization of patient feedback describing internal physiological processes has been termed "visuomotor therapy".[28,241] Visuomotor therapy has been used within pathologic populations such as stroke, TBI, and even chronic immobilization with the goal of providing neuroplasticity within the motor cortex and spinal motor neurons.[29,242]

Visuomotor therapy is used with the aim to induce use-dependent plastic changes in response to activation of higher-motor cortical areas. Use-dependent changes describes the ability of behaviors to be shaped not only by current sensory signals but also by past experiences.[243] For example, repeated movements toward a target will bias the subsequent movements toward that target direction.[243] The aim of the visuo-motor intervention is to stimulate visual processing centers which then activate cortical areas responsible for movement

execution; with the goal of creating use-dependent changes for later motor tasks. Within these cortical areas of movement execution lie a population of mirror neurons in the pre-motor cortex that have been found to discharge during tasks incorporating visual feedback and merely from the observation of motor tasks executed by others.[244-247] These neurons have been hypothesized to connect cortical structures of action observation and motor execution,[248,249] with evidence facilitating motor activity and cortical plasticity.[250]

In populations that have demonstrated a decrease in corticospinal excitability, interventions targeting the activation of the fronto-parietal motor network of mirror neurons are aimed to reduce or inhibit the cortical reorganization that may occur. Electrophysiological research on action observation has showed corticospinal facilitation of the primary motor cortex based on the mirror neuron system.[251] In stroke patients with ankle dorsiflexion deficits, the use of mirror therapy was found to induce ipsilesional sensorimotor and pre-motor cortex activation.[251] Four presented hypotheses have been presented for the influence of mirror therapy has on the human brain: 1) Visual feedback dominates somatosensory feedback or cortical proprioception representation, 2) mirror therapy increases spinal and cortical excitability, 3) sensory experiences can be evoked on the basis of visual information alone, and 4) visual input enhances tactile sensitivity.[252]

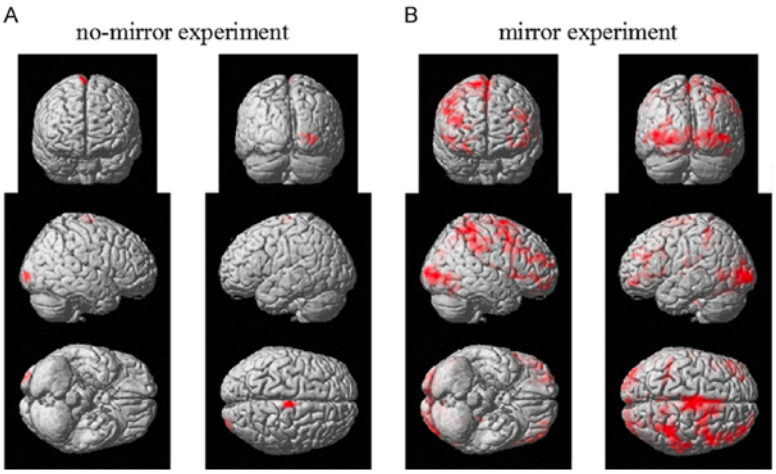


Figure 8: Brain activation during ankle dorsiflexion within a stroke patient. Gou et. al., 2016.

Visuomotor therapy does not have to necessarily be mirror therapy, but rather an exercise incorporating similar goals of providing visual feedback of an internal process. These have commonly been expressed through quantifying joint motion and torque.[253,254] Electromyographic (EMG) biofeedback has been used in the strength literature with the goal of improving motor unit recruitment and optimizing firing rates.[255,256] Factors that define learning a visuomotor task have been proposed as 1) the novelty of the task, 2) visual feedback, 3) complexity of the task, and 4) a pattern of somatosensory feedback related to the training.[257] The use of sub-maximal torque matching tasks have been utilized within studies as a novel task to challenge the patient's motor precision informed through the visual feedback.[257,258] In comparison to a kinematic task, challenging a patient to create a joint position, an active torque producing task has been shown to have greater improvements in motor performance and cortical reorganization.[259]

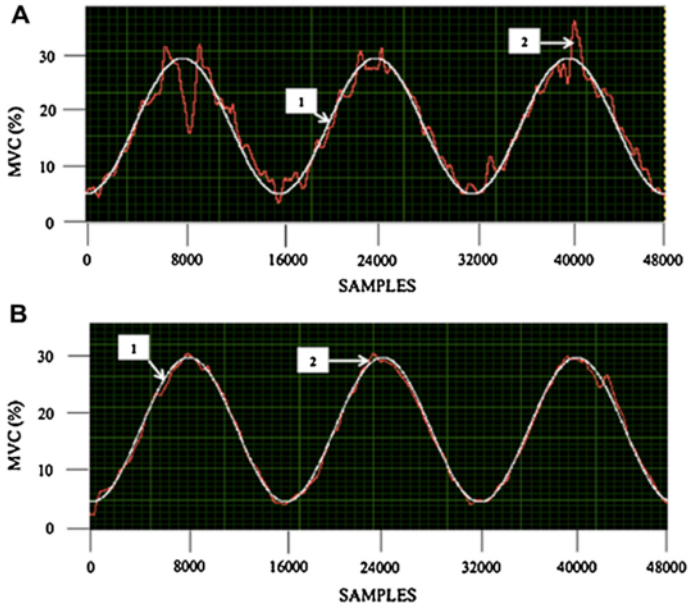


Figure 9: Example of torque matching task. A) low motor control. B) high motor control.[257]

Visuomotor therapy incorporates two parts: complex skill training and visual feedback providing as external focus. Training-induced changes are related to a decrease GABAergic inhibition within intracortical circuits.[260] Short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF) describe intracortical facilitation and inhibition of the motor cortices.[261] These have been studied within individuals post-ACLR and found to be inhibited compared to healthy controls.[185] SICI and ICF are produced by separate populations of cortical interneurons and have been shown to change within a single session skill training task.[259,262,263] Additionally, visuomotor therapy has been found to increase cortical excitability (Figure xx).[264] Compared to passive movement tasks, skill training, defined as sub-maximal, precision oriented tasks, has been found to increase motor evoked potentials and cortical motor representation of the tibialis anterior muscle.[258]

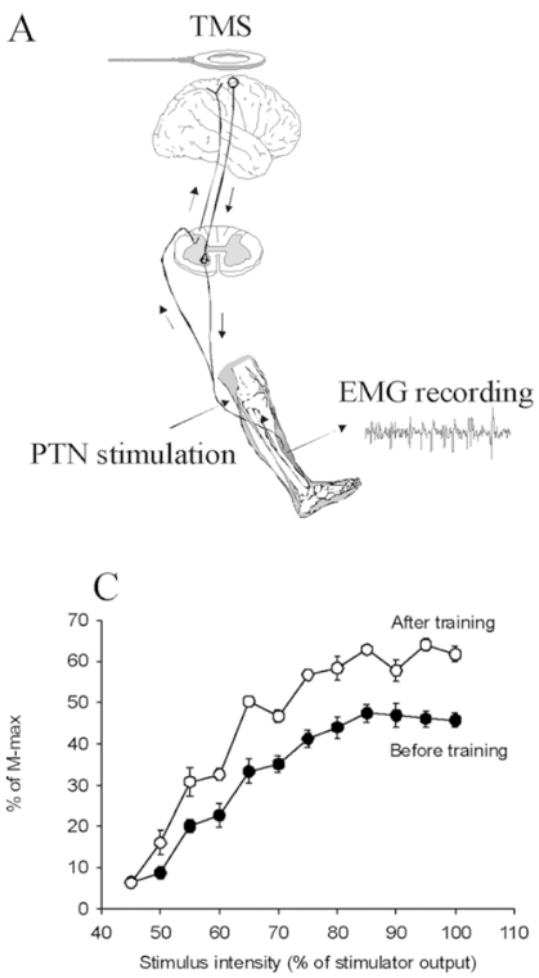


Figure 10: A) Model of recording corticospinal excitability in the Tibialis Anterior muscle. C) Change in MEP following visuomotor training.[258]

The goal of motor skill learning involves a collection of neural processes in in response to activity that eventually leads to lasting changes and capacity for performed that specific skill action. The primary motor cortex, commonly thought to only direct descending motor commands, has been found to alter when exposed to motor learning tasks.[265] These findings suggest the primary motor cortex plays a key role within interpersonal motor acquisition and information processing.[253,266] These changes can then be observed though non-invasive TMS methods. When a novel skill is introduced, short-term changes in cortical excitability and connectivity are observed.[267] The use of goal-directed, continuous, visuomotor skill learning is used for dynamic motor learning processes. Visually-guided finger tracking has been shown to relate to cortical reorganization to multiple brain regions in addition to motor performance movements.[268,269] A single session of goal-directed visuomotor skill task has been found to be associated with an increase in intracortical excitability.[253]

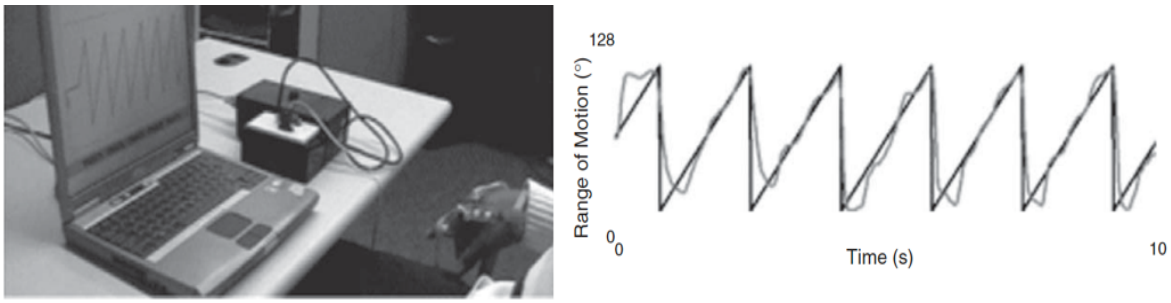


Fig. 1. A) Schematic of study design. B) Finger tracking apparatus with assessment waveform displayed on computer screen. C) Representative tracking response from one subject.

Figure 11: Torque matching task for the 1st metatarsal joint. Dark line is the directed goal and the lighter shade line is the produced torque. [253]

fMRI studies have also characterized dynamic changes in brain activation associated with improved motor performances and greater automaticity for execution of a visually guided motor tracking task.[270] An acute decrease in the primary motor cortex was observed following the task, and is thought to be towards increasingly specific afferent input to the primary motor cortex as the movement pattern becomes better defined.[270]

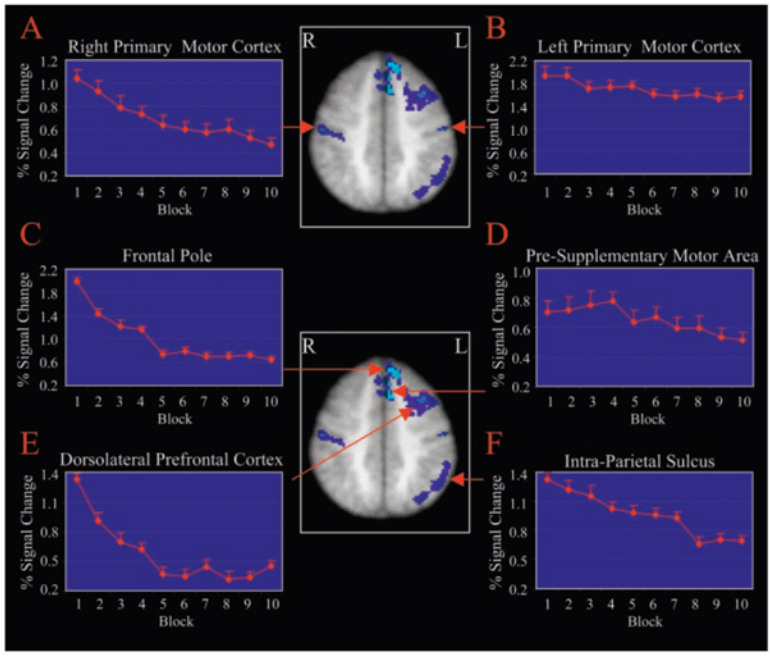


Figure 12: Changes in the primary motor cortex (A, B) following a visually guided motor tracking task of the 1st metatarsal.[270]

Corticospinal excitability is modulated by a variety of sensory inputs. Visual inputs have be viewed as having a relatively low influence on corticospinal excitability with less than 3% of neurons in a primary motor cortex activating in response to a visual stimuli;[271] however, other area of the human brain have been found to be visually responsive.[272] Cortico-cortical pathways between the primary visual cortex (V1) and the primary motor cortex (M1) have been assessed through the measure of corticospinal excitability following a visual stimuli[273] or from reaction time studies.[274] Studies

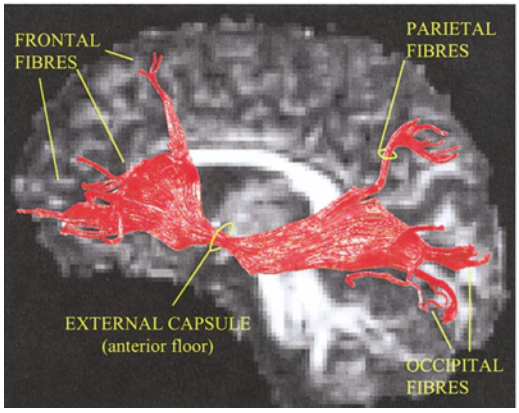


Figure 13: Lateral view of the left inferior fronto-occipital fasciculus connecting the occipital lobe to pre-motor cortical areas.[276]

using TMS to stimulate the occipital region has found that the visual cortex can modulate corticospinal excitability.[275] Visuomotor neuronal circuits within the human cortex have been established in diffusion tensor imaging[276] and dissection studies[277,278] showing connection between visual and motor regions of the human cortex. These pathways are thought to be reciprocal and can have both inhibitory or excitatory effects of the primary motor cortex.[275]

Neuroplastic changes are evaluated through changes of MEP responses and MT elicited through the use of TMS. An increase in MEP and decrease in MT is thought to reflect long-term potentiation-like changes in synaptic efficiency that predominately occur in cortical circuits. Short-term changes, observed through simple yet repetitive tasks, have been attributed to the neural projections to multiple areas of the cerebral cortex and are measured through a change in cortical excitability.[279-281] Longer duration changes is thought to be from synaptic long-term potentiation of cortical projections to the muscle. These studies measuring cortical excitability following motor tasks all find that cortical activity changes through movement tasks requiring greater motor demand. Cortical excitability has been found to increase following

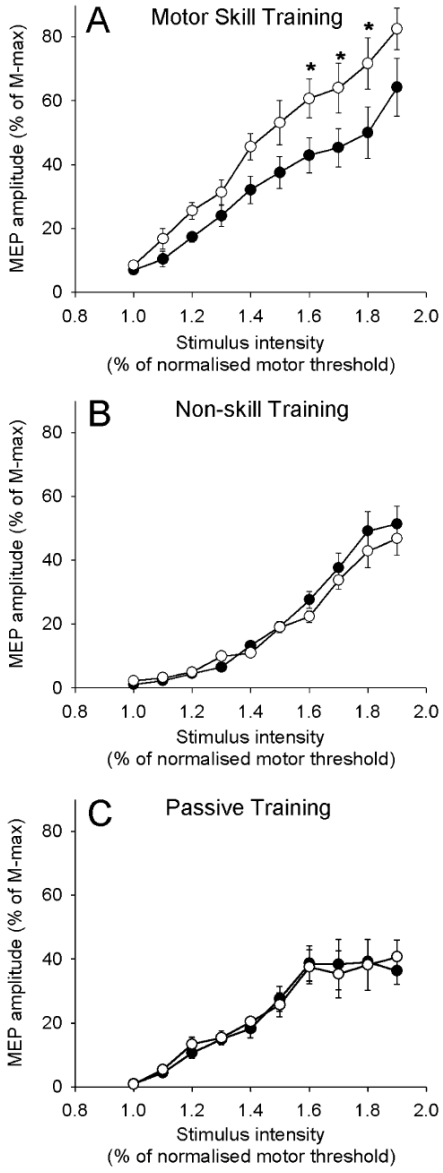


Figure 14: Influence of tibialis anterior motor evoked potentials following strength training(A), skill training (B), and passive training (C)[22,258]

visuomotor tasks that require greater precision compared to an easier motor task.[279] These finding suggest that corticospinal neurons not only modulate their threshold to reflect the type of task but to also accommodate the demands of such task.[279] Results from studies comparing the ability to modulate human corticospinal excitability also suggest that increases in corticospinal excitability are due to the activation of a larger number of corticomotoneuronal cells during different motor tasks that require different levels of precision.[282,283]

The effect of visuomotor tracking tasks to alter corticomotor plasticity has been assessed within single session interventions.[284] Motor learning has been defined as the short-term (single session) acquisition of a visuomotor task resulting in improved motor performance beyond pre-existing levels.[254,285,286] Complex visuomotor tasks requiring an increase in attentional demand require greater activation of corticospinal neurons that have direct projections to motor neurons. Tasks requiring low-intensity, precise voluntary control of muscle activation, compared to less complex tasks such as joint position, have shown neurons in the motor cortex to be more active.[287,288] Studies assessing neuroplastic changes are commonly directed to hand and finger musculature due to the large motor representation of the homunculus; however, studies evaluating visuomotor skill training compared to non-skill and passive training of the tibialis anterior found increased cortical excitability and a larger motor representation.[289]

The combination of visual feedback with sub-maximal low-intensity exercise may be a feasible intervention for individuals following musculoskeletal injuries presenting with corticospinal adaptations. Visual feedback provides a real-time reference depicting motor activity. In order for successful movements to occur, the motor command is needed to be confirmed or denied through sensory input.[290] The feedback utilized in visuomotor tasks allow

the patient to confirm the appropriate motor command or adapt subsequent commands to modify the output, essential for motor learning. Sub-maximal, precision tasks (often labeled as motor skill training) have been shown to have a greater ability to modulate corticospinal excitability due to the larger number of corticomotoneuronal cells activated to elicit the appropriate response.[282] Together, visual feedback and sub-maximal, precision tasks have been shown to increase corticospinal excitability.[257]

Individuals that demonstrate unsatisfactory levels of quadriceps strength following ACLR have been shown to have lower measures of corticospinal excitability.[9] To date, no intervention has been assessed to intervene on these adaptations in patients following ACLR. It is unknown if the application of visuomotor therapy would modify corticospinal adaptations in these individuals. In the present study we plan to develop a visuomotor rehabilitation to counter cortical adaptations seen at the time point of returning to activity following ACLR.

Conclusion

Injury and reconstruction of the ACL presents patients with sub-optimal health outcomes both acutely and chronically following their injury. Not only are these patients at a greater risk for subsequent injury, but they demonstrate lower amounts of physical activity and greater risk for post-traumatic osteoarthritis. Establishment of evidence-based strength thresholds possesses the possibility to improve the health and financial burden that presents to individuals following ACLR. However, underlying neurological contributors to muscular strength may impede the ability for fully restore muscular function. Currently, there is no clinical measure that can identify an individual resistant to traditional rehabilitation, which may lead to the unbeneficial therapeutic prescriptions and referrals. Furthermore, of individuals that may be identified, there

is no current therapy that has been shown to address neurological adaptations observed following ACLR. The following study will present with aims to address these gaps in the literature.

APPENDIX C

Additional Methods

Table C1. Overall Study Procedures

1. Attend Visit 1 (V1) at Memorial Gymnasium, Room 224A. Strength and Endurance Protocol (STEP) (Figure C1)
    a. Obtain informed consent
    b. Complete patient screening
        i. Assess eligibility criteria
    c. Obtain anthropometric measures and patient demographics
        i. Take patient's body mass (kg)
        ii. Take patient's body height (m)
        iii. Determine Limb dominance
        iv. Determine the "involved" limb (ACL-Reconstructed limb)
    d. Complete patient reported outcomes
    e. Assess quadriceps and hamstring isokinetic Torque
    f. Assess quadriceps and hamstring Fatigue index
    g. Assess single-leg balance
    h. Provide patient with the rehabilitation log
    i. Dismiss subject for Visit 1
2. Attend Visit 2 (V2) at Memorial Gymnasium, Room 224A. Lower Extremity Assessment Protocol (LEAP)
    a. Return Rehabilitation Questionnaire
    b. Obtain anthropometric measures and patient demographics
        i. Take patient's body mass (kg)
        ii. Take patient's body height (m)
    c. Complete patient reported outcomes
    d. Assess quadriceps and hamstring isokinetic torque
    e. Assess quadriceps and hamstring fatigue index
    f. Assess single-leg balance
    g. Complete the Landing Error Scoring System (LESS)
    h. Complete single-leg hopping
    i. Dismiss subject for Visit 2
    j. Patient Chart Review
    k. Patient Call-Back
3. Attend Visit 3 (V3) at Memorial Gymnasium, Room 224A
    a. Assess active motor threshold
    b. Assess recruitment curve
    c. Reveal Treatment Randomization
    d. Perform Sub-maximal visuomotor therapy OR Sham
    e. Assess active motor threshold
    f. Assess recruitment curve
    g. Assess quadriceps and hamstring isokinetic Torque

   h. Assess M-wave reflex
   i. Dismiss subject for Visit 3
4. Attend Visit 4 (V3) at Memorial Gymnasium, Room 224A
   a. Assess active motor threshold
   b. Assess recruitment curve
   c. Perform Cross-over therapy
   d. Assess active motor threshold
   e. Assess recruitment curve
   f. Assess quadriceps and hamstring isokinetic Torque
   g. Assess M-wave reflex
   h. Assess Central Activation Ratio
   i. Dismiss subject from the study

Figure 1: Flow chart of study procedures.

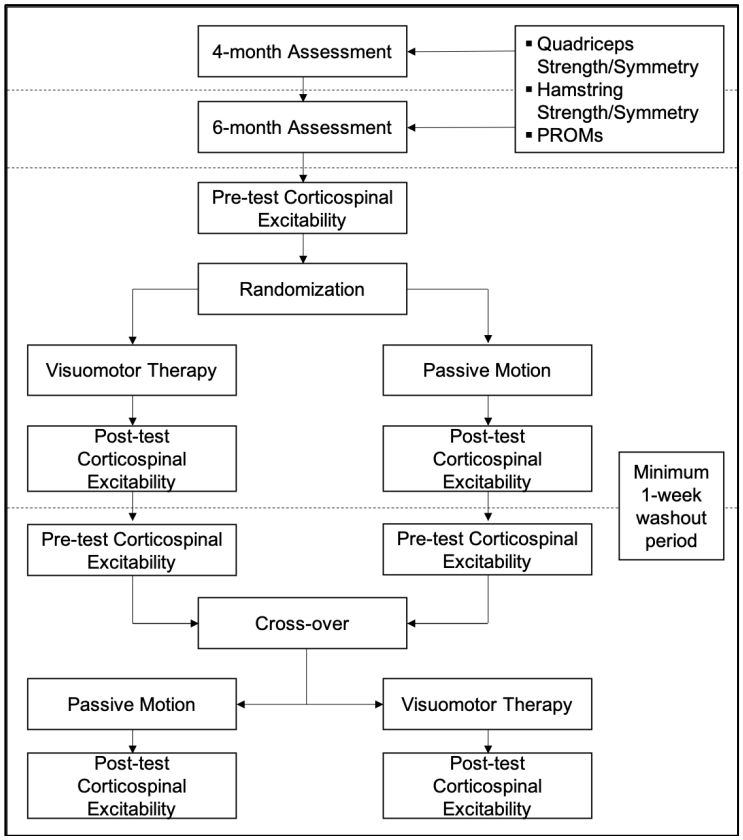
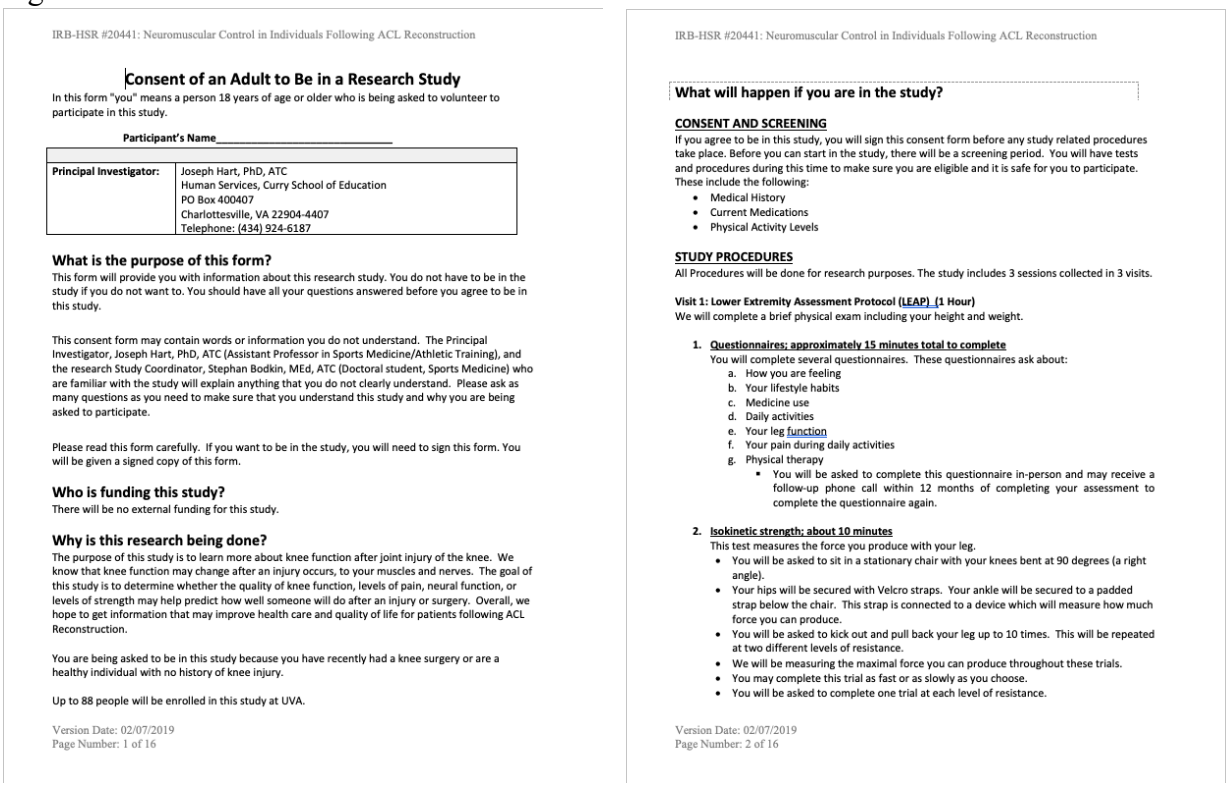


Table C1.1: Attend Visit 1 (V1) at Memorial Gymnasium, Room 224A.
Strength and Endurance Protocol (STEP)

A. Patient should be referred within 3-5 months following ACL-Reconstruction

Figure C1.1.a: Informed Consent for IRB-HSR 20441



IRB-HSR #20441: Neuromuscular Control in Individuals Following ACL Reconstruction

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

Principal Investigator:	Joseph Hart, PhD, ATC Human Services, Curry School of Education PO Box 400407 Charlottesville, VA 22904-4407 Telephone: (434) 924-6187

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

This consent form may contain words or information you do not understand. The Principal Investigator, Joseph Hart, PhD, ATC (Assistant Professor in Sports Medicine/Athletic Training), and the research Study Coordinator, Stephan Bodkin, MEd, ATC (Doctoral student, Sports Medicine) who are familiar with the study will explain anything that you do not clearly understand. Please ask as many questions as you need to make sure that you understand this study and why you are being asked to participate.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

There will be no external funding for this study.

Why is this research being done?

The purpose of this study is to learn more about knee function after joint injury of the knee. We know that knee function may change after an injury occurs, to your muscles and nerves. The goal of this study is to determine whether the quality of knee function, levels of pain, neural function, or levels of strength may help predict how well someone will do after an injury or surgery. Overall, we hope to get information that may improve health care and quality of life for patients following ACL Reconstruction.

You are being asked to be in this study because you have recently had a knee surgery or are a healthy individual with no history of knee injury.

Up to 88 people will be enrolled in this study at UVA.

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IRB-HSR #20441: Neuromuscular Control in Individuals Following ACL Reconstruction

What will happen if you are in the study?

CONSENT AND SCREENING

If you agree to be in this study, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate. These include the following:

- Medical History
- Current Medications
- Physical Activity Levels

STUDY PROCEDURES

All Procedures will be done for research purposes. The study includes 3 sessions collected in 3 visits.

Visit 1: Lower Extremity Assessment Protocol (LEAP) (1 Hour)

We will complete a brief physical exam including your height and weight.

1. **Questionnaires; approximately 15 minutes total to complete**
   You will complete several questionnaires. These questionnaires ask about:
   a. How you are feeling
   b. Your lifestyle habits
   c. Medicine use
   d. Daily activities
   e. Your leg function
   f. Your pain during daily activities
   g. Physical therapy
      - You will be asked to complete this questionnaire in-person and may receive a follow-up phone call within 12 months of completing your assessment to complete the questionnaire again.

2. **Isokinetic strength; about 10 minutes**
   This test measures the force you produce with your leg.
   - You will be asked to sit in a stationary chair with your knees bent at 90 degrees (a right angle).
   - Your hips will be secured with Velcro straps. Your ankle will be secured to a padded strap below the chair. This strap is connected to a device which will measure how much force you can produce.
   - You will be asked to kick out and pull back your leg up to 10 times. This will be repeated at two different levels of resistance.
   - We will be measuring the maximal force you can produce throughout these trials.
   - You may complete this trial as fast or as slowly as you choose.
   - You will be asked to complete one trial at each level of resistance.

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- This will be performed on both legs.

3. **Isometric strength and fatigue; about 10 minutes**
   This test will measure the force you are produce with your leg.
   - You will be seated in a stationary chair. The chair has handles on each side.
   - Your hips will be secured with Velcro straps. Your ankle will be secured to a padded strap below the chair. This strap is connected to a device designed to measure how much force you can produce.
   - You will be asked to kick out and pull back as hard as you can several times in order to estimate the most force you can produce. We will ask you to do this three times. You will rest for 2 minutes between each time.
   - You will then be asked to kick out and pull back at your maximum effort and hold your leg out for 30-60 seconds to measure how quickly your muscles become tired, also called motor fatigue. We will ask you to try to keep the same amount of force for as long as you can.
   - This will be performed on both legs.

5. Postural Control (Balance); about 5 minutes
- We will ask you to stand with both legs on a large plate, which measures force.
- Once balanced, you will be asked to pick one leg up, and balance on the other with your eyes closed. Each trial will last for 20 seconds.
- We will ask you to do this four times on each leg, 2 with your eyes open, 2 with your eyes closed.

4. **Landing Error Scoring System (jump landing task); about 5 minutes**
   - You will be asked to stand on a raised platform (about 12 inches high)
   - You will then be asked to step down and then jump straight up
   - We will ask you to do this three times
   - Video cameras will be used to record this activity from the front and side views.

7. **Single leg hop tests; about 15 minutes**
   - You will be asked to lie down on a treatment table so that the length of your leg can be measured.
   - You will then be asked to hop as far as you can on each leg multiple times in different directions.
   - The distance you hop will be measured along a tape measure.
   - We will also ask you to hop as quickly as possible over a distance of about 20 feet.
   - You will be given 4 practice hop trials in order to practice before testing begins.
   - Once testing begins, three hop trials will be measured for each hop test.
   - This will be performed on both legs.

Visit 2 (2 Hours)

1. **Supra-Imposed Burst Technique; up to 20 minutes**
   - You will be asked to remain in the chair with your lower leg strapped in.
   - You will be asked to kick out as hard as you can against resistance.
   - A stimulation will be provided to your thigh once during your maximal force trial though stimulating electrodes placed on your thigh. The device used to deliver the stimulation is not approved by the FDA, however, it is commercially available and has been used in our lab for other research studies.
   - This will be asked to be performed on both legs

2. **Cortical Excitability Assessment using Transcranial Magnetic Stimulation (TMS); up to 45 minutes**
   - Prior to the start of the study visit, you will be asked if they slept 6 or more hours the night before the study visit. If you have not had adequate sleep, the TMS session will be rescheduled for another time
   - You will be asked to seat in a chair with your leg strapped in at the lower leg.
   - You will be asked to wear a non-latex swim cap for the duration of collection. The purpose of the swim cap is mark (with an ink pen) certain points or features of your head that will be used to determine the best areas of magnetic coil placement for the TMS equipment that will provide stimulation (magnetic energy).
   - The electrodes will remain on your quadriceps from the task above
   - The TMS device will be placed against your head, resting against the swim cap; this device is a magnetic stimulator that is capable of delivering a non-painful stimulus through the scalp and underlying skull. This magnetic response is detected by the brain as an electrical potential and will be recorded by the electrodes placed on your quadriceps. The magnetic impulse used to stimulate the brain causes an audible "click" associated with the magnetic stimulating coil, and a brief muscle contraction (similar to a muscle "twitch") in the muscles of your thigh or leg, which will feel like what is felt during standard medical reflex testing.
   - You will be asked to kick out your leg to match a particular force that is provided to you on a screen in front of you.
   - While you kick out, the investigator with provide a stimulation to your scalp from the TMS device.
   - The investigator will provide a stimulus approximately once every ten seconds until the collection is completed.
   - If at any point you are uncomfortable with the stimulation, let the investigator know and the session will be ended
   - This will be asked to be performed on both legs

3. **Intervention: Motor Control Tasks Biofeedback Exercises OR Sham Treatment**

   a. **You will be randomly assigned (like flipping a coin) to one the following two treatments (Motor Control Tasks Biofeedback Exercises OR Sham Treatment). You have an equal chance of being assigned to any one of the groups. You cannot choose to which group you are assigned.**
   b. **At Visit 3, you will receive the other treatment.**

Motor Control Tasks Biofeedback Exercises
- You will be asked to sit in the Biodex chair with your limb secured similar to the strength testing.
- You will be provided live feedback of the force that you are producing
- You will be asked to try to match your force to the presented target for all trials. (Figure 2)
- There will be a warm up session for familiarization followed by 10 30-second trials.
- You will be given a 15 second rest break between each trial

OR

Sham Treatment
- You will be asked to sit in the Biodex chair with your limb secured similar to the strength testing.
- You will be asked to produce a certain force relative to your perceived maximum
  - (i.e.: "Produce 20% of your maximum force output")
- No Feedback will be provided
- There will be 10 30-second trials of this exercise with a 15 second rest between each trial.

4. **Re-assessment: Supra-Imposed Burst Technique; up to 20 minutes**
   - You will be asked to remain in the chair with your lower leg strapped in.
   - You will be asked to kick out as hard as you can against resistance.
   - A stimulation will be provided to your thigh once during your maximal force trial though stimulating electrodes placed on your thigh. The device used to deliver the stimulation is not approved by the FDA, however, it is commercially available and has been used in our lab for other research studies.
   - This will be asked to be performed on both legs

5. **Re-Assessment: Cortical Excitability Assessment using Transcranial Magnetic Stimulation (TMS); up to 45 minutes**
   - Prior to the start of the study visit, you will be asked if they slept 6 or more hours the night before the study visit. If you have not had adequate sleep, the TMS session will be rescheduled for another time
   - You will be asked to seat in a chair with your leg strapped in at the lower leg.
   - You will be asked to wear a non-latex swim cap for the duration of collection. The purpose of the swim cap is mark (with an ink pen) certain points or features of your head

that will be used to determine the best areas of magnetic coil placement for the TMS equipment that will provide stimulation (magnetic energy).
- The electrodes will remain on your quadriceps from the task above
- The TMS device will be placed against your head, resting against the swim cap; this device is a magnetic stimulator that is capable of delivering a non-painful stimulus through the scalp and underlying skull. This magnetic response is detected by the brain as an electrical potential and will be recorded by the electrodes placed on your quadriceps. The magnetic impulse used to stimulate the brain causes an audible "click" associated with the magnetic stimulating coil, and a brief muscle contraction (similar to a muscle "twitch") in the muscles of your thigh or leg, which will feel like what is felt during standard medical reflex testing.

5. **Re-assessment: Isokinetic strength; about 10 minutes**
   This test measures the force you produce with your leg.
   - You will be asked to sit in a stationary chair with your knees bent at 90 degrees (a right angle).
   - Your hips will be secured with Velcro straps. Your ankle will be secured to a padded strap below the chair. This strap is connected to a device which will measure how much force you can produce.
   - You will be asked to kick out and pull back your leg up to 10 times. This will be repeated at two different levels of resistance.
   - We will be measuring the maximal force you can produce throughout these trials.
   - You may complete this trial as fast or as slowly as you choose.
   - You will be asked to complete one trial at each level of resistance.
   - This will be performed on both legs.

6. **Hoffman's Reflex; about 30 minutes**
   - We will ask you to lie on your back on a treatment table with your knees propped up under towels
   - We will ask you to wear ear-plugs to eliminate noise to be as relaxed as possible.
   - A stimulating EMG electrode will be placed on your quadriceps nerve located just under your waistband near your hip.
   - Other electrodes will be placed on your thigh. These sticky electrodes will measure your muscle activity.
     - A small area on your thigh may need to be shaved and cleaned prior to placement
   - You will be given a stimulation (electrical energy) at a low intensity to become familiar with the sensation during collection. The device that will deliver the stimulation is not approved by the FDA, however, it is commercially and has been used in our lab for other research studies.
   - We will ask you to lie as still as possible in a relaxed state while a stimulation occurs about once every 10 seconds
   - If at any point you are uncomfortable with the stimulation, let the investigator know and the session will be ended

- This will be performed on both legs

Visit 3: Cross-over Treatment Session (2 Hours)

- **All procedures will be the same except the intervention provided. IF you received the Motor Control Tasks Biofeedback Exercise during visit 2, then you will receive the control treatment for visit 3 and vis-versa**

1. **Supra-Imposed Burst Technique; up to 20 minutes**
   - You will be asked to remain in the chair with your lower leg strapped in.
   - You will be asked to kick out as hard as you can against resistance.
   - A stimulation will be provided to your thigh once during your maximal force trial though stimulating electrodes placed on your thigh. The device used to deliver the stimulation is not approved by the FDA, however, it is commercially available and has been used in our lab for other research studies.
   - This will be asked to be performed on both legs
2. **Cortical Excitability Assessment using Transcranial Magnetic Stimulation (TMS); up to 45 minutes**
   - Prior to the start of the study visit, you will be asked if they slept 6 or more hours the night before the study visit. If you have not had adequate sleep, the TMS session will be rescheduled for another time
   - You will be asked to seat in a chair with your leg strapped in at the lower leg.
   - You will be asked to wear a non-latex swim cap for the duration of collection. The purpose of the swim cap is mark (with an ink pen) certain points or features of your head that will be used to determine the best areas of magnetic coil placement for the TMS equipment that will provide stimulation (magnetic energy).
   - The electrodes will remain on your quadriceps from the task above
   - The TMS device will be placed against your head, resting against the swim cap; this device is a magnetic stimulator that is capable of delivering a non-painful stimulus through the scalp and underlying skull. This magnetic response is detected by the brain as an electrical potential and will be recorded by the electrodes placed on your quadriceps. The magnetic impulse used to stimulate the brain causes an audible "click" associated with the magnetic stimulating coil, and a brief muscle contraction (similar to a muscle "twitch") in the muscles of your thigh or leg, which will feel like what is felt during standard medical reflex testing.
   - You will be asked to kick out your leg to match a particular force that is provided to you on a screen in front of you.
   - While you kick out, the investigator with provide a stimulation to your scalp from the TMS device.
   - The investigator will provide a stimulus approximately once every ten seconds until the collection is completed.

- If at any point you are uncomfortable with the stimulation, let the investigator know and the session will be ended
- This will be asked to be performed on both legs

3. **Intervention: Motor Control Tasks Biofeedback Exercises OR Sham Treatment. You will receive the treatment that you did NOT get at Visit 2.**

Motor Control Tasks Biofeedback Exercises
- You will be asked to sit in the Biodex chair with your limb secured similar to the strength testing.
- You will be provided live feedback of the force that you are producing
- You will be asked to try to match your force to the presented target for all trials. (Figure 2)
- There will be a warm up session for familiarization followed by 10 30-second trials.
- You will be given a 15 second rest break between each trial

OR

Sham Treatment
- You will be asked to sit in the Biodex chair with your limb secured similar to the strength testing.
- You will be asked to produce a certain force relative to your perceived maximum
  - (i.e.: "Produce 20% of your maximum force output")
- No Feedback will be provided
- There will be 10 30-second trials of this exercise with a 15 second rest between each trial.

4. **Re-assessment: Supra-Imposed Burst Technique; up to 20 minutes**
   - You will be asked to remain in the chair with your lower leg strapped in.
   - You will be asked to kick out as hard as you can against resistance.
   - A stimulation will be provided to your thigh once during your maximal force trial though stimulating electrodes placed on your thigh. The device used to deliver the stimulation is not approved by the FDA, however, it is commercially available and has been used in our lab for other research studies.
   - This will be asked to be performed on both legs
5. **Re-Assessment: Cortical Excitability Assessment using Transcranial Magnetic Stimulation (TMS); up to 45 minutes**
   - Prior to the start of the study visit, you will be asked if they slept 6 or more hours the night before the study visit. If you have not had adequate sleep, the TMS session will be rescheduled for another time
   - You will be asked to seat in a chair with your leg strapped in at the lower leg.
   - You will be asked to wear a non-latex swim cap for the duration of collection. The purpose of the swim cap is mark (with an ink pen) certain points or features of your head

that will be used to determine the best areas of magnetic coil placement for the TMS equipment that will provide stimulation (magnetic energy).
- The electrodes will remain on your quadriceps from the task above
- The TMS device will be placed against your head, resting against the swim cap; this device is a magnetic stimulator that is capable of delivering a non-painful stimulus through the scalp and underlying skull. This magnetic response is detected by the brain as an electrical potential and will be recorded by the electrodes placed on your quadriceps. The magnetic impulse used to stimulate the brain causes an audible "click" associated with the magnetic stimulating coil, and a brief muscle contraction (similar to a muscle "twitch") in the muscles of your thigh or leg, which will feel like what is felt during standard medical reflex testing.

6. **Re-assessment: Isokinetic strength; about 10 minutes**

This test measures the force you produce with your leg.
- You will be asked to sit in a stationary chair with your knees bent at 90 degrees (a right angle).
- Your hips will be secured with Velcro straps. Your ankle will be secured to a padded strap below the chair. This strap is connected to a device which will measure how much force you can produce.
- You will be asked to kick out and pull back your leg up to 10 times. This will be repeated at two different levels of resistance.
- We will be measuring the maximal force you can produce throughout these trials.
- You may complete this trial as fast or as slowly as you choose.
- You will be asked to complete one trial at each level of resistance.
- This will be performed on both legs.

7. **Hoffman's Reflex; about 30 minutes**
   - We will ask you to lie on your back on a treatment table with your knees propped up under towels
   - We will ask you to wear ear-plugs to eliminate noise to be as relaxed as possible.
   - A stimulating EMG electrode will be placed on your quadriceps nerve located just under your waistband near your hip.
   - Other electrodes will be placed on your thigh. These sticky electrodes will measure your muscle activity.
     - A small area on your thigh may need to be shaved and cleaned prior to placement
   - You will be given a stimulation (electrical energy) at a low intensity to become familiar with the sensation during collection. The device that will deliver the stimulation is not approved by the FDA, however, it is commercially and has been used in our lab for other research studies.
   - We will ask you to lie as still as possible in a relaxed state while a stimulation occurs about once every 10 seconds
   - If at any point you are uncomfortable with the stimulation, let the investigator know and the session will be ended

- This will be performed on both legs

Study Schedule

		Visit 1	Visit 2	Visit 3
LEAP	Informed Consent	x		
	Review study eligibility	x		
	Medical History	x		
	Patient Reported Outcomes	x		
	Physical Exam	x		
	Measurements/tasks	x		
	Neurophysiological Assessment		x	x
	Motor Control Feedback **OR** Control		x	x
	Neurophysiological Re-Assessment		x	x
	Strength Re-assessment		x	x

WHAT ARE YOUR RESPONSIBILITIES IN THE STUDY?
You have certain responsibilities to help ensure your safety.

These responsibilities are listed below:
- You must sleep six of more hours the night prior to the third study session or the TMS procedure will have to be rescheduled
- You must come you to each study visit.
- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Answer all of the study-related questions completely.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over-the-counter), including herbal supplements and vitamins.

How long will this study take?

Your participation in this study will require 3 study visits over 4-week period of time. Each visit will last about from about 1 hour to 2 hours. All 3 testing sessions will last 5 hours in total.

If you want to know about the results before the study is done:
During the study your study leader will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to the study procedures include:

Likely
- You may experience a mild, short-lasting muscle soreness after testing
- You may experience temporary discomfort from electrical stimulation during the supra-imposed burst and Hoffmann's Reflex testing

Less Likely
- Falling from jump landing and single leg hopping tasks
- You could experience minor, short-lasting skin irritation where the elf adhesive electrodes have been placed
- You may experience a mild, transient headache after receiving the Cortical Excitability Assessment

Rare but serious
- You may produce a seizure if you have a history of epilepsy or other seizure disorders. It is important you let us know if you have a history of this condition.

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?
You may or may not benefit from being in this study. Possible benefits include learning more about how your joint injury is doing. In addition, information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?
You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study.

Will you be paid for being in this study?

Healthy participants will not be paid for this study.

If you have had ACL-Reconstruction, you will be paid $100 for finishing this study by check.
If you do not finish the study, you will be paid as follows:
1) Visit 1: $20.
2) Visit 2: $20.
3) Visit 3: $20.
4) Completion of all 3 Visits: $40

You will not be paid at all if **you** decide not to finish this study. If the study leader says you cannot continue, you will be paid the full amount for the study.

The payment should be processed in 4-6 weeks following the your last study visit. The income may be reported to the IRS as income. You will not be paid at all if **you** decide not to finish this study. If the study leader says you cannot continue, you will be paid the full amount for the study.

If you owe money to any Virginia state agency, the state can use the money you earn in this study to pay those debts. These state agencies include the UVa Medical Center, VCU Medical Center or a college or university. The money may be withheld to pay back debt for such things as unpaid medical bills, taxes, fines, child support. Even if this happens, the money you earn may be reported to the IRS as taxable income.

Will being in this study cost you any money?
All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study visit. Parking will be validated from the Department of Kinesiology for the Central Grounds Parking Garage.

What if you are hurt in this study?
If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?
You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader (Dr. Joseph Hart) can take you out of the study. Some of the reasons for doing so may include:
a) Your study physician is concerned about your health
b) Your disease gets worse

If you decide to stop being in the study, we will ask you to please notify Dr. Joe Hart in writing at 210 Emmet Street South, P.O. Box 400407, Charlottesville, VA 22904-4407.

How will your personal information be shared?
The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:
- Personal information such as name, address, date of birth,
- Social Security number ONLY IF you are being paid to be in this study
- Your health information. If required for this study, this may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers (if required for this study, this may include mental health care records, substance abuse records, and/or HIV/AIDS records).

Who will see your private information?
- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

A description of this clinical trial will be available on *http:// www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What if you sign the form but then decide you don't want your private information shared?
You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your medical records will be able to find out that you are in this study. This is done so your regular doctors will know what you receive as part of this study. If you have other health problems during the study, they will be able to treat you properly.

Please contact the researchers listed below to:
- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Joseph Hart, PhD, ATC
Human Services, Curry School of Education
PO Box 400407
Charlottesville, VA 22904-4407
Telephone: (434) 924-6187

What if you have a concern about this study?
You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908
Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the

problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE	

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Signature of Impartial Witness

If this consent form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The subject may place an X on the Participant Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the **identified individual(s)** who has had the opportunity to ask any questions he/she had about the study. I also agree that the **identified individual(s)** freely gave their informed consent to participate in this trial.

Please indicate with check box the identified individual(s):

☐ Subject

IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE

Leaving the Study Early

Signatures should be obtained in this section if the subject decides to leave the study early.

If you leave the study early the study leader will keep the data collected about you up until the time you leave the study to help determine the results of the study.

Signature From Adult

PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE	

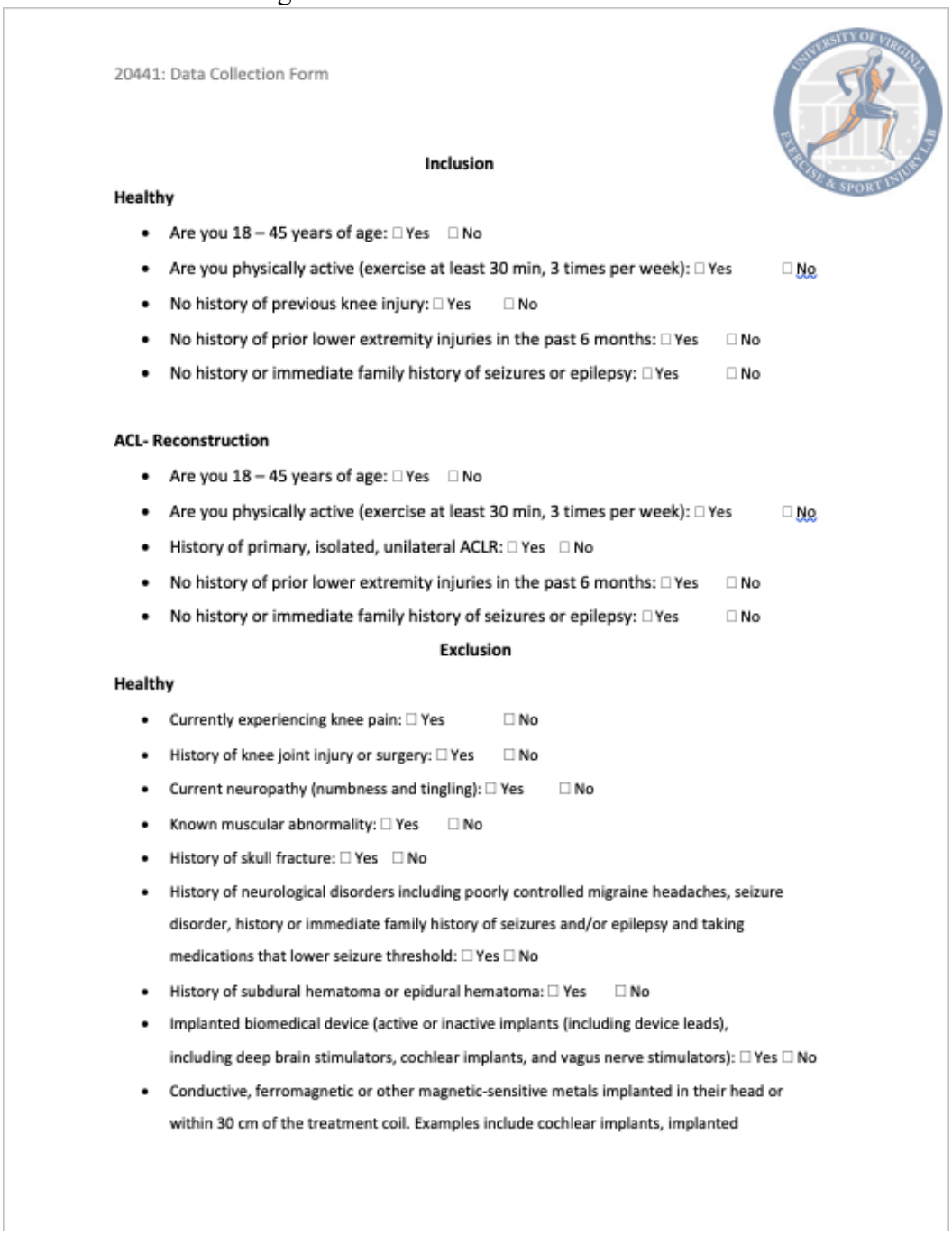
To be completed by participant if 18 years of age or older.

Person Obtaining Signature

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Figure C1.1.b: Patient Screening



20441: Data Collection Form

Inclusion

Healthy

- Are you 18 – 45 years of age: ☐ Yes ☐ No
- Are you physically active (exercise at least 30 min, 3 times per week): ☐ Yes ☐ No
- No history of previous knee injury: ☐ Yes ☐ No
- No history of prior lower extremity injuries in the past 6 months: ☐ Yes ☐ No
- No history or immediate family history of seizures or epilepsy: ☐ Yes ☐ No

ACL- Reconstruction

- Are you 18 – 45 years of age: ☐ Yes ☐ No
- Are you physically active (exercise at least 30 min, 3 times per week): ☐ Yes ☐ No
- History of primary, isolated, unilateral ACLR: ☐ Yes ☐ No
- No history of prior lower extremity injuries in the past 6 months: ☐ Yes ☐ No
- No history or immediate family history of seizures or epilepsy: ☐ Yes ☐ No

Exclusion

Healthy

- Currently experiencing knee pain: ☐ Yes ☐ No
- History of knee joint injury or surgery: ☐ Yes ☐ No
- Current neuropathy (numbness and tingling): ☐ Yes ☐ No
- Known muscular abnormality: ☐ Yes ☐ No
- History of skull fracture: ☐ Yes ☐ No
- History of neurological disorders including poorly controlled migraine headaches, seizure disorder, history or immediate family history of seizures and/or epilepsy and taking medications that lower seizure threshold: ☐ Yes ☐ No
- History of subdural hematoma or epidural hematoma: ☐ Yes ☐ No
- Implanted biomedical device (active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators): ☐ Yes ☐ No
- Conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or within 30 cm of the treatment coil. Examples include cochlear implants, implanted

20441: Data Collection Form

electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair

barrettes: ☐ Yes ☐ No

- History of cardiopulmonary disorder: ☐ Yes ☐ No
- Pregnant women: ☐ Yes ☐ No
- Significant activity change 48 hours prior to enrollment: ☐ Yes ☐ No

ACL- Reconstructed

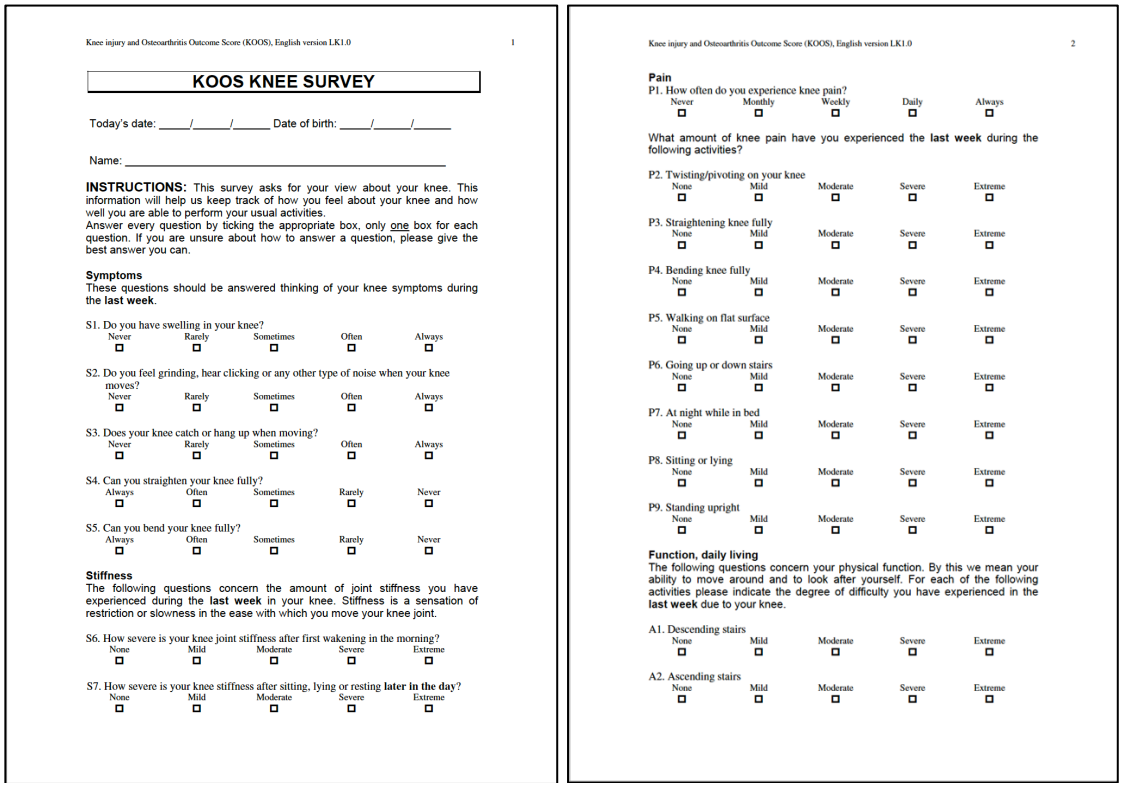
- Multiple ligament reconstruction or a history of graft failure: ☐ Yes ☐ No
- Serious surgical complication following ACL reconstruction: ☐ Yes ☐ No
- Chondral resurfacing procedure (microfracture or OATS procedure): ☐ Yes ☐ No
- History of cardiopulmonary disorder: ☐ Yes ☐ No
- Current symptoms of meniscal injury or failed meniscal repair: ☐ Yes ☐ No
- Current neuropathy (numbness and tingling): ☐ Yes ☐ No
- Known muscular abnormality: ☐ Yes ☐ No
- History of skull fracture: ☐ Yes ☐ No
- History of neurological disorders including poorly controlled migraine headaches, seizure disorder, history or immediate family history of seizures and/or epilepsy: ☐ Yes ☐ No
- Taking medications that lower seizure threshold: ☐ Yes ☐ No
- History of subdural hematoma or epidural hematoma: ☐ Yes ☐ No
- History of neurological disorders: ☐ Yes ☐ No
- Implanted biomedical device (active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators): ☐ Yes ☐ No
- Conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes: ☐ Yes ☐ No
- Pregnant women: ☐ Yes ☐ No
- Significant activity change 48 hours prior to enrollment: ☐ Yes ☐ No

C1.1.c: Patient Demographics

1. Take patient's weight on the standing scale
2. Determine the patient's dominant limb by asking "which leg would you use to kick a ball for distance?"
3. Administer patient demographic and health history form

Figure C1.1.d: Patient Reported Outcomes (PROs)

Knee Osteoarthritis Outcome Score



Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 1

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?
Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S3. Does your knee catch or hang up when moving?
Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S4. Can you straighten your knee fully?
Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

S5. Can you bend your knee fully?
Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 2

Pain
P1. How often do you experience knee pain?
Never ☐ Monthly ☐ Weekly ☐ Daily ☐ Always ☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P3. Straightening knee fully
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P4. Bending knee fully
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P5. Walking on flat surface
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P6. Going up or down stairs
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P7. At night while in bed
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

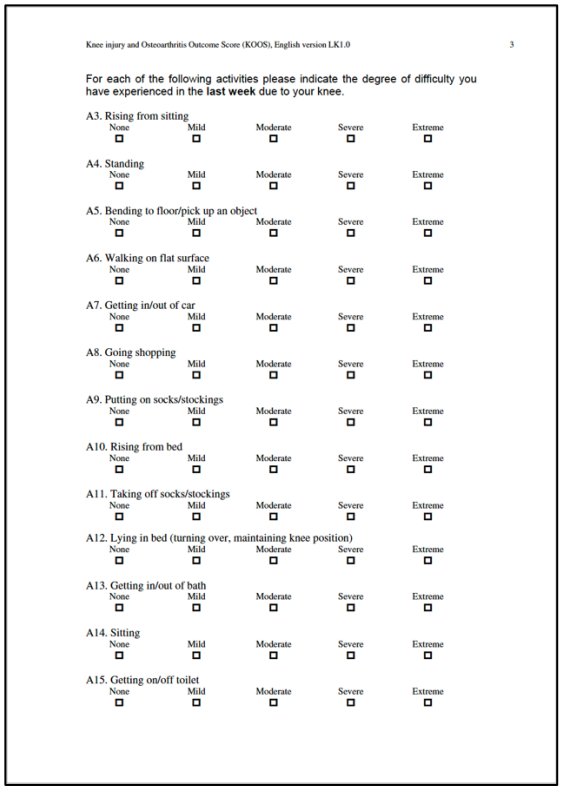
P8. Sitting or lying
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P9. Standing upright
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Function, daily living
The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A2. Ascending stairs
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐



Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 3

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A4. Standing
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A5. Bending to floor/pick up an object
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A6. Walking on flat surface
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A7. Getting in/out of car
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A8. Going shopping
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A9. Putting on socks/stockings
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A10. Rising from bed
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

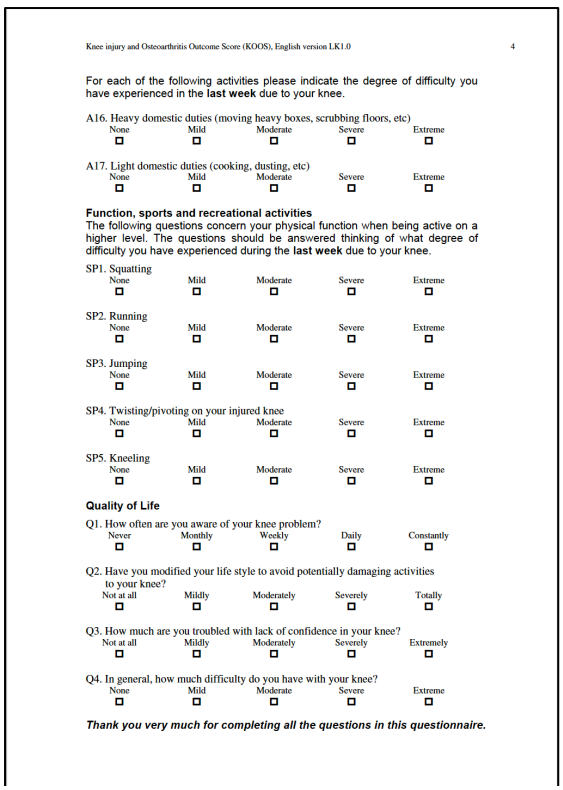
A11. Taking off socks/stockings
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A12. Lying in bed (turning over, maintaining knee position)
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A13. Getting in/out of bath
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A14. Sitting
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A15. Getting on/off toilet
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐



Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 4

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A17. Light domestic duties (cooking, dusting, etc)
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Function, sports and recreational activities
The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

SP2. Running
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

SP3. Jumping
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

SP4. Twisting/pivoting on your injured knee
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

SP5. Kneeling
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Quality of Life

Q1. How often are you aware of your knee problem?
Never ☐ Monthly ☐ Weekly ☐ Daily ☐ Constantly ☐

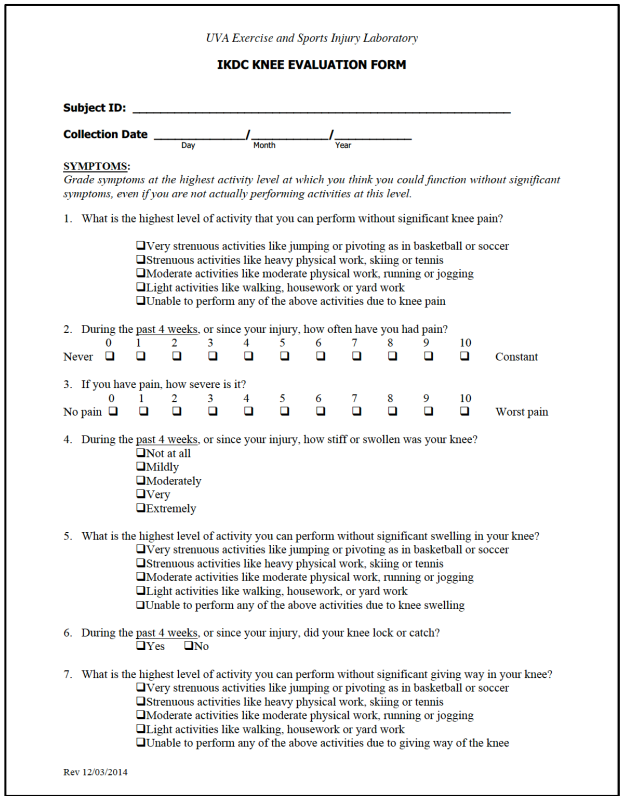
Q2. Have you modified your life style to avoid potentially damaging activities to your knee?
Not at all ☐ Mildly ☐ Moderately ☐ Severely ☐ Totally ☐

Q3. How much are you troubled with lack of confidence in your knee?
Not at all ☐ Mildly ☐ Moderately ☐ Severely ☐ Extremely ☐

Q4. In general, how much difficulty do you have with your knee?
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Thank you very much for completing all the questions in this questionnaire.

International Knee Documentation Committee (IKDC) Subjective Questionnaire



UVA Exercise and Sports Injury Laboratory

IKDC KNEE EVALUATION FORM

Subject ID: _____

Collection Date _____/_____/_____
Day Month Year

SYMPTOMS:
Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

❑Very strenuous activities like jumping or pivoting as in basketball or soccer
❑Strenuous activities like heavy physical work, skiing or tennis
❑Moderate activities like moderate physical work, running or jogging
❑Light activities like walking, housework or yard work
❑Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?
0 1 2 3 4 5 6 7 8 9 10
Never ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ Constant

3. If you have pain, how severe is it?
0 1 2 3 4 5 6 7 8 9 10
No pain ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ Worst pain

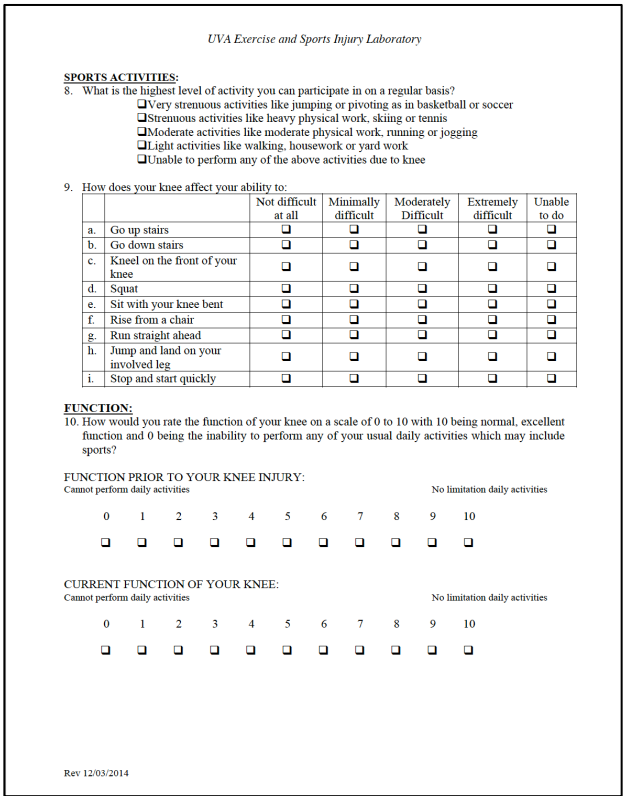
4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?
❑Not at all
❑Mildly
❑Moderately
❑Very
❑Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?
❑Very strenuous activities like jumping or pivoting as in basketball or soccer
❑Strenuous activities like heavy physical work, skiing or tennis
❑Moderate activities like moderate physical work, running or jogging
❑Light activities like walking, housework, or yard work
❑Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?
❑Yes ❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
❑Very strenuous activities like jumping or pivoting as in basketball or soccer
❑Strenuous activities like heavy physical work, skiing or tennis
❑Moderate activities like moderate physical work, running or jogging
❑Light activities like walking, housework or yard work
❑Unable to perform any of the above activities due to giving way of the knee

Rev 12/03/2014



UVA Exercise and Sports Injury Laboratory

SPORTS ACTIVITIES:
8. What is the highest level of activity you can participate in on a regular basis?
❑Very strenuous activities like jumping or pivoting as in basketball or soccer
❑Strenuous activities like heavy physical work, skiing or tennis
❑Moderate activities like moderate physical work, running or jogging
❑Light activities like walking, housework or yard work
❑Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	❑	❑	❑	❑	❑
b.	Go down stairs	❑	❑	❑	❑	❑
c.	Kneel on the front of your knee	❑	❑	❑	❑	❑
d.	Squat	❑	❑	❑	❑	❑
e.	Sit with your knee bent	❑	❑	❑	❑	❑
f.	Rise from a chair	❑	❑	❑	❑	❑
g.	Run straight ahead	❑	❑	❑	❑	❑
h.	Jump and land on your involved leg	❑	❑	❑	❑	❑
i.	Stop and start quickly	❑	❑	❑	❑	❑

FUNCTION:
10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:
Cannot perform daily activities — No limitation daily activities

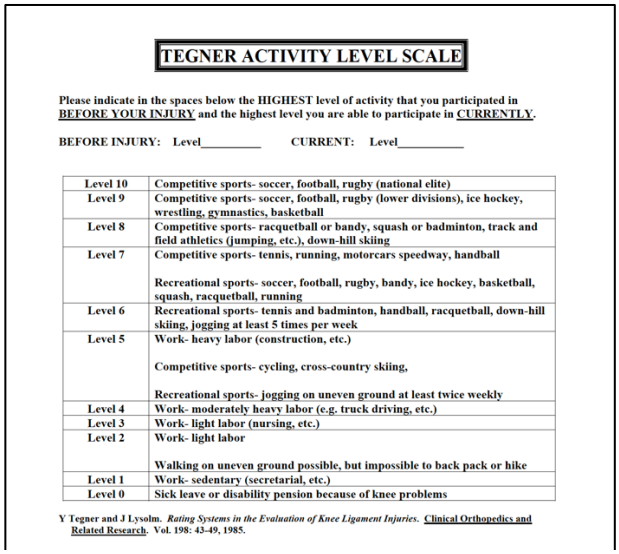
0 1 2 3 4 5 6 7 8 9 10
❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑

CURRENT FUNCTION OF YOUR KNEE:
Cannot perform daily activities — No limitation daily activities

0 1 2 3 4 5 6 7 8 9 10
❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑

Rev 12/03/2014

Tegner Leisure Activity Scale



TEGNER ACTIVITY LEVEL SCALE

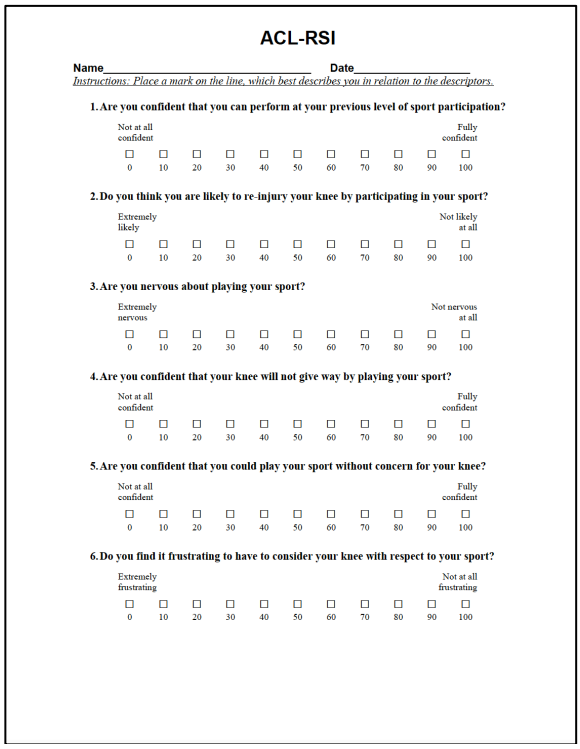
Please indicate in the spaces below the HIGHEST level of activity that you participated in BEFORE YOUR INJURY and the highest level you are able to participate in CURRENTLY.

BEFORE INJURY: Level_____ CURRENT: Level_____

Level 10	**Competitive sports- soccer, football, rugby (national elite)**
Level 9	**Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball**
Level 8	**Competitive sports- racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing**
Level 7	**Competitive sports- tennis, running, motorcars speedway, handball** **Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running**
Level 6	**Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week**
Level 5	**Work- heavy labor (construction, etc.)** **Competitive sports- cycling, cross-country skiing,** **Recreational sports- jogging on uneven ground at least twice weekly**
Level 4	**Work- moderately heavy labor (e.g. truck driving, etc.)**
Level 3	**Work- light labor (nursing, etc.)**
Level 2	**Work- light labor** **Walking on uneven ground possible, but impossible to back pack or hike**
Level 1	**Work- sedentary (secretarial, etc.)**
Level 0	**Sick leave or disability pension because of knee problems**

Y Tegner and J Lysolm. ***Rating Systems in the Evaluation of Knee Ligament Injuries.*** **Clinical Orthopedics and Related Research. Vol. 198: 43-49, 1985.**

ACL-Return to Sport Index (ACL-RSI)



ACL-RSI

Name_____ **Date**_____

Instructions: Place a mark on the line, which best describes you in relation to the descriptors.

1. Are you confident that you can perform at your previous level of sport participation?

Not at all confident — Fully confident

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

2. Do you think you are likely to re-injury your knee by participating in your sport?

Extremely likely — Not likely at all

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

3. Are you nervous about playing your sport?

Extremely nervous — Not nervous at all

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

4. Are you confident that your knee will not give way by playing your sport?

Not at all confident — Fully confident

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

5. Are you confident that you could play your sport without concern for your knee?

Not at all confident — Fully confident

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

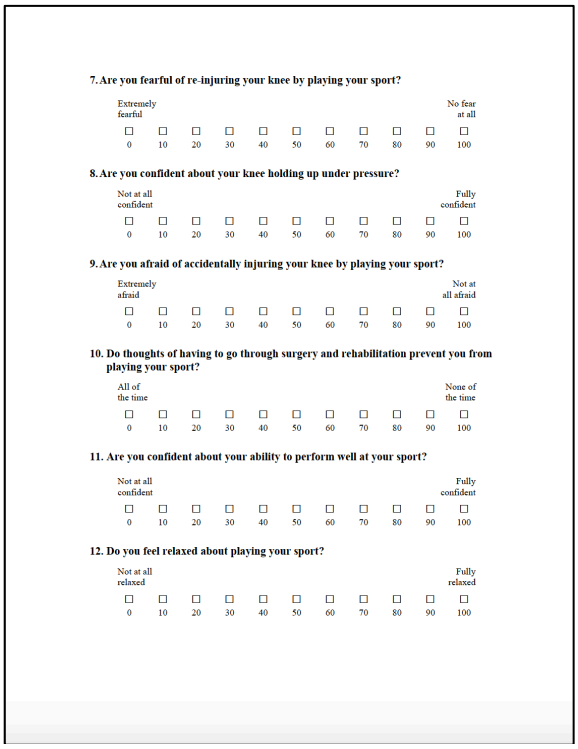
0 10 20 30 40 50 60 70 80 90 100

6. Do you find it frustrating to have to consider your knee with respect to your sport?

Extremely frustrating — Not at all frustrating

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100



7. Are you fearful of re-injuring your knee by playing your sport?

Extremely fearful — No fear at all

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

8. Are you confident about your knee holding up under pressure?

Not at all confident — Fully confident

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

9. Are you afraid of accidentally injuring your knee by playing your sport?

Extremely afraid — Not at all afraid

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

10. Do thoughts of having to go through surgery and rehabilitation prevent you from playing your sport?

All of the time — None of the time

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

11. Are you confident about your ability to perform well at your sport?

Not at all confident — Fully confident

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 10 20 30 40 50 60 70 80 90 100

12. Do you feel relaxed about playing your sport?

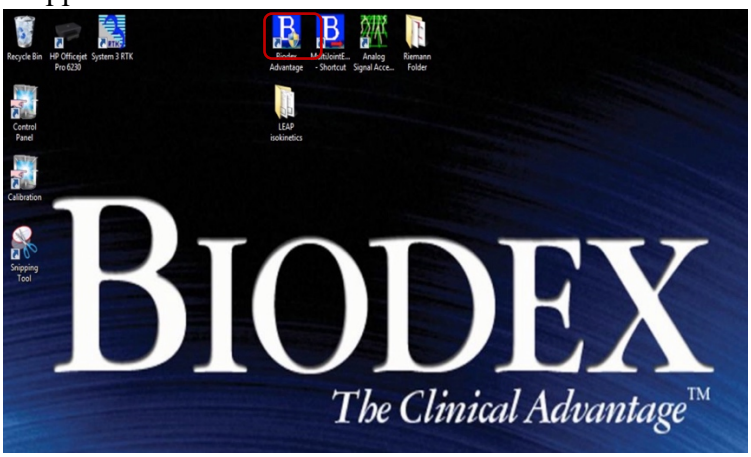
Not at all relaxed — Fully relaxed

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

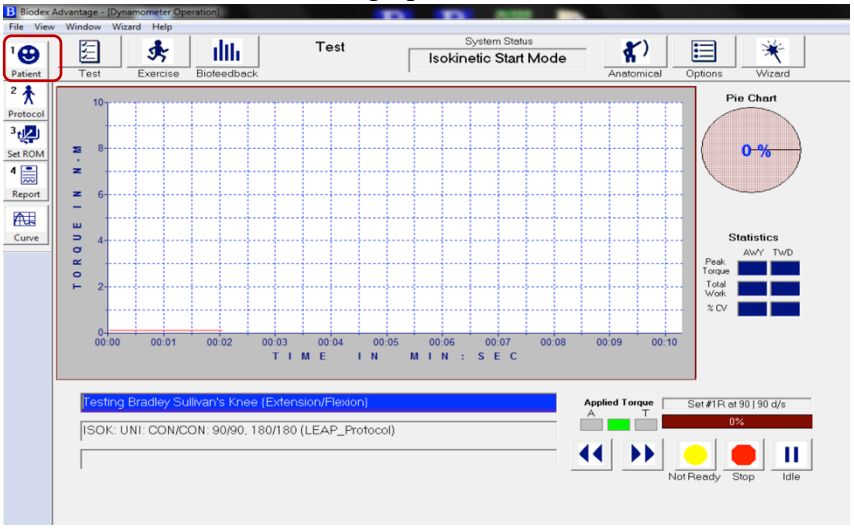
0 10 20 30 40 50 60 70 80 90 100

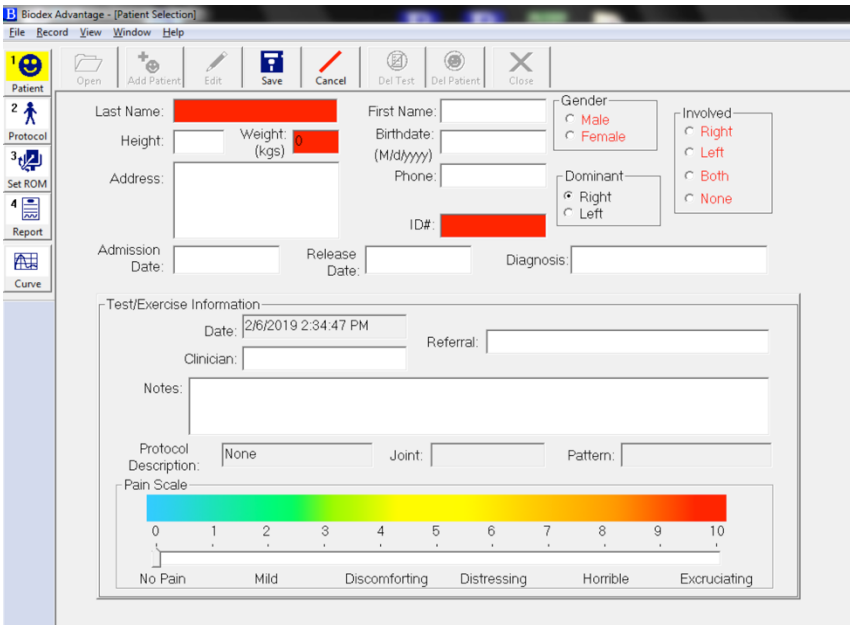
Table C1.1.e: Quadriceps and Hamstring Isokinetic Torque Setup and Procedures

1. Biodex Set-up
    a. Turn on Biodex
    b. Wait for Biodex calibration to occur
    c. Position the back of the chair to 80 degrees
    d. Attach limb to assess the uninvolved limb
2. Computer Setup
    a. Open Biodex Application

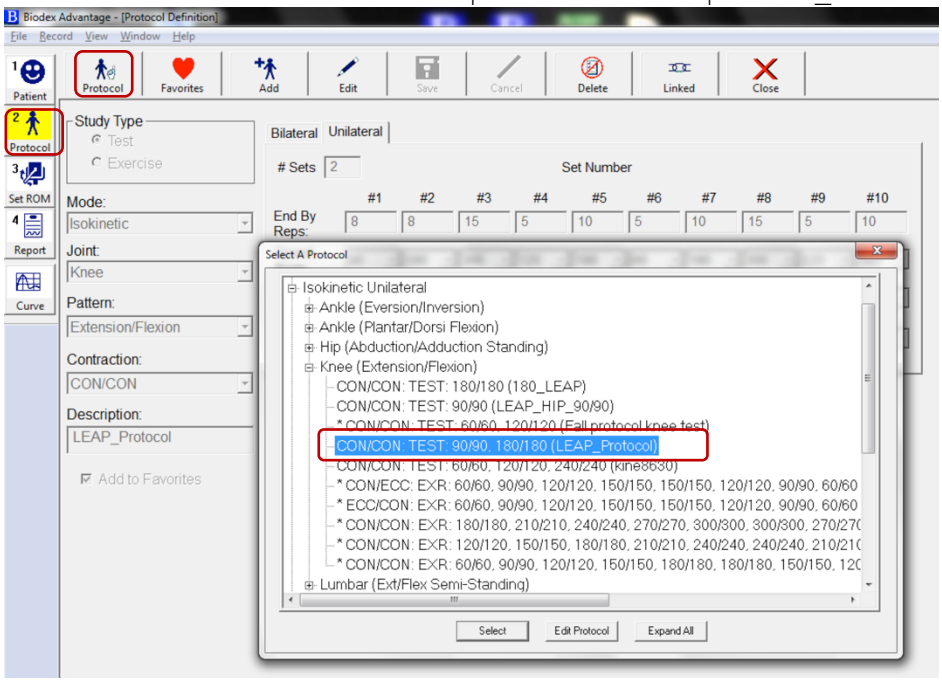


    b. File | Setup | Simulation Mode: OFF
    c. Select “Patient” Icon
        i. Enter in Patient demographics

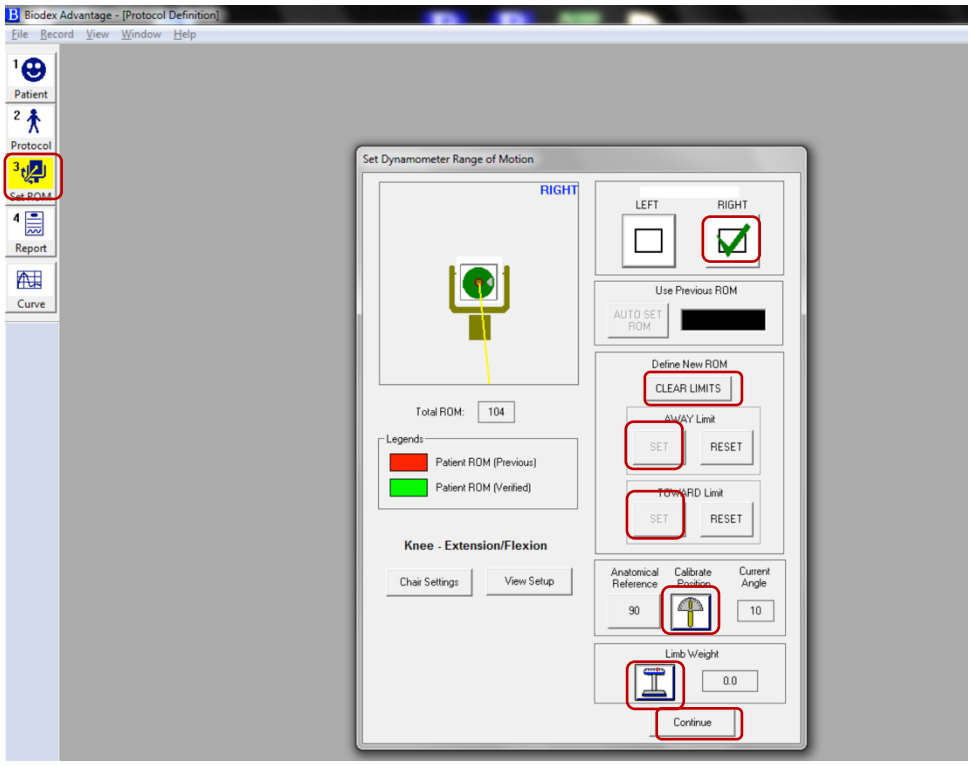




d. Select “Protocol” Icon
    i. Select “Unilateral Isokinetic” | “Knee Ext/Flex” | “LEAP_Protocol” | close



e. Select “Range of motion” Icon



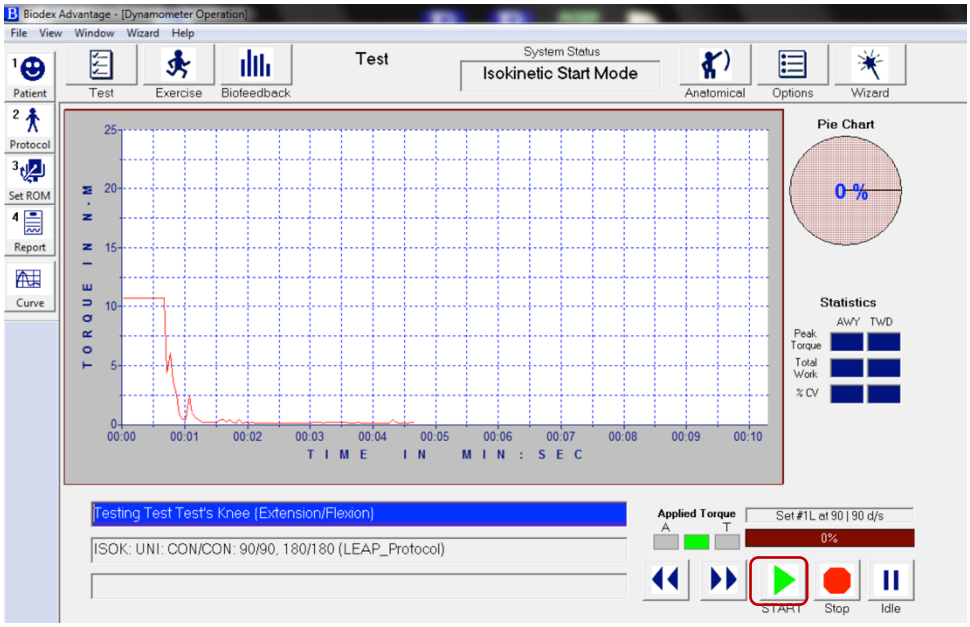
i. Select the appropriate side “Left”/“Right”
ii. Click “Define New Range” | “Clear”
iii. Attach magnetic goniometer to the arm of the limb attachment
iv. Extend the patient’s knee to 0 degrees of extension | Press “Hold” button
v. Select “Away” on Biodex computer | Press “Hold” button
vi. Flex the patient’s knee to 70 degrees of flexion | Press “Hold” button
vii. Select “Towards” on the Biodex computer | Press “Hold” button
viii. Place the patient’s knee in 90 degrees of flexion (Neutral) | Press “Hold” button
ix. Select “Position” on the Biodex computer | Press “Hold” button
x. Extend the patient’s knee to 0 degrees of extension | Press “Hold” button
xi. Ask the patient to relax their leg
xii. Select “limb weight” on the Biodex computer
xiii. Select “Continue” on the Biodex computer

f. Select “Start” on the Biodex computer to begin testing

3. Patient Preparation
   a. Position the Patient in the Biodex Chair
      i. Move the back of the chair so that ~5 cm of the patient’s thigh overhang the edge of the chair
      ii. Move chair forward/backward so that the lateral epicondyle aligns with the axis of rotation of the Biodex
      iii. Move chair up/down so that the lateral epicondyle aligns with the axis of rotation of the Biodex
   b. Flex patient’s knees to 90 degrees
   c. Restrain the patient with the lap belt
   d. Strap distal shank (2 cm above lateral malleolus) to Biodex attachment

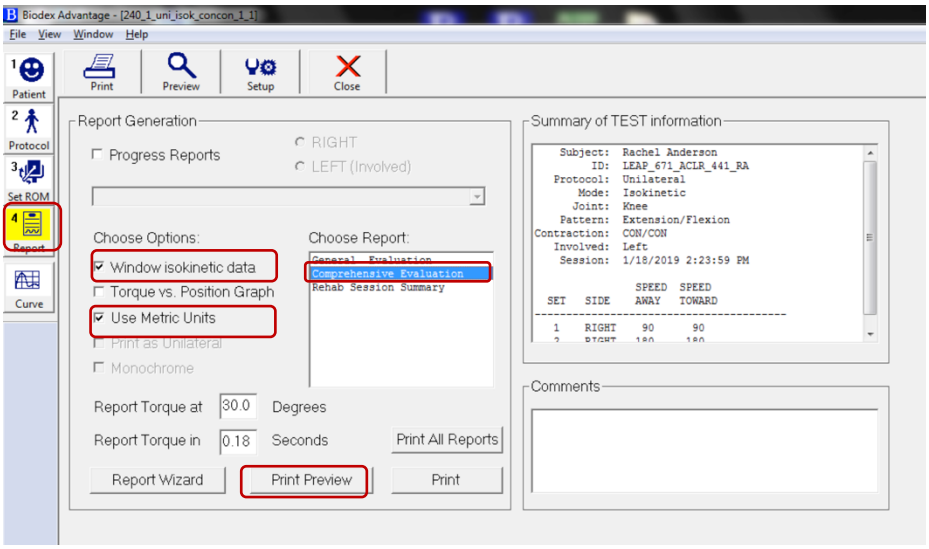
e. Provide instructions for proper testing procedures
    i. “Sit up straight with your back against the backrest”
    ii. “Do not rotate or arch or back”
    iii. “Cross your hands across your chest for the duration of testing”
    iv. “Focus on kicking out and pulling back in as fast and as hard as you can with just your thigh muscles”

4. Data Collection

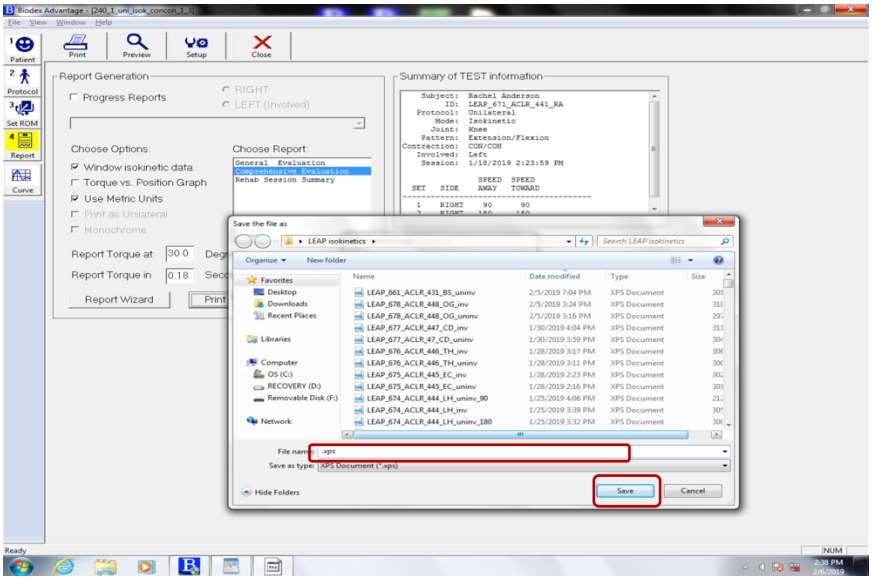


a. Click the start button on the Biodex computer to initiate the assessment
b. Inform the patient to perform as many practice trials as necessary until they are familiar with the task
c. Patient will perform 8 repetitions at 90 deg/sec
d. Patient will rest for 30 seconds
e. Inform the patient to perform as many practice trials as necessary until they are familiar with the task
f. Patient will perform 8 repetitions at 180 deg/sec
g. Select Continue button on the screen

5. Data Processing
    a. Select the “Report” Icon



b. Under options, select “Window Isokinetic Data” and “Use Metric Units”
c. Under Choose Report, select “Comprehensive Evaluation”
d. Select “Print Preview”
e. Save as PDF in “Isokinetic Data” Folder

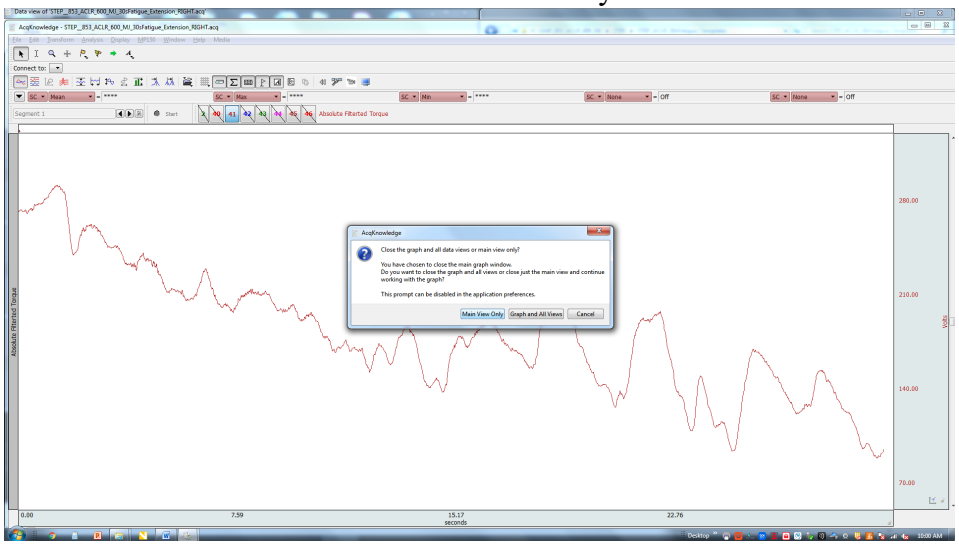


f. Save as “*Patient_ID*_Uninv”

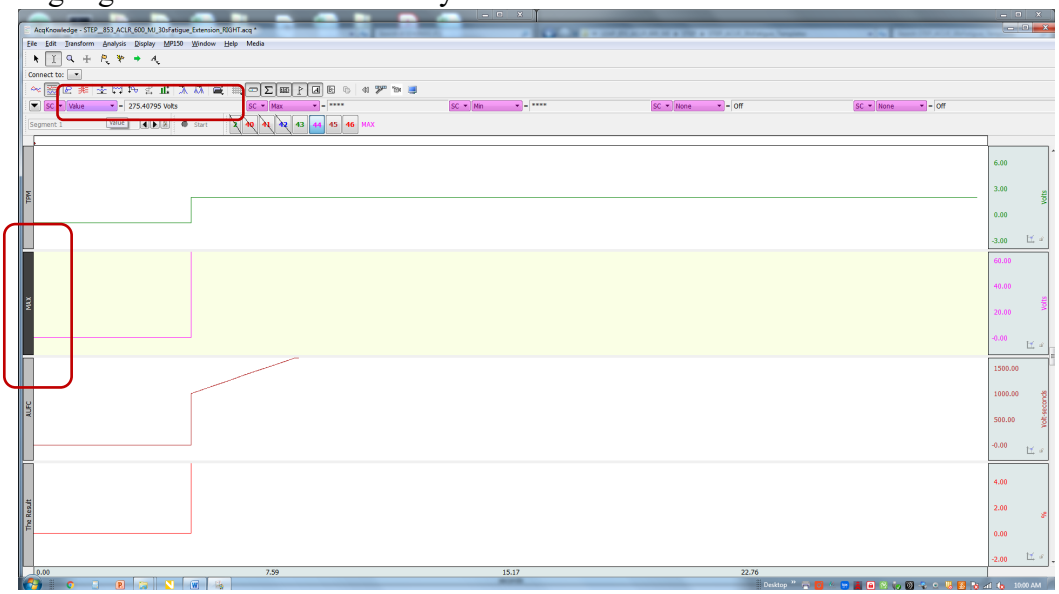
Table C1.1.f: Quadriceps and Hamstring Fatigue Index Setup and Procedures

1. Biodex Set-up
    a. Turn on Biodex
    b. Wait for Biodex calibration to occur
    c. Position the back of the chair to 80 degrees
    d. Attach limb to assess the uninvolved limb
    e. Attach magnetic goniometer to the arm of the limb attachment
    f. Position attachment to 90 degrees
2. AcqKnowledge Setup
    a. Open AcqKnowledge 4.2.0 for Windows on the Standing Computer
    b. Select the attached MP150 Unit
    c. Select MP150 | Acquire
        i. Change the menus to “record” and “append”
        ii. Change sampling rate to 2000 Hz
        iii. Change the acquisition length to 30 seconds
        iv. Select Exit
    d. Select MP150 | Setup Channels
        i. Select the Analog Tab
        ii. Label Channel 1: “Force”
        iii. Select the Acquire, Plot, and Value boxes
        iv. Change sampling rate to 125 Hz
        v. Select Exit
3. Data Collection
    a. Educate the patient of the test trial
        i. “Sit up tall with your back firmly against the back of the chair and your arms crossed across your chest. Throughout the trial, do not lean or twist your back but rather focus on exerting all force through your knee and thigh. I will count down, ‘3, 2, 1, Kick.’ As I count down I want you to slowly ramp up your force but to make sure you are exerting maximal volitional force when I get to ‘kick’. Try to exert your maximal effort for the 30-second trial. You are expected to get tired throughout the trial. Do you have any questions?”
        ii. Count down the patient into the trial and select the “Start” button in Acqknowledge when you finish the countdown.
        iii. Inform thee patient to “Relax” when the 30-second trial concludes
4. Data Processing
    a. Open Acqknowledge file

b. Exit out of main view. Select “Main View Only”



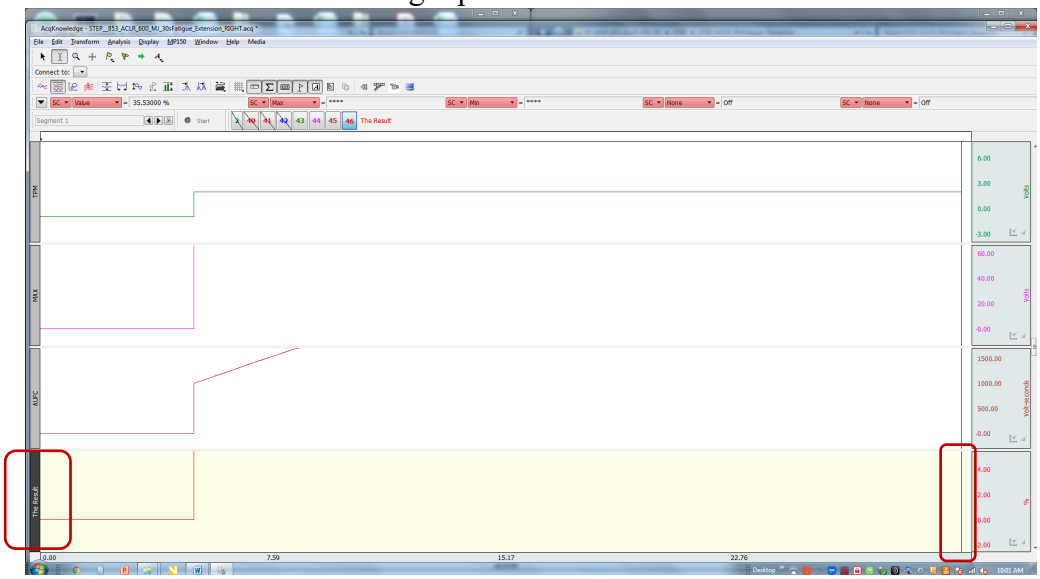
c. Highlight the “MAX” tab on the y-axis and select “Value” for “SC”



d. Enter value into the LEAP report

e. Select the “Result” tab on the y-axis.

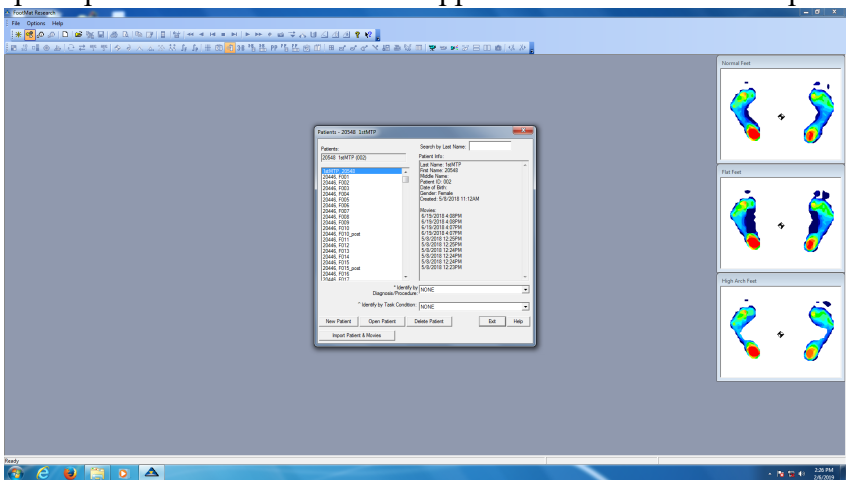
f. Move the curser to the most right point of the trial.



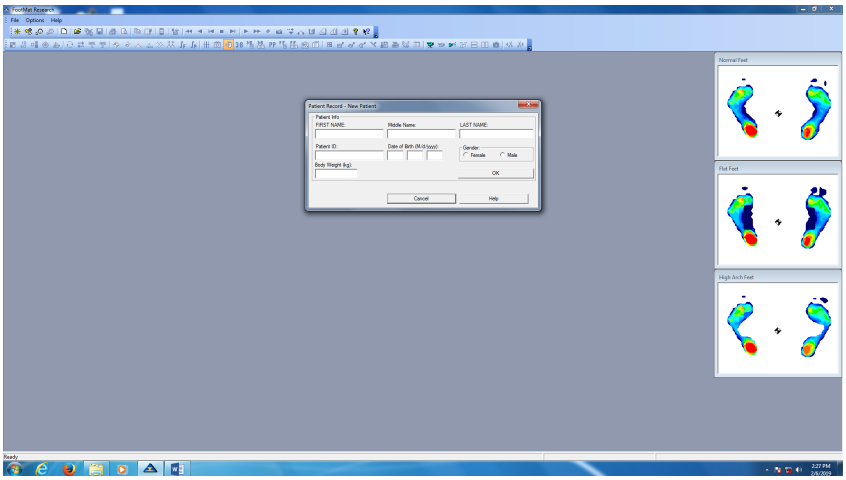
g. Enter value into the LEAP report

Table C1.1.g: Single-Leg Balance Setup and Procedures

1. Equipment Setup
    a. Turn on Balance Computer
    b. Plug in both USB cables from the TekScan into the computer
    c. Open up FootMat Research 7.10 Application on Balance Computer

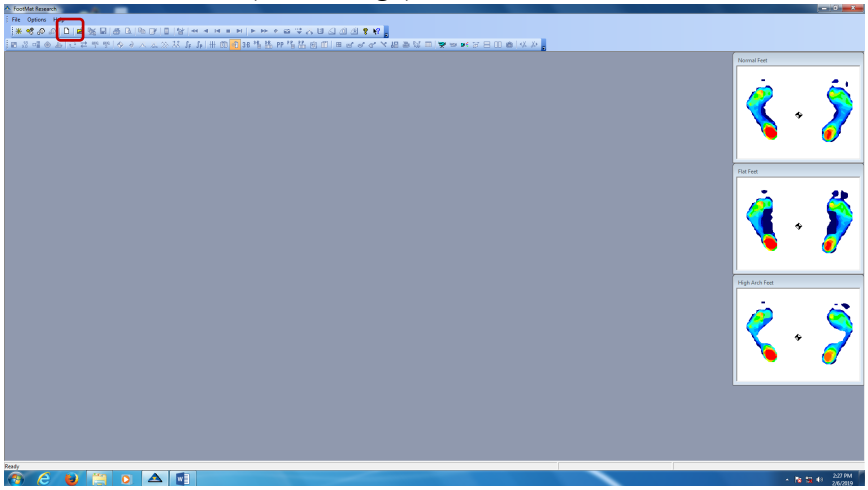


d. Select New Patient

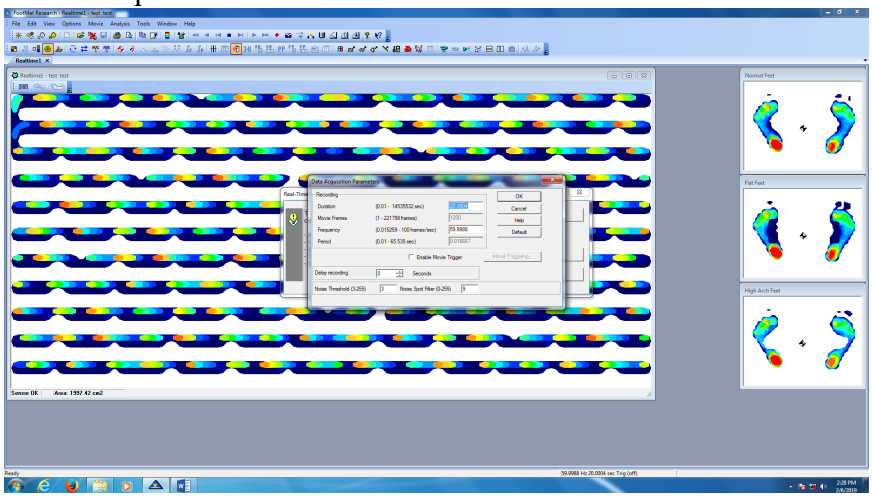


i. Insert patient demographics
ii. Select OK

e. Select New Movie (White Page)

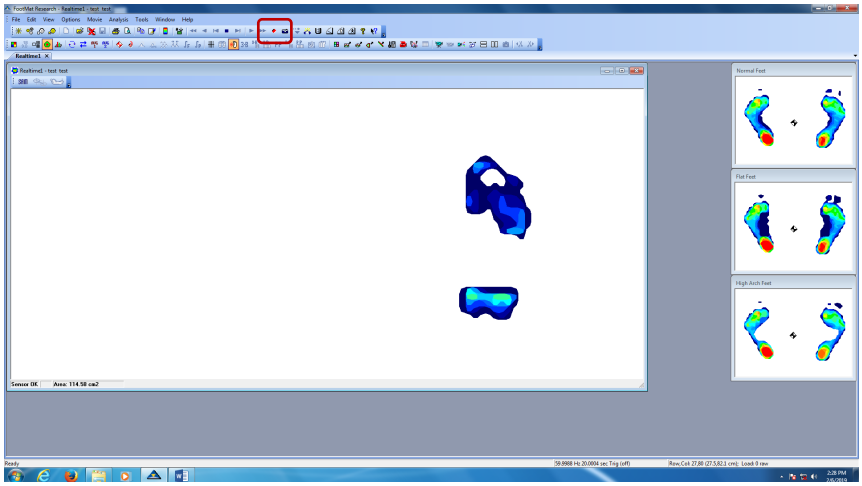


f. Select Acquisition Parameters



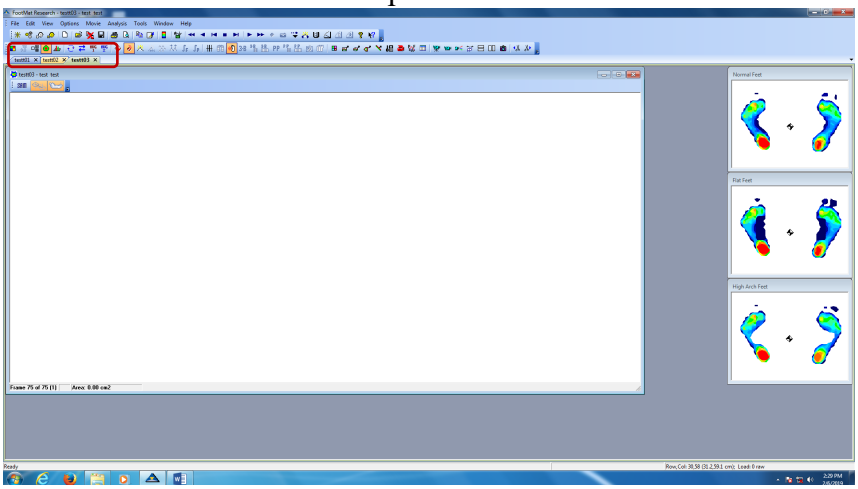
i. Trial Length: 20 seconds
ii. Frequency: 60 Hz
iii. Select OK

g. Place Tekscan Mat on a hard surface
h. Have the patient stand on the mat in proper position
i. Select red record button to start the collection



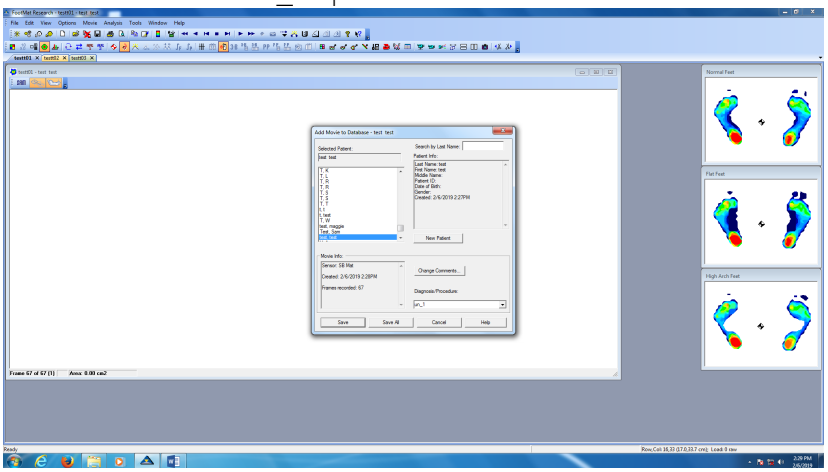
j. After each trial, select the white paper icon for a new trial window
k. Repeat steps 1g – 1i for the contralateral limb

2. Patient Preparation
    a. Identify the patient's uninvolved limb
    b. Have the patient stand on the mat with their test limb while placing the non-test limb's toe on the ground to stabilize
    c. Using a plastic goniometer, place the knee in 30 degrees of flexion
        i. Axis of rotation: Lateral Epicondyle
        ii. Proximal landmark: greater trochanter of the femur
        iii. Distal landmark: lateral malleolus
    d. Instruct the patient to place hands on hips
    e. Instruct the patient to look straight ahead and to pick up the non-test limb when ready
    f. Start trial
3. Data Acquisition
    a. Four Trial windows should be present within the FootMat Research Application

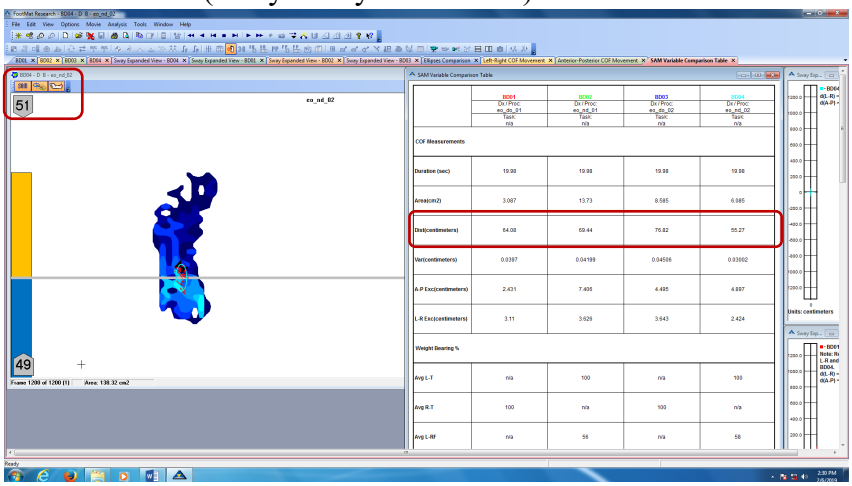


    b. Select the first trial window and press *control + s*

i. Label trial “Un_1” | Save



c. Select the second trial window and press *control + s*
   i. Label trial “Inv_1” | Save
d. Select the third trial window and press *control + s*
   i. Label trial “Un_2” | Save
e. Select the forth trial window and press *control + s*
   i. Label trial “Inv_2” | Save
f. Select the SAM (Sway Analysis Measure) Icon



g. Record the COP distance on the Data Collection Form for each trial
h. Close all windows

Figure C1.1.h: Rehabilitation Log

Exercise and Sports Injury Lab
Rehabilitation Log

Please document all activity that is completed with the goal of rehabilitating your knee.
Do not include exercise that takes part in activities of daily living.

Date	Setting	Type of Exercise		Duration (Minutes)
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	
	☐ Clinic ☐ Home/Gym	☐ Strength ☐ Agility	☐ Cardio ☐ Balance ☐ Other: ____	

Common Exercise Examples:

Strengthening	**Agility**	**Cardio**
Resistance/Weight Training	Sport Specific Exercise	Running
Plyometrics		Biking
Lunges, Squats, etc.		

1. Provide the rehabilitation log to the patient and inform them of the purpose
2. All therapy sessions performed for post-ACLR treatment should be administered
    a. For setting, select clinic if the session was observed by a physical therapist or athletic trainer.
    b. For type, have the patient select the type of therapy administered (examples are provided at the bottom of the page)
    c. For duration, provide the length of the TOTAL session (minutes)
3. The protocol should be completed for every session until the next visit (LEAP) approximately 2 months following the STEP

Table C1.1.i: Dismiss the patient for Visit 1

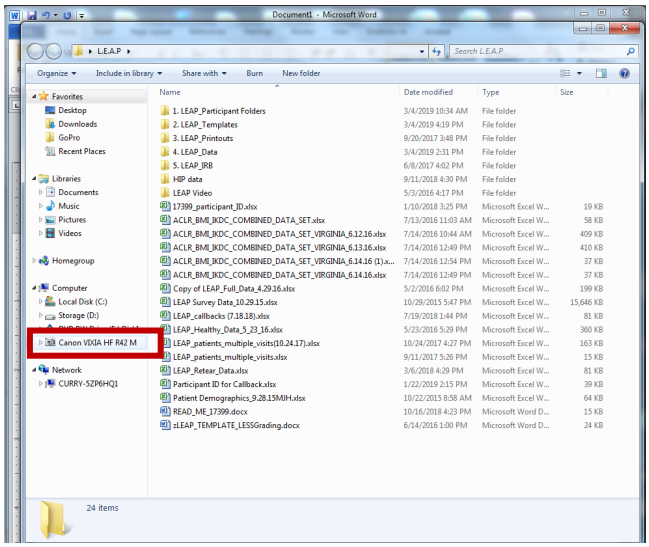
Table C1.2: Attend Visit 2 (V2) at Memorial Gymnasium, Room 224A.

Lower Extremity Assessment Protocol (Patient should be referred within 5-7 months following ACL-Reconstruction)

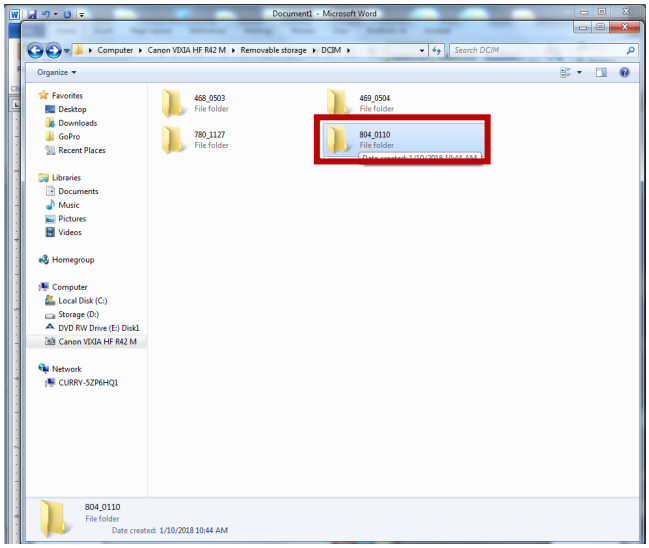
1. Collect Rehabilitation Log from the patient
2. Repeat Steps **C1.1.c through C1.1.g** to assess the following
    a. Obtain anthropometric measures and patient demographics
        i. Take patient's body weight (lbs)
        ii. Take patient's body height (m)
    b. Complete patient reported outcomes
    c. Assess quadriceps and hamstring isokinetic torque
    d. Assess quadriceps and hamstring fatigue index
    e. Assess single-leg balance

Table C1.2.g: Landing Error Scoring System

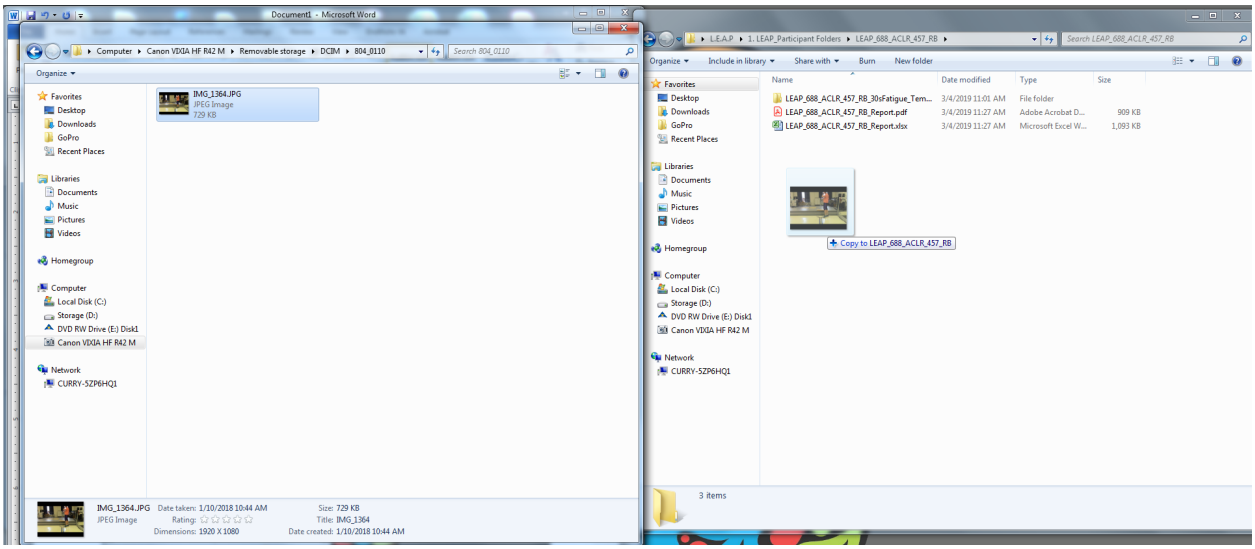
1. Camera Set-up and patient instruction
    a. Place cameras 3 m from the jump platform in the frontal and sagittal plane
    b. Educate the patient on the task
        i. Obtain patient's height from demographics and health history form
        ii. Tell the patient to jump out with both feet at the same time and to aim for their toes to land at the instructed line (Line should approximately match the patient's height)
        iii. Upon landing, instruct the patient to jump up as high as they can while landing back in the same spot
        iv. Have the patient perform as many practice trials until they feel comfortable with the task
    c. Start recording
    d. Have the patient complete three trials
    e. Stop recording
2. Data Preparation
    a. Plug the camera into the standing computer through the micro-USB hub
    b. Press "play" on the camera
    c. Open the camera's files through any desktop folder



d. Select “Removable Storage”
e. Select “DCIM”
f. Select the <u>last folder</u>

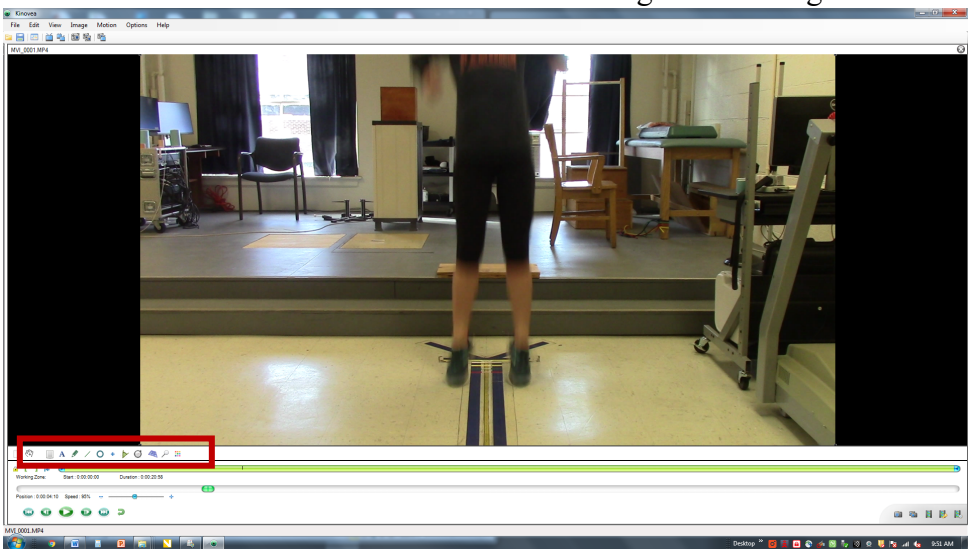


g. Drag the file to the patient’s folder



h. Perform steps **C1.2.g.2.a though C1.2.g.2.f** with the other camera

3. Data Processing
    a. Load data from the patient's LEAP folder
    b. Find the correct time of video for scoring (i.e. initial contact)
        i. Use the *space bar* to start and stop the video
        ii. Use the *right arrow* to progress by a dingle frame
        iii. Use tools on tool bar to reference straight line or angle tool



c. Score the trial by placing a "1" or "0" in the Excel LEAP File
d. Repeat steps **C1.2.g.3.a through C1.2.g.3.c** for each trial

Table C1.2.h: Single-Leg Hopping Setup and Procedures

1. Clean the floor and let dry prior testing
2. Single Hop
    a. Have the patient stand behind the "Start" line on the testing foot
    b. Instruct the patient to "jump as far as possible while maintaining the landing on the tested limb"

i. If the contralateral limb touches down, or the testing limb does not stick a firm landing – then the trial is performed again

c. Record the distance from the heel of the test foot in cm

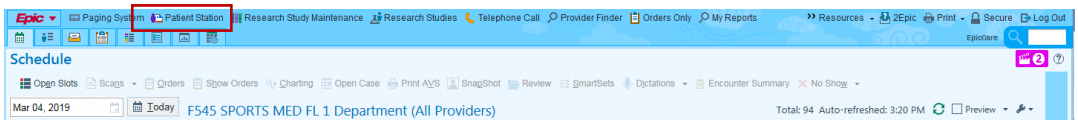
d. Perform 3 Trials (a-c) on each limb, starting on the uninvolved limb and alternating limbs between each trial

3. Triple Hop
    a. Have the patient stand behind the "Start" line on the testing foot
    b. Instruct the patient to "jump as far as possible in three consecutive jumps while maintaining the landing on the tested limb"
        i. If the contralateral limb touches down, or the testing limb does not stick a firm landing – then the trial is performed again
    c. Record the distance from the heel of the test foot in cm
    d. Perform 3 Trials (a-c) on each limb, starting on the uninvolved limb and alternating limbs between each trial
4. 6-m Timed Hop
    a. Set up Fit-Light Timers
        i. Take sensors (lights) 1 & 2 and secure them on the standing poles 50 cm above the ground
        ii. Turn on Android *Fitlight* Tablet
        iii. Select the *Fitlight* Application
        iv. Allow time for the tablet to recognize both sensors (lights)
        v. Select Performance & Training
        vi. Select Split Time trial
        vii. Select Start
    b. Have the patient stand behind the "Start" line on the testing foot
    c. Instruct the patient to "jump as fast as possible until the testing foot crosses the 6-meter line"
    d. Perform 3 Trials (b-c) on each limb, starting on the uninvolved limb and alternating limbs between each trial
    e. Measure leg length of the patient from the Anterior Superior Iliac Spine to the

Table C1.2.i: Dismiss subject from Visit 2 (LEAP)

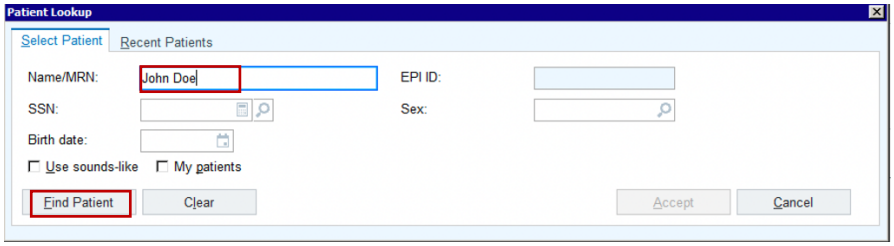
Table C1.2.j: Patient Chart Review

1. Log onto Epic
2. Search Patient



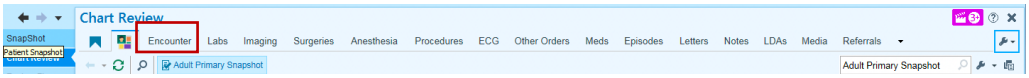
    a. Select patient station
    b. Search subjects name

i. Press “Select”



c. Select “Chart Review”

d. Select “Encounter”



3. Review Medical History
   a. Initial ACLR Documentation
      i. Find “Procedure Visit” of the ACLR
      ii. Select “Op/Procedural notes”
   b. Follow-up Documentation
      i. Find the “Office Visit” occurring subsequently to the “Procedural Visit”
      ii. Review Documentation for patient notes
   c. Prior Medical History
      i. Review patient’s chart to assure that the patient did not have prior history of lower extremity surgery or history of lower extremity injuries within 6-months of ACLR

Figure C1.2.k: Patient Call-Back Script

1. Obtain the patients phone number from EPIC (step **C1.2.e**)
2. Call patient and read the following script

LEAP Follow-up Appointment Scheduling Telephone Script

Hello (subject name),
My name is Katie Carr, and I'm an employee of the Exercise and Sport Injury Lab here at UVA. We previously performed a Lower Extremity Assessment (or LEAP) with you for Dr. _____ following your ACL Reconstruction. It's been about (time period) *since your last visit with us and I'm calling you (and your child) to see if you would be willing to come in and do a follow up appointment. This is a free assessment that would inform you about your knee function following your surgery and would take about an hour of your time. If you're interested in doing this, please call me at 434-924-6184.*

Is this something you would be interested in doing?

- YES → schedule day/time according to lab and personnel availability (if nights/weekends, schedule and follow-up with confirmation email within 24 hours)
  - Perform LEAP test/questionnaires on scheduled day/time
  - Deliver LEAP Follow-up Questionnaire
- NO → *That's okay, I understand. Would you be willing to complete a few questionnaires?*
  - YES → *Would you like to answer the questionnaires via email or in writing?*
    - EMAIL → send email-able forms of 1) LEAP Follow-up Questionnaire and 2) LEAP questionnaires directly to patient's personal email
    - MAIL → send hard copies of 1) LEAP Follow-up Questionnaire and 2) LEAP questionnaires directly to patient's provided address
    - NEITHER (PHONE) → ask 1) follow-up questions (below) over the phone
  - NO → *Is there a better time to contact you?*

Thank you for taking the time to answer these questions! Do you have any questions for me?

Would you mind confirming your first and last name, home address, email, and cell phone number if any issues arise?

Thank you again for your time, and I hope you have a great day!

Follow-up Questions

1) What type of activity/sport were you participating in before your injury?
2) Did you return to your pre-injury level of activity/sport? When? Did you feel ready to return to your pre-injury activity/sport at time of discharge from physical therapy?
3) What date did your knee feel 100%?
4) What is your current level of participation in activity/ sport?
5) How much activity (and what type) are you involved with each week?
6) Have you experienced any pain in the knee since completing the research study/return to activity?
7) Have you re-injured your previously tested knee or your other knee since your surgery? If so, when?
8) Have you had any additional lower extremity injuries since completing the study? (ankle sprains, etc.) If so, when? Did you have any surgeries to treat those injuries?
9) Did you go back to physical therapy or look for follow up care for your original injury at any point after completing the study? (yes: describe treatment and list reason for return)
10) Are you currently doing regular exercise for your knee? If so, how many days per week?
11) Have you experienced any problems completing certain activities over the past (time frame) from your injury?
12) Are you satisfied with your surgery?
13) On a scale of 1-100, how would you currently rate the global function of your knee?
14) If you were to go back and go through this process again, would you elect to have ACL-reconstruction?

Potential Questions from Patients (And Answers):

-Why is this important?
→We see a pretty steady trend of young people experiencing unexpected declines in strength that are subtle at first. Your strength might be slightly less than you can feel or would expect.
→Longitudinal care can help address concerns with knee re-injury and deteriorating strength.

-Why should I come back?
→When you signed your consent form, it gave info on being able to come in again.
→Longitudinal care helps address concerns with knee re-injury and deteriorating strength.
→This re-evaluation can give you a good idea of where you are. We can talk to your doctor or physical therapist following your evaluation for further steps.
→We can schedule around your commitments. If you need a weekend/night appointment, I can set that up and email you with confirmation in the next 24 hours.

-Are you going to do rehab on me?
→We are not a physical therapy clinic, but we can talk about potential exercises, present research studies, etc. relating to your injury.
→Feel free to talk to your evaluator about these things.

-I feel fine, so why should I come?
→This is a free opportunity to evaluate where you really are physically.
→We see a pretty steady trend of young people experiencing unexpected declines in strength that are subtle at first. Your strength might be slightly less than you can feel or would expect.
→Besides, getting a clean bill of health is always a good thing (especially when it's free). We will even validate your parking, so it truly costs you nothing.

3. Administer the follow-up questionnaire via phone to the patient

Attend Visit 3 (V3) at Memorial Gymnasium, Room 224A

a. Assess active motor threshold and Motor Recruitment Curve
b. Reveal Treatment Randomization
c. Perform Sub-maximal visuomotor therapy OR Sham
d. Assess active motor threshold
e. Assess recruitment curve
f. Assess quadriceps and hamstring isokinetic Torque
g. Assess quadriceps and hamstring MVIC and Fatigue index
h. Assess M-wave reflex
i. Dismiss subject for Visit 3

Table C1.3.a: Assess Active Motor Threshold (AMT) and Motor Response Curve

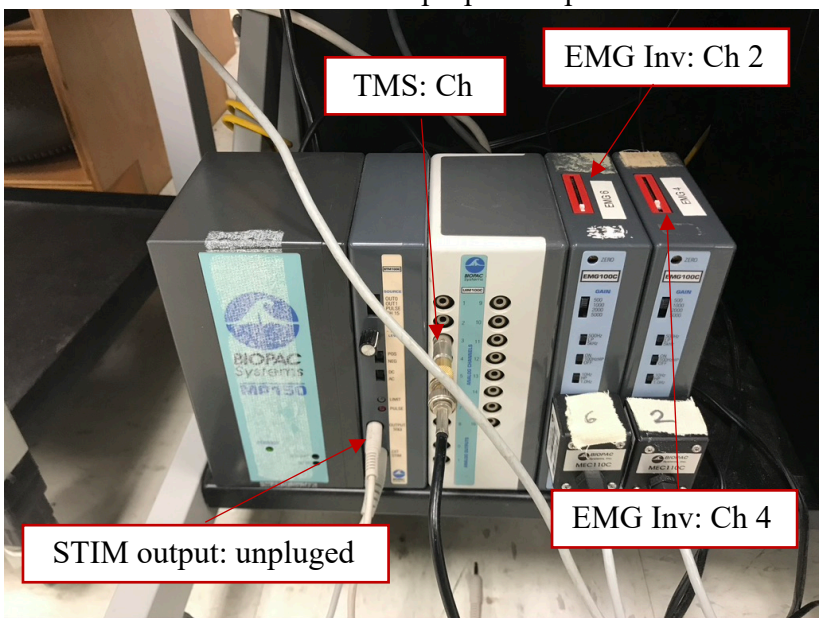
1. Biopac System Setup
    a. Connect an UIM100C and EMG100C to the MP150 unit
    b. Connect the MP150 to the computer using a LAN wire
    c. Turn on the MP150 unit and the computer
    d. EMG100C settings
        i. Gain: 1000
        ii. Filter: Off
        iii. LP: 5 kHz
        iv. HP: 1.0 Hz

2. Magstim Rapid Setup
    a. Insert the footswitch connector in the “Foot Switch” port on the back of the Magstim device
    b. Insert the Magstim output cable to the “Trigger Out” port on the back of the Magstim device, and to channel 3 of the UIM100C (Biopac Attachment)
    c. Connect the output cable of the Booster Module Plus to the front of the Booster Module device and back of the Magstim device
    d. Connect the stimulating coil to the Magstim device using the port on the front of the machine
    e. Turn the main power switch located on the front of the Booster Module device to the ON position
    f. Turn the Magstim device on using the ON/OFF button on the front panel
        i. The Unit Power Status Indicator should remain lit throughout the testing session
    g. Press the green RUN button to charge the unit and illuminate the ready indicator

3. AcqKnowledge Setup (TMS_Output_Template)
    a. Open AcqKnowledge 4.2.0 for Mac and select the attached MP150 unit (Laptop used for this)
    b. MP150| Setup Channels| Analog menu
        i. Channel 1
            1. Sample Rate = 125 Hz
            2. Label = Torque
            3. Check all boxes associated with this channel

ii. Channel 2
    1. Sample Rate = 2000 Hz
    2. Label = MEP_involved
    3. Check all boxes associated with this channel
iii. Channel 3
    1. Sample Rate = 125 Hz
    2. Label = TMS
    3. Check all boxes associated with this channel
iv. Channel 4
    1. Sample Rate = 2000 Hz
    2. Label = MEP_Contralateral
    3. Check all boxes associated with this channel

c. MP150| Set Up Acquisition
    i. Change menus to "Record" and "Append"
    ii. Sample Rate = 2000 Hz
    iii. Acquisition Length = 80 msec
d. Open the data journal and graph window
e. Click the start button to confirm proper setup



4. AcqKnowledge 4.2.0 Setup (Torque_Response_Template)
    a. Open AcqKnowledge 4.2.0 for Windows and select the attached MP150 unit
    b. MP150| Setup Channels| Analog menu
        i. Channel 2
            1. Sample Rate = 200 Hz
            2. Label = Force
            3. Check all boxes associated with this channel
    c. MP150| Setup Channels| Calculation menu
        i. Channel 0
            1. Label = C0 – Expression
            2. Preset = Expression
            3. Sample Rate = 200 Hz

ii. Setup (C0 – Expression) 1. Preset = None
    1. Label = C0 – Expression
    2. Evaluate Expression = <<Insert voltage = 5% MVIC>>
    3. Sources = A2, Force
    4. Functions = ABS()
    5. Operators = +
iii. Setup (C1 – Math) 1. Preset = None
    1. Label = C1 – Math
    2. Source 1 = A2, Force
    3. Operation = a
    4. Source 2 = K, Constant
    5. Constant = 0.05

d. MP150| Set Up Acquisition
    i. Change menus to "Record" and "Append"
    ii. Sample Rate = 200 Hz
    iii. Acquisition Length = 10 min
e. Open the data journal and graph window
f. Click the start button to confirm proper setup

5. Subject Preparation (Figure C6)
    a. Identify the vastus medialis during isometric knee extension
        i. Shave the area
        ii. Debride with an abrasive pad
        iii. Clean with isopropyl alcohol
    b. Place 2 EMG electrodes in the prepared area
        i. Parallel to the muscle fiber orientation
        ii. Interelectrode distance of 2 cm
    c. Identify an area on the distal anteromedial tibia for the ground electrode
        i. Shave the area
        ii. Debride with an abrasive pad
        iii. Clean with isopropyl alcohol
    d. Place 1 EMG electrode in the prepared area
    e. Perform steps **C1.5.a through C1.5.d** for the contralateral limb
    f. Position the subject in the dynamometer chair in an upright seated posture
        i. Knees flexed to 90 degrees
        ii. Restrain the subject using the lap strap
        iii. Secure the ankle strap 2 cm proximal to the lateral malleolus
    g. Attach the leads from the EMG100C unit to the active and reference electrodes
        i. Proximal active = Red lead
        ii. Distal active = White lead
        iii. Reference = Black lead
    h. Place a new, clean nylon swim-cap on the subject's head
        i. Mark with two perpendicular lines from left tragi to right tragi
        ii. External occipital protuberance to midline near the midline
    i. Provide earplugs for the subject to be worn throughout testing
    j. Ask the subject to relax, breathe normally, fold hands in lap, and keep head back against the headrest.

k. Ask the subject to "kick" to a red line, indicating 5% MVIC, then to relax the leg after the stimulus is delivered

6. Data Collection
    a. Active Motor Threshold (AMT) Collection
        ii. Position the stimulating coil over the contralateral homunculus of the testing limb near the central sulcus
        iii. Set the Magstim output to 60%
        iv. Click the START button within the Acqknowledge software (on each computer)
        v. Depress the Magstim footswitch
        vi. Press and hold the trigger on the stimulating coil
        vii. Review the data for motor response in the EMG (MEP) channel
        viii. If positive for motor response:
            1. Record MEP amplitude in journal
            2. Repeat stimulus in radius around this point
            3. Move the stimulator in the frontal and sagittal plane until the maximum MEP amplitude has been found, and a 1-cm radius around this point has been assessed. This location is termed the "Hot Spot".
            4. Decease the stimulation intensity by 5%, and re-stimulate
            5. When no response is observed, increase the stimulation intensity by 1% and repeat stimulus until MEP is detected
            6. Wait at least 10 seconds between stimulations
        ix. If negative for motor response:
            1. Re-position and repeat at same stimulus intensity
            2. Continue until 1-cm radius has been stimulated
            3. If no response, increase stimulus intensity by 5%, and re-stimulate
        x. Continue to decrease the stimulus intensity until MEP is measured
            1. Once confirmed, deliver 10 stimulations
            2. If positive for MEP in at least 50% of trials, end testing
            3. If negative for MEP in at least 60% of trials, increase stimulus intensity 1% and test again.
    b. Motor Reponses (Recruitment) Curve Collection
        xi. Position the TMS coil above the "Hot Spot" location found in Step C1.6.a.vii.3
        xii. Adjust the stimulation intensity 80% of the AMT found in Step C9.6.a
            1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial
        xiii. Adjust the stimulation intensity 90% of the AMT found in Step C9.6.a
            1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial
        xiv. Adjust the stimulation intensity 100% of the AMT found in Step C9.6.a
            1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial
        xv. Adjust the stimulation intensity 110% of the AMT found in Step C9.6.a

1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial

xvi. Adjust the stimulation intensity 120% of the AMT found in Step C9.6.a
1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial

xvii. Adjust the stimulation intensity 130% of the AMT found in Step C9.6.a
1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial

xviii. Adjust the stimulation intensity 140% of the AMT found in Step C9.6.a
1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial

xix. Adjust the stimulation intensity 150% of the AMT found in Step C9.6.a
1. Provide 5 stimulation at this intensity and record the Motor Output in the Journal for each trial

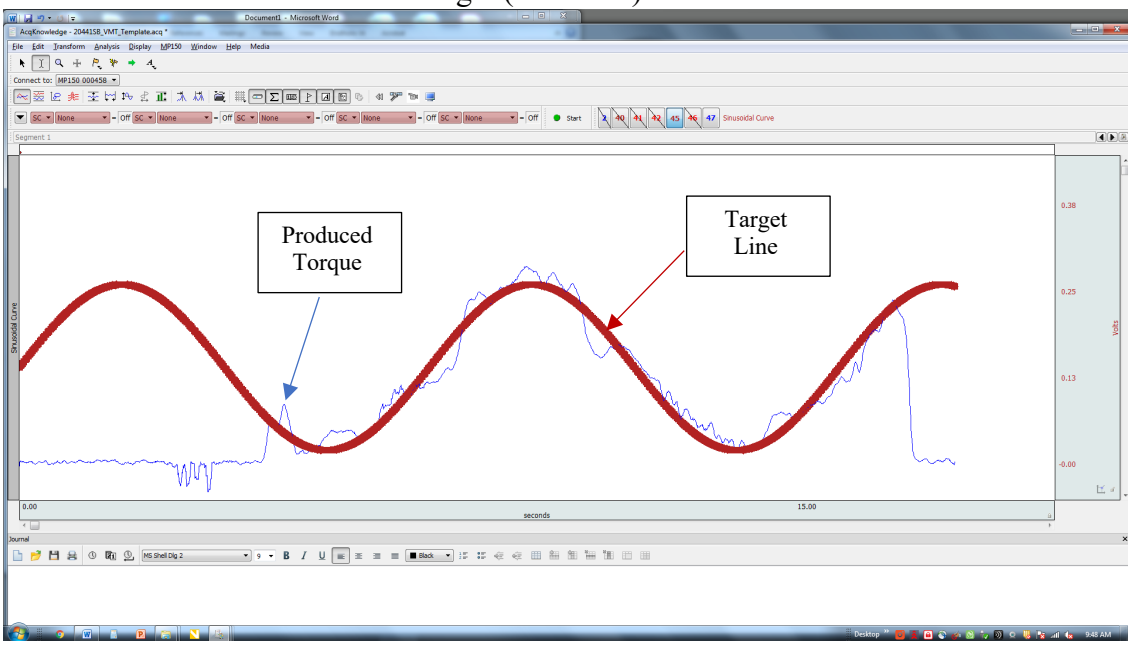
7. Data Processing
   g. During testing, record the peak-to-peak amplitude (P-P), time from stimulus artifact to onset of MEP (delta T), and time for each MEP in the journal of AcqKnowledge – coordinates should be documented when searching for the ideal coil position, or "hotspot," during subsequent testing
   h. Record the active motor threshold (AMT) as the intensity required for 50% success during 10 consecutive trials
   i. Record P-P, Delta T, and time for MEPs detected at 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150% MEP
      i. Record the stimulus intensity at each percentage
      ii. Record a minimum of five acceptable trials

Table C1.3.b: Treatment Randomization

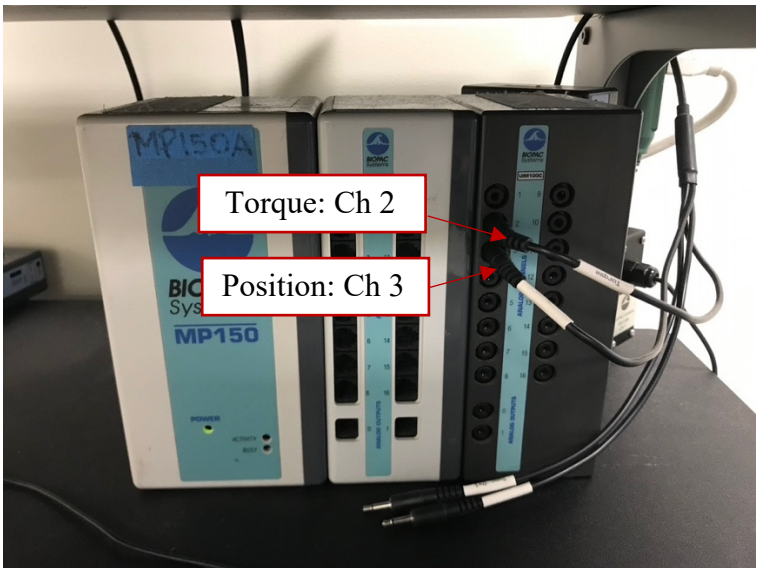
1. Pre-Study Randomization Scheme
   a. 4-block design made by study investigator by associated with treatment administration or data collection
      i. Possible randomizations: aabb, abba, abab, bbaa, baab, baba
      ii. 10 total blocks
   b. Place randomized treatments in opaque sealed envelopes
2. Patient Randomization
   a. During Visit 3, the unblinded researcher will open the next available randomization envelope revealing the treatment to be administered during Visit 3
      i. Visuomotor Therapy
      ii. Sham Therapy
   b. Unblinded researcher will replace blinded researcher in the lab to administer the assigned therapy
   c. The randomization card will be placed back into the envelope and within the subject's study folder

Table C1.3.c: Perform Assigned Therapy

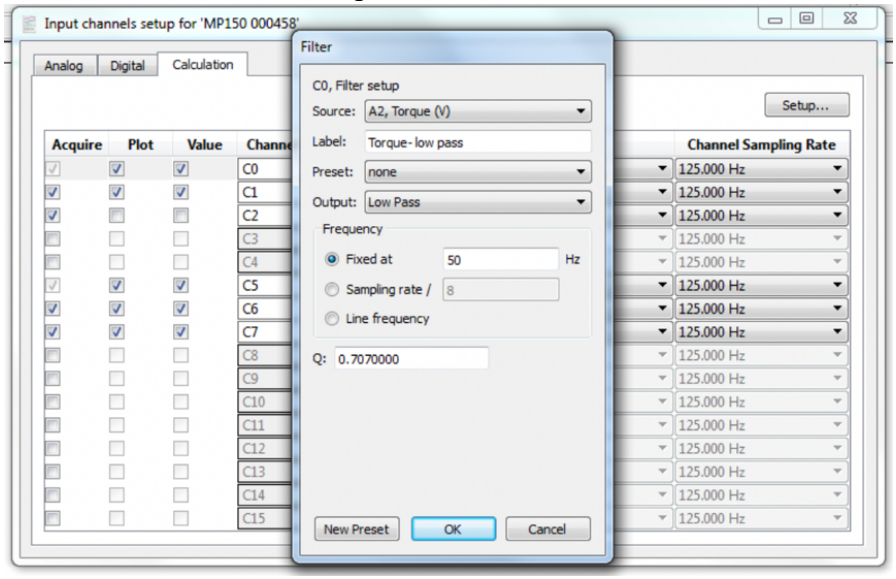
1. Visuomotor Therapy
    a. Biodex System Setup
        i. Position the Patient in the Biodex Chair
            1. Move the back of the chair so that ~5 cm of the patient's thigh overhang the edge of the chair
            2. Move chair forward/backward so that the lateral epicondyle aligns with the axis of rotation of the Biodex
            3. Move chair up/down so that the lateral epicondyle aligns with the axis of rotation of the Biodex
        ii. Flex patient's knees to 90 degrees
        iii. Restrain the patient with the lap belt
        iv. Strap distal shank (2 cm above lateral malleolus) to Biodex attachment
        v. Provide instructions for proper testing procedures
            1. "Sit up straight with your back against the backrest"
            2. "Do not rotate or arch or back"
            3. "Cross your hands across your chest for the duration of testing"
            4. "Focus on kicking out to match your produced torque (Blue Line) to the Target (Red Line)"



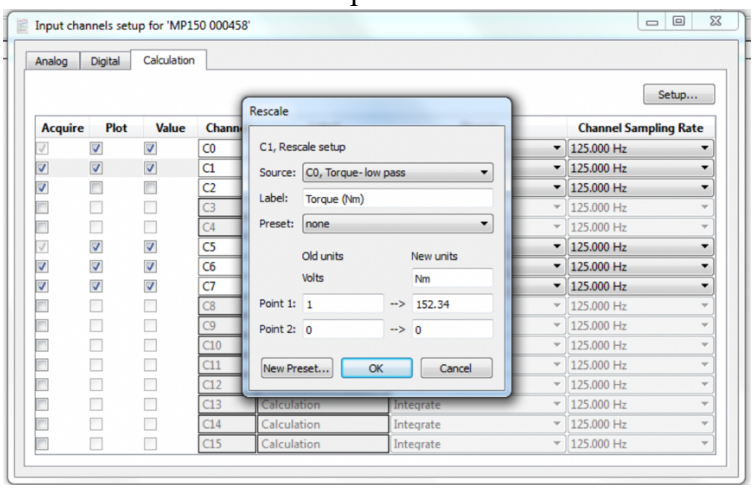
    b. Biopac System Setup
        i. Insert "Torque" input (from Biodex Tower) into Channel 2
        ii. Insert "Position" input (from Biodex Tower) into Channel 3
        iii. Assure that the MP150 is connected to the standing computer via ethernet cable



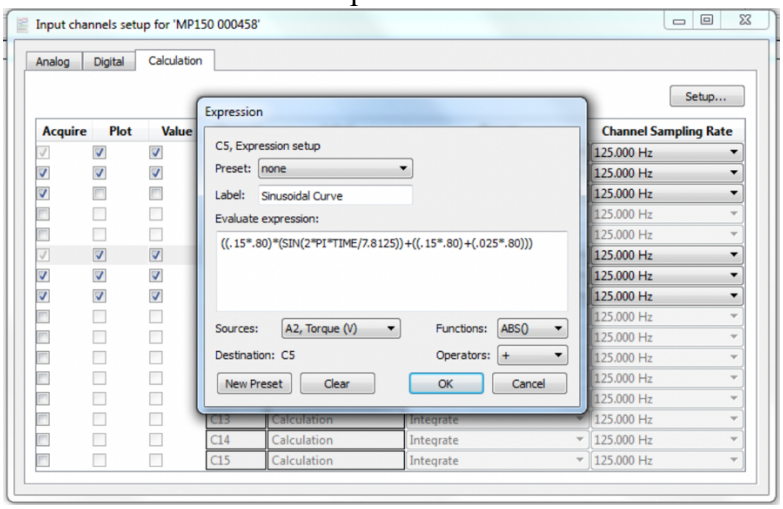
c. AcqKnowledge Setup (20441_VMT)
    i. Open AcqKnowledge 4.2.0 for Windows and select the attached MP150 unit
    ii. MP150|Setup Channels|Analog Menu
        1. Channel 2
            a. Sample Rate = 200 Hz
            b. Label = “Force”
            c. Check all boxes associated with this channel
    iii. MP150|Setup Channels|Calculation Menu
        1. Channel C0
            a. Sampling rate = 125 Hz
            b. Label = “Torque – Low Pass”
            c. Check all boxes associated with this channel
            d. Preset = Filter
            e. Select “Setup”. Follow Screenshot Below:



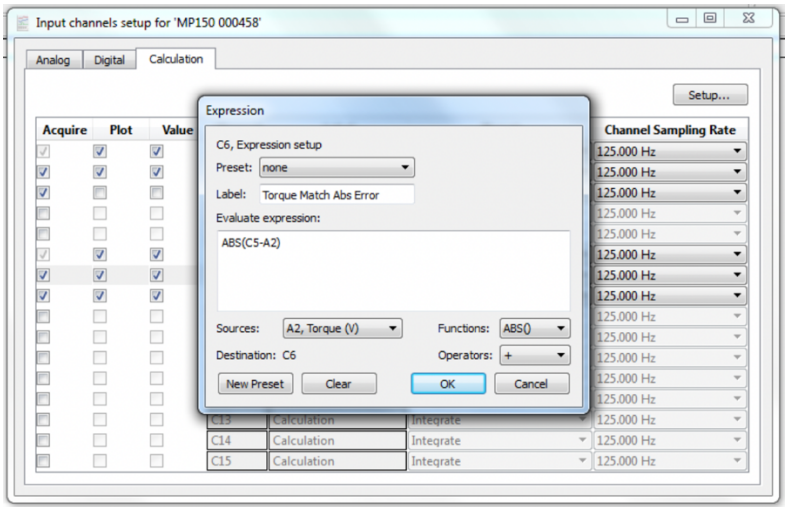
1. Channel C1
    a. Sampling rate = 125 Hz
    b. Label = “Torque (Nm)”
    c. Check all boxes associated with this channel
    d. Preset = Rescale
    e. Select “Setup”. Follow screenshot below:



2. Channel C5
    a. Sampling Rate = 125 Hz
    b. Label = “Target Line”
    c. Check all boxes associated with this channel
    d. Preset = Expression
    e. Select “Setup”. Follow Screenshot below:

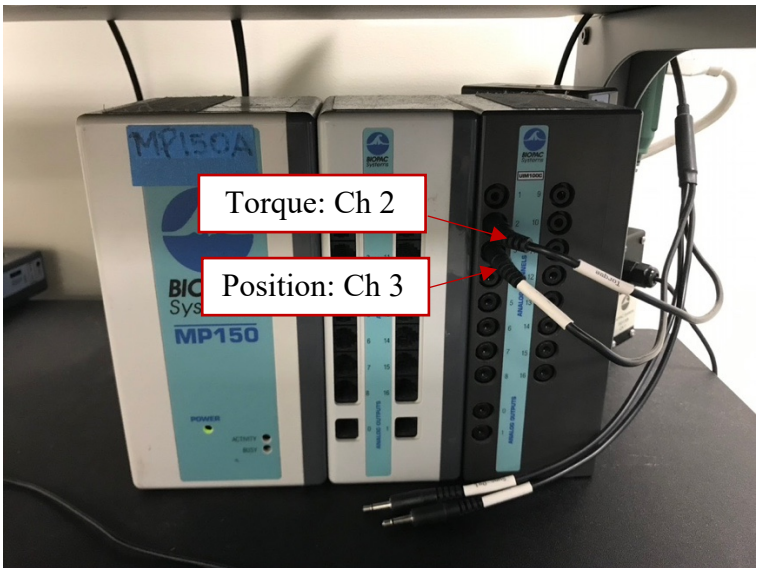


3. Channel C6
    a. Sampling Rate = 125 Hz
    b. Label = “Torque Match Abs. Error”
    c. Check all boxes associated with this error
    d. Preset = Expression
    e. Select “Setup”. Follow Screenshot below:

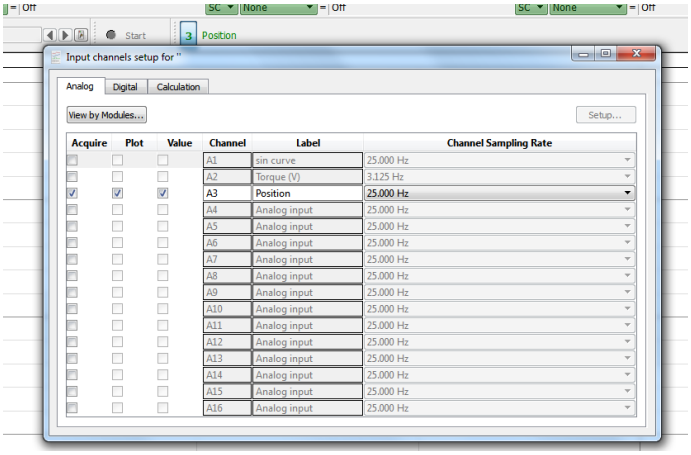


f. Data Collection

2. Sham Therapy
    a. Biodex System Setup
        i. Position the Patient in the Biodex Chair
            1. Move the back of the chair so that ~5 cm of the patient's thigh overhang the edge of the chair
            2. Move chair forward/backward so that the lateral epicondyle aligns with the axis of rotation of the Biodex
            3. Move chair up/down so that the lateral epicondyle aligns with the axis of rotation of the Biodex
        ii. Flex patient's knees to 90 degrees
        iii. Restrain the patient with the lap belt
        iv. Strap distal shank (2 cm above lateral malleolus) to Biodex attachment
        v. Provide instructions for proper testing procedures
            1. "Sit up straight with your back against the backrest"
            2. "Do not rotate or arch or back"
            3. "Cross your hands across your chest for the duration of testing"
            4. "Relax your limb and let the attachment move your limb through the duration of testing."
    b. Biopac System Setup
        i. Insert "Torque" input (from Biodex Tower) into Channel 2
        ii. Insert "Position" input (from Biodex Tower) into Channel 3
        iii. Assure that the MP150 is connected to the standing computer via ethernet cable



c. AcqKnowledge Setup (20441_VMT)
    i. Open AcqKnowledge 4.2.0 for Windows and select the attached MP150 unit
    ii. MP150|Setup Channels|Analog Menu
        2. Channel 3
            a. Sample Rate = 25 Hz
            b. Label = "Position"
            c. Check all boxes associated with this channel



d. Data Collection
    i. Biodex Computer and Application
        1. Open up Biodex application on the Biodex Computer (Left corner of Lab)
        2. Sect "Patient"
            a. Type in patient's last name
        3. Select "Protocol"→ Open
            a. Select Passive Unilateral → Knee
            b. Select "(20441)"
            c. Select *involved (right/left)* limb
            d. Clear limits

e. Set Towards at 80 degrees
f. Set Away at 120 degrees
g. Set reference at 90 degrees
h. Take limb weight

4. Educate the patient on the task
    a. Your knee is going to move in a short range of motion for 60 seconds. I want you to relax your limb and let the Biodex move it. Do not exert any force during the trial. After the 60 seconds, you will get a 30 second break. We will do this for 10 trials."
5. Press "Start"
6. Press "Hold/resume" button on the dynamometer
7. Quietly stand with patient during collection

ii. Acqknowledge (Visual Feedback Computer)
1. Open Patient's "Passive.Acq" file
2. Select "Start"

iii. At the end of the 15 minute session, exit out of all applications and notify the blinded researcher

Table C1.3.d: Post-Treatment Assess Active Motor Threshold (AMT) and Motor Response Curve

1. Biopac System Setup
    a. Repeat **Table C1.3.a.1 through C1.3.a.5**

2. Data Collection
    a. Active Motor Threshold (AMT) Collection
        i. Position the stimulating coil over previously established "Hot Spot"
        ii. Set the Magstim output to previously established AMT
        iii. Click the START button within the Acqknowledge software (on each computer)
        iv. Depress the Magstim footswitch
        v. Press and hold the trigger on the stimulating coil
        vi. Collect 5 trials with 10 seconds between each stimulation
    b. Motor Reponses (Recruitment) Curve Collection
        i. Repeat steps 2.a.i to 2.a.vi for 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150% of the patients established AMT.
3. Data Processing
    a. During testing, record the peak-to-peak amplitude (P-P), time from stimulus artifact to onset of MEP (delta T), and time for each MEP in the journal of AcqKnowledge – coordinates should be documented when searching for the ideal coil position, or "hotspot," during subsequent testing
    b. Record the active motor threshold (AMT) as the intensity required for 50% success during 10 consecutive trials
    c. Record P-P, Delta T, and time for MEPs detected at 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150% MEP

i. Record the stimulus intensity at each percentage
ii. Record a minimum of five acceptable trials

Table C1.3.e: Assess quadriceps and hamstring isokinetic Torque
a. Repeat **Table C1.1.e**
Table C1.3.f: Assess quadriceps and hamstring MVIC and Fatigue index
a. Repeat **Table C1.2.f**
Table C1.3.g: Dismiss from Visit 3

Attend Visit 4 (V3) at Memorial Gymnasium, Room 224A
a. Assess active motor threshold and motor recruitment curve
b. Perform Cross-over therapy
c. Assess active motor threshold and motor recruitment curve
d. Assess quadriceps and hamstring isokinetic Torque
e. Assess quadriceps and hamstring MVIC and Fatigue index
f. Assess M-wave reflex
g. Dismiss subject from the study

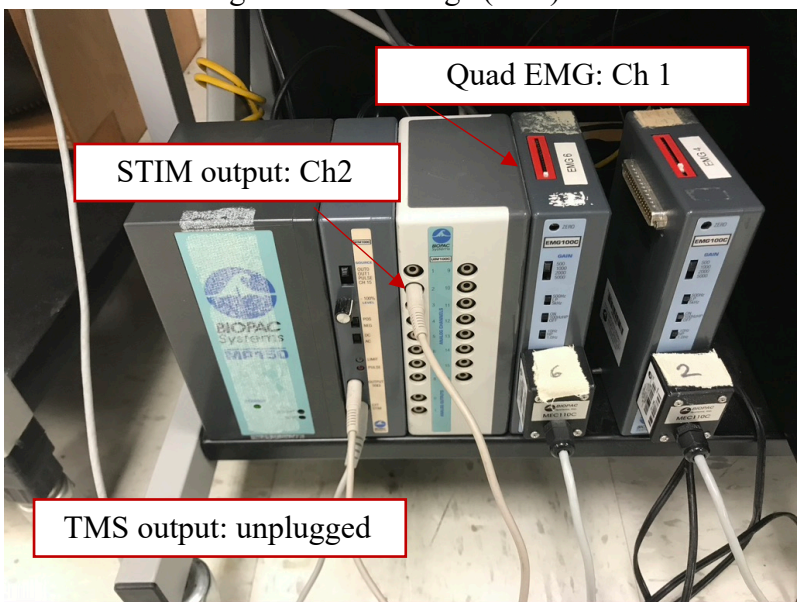
Table C1.4.a: Assess Active motor Threshold and Motor Recruitment Curve
1. Repeat Table **C1.3.a**
Table C1.4.b: Perform Cross Over Therapy
1. Only the blinded researcher should administer the assigned therapy
2. If the patient received the Visuomotor Therapy in Visit 3 (**Table C1.3.b**)
    a. Administer the Sham Therapy
    b. Table C1.3.c.2
3. If the patient received the Sham therapy in Visit 3 (Steps **Table C1.3.b**)
    a. Administer the Sham Therapy
    b. Table C1.3.c.1

Table C1.4.c: Post-Assessment Active Motor Threshold and Motor Recruitment Curve
1. Repeat **Table C1.3.d**
Table C1.4.d: Assess quadriceps and hamstring isokinetic Torque
1. Repeat **Table C1.1.e**
Table C1.4.e: Assess quadriceps and hamstring MVIC and Fatigue index
1. Repeat steps **Table C1.2.f**
Table C1.4.f: Assess M-wave reflex
1. Biopac Setup computer and MP150
    a. Connect the MP150 to the computer (neuro computer) via LAN
    b. Connect the UIM100C, STIM1003 and EMG100C to the MP150 Unit
    c. Connect the STMISOC to the output port of the STM100C
        i. STMISOC Parameters
            1. Source: OUT0
            2. Level: 100%
            3. Polarity: POS
            4. Current: DC
        ii. EMG100C Parameters
            1. Gain: 1000

2. Filter: Off
3. LP: 5 kHz
4. HP: 1.0Hz

iii. STMISOC Parameters

1. Voltage Monitor: 0.5 V
2. Voltage Switch: Voltage (1:10) 200 V Max



2. Subject Preparation
   a. Position the subject supine on the treatment table in reach of the computer
   b. Place a foam roller (half or full) under the patients' knees
   c. Resist knee extension to identify the bulk of the vastus medialis muscle
      i. Shave the area
      ii. Debride with abrasive pad
      iii. Clean with isopropyl alcohol
      iv. Let surface dry
   d. Place two EMG Electrodes on the cleaned surface
      i. Position the electrodes in parallel to muscle fibers
         1. Approximately 50 degrees medially from line intercepting the ASIS to patellar midpoint
      ii. Interelectrode distance: 2.0 cm
   e. Find the contralateral distal medial tibia for the reference/ground electrode
      i. Shave the area
      ii. Debride with abrasive pad
      iii. Clean with isopropyl alcohol
      iv. Let surface dry
      v. Place a single electrode on the cleaned surface
   f. Attach the leads from the EMG100C unit to the EMG electrodes
      i. Red Lead: Proximal Active Electrode
      ii. White Lead: Distal Active Electrode
      iii. Black Lead: Ground/Reference Electrode
   g. Place gel on the stimulating electrode

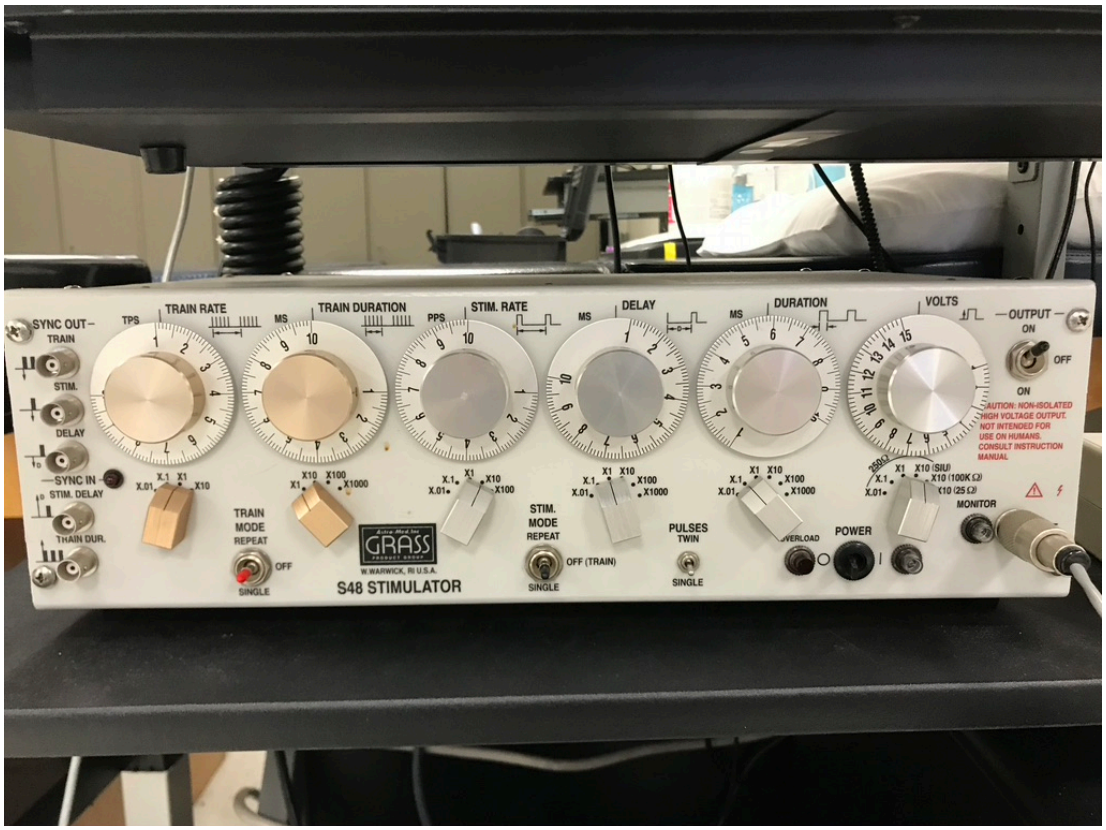
h. Palpate the inguinal fold and identify the femoral artery (pulse)
i. Move slightly laterally to be directly over the femoral nerve
j. Place the stimulating electrode over the femoral nerve
k. Place gel on the dispersive pad and place under the posterior thigh near the gluteal fold
l. Instruct the patient to close their eyes and be as relaxed as possible
m. Close all blinds, turn off all lights, and turn off any unnecessary electronic equipment in the testing room
n. Let subject rest for 5 minutes before beginning the assessment

3. Acknowledge Setup (Neuro Computer)
    a. Make sure all leads are unplugged from the STMISOC unit while manipulating AcqKnowledge parameters
    b. Open AcqKnowledge 4.2.0 for Windows on the "Neuro Computer" and select the attached MP150 unit
    c. Select MP150 | Setup Channels | Analog Menu
        i. Channel 1
            1. Sample Rate: 2000 Hz
            2. Label: Quadriceps
            3. Check all boxes
        ii. Channel 2
            1. Sample Rate: 2000 Hz
            2. Label: Stim
            3. Check all boxes
    d. Select MP150 | Set up acquisition
        i. Change menus to "Record and Append"
        ii. Sample Rate: 2000 Hz
        iii. Acquisition Length: 80 ms
    e. Select MP150 | Set Up stimulator
        i. Select "Square wave" Icon
        ii. Duration: Output once
        iii. Stimulator Sample Rate: 2000 Hz
        iv. Segment 1 Width: 3.0 msec
        v. Segment 2 Width:1.0 msec
        vi. Segment 3 Width: 0.0 msec
        vii. Segment 4 Width:0.0 msec
        viii. Segment 5 Width: 33.5 msec
    f. MP150 | Show Manual Control
        i. Analog Control: Out 1: Drag to 0.0 **(While Stim output is unplugged)**
        ii. Analog Outputs: Out 2: Drag to 0.0 **(While Stim output is unplugged)**
        iii. Open data journal and stimulator window
4. Data Collection
    a. Select the measurement variables to show "P-P" and "Delta T" for Channel 1 or 2
    b. Change the Seg #2 in the Stimulator window to 2.0
    c. Apply the stimulus by clicking "start" or *control+space*
    d. Progressively increase the stimulus intensity by 0.5 V until a measurable M-response is present and the H-reflex diminishes

        i. Save response to journal
    e. Progressively increase the stimulus intensity by 0.5 V until the motor response no longer increases
    f. Conform the maximal M-Wave and complete 3 trials
        i. Save each response to journal
    g. Save data file
5. Data Processing
    a. Open the patients data file
    b. Select | Transform |Digital Filters | FIR | Band Pass
        i. Select Low Frequency Cutoff | Fixed at | 50.5 Hz
        ii. Select High Frequency Cutoff | Fixed at | 60.5 Hz
        iii. Select Number of Coefficients | Optimize for sample rate and cutoff
        iv. Check “Filter Entire Waveform”
    c. Start Processing the trials.

Table C1.4.h: Assess Central Activation Ratio

1. Biodex Set-up
    a. Turn of Biodex System 4
    b. Set limb attachment to 90 degrees
    c. Set the back of the seat at 80 degrees of hip flexion
    d. Connect the “Force” Output Wire from the Biodex to “Channel 2” of the MP150
2. Acqknowledge Set-up
    a. Open AcqKnowledge 4.2.0 and select the attached MP150 unit
    b. Select MP150 | Acquire
        i. Change menus to record and append
        ii. Change sampling rate to 125 Hz
        iii. Change acquisition length to 10000 seconds
    c. Select MP150 | Setup Channels
        i. Click “Analog”
        ii. Label Ch 2 “force”
        iii. Select all boxes with this channel
        iv. Change sampling rate to 125
    d. Select start. Stop recording after each trial.
3. GRASS S48 Stimulator
    a. Stimulator settings
        i. Train Rate: 1.0 TPS
        ii. Train Duration: 10.0 ms
        iii. Stim Rate: 10.0 PPS
        iv. Delay: 1.0 ms
        v. Duration: 0.6 ms
        vi. Volts: Max (for test trials, can provide practice trial at lower intensity)
        vii. Output: On
        viii. Stim Mode: Single



b. Isolation Unit settings (SIU8T)
    i. Constant Voltage: Low
    ii. Polarity: Normal
    iii. Stimulus Intensity: 20
c. Connect wires from SIU8T unit to electrodes when ready for trials

4. Subject Preparation and Instruction
    a. Shave quadriceps at locations of electrodes if needed
    b. Place self-adhesive carbon impregnated electrodes over the proximal vastus lateralis and the distal vastus medialis
    c. Seat patient in the Biodex chair with hip flexed to 80 degrees and knee flexed to 90 degrees
    d. Provide instruction to the patient.
        i. Sit up tall with your back firmly against the back of the chair and your arms crossed across your chest. Throughout the trial, do not lean or twist your back but rather focus on exerting all force through your knee and thigh. I will count down, '3, 2, 1, Kick.' As I count down, I want you to slowly ramp up your force but to make sure you are exerting maximal volitional force when I get to 'kick'. Try to exert your maximal effort for the 30-second trial. You are expected to get tired throughout the trial. Do you have any questions?"
    e. Allow the subject to practice at 25%, 50%, 75%, and 100% of their perceived maximal effort

5. Data Collection
    a. Click the start button in the AcqKnowledge File
    b. Perform practice trial with patient to exert 25%, 50%, 75%, and 100% knee extensor torque
    c. Have the patient perform maximum volitional force trial
    d. Trigger a single stimulation pulse through the GRASS S48 stimulator when the maximal force is reached.
    e. Click the stop button in AcqKnowledge
    f. Perform 2 additional trials
    g. Allow at least 30-seconds between each trial
    h. Save data file

6. Data Processing
    a. Open the data file
    b. Click Transform | Digital Filters | FIR | Low Pass
        i. Frequency cutoff: 10 Hz
        ii. Rate of Coefficients = Optimized for sampling rate and cutoff
        iii. Select Entire waveform
    c. Highlight the 100 ms directly prior to the superimposed burst
        i. Record the max value
    d. Highlight the bout of torque during the superimposed burst
        i. Record the max value
    e. Repeat for subsequent trials

Table C1.4.i: Dismiss subject from the study

Table C1: Sample Size Estimate

Manuscript	Outcome	Logistic Regression		Group Comparisons			Sample Size
		Independent variables of interest	Incidence Rate	Minimal Difference	Effect size	Expected Variance	
1	Reinjury Rate	4	20%	-	-	-	200
2	Quadriceps Strength	1	45%	-	-	-	23
3	MEP	-	-	-	.71	417.1	15

APPENDIX D

Additional Results

MANUSCRIPT I: Predicting ACL Reinjury from Return to Activity Assessments at 6-months Post-Surgery: A Prospective Cohort Study

Table 1: Patient demographics in all participants.

All Patients	
Patients, n	193
Age, years	21.2±9.2
Sex (Female:Male)	104:88
Mass, kg	73.7±17.8
Height, cm	172.0±17.8
Time Since Surgery, Months	6.73±1.4
Pre-Injury Activity Level (Tegner)	8.55±1.3

Table 2: Patients primary activity prior to ACLR.

Activity	Number
Recreational Sports	8
Baseball	1
Basketball	20
Cheer/Dance/Gymnastics	6
Field Hockey	1
Football	30
Lacrosse	15
Military	3
Rugby	5
Running	2
Ski	6
Soccer	38
Softball	4
Tennis	1
Volleyball	6
Wrestling	3
Primary sport unknown	6
Total	**155**

Table 3: Sport Competition Level in Patients that RTA.

Activity Level	Number
High School	78
College	25
Military	3
Recreational	41
Unknown	8
Total	**155**

Table 4: Comparison of the distribution of subsequent ACL injuries by sex. X^2= 0.13, P=0.86

Reinjury	Males	Female	Total
Yes	20	24	44
No	54	57	111
Total	74	81	155

Table 5: Graft Type Distribution. Abbreviations: PT=Patellar Tendon, HS=Hamstring, QT=Quadriceps Tendon

Graft	n	%
PT	95	61.3
HS	58	37.4
QT	2	1.3
Total	155	100

Table 6: Comparison of the distribution of subsequent ACL injuries by Graft Type. X^2= 0.24, P=0.71

Reinjury	PT	HS	Total
Yes	26	18	44
No	69	40	109
Total	95	58	153

Table 7: Comparison of the distribution of subsequent ACL injuries by Graft Type in Males. X^2= 0.95, P=0.41

Reinjury	PT	HS	Total
Yes	11	9	20
No	35	17	52
Total	46	26	72

Table 8: Comparison of the distribution of subsequent ACL injuries by Graft Type in Females. X^2= 0.06, P=0.99

Reinjury	PT	HS	Total
Yes	15	9	24
No	34	23	57
Total	49	32	81

Table 9: Comparison of the side of subsequent ACL injury by Graft Type. X^2= 1.80, P=0.23

Reinjury Side	PT	HS	Total
ACL Graft	12	12	24
Contralateral ACL	14	6	20
Total	26	18	44

Table 10: Comparison of the side of subsequent ACL injury by Graft Type in Males. X^2= 0.07, P=0.99

Reinjury Side	PT	HS	Total
ACL Graft	8	7	15
Contralateral ACL	3	2	5
Total	11	9	20

Table 11: Comparison of the side of subsequent ACL injury by Graft Type in Females. X^2= 2.00, P=0.21

Reinjury Side	PT	HS	Total
ACL Graft	4	5	9
Contralateral ACL	11	4	15
Total	15	9	24

Table 12: Descriptive statistics for covariates used in the logistic regression analyses.

Reinjury	Yes	No	*P*-value	ES(95% CI)
Patients, n	44	111	-	-
Age, years	18.49±7.0	20.69±8.7	.139	.27(-.08,).62
Sex (F:M)	24:20	57:54	.859	-
Pre-Injury Activity Level (Tegner)	8.91±.93	8.55±1.4	.116	.28(-.07, .63)

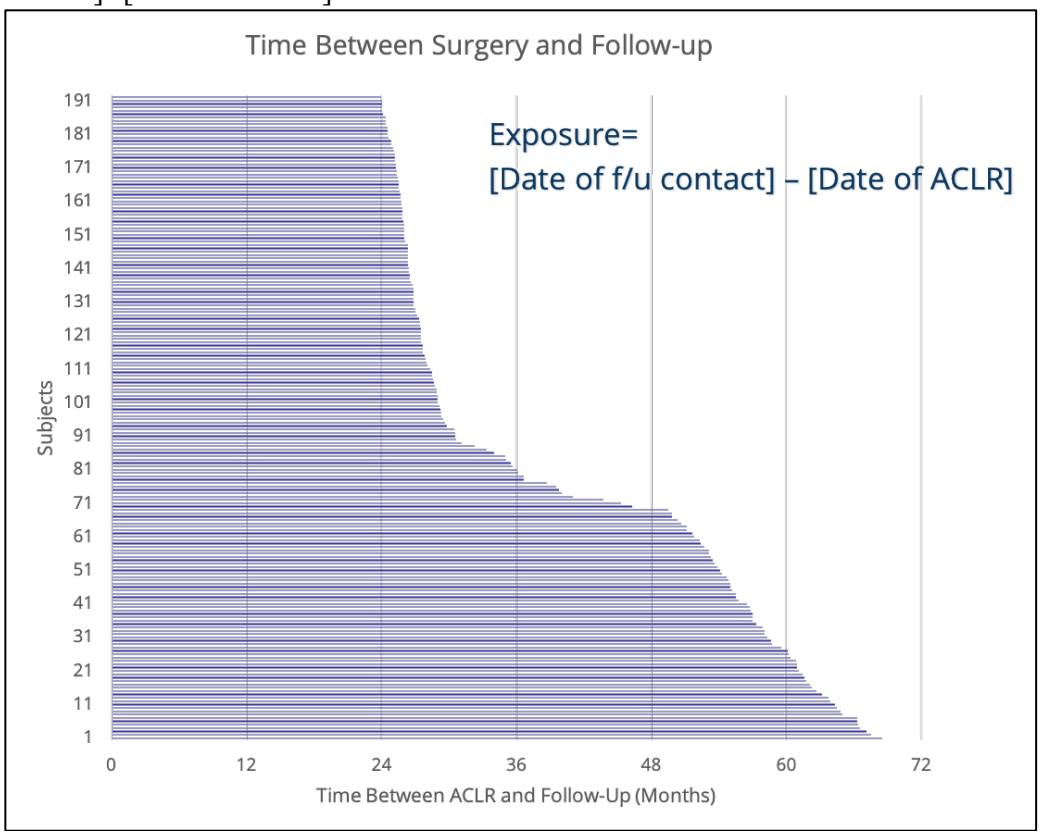
Table 13: Predictors of subsequent ACL injury of the ACLR graft (ACLR Graft: n=24, No Reinjury: n=111, Total Cohort: n=135). Each Variable was entered into separate models controlling for Age, Sex, and Activity Level.

	Beta	OR [95% CI]	*P*-value
Quadriceps Peak Torque (Nm/kg)	1.01	2.75 [1.04, 9.25]	.03
Quadriceps Symmetry (%)	2.50	1.03 [1.00, 1.06]	.02
Time to RTA	-.062	.94 [0.80, 1.10]	.39

Table 14: Predictors of subsequent ACL injury of the Contralateral ACL (Contralateral ACL: n=20 No Reinjury: n=111, Total Cohort: n=131). Each Variable was entered into separate models controlling for Age, Sex, and Activity Level. Model for Sex was controlled for Age and Activity Level.

	Beta	OR [95% CI]	*P*-value
Quadriceps Peak Torque (Nm/kg)	.24	1.27 [0.41, 4.22]	.66
Quadriceps Symmetry (%)	0.7	1.00 [0.98, 1.04]	.55
Time to RTA	-.09	.92 [0.77, 1.07]	.26
Sex(Female)	1.20	3.27 [1.07, 10.4]	.03

Figure 1: Participant Exposure Time following ACLR. Exposure Time = [Date of follow-up contact]- [Date of ACLR]



MANUSCRIPT II: Quadriceps and Patient Function in Serial Assessments Throughout the Post-ACL Reconstruction Progression

Table 15: Patient Demographics of all participants.

Patient Demographics	
Patients, n	48
Age, years	24.3±11.1
Sex (Female:Male)	27:20
Mass, kg	75.4±19.3
Height, cm	175.4±24.7
Time Since Surgery Visit 1, Months	4.03±.49
Time Since Surgery Visit 2, Months	6.46±.68
Pre-Injury Activity Level (Tegner)	8.04±1.4

Figure 2: Change in the IKDC between the 4-month (STEP) and 6-month (LEAP) visits. Box plot represents the Median, Interquartile range, and range. Each point represents one subject.

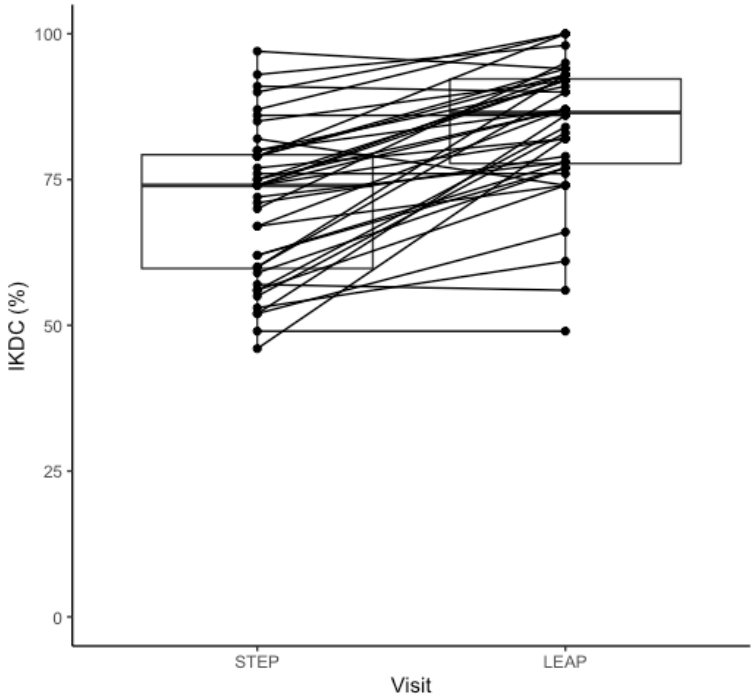


Figure 3: Change in the KOOS Sport between the 4-month (STEP) and 6-month (LEAP) visits. Box plot represents the Median, Interquartile range, and range. Each point represents one subject.

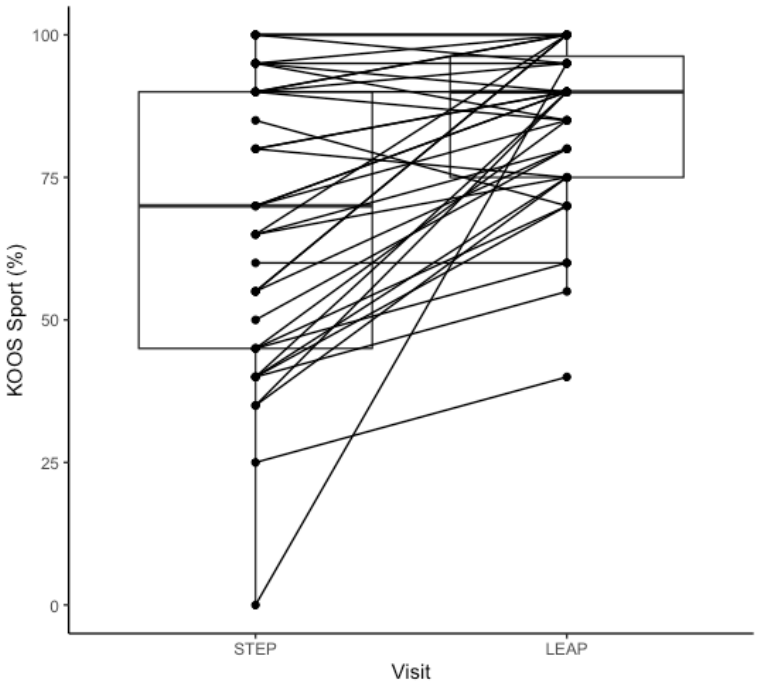


Figure 4: Change in the ACL-RSI between the 4-month (STEP) and 6-month (LEAP) visits. Box plot represents the Median, interquartile range, and range. Each point represents one subject.

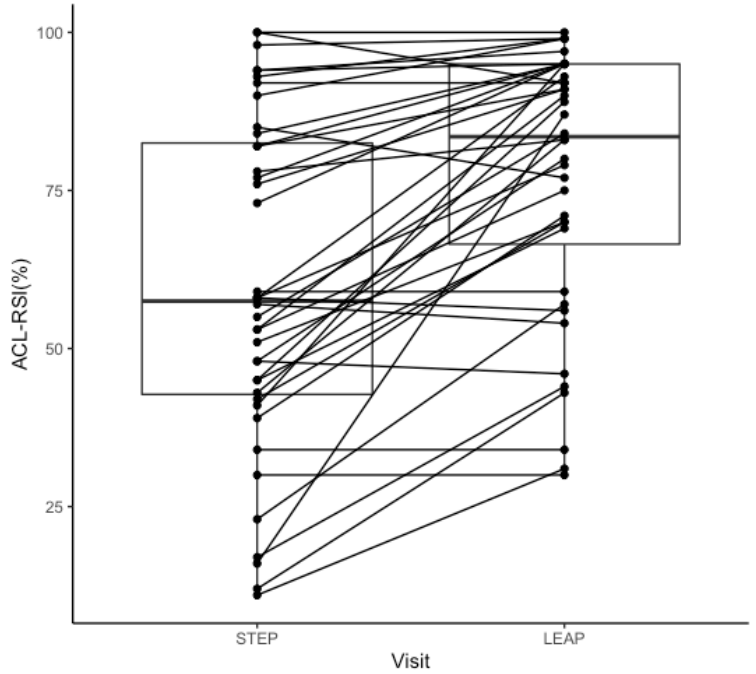


Figure 5: Change in quadriceps peak torque (Nm/kg) between the 4-month (STEP) and 6-month (LEAP) visits. Box plot represents the Median, Interquartile range, and range. Each point represents one subject.

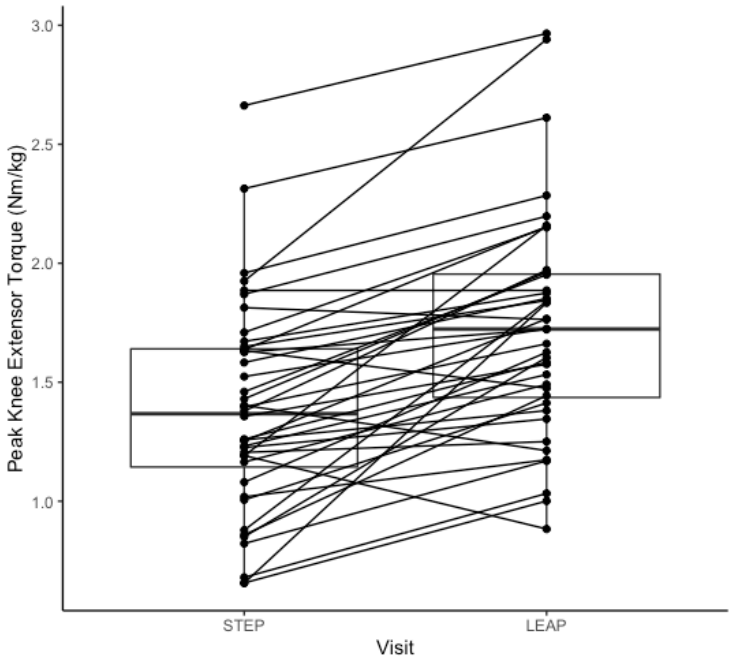


Figure 6: Change in quadriceps symmetry (%) between the 4-month (STEP) and 6-month (LEAP) visits. Box plot represents the Median, Interquartile range, and range. Each point represents one subject.

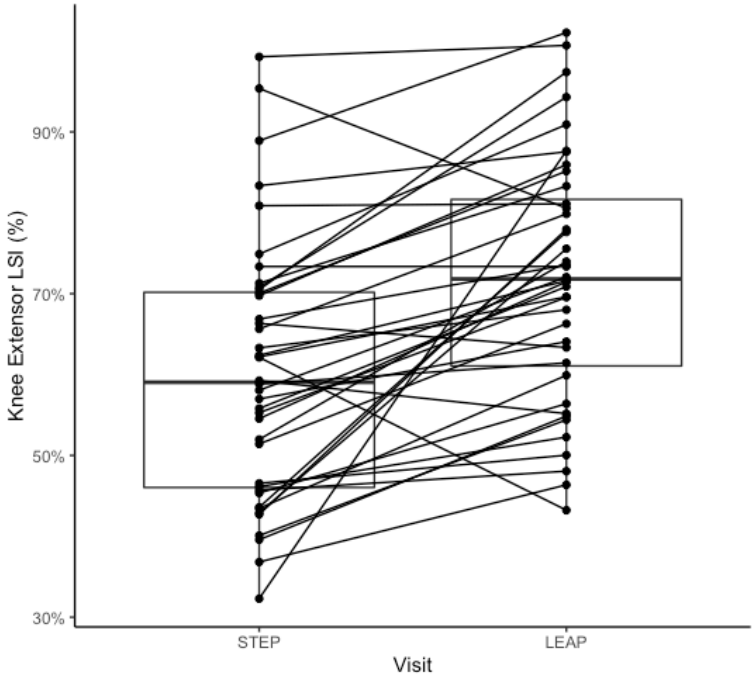


Table 16: Changes in patient strength and symmetry in those with a Patellar Tendon graft from the 4-month to 6-month visits.

Patellar Tendon Graft (n=38)	4-month Visit	6-month Visit	Change	P-value
Involved Knee Extensor Peak Torque (Nm/kg)	1.40±0.36	1.73±0.45	0.33±0.33	<.001
Uninvolved Knee Extensor Peak Torque (Nm/kg)	2.35±0.38	2.45±0.38	0.09±0.21	.002
Knee Extensor Symmetry (%)	59.4±13.0	70.8±14.4	11.4±12.7	<.001
Involved Knee Flexor Peak Torque (Nm/kg)	.92±0.30	1.06±0.25	0.14±0.27	.001
Uninvolved Knee Flexor Peak Torque (Nm/kg)	1.04±0.33	1.09±0.22	0.04±0.29	.002
Knee Flexor Symmetry (%)	87.4±15.8	95.4±15.35	8.1±17.6	.012

Table 17: Changes in patient strength and symmetry in those with a Hamstring graft from the 4-month to 6-month visits.

Hamstring Graft (n=8)	4-month Visit	6-month Visit	Change	P-value
Involved Knee Extensor Peak Torque (Nm/kg)	1.55±.65	1.87±.61	0.35±0.38	.049
Uninvolved Knee Extensor Peak Torque (Nm/kg)	2.20±.60	2.29±.55	0.09±.20	.254
Knee Extensor Symmetry (%)	70.0±21.1	81.2±13.0	11.2±20.5	.165
Involved Knee Flexor Peak Torque (Nm/kg)	.73±.16	.89±.23	0.17±.15	.013
Uninvolved Knee Flexor Peak Torque (Nm/kg)	.95±.27	1.05±.27	0.10±.27	.100
Knee Flexor Symmetry (%)	77.5±11.3	85.4±9.3	7.9±4.8	.002

Table 18: Comparison of patient outcomes at the 4-month assessment in those with patellar tendon vs hamstring grafts.

	PT	HS	P-value
IKDC	70.4±13.2	76.0±16.3	.302
KOOS Sport	64.2±24.9	80.6±27.7	.104
ACL-RSI	54.7±23.7	73.5±25.7	.051
Involved Knee Extensor Peak Torque (Nm/kg)	1.40±.36	1.55±.65	.350
Knee Extensor Symmetry (%)	59.4±13.0	70.0±.21	.069
Involved Knee Flexor Peak Torque (Nm/kg)	0.92±0.30	0.72±0.15	.084
Knee Flexor Symmetry (%)	88.7±16.4	77.4±11.3	.072

Table 19: Comparison of patient outcomes at the 6-month assessment in those with patellar tendon vs hamstring grafts.

	PT	HS	P-value
IKDC	82.3±11.2	88.8±12.0	.155
KOOS Sport	85.0±14.5	89.4±11.2	.429
ACL-RSI	74.0±20.5	77.8±22.2	.645
Involved Knee Extensor Peak Torque (Nm/kg)	1.73±.45	1.87±.61	.429
Knee Extensor Symmetry (%)	70.7±14.4	81.3±13.0	.065
Involved Knee Flexor Peak Torque (Nm/kg)	1.05±.25	0.89±.13	.101
Knee Flexor Symmetry (%)	96.8±15.8	85.4±9.3	.056

Table 20: Comparison of patient function at the 4-month assessments between patients that increased quadriceps strength (≥.22 Nm/kg) and those with persistent muscle weakness (<.22 Nm/kg). **Bolded** variables are identified as statistically significant.

	Significant variables from 4-month Visit		
	<.22 Nm/kg	≥ .22 Nm/kg	*P*-Value
n	14	27	-
Age (Years)	**28.8±15.0**	**21.2±6.1**	**.02**
Height (cm)	171±13.6	179.4±31.1	.41
Mass (kg)	78.2±24.9	76.5±17.0	.79
Pre-Injury Activity Level (Tegner)	**7.4±1.3**	**8.5±1.3**	**.02**
IKDC	70.64±14.4	71.9±12.4	.78
KOOS Symptom	82.1±16.0	82.8±13.1	.89
KOOS Pain	86.9±11.6	89.4±8.8	.45
KOOS ADL	95.5±8.5	96.8+3.8	.51
KOOS Sport	68.2+25.3	69.4±25.1	.89
KOOS QoL	56.3±24.2	56.7±19.4	.94
ACL-RSI	58.6±26.5	60.3+26.8	.86
Quadriceps Peak Torque (Nm/kg)	1.46±.26	1.34±.50	.42
Quadriceps Strength Symmetry (%)	**66.3±12.5**	**57.4±14.6**	**.04**
Hamstring Peak Torque (Nm/kg)	0.83±.24	0.91±.33	.47
Hamstring Strength Symmetry (%)	86.4±13.5	87.7±18.1	.81

Table 21: Relationships between the number of rehabilitation visits completed between visits and changes in quadriceps and hamstring strength.

		Change in Quadriceps Peak Torque	Change in Hamstring Peak Torque	Changes in Quadriceps LSI	Changes in Hamstring LSI
Total Rehabilitation Visits	*r*	.134	-.224	.155	.092
	P	.403	.158	.334	.568

Figure 7: Relationship between changes in patient quadriceps strength and changes in IKDC. Blue line represents the linear regression line and the shaded areas are the 95% CI.

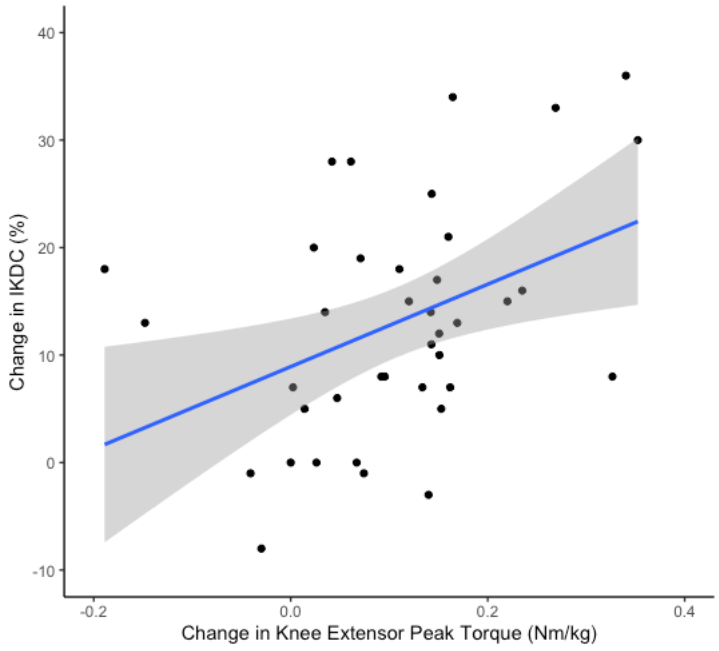
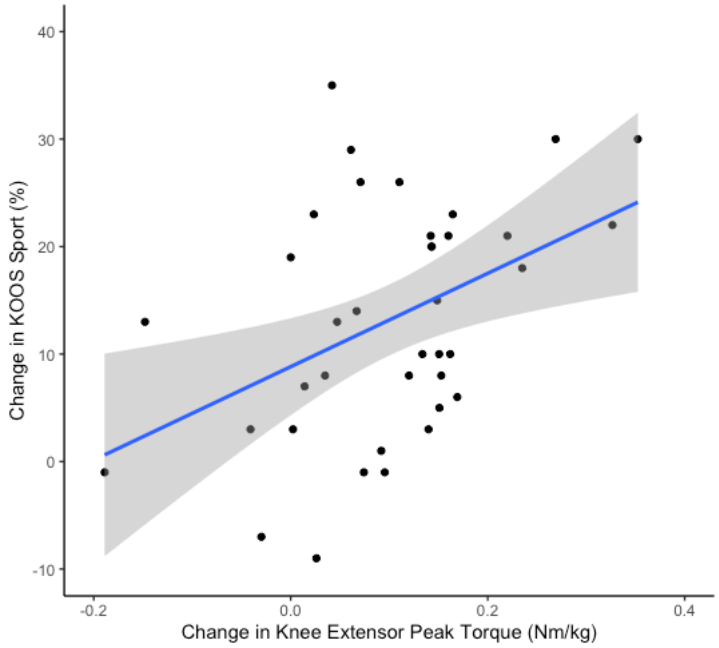


Figure 8: Relationship between changes in patient quadriceps strength and changes in KOOS Sport. Blue line represents the linear regression line and the shaded areas are the 95% CI.



MANUSCRIPT III: Visuomotor Therapy Modulates Corticospinal Excitability in Patients following ACL-Reconstruction

Table 22: Change in Patient function between the 4 and 6 month visits.

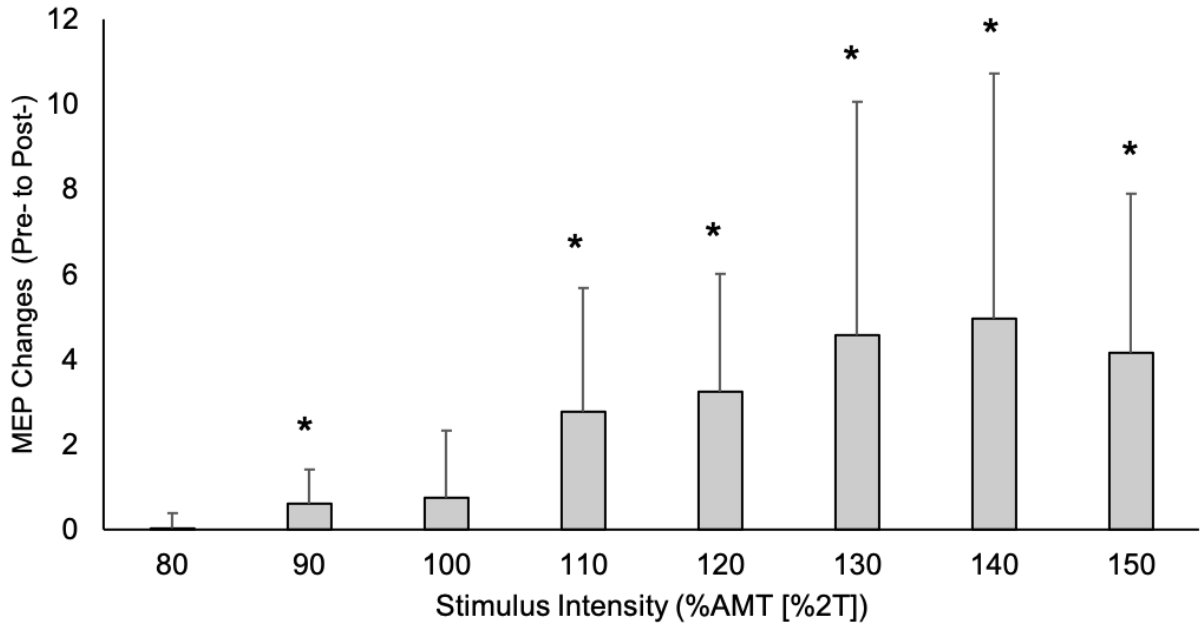
	4-Month (STEP)	6-Month (LEAP)	Change	*P*-value
	Mean±SD	Mean±SD	Mean±SD	
Knee Extensor Peak Torque	1.15±.34	1.64±.33	0.49±.37	<.001
IKDC STEP	66.7±12.1.9	82.8±7.13	16.1±12.0	<.001
ACL RSI STEP	54.6±27.6	77.0±19.9	22.4±20.7	<.001

Table 23: Changes ([Post]-[Pre]) in Quadriceps MEP following single session of therapy. Median [IQR]

		80% AMT	90% AMT	100% AMT	110% AMT	120% AMT	130% AMT	140% AMT	150% AMT
MEP Changes (% of M-max)	Visuomotor Therapy	0.11 [-.01,.17]	.21* [.08,1.1]	0.58 [-.18,1.3]	2.25* [1.1,5.2]	2.84* [1.17,5.4]	4.29* [.92,5.4]	2.77* [1.1,7.3]	4.77* [3.1,6.4]
	Passive Motion	.002* [.00, .01]	-.0003 [.00, .002]	.001 [.00, .002]	.003 [.00, .011]	.003 [-.03, .02]	-.008 [-.01, .01]	-.002 [-.03, .02]	-.004 [.-.02, .01]

*Represent a significant increase in Quadriceps MEP. Positive values represent an increase in MEP. Abbreviations; MEP: Motor evoked potential

Figure 9: Changes in quadriceps MEP following visuomotor therapy. *Represents a statistically significant change from pre- to post-therapy assessment.



APPENDIX E

BACK MATTER

Recommendations for future research

1. Do 6-month functional outcomes differ between patients that had a contact vs. non-contact ACL injury mechanism?
2. Do functional assessments administered at 8-months post-ACLR better predict secondary injury compared to 6-month assessments?
3. Do pre-operative functional assessments influence post-operative outcomes at the time of return to activity?
4. Examine the relationships between components of post-ACLR rehabilitation to strength changes throughout return to activity progression.
5. Can serial functional assessments at 4- and 6-months post-ACLR be used to predict the time needed to reach functional targets?
6. Examine the feasibility of a 4-week intervention of visuomotor therapy in patients following ACLR.
7. Does the torque matching accuracy relate to neuromuscular function in patients following ACLR?
8. Examine the lasting effects of visuomotor therapy of quadriceps neuromuscular function following a 4-week intervention randomized control trial.

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