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INJURY-RELATED FEAR IN PATIENTS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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INJURY-RELATED FEAR IN PATIENTS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Health Sciences at the University of Kentucky

By
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Lexington, Kentucky

2019

ABSTRACT OF DISSERTATION

INJURY-RELATED FEAR IN PATIENTS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Approximately 200,000 anterior cruciate ligament (ACL) injuries occur each year with about 100,000 of these injuries undergoing reconstruction (ACLR). The impetus of ACLR is to allow previously high functioning, physically active individuals to return to desired levels of sports participation and to engage in recommended levels of physical activity. However, 1 out of 3 patients after ACLR fail to return to competitive levels of sport and meet recommended levels of physical activity. Injury-related fear has been cited as the primary barrier for failure to return to sport. However, the research has been primarily qualitative in nature and limited research has quantitatively examined the impact of injury-related fear on return to sport and physical activity engagement in this population.

In addition to quantifying the impact of injury-related fear, no research has examined the underlying neural substrates associated with injury-related fear after ACLR. Previous research has demonstrated that patients after ACLR undergo neuroplasticity in sensorimotor regions of the brain and exhibit changes in neurocognitive functioning. Despite previous research in other musculoskeletal pathologies demonstrating neuroplasticity in emotional regulation centers of the brain, no research has examined these brain regions in patients after ACLR. Furthermore, previous research in healthy athletes has suggested that psychosocial impairments can lead to changes in neurocognitive functioning, including reaction time. Understanding these neural substrates could provide insight into appropriate intervention strategies to decrease injury-related fear, increase return to sport and physical activity engagement, and potentially improve neurocognitive functioning in patients after ACLR.

The purpose of this dissertation was to further investigate the effects of injury-related fear on patients after ACLR and to determine the efficacy of a cognitive behavioral intervention to decrease injury-related fear in this population. The purposes of these studies were to determine whether patient-based, specifically psychological, and functional outcomes were associated with return to sport and physical activity levels in individuals with a history of ACLR, to determine differences in brain activation patterns when exposed to fear-eliciting stimuli in individuals with a history of ACLR compared healthy matched controls, and to determine the efficacy of *in vivo* exposure therapy on self-reported fear and reaction times in participants post-ACLR.

The results of these studies indicate that injury-related fear was quantitatively associated with return to sport and physical activity engagement in patients after ACLR. Additionally, individuals with a history of ACLR activated emotional regulation centers of the brain in greater depth when compared to healthy matched controls. Lastly, *in vivo* exposure therapy decreased self-reported injury-related fear for specific functional tasks but did not improve general fear response or reaction time in post-ACLR participants. The results of these studies objectively elucidate the negative impact of injury-related fear in patients with a history of ACLR.

Keywords: Anterior Cruciate Ligament Reconstruction, Injury-Related Fear, Neuroplasticity, In Vivo Exposure

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April 26th, 2019
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INJURY-RELATED FEAR IN PATIENTS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Chapter One: Introduction

Background

Anterior cruciate ligament (ACL) injuries commonly occur in the highly active population and most injuries transpire in sports that require frequent pivoting and cutting.[1] Rupture to the anterior cruciate ligament is often traumatic and affects approximately 200,000 people each year.[1] Additionally, 42.5 out of 100,000 people each year undergo ACL reconstruction (ACLR).[1] While the impetus of reconstruction and subsequent rehabilitation is to return patients to their pre-injury levels of physical activity, this does not always occur.[2,3] Only 55% of patients return to competitive levels of sport participation, and only 65% of patients return to pre-injury levels of sports participation after ACL injury.[4] Therefore, while participation in physical activity is vital for overall health, it can lead to musculoskeletal injury; which in turn can lead to physical inactivity.[5]

Physical inactivity can predispose individuals to early death, stroke, coronary artery disease, multiple cancers, type 2 diabetes, falls, and depression.[6] Previous literature reports that individuals with a history of ACLR have reduced physical activity levels[7] and a decreased health-related quality of life (HRQL).[3,8] In a qualitative study that examined activity preferences, lifestyle modifications, and HRQL in patients after ACLR, each of the patients in the study reported having injury-related fear throughout their recovery.[3] Injury-related fear is a contextual factor that may affect physical activity levels, clinical outcomes, and HRQL following ACL injury and reconstruction.[3,9,10] Injury-related fear has been studied in various patient populations with musculoskeletal injuries including chronic low back pain,[11] chronic ankle instability,[12] and post-ACLR.[13] Specific to the chronic low back pain literature, the fear-avoidance model has been used to examine how two types of injury-related fear, fear-avoidance beliefs and fear of re-injury, can develop following injury.[11] Fear-avoidance beliefs and fear of re-injury have been frequently researched in patients with chronic low back pain, but few have examined how the fear-avoidance model can affect clinical outcomes after ACLR.

The premise of the fear-avoidance model is that pain catastrophizing behaviors, which occur after a painful experience, lead to fear-avoidance beliefs, avoidance of activity, and eventually disuse, depression, and disability (Figure 1.1).[10] It has been suggested that patients who do not develop fear-avoidance beliefs and pain catastrophizing behaviors experience a more efficient recovery and a better outcome.[14] However, those who do develop fear-avoidance beliefs or fear of re-injury, may be susceptible to poorer clinical outcomes, such as lower patient-reported outcome measures, functional outcomes, and decreased physical activity levels.[3] Unfortunately, decreased physical activity levels following injury can create long-term problems that can also affect HRQL.[3] These poor long-term outcomes are often observed in patients following ACLR.[3,8]

Health-related quality of life is a multidimensional patient-centered concept of health that incorporates the patient's personal, societal, and spiritual beliefs, values, and preferences.[15] The 6 domains of HRQL are: physical, social, emotional, psychological, spiritual, and economical.[15] It has been reported that an injury to the ACL marks the beginning to lifelong persistent knee difficulties in patients.[8] In a qualitative study that interviewed ACLR patients between 5 and 20 years after reconstruction, the researchers discovered that activity preferences, lifestyle modifications, and fear of re-injury influenced HRQL.[3] As expected, those patients who did not participate in recreational exercise were at a heightened risk of poor HRQL compared to those who participated in regular physical activity. In patients who did return to pre-injury sport or recreational activity after ACLR, the most important factor influencing their return was psychological readiness.[3] Previous literature reports that injury-related fear and psychological readiness are common barriers, and potentially the most influential barriers, in the ACLR population when returning to pre-injury sport participation.[2] Measuring clinical outcomes throughout the rehabilitation process could provide insight into these psychological barriers after ACLR.

Throughout the rehabilitation process, clinicians measure and evaluate outcomes to track progress of the patient and to determine treatment efficacy.[16,17] The most common outcomes collected following ACLR include both clinician and patient-based outcome measures.[16,17] Patient reported outcome measures (PRO) are patient-based outcome assessments that provide a quantifiable measurement of subjective information from the patient about their health status.[18] Generic PROs, such as the Disablement of the Physically Active Scale[19] and the Medical Outcomes Study 36-item Short Form Health Survey,[20] and region specific PROs, such as the Knee Injury and Osteoarthritis Outcome Score (KOOS)[21] and the International Knee Documentation Committee,[22] are used to evaluate constructs of HRQL and knee-related function in patients with musculoskeletal injuries. Alongside their respective health status, PROs are also used to evaluate injury-related fear. Two frequently used PROs that examine injury-related fear include the Fear-Avoidance Belief Questionnaire (FABQ)[23] and the Tampa Scale of Kinesiophobia-11 (TSK-11).[24] These two instruments target aspects of the fear-avoidance model, which could help to explain the relationship between injury-related fear, clinician-based outcomes, and overall health outcomes in post-ACLR patients.

Functional outcomes are clinician-based outcomes that evaluate a patient's ability to run, jump, cut, and other physical tasks with the involved pathology.[25] In rehabilitation sciences, functional outcomes are frequently used to assess a patient's ability to return to sport or desired physical activity.[26] Frequently used functional outcomes for knee patients include the landing error scoring system (LESS),[27] the single-leg hop series,[28] the star excursion balance test,[29] and isokinetic quadriceps and hamstring strength testing.[30] It has been demonstrated that increased levels of injury-related fear are associated with stiff jump-landing mechanics in patients after ACLR,[31] and potentially other functional outcome measure are influenced by this psychosocial construct.

<u>Overall Outcomes</u>

In a previous study using the fear-avoidance model, Tichonova et al.[32] examined the relationship between pain catastrophizing, kinesiophobia, and subjective knee function during rehabilitation following ACLR and menisectomy. Participants completed the TSK-11, Pain Catastrophizing Scale,[33] Numerical Pain Rating Scale,[34] and the KOOS before and after a 14-session rehabilitation program. Researchers concluded that pain catastrophizing and kinesiophobia decreased throughout rehabilitation; however, higher pain catastrophizing was related to greater levels of knee pain before and after rehabilitation. In a similar study that examined the implications of fear of re-injury in athletes on their rehabilitation outcomes, Hsu et al.[35] discovered similar changes in reduced self-reported function, but also noted that fear of re-injury negatively affected the recovery of physical impairments and successful return to sport.

In a cross-sectional study that examined the impact of psychological readiness to return to sport following ACLR, researchers demonstrated that only 40% of participants return to pre-injury activity.[2] In those who did not return to activity, 28% reported that they did not return because they did not trust their knee, 24% reported fear of a new injury, and 22% reported poor knee function. Ardern at el.[2] stated that psychological readiness to return to sport was the factor most strongly associated with returning to pre-injury levels of sport. It has also been suggested that interventions aimed to improve psychological readiness throughout rehabilitation could improve the rate of return to high levels of activities and improve rehabilitation outcomes.[2] However, there is limited knowledge on how to treat lack of psychological readiness and injury-related fear in patients after ACLR. Implementation of a psychological intervention may help to improve these poor overall health outcomes observed in this population.

Neurocognitive Functioning and Neuroplasticity

In addition to deficits in physical activity and HRQL, patients after ACLR also exhibit deficits in neurocognitive functioning[36] and neuroplastic alterations[37,38] as a result of their injury. In a case-control study designed to explore the connection between neurocognitive functioning and knee injuries in eighty collegiate intercollegiate athletes, Swanik et al.[36] discovered that individuals who sustained a non-contact ACL injury had deficits in reaction time, processing speed, and visual and verbal memory scores prior to their injury compared to matched controls.[36] It was suggested that the neurocognitive differences prospectively were associated with a loss of neuromuscular control which predisposed these individuals to sustain a non-contact ACL injury. This is supported by additional research which has reported a relationship between deficits in reaction times and risk of sustaining a lower extremity injury.[39,40]

Athletic individuals with slower neurocognitive reaction times and visuomotor reaction times have an increased risk of lower extremity sprain and strains.[39,40] Visuomotor reaction times refer to the ability of a person to effectively respond to central and peripheral visual stimuli during a task, which is important for an athletic population as they must be able to recognize and respond to changing environmental conditions during their respective sport.[40] Interestingly, psychological influences, such as increased levels of life stress, have been associated with decreased visuomotor reaction times in athletes.[41] Despite this evidence, visuomotor reaction times and neurocognitive reaction times have not been examined in patients after ACLR with self-reported levels of injury-related fear.

Neuroplastic alterations have also been observed in patients after ACLR. These patients exhibit compensatory sensorimotor brain activation changes compared to healthy matched controls.[37] As measured by functional magnetic resonance imaging (fMRI) during a knee extension-flexion task, Grooms et al.[37] discovered that post-ACLR patients have increased activation in the contralateral motor cortex and lingual gyrus. Interestingly, these patients also demonstrated increased activation in the ipsilateral secondary somatosensory area,[37] which is an area of the brain responsible for addressing painful stimuli. However, none of the patients in this study reported pain or discomfort during the fMRI.[37] This suggests that other factors, including psychological factors, may influence brain activation patterns in patients after ACLR, and warrants further exploration of the emotional regulation centers of the brain.

Examination of the emotional regulation centers of the brain in patients after musculoskeletal injury has previously been completed.[42] Patients with medial patellofemoral ligament deficiency demonstrated increased activation in the limbic and hypothalamic regions of the brain during a patellar glide when compared to healthy controls.[43] In another fMRI study that examined the emotional regulation centers of the brain in patients with chronic musculoskeletal pathologies, the researchers discovered that these patients experienced increased activation in the emotional regulation centers while completing a picture imagination task of functional activities.[42] Despite evidence of neuroplastic alterations in patients after ACLR, the emotional regulation centers in these patients have not been explored even though strong evidence suggests that these patients exhibit increased levels of injury-related fear. Understanding the neural substrates associated with injury-related fear will enhance our ability to develop appropriate cognitive behavioral therapies to treat these psychological impairments in this population.

Cognitive Behavioral Therapies

As previously discussed, patients post-ACLR have increased injury-related fear which may be associated with deficits in clinical outcomes observed in this population.[2,36,41] Therefore, these individuals may benefit from the implementation of cognitive behavioral therapies, which are short-term interventions designed to alter how a person thinks to lead to a behavior change.[44] Cupal et al.[45] demonstrated that guided imagery and relaxation training improved knee strength and decreased re-injury anxiety and pain in patients 24 months after ACLR. Unfortunately, the efficacy of psychological interventions, specifically imagery and relaxation training, on improving postoperative quality of life, anxiety, and injury-related fear in patients after ACLR is inconsistent.[46]

However, *in vivo* exposure therapy has been demonstrated to decrease injury-related fear and increase physical activity in patients with chronic low back pain.[47] Moreover, this cognitive behavioral intervention can be successfully and effectively implemented by rehabilitation specialists.[47,48] *In vivo* exposure therapy is a cognitive behavioral therapy designed to gradually expose patients to their most fear-eliciting functional tasks in an attempt to reframe maladaptive views of the respective functional tasks.[47] Instead of imagery techniques and relaxation training, a psychological intervention like *in vivo* exposure therapy may decrease injury-related fear in patients after ACLR.

The Problem

Patients after ACLR are not returning to pre-injury levels of sports participation despite medical clearance and full objective knee function.[49] Physical function is necessary but insufficient to return to sport. Therefore, rehabilitation specialists must be equipped to recognize and address underlying psychosocial impairments, specifically injury-related fear, that impede return to sport and physical activity engagement. At this time, the relationship between injury-related fear, clinical outcomes, and PA is unknown, and whether injury-related fear is associated with maladaptive neuroplastic alterations in patients after ACLR. Moreover, it is unknown whether rehabilitation specialists can successfully implement cognitive behavioral therapies to treat injury-related fear in the post-ACLR population. There is a critical need to further examine the effects of injury-related fear on health outcomes and to determine an effective cognitive behavioral intervention to mitigate injury-related fear in patients after ACLR. In the absence of such knowledge, injury-related fear will likely remain and will continue to influence long-term sports participation, physical activity, and health outcomes in a previously high functioning, physically active population.

Purpose

There are 3 purposes of this dissertation. The first purpose is to determine which patient-based and functional outcome measures are associated with return to sport participation (RTS) and physical activity levels in patients with a history of ACLR. The second purpose is to determine the differences in activation patterns in corticolimbic brain regions between individuals with a history of ACLR and healthy matched controls. The third purpose is to examine the efficacy of *in vivo* exposure therapy on decreasing injury-related fear and improving reaction times in individuals with a history of ACLR. These studies were designed to address the following aims:

1. To examine functional and patient-based outcomes that are associated with RTS in individuals with a history of ACLR.
2. To examine functional and patient-based outcomes are associated with physical activity levels in individuals with a history of ACLR.
3. To determine difference the neural substrates of injury-related fear during a visually-based picture imagination task in individuals with a history of ACLR compared to healthy age-mated controls.
4. To determine the effectiveness of an *in vivo* exposure intervention on self-reported injury-related fear and reaction times in post-ACLR participants.

Overview

The methods, results, discussion, limitations, and conclusion for each of the four aims are as follows. Chapter 2 will summarize the theoretical implications for each of the studies by examining the stress and injury model and the cognitive appraisal model. Additionally, Chapter 2 will discuss the neural mechanisms of the fear response and will also provide a review of cognitive behavioral therapies that have been implemented by rehabilitation specialists to treat chronic low back pain. Chapter 3 will determine the patient-based and functional outcomes that are associated with RTS and physical activity levels. Chapter 4 will examine the differences in brain activation patterns in individuals with a history of ACLR compared to healthy controls. Lastly, Chapter 5 will determine the efficacy of *in vivo* exposure therapy on decreasing injury-related fear in individuals with a history of ACLR. Additionally, this chapter will discuss the effects of *in vivo* exposure therapy on visuomotor reaction times.

Operational Definitions

Throughout these studies, the following definitions will be used:

1. Psychosocial: The interrelation of psychological factors (i.e. injury-related fear) and social factors (i.e. social support) that can influence thoughts and behaviors, specifically after musculoskeletal injury.
2. Fear: An unpleasant and strong emotion caused by a specific and identifiable threat.
3. Fear-Avoidance Beliefs: A fear of pain and/or re-injury that leads to avoidance of activities that could lead to pain and/or re-injury.
4. Health-Related Quality of Life (HRQL): A multidimensional patient-centered concept of health that incorporates the patient's personal, societal, and spiritual beliefs, values, and preferences.

5. Neurocognitive Functioning: How well neural processes, such as reaction times, and structures involved in cognition are performing.
6. Neuroplasticity: The ability for the brain to form and recognize synaptic connections in context-dependent situations.
7. *In Vivo* Exposure Therapy: A type of cognitive behavioral therapy used to reduce fear associated with specific triggers in real life situations.

Assumptions

The primary assumptions for the dissertation are as follows:

Chapter 3:

1. Participants were cleared to return to pre-injury levels of sports participation.
2. Participants answered PROs honestly and to the best of their abilities.
3. Participants completed functional testing to the best of their abilities.
4. Participants wore their pedometer every day and accurately reported their step counts on their daily step log.

Chapter 4:

1. Participants were cleared to return to pre-injury levels of sports participation.
2. Participants answered PROs honestly and to the best of their abilities.
3. Participants were not claustrophobic while completing the fMRI scan.
4. Participants completed the picture imagination task appropriately while completing the fMRI scan.
5. Participants accurately reported their medical history and previous sports participation.

Chapter 5:

1. Participants were cleared to return to pre-injury levels of sports participation.
2. Participants answered PROs honestly and to the best of their abilities.
3. Participants completed reaction time testing to the best of their abilities.
4. Participants enrolled in the intervention group viewed the YouTube video link.
5. Participants enrolled in the intervention group completed their tasks throughout the week and accurately tracked it on their compliance log.
6. Participants in the control group wore their pedometer every day and accurately reported their step counts on their daily step log.

Delimitations

The delimitations of this dissertation are as followed:

Chapter 3:

1. Participants were males and females between the ages of 18-35.
2. Participants were at least 1 year post-operative index ACLR.
3. Participants had no other ligamentous damage at the time of their index ACLR.
4. Participants had history of unilateral ACLR.
5. Participants with or without meniscal pathology and with ACL revision surgeries were included.
6. Participants had no history of lower extremity surgery or injury within the past 3 months.

Chapter 4 and Chapter 5:

1. Participants were females between the ages of 18-35.
2. Participants were at least 1 year post-operative index ACLR.
3. Participants had no other ligamentous damage at the time of their index ACLR.

4. Participants had history of unilateral ACLR.
5. Participants with or without meniscal pathology and with ACL revision surgeries were included.
6. Participants had no history of lower extremity surgery or injury within the past 3 months.
7. Participants were right-hand dominant.
8. Participants with a history of ACLR sustained a left-sided ACL injury.
9. Participants had to score at least a 5 on the Tegner Physical Activity Assessment prior to their index ACLR.
10. Participants did not have any neurological conditions affecting their nervous system.

<u>Limitations</u>

Chapter 3:

1. Participants self-reported their daily step counts to the investigators.
2. The Tegner Physical Activity Assessment was used to determine RTS and it is possible that some participants did not RTS due to other factors unrelated to their ACLR, including lifestyle changes.
3. Documentation of occupation of participants did not occur.
4. Some of the PROs used in this study have not been validated for the ACLR population.

Chapter 4:

1. Participants may have had increased activation in their emotional regulation centers as a result of anxiety or pain from being in the scanner.

2. Some of the PROs used in this study have not been validated for the ACLR population.
3. Participants were only female and the results may not be generalizable for all ACLR patients.

Chapter 5:

1. Some of the PROs used in this study have not been validated for the ACLR population.
2. Participants self-reported daily step counts and task completion on the compliance logs to the investigators.
3. Participants were only female and the results may not be generalizable for all ACLR patients.
4. The investigator completing outcome assessments were not blinded to group membership.

Abbreviations

ACL = Anterior Cruciate Ligament

ACLR = Anterior Cruciate Ligament Reconstruction

RTS = Return to Pre-injury Sports Participation

HRQL = Health Related Quality of Life

PRO = Patient Reported Outcome Measure

FABQ = Fear-Avoidance Beliefs Questionnaire

FABQ-PA = Fear-Avoidance Beliefs Questionnaire – Physical Activity Subscale

FABQ-S = Fear-Avoidance Beliefs Questionnaire – Sport Subscale

KOOS-Sy = Knee Injury and Osteoarthritis Outcome Score – Symptoms

KOOS-P = Knee Injury and Osteoarthritis Outcome Score – Pain

KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score – Activities of Daily Living

KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score – Quality of Life

KSES-ADL = Knee Self-Efficacy Scale – Activities of Daily Living

KSES-Sport = Knee Self-Efficacy Scale – Sports and Leisure

KSES-PA = Knee Self-Efficacy Scale – Physical Activity

KSES-Future = Knee Self-Efficacy Scale – Future

KSES-Total = Knee Self-Efficacy Scale – Total Score

mDPA-PSC = Modified Disablement in the Physically Active Scale – Physical Component Score

mDPA-MSC = Modified Disablement in the Physically Active Scale – Mental Component Score

PCS = Pain Catastrophizing Scale

TSK-11 = Tampa Scale of Kinesiophobia-11

Tegner = Tegner Physical Activity Assessment

LESS – RT = Landing Error Scoring System – Real Time

SL Hop for Distance = Single-Leg Hop for Distance

TL Hop for Distance = Triple-Leg Hop for Distance

CO Hop for Distance = Crossover Hop for Distance

LSI = Limb Symmetry Index

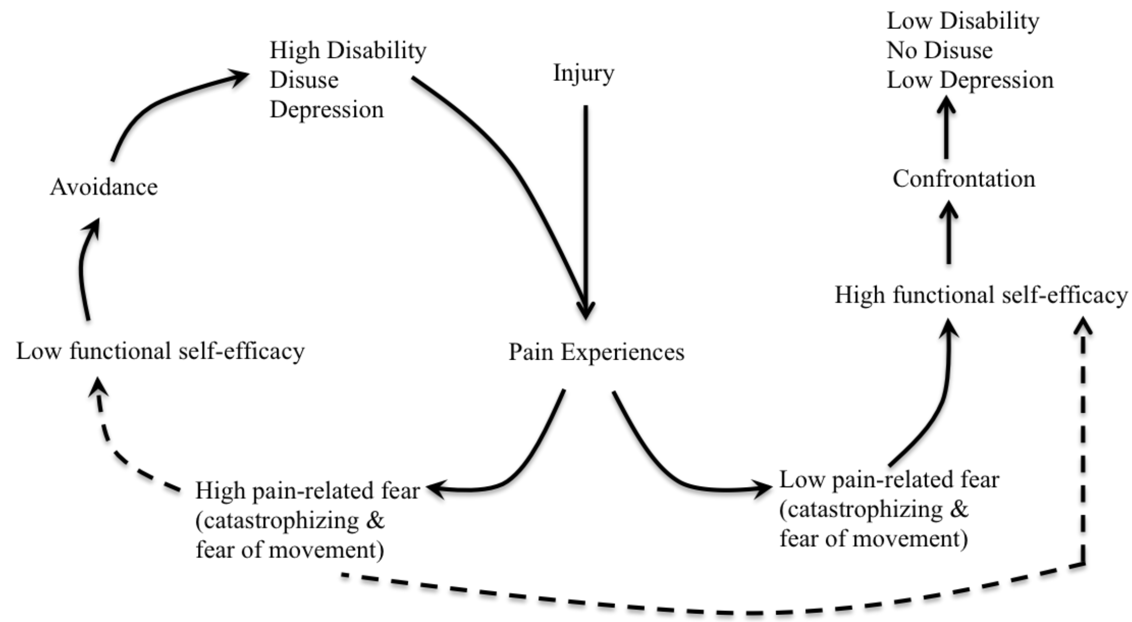
PIT = Picture Imagination Task

MDT = Mediodorsal Thalamus

IPL = Inferior Parietal Lobule

DMN = Default Mode Network

Figure 1.1. Fear-Avoidance Model



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Chapter Two: Literature Review

Part I: The Stress and Injury Model and the Cognitive Appraisal Model: Implications for Patients after Anterior Cruciate Ligament Reconstruction

Introduction

Health-related quality of life (HRQL) is a balance of physical, mental, and social well-being.[15] While the literature has reported athletes have increased physical HRQL compared to their peers, sports participation has recently been associated with poor mental and social HRQL.[50,51] Factors such as increased life pressures, including separation from family or worries of public perception in the media, have contributed to these detriments.[50] Unfortunately, increased life stressors can negatively affect an athlete's ability to successfully, and safely, perform their respective sport which may lead to sustaining a musculoskeletal injury.[52] Athletic injuries can affect all aspects of HRQL.[51] However, emphasis of musculoskeletal rehabilitation is to improve the physical domain of HRQL, often neglecting mental and social well-being. Two common psychological factors that are observed after sustaining a musculoskeletal injury is increased injury-related fear and decreased levels of self-efficacy.[53] These psychosocial barriers can prevent a previously high functioning, physically active athlete from returning to sport after sustaining a musculoskeletal injury.[53-55] For example, in patients after anterior cruciate ligament reconstruction (ACLR), 1 out of 3 patients fail to return to competitive levels of sports and injury-related fear has been cited as the primary barrier.[4] In those who do return to sport after ACLR, injury-related fear has been associated with sustaining a secondary injury to their ACL limb within 24 months of reconstruction.[56] Rehabilitation that addresses all aspects of HRQL could help to mitigate these negative responses after ACLR.

Psychosocial factors have also affect neurocognitive functioning in healthy athletes, specifically, reaction times.[52] Consequently, deficits in reaction time can increase susceptibility to injury in the highly active population.[39,40] This further suggests that other factors may influence injury. Two models have been developed to explain the impact of psychological factors on sustaining an athletic injury and how these factors can impact the rehabilitation and recovery process. The stress and injury model was designed to explain the effects of pre-injury psychological factors on athletic injury[57] and the cognitive appraisal model was developed to explain post-injury psychological responses to athletic injury.[58] Knowledge and application of these models will allow clinicians to implement appropriate theory-based psychological intervention strategies before injury to decrease injury risk. These models will also enhance rehabilitation strategies to improve recovery outcomes, especially in patients after sustaining an ACLR. Therefore, the purpose of this paper is to discuss the stress and injury model and the cognitive appraisal model. Furthermore, we will evaluate the current literature that examines psychosocial factors in individuals with a history of ACLR and how these factors can influence recovery outcomes and risk for re-injury. In addition to theoretical discussion, recommendations for clinical practice will be provided.

Stress and Injury Model

Williams & Andersen developed a theoretical framework to describe the relationship between the stress response and injury rates in high functioning, physically active individuals.[57] The stress and injury model was then used as a theoretical framework to predict and prevent stress-related athletic injuries (Figure 2.1). The authors proposed that when an athlete encounters a stressful athletic situation, there are multiple factors that contribute to sustaining an athletic injury related to the stress response. The stress and injury model suggests that cognitive, physiological, attentional, behavioral, intrapersonal, social, and stress history can affect how an athlete responds to stress.[57]

When an athlete encounters a potentially stressful athletic situation, a stress response will occur. This stress response consists of a reciprocal interaction between the athlete's cognitive appraisal of the stressful athletic situation and changes in physiological/attentional demands. If an athlete has a negative stress response, then the athlete may experience increased general muscle tension, a narrowing of the visual field, and increased distractibility. Each of these can lead to sustaining an athletic injury.[57]

Four different factors can influence the stress response of the athlete. These factors include the athlete's personality, history of stressors, coping resources, and interventions. Firstly, the personality of the athlete, such as locus of control and trait anxiety, can influence the cognitive appraisal and changes in physiological/attentional demands associated with a stressful athletic situation. Athletes who feel more in control of the situation may respond differently than an athlete who feels lack of control. Secondly, history of stressors can impact an athlete's ability to maintain attention and appropriately appraise stressful situations. Previous musculoskeletal injury is a stressor that could potentially negatively impact the stress response. Thirdly, coping resources, such as mental skills training, can alter how an athlete perceives and responds to a stressful athletic situation. If an athlete has the mental skills to mitigate increased levels of performance anxiety, then that athlete may have a decreased stress response during a stressful athletic situation compared to an athlete without those coping resources. Lastly, Williams & Andersen proposed that interventions, such as cognitive restructuring and relaxation skills, can positively influence the stress response.[57]

Cognitive Appraisal Model

After sustaining an athletic injury, athletes may experience a shift in their cognitive appraisal due to an introduction of a new life stressor as a result of their athletic injury.[58] Wiese-Bjornstal et al.[58] developed the cognitive appraisal model to allow for clinicians to understand how cognitive changes can affect rehabilitation and recovery outcomes after sustaining an athletic injury (Figure 2.2). In the model, cognitive appraisal is defined as how the athlete judges, or appraises, their injury and this appraisal will affect the emotional responses and recovery outcomes in the athlete. Negative cognitive appraisal of their injury and rehabilitation can affect short-term and long-term health outcomes. The cognitive appraisal model suggests that four different factors can influence the cognitive appraisal of an athlete who has sustained an injury: personal factors, situational factors, emotional responses, and behavioral responses.[58]

Personal factors, including psychological, demographic, and physical factors, can influence the cognitive appraisal of an injured athlete. If an athlete has poor coping skills, then this could negatively influence their cognitive appraisal of their injury and rehabilitation. Situational factors, such as the environment, can influence the cognitive appraisal processes. For instance, if an athlete does not feel social support from their rehabilitation specialists, or feels that the environment itself is not conducive for their success, then a negative appraisal of their injury and subsequent poor outcome may occur. [59] Emotional responses, including injury-related fear, can influence an athlete's cognitive appraisal. Development of injury-related fear can not only impact ability to return to sport after injury, but can negatively affect long-term engagement in physical activity in previously high functioning, physically active individuals.[3] Lastly, behavioral responses, such as adherence to rehabilitation and usage of psychological strategies, can alter the cognitive appraisal of an injured athlete and long-term recovery outcomes. If an athlete does not report to rehabilitation, or begins to engage in avoidance behaviors, then their health outcomes may be negatively altered.[58]

Cognitive Appraisal Model and Return to Sport after ACLR

Individuals who sustain an ACL injury during athletics often undergo ACLR to improve the stability of their knee, which would theoretically allow the patient to return to previous levels of sports participation.[60] However, the decision to return to sport after ACLR can be influenced by a multitude of factors, including personal and situational factors.[3,59,61] Use of the cognitive appraisal model could help to explain the poor physical and psychosocial recovery outcomes observed in patients after ACLR. Previous literature has demonstrated that the primary barrier for return to sport after ACLR is injury-related fear.[4] As depicted by the cognitive appraisal model, injury-related fear is an emotional response after musculoskeletal injury that can affect recovery outcomes. As explained by the model, those individuals with increased levels of injury-related fear after ACLR may experience a shift in their cognitive appraisal associated with their ability to participate in sports. This change in cognitive appraisal may negatively influence behavioral responses, such as adherence to rehabilitation, effort, or intensity. In cohesion, each of these factors could contribute to an athlete failing to return to sport. Previous literature supports this hypothesis.

In a qualitative analysis of factors that impact health-related quality of life (HRQL) and physical activity engagement in individuals between 5 to 20 years post ACLR, injury-related fear emerged as a prominent theme.[3] Throughout their entire ACLR experience, all participants described experiencing injury-related fear, ranging from their index ACL injury until their interview day for participation in the study. Participants either engaged in one of three behavioral responses, including fear suppression, fear accommodation, or fear avoidance. Those individuals interviewed who reported suppression of injury-related fear, also demonstrated the ability to cope with their fears and were able to maintain their previous level of sports participation. These individuals stated that they used their injury-related fear as motivation to return to sport. Participants who reported fear accommodation did not return back to previous levels of sport, but were satisfied with their activity level and quality of life. Lastly, participants who engaged in fear avoidance reported cessation of all physical activity and deficits in their quality of life.[3]

As demonstrated by Filbay et al.,[3] how an individual cognitively appraises their ACLR and the factors associated with their injury can influence behavioral responses. Emotional responses, specifically injury-related fear in this population, severely impacted the patient's ability to return back to sport and their HRQL. It is also important to appreciate that emotional responses work in unison with other factors, such as personal and situational factors, to influence the cognitive appraisal process of athletes after ACLR. Those individuals who utilized their injury-related fear as motivation were able to overcome their emotional responses to have a successful recovery. Those who did not, or did not possess the necessary coping skills to overcome their injury-related fear, engaged in avoidance behaviors, which led to a poorer recovery outcomes.[3]

Echoing results demonstrated by Filbay et al.,[3] Burland et al.[59] completed a qualitative analysis to determine the psychosocial factors that influenced return to sport decisions after ACLR. Only six of twelve participants returned to sport. Results demonstrated that psychosocial factors were very influential on the decision to return or not to return to sport after ACLR. Factors that influenced failure to return to sport included hesitancy, lack of confidence, and injury-related fear. However, intrinsic characteristics, including a strong sense of athletic identity, in combination with competitive rehabilitation environments, facilitated return to sport after ACLR. Additionally, the researchers discovered that having a strong support system within and outside of rehabilitation led to increased confidence for patients after ACLR.[59] Use of the cognitive appraisal model can be used to explain the observed results. Personal factors, including the strong sense of athletic identity, positively affected the cognitive appraisal of athletes and led to return to sport. The situational factors observed (competitive rehabilitation environments and social support) also positively influenced cognitive appraisals and facilitated return to sport. However, those individuals after ACLR with increased levels of negative emotional responses led to failure to return to sport, while increased levels of positive emotional responses led to return to sport. Ultimately, each of these factors worked in combination to influence the athlete's cognitive appraisal of return to sport.

<u>Stress and Injury Model and Re-injury after ACLR</u>

The stress and injury model can be used to explain re-injury outcomes in patients after ACLR. Paterno et al.[56] further evaluated the effects of injury-related fear on health outcomes after ACLR. The purpose of their study was to examine the relationship between injury-related fear, objective measures of function, and rates of secondary injury after ACLR and return to sport. All participants completed rehabilitation for a primary ACLR and were cleared to return back to previously levels of function. Participants were tracked for 24 months after clearance for return to sport to identify secondary ACL injury. Results demonstrated that individuals with increased levels of injury-related fear were 4 times more likely to report lower activity levels, 7 times more likely to have hop test scores less than 95%, and 6 times more likely to have quadriceps strength symmetry less than 90%.[56] However, one of the most compelling aspects of their results was that participants with elevated levels of injury-related fear were 13 times more likely to suffer a secondary ACL injury. Thus, individuals with self-reported injury-related fear were less active, had lower functional performance, and were at an increased risk of sustaining a secondary ACL injury.[56]

As suggested by the stress and injury model, history of stressors can negatively affect the stress response and lead to injury. Individuals who return to sport after ACLR may encounter potentially stressful athletic situations. The stress response associated with this situation may be negatively influenced by previous injury and injury-related fear. If an individual after ACLR exhibits increased injury-related fear and decreased coping resources, then a negative stress response may occur. Potentially, individuals with a history of ACLR who return to sport with injury-related fear are unable to overcome their stress response, experience a shift in physiological/attentional demands, and sustain an re-injury to their ACL limb. Previous research has demonstrated that individuals prior to their index ACLR exhibit deficits in attentional demands, specifically in reaction times, and slower reaction times have been associated with injury risk.[36] The current literature about return to sport after ACLR highlights the importance of addressing other factors of HRQL, including psychological, to improve return to sport rates and mitigate re-injury risks in patients after ACLR.

Limitation of the Models

These models are not without limitations. The stress and injury model was designed to describe psychosocial factors that led to initial injury rather than psychosocial factors after the injury has been sustained. While this model is not traditionally used in a post-pathological population, this model can be adapted to explain reinjures after ACLR. Currently, a majority of the ACLR literature examines emotional responses throughout the rehabilitation process prior to return to sports participation. The stress and injury model can be modified to characterize these observed recovery outcomes after ACLR and can provide theoretical support for the implementation of psychoeducation in this population. As demonstrated in the stress and injury model, implementation of appropriate psychosocial interventions can alter the stress response and help to mitigate risk of sustaining an athletic injury during stressful athletic situations.[14] It is important that athletes possess the interventions and appropriate coping resources needed to overcome the stress response during an athletic situation and potentially decrease the risk of re-injury. This could prevent history of previous injury impeding the athlete's ability to perform.

A limitation of the cognitive appraisal model is that the model was designed to understand the recovery process and was not intended to be used as an injury prediction model in this population. The cognitive appraisal model should not be used to explain the relationship between psychosocial factors and sustaining an athletic injury. Rather, this model characterizes the relationship between psychosocial factors and rehabilitation outcomes after ACLR which can help to explain outcomes observed in ACLR literature. However, it is important to utilize the stress and injury model and the cognitive appraisal model in unison to provide a big picture view on the overall impact of psychosocial impairments in the ACLR population.

Recommendations for Clinical Practice

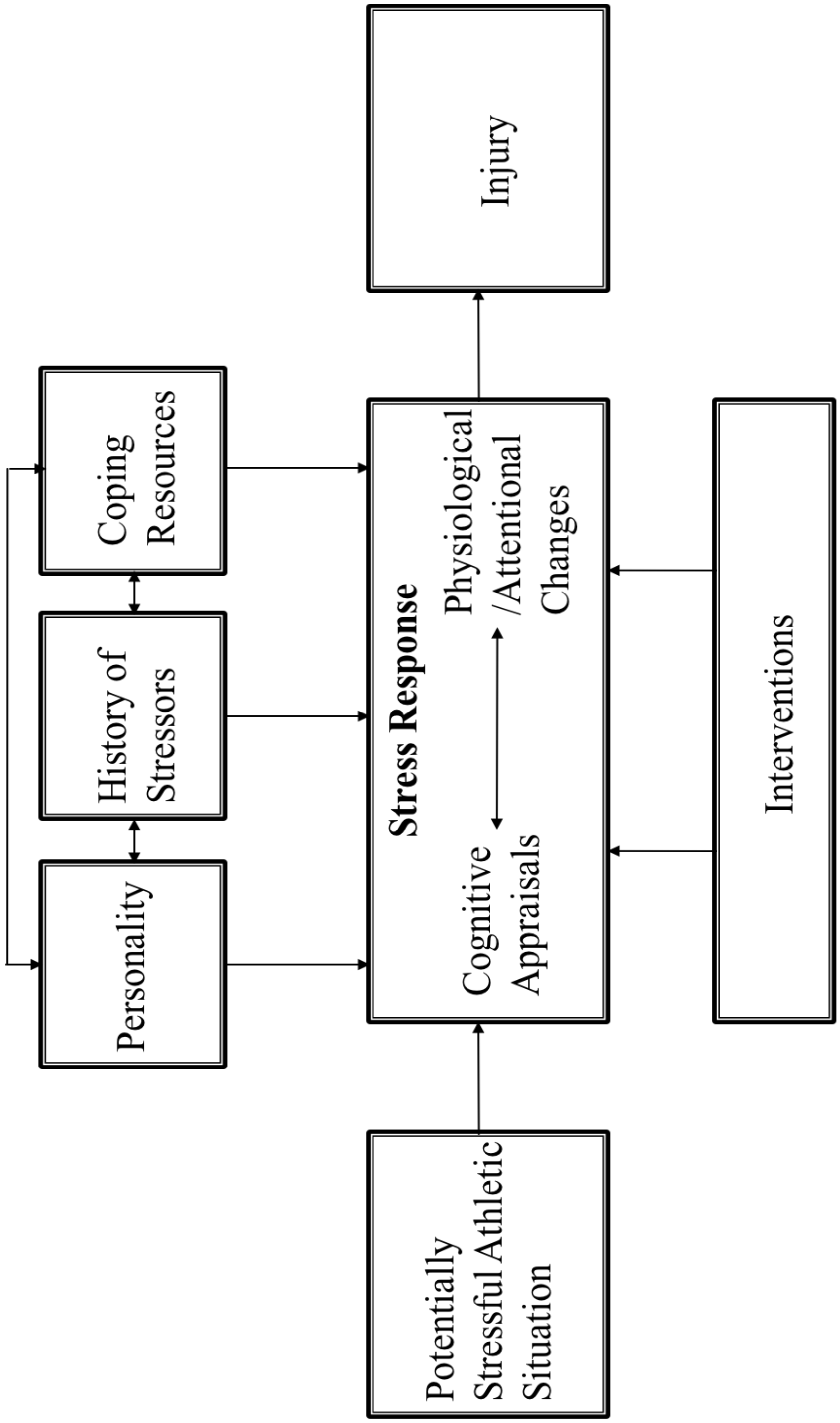
After undergoing ACLR, rehabilitation specialists should consider other factors, besides physical impairments, that can negatively affect recovery and HRQL. Psychosocial factors, including injury-related fear, should be addressed throughout the rehabilitation process after ACLR. Poor recovery outcomes after ACLR linked to psychosocial impairments demonstrates the need for interprofessional collaboration to eliminate psychosocial impairments throughout musculoskeletal rehabilitation. Rehabilitation specialists and sports psychology professionals should work together to develop a rehabilitation plan that would allow for a holistic approach to rehabilitation after ACLR. Instead of focusing on physical health or psychological health in isolate, interprofessional collaboration would allow for a cohesive rehabilitation plan that would provide effective patient-centered care. Moreover, implementation of these psychological interventions throughout rehabilitation can provide the patient with interventions to use independently to decrease the stress response during competition after return to sport has occurred.

Additionally, it is important to objectively evaluate psychosocial impairments throughout the ACLR rehabilitation and recovery process. Throughout the rehabilitation process after ACLR, previous literature has demonstrated fluctuations of injury-related fear.[32] Thus, use of patient-reported outcome measures can provide clinicians with objective measures to evaluate psychosocial impairments. Furthermore, use of patient-reported outcome measures can be used to determine treatment effectiveness of psychosocial interventions. An array of valid and reliable patient-reported outcome measures can be used in this population to address psychosocial impairments, including the Anterior Cruciate Ligament Return to Sport after Injury Scale [62], the Tampa Scale of Kinesiophobia [63], Knee Self-Efficacy Scale [64], the Athlete Fear Avoidance Questionnaire [65], and the Fear-Avoidance Beliefs Questionnaire [23].

Conclusion

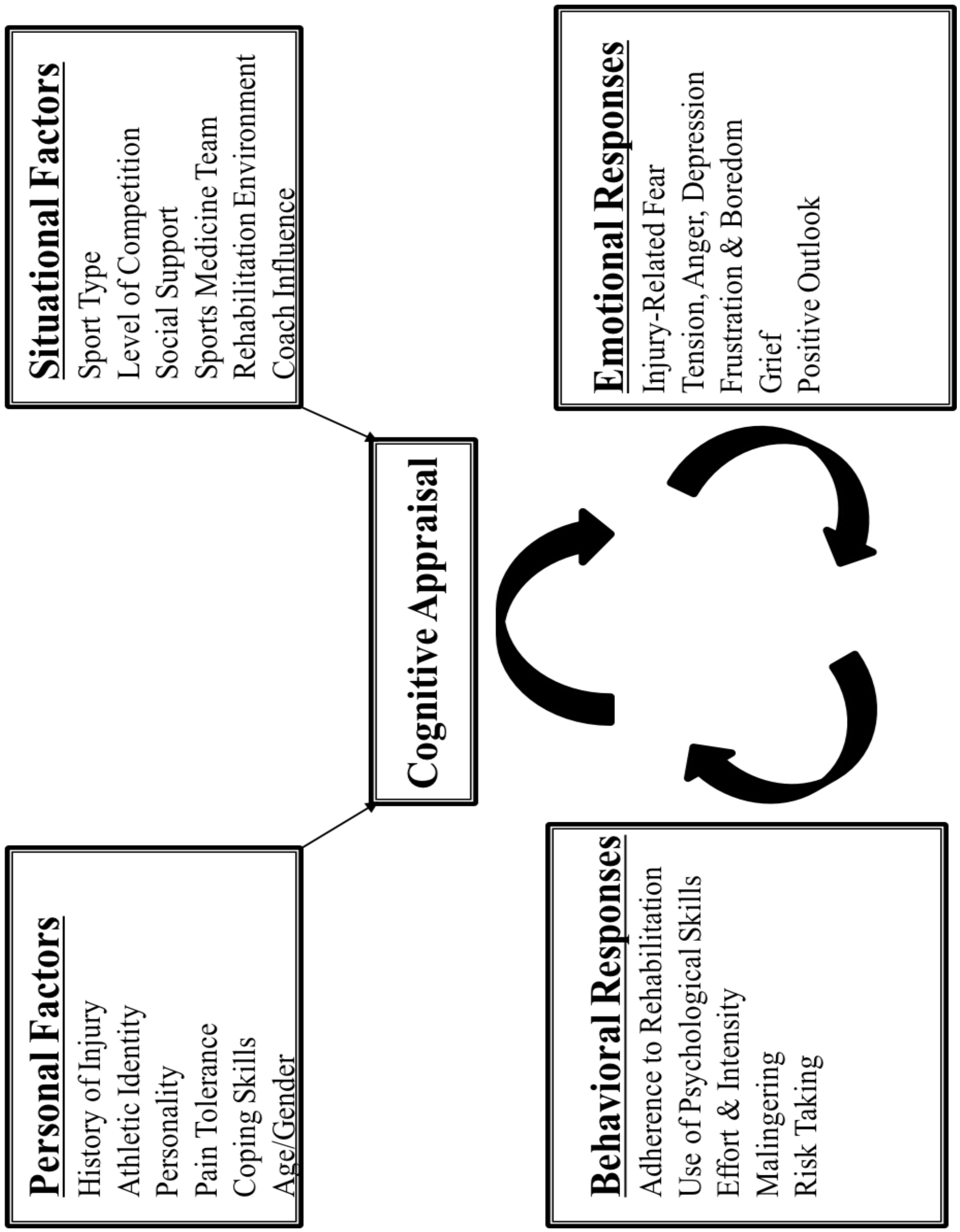
The stress and injury model and the cognitive appraisal models can be used to understand the impacts of psychosocial factors on injury recovery and re-injury after ACLR. Clinicians should utilize these models to provide patient-centered, holistic healthcare by developing intervention strategies to address the psychosocial factors that may impede recovery or lead to secondary injury. Mitigating psychosocial impediments of return to sport can help to prevent previously high functioning, physically active individuals, from failure to return to sport or engage in physical activity. Lastly, interprofessional collaboration between rehabilitation specialists and sports psychology professionals should be considered to optimize recovery after ACLR.

Figure 2.1. Stress and Injury Model



Reprinted with permission from: Taylor & Francis Group
From: Williams JM, Andersen MB. Psychosocial antecedents of sport injury: review and critique of the stress and injury model. *J App Sports Psychol.* 1998;10(1):5-25

Figure 2.2. Cognitive Appraisal Model



Reprinted with permission from: Taylor & Francis Group
From: Wiese-Bjornstal DM, Smith AM, Shaffer SM, Morrey MA. An integrated model of response to sport injury: Psychological and sociological dynamics. *J App Sports Psychol.* 1998;10(1):46-69

Part II: Evaluation of Cognitive Behavioral Interventions and Psychoeducation Implemented by Rehabilitation Specialists to Treat Fear-Avoidance Beliefs in Patients with Low Back Pain: A Systematic Review

Introduction

The fear-avoidance model (FAM) provides a conceptual framework to illustrate how fear-avoidance beliefs can impact a patient's health-related quality of life and physical activity levels.[10,23] Specifically, this model suggests why patients who engage in avoidant behaviors after initial injury enter a cycle of pain, depression, and disability.[10,23] This phenomenon is commonly evaluated in patients with acute, sub-acute, or chronic low back pain (LBP), and recent literature has established a relationship between fear-avoidance beliefs, kinesiophobia, and poor long-term outcomes in patients with LBP.[14,66,67] For example, some patients with LBP have elevated pain-related fear, which may help explain why these patients report chronic disability and do not return to work or desired physical activity.[67] Specific treatments have been developed to help combat psychosocial factors such as fear-avoidance beliefs and/or kinesiophobia.[68,69] Specifically for patients with acute, sub-acute, or chronic LBP, cognitive behavioral therapies (CBT) and psychoeducation are often utilized as an interventions to decrease fear-avoidance beliefs and/or kinesiophobia.[68,69]

Cognitive behavioral therapy (CBT) emphasizes the interrelations between patient's thoughts, feelings, and behaviors.[70] Compared to other forms of psychotherapy, CBT is short-term, goal-oriented, and focuses on the modification of dysfunctional beliefs and behaviors to reduce distress and improve long-term function.[44] Cognitive behavioral therapy techniques include cognitive restructuring,[70] patient education and effective communication,[71] and cognitive functional therapies, such as in vivo exposure technique.[14] Some CBT treatments must be employed by trained mental health professionals,[68,69] but other techniques, such as graded exposure, and psychoeducation, can be provided by a rehabilitation specialist.[14,70] While it is very important to engage in interprofessional collaboration with mental health specialists, it is also important to evaluate treatments or interventions that can be implemented in the musculoskeletal rehabilitation setting to treat fear after injury. Previous systematic reviews have examined the interventions and the efficacy of these interventions utilized to combat psychosocial risk factors in patients with LBP;[68,69] however, to our knowledge, there is not a systematic review that focuses on interventions that can be implemented by a rehabilitation specialist during the patient's musculoskeletal rehabilitation. Therefore, the purpose of this systematic review is to systematically locate, critically appraise, and synthesize the available evidence regarding the effectiveness of CBTs and psychoeducation on fear-avoidance beliefs and/or kinesiophobia, which were implemented by a rehabilitation specialist, in the treatment of patients with LBP compared to a control treatment. For the purpose of this review, rehabilitation specialists included athletic trainers, physical therapists, occupational therapists, physios, and physiotherapists.

Methods

This systematic review was performed utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy

The electronic databases CINAHL, PUBMED, PSYCHOLOGY AND BEHAVIOR SCIENCES COLLECTION, SPORTDISCUS, and PSYCH INFO were systematically searched from their inception through September 1, 2017 by the primary investigator. A combination of key words related to fear-avoidance beliefs, kinesiophobia, LBP, CBT and psychoeducation were searched in the databases (Table 2.1). Boolean operators "OR" and "AND" were used to merge search terms. Additional articles were identified through a hand search of the reference lists of articles that were identified through database searches. Duplicates retrieved from different databases were removed.

Eligibility Criteria

The primary author reviewed articles identified by the systematic search for inclusion in the review. Abstracts and titles were screened by two independent reviewers (SEB and JMH) to determine whether the study met inclusion criteria for this review. Thus, each abstract was read twice for inclusion. Once the independent reviewers determined the study would be included, the full text of the article was reviewed. Only the full text of the abstracts that met the inclusion criteria were reviewed. If disagreements occurred about study eligibility, a third reviewer (MCH) who was blinded to the decisions of the independent reviewers, made the final decision on whether the study would be included into the final review.

Inclusion criteria

Studies were included in the systematic review if they met the following criteria:

- Studies that utilized a randomized controlled trial (RCT) study design.
- Studies that included cognitive functional therapy, CBT patient education/psychoeducation techniques, or fear-avoidance based rehabilitation. CBT was operationally defined as previously described by Beck et al.[44]

- Studies that included adults (>18 years of age) with acute, sub-acute, or chronic LBP.
- Studies that evaluated an intervention that could be implemented by a rehabilitation specialist (physical therapists, athletic trainers, occupational therapists, physios, and physiotherapists).
- Studies that included a patient-reported outcome (PRO) measure as a measure of effectiveness specific to fear-avoidance beliefs, (i.e. Fear Avoidance Beliefs Questionnaire (FABQ)) or kinesiophobia (i.e. Tampa Scale of Kinesiophobia).

Exclusion criteria

Studies were excluded from the systematic review if they:

- Did not evaluate fear, fear-avoidance beliefs, or kinesiophobia in the participants.
- Included post-surgical patients (i.e. lumbar fusions, disc surgery, etc) or specified pathologies (i.e. disc degeneration).
- Included an intervention that could only be implemented by a mental health specialist.
- Studies that were not published in English.

Quality Assessment

The quality of each of the included studies was determined using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale was developed to identify RCTs that were internally valid and to determine whether RCTs provided sufficient statistical information to allow results to be interpretable.[72] Two investigators (SEB and JMH) independently reviewed each study, completed the PEDro, and then came to a consensus on the quality of each study. In the event of disagreement, a third investigator (MCH) blind to the previous assessment results, made the final decision on final scoring of each study. Studies were considered high quality if a PEDro score was ≥ 6.[72]

Study Characteristics

Characteristics associated with each study were extracted. All studies included interventions to treat fear-avoidance beliefs in patients with acute, subacute, or chronic LBP. The characteristics extracted for each study were as follows: subject demographics, information regarding the experimental and control intervention utilized, data collection time points, specific outcome measures for each study, and the results associated with each respective study.

Level of Evidence and Strength of Recommendation

Quality assessment of the evidence for recommendations was evaluated using the Strength of Recommendation Taxonomy (SORT).[73] The SORT is a patient-centered method to grading evidence in healthcare literature.[73] Individual study quality was assessed using the following SORT levels: Level 1 evidence represents good-quality patient-oriented evidence, Level 2 evidence represents limited-quality patient-oriented evidence, and Level 3 represents other evidence. Strength-of-recommendation was also assessed using the SORT grades. A grade of A represents consistent, good-quality patient oriented evidence. A grade of B represents inconsistent or limited-quality patient-oriented evidence. A grade of C represents consensus, disease-oriented evidence.[73]

Data Extraction

Two reviewers (SEB and JMH) extracted data during initial review of each study. This included: study sample, subject demographics, CBT and psychoeducation intervention details, data collection time points, outcome assessments, statistical analysis, results, and conclusions (Table 2.2). Extracted data was reviewed a second time for accuracy once final inclusion of all studies was determined. In addition, the magnitude of the difference between the two groups at each of the time points was examined using Hedge's g effect sizes.[74] Effect sizes were interpreted as weak if $\leq$0.39, moderate if between 0.40 and 0.69, and strong if $\geq$0.70. Effect sizes were only calculated for studies reporting the appropriate measure of central tendency and variability.

Results

Literature Search

The search and review process of articles is demonstrated in Figure 2.3. After examining 30 articles, five[48,75-78] met the inclusion criteria and were eligible for this systematic review. Of the 25 studies excluded, 20 of the studies were deemed ineligible because a rehabilitation specialist did not complete the intervention and one[47] study was excluded due to a crossover RCT study design. Four other articles[79-82] were excluded because their intervention was not designed specifically to target fear-avoidance or kinesiophobia in patients with LBP. A summary of study characteristics for the included studies is located in Table 2.2.

Methodological Quality

The results of the quality assessment for each study are located in Table 2.3. The investigators (SEB, JMH) initially agreed upon 90.9% of items on the PEDro. Disagreements were resolved between the two researchers for 4 out of the 6 items, while a third reviewer (MCH) was consulted to make a final decision on the remaining 2 items. The average total PEDro scores for the 5 included studies was 6.8 with a range of 6-9. All included studies scored ≥6 on the PEDro and were all classified as moderate to high quality.[72]

Study Characteristics

The study characteristics of the included studies are located in Table 2.2. All studies utilized interventions to treat fear-avoidance in patients with acute, sub-acute, or chronic LBP by a rehabilitation specialist. None of the included studies addressed kinesiophobia. Secondary outcomes extracted from these studies included: disability,[48,75-78] pain intensity,[48,75-78] self-efficacy,[78] patient satisfaction,[76] and general health and well-being.[76-78]

Outcome Measures

Patient-reported outcome measures that assessed fear-avoidance beliefs and kinesiophobia were the primary outcomes of interest for this systematic review. Patient-reported outcome measures are self-report surveys that query information about the patient's health status directly from the patient.[18] All studies that assessed fear-avoidance beliefs utilized the Fear-Avoidance Beliefs Questionnaire (FABQ). The FABQ is a 15-item questionnaire that assesses fear-avoidance beliefs in patients with musculoskeletal conditions.[23] The FABQ consists of two subscales. The physical activity subscale (FABQ-PA) consists of 5 items and examines fear-avoidance beliefs associated with physical activity. The work subscale (FABQ-W) consists of 10 items and examines fear-avoidance beliefs associated with work. A 6-point Likert scale is used to score each question, and higher scores represent greater fear-avoidance beliefs. A score >15 on the FABQ-PA[67] and >34 on the FABQ-W[83] indicates high fear-avoidance beliefs. In patients with LBP, the FABQ demonstrates excellent reliability (ICC = 0.90 (FABQ-PA) and 0.96 (FABQ-W)).[23]

<u>Interventions</u>

Interventions included psychoeducation through usage of *The Back Book,*[48,75,77] graded exercise,[48,78] and cognitive functional therapy.[76] *The Back Book* is an educational booklet with a "stay-active approach" which was designed for patients with nonspecific LBP.[75] The book promotes self-care as it provides patients with information about the fear-avoidance model, appropriate strategies on how to cope with LBP, and encouragement to return to normal activities.[75] A graded exercise technique, included in a fear-avoidance-based treatment, consisted of predetermined intensity, duration, and repetition of specific exercises.[48,78] Finally, a classification based cognitive functional therapy (CFT) was utilized in one included study. This treatment included outlining the patient's pain on a diagram and focused on integration of functional activities that the patient avoided in daily life.[76] Cognitive functional therapy is multi-faceted and patient specific. This technique is also similar to cognitive behavioral exposure treatments and/or activities pacing.[76]

<u>Statistical and Clinical Significance</u>

Of the five included studies, two[48,76] studies demonstrated significant differences between the experimental and control groups. Means, standard deviations and effect sizes for outcomes of interest in each study are located in Table 2.4. Of the 39 effect sizes that were calculated, ten[48,76] were interpreted as strong with 95% CI that did not encompass zero, while one[48] was interpreted as moderate and 28[48,75-77] were interpreted as weak with 95% CIs that crossed zero. Of the large effect sizes, 3 were observed in the FABQ-PA, 1 was observed in the FABQ-W subscales, 2 were observed for the Oswestry Disability Index (ODI), 2 were observed for the pain intensity numerical rating scale (PINRS), and 2 were observed for the Hopkins Symptoms Checklist (HSC). Large effect sizes were demonstrated at 4-weeks,[48] 3-months,[76] and 12-months,[76] post CBT intervention for FABQ-PA, ODI, PINRS, and HSC and were observed at 3-months[76] for the FABQ-W. The moderate effect size was observed in the FABQ-PA subscale at 6 months post CBT intervention.[48] Rasmussen-Barr et al.[78] did not include appropriate data for effect size calculation.

Level of Evidence

The results of this systematic review demonstrate there is Grade B evidence to support the use of CBT and/or psychoeducation interventions, implemented by rehabilitation specialists, to treat fear-avoidance beliefs in patients with LBP. This grade was given due to inconsistent Level 1 patient-oriented evidence on the effectiveness of these interventions when compared to control treatments.

Discussion

Summary of Results

The purpose of this systematic review was to evaluate the effectiveness of CBT and/or psychoeducation interventions implemented by rehabilitation specialists, compared to a control treatment, to treat fear-avoidance beliefs and/or kinesiophobia in patients suffering with acute, sub-acute, or chronic LBP. A total of two[48,76] out of 5 studies included in this systematic review demonstrated significant and clinically meaningful improvements in fear-avoidance beliefs for patients that underwent a CBT and/or psychoeducation intervention to treat psychosocial factors compared to a control condition. None of the included studies assessed kinesiophobia.

Effectiveness of Psychoeducation and Cognitive Behavioral Therapies

George et al.[48] examined the effectiveness of a fear-avoidance based physical therapy treatment that included *The Back Book*, treatment based classification (TBC) therapy, and graded exercise technique compared to TBC therapy alone. Treatment based classification therapy uses key findings on a physical examination to classify the patient with acute LBP into one of four separate treatment categories.[84] The standard of care treatment group received an educational pamphlet, which discussed spinal anatomy and pathology, and a standardized exercise progression. The fear-avoidance-based treatment received psychoeducation that encouraged the patient to assume a participatory role in their rehabilitation, and also educated the patient to view their back pain as a common condition, instead of a debilitating disease.[48] Patients in the experimental group completed a graded exercise program, and were provided positive reinforcement and a new exercise quota once an established exercise quota was reached. The graded exercise program utilized predefined guidelines to standardize the treatment for those enrolled within the fear-avoidance-based physical therapy treatment group. The fear-avoidance group had significantly lower FABQ-PA scores compared to the standard of care group (Table 4) at both 4-weeks and 6-months which was further supported by moderate and large effect sizes. No significant differences were demonstrated for the FABQ-W at any time period within this study.

Vibe Fersum et al.[76] implemented CFT and compared these effects to traditional exercise and manual therapy. Cognitive functional therapy addresses cognitive, functional, and lifestyle factors that are individualized for each patient. For example, psychoeducation regarding the nature of the patient's pain and graded exposure exercise techniques specific to the patient's impairments could be implemented in CFT. The inclusion of therapy to address a lifestyle factor, such as sedentary behaviors, may also be included. The CFT in this study consisted of four main components: outlining each patient's pain in a diagram with the physiotherapist, incorporating specific movement exercises to normalize maladaptive movements, integrating activities of daily living that were avoided by the patient, and designing a physical activity program based on the classification system that was best suited for the patient.[76] The control group was treated with mobilization or manipulation, and were also provided exercises to be completed at home. The results demonstrated that CFT led to decreases in fear-avoidance beliefs as measured by the FABQ when compared to the traditional exercise and manual therapy group at 3 months and 12 months on the FABQ-PA, which was also supported by large effect sizes between groups at both time points. Furthermore, the experimental group demonstrated significantly improved FABQ-W scores at 3 months. This study provides further information regarding the efficacy of additional intervention besides psychoeducation strategies, specifically for chronic LBP patients. When compared to the other studies in cohorts of patients with chronic LBP, significant and clinical differences only occurred in combination with further cognitive behavioral intervention techniques.

Vibe Fersum et al.[76] also included the ODI, the PINRS, the HSC (a screening tool to measure symptoms of anxiety and depression), total lumbar spine range of motion, a patient satisfaction questionnaire, and the Orebro screening questionnaire (a screening tool that predicts long-term disability and failure to return to work). Cognitive functional therapy led to statistical and clinical meaningful differences in decreasing pain and disability, and increasing range of motion and patient satisfaction.[76] Large effect sizes were observed for ODI, PINRS, and the HSC. George et al.[48] also collected the ODI and PINRS to measure disability and pain, respectively. However, significant between group differences were not observed.

Three included studies did not find significant results. Rasmussen-Barr et al.[78] included similar methodologies as George et al.[48]; however, George et al.[48] included a stronger psychoeducation component (i.e. The Back Book). The stronger psychoeducation component may have provided the active ingredient necessary to demonstrate significant and clinical differences between groups. Additionally, Rasmussen-Barr et al.[78] included a chronic LBP population while George et al.[48] examined these methodologies in an acute LBP population. It is possible these methodologies are more effective for patients with acute LBP. Sparkes et al.[75] and Ranton et al.[77] also utilized a psychoeducation component, but did not include further strategies, such as a graded exercise program. Thus, it appears psychoeducation strategies alone are not effective in decreasing fear-avoidance beliefs in patients with LBP.

Methodological Considerations

All studies included in this review were considered moderate to high quality evidence, but methodological concerns did affect PEDro scores. All of the studies lost one point on the quality assessment due to lack of participant blinding. In addition, only one study blinded the therapists and only two studies blinded assessors of at least one outcome measure. While blinding of the patients and outcome assessors in future studies could be relatively easily addressed; blinding of the therapist implementing the treatment may not always be possible. Future studies should examine ways to blind patients and outcome assessors, provide further consideration on the description of how therapists are trained, and discussion regarding whether blinding was possible should be made.

Outcome Measures

While not included in this systematic review due to methodological design, Vlaeyen et al.[47] examined the effectiveness of a cognitive behavioral exposure treatment, in vivo exposure, compared to graded activity. Vlaeyen et al.[47] included the PCS to assess pain catastrophizing in patients with LBP. The PCS is a valid and reliable 13-item questionnaire that is scored using a 5-point Likert scale, where higher scores indicate greater levels of catastrophizing.[33] In this study, patients who had the in vivo exposure treatment had decreased pain catastrophizing scores compared to those in the graded activity treatment. The FAM illustrates how pain catastrophizing can lead to fear-avoidance beliefs, which in turn leads to chronic disability, depression, and disuse.[10] Other behavioral interventions that have been utilized to specifically target pain include relaxation training[85] and mindfulness[86]. Future research should consider using the PCS, which can provide another perspective into the patient's attitudes toward and beliefs about pain, which can be affected prior to the engagement in avoidant behaviors. Early recognition of pain catastrophizing behaviors and early intervention may prevent development of avoidant behaviors. Lastly, depression and anxiety may be important variables to consider that could affect fear avoidance beliefs and/or kinesiophobia in patients with acute, subacute, or chronic LBP.

Practical Implications

Patient-centered care has been demonstrated to improve treatment outcomes and should be further incorporated into the orthopaedic rehabilitation setting.[87] One of the two studies[76] that demonstrated significant and clinically meaningful differences between groups incorporated CBT techniques that were personalized treatment plans to treat patient specific fears. Emphasis on the patient's specific fears and treating those issues appears to have led to a more successful long-term outcome. While *The Back Book* emphasizes patient education, this modality in isolate was not effective in decreasing fear in patients with LBP.[75,77] Thus, while patient education is necessary to provide patient-centered care, the reduction of fear-avoidance beliefs may not occur with patient education alone. The results of this review suggest that long-term changes in patient behavior and psychological well-being may need further intervention beyond patient education. The combination of a gradual completion of the fearful task through patient-specific cognitive functional therapies and psychoeducation appear to be more effective at decreasing fear-avoidance beliefs.

This concept is further supported by George et al.[48] who included *The Back Book,* in combination with graded exercise treatments. While George et al.[48] did not find statistical or clinically meaningful differences for any other outcome measure besides fear-avoidance beliefs, interaction was discovered between individuals with elevated fear-avoidance beliefs and less disability in those assigned in the fear-avoidance treatment group. Those patients enrolled into a fear-avoidance based treatment group who exhibited lower levels of fear-avoidance beliefs at baseline had increased disability at follow-up time points when compared to those receiving standard of care physical therapy. It appears the intervention may negatively affect their disability and pain. These results further emphasize the importance for patient-centered care, as, it is important to design an appropriate treatment based on the information gleaned from the patient by the rehabilitation specialist. [48] Clinicians should utilize PROs that assess these psychological factors to detect identify elevated levels of fear that warrant proper treatment. Furthermore, the utilization of cut-off scores on these PROs may assist rehabilitation specialists with determining whether patients should be enrolled in a fear-avoidance based interventions.[48] However, clinicians should utilize caution when employing cut-off scores in clinical practice. While cut-off scores can be utilized as a crude strategy for the identification patients who may benefit from fear-avoidance based interventions, a patient-by-patient assessment of their psychological schema should be assessed, in combination with the usage of dimension specific PROs, to foster personalized and patient-centered care for each individual patient.

Future research should further examine the effects of CBTs on different types of psychosocial factors such as self-efficacy. Rasmussen Barr et al.[78] included a measure of self-efficacy in their study. The patients enrolled in the CBT demonstrated significant and clinically meaningful differences in self-efficacy when compared to patients that completed the daily walking and traditional home exercise treatment.[78] Self-efficacy may be a mediating factor between the development of pain-related fear and outcomes in chronic LBP.[88] Thus, future research should include a measure of self-efficacy in this population.

Limitations

This review is not without limitations. Firstly, the databases that were searched were considered to be best for the purposes of this review. There is always a possibility that relevant articles may have failed to be retrieved during the search process. Secondly, the authors defined rehabilitation specialist to include physical therapists, athletic trainers, occupational therapists, physios, and physiotherapists. While these rehabilitation specialists traditionally treat patients with LBP, studies that included other healthcare providers that treat these patients could have been missed in this review. Furthermore, included studies were not equivalent in the type of "dose" of cognitive behavioral intervention or psychoeducation provided and the samples only represent patients with LBP in certain settings. These factors could affect generalizability of these results.

An additional limitation of this review is the lack of information provided in the individual studies regarding the training of the rehabilitation specialists to implement the CBTs and/or psychoeducation intervention. One study[76] provided this information , and was one of the two studies to demonstrate statistical and clinical significance with their intervention. Thus, it is possible a lack of education and/or training on how to appropriately administer the interventions impacted the results. Further information regarding the training of the rehabilitation specialist should be included in future studies. Lastly, due to the limited number of studies, there is limited strength associated with the conclusions and recommendations in this review.

None of the studies presented in this review utilized the FABQ and Tampa Scale of Kinesiophobia (TSK) together to evaluate these two different constructs of fear. Fear-avoidance beliefs, measured by the FABQ, are dysfunctional beliefs about pain or fear of pain.[10] Kinesiophobia, measured by the TSK, is a debilitating or irrational fear of movement or vulnerability to re-injury.[89] Measuring both constructs of fear may provide be beneficial in future research and clinical practice. Additionally, in order to gain a better perspective of the patient's psychosocial wellbeing other outcome measures such as the Pain Catastrophizing Scale (PCS) and Self-Efficacy Scale could be utilized in combination with the FABQ or TSK. Lastly, inclusion of an outcome measure, such as HSC[90], to screen for anxiety and depression, could be of benefit for clinicians and should also be considered.

Conclusion

There is inconsistent, patient-oriented evidence (grade B) that CBT and/or psychoeducation interventions implemented by a rehabilitation specialist to treat fear-avoidance beliefs and/or kinesiophobia in patients with LBP are effective. Patient-centered interventions, such as cognitive functional therapy with psychosocial patient education, demonstrated favorable outcomes, while patient-education techniques alone were not sufficient to reduce these psychosocial factors in this population. However, continued research is needed to determine the most effective combination of treatments to treat fear-avoidance beliefs. Future research should further explore which components of CBTs are the most beneficial, determine best practices for training rehabilitation specialists in the delivery of CBTs, and should also examine how to match these interventions for individualized patient problems.

Acknowledgments: This study was published in Archives of Physical Medicine and Rehabilitation and was reprinted in this dissertation with permission.

Table 2.1 Search strategy

Step	Search terms	Boolean Operator	EBSCO Host
1	Low Back Pain Non Specific Low Back Pain Backache Lumbago Chronic Low Back Pain Low Back Dysfunction Back Pain Acute Low Back Pain Subacute Low Back Pain	OR	58, 715
2	Fear Avoidance Fear Avoidance Beliefs Fear of Movement Kinesiophobia Fear of Re-injury Biopsychosocial	OR	22, 853
3	Intervention Treatment Rehabilitation Rehab Therapy Cognitive Therapy Behavioral Therapy Cognitive Behavioral Therapy Psychoeducation	OR	9, 722, 072
4	1+2+3	AND	1, 608
5		Limited to ALL ADULT	438
6		Limited to English	428
Hand Search			3
Total Identified			431

Table 2.2 Characteristics of the included studies

Author	Level of Evidence	PEDro Score	Type of LBP	Subject Characteristics	Intervention	Data Collection Time points	No. Control Patients	No. Experimental Patients	Depend. Variable	Results
George et al. 2003	1	7	Acute LBP	*Inclusion:* Between ages 18-55, LBP within the last 8 weeks, English speaking /reading *Exclusion*: Nerve root compression, low back surgery within the last 6 months, tumor,	*Intervention:* Patients were enrolled in a fear avoidance-based physical therapy treatment that consisted of distribution of the *Back Book* to complete during HEP and graded exercise supervised by a physical therapist. Graded exercise consisted of	Pre-assessment, 4-weeks and 6-month follow-up	32	34	ODI, Pain Intensity, FABQ	The intervention group had significantly lower FABQ scores at both follow-ups compared to the control group. There were no other signific

Table 2.2 (continued)

				fracture, osteoporosis, or pregnancy	a predetermined quota of intensity of exercise, duration of exercise, or repetition of exercise. *Control*: Patients were enrolled in appropriate TBC therapy and were provided *Handy Hints*, an educational pamphlet. to read as part of their HEP.					ant differences between groups at any of the time-points for the ODI or Pain Intensity outcome measures.
Sparkes et al. 2011	1	9	Chronic LBP	*Inclusion:* Over 18 yrs, LBP with or without referred pain,	*Intervention:* Patients received the *Back Book* while waiting for their appointment	Pre-appointment and post-appointment	32	34	BBQ, FABQ, RMDQ, VAS	No statistical differences between groups

Table 2.2 (continued)

	and referral to the spine clinic by general practitioner *Exclusion:* Serious spinal disease, history of drug or alcohol abuse, psychiatric illness, or inability to read, write, or understand English	with SPC. The patients completed the outcome questionnaires prior to reading the *Back Book*. The patients completed the post-assessments at their first appointment with SPC. *Control:* No additional information was provided while waiting for appointment with SPC. The patient's completed the pre-appointment questionnaires while waiting for	for any of the outcome measures.

Table 2.2 (continued)

					an appointment with the SPC and the post-appointment at their first appointment with the SPC.					
Rasmussen Barr et al. 2009	1	6	Chronic LBP	*Inclusion*: Ages18-60, working, back pain lasting >8 weeks, 1 pain-free period in the previous year. *Exclusion:* First-time LBP, radiating	*Intervention:* Patients met with a physical therapist and completed an exercise program which was based on pain level and observed movement control and quality (graded exercise). Patients were also given a HEP and were	Pre-physical therapy, Post physical therapy, 6, 12, and 36 months	35	36	ODI, VAS, SF-36, SES, FABQ-PA	No significant differences between groups for fear-avoidance beliefs or pain. There were significant differences in

Table 2.2 (continued)

	pain, lumbar disc hernia or fracture, back surgery, diagnosed inflammatory joint disease, severe osteoarthritis, or malignant disease	instructed to complete the HEP indefinitely to avoid recurrent back pain. Finally, patients were educated on the importance of activating stabilizing muscles for activities of daily living. *Control:* Patients were instructed to take a 30-minute walk every day. They were given a general HEP but received no follow-up instructions. The patients		OSD scores. Participants enrolled in the exercise group demonstrated significant decreases in perceived disability at post-intervention, 6, and 12 months after baseline. Additionally, there

Table 2.2 (continued)

	documented their walks in a diary and returned it to their physical therapist. No formal physical therapy occurred.	was a significance difference in pain reduction from baseline between groups immediately post-intervention. Lastly, there was a significant group difference at the follow-up time

Table 2.2 (continued)

points in physical health. The exercise group had significantly better physical health immediately post-intervention and at 6, 12 and 36 month follow-ups. They also had improved and self-

Table 2.2 (continued)

									efficacy at both the 12 and 36 month follow-ups compared to the control group.
Rantonen et al. 2014	1	6	Mild LBP	*Inclusion:* <57 years old, reported LBP intensity between 10-34mm on VAS in the past week, and fulfilled one of	*Intervention:* The patients were given the Back Book by an occupational health nurse who reviewed the book in detail, and provided an additional PowerPoint presentation prepared by	Pre-*Back Book* distribution, 3, 6, 12, 24, 48 months post		RM-18, FABQ, VAS, HRQL	No statistical differences between groups for any outcome measure

Table 2.2 (continued)

the following criteria: LBP duration of ≥2 weeks in the past 12 months; LBP that radiates below the knee; Recurrent LBP (≥2 episodes in past year), and Self-reported work absence due to LBP in the past year.	the primary author. *Control:* Patients only received the *Back Book* without any further information or advice.

Table 2.2 (continued)

Exclusion: Retirement within the follow-up period, pregnancy, acute nerve root compression symptoms, malignant tumors, recent fracture, sever osteoporosis, or other disease.

Table 2.2 (continued)

Vibe Fersum et al. 2013	1	6	Chronic Non-Specific LBP	*Inclusion*: Localized back pain as a results of mechanical dysfunction *Exclusion:* Continuous sick-leave for >4 months, specific LBP diagnosis, any low limb surgery in the previous 3 months, surgery involving the lumbar spine, pregnancy, diagnosed with psychiatric disorder, widespread constant non-specific pain disorder, pain without clear mechanical behavior, active rheumatologic disease, progressive neurological disease, serious cardiac or internal medical condition, malignant diseases, acute traumas, infection or acute vascular catastrophes.	*Intervention:* After examination by a physical therapist the patients completed Classification Based – Cognitive Functional Therapy (CB-CFT) which had four main components; 1) An outline of the patient's pain in a diagram 2) completed specific movement exercises to normalize maladaptive movement behaviors, 3) focused on a functional integration of activities avoided in activities of daily living, and 4) physical activity program designed for the movement classification. Patients were seen 2-3 times per week for 30-45 minutes session for 12 weeks.	3 months, 12 months	43	51	ODI, PINRS, HSCL-25, FABQ, Patient Satisfaction Questionnaire Orebro Screening Questionnaire	Statistical and clinical significance between groups for all outcomes measures at 3 and 12 months.

Table 2.2 (continued)

Control: Treated with joint mobilization or manipulation techniques to the spine or pelvis. Patients were also given general exercise or motor control exercise. Patients were not assigned into a classification group.

Abbreviations: BBQ = Back Beliefs Questionnaire, FABQ = Fear Avoidance Beliefs Questionnaire, RMDQ = Roland-Morris Disability Questionnaire, VAS = Visual Analog Scale, SF-36 = Short Form-36 Health Survey, SES = Self-Efficacy Scale, FABQ-PA = Fear Avoidance Beliefs Questionnaire – Physical Activity Subscale, RM-18 = Roland-Morris Disability Questionnaire – 18 Items, HRQL = Health Related Quality of Life, HSCL-25 = Hopkins Symptoms Checklist, SPC = Spinal Pain Clinic, PT = Physical Therapist, OH = Occupational Health

Table 2.3. Risk of bias of included studies

PEDro Item	Sparkes et al. 2011	Rasmussen Barr et al. 2009	Ranton et al. 2014	Vlaeylen et al. 2002	VibeFersum et al. 2013	George et al. 2003
1. Eligibility criteria were specified.	Yes	Yes	Yes	Yes	Yes	Yes
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).	Yes	Yes	Yes	Yes	Yes	Yes
3. Allocated was concealed.	Yes	Yes	Yes	Yes	Yes	Yes
4. The groups were similar at baseline regarding the most important prognostic factors.	Yes	Yes	Yes	Yes	Yes	Yes
5. There was blinding of all subjects.	No	No	No	No	No	No
6. There was blinding of all therapists who administered the therapy.	Yes	No	No	No	No	No
7. There was blinding of all assessors who measured at least one key outcome.	Yes	No	No	No	Yes	No
8. Measures of at least one key outcome were	Yes	No	No	Yes	No	Yes

Table 2.3. (continued)

obtained from more than 85% of the subjects initially allocated to groups.						
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat."	Yes	Yes	Yes	Yes	No	Yes
10. The results of between-group statistical comparisons are reported for at least one key outcome.	Yes	Yes	Yes	Yes	Yes	Yes
11. The study provides both point measures and measures of variability for at least one key outcome.	Yes	Yes	Yes	Yes	Yes	Yes
Total	9/10	6/10	6/10	7/10	6/10	7/10

Table 2.4. Hedge's g effect sizes and 95% confidence intervals for all time points for the included studies.

Studies	Outcome Measures	Time Point	Mean (SD) Experimental	Mean (SD) Control	Effect Size (95% CI)
George et al. 2003	FABQ-PA	4-weeks	10. 7 (5.4)	14.9 (6.5)	-0.70 (-1.19, -0.20)
George et al. 2003	FABQ-PA	6-months	10.1 (5.9)	13.5 (7.0)	-0.52 (-1.01, -0.03)
George et al. 2003	FABQ-W	4-weeks	11.1 (10.5)	13.4 (12.4)	-0.20 (-0.68, 0.29)
George et al. 2003	FABQ-W	6-months	9.7 (10.2)	12.3 (12.3)	-0.23 (-0.71, 0.26)
George et al. 2003	ODI	4-weeks	17.7 (19.5)	21.5 (18.3)	-0.20 (-0.68, 0.20)
George et al. 2003	ODI	6-months	11.9 (10.0)	15.5 (17.9)	-0.25 (-0.73, 0.24)
George et al. 2003	Pain	4-weeks	1.9 (2.4)	2.6 (2.4)	-0.29 (-0.77, 0.20)
George et al. 2003	Pain	6-months	1.7 (2.2)	1.5 (2.0)	0.09 (-0.39, 0.58)
Sparkes et al. 2011	FABQ	Post	11.3 (6.0)	12.4 (3.9)	-0.21 (-0.73-0.31)
Sparkes et al. 2011	BBQ	Post	27.7 (8.5)	27.1 (8.3)	0.07 (-0.45 0.31)
Sparkes et al. 2011	RMDQ	Post	8.3 (5.4)	6.5 (4.6)	0.35 (-0.17, 0.88)
Sparkes et al. 2011	VAS	Post	4.22 (3.2)	3.74 (2.6)	0.16 (-0.36, 0.68)
Rantonen et al. 2014	FABQ	3 months	28 (11)	26 (10)	0.19 (-0.10-0.48)
Rantonen et al. 2014	FABQ	6 months	25 (10)	25 (10)	0.00 (-0.29- 0.29)
Rantonen et al. 2014	FABQ	12 months	27 (11)	25 (9)	0.20 (-0.09- 0.49)
Rantonen et al. 2014	FABQ	24 months	26 (12)	25 (9)	0.09 (-0.20- 0.39)
Rantonen et al. 2014	RM-18	3 months	3 (3)	2 (3)	0.33 (0.04, 0.63)
Rantonen et al. 2014	RM-18	6 months	2 (3)	2 (3)	0.00 (-0.29, 0.29)

Table 2.4. (continued)

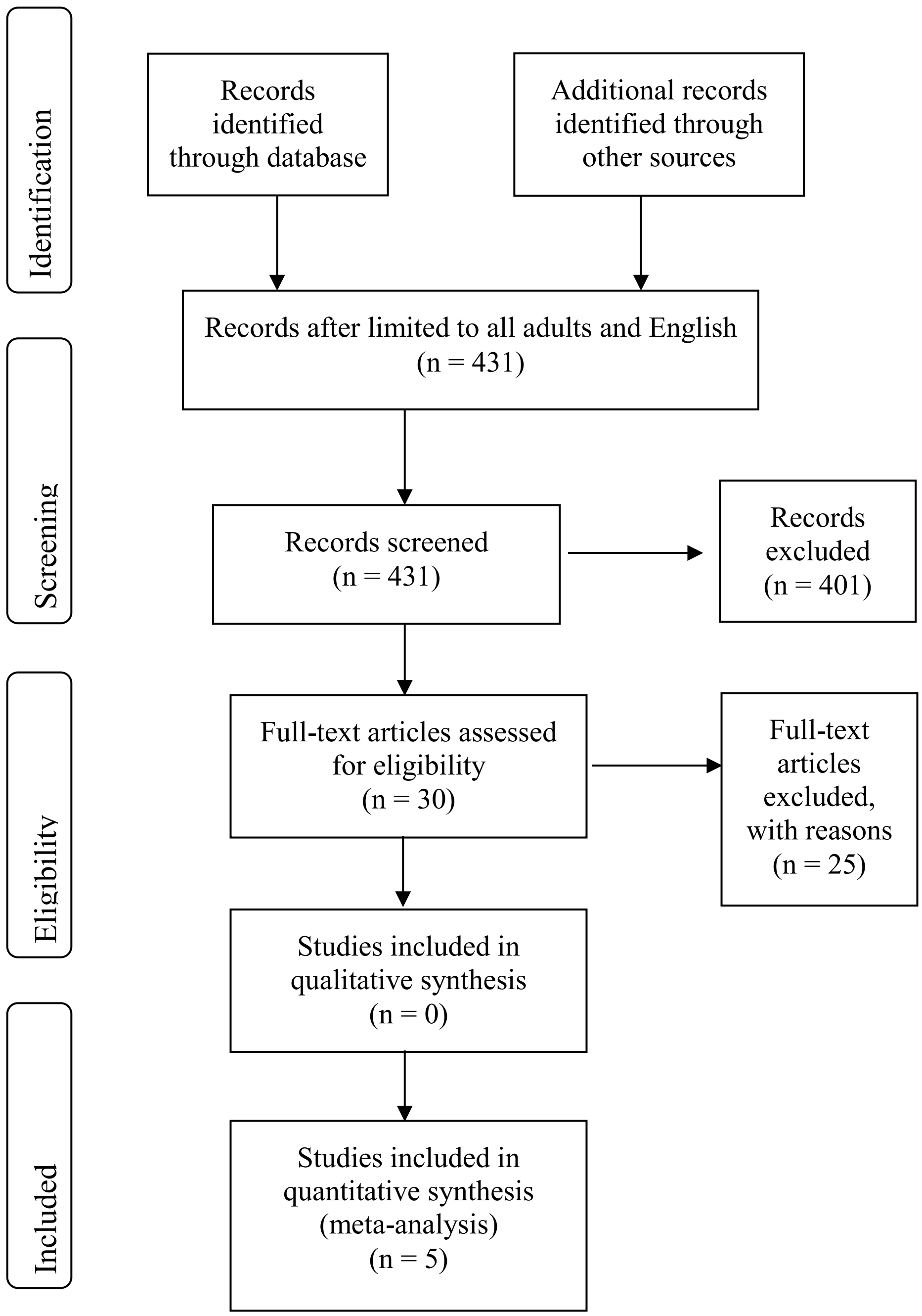
Rantonen et al. 2014	RM-18	12 months	2 (3)	2 (3)	0.00 (-0.29, 0.29)
Rantonen et al. 2014	RM-18	24 months	2 (4)	2 (3)	0.00 (-0.29, 0.29)
Rantonen et al. 2014	VAS	3 months	16 (16)	20 (21)	-0.21 (-0.51, 0.08)
Rantonen et al. 2014	VAS	6 months	14 (16)	17 (17)	-0.18 (-0.48, 0.11)
Rantonen et al. 2014	VAS	12 months	19 (20)	17 (19)	0.10 (-0.19, 0.40)
Rantonen et al. 2014	VAS	24 months	20 (23)	18 (20)	0.09 (-0.20, 0.39)
Rantonen et al. 2014	HRQL	3 months	0.92 (0.07)	0.93 (0.06)	-0.15 (-0.45, 0.14)
Rantonen et al. 2014	HRQL	6 months	0.92 (0.09)	0.93 (0.07)	-0.12 (-0.42, 0.17)
Rantonen et al. 2014	HRQL	12 months	0.92 (0.09)	0.93 (0.06)	0.00 (-0.29, 0.29)
Rantonen et al. 2014	HRQL	24 months	0.91 (0.10)	0.92 (0.07)	-0.12 (-0.41, 0.18)
Vibe Fersum et al. 2013	FABQ-PA	3 months	6.1 (5.0)	10.3 (6.0)	-0.76 (-1.18,-0.34)
Vibe Fersum et al. 2013	FABQ-PA	12 months	5.8 (5.5)	10.9 (5.5)	-0.92 (-1.35, -0.49)
Vibe Fersum et al. 2013	FABQ-W	3 months	8.3 (8.4)	17.4 (10.8)	-0.94 (-1.37,-0.52)
Vibe Fersum et al. 2013	FABQ-W	12 months	7.7 (9.0)	16.6 (12.2)	-0.21 (-0.73, 0.31)
Vibe Fersum et al. 2013	ODI	3 months	7.6 (6.7)	18.5 (8.1)	-1.48 (-1.94,-1.02)
Vibe Fersum et al. 2013	ODI	12 months	9.9 (9.8)	19.7 (11.7)	-0.91 (-1.22, -0.48)
Vibe Fersum et al. 2013	PINRS	3 months	1.7 (1.7)	3.8 (1.9)	-1.16 (-1.60, -0.72)
Vibe Fersum et al. 2013	PINRS	12 months	2.3 (2.0)	3.8 (2.1)	-0.73 (-1.15, -0.31)
Vibe Fersum et al. 2013	HSC	3 months	1.20 (0.27)	1.43 (0.37)	-0.71 (1.13, -0.30)
Vibe Fersum et al.	HSC	12 months	1.22 (0.32)	1.51 (0.47)	-0.73 (-1.13, -0.30)

Table 2.4. (continued)

Vibe Fersum et al. 2013	ROM	3 months	49.7 (14.0)	45.6 (12.7)	0.30 (-0.11, 0.71)

Abbreviations: FABQ-PA = Fear Avoidance Beliefs Questionnaire- Physical Activity Subscale, FABQ-W = Fear Avoidance Beliefs Questionnaire- Work Subscale, ODI = Oswestry Disability Index, Pain = Pain intensity, BBQ = Back Beliefs Questionnaire, RMDQ = Roland Morris Disability Questionnaire, VAS = Visual Analog Scale, RM-18 = Roland Morris Disability Questionnaire – 18 items, HRQL = Health-Related Quality of Life, PINRS = Pain Intensity Numerical Rating Scale, HSC = Hopkins Symptoms Checklist, ROM = Total Lumbar Range of Motion

Figure 2.3. Flow Chart of Literature Review



This figure was adapted from the PRISMA statement created by Moher et al.

Part III: Neural Substrates of the Fear Response and Health Outcomes after Anterior Cruciate Ligament Reconstruction

Introduction

The impetus of anterior cruciate ligament reconstruction (ACLR) is to allow previously high functioning, physically active people to return back to desired levels of sports participation.[60] However, this does not always occur. Approximately 1 out of 3 patients after ACLR will not return to competitive levels of sports participation and injury-related fear has been cited as the primary reason for this failure to return.[4] However, the development of injury-related fear is not the only maladaptive health outcome that has been observed in this population. Individuals after ACLR have demonstrated neuroplastic alterations as well as neurocognitive deficits as a result of their ACL injury and subsequent reconstruction.[36-38] Specifically, patients after ACLR exhibit compensatory sensorimotor brain activation patterns, including increased activation in the contralateral motor cortex and lingual gyrus, when compared to healthy matched controls.[37] Furthermore, these patients also exhibit prospective deficits in reaction times compared to healthy matched controls.[36]

Despite suggestions by Dingenen & Gokeler,[91] traditional rehabilitation practices often do not examine the sensorimotor spectrum as a criteria for progression throughout rehabilitation or return to sport. Effective rehabilitation practices should integrate neurobiological principles, including integration of activities that challenges the relationship between the individual and the environment, to improve health outcomes in a population vulnerable to maladaptive neuroplastic alterations.[91] However, sensorimotor alterations may be just one type of neuroplasticity observed in this population.

As demonstrated by Kadowoki et al.,[43] patients with medial patellofemoral ligament deficiency experience diminished activation in the contralateral somatosensory cortical area. Interestingly, these patients also demonstrated increased activity in the anterior cingulate cortex, prefrontal cortex, and inferior parietal lobule.[43] Very similar to patients after ACLR, changes in the somatosensory areas of the brain did occur, but they were also accompanied by neuroplastic alterations in the emotional regulation centers when compared to healthy matched controls. A similar phenomenon was present in patients with chronic musculoskeletal pain.[42,43] These patients exhibited increased activation in the amygdala, orbitofrontal cortex, substantia nigra/ventral tegmentum, putamen, thalamus, pallidum, inferior parietal lobule, and cingulate cortex compared to healthy matched controls. These two studies demonstrate that alterations in the limbic system, specifically in the amygdala, can occur as a result of musculoskeletal injury.[92] The amygdala is a subcortical structure responsible for detecting fear.[92] Potentially, similar neuroplasticity may be occurring in patients after ACLR, especially as injury-related fear has been cited as the primary barrier for return to sport.[4]

It is imperative to understand neurobiological principles associated with musculoskeletal rehabilitation, especially as it relates to the amygdala and other corticolimbic brain structures. In patients after ACLR with known susceptibility to neuroplastic alterations, emphasis on neuroplasticity associated with emotional regulation centers should be discussed. Therefore, the purpose of this paper is to discuss the structure and function of the amygdala and corticolimbic brain regions and to apply these concepts to ACL rehabilitation and return to sport.

Emotions and the Fear Response

Emotions are an automatic and largely unconscious behavioral and physiological response to challenging situations.[92] Changes in emotional states triggers the autonomic system and endocrine system to drive processes like hunger, thirst, or response to pain.[92] These mechanisms are mediated by the amygdala, prefrontal cortex, dorsal anterior cingulate cortex, hypothalamus, and the brain stem.[93] Lesion studies have demonstrated that the amygdala is the critical regulatory site for emotions, specifically the emotion of fear.[94,95] Fear is an emotion that is important for survival, but fear expression in the absence of threat can be dangerous to the organism.[93] Emotions like fear are often a result of Pavlovian conditioning.[92,93]

Pavlovian conditioning, also known as classical conditioning, is a type of implicit learning associated with instinctual responses.[96] During Pavlovian fear conditioning, humans and animals begin to associate a previously neutral conditioning stimulus (CS) with an aversive unconditioned stimulus (US).[96,97] The pairing of the CS and US can lead to a conditioned fear response.[96,97] For example, a tone (CS) and a shock (US) are delivered to an animal at the same time. Eventually, the tone itself will be enough to elicit a fear response in the animal. This type of conditioning is the first phase of avoidance conditioning.[92] Avoidance conditioning occurs when the human or animal learns to successfully avoid the US.[92] In patients after ACLR, it has been suggested that patients with increased levels of injury-related fear engage in avoidance behaviors.[3] Other musculoskeletal populations, including patients with chronic low back pain, often exhibit increased levels of fear-avoidance beliefs.[98] However, this construct has rarely been examined in patients after ACLR, despite basic principles of Pavlovian fear conditioning.

To truly understand Pavlovian fear condition, it is important to appreciate the structures involved in the acquisition of fear. The primary structure associated with Pavlovian fear conditioning is the amygdala.[92,93,95]

Amygdala Structure, Function, and Fear Acquisition

The amygdala is the structure of the brain responsible for autonomic responses associated with fear.[92] The amygdala is an almond-shaped structure that consists of approximately 12 nuclei.[92] However, the lateral and central nuclei are the primary nuclei associated with fear acquisition.[95] The lateral nucleus of the amygdala receives information about the CS from the thalamus.[93] The thalamus is part of the diencephalon and is responsible for relaying signals to the cerebral cortex and other subcortical structures.[92] Functionally, the lateral nucleus is divided into two regions. The dorsal division of the lateral nuclei initiates learning of the paired CS-US and ventral division is thought to control fear memory.[92] During fear acquisition, the lateral nucleus transfers the information to the central nucleus.[93] The central nucleus then drives the expression of the fear response.[95]

The central nucleus is connected to the brain stem and hypothalamus.[93] The brain stem connects the messages from the brain to the lower motor neurons (behavioral response) and the hypothalamus which regulates the autonomic nervous system (i.e. physiological response).[93] The connectivity of the thalamus, amygdala, brainstem and hypothalamus lead to fear expression.[93] Long-term potentiation, which is the persistent strengthening of the synapses between two neurons, between the lateral nucleus and central nucleus of the amygdala, has been observed as a result of frequent exposure of a paired CS and US.[92,99] However, one single paired exposure of the CS and US can be strong enough to acquire learned fear that is sustained throughout life.[93] Potentially, an ACL injury and/or ACLR may be a strong enough US to lead to avoidance of sports participation (CS).

The amygdala also has connections to other cortical and subcortical structures during fear expression. Firstly, the thalamus also sends signals to the cortex once it receives signaling information.[92] For example, the thalamus sends sensory information to the dorsal anterior cingulate cortex, which is a structure located in the frontal lobe that assists with regulation of emotions and has high connectivity to the amygdala, striatum, and hippocampus. The amygdala then indirectly receives additional information about the cognitive processing of fear from the dorsal anterior cingulate cortex.[92,100] After fear conditioning, the ventromedial prefrontal cortex, which is extensively connected to the amygdala, is activated when the CS is presented and drives fear expression.[93] The ventromedial prefrontal cortex is a structure in the frontal lobe that receives context-dependent information about the CS from the hippocampus. The hippocampus, located in the medial temporal lobe, is associated with long-term memory.[92] Memory associated with the paired CS-US can lead to fear expression or fear extinction.[93] One cortical area that is a key structure not only for fear conditioning, but also for fear extinction, is the ventromedial prefrontal cortex.

Fear Extinction

Extinction of fear occurs when the presentation of the CS without the US no longer leads to a fear response.[93] Many cortical and subcortical structures are involved during fear extinction, however initial fear extinction begins in the amygdala. After receiving the CS from the thalamus, the lateral nuclei and the basal nuclei are activated.[93]

The hippocampus detects whether the CS is a threat and send signals about the context of the threat to the lateral nuclei and to the ventromedial prefrontal cortex.[92,93] The ventromedial prefrontal cortex is not only important for emotional regulation, but also for decision-making.[101] The ventromedial prefrontal cortex is also reciprocally connected to the basal nuclei of the amygdala that consists of extinction neurons.[101] After receiving information from the basal nuclei and the hippocampus, neurons in the ventromedial prefrontal cortex sends feedback to the amygdala through intercalated cell masses.[93] This cell mass functions as an inhibitory mechanism between the lateral nuclei and central nuclei.[93] This inhibitory mechanism prevents the activation of the conditioned fear response. [93] Thus, the ventromedial prefrontal cortex indirectly inhibits the central nuclei and the expression of the fear response. [93]

In a previous functional magnetic resonance imaging (fMRI) study, it was demonstrated that increased activation in the ventromedial prefrontal cortex and decreased activation in the amygdala correlated with fear extinction.[102] Exposure therapies, such as *in vivo* exposure, have been developed to induce this neural response and lead to fear extinction in patients after musculoskeletal injury.[47,103,104] It is important to understand the neural substrates of the fear response to effectively implement exposure therapies. Integration of these therapies without an understanding of the neural response may lead to the implementation of poor intervention strategies. Musculoskeletal rehabilitation is a dynamic process and should integrate a combination of physical and psychosocial rehabilitation. Rehabilitation is a dynamic system and failing to address a part of the system can lead to poor health outcomes. Specifically, as it relates to ACLR, failing to address the psychological responses after ACL injury can lead to sustenance of a secondary injury. Therefore, it is important to understand the consequences of not addressing the fear response during ACLR rehabilitation.

Stress and Injury Model

Previous literature has demonstrated that increased levels of injury-related fear have been associated with re-injury within 24 months of initial ACLR.[56] One model that could help to explain the consequences of failing to address the fear response after ACL injury is the stress and injury model.[58] When an athlete faces a potentially stressful athletic situation, then the athlete will undergo a stress response. During the stress response, the hypothalamus will signal physiological changes as a result of the stress response.[58,92] This evocation of emotions during a stress response can lead to muscle tension, increased heart rate, and divided attention.[58]

The stress and injury model suggests that an individual's personality, history of stressors, and coping strategies can all influence the stress response when exposed to a potentially stressful athletic situation.[58] History of stressors can include previous athletic injury. Unfortunately, this previous athletic injury may be a CS that may trigger the fear response and contribute to stress. A negative stress response can ultimately lead to sustaining another injury.[58] As demonstrated by Paterno et al.,[56] individuals with injury-related fear are 13 times more likely to sustain a re-injury within 24 months after ACLR. Thus, it is imperative that fear extinction occur in this population to mitigate re-injury risk to a population already vulnerable to re-injury. This begins with a foundational understanding of the neurobiological principles of the fear response in these patients to develop appropriate intervention strategies that will lead to extinction of fear.

Conclusion

Patients after ACLR exhibit increased levels of injury-related fear that inhibits their ability to return to pre-injury levels of sport. The amygdala is the primary injury-related fear in the human brain. This structure is connected to cortical and subcortical structures to elucidate a fear response. The fear response is a result of pavlovian learning and the fear response should be mitigated to allow for successful outcomes after ACLR. It is important to understand the neural substrates of injury-related fear to develop appropriate interventions to decrease the fear response. Failure to understand these neural substrates may lead to the implementation of subpar intervention strategies. Modulation of the fear response can take time. Even at the level of the neuron, change takes time. However, the more frequently an individual is exposed to the desired environmental stimuli, the more likely the individual is to undergo synaptic plasticity and lead to long-term changes in neuronal processes.

Chapter Three: Examination of Physical Activity, Patient-Based and Functional Outcomes after ACL Reconstruction: A Modified Cross-Sectional Study

Introduction

According to the 2008 Physical Activity Guidelines, engaging in regular physical activity can decrease the risk of chronic diseases development and associated comorbidities.[6] However, a consequence of physical activity is musculoskeletal injury and if not treated effectively, these injuries could lead to a sedentary lifestyle and the health benefits associated with physical activity abated.[105] Injury to the anterior cruciate ligament (ACL) is a common musculoskeletal injury that results from participation in physical activity, and individuals will often undergo ACL reconstruction (ACLR) with subsequent rehabilitation to return to pre-injury levels of sports participation (RTS).[3,106] However, RTS is not always the case. It is estimated only 55% of patients who undergo ACLR return to competitive levels of sport participation and only 65% return to pre-injury sports participation.[4] Furthermore, it has been demonstrated that patients who have undergone ACLR spend less time in moderate-to-vigorous physical activity and have lower daily step count compared to their healthy counterparts.[7,107]

In addition to deficits in physical activity, previous research has also suggested that individuals post-ACLR report decreased health related quality of life (HRQL).[3] Health-related quality of life is a multidimensional patient-centered concept of health that incorporates the patient's personal, societal, and spiritual beliefs, values, and preferences.[15] The domains of HRQL include: physical, social, emotional, psychological, spiritual, and economical.[15] A decrease in HRQL, function, and inability to RTS may cause some individuals with a history of ACLR to adopt inactive lifestyles which could lead to severe health consequences.[6]

The majority of evidence regarding RTS after ACLR has focused on the physical domain of HRQL such as impairments, limitations, or restrictions.[3,9] While the evidence has included both functional and patient-based outcomes,[9] little evidence exists examining other contextual factors that could affect RTS and physical activity participation such as injury-related fear.[3,106] Evidence has suggested that injury-related fear can negatively influence HRQL, functional outcomes, and increase risk for subsequent re-injury in individuals post-ACLR.[3,56] In addition, the most important factor influencing return to sport after ACLR is psychological readiness.[9] In a recent qualitative study, it was determined that injury-related fear was directly related to self-reported knee function and largely influenced the decision to RTS after ACLR.[59] Thus the examination of psychological factors on the ability to RTS is imperative for the long term health and wellness of these patients. Therefore, the purpose of this study is to examine functional and patient-based outcomes that are predictive of RTS and physical activity levels in individuals with a history of ACLR. We hypothesize a combination of functional and patient-based outcomes will explain a significant amount of variance associated with RTS and physical activity levels in individuals with a history of ACLR.

Methods

Design

A modified cross-sectional design was used for this study. All participants reported to the laboratory for one testing session. This study consisted of a single group of individuals with a history of ACLR. The predictor variables included scores on patient-based and functional outcomes and the dependent variables were RTS (Yes/No) and average daily step counts (number).

Participants

A convenience sample of 40 participants with a history of ACLR were recruited from a local physical therapy clinic and in the general student population at a Division 1 university. Participants were eligible if they had a history of unilateral ACLR with or without concomitant meniscal pathology, were between the ages of 18-35, and had been cleared to RTS. Participants were excluded from the study if they were currently injured, reported concomitant collateral ligament or posterior cruciate ligament injury at the time of their index ACL injury, or had a history of concussion in past 3 months. Informed consent was obtained prior to the start of the study and the study was approved by the Institutional Review Board.

Procedures

After informed consent, participants completed a demographic questionnaire and the following patient-reported outcome measures (PROs): FABQ, KOOS, K-SES, the mDPA, PCS, TSK-11, and the Tegner Physical Activity Assessment. Once the PROs were completed, the participants completed a series of functional tests. The battery of functional tests included: SL hop for distance, TL hop for distance, CO hop for distance, the LESS-RT, and peak torque concentric isokinetic quadriceps and hamstring strength testing. In addition to PROs and functional measures, the participants were given a pedometer to wear for 1-week. All participants were encouraged to follow their normal routines throughout the 1-week period. After 1-week, the participants followed-up with the investigators to return the pedometer and step log. Completion of clinical outcome measures and use of the pedometer were counterbalanced to control for order effect. All data were collected by the primary author (S.E.B), who is a certified athletic trainer, and was not involved in the treatment or rehabilitation of any participant.

Instrumentation

Demographic Health History Questionnaire

The demographic health history questionnaire assessed self-reported physical activity history, previous orthopedic history, and anthropomorphic measurements such as age, weight, sex, and ethnicity. Additional questions regarding the ACL surgery and rehabilitation were assessed.

Patient Reported Outcome Measures (PROs)

Fear-Avoidance Belief Questionnaire: The Fear-Avoidance Belief Questionnaire (FABQ) is a 15-item questionnaire designed to evaluate fear-avoidance beliefs in patients with low back pain.[23] The FABQ has 2 subscales: the FABQ-Physical Activity (FABQ-PA) and the FABQ-Work (FABQ-W). A 6-point Likert scale is used to score each question, where higher scores indicate elevated fear-avoidance beliefs. In patients with low-back pain, the FABQ-PA and FABQ-W demonstrated excellent reliability (Intraclass correlation coefficient, ICC=0.90 and 0.96, respectively).[108] The original FABQ was amended for use in patients with knee pathology, where "back" was changed to "knee" throughout the questionnaire.[109] In addition, the FABQ-W was modified to the FABQ-Sport (FABQ-S) where questions were adjusted for the demands of sport.[109]

Knee Injury and Osteoarthritis Outcome Score: The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a 42-item questionnaire that evaluates knee-related disability for individuals with a variety of knee conditions.[21] The KOOS consists of 5 domains:

symptoms (KOOS-Sy), pain (KOOS-P), activities of daily living (KOOS-ADL), function in sport and recreation (KOOS-Sport), and quality of life (KOOS-QOL).[21] A score of 100 on each subscale represents no disability. The reliability for the KOOS in individuals post-ACLR is clinically acceptable (ICC>0.75).[21]

Knee Self-Efficacy Scale: The Knee Self-Efficacy Scale (KSES) is an 22-item questionnaire that was designed to evaluate patient self-efficacy following ACL injury.[64] The K-SES assesses the patient's perspective on their ability to complete tasks, regardless of discomfort or pain. There are four subscales of the KSES. The "daily activities" subscale has 7 questions, the "sports and leisure activities" subscale has 5 questions, the "physical activities" subscale has 6 questions, and the "your knee function in the future" subscale has 4 questions. The KSES has an intraclass correlation coefficient of 0.75 and internal consistency of 0.94.[64]

The Modified Disablement in the Physically Active Scale: The Modified Disablement in the Physically Active Scale (mDPA) is a 16-item questionnaire that is designed to examine HRQL in the physically active population.[110] There are two domains of the mDPA: physical summary component (mDPA-PSC) and mental summary component (mDPA-MSC). A 5-point Likert scale is used to score each item, with higher scores representing higher levels of disability. The scores range from 0-48 and 0-16 for the mDPA-PSC and mDPA-MSC, respectively.[110] The mDPA-PSC (α=0.94) and mDPA-MSC (α=0.89) demonstrated excellent internal consistency.[110]

Pain Catastrophizing Scale: The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire that examines a patient's frequency in engaging in pain catastrophizing behaviors.[33] The PCS is scored on a 5-point Likert scale with a higher score indicating higher levels of pain catastrophizing and a lower scores indicating lower levels of pain catastrophizing. In patients with low-back pain, the PCS has an intraclass correlation coefficient of 0.93 and a minimal detectable change of 9.1 points.[108] The PCS is a valid and reliable measure of the three components of pain catastrophizing.[33] These include rumination (i.e. "I can't stop thinking about how much it hurts", magnification (i.e "I worry that something serious may happen"), and helplessness (i.e "There's nothing I can do to reduce the intensity of the pain").[33] Previous literature has utilized the PCS in patients following ACLR.[32,111,112]

<u>Tampa Scale of Kinesiophobia-11</u>: The TSK-11 is a valid and reliable 11-item questionnaire that evaluates fear of movement and re-injury.[24] A 4-point Likert scale is used to score each item, with higher scores representing higher fear of re-injury/movement. The instrument is scored 11-44; with greater scores indicating increased levels of fear of movement and re-injury. The TSK-11 has acceptable test-retest reliability (ICC=0.81) and internal consistency (α=0.79).[24] The TSK-11 has been used in previous literature investigating fear of re-injury in patients with a history of ACLR.[32]

<u>The Tegner Physical Activity Assessment</u>: The Tegner is a questionnaire used to evaluate an individual's current physical activity level and physical activity level prior to injury.[113] The Tegner is scored from 0 to 10, with 0 representing no physical activity and 10 representing highest competitive levels of physical activity. In the present study, participants were considered to have RTPS if they scored within ±1 of their pre-injury physical activity level status. This method was used to account for changes in life priorities as a limitation associated with the scale.

Functional Testing

Participants completed a series of functional tests which have been suggested as a battery for return to sport decision making for post-ACLR patients.[25] Participants began with a 5-minute stationary bike warm up. The uninvolved limb was tested first and participants received a 3-minute rest period between tests.

The Landing Error Scoring System-Real Time: The LESS-RT is a valid and reliable clinical assessment that is used to identify individuals at risk of lower extremity injury.[114] The participants were instructed to perform the task as previously reported.[114] The participants completed 2 practice trials followed by 4 test trials. During the test trials, if participants did not complete a successful jump they were instructed to repeat the task. Jump-landing mechanics were assessed using the defined criteria by Padua et al.[114] The total score based on the number of errors was used for the analysis.

Single-Leg Hop Tests: The SL hop for distance, TL hop for distance, and CO hop for distance were used to measure limb power. For SL, the participant was instructed to stand on test leg, and then jumped forward as far as possible while landing on the same limb. For TL, the participant was instructed to stand on the test leg, and then jump forward as far as possible while landing on the same limb for 3 consecutive jumps. For CO, the participant began by standing on one leg and then jumped forward as far as possible 3 times while crossing over a 6cm wide strip on the floor for each jump. The total distance hopped was recorded (cm). The participant completed 1 practice trial followed by 3 test trials, with 30-seconds for recovery between each trial. The average score of the 3 trials for each limb was used to calculate the limb symmetry index (LSI).

Isokinetic Testing: The Biodex Isokinetic Dynamometer (Biodex System 4 Pro; Biodex Medical Systems, Inc., Shirley, NY) was used to assess concentric isokinetic quadriceps and hamstring strength at 60°/sec, 180°/sec, and 300°/sec (Nm/kg). Testing speed and protocol were implemented based on the previous literature.[25] One practice trial of ten repetitions and one test trial of ten repetitions occurred at each speed. Peak torque LSI was measured at each speed with 100% representing full symmetry and 0% representing full asymmetry. There was a 1-minute rest between each speed.

Pedometers

A Pedometer (Digi-Walker SW-200; New Lifestyles Inc., Lees Summit, MO) was used to measure PA as described in previous literature.[105] The participants were instructed to put the pedometer on in the morning near the hip joint, and to wear the pedometer at all times during the week except when showering, swimming, or sleeping.[105] They were instructed to log their steps each night on the step log. Throughout the 1-week period, the participants received a daily reminder to log their steps each night, and to reset the pedometer before going to sleep.[105] Average steps over the 1-week period were used for analysis.

Statistical Analyses

All statistical analyses were conducted with SPSS software (v23.0, SPSS, Inc., Chicago, IL, USA). Independent t-tests and chi square analyses were used to determine between group differences in demographics. Mean values for the SL hop series and peak torque for the uninvolved and involved limbs were used to calculate LSI for each participant, and were calculated by: involved limb/uninvolved limb x 100. For regression analyses, it has been suggested a total of 10 participants be included per predictor variable.[115,116] We anticipated variables will exhibit collinearity ($r \geq 0.70$); thus, decreasing the number of variables that were included in the final models. We hypothesized that the final models would include no more than 4 predictor variables, thus a sample size of 40 participants was sufficient. A binary logistic regression was used to determine patient-based and functional outcomes associated with RTS (yes or no). Bivariate analyses were completed between the predictor variables and the dependent variable to identify which factors to include into the initial model. A significance level of ≤0.10 was used to determine which predictor variables entered the initial model. The predictor variables in the initial model were assessed for multicollinearity using a Variance Inflation Factor based on linear regression methods. Then, the remaining variables were entered into a backwards stepwise model with a significance level of ≤0.05.

Separate stepwise multiple linear regression analysis was conducted with PRO scores and functional outcome scores as predictor variables and average daily steps counts serving as the dependent variable. Univariate analyses between predictor variables and the dependent variable were performed to reduce the number of predictor variables. All predictor variables with $r>0.20$ were eligible for inclusion in the model. Predictor variables were assessed for collinearity and if strongly correlated ($r>0.70$), only one variable was moved forward. Next, at each step a predictor variable was removed if it did not significantly contribute to the predictive value of the model (R^2). In conjunction with the "1 in 10" rule for linear models, 4 variables were entered into the initial model (n=40).[115,116] The overall percent of the explained variance (R^2) for the regression analysis was identified. The regression coefficient (β), the constant, the p-values, confidence intervals, and the individual predictive power of each variable were calculated. Significance was set a priori at $P<0.05$. All data were collected, stored, and managed in REDCap (Research Electronic Data Capture), an electronic data capture tool at the University of Kentucky.

Results

Forty participants (24 female, mean age = 24.3±4.1 years) were included in this study. No participants were lost to follow-up. Participants were a median of 5 [7] years from index ACLR. Descriptive statistics for participant demographics are presented in Table 3.1. Sixty-two percent (n=11) of participants did not RTS and 72% (n=29) of participants did not average 10,000 steps per day. There was a significant difference between the RTS and NRTS groups for current level of activity on the Tegner ($p=0.00$), but there were no significant differences in pre-injury Tegner scores between the RTS and NRTS groups ($p=0.15$). There were no significant differences in anthropometric measures and time since index ACLR between the RTS and NRTS groups (Table 3.1). Means and SD for predictor variables are presented in Table 3.2.

Predictors of Self-Reported Return to Pre-injury Sport

Bivariate analyses demonstrated that the TSK-11 (18.22±5.28), KOOS-Sy (81.46±13.18), and KSES-Future (5.73±2.57), with time from index ACLR included as a covariate, were associated with RTS and met inclusion criteria for the model (Table 3.3). After completion of the backwards logistic regression, KOOS-Sy was removed, and the final model included the TSK-11, KSES-Future, and time from index ACLR (Table 3.4). Those individuals who did not RTS were a median of 7 [7] years after index ACLR compared to those who did RTS with a median of 4 [4] years after index ACLR. Holding future knee self-efficacy and time from index ACLR constant, for every point increase on the TSK-11, individuals were 17% less likely to RTS (no RTS= 19.72±5.30, RTS=15.73±4.35).

Predictors of Average Daily Step Count

Univariate analysis demonstrated LESS-RT, CO hop for distance, peak torque concentric hamstring strength at 180°/sec and 300°/sec, KOOS-Sport, KOOS-QOL, KSES-ADL, KSES-Total, FABQ-S, FABQ-Total, PCS, and RTS were associated with average daily step counts (Table 3.4). The LESS-RT, KOOS-QOL, KSES-ADL and RTS were selected for the model (Table 3.5). Explanation for selection of predictive variables for the initial model is presented in Table 3.3. The average LESS-RT score was 6.07±3.2, average KOOS-QOL score was 74.22±17.63, average KSES-ADL was 8.95±2.21 and 37.5% of the sample RTS. In the stepwise multiple linear regression model, the KSES-ADL and KOOS-QOL accounted for 27.1% of the variance of average daily step counts in individuals with a history of ACLR (Table 3.5).

Discussion

The purpose of this study was to determine predictive factors associated with RTS and physical activity levels in individuals at least 1-year post-ACLR. We hypothesized that patient-based outcomes and functional outcomes would be predictive of RTS and physical activity levels. Overall, our hypothesis was not supported as only patient-based outcomes were predictive of RTS and physical activity levels. Specifically, injury-related fear was significantly predictive of RTS, even after controlling for future knee self-efficacy and time since index ACLR. While knee self-efficacy and knee-related quality of life were predictive of step-counts in patients after ACLR.

Predictive Factors of RTS

This study contributes to the growing body of literature that demonstrates the impact of psychosocial factors on RTS in patients after ACLR. Patients after ACLR are not only experiencing deficits in physical HRQL, but as well as psychological HRQL. While most of the current literature examines psychosocial factors in an acute ACLR population, this study examines these factors in individuals ranging from 1 to 14 years post index ACLR. Our results indicate injury-related fear, as measured by the TSK-11, and time from index ACLR were associated with RTS. In a recent qualitative study, Burland et al.[59] interviewed a cohort of individuals with a history of ACLR who were at least 1 year post-operative to determine what factors were associated with their decision to RTS. It was discovered that the decision to RTS was based primarily on psychosocial factors, including injury-related fear and self-efficacy.[59] In conjunction with Burland et al.,[59] our study quantitatively highlights that psychosocial factors may still be present years after ACLR and still affect the patient's ability to RTS.

The present study also highlights the importance of the usage of PROs in clinical practice. Patient-reported outcome measures provide information about a patient's health directly from the patient.[18] Psychological readiness has been demonstrated as the strongest predictor of RTS after ACLR in previous literature[2,54,61,117] including our current findings, and the most clinically applicable method to measure this variable is through PROs. The TSK-11[24] is one of many PROs that provide information about psychological readiness after musculoskeletal injury. Recent literature has also demonstrated that the Anterior Cruciate Ligament Return to Sport after Injury (ACL-RSI) scale is predictive of RTS in patients after ACLR, and has been included as a variable in the battery of functional outcomes and PROs for RTS decision making.[117] PROs are easy to administer and score, and provide very valuable information about the psychological readiness in patients after ACLR.

Predictive Factors of Physical Activity

This sample of individuals with a history of ACLR averaged approximately 8657 daily steps. This is 1350 daily steps less than the recommended daily step count of 10,000 steps per day by the 2008 Physical Activity Guidelines.[6] Similar results were demonstrated by Bell et al.[7] and Kuenze et al.,[107] who both included populations post-ACLR. Despite the impetus of ACLR to allow individuals to return to a physically active lifestyle, it appears that patients after ACLR are consistency failing to engage in the recommended levels of daily steps suggested for maintenance of long-term health. This is concerning as failure to engage in regular physical activity can increase the risk for the development of chronic disease and comorbidities.[6]

While the included participants did not meet the 10,000 steps per day to be considered physical active, the present study demonstrated that the KSES-ADL and KOOS-QOL were predictive of average daily step counts. While preoperative knee self-efficacy can predict return to previous levels of physical activity, symptoms, and muscle function at 1-year post reconstruction,[118] our study demonstrates that deficits in self-efficacy post-operatively were associated with decreased levels of physical activity years after ACLR. These results further highlight the importance of addressing psychological factors throughout the rehabilitation process after ACLR. If knee confidence is not addressed throughout the rehabilitation, deficits in long-term physical activity may occur.

Interestingly, lower KOOS-QOL scores were associated with increased daily step counts. We believe this is due to the time since index ACLR. This sample was a median of 5 years post index ACLR, it may be that those individuals who did not average 10,000 steps per day may have modified their activity preferences after ACLR which could have led to an increase in knee-related quality of life. These individuals may have recalibrated their knee-related quality of life because they are no longer engaging in activities that make them aware of their knee. Previous research has demonstrated that orthopaedic populations can undergo a phenomenon called response shift.[119] A response shift is a change in self-evaluation and appraisal that can affect perceived HRQL.[119] In this particular sample, those patients who are no longer engaging in physical activity may have undergone response shift and have reconceptualized how they view their knee to improve their perceived quality of life. Therefore, individuals who RTS may experience decreased knee-related quality of life as a result of increased exposure to situations that make them aware of the discomfort in their knee.

Psychologically Informed Clinical Practice

Participants in this study exhibited elevated levels of injury-related fear and decreased knee self-efficacy. Interestingly, traditional functional assessments (i.e. single leg hop testing) far exceeded recommended values for RTS in this sample of participants after ACLR.[25,120] These individuals may have benefited from the implementation of psychoeducational techniques which could have facilitated RTS and physical activity engagement. Thus, these results support the integration of psychosocial techniques into traditional musculoskeletal rehabilitation to enhance clinical outcomes.

Psychologically informed clinical practice is a biopsychosocial approach to traditional musculoskeletal rehabilitation by integrating cognitive-behavioral techniques into rehabilitation.[121] The integration of cognitive-behavioral techniques has been demonstrated to decrease injury-related fear, increase self-efficacy, and improve clinical outcomes in patients with musculoskeletal injuries.[121] Cognitive-behavioral techniques that have been used to improve clinical outcomes include motivational interviewing,[122] goal-setting,[53] and activity-based treatments, such as *in vivo* exposure therapy,[47] among many others. Additionally, these techniques have been successfully implemented by rehabilitation specialists.[123] Specifically associated with patients after ACLR, integration of relaxation training and imagery during ACLR rehabilitation has previously led to increased knee strength, decreased pain, and less re-injury anxiety at 24 weeks post-operatively for those who received the treatment compared to a placebo and control group.[45] Using these skills in individuals with a history of ACLR could help to increase physical activity engagement and encourage RTS.

Limitations

This study is not without limitations. Firstly, all step counts were self-reported by each participant. We assumed that all participants used the pedometer and accurately reported their step counts on the log. Secondly, we have used the Tegner to determine RTS. While we have attempted to adjust for maturation by including individuals within 1 of their pre-injury Tegner scores into the RTS group, there is a possibility that individuals dichotomized into the NRTS group did not return due to other factors unrelated to their ACLR. While not statistically significant, those individuals who were dichotomized into the NRTS were further out from their index ACLR compared to those in the RTS group. Individuals may not have RTS because of transitions from high school to college or beyond. It has been reported in previous literature that life changes can lead to adjustments in activity preferences in individuals with a history of ACLR.[3] Lastly, we did not document occupation status of all participants which could have influenced daily step counts.

Future Research

Future research should explore factors associated with other aspects of physical activity, including moderate-to-vigorous active minutes. This outcome may serve as a better representation of physical activity in patients after ACLR. Additionally, future research should explore the efficacy of psychosocial interventions to decrease injury-related fear and improve knee-self efficacy. Integration of these interventions may improve RTS and physical activity engagement in patients after ACLR.

Conclusion

Patient-based outcomes explained the variance observed in physical activity and RTS in individuals with a history of ACLR. The TSK-11 and time from index ACLR were predictive of RTS and the KSES-ADL and KOOS-QOL were predictive of average daily step counts. Specific to the psychological domain of HRQL, increased levels of injury-related fear and decreased levels of self-efficacy were still present in patients after ACLR even at midterm follow-up. Engaging in psychologically informed clinical practice could decrease injury-related fear observed in these patients.

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Table 3.1. Participants' demographics

	RTS (n=15) Mean (SD) Frequency (%) Median [IQR]	NRTS (n=25) Mean (SD) Frequency (%) Median [IQR]	TOTAL (n=40) Mean (SD) Frequency (%) Median [IQR]	P-Value
Height (cm)	170.8 (8.6)	169.4 (9.6)	169.9 (9.1)	0.65*
Weight (kg)	75.3 (17.21)	71.9 (13.8)	73.2(15.1)	0.50*
Age (years)	23.3 (4.4)	25.1 (4.4)	24.28 (4.2)	0.11#
Sex				0.613^
Females	11 (73.3%)	18 (72%)	25 (62.5%)	
Males	4 (26.7%)	7 (28%)	15 (37.5%)	
Time from Index ACLR (years)	4 [4]	7 [7]	5 [7]	0.07#
Average Daily Step Counts	7754.3 (2399.4)	9198.9 (2385.3)	8657.2 (2467.2)	0.07*
Tegner Score (Before Injury)	8 [2]	9 [2]	9 [2]	0.15#
Tegner Score (Current Level)	7.7 (1.5)	6.0 (1.2)	6.6 (1.5)	0.00*

RTS = Return to Pre-injury Sports Participation, NRTS = No Return to Pre-injury Sports Participation Tegner = Tegner Physical Activity Assessment *Independent T-Test, #Mann-Whitney U Test, ^Fishers Exact

Table 3.2. Means and standard deviations for the predictor variables

	RTS (n=15) Mean (SD)	NRTS (n=25) Mean (SD)	TOTAL (n=40) Mean (SD)	P-Value
mDPA-PSC	6.27 (4.50)	9.40 (7.86)	8.23 (6.90)	0.16
mDPA-MSC	1.73 (2.15)	2.00 (2.48)	1.90 (2.34)	0.73
mDPA-Total	8.00 (5.09)	11.40 (9.27)	10.13 (8.06)	0.20
KOOS-Sy	87.48 (7.56)	77.86 (14.59)	81.46 (13.18)	0.07
KOOS-Pain	92.04 (5.02)	87.78 (11.42)	89.37 (9.68)	0.18
KOOS-ADL	98.33 (2.41)	95.59 (7.32)	96.62 (6.07)	0.17
KOOS-Sport	86.00 (9.10)	83.40 (15.46)	84.37 (13.36)	0.56
KOOS-QOL	78.33 (13.34)	71.75 (19.61)	74.22 (17.63)	0.26
Tegner_Pre	8.07 (1.28)	8.88 (1.05)	8.58 (1.20)	0.15
Tegner_Current	7.67 (1.50)	6.00 (1.16)	6.63 (1.51)	0.00*
TSK-11	15.73 (4.35)	19.72 (5.30)	18.22 (5.28)	0.02*
KSES-ADL	8.94 (2.57)	8.94 (2.01)	8.95 (2.21)	0.99
KSES-Sport	8.81 (1.36)	7.80 (2.15)	8.18 (1.94)	0.11
KSES-PA	8.28 (1.11)	7.61 (1.86)	7.86 (1.64)	0.23
KSES-Future	6.88 (1.76)	5.03 (2.75)	5.73 (2.57)	0.03*
FABQ-Sport	10.53 (11.16)	11.12 (8.27)	10.90 (9.32)	0.85
FABQ-PA	6.40 (5.96)	9.68 (7.31)	8.45 (6.94)	0.51
FABQ-Total	16.92 (15.49)	20.80 (13.03)	19.35 (13.94)	0.26
PCS	3.79 (5.12)	4.20 (6.48)	4.05 (5.96)	0.61
SL Hop LSI	94.64 (8.14)	96.83 (13.36)	96.00 (11.61)	0.33
TL Hop LSI	93.95 (11.51)	98.15 (11.38)	98.28 (10.15)	0.15
CO Hop LSI	94.72 (12.07)	100.42 (8.35)	98.28 (10.15)	0.07
LESS-RT	5.07 (2.58)	6.68 (3.90)	6.07 (3.52)	0.16
Peak Torque Quad LSI 60	85.94 (13.87)	84.91 (12.13)	85.30 (12.64)	0.80
Peak Torque Ham LSI 60	89.86 (17.53)	86.80 (9.68)	87.89 (13.06)	0.47
Peak Torque Quad LSI 180	93.02 (7.81)	94.82 (8.54)	94.15 (8.22)	0.52
Peak Torque Ham LSI 180	102.42 (15.13)	92.51 (13.80)	95.85 (21.04)	0.04*
Peak Torque Quad LSI 300	98.06 (12.74)	94.53 (12.74)	95.85 (21.04)	0.78
Peak Torque Ham LSI 300	102.47 (44.64)	96.87 (17.67)	98.98 (30.25)	0.61

*Statistically Significant, mDPA = Modified Disablement in the Physically Active Scale, PCS = Physical Component Score, MCS = Mental Component Score, KOOS = Knee Injury and Osteoarthritis Outcome Score, Sy = Symptoms, ADL = Activities of Daily Living, QOL = Quality of Life, TSK-11= Tampa Scale of Kinesiophobia-11, KSES= Knee Self-Efficacy Scale, PA = Physical Activity, FABQ = Fear-Avoidance Beliefs Questionnaire, PCS = Pain Catastrophizing Scale, SL = Single Leg, LSI = Limb Symmmetry Index, TL = Triple Leg, CO = Crossover

Table 3.3. Logistic regression model to determine predictors of return to sport

Model	Independent Variables	β	SE	Wald Statistic	P-Value	OR (95% CI)
1	TSK-11	-0.20	0.10	4.15	0.04	0.82 (0.68-0.99)*
	Time from Index Surgery	-0.30	0.13	5.63	0.02	0.74 (0.57-0.95)*
	KOOS-Symptoms	0.03	0.05	0.45	0.50	1.03 (0.94-1.14)
	KSES-Future	0.19	0.28	0.45	0.50	1.21 (0.70-2.14)
2	TSK-11	-0.19	0.09	4.14	0.04	0.83 (0.69-0.99)*
	Time from Index Surgery	-0.31	0.13	6.25	0.01	0.73 (0.57-0.94)*
	KSES-Future	0.33	0.21	2.60	0.11	1.39 (0.93-2.09)

*Statistically Significant, RTS = Return to Pre-injury Sports Participation, TSK-11 = Tampa Scale of Kinesiophobia-11, KOOS = Knee Injury and Osteoarthritis Outcome Score, KSES = Knee Self-Efficacy Scale

Table 3.4. Selection of eligible predictor variables for stepwise regression model

Predictor Variable	Correlation Coefficient	Included	Reason for Inclusion/Exclusion
LESS-RT	-0.403	Yes	Strongest functional outcomes associated with physical activity in this sample
Crossover Hop for Distance LSI	-0.216	No	Ceiling effect with LSI present in this sample
Peak Torque Hamstring 180°/sec LSI	0.370	No	Ceiling effect with LSI present in this sample
Peak Torque Hamstring 300°/sec LSI	0.230	No	Ceiling effect with LSI present in this sample
KOOS-Sport	-0.252	No	Eliminated due to collinearity with KOOS-Quality of Life
KOOS-Quality of Life	-0.356	Yes	Changes in quality of life have been associate with physical activity modification
KSES-ADL	0.427	Yes	Strongest patient-oriented outcome associated with physical activity in this sample
KSES-Total	0.216	No	Eliminated due to collinearity with KSES-ADL
FABQ-S	0.276	No	Eliminated due to collinearity with KOOS-Quality of Life
FABQ-Total	0.250	No	Eliminated due to collinearity with KOOS- Quality of Life
PCS	0.306	No	Eliminated due to floor effect of the instrument observed in this sample
RTS	-0.287	Yes	Tegner Physical Activity Assessment is responsive to physical activity change in ACLR patients.

LESS-RT = Landing Error Scoring System – Real Time, LSI = Limb Symmetry Index, KOOS = Knee Injury and Osteoarthritis Outcome Score, KSES = Knee Self-Efficacy Scale, ADL = Activities of Daily Living, FABQ-S = Fear-Avoidance Beliefs Questionnaire Sports Subscale, PCS = Pain Catastrophizing Scale, RTS = Return to Pre-injury Sports Participation

Table 3.5. Significant predictors for physical activity after ACLR

Model	Independent Variables	β (95%CI)	R^2	Adjusted R^2	Constant	F	P-Value
1	KSES-ADL	477.25 (144.97 to 809.52)	0.18	0.16	4387.78	8.45	0.006*
2	KSES-ADL	476.85 (167.00 to 786.70)	0.31	0.27	8087.07	8.26	0.004*
	KOOS-QOL	-49.80 (-88.56 to -11.04)					0.013*
3	KSES-ADL	433.57 (129.75 to 737.40)	0.37	0.32	8773.37	7.04	0.006*
	KOOS-QOL	-38.76 (-78.17 to 0.656)					0.054
	LESS-RT	-184.13 (-383.81 to 15.56)					0.070
4	KSES-ADL	415.66 (132.12 to 699.19)	0.47	0.41	9049.55	7.72	0.005*
	KOOS-QOL	-25.70 (-63.87 to 12.47)					0.180
	LESS-RT	-258.39 (-453.64 to -63.14)					0.011*
	RTS	-1689.67 (-3032.62 to -346.71)					0.015*

*Statistically Significant, PA = Physical Activity, LESS-RT = Landing Error Scoring System – Real Time, RTS = Return to Pre-injury Sports Participation, FABQ = Fear-Avoidance Beliefs, Questionnaire

Chapter Four: Neuroplasticity in Corticolimbic Brain Regions in Individuals with a History of Anterior Cruciate Ligament Reconstruction

Introduction

Injury to the anterior cruciate ligament (ACL) is a serious athletic injury that often results in surgical reconstruction (ACLR) to repair and augment knee stability.[60] The principle goal of this surgical procedure is to allow patients to return to previous levels of sports participation and physical activity.[60] However, 1 out of 3 patients will not return to previous levels of sport participation, with injury-related fear often cited as the primary barrier for this failure.[4,13,125] Unfortunately, injury-related fear has not only been associated as a barrier for return to sport but also with an increased rate of secondary injury risk.[56] Previous research has suggested that patients with increased injury-related fear at return to sport (RTS) are 13 times more likely to sustain a secondary ACL injury within 24 months of RTS clearance.[56] Despite the negative impact of injury-related fear in this population, interventions to mitigate injury-related fear post-ACLR have yet to be explored.

Patients after ACLR also experience neuroplasticity in sensorimotor brain regions after their injury.[37,38] Previous research has demonstrated that patients after ACLR exhibit increased activation in the contralateral motor cortex, lingual gyrus, and the ipsilateral secondary somatosensory area during a knee extension-flexion task when compared to healthy controls.[37] These results suggest that patients after ACLR have shifted from a sensory-motor strategy to a compensatory visual-motor to complete functional tasks.[37,126] Interestingly, the secondary somatosensory area is an area of the brain responsible for addressing painful stimuli and exhibited increased activation in this cohort of patients an average of 38 months post-ACLR.[37] However, these patients did not report discomfort during their scans. These results suggest that other factors, specifically psychological, may have influenced the observed brain activation changes. This implies that neuroplasticity in emotional processing brain regions, or corticolimbic regions, may have also occurred in this population.[37]

Other populations with musculoskeletal conditions have demonstrated neuroplasticity in corticolimbic brain regions. In patients with medial patellofemoral ligament deficiency, increased activation in corticolimbic regions was observed during a patellar mobilization task when compared to healthy matched controls.[43] In addition, patients with chronic musculoskeletal pain also exhibited increased activation in corticolimbic regions of the brain.[42] Taylor et al.[42] utilized a blocked picture imagination task paradigm to examine corticolimbic activation, whereby patients were instructed to view pictures of activities of daily living and to imagine themselves completing those tasks. This picture imagination paradigm may be useful to examine neuroplasticity in corticolimbic brain regions in patients with different musculoskeletal pathologies, including ACLR.

There is a critical need to characterize the underlying neural substrate of injury-related fear in patients post-ACLR. Characterizing injury-related fear may allow for the development of more appropriate intervention strategies that may better mitigate injury-related fear after ACLR. By developing appropriate intervention strategies to address injury-related fear, patients may be able to more successfully RTS and lower their risk for sustaining a secondary ACL injury. As such, the purpose of this study is to determine the neural substrate of injury-related fear during a visually-based picture imagination task (PIT) in individuals with a history of ACLR compared to healthy age-matched controls.

We hypothesized that individuals with a history of ACLR would exhibit increased blood oxygen level dependent (BOLD) percent signal changes in corticolimbic brain regions, specifically the medial prefrontal cortex and cingulate cortex, when compared to healthy matched controls.

Methods

Design

A case-control study design was used to examine BOLD signal changes in corticolimbic regions in a cohort of individuals post- ACLR compared to healthy matched controls. The dependent variable was mean BOLD percent signal change and the independent variable was group identification (ACLR vs. healthy controls).

Participants

Twelve female participants post-ACLR and 12 healthy matched controls were recruited for this study. Females were selected for this study due to internal validity concerns as there are sex differences in brain activation patterns in corticolimbic brain regions.[127] Furthermore, females have a higher incidence of ACL injuries compared to their male counterparts.[128] Participants in the post-ACLR group were between 18-35 years, injured their knee playing or training for sports (recreational or organized), had a history of unilateral left-side ACLR, were right-hand dominant, were a minimum of 1-year post-surgery, were cleared for full return to activity by a physician, and lastly, demonstrated magnetic resonance imaging compliance. Healthy matched controls were right-hand dominant, and matched for age (+/- 20% of age in years), height (+/- 20%), mass (+/- 20%), and physical activity history of participating in the same sport. Additionally, participants enrolled in this study must have reported a minimum score of 5 on the Tegner Physical Activity Assessment[113] for activity levels prior to index ACL injury. All participants had to be compliant with magnetic resonance imagining (MRI), including: no presence of metal or other devices in the body or any conditions that may put the participant at risk for having metal in the body. All participants reviewed and signed a University of Kentucky approved IRB informed consent form prior to participation.

Sample Size Calculation

An a priori power analysis was completed. With a sample of 12 participants post-ACLR and 12 healthy matched controls we calculated an 80% power for detecting a 1.25 effect size in the BOLD signal change in prefrontal cortex[42] between the two groups. This calculation was based on an independent t-test with a common standard deviation of 1 and a two-tailed alpha level of 0.05.

Procedures

After informed consent, post-ACLR participants and healthy matched controls completed a demographic questionnaire to assess anthropometric measures and injury history. After completion of the demographic questionnaire, participants underwent a functional magnetic resonance imaging (fMRI) scan. During this scan, participants were presented 40 sports-specific “active” pictures (i.e. jumping) and 20 “resting” or neutral pictures (i.e. sitting). Exposure to sports-specific active pictures followed a modified protocol (Figure 4.1) implemented by Taylor et al.[42] Images selected for the task were selected from the International Affective Picture System (IAPS)[129] and the Photographic Series of Sports Activities for ACLR (PHOSA-ACLR).[130]

Participants first focused on a visual fixation cross to allow the participant's hemodynamic response to return to baseline levels. The stimulus presentation followed a slow event-related design with picture category in a random order and were distributed across two fMRI runs. The duration associated with the fixation cross was counterbalanced and was presented in a random fixed order across the photographs. Based on the previously established protocol by Taylor et al.,[42] participants were instructed to carefully imagine themselves physically and mentally completing the task demonstrated in the picture. All images were presented once for 3 seconds and a fixation cross was presented for a randomized duration ranging between 4.5 seconds and 12 seconds. At the conclusion of the fMRI, all participants completed the Fear-Avoidance Beliefs Questionnaire (FABQ),[23] the PHOSA-ACLR,[130] and the Tampa Scale of Kinesiophobia-11 (TSK-11)[63] to measure injury-related fear.

<u>Instrumentation</u>

Photos of Fear Eliciting Tasks

The IAPS[129] consists of a set of images of normative emotional stimuli for investigations of emotion. A total of 28 sports-specific pictures and 20 neutral images were selected from the IAPS. All sports-specific images were selected if the description included a sports activity (i.e. weightlifting, boxers, runners, etc) and neutral images were of people engaging in activities of daily living (i.e. sitting, laying, reading, etc) with low arousal ratings. PHOSA-ACLR[130] is a patient-reported outcome measure that includes images to assess "fear of harm" while completing functional tasks. All 12 images from the PHOSA-ACLR were utilized in the protocol.

Patient-Reported Outcome Measures

All participants completed three measures of injury-related fear (FABQ, TSK-11 and PHOSA-ACLR). The FABQ is a 15-item questionnaire designed to assess fear-avoidance beliefs in patients with musculoskeletal injury.[23] The FABQ has 2 subscales: the FABQ-Physical Activity (FABQ-PA) and FABQ-Sport (FABQ-S) subscale which have both been modified for the knee.[109] A 6-point Likert scale is used to score each question, where higher scores represent elevated levels of fear-avoidance beliefs. The FABQ-PA and FABQ-S have excellent reliability (intraclass correlation coefficient, ICC = 0.90 and 0.96, respectively).[108] The TSK-11 is a valid and reliable questionnaire (ICC = 0.81, internal consistency = 0.79) designed to evaluate fear of movement and fear of re-injury in patients with musculoskeletal injury.[24] A 4-point Likert scale is used to score each item, with higher scores equating to elevated levels of fear of movement and re-injury. This instrument will be used to assess another psychological impairment that has been routinely evaluated in this population.[24] The PHOSA-ACLR is a valid and reliable 12-item questionnaire used to assess fear of harm.[130] Participants rank their fear of harm on a scale ranging from 0 to 10. Higher scores represent increased levels of fear and lower scores represent lower levels of fear. These surveys were administered after fMRI testing to not interfere with the fMRI results.

Statistical Analysis

Descriptive statistics were calculated for participant demographics, including PRO scores. Mann-Whitney U tests were used to examine between group differences in baseline demographics and injury-related fear as measured by the PROs.

Image Acquisition, Processing, and Analysis

Whole-brain functional images were collected on a Siemens 3T PRISMA MRI scanner using a 64-channel array, receiver-only head coil at the Magnetic Resonance Imaging and Spectroscopy Center at the University of Kentucky. Functional data were acquired with blood-oxygen level dependent (BOLD) echoplanar imaging using a gradient echo simultaneous multi-slice EPI pulse sequence with repetition time (TR) =1500 msec and an echo time (TE) =32msec. Increases in BOLD signal indicate increased activation and decreases in BOLD signal indicate decreased activation. The acquisition matrix was 64x64, field of view (FOV) of 224 mm, and slice thickness of 3.5mm (n =42 axial slices). Acquisition of the data was synchronized with the presentation of sports-specific and neutral images. A double-echo GRE image data set with resolution matched to the EPI was acquired for geometric distortion correction. Anatomical data consisted of volumetric T_1 –weighted MPRAGE gradient echo images with TR =2530msec and TE =2.3msec with 1100ms inversion time, iPAT acceleration of 2 and GRAPPA reconstruction. The voxel resolution was 1x1x1 mm^3.

Functional data were processed using AFNI (Analysis of Functional NeuroImages, http://afni.nimh.nih.gov/) and FSL (http:// fsl.fmrib.ox.ac.uk/fsl/fslwiki) research software. Images were corrected for motion, slice timing, geometric distortion and spatially smoothed. Image data were then analyzed using multiple regression. A general linear model was used to estimate the mean activation response for each condition measured as percent fractional signal change. Regressors included active images and neutral images, as well as the motion parameter estimates as additional nuisance variables. For the second-level group analysis, voxel-wise maps of the fractional signal change activation responses for each subject were transformed to a common stereotaxic Talairach coordinate space, and objective region-of-interest measurements were made using the AAL atlas template.[131] Post-hoc region of interest (ROI) analyses were performed to further characterize the brain responses during the picture imagination task.

Results

Twenty-four (12 individuals with a history of ACLR and 12 healthy matched controls) were scanned. Participant demographic information are presented in Table 4.1. Statistically significant differences were demonstrated between individuals with a history of ACLR and healthy matched controls on the FABQ-S, FABQ-PA, FABQ-Total, TSK-11, and PHOSA-ACLR (Table 4.1). Individuals with a history of ACLR exhibited increased levels of injury-related fear when compared to healthy controls.

Imaging

Differences in BOLD response occurred between groups during the PIT (Figure 4.2, Figure 4.3). The ROI-analysis demonstrated that participants with a history of ACLR exhibited increased activation in corticolimbic brain regions, including the mediodorsal thalamus (MDT) (Figure 4.2), the inferior parietal lobule (IPL) (Figure 4.3), and cerebellar lobule IX, irrespective to picture category when compared to controls. ACLR participants exhibited reduced deactivation in the default mode network (DMN) (i.e posterior cingulate/precuneus and medial prefrontal cortex) irrespective to picture category when compared to healthy controls (Table. 4.2). Statistically significant differences in activation during the PIT are presented in Table 4.2.

Discussion

The purpose of this study was to examine differences in brain activation in corticolimbic brain regions in individuals with a history of ACLR compared to healthy age-matched controls. Our hypothesis that individuals with a history of ACLR would exhibit increased activation in corticolimbic brain regions was confirmed. Increased activation in the inferior parietal lobule, mediodorsal thalamus, and cerebellar lobe IX were observed in the ACLR group. It was also noted that less deactivation in the DMN was present in the ACLR group compared to controls, a finding which has been previously correlated to depression, anxiety, and chronic pain in other populations.[42,132-134] To the best of our knowledge, this is the first study to examine neural substrates of injury-related fear in patients after ACLR. These results indicate that injury-related fear after ACLR is not merely subjectively occurring as a response to injury, but may induce neuroplastic adaptations in corticolimbic brain regions, changes that can be objectively measured and quantified in this population.

Inferior Parietal Lobule and Mediodorsal Thalamus Activation

When compared to healthy controls, patients after ACLR exhibited increased activation in the IPL, MDT, and cerebellar lobule IX. The IPL is the junction of the auditory, visual, and somatosensory cortices and is involved in the perception of emotions in facial stimuli and body images.[135] Traditionally, the IPL processes body and facial images that are exhibiting fearful behaviors, such as screaming or crying.[135] For example, Engelen et al.[135] utilized an image of a male actor jumping backwards with his hands forward as a response to something fearful. Interestingly, none of the sports-specific or neutral images showed athletes being “afraid” of their sports participation, and all athletes were simply performing their sport. However, the post-ACLR group associated these sports-specific images as emotional bodies when compared to healthy controls. This indicates that sports participation may be an emotional, specifically fearful, task for these individuals.

In addition to the IPL, increased activation in the MDT in the post-ACLR group suggests that the MDT has an important role for the acquisition, consolidation, or retrieval of Pavlovian contextual fear conditioning.[136,137] Activation of the thalamus is typically associated with somatosensory inputs, but the MDT serves as an associative hub into and from limbic and hypothalamic brain regions. This connectivity allows for the MDT to influence autonomic processing, such as increased heart rate, which is also related to the sympathetic autonomic response (i.e. fight or flight). Furthermore, the MDT has been associated with the mediation of emotional responses specifically related to pain-evoking stimuli.[138] Viewing sports-specific images may have trigged an emotional response in the post-ACLR group due to episodic memories associated with a painful ACL injury. Sports participation can potentially lead to painful experiences, such as sustaining an ACL injury, thus the post-ACLR group may have experienced a sympathetic autonomic response as a result of these memories. The post-ACLR group did exhibit increased activation in the angular gyrus, an area of the brain associated with recall of episodic memories, when compared to the control group (Table 4.3). This activation further supports the hypothesis of increased episodic memory retrieval in the post-ACLR group during the PIT.

Lastly, it is important to appreciate that the MDT can mediate whether emotional responses to pain-evoking stimuli are processed in the prefontal cortex, an area of the brain associated with executive function, judgement, and decision making.[139,140] Fear-avoidance beliefs, a type of injury-related emotional state that was elevated in this sample, is a fear of pain/and or re-injury that is correlated with learned avoidance behaviors.[23] Pain memories associated with their ACLR experience may not have only led to increased activation in the MDT, but may have also contributed to the observed increased levels of fear-avoidance beliefs in the ACLR group. Increased fear-avoidance beliefs may subjectively represent the objective feedback loop between the MDT and the prefrontal cortex. Activation in the MDT may allow for rumination of painful memories in the prefrontal cortex which then creates a feedback loop to allow the pain memory to consistently be processed in the person's consciousness during sports participation. This feedback loop may negatively change the cognitive appraisal of sports participation in patients after ACLR, thus changing the patient's subjective views and lead to increased fear-avoidance beliefs. Furthermore, previous research has established that damage to the MDT is accompanied with an inability to process the emotional consequences of pain as the connection to the prefrontal cortex is no longer present.[141] This connection between the MDT and the prefrontal cortex may also explain why this sample of ACLR patients exhibited reduced deactivation in the DMN.

Default Mode Network

The DMN is a cortical network that shows greater activity during resting state conditions when compared to the active performance of a goal task (i.e. picture imagination task).[133,134,142] The functional hubs associated with the DMN include the posterior cingulate cortex (PCC) and precuneus, the medial prefrontal cortex, and the angular gyrus.[134,142,143] The PCC is activated in in all tasks associated with the self, relating to others, past memories, and thinking about the future. The precuneus is activated with the processing of attentional and spatial information.[143] Previous research has demonstrated that less deactivation in the DMN is associated with psychopathological conditions, including depression,[144,145] and anxiety,[146,147] and chronic pain.[42,132] Echoing the results demonstrated in Taylor et al.[42] in a sample of patients with chronic musculoskeletal pain, the post-ACLR group exhibited less deactivation of the DMN when compared to healthy controls. Specifically, the post-ACLR group exhibited less deactivation in the PCC, precuneus, and medial prefrontal cortex. Inability to suppress the DMN may indicate that patients after ACLR are predisposed to processing fear, anxiety, and/or pain. Taylor et al.[42] suggested that reduced deactivation in the DMN may also occur because the brain is constantly processing pain. However, we hypothesize that rather than processing pain, the ACLR group may constantly process the memory of the painful event. Very similar to the results of Grooms et al.,[37] our participants were approximately 5.5 years from index ACLR and none of the participants complained of pain while in the scanner. Grooms et al.[37] noticed increased activation in the ipsilateral secondary somatosensory area and attributed this to a functional cortical sensory processing reorganization as a result of knee trauma. However, our results suggest that the ipsilateral secondary somatosensory area may have been activated during the knee flexion/extension task as the DMN may have been continuously processing pain memory in these patients.

Cerebellar Activation

Increased activation in the cerebellum was also observed in patients after ACLR when compared to healthy controls. Activation in the cerebellar lobule IX is consistent with results from Grooms et al.,[37] suggesting that patients after ACLR exhibit increased reliance on their vision to complete functional tasks. The cerebellar lobule IX is an area considered to be essential for the visual guidance of movement.[148,149] These results add to the growing body of literature that suggests patients after ACLR are compensating for changes in their sensorimotor system by relying on their vision to complete functional tasks.[37,126,150] However, activation in the cerebellum may not only be a result of increased visual reliance.

Traditionally, cerebellar activity has only been described in the context of motor function, but recent research has begun to explore the involvement of the cerebellum in Pavlovian fear conditioning.[151,152] It has been demonstrated that the cerebellum, specifically the vermis, is associated with high arousal and negative emotional regulation.[151] The cerebellum has direct connections with limbic regions, including the amygdala and the hippocampus.[151] Recognition of potentially fear eliciting stimuli and activation of cerebello-hypothalamic brain regions may be a result of the sympathetic autonomy response (fight or flight). During the PIT, individuals with a history of ACLR may have undergone a sympathetic autonomic response as a result of the PIT.

As proposed by the stress and injury model, maladaptive stress responses can increase the risk of sustaining an athletic injury.[52] The stress and injury model proposes that an athlete's cognitive appraisal of an athletic situation can lead to physiological and attentional changes.[52] However, multiple factors can influence this stress response, including previous injury.[52] If the athlete experiences increased levels of stress and is unable to overcome the physical and psychological demands of the situation, then the athlete is at an increased risk of sustaining an injury.[52] The results of our research align with the present model, as the brain areas associated with physiological and attentional responses to stress are activating in these patients. The corticolimbic regions activated in these patients have direct connections to the hypothalamus which regulates the physiological stress response.[153] Previous research has demonstrated that patients after ACLR who exhibit increased injury-related fear are 13 times more likely to sustain a secondary ACL injury within 24 months of RTS.[56] The stress response as a result of increased activation in corticolimbic brain regions may be partially related to this increased risk of re-injury associated with increased levels of injury-related fear in ACLR patients .

Psychologically Informed Clinical Practice

The results from this study highlight the potential significance and importance of integrating psychologically informed clinical practice techniques during the treatment of patients after ACLR. Psychologically informed clinical practice emphasizes the integration of cognitive behavioral therapies and psychoeducation techniques in conjunction with traditional musculoskeletal rehabilitation.[121] It has been established that rehabilitation specialists can effectively implement cognitive behavioral therapies and psychoeducation techniques to decrease injury-related fear after ACLR.[123] Specifically, integration of *in vivo* exposure therapy has been successfully integrated and used by rehabilitation specialists to decrease injury-related fear in patients with chronic low back pain.[123] *In vivo* exposure is a cognitive behavioral technique that gradually exposes patients to functional tasks they are fearful to complete.[47] Rather than using pain or soreness as a guide for progression, rehabilitation specialists utilize fear as their guide for progression through different levels of exercises with the goal of decreasing the patient's fear response to that specific exercise.[47] This technique may not only decrease injury-related fear in patients after ACLR, but it may be able to induce long-term adaptive neuroplasticity in patients after ACLR.

Limitations

The following limitations have been identified for this study. First, the activation patterns observed in the ACLR group may have been present prior to their ACL injury. We are unable to definitively state that the ACL injury led to these changes in activation, although the lack of similar activity in the control population does suggest that activation patterns in the ACLR group were likely related to ACL injury or repair. Secondly, fMRI is an indirect measure of neural activity and we are unable to distinguish connectivity between brain regions. Thus, we are only able to speculate the connectivity between corticolimbic regions in the brain from the activation patterns. Thirdly, while the questionnaires used in this study to examine injury-related fear have been previously used in patients after ACLR, these questionnaires have not been validated for an ACLR population. Lastly, we were unable to quantify pain levels in these patients, and instead of injury-related fear, pain may have led to the activation patterns observed in the post-ACLR group. However, no participant complained of pain during the fMRI scan.

Conclusion

The present study found brain activation differences in corticolimbic brain regions in individuals with a history of ACLR when compared to healthy matched controls during the PIT. The brain activation patterns observed indicated that neuroplasticity in corticolimbic brain regions may have occurred, which may be a result of increased levels of injury-related fear. Future research should explore the effectiveness of cognitive behavioral therapies, specifically *in vivo* exposure, on decreasing injury-related fear and mitigating brain activation differences in patients after ACLR. Lastly, future research should characterize the structural connectivity between corticolimbic brain regions in patients after ACLR.

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Table 4.1. Participants' demographics

	ACLR Group (n=12) Median [IQR]	Control Group (n=12) Median [IQR]	TOTAL (n=24) Median [IQR]	Mann-Whitney Test P-Value
Height (cm)	168.91 (16.51)	166.37 (14.61)	167.64 (14.61)	0.98
Weight (kg)	68.49 (22.80)	66.90 (19.28)	68.04 (17.92)	0.32
Age (years)	21.50 (6.75)	23.00 (1.75)	22.5 (3.75)	0.27
Time from Index ACLR (years)	5.5(4.25]			
FABQ-PA	7.50 (12)	0.00 (5)	4.00 (10)	0.008
FABQ-S	13.00 (17)	0.00 (6)	4.00 (17)	0.006
FABQ-T	19.50 (30)	0.00 (11)	8.00 (26.00)	0.006
TSK-11	20.00 (6)	14.00 (7)	17.50 (8.00)	0.01
PHOSA-ACLR	1.92 (2.04)	0.17 (1.54)	1.08 (2.23)	0.04

*ACLR = Anterior Cruciate Ligament Reconstruction, FABQ = Fear-Avoidance Beliefs Questionnaire, FABQ-PA = Physical Activity Subscale, FABQ-S = Sports Subscale, TSK-11 = Tampa Scale of Kinesiophobia-11, PHOSA-ACLR = Photographic Series of Sports Activities after Anterior Cruciate Ligament Reconstruction, ACLR = Anterior Cruciate Ligament Reconstruction

Table 4.2. Statistically significant group differences for picture imagination task

	Mean Fractional % Signal Change (SD)		T-stat	P-value
	ACLR Group	Control Group		
Frontal Superior R	3.17 (6.40)	-4.35 (8.07)	2.52	0.019
Frontal Superior Medial L	8.52 (11.46)	-1.75 (11.28)	2.21	0.038
Frontal Superior Medial R	-3.13 (11.81)	-11.62 (14.31)	2.14	0.043
Frontal Orbital Medial L	9.54 (12.48)	-6.94 (19.10)	2.50	0.020
Cingulum Ant R	-1.39 (7.00)	-8.35 (9.07)	2.10	0.047
Cingulum Mid L	5.15 (5.92)	-2.19 (1.03)	2.14	0.043
Cingulum Post L	9.62 (18.10)	6.45 (15.31)	3.79	0.001
Cingulum Post R	6.45 (15.31)	-12.37 (7.30)	3.84	0.001
Hippocampus R	13.25 (5.26)	6.91 (7.31)	2.43	0.023
Occipital Inferior L	70.00 (20.65)	51.91 (15.13)	2.44	0.023
Angular Gyrus L	5.37 (12.26)	-5.52(11.52)	2.24	0.035
Angular Gyrus R	-1.11 (13.09)	-14.04 (8.33)	2.88	0.009
Caudate L	5.99 (6.63)	-1.90 (8.93)	2.45	0.022
Thalamus L	11.75 (9.00)	0.8 (6.70)	3.36	0.003
Thalamus R	10.21 (8.10)	0.8 (6.83)	3.06	0.006
Cerebellum Crus 2 L	5.79 (7.68)	-2.23 (6.00)	2.90	0.008
Cerebellum Crus 2 R	5.56 (6.00)	0.7 (5.23)	2.08	0.049
Cerebellum 9 L	15.34 (7.88)	5.28 (4.38)	3.85	0.001
Cerebellum 9 R	16.54 (9.34)	6.42 (6.06)	3.14	0.005
Cerebellum 10 L	23.67 (12.07)	13.22 (8.54)	2.44	0.023
Vermis 1	5.01 (9.40)	-3.21 (9.96)	2.08	0.049
Vermis 9	16.44 (5.08)	5.97 (6.75)	4.29	0.000

*Region-Of-Interest Analysis using the Automated Anatomical Labeling (AAL) atlas

Figure 4.1. Functional magnetic resonance imaging trial timing

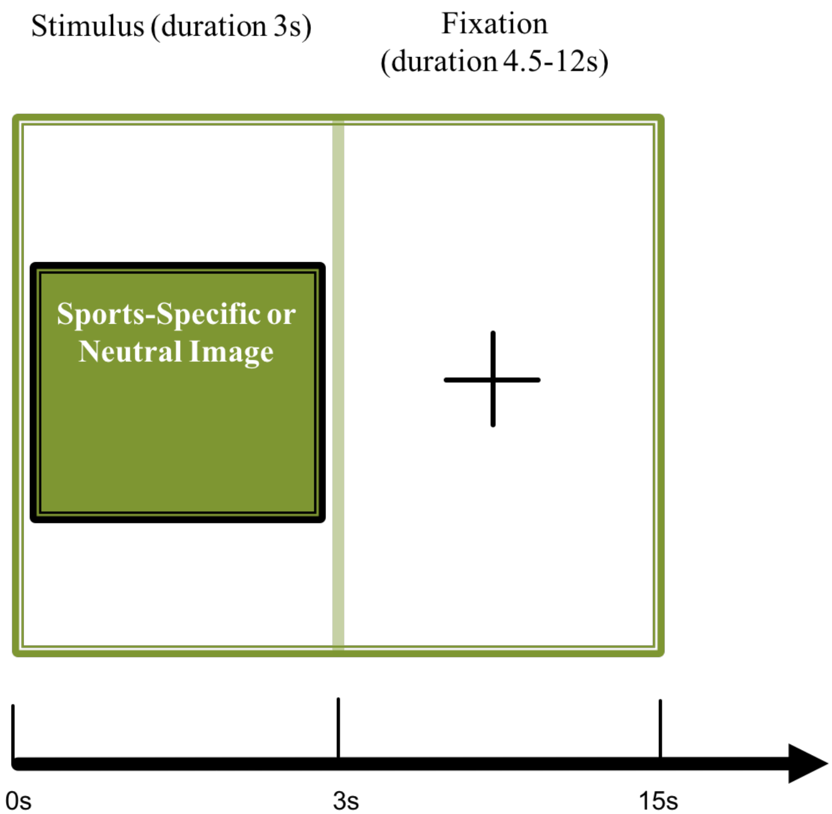


Figure 4.2. Thalamus activation during the picture imagination task.

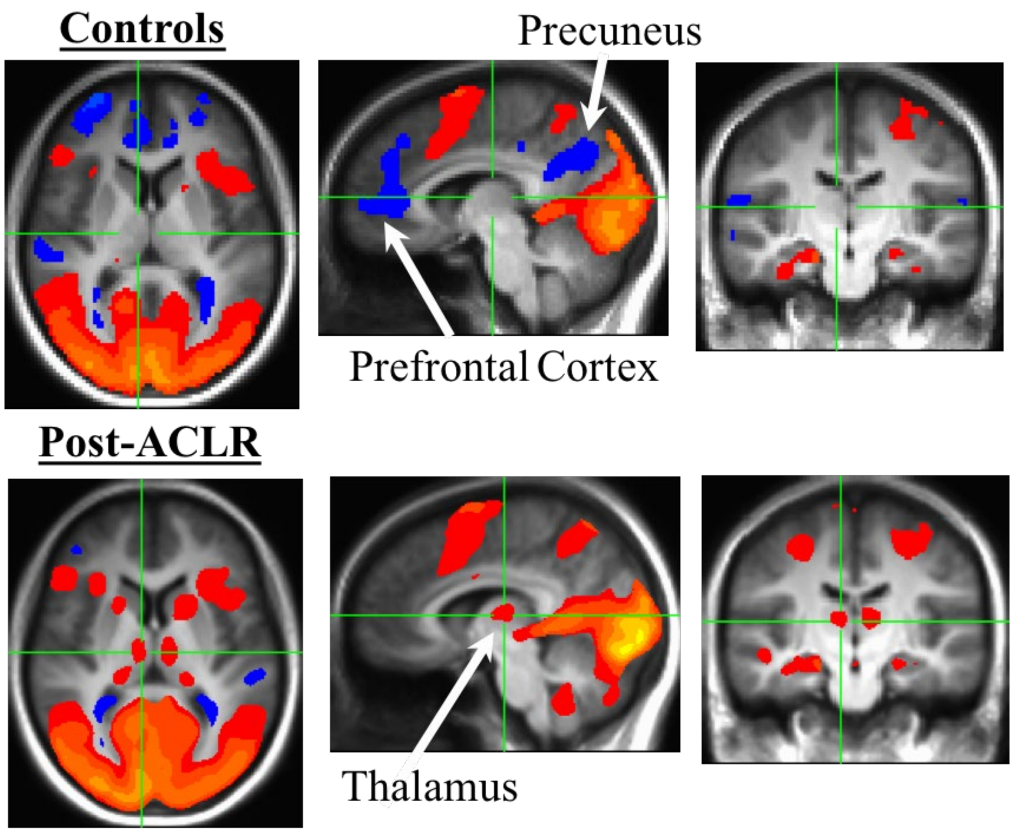


Figure 4.2. fMRI activation map in a transformed Talairach coordinate frame of reference. Response to picture stimuli measured as % fractional signal change. Crosshair at location (8 [R], -14[P], 10[S]) in the thalamus irrespective to picture category. Red indicates increased activation in the area and blue indicates decreased activation in the area.

Figure 4.3. Inferior parietal lobule activation during the picture imagination task.

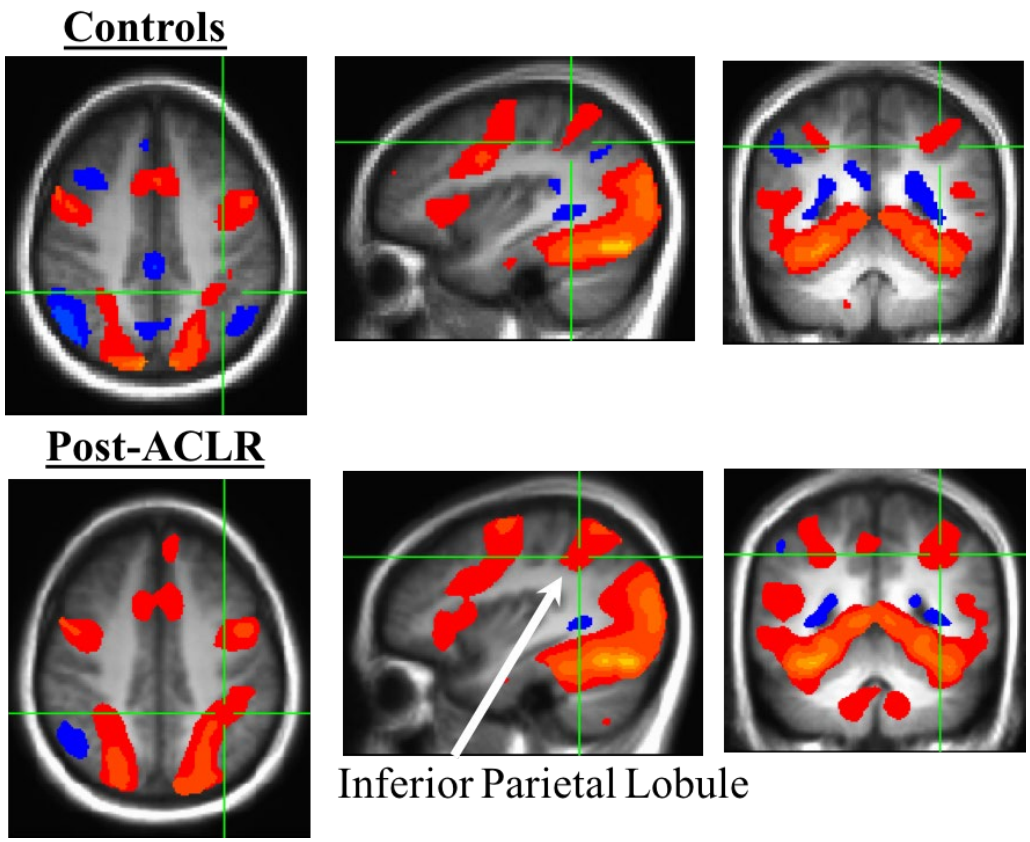


Figure 4.3. fMRI activation map in a transformed Talairach coordinate frame of reference. Response to picture stimuli measured as % fractional signal change. Crosshair at location (-34 [L], -44[S], 40[P]) in the inferior parietal lobule irrespective to picture category. Red indicates increased activation in the area and blue indicates decreased activation in the area.

Chapter Five: Implementation of *In Vivo* Exposure Therapy to Decrease Injury-Related Fear in Females after ACL-Reconstruction: A Pilot Study

Introduction

Engagement in a physically active lifestyle is pertinent for health.[154] However, an associated risk of physical activity is musculoskeletal injury.[105] Individuals who participate in high-levels of competitive sports, like soccer or football, are at an increased risk of sustaining injury to the anterior cruciate ligament (ACL).[155] Unfortunately, females tear and re-tear their ACLs at a significantly higher rate than their male counterparts,[128] which can lead to poorer health outcomes compared to male counterparts. Individuals who sustain an ACL injury often undergo ACL reconstruction (ACLR) with the goal of returning to pre-injury levels of function.[60] Unfortunately, return to previous levels of function does not always occur, as approximately 1 out of 3 patients after ACLR will not return to competitive levels of sports and only 65% will return to pre-injury level of sport.[4] Psychosocial impairments, such as injury-related fear, have been cited as the primary reason for failure to return in these previously high-functioning, physically active individuals.[2,4] Rehabilitation specialists are often the healthcare provider that communicates with the patient most frequently during their rehabilitation and return to sport process. Therefore, rehabilitation specialists are more likely to recognize psychosocial impairments, such as injury-related fear, that may be affecting their patient compared to other members of the patient's healthcare team. Rehabilitaiton specialists may also be in a position to implement effective intervention strategies, such as cognitive behavioral therapies, to address these impairments.

Cognitive behavioral therapies are short-term intervention strategies designed to modify an individual's cognitions, in an effort to incite a behavioral change.[44] Cognitive behavioral therapies and psychoeducation can be successfully implemented by rehabilitation specialists to treat chronic low back pain.[123] In a recent systematic review regarding effective cognitive behavioral and psychoeducational interventions to decrease fear-avoidance beliefs in patients with chronic low back pain, the most effective intervention strategies were exposure therapies and classification based cognitive functional therapy.[123] While classification based cognitive functional therapy is appropriate for intervening on patients with chronic low back pain, *in vivo* exposure therapy may be appropriate to intervene in other populations, such as patients after ACLR. *In vivo* exposure therapy is a cognitive behavioral therapy designed to gradually expose patients to their most fear-eliciting functional tasks in an attempt to reframe maladaptive views of the respective functional tasks.[47] *In vivo* exposure therapy has been demonstrated to decrease fear of movement/re-injury,[47,104] and patients also increased their physical activity levels.[47] These interventions may be useful in the post-ACLR rehabilitation and return to sport process to decrease psychosocial impairments, and improve physical activity outcomes.

Interestingly, none of the studies included in the systematic review examined other outcomes, including the effects of *in vivo* exposure on neurocognitive functioning. This is important because, in addition to increased levels of injury-related fear after ACLR, these patients also demonstrate deficits in neurocognitive functioning prior to their injury and neuroplastic alterations after their subsequent reconstruction.[36] Previous literature has demonstrated that healthy athletes with psychosocial impairments also demonstrate decreases in reaction times.[41] Unfortunately, deficits in neurocognitive function, specifically reaction time, can predispose an athlete to increased risk of injury or re-injury.[39,40] Therefore, the identification of an effective cognitive behavioral therapy that can reduce injury-related fear and also improve reaction times is pertinent. Since reaction time has been associated with injury risk, improvements in reaction times through *in vivo* exosure therapy may allow for another tertiary prevention strategy to mitigate re-injury risk in patients after ACLR.

Given the positive influence on outcomes in patients with low back pain,[123] and occurrence of injury-related fear in a post-ACLR population, there is a critical need to examine the effectiveness of these intervention strategies in individuals post-ACLR. Therefore, the purpose of this pilot study was to examine the effectiveness of *in vivo* exposure therapy on injury-related fear and neurocognitive functioning in post-ACLR female participants. We hypothesized that post-ACLR participants who complete the intervention would have decreased injury-related fear and faster reaction times when compared to post-ACLR controls.

Methods

Design

A randomized control trial (Figure 5.1) was used to examine the efficacy of *in vivo* exposure therapy in post-ACLR participants. Twelve females post-ACLR were randomized into an intervention group or control group. A random number generator was used to randomly generate a list of numbers, and an outside investigator assigned each number to the experimental [1] or control [2] group. This investigator sequentially numbered the opaque envelopes and placed a numbered card [1 or 2] inside which corresponded to group assignment. The independent variables were group and time. The dependent variables were scores on the Photographic Series of Sports Activities for ACLR (PHOSA-ACLR), Tampa Scale of Kinesiophobia-11 (TSK-11), Fear-Avoidance Belief Questionnaire (FABQ), Anterior Cruciate Ligament Return to Sport after Injury scale (ACL-RSI), the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), upper extremity visuomotor reaction time via the Dynavision D2 systems (s), and lower extremity visuomotor reaction time via the FitLight Trainer™ (ms).

Participants

Twelve post-ACLR participants were recruited (Table 5.1). Participants were female, ages 18-35 years, had self-reported levels of injury-related fear as measured by the PHOSA-ACLR, injured their knee playing or training for sports (recreational or organized), had a history of unilateral left-side ACLR, were right-hand dominant, were a minimum of 1-year post-surgery, and were cleared for full return to activity by a physician. Additionally, participants enrolled in this study must have reported a minimum score of 5 on the Tegner Physical Activity Assessment[113] for activity levels prior to index ACL injury. This study was approved by the University of Kentucky Institutional Review Board. All participants reviewed and signed a University approved IRB informed consent prior to participation.

Procedures

After informed consent, participants completed a demographic questionnaire and the Knee Injury and Osteoarthritis Outcome Score (KOOS). The demographic questionnaire collected information regarding anthropometric information and health history and the KOOS collected information about knee symptoms, pain, function specific to activities of daily living and sport activities, and knee-related quality of life.

After completion of the demographic questionnaire and the KOOS, the participants completed a series of patient-reported outcome measures (PROs): PHOSA-ACLR, TSK-11, FABQ, and ACL-RSI. Once the participants completed all of the PROs, participants completed three neurocognitive assessments: the ImPACT, Dynavision D2 systems, and FitLight Trainer™. Finally, after all baseline measures were captured, the participants were randomized in to the control or intervention group.

Intervention

After completion of baseline assessments, the investigator that completed the baseline assessments opened the numbered envelope to reveal group allocation. Participants randomized to the experimental group completed a 5-week *in vivo* exposure therapy designed to treat injury-related fear (Figure 5.2). Participants randomized to the control group were asked to document their weekly physical activity on a physical activity log and returned the physical activity log to the investigator at the beginning of each week.

Post-ACLR Control Group

Control participants were given a pedometer (3D Active PW-300), asked to wear the pedometer on their non-dominant wrist, and were instructed to wear their pedometer at all times except when showering, swimming, or sleeping. Participants were asked to document their physical activity levels throughout the five weeks on a weekly step log. Control participants reported to the lab once per week to assess any changes in health status and to receive a new weekly step log. On week 5, all participants repeated the PROs and neurocognitive assessments described above.

Intervention Group

Scores on the baseline PHOSA-ACLR were used to develop the graded-hierarchy of fear-eliciting situations, and these fear-eliciting situations were addressed in the *in vivo* exposure therapy. The *in vivo* exposure therapy began on week 2 (Figure 5.2) with Task 1. During this first week after baseline assessments, participants were instructed to watch an 8-minute video that provided education on the rationale of cognitive behavioral therapies, specifically the benefits of exposure therapy. The video also provided education on passive and active coping patterns, specifically addressed through the fear-avoidance model, and the benefits of positive self-talk. The information in the video was presented by the primary investigator (S.B.) and was recorded to ensure consistency in information delivered to all participants.

Upon completion of the patient education session the participants were gradually exposed to their most fear-eliciting task (Task 1) as determined by their graded hierarchy of fear-eliciting situations. First, the investigator modeled the activity and the participants were asked to rate their current level and expected level of fear while performing the respective task on a 0-10 point scale (0 = no fear and 10 = most fear possible). The participants were then gradually exposed to the fear-eliciting situation through a graded exposure technique (Figure 5.2). Upon completion of each stage of the graded exposure, the participants were asked to rate the fear actually experienced while completing the task on the same 0-10 scale. If the ranking decreased, then it was appropriate to move to the next progression of the fear-eliciting task.

For example, Participant A's graded hierarchy of fear-eliciting situations indicated they had increased fear of completing the single-leg hop. A progression for graded exposure for this task would be completion of a) double-leg vertical hop, b) double-leg forward hop, c) single-leg vertical hop, and d) single-leg forward hop (Figure 5.2). Therefore, the investigator began by demonstrating the double-leg vertical hop. The participant would then rate their current level of fear while performing the double-leg vertical hop. The participant would then complete the double-leg vertical hop and then rate the fear actually experienced while completing the double-leg vertical hop. If the ranking decreased, then the participant would be progressed to complete the double-leg forward hop. The investigator would model the behavior, have the participant rank their fear, have the participant complete the task, and then have them rank their fear, again. If the ranking decreased, then the participant would be progressed to the next task. The investigator would continue this method for tasks completion throughout the entire progression (Part A - Part D; Figure 5.2). Additionally, participants were encouraged to engage in positive self-talk while completing each task as cognitive restructuring in combination with *in vivo* exposure has been theorized to aid in improving successful performance of functional tasks.[156]

After session I, participants were encouraged to engage in Task 1 throughout the next week. Participants documented their engagement in Task 1 on a compliance log and received a new compliance log each week to document their engagement compliance with each subsequent task. Participants in the experimental group returned to the lab on week 3 and week 4 to complete Tasks 2 and Tasks 3, respectively. The same methodology described above occurred on each of those weeks. On week 4, participants did not come to the lab for a formal exposure session but were instructed to engage in all tasks from weeks 2-4 throughout the week. They were asked to document compliance with engaging in these tasks on their compliance log. The participants then returned to the lab on week 5 and returned their week 4 compliance log and repeated the PROs and neurocognitive assessments.

Instrumentation

Patient-Reported Outcome Measures

The Knee Injury and Osteoarthritis Outcome Score

The KOOS consists of 5 domains: symptoms (KOOS-S), activities of daily living (KOOS-ADL), function in sport and recreation (KOOS-Sport), and quality of life (KOOS-QOL).[21] A 5-point Likert Scale is utilized for each item, and a score of 100 on each subscale represents no disability. The reliability for the KOOS in individuals post-ACLR is clinically acceptable (ICC>0.75).[21] This measure was used to understand the participant's perceived symptoms, pain, and knee related function.

The Photographic Series of Sports Activities for ACLR

The PHOSA-ACLR is a questionnaire designed to measure fear of harm of specific tasks through photographical assessment.[130] Patients were instructed to rate each photograph of sports activities on a scale of 0 to 10, with 0 representing "not harmful at all" and 10 representing "extremely harmful." This instrument provides information about fear-eliciting stimuli that are not measured by the TSK-11 and FABQ including running, landing after a jump, singe leg jump, pivoting movement, and other functional tasks. The minimal detectable change for the PHOSA-ACLR is 2 points ($1.96 \times 0.63 \times \sqrt{2} = 1.74$).[130] The PHOSA-ACLR demonstrates excellent internal consistency (Cronbach's alpha = 0.95), is strongly correlated with the TSK ($r = 0.59$), and demonstrates excellent test-retest reliability (ICC = 0.86).[130]

The Fear-Avoidance Beliefs Questionnaire

The FABQ has 2 subscales: the FABQ-Physical Activity (FABQ-PA) and FABQ-Sport (FABQ-S) subscale which have been modified for the knee.[109] A 6-point Likert scale is used to score each question, where higher scores represent elevated levels of fear-avoidance beliefs. The FABQ-PA and FABQ-S have excellent reliability (intraclass correlation coefficient, ICC = 0.90 and 0.96, respectively).[108]

The Tampa-Scale of Kinesiophobia-11

The TSK-11 is a valid and reliable questionnaire (ICC = 0.81, internal consistency = 0.79) designed to evaluate fear of movement and fear of re-injury in patients with musculoskeletal injury.[24] A 4-point Likert scale is used to score each item, with higher scores equating to elevated levels of fear of movement and re-injury. This instrument was used to assess another psychological impairment that has been routinely evaluated in this population.[24]

Anterior Cruciate Ligament – Return to Sports after Injury Scale

The ACL-RSI is a 12-item questionnaire that measures psychological readiness to RTS after ACLR. This questionnaire measures emotions (five items), confidence in performance (five items), and risk appraisal (two items). This questionnaire using a Likert scale ranging from 0-5 and is scored from 0-100. Lower scores represent poor psychological readiness to RTS and higher scores represent good psychological readiness to RTS. The ACL-RSI has high validity and internal consistency (Cronbach's alpha=0.96).[62]

Neurocognitive Assessments

Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

The ImPACT[157] is a scientifically validated computerized neurocognitive test that asks questions to assess different domains of neurocognitive function. Using a computer, participants selected answers by hitting keys on a keyboard and by clicking a mouse. Participants completed the ImPACT and a composite score was generated for neurocognitive reaction time.[157] The ImPACT composite score is a reliable measure to assess neurocognitive function,[158] and has demonstrated higher sensitivity and specificity for diagnosis of concussion.[159]

Dynavision D2 System

The Dynavision D2 System (Dynavision International, LLC, West Chester, OH) provides information regarding visuomotor processing speed and reaction time. The system consists of 64 raised 3D color changing targets arranged in 5 rings on a 4' x 4' impact resistant, square board with an adjustable height ranging from (65.75 cm to 95.5 cm).[160-163] Participants completed the "proactive" mode of the system. During this mode, the Dynavision generated a random activation sequence of one target button at a time. Participants were instructed to press the activated buttons as quickly as possible. Participants were allowed to use either hand to complete this task. There were three 30-second familiarization trials which were followed by one 60-second test trial. The number of targets hit and the average time (milliseconds) between the targets hits was used to assess visuomotor reaction times. Unpublished data demonstrates a minimal detectable change of 0.29ms as a clinically meaningful difference.

FitLight Trainer™

The FitLight Trainer™ (FITLIGHT Sports Corporation, Aurora, ON) is a speed and agility trainer designed to measure visuomotor reaction time. The FitLight Trainer™ consists of a series of LED wireless sensor light discs that are designed to be deactivated by hands, feet, head, and/or sports equipment. Deactivation of lights can occur through contact with the target or through proximity of the target (i.e. 10cm above the target). The FitLight Trainer™ has been previously used to examine visuomotor reaction time in athletes.[164] Participants were instructed to respond to a visual stimulus and deactivate a series of 5 targets arranged in a semicircle with their feet. Each light disc has a velcro back and will be stuck to a mat in increments of 45 degrees around the 180-degree semicircle. The distance for each light was normalized to the length of the shank of each participant. The target deactivated when the participant's foot touched the target. A random sequence of visual stimuli configured by the tablet controller (Android operating systems) was used to measure visuomotor reaction time in seconds. Participants completed the test bilaterally, and test limb order was counterbalanced between participants. Participants completed three 30-second familiarization trials followed by one 60-second test trial. Unpublished data demonstrates a minimal detectable change of 0.074s as a clinically meaningful difference.

Statistical Analysis

All statistical analyses were performed using SPSS software (v.25.0, SPSS, Inc., Chicago, IL, USA). Independent t-tests were used to examine between group differences in baseline demographics. The dependent variables were scores on the PHOSA-ACLR, TSK-11, FABQ, and ACL-RSI, upper extremity visuomotor reaction time (ms), lower extremity visuomotor reaction time (s), and neurocognitive reaction time (s). The independent variables were group and time. Descriptive statistics (mean±standard deviation) were calculated for each dependent variable. A group x time repeated measures two-way analysis of variance (ANOVA) was completed for each dependent variable. Partial η^2 effect sizes were calculated to examine the magnitude of differences between group and time. Effect sizes were interpreted as small if between 0.01 and 0.08, medium if between 0.09 and 0.24, and large if $\geq$0.25.[165]

Results

A total of 12 participants were included in the analysis. No participants were lost to follow-up and all participants in the intervention group were able to complete the 3 tasks as described. Participants were an average of 22.50±4.60 years old and a median of 5 [5] years from index ACLR. No statistical differences in baseline demographics were observed between groups (Table 5.1). Functional tasks addressed in the intervention included pivoting, running, landing after a jump, lateral lunging, single-leg jumping, sliding, sudden deceleration, hopping, and jumping on a trampoline (Table 5.2). Three out of the 6 participants in the intervention group selected the pivoting task as the most fear-eliciting task, and 5/6 participants in the intervention group addressed pivoting during their exposure therapy. Individual item scores for the PHOSA-ACLR in the intervention and control groups are presented in Table 5.2 and Table 5.3, respectively. Participants in the control group averaged a total of 8709.04±2995.04 steps during the 5-weeks. However, only 33% (2/6) of participants in the control group averaged 10,000 steps during the 5-weeks.

The means and SD for each of the dependent variables at pre-test and post-test are presented in Table 5.4. The PHOSA-ACLR exhibited a significant main effect for time ($F(1,10) = 9.92$, $p = 0.01$, partial $\eta^2 = 0.50$), however a main effect for group was not observed ($F(1,10) = 0.21$, $p = 0.659$, partial $\eta^2 = 0.02$). A statistically significant group x time interaction effect was not observed for the PHOSA-ACLR but a medium effect size was present ($F(1,10) = 1.102$, $p = 0.32$, partial $\eta^2 = 0.09$). We failed to reach the MDC for the PHOSA-ACLR, but individual item scores demonstrated changes in PHOSA-ACLR items that were addressed in the intervention (Table 5.2). No other statistical significance was observed for any other outcome measure. However, medium to large effect sizes were present for other outcome measures. Medium effect sizes for group were present for the FABQ-S, TSK-11, Dynavision D2 System, ImPACT RT, and FitLight uninjured limb. Medium effect sizes for time were present for the Dynavision D2 system. Large effect sizes for group were present for the FitLight Trainer injured limb. Large effect sizes for time were present in the PHOSA-ACLR. All effect sizes for group and time are presented in Table 5.4. Despite medium to large effect sizes, we failed to reach the MDC for any outcome measure.

Discussion

The purpose of this study was to examine the efficacy of *in vivo* exposure therapy on decreasing self-reported injury-related fear and improving visuomotor reaction time in individuals post-ACLR. We hypothesized that those individuals who underwent *in vivo* exposure therapy would exhibit decreased injury-related fear and faster reaction times when compared to the post-ACLR control group. However, our hypothesis was not supported. Individuals post-ACLR who underwent *in vivo* exposure did not exhibit statistically or clinically meaningful decreases in injury-related fear, as measured by the FAQB and TSK-11, or improvements in upper extremity or lower extremity VMRT when compared to the post-ACLR control group. Although not clinically meaningful, 100% of the participants in the intervention group reported lower levels of injury-related fear on the specific items from the PHOSA-ACLR addressed in the intervention. This result supports the efficacy of the current *in vivo* exposure paradigm to reduce injury-related fear associated with specific functional tasks, but not general phobic responses.

In Vivo Exposure Therapy and Injury-Related Fear

Although we did not see a statistically significant or clinically meaningful change in total score on the PROs, we did see changes in specific functional tasks addressed in the intervention. These results raise the possibility that the proposed gradual exposure paradigm could decrease self-reported injury-related fear for specific functional tasks. If a patient post-ACLR reports to a rehabilitation specialist with a specific fear associated with a particular functional task, *in vivo* exposure therapy may be an appropriate intervention to address patient-specific fears. The developed intervention replicates traditional progressions implemented throughout ACL rehabilitation. Based on these results, rather than using traditional clinical outcomes, such as a pain or strength as the progressive factor, the rehabilitation specialist would utilize injury-related fear as the progressive factor. This intervention slightly deviates from traditional clinical practice, but these results suggest that this deviation may be of benefit to patients after ACLR. However, *in vivo* exposure therapy may not be effective in decreasing general phobic responses in patients after ACLR, as the *in vivo* exposure therapy was not effective in decreasing overall injury-related fear as measured by the TSK-11, FABQ, or ACL-RSI.

In Vivo Exposure and Neuroplasticity

Implementation of *in vivo* exposure therapy did not lead to statistically significant or clinically meaningful differences in VMRT between the intervention group and control group. This suggest that *in vivo* exposure therapy did not lead to changes in neurocognitive functioning and failed to induce neuroplasticity in this sample. Previous research has examined neuroplasticity after implementation of *in vivo* exposure therapy in individuals with PTSD. [103] King et al.[103] implemented a 16-week non-trauma-focused *in vivo* exposure therapy in combination with mindfulness training to decrease combat PTSD in military veterans. The intervention in this study consisted of four modules which included: 1) PTSD psychoeducation and relaxation, 2) mindfulness of body and breath exercise and *in vivo* exposure, 3) mindfulness of emotion and *in vivo* exposure, and 4) self-compassion training. Each of the sessions were 2 hours and all participants completed daily homework between each session. *In vivo* exposure was only conducted for avoided and objectively safe situations and/or activities. Results demonstrated that implementation of the 16-week intervention in addition to mindfulness training led changes in neural activity associated with symptom reduction.[103] The length of the intervention, frequency of the exposure, and combination of mindfulness training may have led to the neuroplasticity observed in their patients compared to the intervention included in this study.

The 5-week intervention completed in the present study may not have been long enough to induce neuroplasticity and lead to statistically significant or clinically meaningful differences in VMRT in the post-ACLR group. Specially, each session with the participants in the intervention group lasted approximately 30 minutes. Furthermore, participants in the present study were instructed to only complete the functional tasks at least 3 times per week. However, King et al.[103] instructed their participants to address activities and/or situations that were avoided everyday with their daily homework assignment. These results highlight the importance of saliency and experience on inducing neuroplasticity. It is possible that differences in VMRT may have been observed in this sample if *in vivo* exposure sessions were longer, and if participants were instructed to complete the exercises each day for longer periods of time. Given the reduction in item scores on the PHOSA-ACLR, future research should explore neural correlates of the current *in vivo* exposure therapy paradigm implemented for a longer duration and increased frequency in patients after ACLR.

Physical Activity, Injury-Related Fear, and Visuomotor Reaction Time

Although not statistically significant or clinically meaningful, individuals in the physical activity control group also exhibited lower scores on functional tasks of the PHOSA-ACLR at post-test. While there was not a significant increase observed in average daily step counts throughout the course of the 5-weeks, these participants also exhibited faster reaction time that led to medium and large effect sizes at the post-test assessment. Although the number of steps was documented, we did not examine the quality of the steps. Specifically, it is unknown whether these participants began to engage in increased levels of physical activity that was not accounted for via daily step counts throughout the 5 weeks that may have led to changes in injury-related fear and VMRT. These results further call into question whether daily step counts are a good representation of physical activity in patients after ACLR.

Kuenze et al.[107] and Bell et al.[7] have previously measured moderate-to-vigorous active minutes to examine physical activity levels in patients after ACLR. Potentially, this sample may have exhibited increased levels of moderate-to-vigorous active minutes that were not accounted for in active daily steps. Examination of the quality of physical activity, via moderate-to-vigorous active minutes, may have provided insight into the changes observed. While not statistically significant or clinically meaningful, monitoring of physical activity may have led to increased exposure to all of the tasks on the PHOSA-ACLR which led to individual item decreases. Furthermore, this increased exposure may have also led to improvements in VMRT. Future research should explore the effect of moderate-to-vigorous active minutes on injury-related fear and VMRT in patients after ACLR.

Limitations

This study is not without limitations. Firstly, it is important to acknowledge that participants in the intervention group were aware that the purpose of the intervention was to decrease their injury-related fear associated with specific functional tasks. While an interaction was not present, individuals in the intervention group may have self-reported decreases in injury-related fear on those specific tasks because they knew that was the intention of the study. Secondly, this is a pilot study with a small sample size and a Type II error may have occurred as a result of the small sample. It is also possible that individuals in the intervention group did not complete their home exercises as prescribed for the *in vivo* exposure therapy. Lack of compliance of the intervention may have also led to failure to detect statistical significance.

Conclusion

Physical activity is important for health and wellness across the lifespan. Individuals post-ACLR fail to return to pre-injury levels of activity[4] and participate in less moderate-to-vigorous physical activity when compared to healthy counterparts.[7,107] Injury-related fear has been cited as the primary barrier for this failure.[4] Thus, it is important to investigate the efficacy of intervention strategies to mitigate injury-related fear in this population. Implementation of *in vivo* exposure therapy did not lead to statistically significant or clinically meaningful decreases in self-reported injury-related fear or improvements in VMRT. Length of the intervention and frequency of completing the intervention may have led to failure to detect between group differences. Future research should explore the efficacy of *in vivo* exposure therapy on decreasing injury-related fear and improving VMRT for a longer study period with increased frequency of intervention completion. Additionally, future research should explore the efficacy of *in vivo* exposure therapy in combination with mindfulness training on decreasing injury-related fear and improving VMRT in patients after ACLR.

Table 5.1. Baseline demographics of participants

	Intervention (n=6) Mean (SD)	Control (n=6) Mean (SD)	Total (n=12) Mean (SD)	P-Values
Age (yrs)	23.50 (5.43)	21.50 (3.83)	22.50 (4.60)	0.48
Height (cm)	166.37 (9.47)	166.98 (10.62)	166.57 (9.60)	0.94
Weight (kg)	69.02 (8.78)	64.94 (10.76)	67.21 (9.66)	0.44
Time since ACLR	3.50 [7]	5.00 [6]	5.00 [5]	0.59^
Tegner Score (Before Injury)	8.00 (1.41)	8.00 (0.90)	8.00 (1.13)	1.00
Tegner Score (Current Level)	6.67 (2.42)	5.17 (1.60)	5.92 (2.11)	0.23
KOOS-Sy	79.76 (13.30)	80.95 (12.51)	80.36 (12.33)	0.88
KOOS-P	90.74 (4.18)	85.19 (13.91)	87.96 (10.21)	0.37
KOOS-ADL	97.31 (3.00)	94.36 (8.40)	95.83 (6.20)	0.44
KOOS-Sport	74.17 (15.63)	78.33 (22.06)	76.25 (18.36)	0.71
KOOS-QOL	76.04 (10.77)	61.46 (28.90)	68.75 (22.14)	0.27

^ Mann-Whitney U, KOOS = Knee Injury and Osteoarthritis Outcome Score, Sy = Symptoms, P = Pain, ADL = Activities of Daily Living, Sport = Sports and Recreation, QOL = Quality of Life

Table 5.2. Individual item scores for the photographic series of sports activities for ACLR in intervention group

	Run	Land after a Jump	Squat	Lat. Lunge	SL Jump	Slide	Sudden Deceler.	Hop	Lunge	Jump and Land on Trampoline	Pivot	Start a Sprint	Total
PRE													
1	2	4**	0	5*	2	3	3	0	0	4	5***	2	2.50
2	1	2	0	0	3*	0	2	0	0	4**	4***	0	1.30
3	3	3*	2	0	2	0	1	3**	1	1	4***	0	1.67
4	5*	3	2	0	4	3	2	5***	5	1	5**	1	3.00
5	2	2	1	1	2***	0	3**	3	1	2	2*	2	1.75
6	1	0	0	3**	3***	2*	0	1	0	0	0	0	0.83
POST													
1	2	1**	1	1*	2	2	2	0	1	3	1***	0	1.33
2	2	1	0	1	2*	0	0	1	0	0**	0***	0	0.58
3	1*	1*	0	1	1	0	1	1**	1	1	1***	0	0.75
4	4	3	4	3	2	3	3	3***	3	1	3**	1	2.75
5	0	0	0	1	0***	0	1**	0	0	1	0*	1	0.33
6	1	1	0	0**	1***	1*	0	0	1	0	1	0	0.50

Lat = Lateral, SL = Single-Leg, Deceler. = Deceleration, *** = Selected as most fearful task, ** = Selected as second most fearful task, * = Selected as third most fearful task; Green indicates decrease in fear

Table 5.3. Individual item scores for the photographic series of sports activities for ACLR in control group

	Run	Land after a Jump	Squat	Lat. Lunge	SL Jump	Slide	Sudden Deceler.	Hop	Lunge	Jump and Land on Trampoline	Pivot	Start a Sprint	Total
PRE													
1	3	6	1	8	4	2	3	0	0	0	9	0	3.00
2	0	3	2	3	4	1	2	3	2	1	3	1	2.08
3	0	2	1	0	1	0	1	1	0	0	0	0	0.50
4	7	6	3	7	6	1	4	3	4	4	7	7	4.91
5	0	0	0	2	2	3	2	1	0	0	1	1	1
6	1	0	1	0	0	1	0	0	0	0	0	0	0.25
POST													
1	2	6	1	6	4	2	5	0	1	0	7	0	2.83
2	2	3	4	1	1	0	2	2	1	1	0	1	1.5
3	0	2	1	3	2	0	3	0	1	0	2	1	1.25
4	5	4	3	3	4	1	3	1	2	3	5	4	3.17
5	1	0	0	0	0	0	0	0	0	1	0	0	0.17
6	0	1	0	1	1	1	0	1	0	0	0	0	0.42

Lat = Lateral, SL = Single-Leg, Deceler. = Deceleration, *** = Selected as most fearful task, ** = Selected as second most fearful task, * = Selected as third most fearful task; Green indicates decrease in fear

Table 5.4. Means and standard deviations of patient-reported outcome measures and visuomotor reaction time assessments

	Intervention - Pre (n=8) Mean (SD)	Intervention – Post (n=8) Mean (SD)	Control – Pre (n=8) Mean (SD)	Control – Post (n=8) Mean (SD)	Group partial η^2	Time partial η^2
FABQ-PA	9.83 (4.26)	10.50 (3.08)	8.33 (7.74)	9.33 (5.79)	0.02	0.05
FABQ-S	15.50 (8.12)	17.67 (7.23)	12.83 (9.24)	10.33 (7.84)	0.12*	0.00
FABQ-Total	25.33 (11.33)	28.17 (5.52)	21.17 (16.19)	19.67 (13.05)	0.08	0.00
TSK-11	20.33 (3.01)	17.83 (4.79)	22.17 (6.65)	21.83 (7.03)	0.10*	0.07
ACL-RSI	61.25 (17.03)	66.94 (10.86)	59.58 (27.91)	53.05 (34.60)	0.03	0.00
PHOSA-ACLR	1.85 (0.78)	1.04 (0.90)	1.96 (1.78)	1.55 (1.23)	0.02	0.50^
Dynavision	0.89 (0.13)	0.83 (0.06)	0.82 (0.04)	0.82 (0.05)	0.09*	0.16*
ImPACT RT	0.57 (0.07)	0.59 (0.07)	0.54 (0.05)	0.54 (0.05)	0.12*	0.05
FitLight Injured	0.50 (0.02)	0.52 (0.06)	0.62 (0.13)	0.58 (0.08)	0.29^	0.04
FitLight Uninjured	0.50 (0.05)	0.52 (0.06)	0.59 (0.10)	0.55 (0.05)	0.22*	0.08

*Medium effect size, ^Large effect size, FABQ = Fear-Avoidance Beliefs Questionnaire, FABQ-PA = Fear-Avoidance Beliefs Questionnaire Physical Activity subscale, FABQ-S = Fear-Avoidance Beliefs Questionnaire Sports subscale, TSK-11 = Tampa Scale of Kinesiphobia-11, ACL-RSI = Anterior Cruciate Ligament Reconstruction Return to Sport after Injury Scale, PHOSA-ACLR = Photographic Series of Sports Activities for Anterior Cruciate Ligament Reconstruction, ImPACT RT = Immediate Post-Concussion Assessment and Cognitive Testing Reaction Time

Figure 5.1. Study design

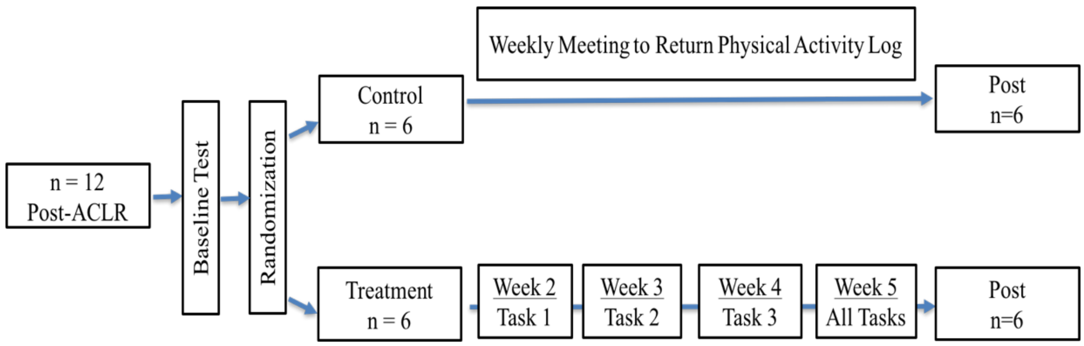
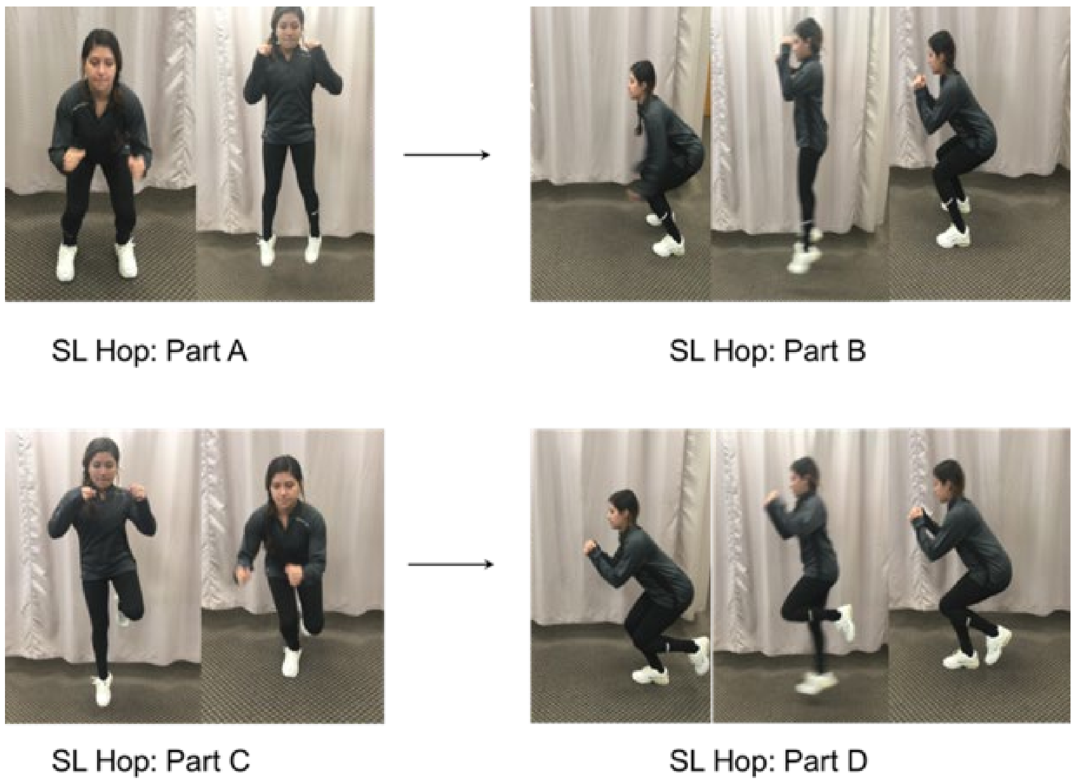


Figure 5.2. Single-leg hop progression



Chapter Six: Summary

Purposes, Aims, and Hypotheses

The purposes of this dissertation were to determine which patient-based and functional outcome measures were predictive of RTS and physical activity levels in patients with a history of ACLR; to determine the differences in brain activation patterns in the limbic and hypothalamic regions between individuals with a history of ACLR and healthy matched controls; and to examine the effectiveness of *in vivo* exposure therapy on decreasing injury-related fear and improving reaction times in individuals with a history of ACLR. These studies were designed to address the following aims and hypotheses:

1. To examine functional and patient-based outcomes that were predictive of RTS in individuals with a history of ACLR.

    Hypothesis: A combination of functional and patient-based outcomes will explain a significant amount of variance associated with RTS in individuals with a history of ACLR.

2. To examine functional and patient-based outcomes that were predictive of physical activity levels in individuals with a history of ACLR.

    Hypothesis: A combination of functional and patient-based outcomes will explain a significant amount of variance associated with physical activity levels in individuals with a history of ACLR.

3. To determine difference the neural substrates of injury-related fear during a visually-based picture imagination task in individuals with a history of ACLR compared to healthy age-mated controls.

Hypothesis: Individuals with a history of ACLR will have greater mean blood oxygen level dependent (BOLD) percent signal changes in corticolimbic brain regions compared to healthy matched controls.

4. To determine the effectiveness of an *in vivo* exposure intervention on self-reported injury-related fear and reaction times in post-ACLR participants.

   Hypothesis: Participants enrolled in the *in vivo exposure* intervention will have decreased injury-related fear and faster reaction times when compared to post-ACLR controls.

Summary of Findings

The summary of findings for each specific aim are presented below. The findings include the following:

1. To examine functional and patient-based outcomes that were predictive of RTS in individuals with a history of ACLR.

Findings: The hypothesis was partially supported, as only patient-based outcomes explained a significant amount of variance associated with RTS in individuals with a history of ACLR. The TSK-11, KSES-Future, and time from index ACLR were included in the final model. Holding future knee self-efficacy and time from index ACLR constant, for every point increase on the TSK-11, individuals were 17% less likely to RTS (no RTS= 19.72±5.30, RTS=15.73±4.35).

2. To examine functional and patient-based outcomes that were predictive of physical activity levels in individuals with a history of ACLR.

   Findings: The hypothesis was partially supported, as only patient-based outcomes explained a significant amount of variance associated with physical activity levels in individuals with a history of ACLR.

The KSES-ADL subscale and KOOS-QOL subscale, in combination, explained 27% of the variance observed in physical activity levels in individuals with a history of ACLR.

3. To determine difference the neural substrates of injury-related fear during a visually-based picture imagination task in individuals with a history of ACLR compared to healthy age-mated controls.

    Findings: The hypothesis was supported as individuals with a history of ACLR exhibited increased activation in the mediodorsal thalamus and inferior parietal lobule, two areas responsible for the regulation of emotions, when compared to healthy controls. Healthy controls exhibited decreased activation in the default mode network when compared to individuals with a history of ACLR. Inability to suppress the default mode network has been associated with depression, anxiety, and chronic pain.

4. To determine the effectiveness of an *in vivo* exposure intervention on self-reported injury-related fear and reaction times in post-ACLR participants.

    Findings: The hypothesis was not supported. Individuals in the intervention group did not exhibit statistically significant or clinically meaningful decreases in injury-related fear or improvements in VMRT when compared to the control group. However, while not statistically significant or clinically meaningful, lower levels of injury-related fear were observed for the specific functional tasks that were addressed in the intervention.

Synthesis of Results and Future Research Implications

Several conclusions and implications for future research can be made based on the results of these studies.

1. Rehabilitation specialists can successfully implement cognitive-behavioral therapies and psychoeducation techniques to decrease injury-related fear in patients with chronic low back pain.[123] Specifically, interventions like *in vivo* exposure therapy can decrease injury-related fear and improve physical activity engagement. Future research should explore the efficacy of this intervention in acute musculoskeletal populations during their rehabilitation.
2. Psychological responses, including injury-related fear and decreased levels of self-efficacy, are associated with failure to return to sport and physical activity modification in individuals after ACLR. Assessment of psychological outcomes, in conjunction with functional outcomes, should occur in post-ACLR patients. Future research should explore the effectiveness of psychological interventions to decrease injury-related fear and enhance self-efficacy after ACLR. Addressing maladaptive psychological responses may influence the patient's ability to successfully return to sport and engage in life-long levels of physical activity.
3. Brain activation changes in emotional regulation centers have occurred in patients after ACLR. Increased activation in the mediodorsal thalamus and inferior parietal lobule are associated with increased emotional processing. Additionally, reduced deactivation in the default mode network was present. These areas have previously been associated with depression, anxiety, and chronic pain.[42,147] Future research should explore the structural and functional

connectivity between corticolimbic regions in the brain after ACLR to further characterize the neuroplasticity observed in patients after ACLR.

4. Our results demonstrated that implementation of *in vivo* exposure therapy in individuals with a history of ACLR who are a minimum of 1-year post surgery did not successfully decrease overall injury-related fear or improve VMRT. The dosage associated with this therapy may not have been enough to reduce general phobic responses or induce neuroplasticity. Future research should explore the efficacy of *in vivo* exposure therapy for a longer duration with increased frequency of the exposure. Secondly, future research should explore the efficacy of mindfulness training in addition to *in vivo* exposure therapy on decreasing injury-related fear and improving VMRT in patients after ACLR.

Conclusions

This dissertation examined the impact of injury-related fear on patients after ACLR. Previous research has demonstrated that injury-related fear can affect a patient's ability to immediately return to sports participation.[4] Our results show these patients continue to fail to return to sports participation years after clearance for sport, and injury-related fear is associated with this failure. Furthermore, our results demonstrate that injury-related fear is associated with physical activity engagement in patients after ACLR. This is of concern as failure to reach recommended levels of physical activity can contribute to the development of chronic disease and comorbidities.

In addition to the association between injury-related fear, return to sport and physical activity outcomes, we examined the neural substrates of injury-related fear in this population. Our results demonstrated that patients after ACLR exhibited increased activation in areas of the brain responsible for emotional processing. Furthermore, these patients also exhibited a reduced deactivation in the default mode network, which has previously been associated with depression, anxiety, and chronic pain. Thus, these results demonstrate the injury-related fear is no longer just a subjective factor affecting this population, but injury-related fear is leading to objective changes in the nervous system after ACLR.

Lastly, implementation of *in vivo* exposure therapy did not lead to decreases in injury-related fear or improve VMRT in patients at least 1-year post ACLR. However, lower levels of injury-related fear for specific functional tasks that were addressed in the intervention group was observed. In summary, it appears that injury-related fear is leading to subjective and objective changes in patients after ACLR and integration of cognitive-behavioral therapies may help to mitigate these observed changes.

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Vita

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EDUCATION

University of Kentucky
Doctor of Philosophy
Major Area of Study: Rehabilitation Sciences
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University of Kentucky
Master of Science
Major Area of Study: Athletic Training
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University of North Carolina at Chapel Hill
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PROFESSIONAL POSITIONS

Midway University, Midway KY
Mental Performance Consultant Intern
March (2018) – May (2019)

Midway University, Midway KY
Graduate Assistant Athletic Trainer
Fall (2014) – Spring (2016)

ActivCare Physical Therapy, Clayton NC
Athletic Trainer
Summer (2013) - Spring (2014)

SCHOLASTIC AND PROFESSIONAL HONORS

1. Valedictorian, E.E. Smith High School, Fayetteville, NC, June 2009.
2. Finalist, Morehead-Cain Scholarship at the University of North Carolina at Chapel Hill, March 2009.
3. UNC Chapel Hill Dean's List (5 semesters), Fall 2009 - Spring 2013.
4. UNC Chapel Hill Athletic Training Quiz Bowl Team, Spring 2013.
5. Lyman T Johnson Fellowship, University of Kentucky, August 2014-May 2016, August 2018-May 2019.

6. National Athletic Trainers' Association Research & Education Foundation Doctoral Scholarship Recipient, June 2018
7. Selected for Leadership Summit for Top 100 Student Leaders, University of Kentucky, May 2018-May 2019
8. University of Kentucky College of Health Sciences Robinson Graduate Award for Research Creativity, March 2019

PROFESSIONAL PUBLICATIONS

Published Referred Manuscripts

1. Genoese FM, **Baez SE**, Hoch JM. The association of fear-avoidance beliefs and self-reported knee function in patients with a knee injury: a critically appraised topic. *Int J Athl Ther Train.* 2018;23(5):187-191.
2. **Baez SE**, Hoch, MC, Hoch, JM. Evaluation of cognitive behavioral interventions and psychoeducation implemented by rehabilitation specialists to treat fear-avoidance beliefs in patients with low back pain: a systematic review. *Arch Phys Med Rehabil*. 2018;99(11):2287-2298.
3. Hoffman E, D'Onofrio A, **Baez SE**, Cavallario J. The effectiveness of kinesio-tape in decreasing kinesiophobia in patients with musculoskeletal pain: a critically appraised topic. *Int J Athl Ther Train.* 2018;23(1):10-15.
4. **Baez SE**, Hoch JM, Uhl TL. The effectiveness of cervical traction and exercise in decreasing neck and arm pain in patients with cervical radiculopathy: a critically appraised topic. *Int J Athl Ther Train.* 2017;22(5):4-11.

Accepted Refereed Manuscripts in Press

1. Hunt E, **Baez SE**, Olson A, Butterfield T, Dupont-Versteegden E. Using massage to combat fear-avoidance and the pain tension cycle. *Int J Athl Train Ther.* Accepted February 18, 2019.
2. Hoch JM, **Baez SE,** Hoch MC. Examination of ankle function in individuals with a history of ACL reconstruction. *Phys Ther Sport.* Accepted January 7, 2019.
3. **Baez SE**, Cramer RJ, Hoch JM. Social cognitive theory and the fear avoidance model: the explanation of poor health outcomes after ACL reconstruction. *Athl Train Sports Health Care*. Accepted May 25, 2018.
4. Hoch JM, **Baez SE**, Cramer RJ, Hoch MC. Differences in the modified disablement in the physically active scale in those with and without chronic ankle instability. *J Sport Rehabil.* Accepted March 6, 2018.

Manuscripts Submitted for Publication

1. Hoch JM, Houston MN, **Baez SE**, Hoch MC. Fear-avoidance beliefs and health-related quality of life in post-ACL reconstruction and healthy athletes: a case control study. *J Sports Rehabil.* In Review.
2. **Baez SE**, Hoch JM, Cormier MC. The Stress and Injury Model and the Cognitive Appraisal Model: Implications for patients after anterior cruciate ligament reconstruction. *Athl Train Sports Health Care.* In Review.
3. Barchek A, **Baez SE**, Hoch MC, Hoch JM. The relationship between musculoskeletal injury and objectively measured physical activity levels: a critically appraised topic. *J Sports Rehabil.* In Review.
4. **Baez SE,** Hoch MC, Hoch JM. Patient-based and functional outcomes predict physical activity and return to preinjury levels of sport after ACL-reconstruction: a modified cross-sectional study. *Knee Surg Sports Traumatol Arthrosc.* In Review.
5. Brinkman C, **Baez SE,** Genoese FG, Hoch JM. Use of goal-setting to enhance self-efficacy after sports-related injury: a critically appraised topic. *J Sports Rehabil.* In Review.
6. **Baez SE,** Hoch JM, Howard JS. Use of response shift to improve agreement between patient-reported outcomes and performance-based measures in patients with knee injury. *J Athl Train.* In Review.