Neuroplastic and Neuromuscular Effects of Knee Anterior Cruciate Ligament Injury

DISSERTATION

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By

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Abstract

Anterior cruciate ligament (ACL) ruptures are common activity-related knee injuries usually requiring surgical reconstruction and extensive rehabilitative therapy to restore knee stability and function. Despite surgical reconstruction and physical rehabilitation, injury of the ACL dramatically increases the risk for a second injury (re-tear or contralateral leg), costly and long-term disabling osteoarthritis as well as decreased lifelong physical activity. The mechanism of this injury is typically non-contact, meaning the individual experiences a loss of neuromuscular control during jump landing, running or a change of direction maneuver without contact from another person or any other external force. Current interventions focus on biomechanical adaptations, mitigating their effectiveness to address the full neuromuscular control system. In spite of the plethora of biomechanical and patient data collected over the last three decades, the re-injury rate has remained high, if returning to activity, and patient dysfunction remains prolonged. Previous investigators have observed central nervous system and somatosensory deficits despite ACL reconstruction and rehabilitation, and we suggest that this is likely due to a neuroplastic adaptation not currently understood. This project connects highly dynamic measures of knee neuromuscular function with whole brain activation patterns to generate a brain-behavior model. The integration of neuroimaging and biomechanics in this investigation identifies the central nervous system components
of ACL injury not accounted for in current assessment and intervention techniques. Quantification of the underlying neurological changes that may be driving the biomechanical outcomes after ACL injury will allow neural correlates of function to be targeted in rehabilitation.
Dedication

To my wonderful family and friends for supporting me in ways they will never know.

Kelly Grooms – Father
Kittie Grooms – Mother
Always believed in and gave me the strength to not fail

I don’t believe it. – Luke Skywalker
That is why you fail. – Yoda

Deanna Bellomo – Sister
Always proved you should never be afraid

Never tell me the odds.
Han Solo

Robert Wallen – Grandfather
Deanna Wallen – Grandmother
Always gave life perspective and wisdom

Life doesn’t give us purpose. We give life purpose.
The Flash
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*If I have seen further than others, it is by standing upon the shoulders of giants.*

- Isaac Newton, *The Correspondence of Isaac Newton*

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Fields of Study

Major Field: Health and Rehabilitation Sciences

Minor Field: Biomechanics

Minor Field: Neuroscience
# Table of Contents

Abstract ......................................................................................................................... ii

Dedication ...................................................................................................................... iv

Acknowledgments ......................................................................................................... v

Vita .................................................................................................................................... vii

Publications .................................................................................................................... vii

Fields of Study ............................................................................................................... viii

Table of Contents .......................................................................................................... ix

List of Tables ................................................................................................................ xiv

List of Figures ................................................................................................................. xv

Chapter 1: Overview ....................................................................................................... 1

Anterior Cruciate Ligament Injury .................................................................................. 2

Limitations of the Structural-Mechanical Model ............................................................ 4

Neuromuscular Control ................................................................................................ 6

Sensorimotor control .................................................................................................... 9

Anterior Cruciate Ligament Specific Neurological Adaptations ................................... 12
Introduction .............................................................................................................. 44
Methods .................................................................................................................... 45
Participants .............................................................................................................. 45
Data Collection ....................................................................................................... 46
Data Analysis .......................................................................................................... 51
Statistical Analysis .................................................................................................. 52
Results ...................................................................................................................... 53
Kinematic – Sagittal ................................................................................................. 55
Kinematic – Frontal .................................................................................................. 58
Kinetic – Ground Reaction Force .......................................................................... 61
Kinetic – Sagittal ..................................................................................................... 64
Kinetic – Frontal ..................................................................................................... 68
Discussion ................................................................................................................. 72
Sagittal ....................................................................................................................... 72
Frontal ....................................................................................................................... 74
Clinical Implications ............................................................................................... 75
Limitations ............................................................................................................... 78
Future work ............................................................................................................... 79
Conclusion ............................................................................................................... 80
Chapter 4: The Brain-Behavior relationship after Anterior Cruciate Ligament Reconstruction ................................................................. 82

Abstract .................................................................................................................. 82

Introduction .............................................................................................................. 84

Methods ................................................................................................................... 86

Participants .............................................................................................................. 86

Neuroimaging - Data Collection ........................................................................... 86

Neuroimaging - Data Analysis ............................................................................... 87

Neuroimaging - Region of Interest Analysis ......................................................... 88

Biomechanics - Data Collection ........................................................................... 89

Biomechanics - Data Analysis ............................................................................... 90

Statistical Analysis ................................................................................................. 91

Results ..................................................................................................................... 91

Discussion ................................................................................................................ 96

Cortical Excitability ............................................................................................... 97

Clinical Implications ............................................................................................... 98

Limitations ............................................................................................................... 100

Future Work ............................................................................................................ 101

Conclusion .............................................................................................................. 102
Chapter 5: Conclusions

Future Work

References

Appendix A: Alternative Chapter 4 Statistical Analysis

Introduction

Kinematic – Sagittal

Kinematic – Frontal

Kinetic – Ground Reaction Force

Kinetic – Sagittal

Kinetic – Frontal
List of Tables

Table 1. Data across all participants by visual condition *Knee adduction angle is degree change from initial contact to peak flexion. Peak vertical ground reaction forces are expressed relative to body weight................................................................. 54

Table 2. Mean of region and peak voxel within region respective and standard deviations for motor cortex activation (percent signal change) and lingual gyrus (percent signal change) in columns 2 and 3. Mean stroboscopic effect on knee flexion and knee adduction (degrees) for each group in column 4. ................................................................. 93

Table 3 Bivariate Pearson correlation between change score from full vision to low stroboscopic visual condition and change score of full vision to high stroboscopic condition. ......................................................................................................................... 127
List of Figures

Figure 1. Illustrating the spectrum of neuromuscular control assessment, with basic controlled sensory function on the left and highly dynamic motor output on the right. adopted and modified from Hertel 2008 \(^{100}\) .......................... 8

Figure 2. Illustrating the sensorimotor control system with sensory-afferent components on the left and motor-efferent on the right with CNS integration in the middle; adopted and modified from Hertel (2008) \(^{100}\) ...................................................... 11

Figure 3. Framework for neurological adaptations post ACL injury.......................... 13

Figure 4. Knee motor control task: Four sets of 30 seconds of rest followed by 30 seconds of 45° extension-flexion completed at 1.2 Hz. ................................................................. 28

Figure 5. Statistically significant region with HIGHER activation in the ACLR cohort during involved knee movement \(p<0.05\) cluster corrected for multiple comparisons..... 32

Figure 6. Statistically significant region with HIGHER activation in the ACLR cohort during involved knee movement \(p<0.05\) cluster corrected for multiple comparisons..... 32

Figure 7. Statistically significant region with HIGHER activation in the ACLR cohort during involved knee movement \(p<0.05\) cluster corrected for multiple comparisons..... 33

Figure 8. Statistically significant region with LOWER activation in the ACLR cohort during involved knee movement \(p<0.05\) cluster corrected for multiple comparisons..... 33
Figure 9. Frame of analysis with 2D video, Vicon model, Visual 3D model respectively. ................................................................. 48

Figure 10. Stroboscopic visual disruption experience ..................................................... 50

Figure 11. Mean peak knee flexion under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition ................................................................. 56

Figure 12. Mean knee flexion degree change under stroboscopic condition compared to full vision. .................................................................................................................... 57

Figure 13. Mean peak knee adduction angle under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition ................................................................. 59

Figure 14. Mean knee adduction degree change under stroboscopic condition compared to full vision. .................................................................................................................... 60

Figure 15. Mean peak ground reaction force under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition ................................................................. 62

Figure 16. Mean peak ground reaction force change under stroboscopic condition compared to full vision. .................................................................................................................... 63

Figure 17. Mean peak knee flexion moment under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition ................................................................. 65
Figure 18. Mean peak knee flexion moment change under stroboscopic condition compared to full vision. ................................................................. 66

Figure 19. Mean peak knee flexion moment change under stroboscopic condition compared to full vision. (mass normalized)................................. 67

Figure 20. Mean peak knee abduction moment under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision).
* indicates significant difference from FV condition ................................ 69

Figure 21. Mean peak knee abduction moment change under stroboscopic condition compared to full vision. ................................................................. 70

Figure 22. Mean peak knee abduction moment change under stroboscopic condition compared to full vision. (mass normalized)................................. 71

Figure 23. Typical lingual gyrus area brain activation for left knee movement. ...... 94

Figure 24. Scatter plot of lingual gyrus activation and change score from full vision to stroboscopic vision for knee flexion. 0 – black circle are controls (r=0.688, p=0.009); 1 – red squares are ACLR (r=0.582, p=0.037) ................................................................. 94

Figure 25. Typical sensorimotor brain activation for left knee movement............... 95

Figure 26. Scatter plot of motor cortex activation and change score from full vision to stroboscopic vision for knee adduction. 0 – black circle are controls( r=0.032, p=0.916); 1 – red squares are ACLR (r=0.683, p=0.005) ................................................................. 95

Figure 27 Mean peak knee flexion under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition ........................................................................................................ 129
Figure 28  Mean knee adduction change from initial contact (IC) to peak knee flexion (PKF) under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition .................................................. 131

Figure 29  Mean peak vertical ground reaction force under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). ................................................................. 133

Figure 30  Mean peak external knee flexion moment under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition .................................................................................................................. 135

Figure 31  Mean peak knee abduction moment under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition .................................................................................................................. 137
Chapter 1: Overview

The purpose of this Dissertation is to provide a link between the neurological and physical results of Anterior Cruciate Ligament (ACL) injury and reconstruction. Integration of neuroimaging with assessment of lower extremity functional biomechanics is a step towards identifying components of injury risk not accounted for in typical assessment and intervention techniques. The goal of this research line is to improve intervention specificity to target dysfunctions that remain in current treatment strategies by bridging neuroscience and movement science.

The combined knowledge across this project culminates in a brain-behavior model for knee neuromuscular control to allow the exploration of novel neuroplastic interventions. The combined ability to target neuromuscular control deficits from the final output (movement) perspective and the internal processes (neurological) that generate movement allows an unprecedented ability to target deficits that remain despite extensive efforts to treat the mechanical dysfunctions.

This work seeks to shift the current clinical practice paradigm of reliance on the postural-structure-biomechanical model to explain post injury adaptations. This classic functionalist approach focuses on the measurable behavioral changes of injury and minimizes the underlying mechanisms that instigate these observations. The last three decades of injury biomechanics research has arguably answered the “what” has changed
after musculoskeletal trauma and treatment, but we have yet to answer the “why” or “how” these changes occur. The application of neuroscience principles and technology may allow us to answer these questions and integrate them into clinical practice.

Anterior Cruciate Ligament Injury

The World Health Organization recommends at least 60 minutes of daily moderate to vigorous physical activity to maintain a healthy lifestyle. Athletic activities are a primary source for many to achieve this physical activity goal. Of concern with this recommendation is the occurrence of musculoskeletal injury, particularly non-contact ACL ruptures. The ACL is an intra-articular ligament providing rotary and translatory mechanical stability to the knee joint as well as being highly innervated with mechanoreceptors that provide afferent signals to the central nervous system (CNS).

ACL ruptures are a common activity-related knee injury usually requiring surgical reconstruction to restore knee stability and function. Despite surgical reconstruction and physical rehabilitation methods, injury of the ACL dramatically increases the risk for costly and long term disabling osteoarthritis and associated decreased lifelong physical activity further increasing the indirect cost. The current standard of care for reconstruction and rehabilitative neuromuscular training have a failure rate up to 25% for re-rupture, after return to activity in young active individuals, and no decrease in future osteoarthritis risk. This high failure rate is further compounded due to a majority of individuals not even returning to pre-injury levels of activity.
opportunity to improve current neuromuscular training interventions for return to
activity.\textsuperscript{59,98,100,223,267}

After injury, ACLR (anterior cruciate ligament reconstruction) is a primary means
to restore mechanical stability to the joint and occurs approximately 350,000 times each
year in the United States.\textsuperscript{294} The direct and societal cost of ACLR is approximately $13 billion/year in the United States (typical patient cost per reconstruction is $38,000), not
including the dramatically accelerated development of costly and long-term disabling
osteoarthritis (up to 36\% in the first decade post injury and as high as 90\% across the
lifespan).\textsuperscript{1,164,173,184} The economic burden of traumatic ACL injury contributes to great societal cost of decreased work status, earnings, disability and quality of life due to the
rapid onset of post-traumatic knee osteoarthritis.\textsuperscript{1,173,259} Surgical reconstruction and
rehabilitation of ACL injury does not alleviate the dramatic increased risk for disabling
osteoarthritis and associated decreased lifelong physical activity that greatly contributes
to the long term societal burden.\textsuperscript{1,52,162,173,248,259,275,284,287}

The current best evidence suggests targeting the neuromuscular control system is
the key to intervention effectiveness, restoring patient function and reducing re-injury
risk.\textsuperscript{90,302} However, reliance on these interventions alone has had mixed results as
reconstruction and rehabilitation have a high failure rate for re-rupture and no decrease in
future osteoarthritis risk.\textsuperscript{173,252} The high risk of re-injury and associated fear causes once
active individuals to become more sedentary, even years after the injury, further
compounding the limitations of current neuromuscular training methods.\textsuperscript{13,15,274} These
psychological and physical components combine to decrease post injury quality of life
and increase risk of activity related mortality and morbidity.\textsuperscript{162} In spite of decades of research into surgical reconstruction and rehabilitation after ACL injury, prolonged pain, instability and depressed neuromuscular control causes over half of patients to not return to their previous functional ability or physical activity level.\textsuperscript{12,32,58,120,155,299} Perhaps even more concerning, is that no intervention, thus far, has been shown to mitigate the development of post-traumatic osteoarthritis.\textsuperscript{164} Rehabilitation efforts must consider other avenues beyond the current standard of care or risk continuing to sentence our patients to early total knee replacement and decreased ability to enjoy an active lifestyle.

\textbf{Limitations of the Structural-Mechanical Model}

Current standard of care interventions, targeting the neuromuscular control system, may be missing vital aspects of sensorimotor function as at return to sport significant deficits remain in neuromuscular function.\textsuperscript{80,90,149,160,302} The decreased function and fear, associated with the high risk of re-injury, leads individuals, who were once active, to become more sedentary, even years after the injury.\textsuperscript{13,15} Our best practice neuromuscular control focused programs may be insufficient to fully address re-injury risk or restore patient function.\textsuperscript{82,100,138,198,218,221} It is likely that aspects of sensorimotor function that are affected by the injury are not adequately addressed in therapy, allowing suboptimal neuroplastic compensations to occur.\textsuperscript{3,76,244} Consideration of neurological post injury adaptations, in addition to restoring mechanical stability, is needed to formulate adjunct therapeutic strategies to improve neuromuscular control.

The very nature of the non-contact ACL injury mechanism illustrates the vital role of the CNS to restore function and prevent second ACL injury.\textsuperscript{136,208} The non-contact
ACL mechanism is due to a loss of neuromuscular control during activities that can range from simple running to jump landing and rapid direction changes. This noncontact injury scenario demonstrates the need to challenge a broad spectrum of sensorimotor control contributions. The noncontact mechanism has repeatedly been associated with a failure to maintain knee neuromuscular control, while attending to an external focus of attention, involving highly complex dynamic visual stimuli, variable surfaces, movement planning, rapid decision-making, variable player positions and environment interactions, and unanticipated perturbations.

While many factors, including hormonal, gender, anatomical, and even genetic influences, have been implicated in injury risk; the primary focus of physical rehabilitation has been dynamic neuromuscular control, since it is modifiable and a prospective predictor of primary and secondary injury. A great deal of evidence suggests targeting the neuromuscular control system is the key to intervention effectiveness, and the ability to mitigate injury risk is with optimizing this system. However, despite a great deal of biomechanical data to support altered movement strategies that continue to exist despite intervention, orthopedic medicine has only just begun to examine how joint injury influences the nervous system.

Recent research has demonstrated CNS changes may be more important to sustained optimization of movement strategies than reliance on biomechanical post-test measures alone. This suggests that the CNS underlies any modification of injury risk, and to decrease risk; a motor learning adaptation is required to cause the
The sustainment of movement strategies to reduce injury risk is highly associated with a neuromuscular motor learning adaptation. These findings elucidate a need to discover the intricacies of neurological processes associated with lower extremity movement and injury. This is especially important as the standard intervention utilizes neuromuscular training programs without any measure of neurological function, which may be limiting program efficacy. These interventions strictly focus on the final output of the neuromuscular control system in the form of biomechanical adaptations that may mitigate their injury protective effects. Due to limitations of the biomechanical model of musculoskeletal injury assessment, current interventions focus on adaptations made in primarily biomechanical terms that have been shown to revert to pre-intervention levels or not induce improvement at all. Determining the neural control of biomechanical performance will provide insight into the design of interventions that leverage neuroplasticity to facilitate long term motor control changes and injury reduction. No research has yet established the relationship between biomechanical performance measures and brain functional activation for knee motor control.

**Neuromuscular Control**

The term neuromuscular control is meant to encompass a spectrum of human function, ranging from the afferent input, the processing of that input, generation of the efferent output and the overall coordination of the system (figure 1). Neuromuscular control also has a temporal component in the continuous feedback back loops between
sensory and motor processing that contributes to the final measurable output. As the bodily segments move and muscles contract, the afferent system is constantly sending new signals to the motor system to update the position, force generation, environmental representation and other factors relative to the output. This constantly updating system represents the neuromuscular control profile.

To experimentally capture the neuromuscular control system, a largely behaviorist and functionalist methodology has dominated the field with reliance on a postural-structural-biomechanical approach. This prevailing method is concerned primarily with measuring the final output of the system in the form of joint biomechanics without any quantification of the underlying mechanisms that generate those mechanics. The classic measure of neuromuscular control in lower extremity physical assessment is the drop vertical jump as it demands rapid landing force attenuation then rapid force generation that challenges coordinated joint stiffness, reflex action, and the CNS via the rapid stretch-shorten cycle. The drop vertical jump is also utilized as a screening and outcome assessment as it incorporates components theorized to be highly related to injury risk primarily that of knee joint control (sagittal and frontal plane stability), force attenuation and movement strategy. As figure 1 demonstrates such high level activities incorporate all of the components of neuromuscular control to varying degrees, but limit the ability to pinpoint specific mechanisms, contributing to the biomechanically measured neuromuscular control profile without a concurrent assessment of the CNS sensorimotor system.
Figure 1. Illustrating the spectrum of neuromuscular control assessment, with basic controlled sensory function on the left and highly dynamic motor output on the right. adopted and modified from Hertel 2008. 
Sensorimotor control

The neuromuscular control system relies on the sensory system’s three primary afferent pathways (vestibular, visual, and somatosensory) to allow the efferent neuromuscular control system to provide adequate stability and control in the presence of a changing environment (figure 2). The proprioception, force control, and kinesthetic contributions of the sensory system are vital to the organization of motor output and maintaining neuromuscular control integrity. The ACL is unique compared to most ligamentous structures in that it has robust afferent connections with the spinal cord and cerebrum. This is due to the high volume of mechanoreceptors such as free nerve endings, ruffini end organs, pacinian corpuscles and golgi receptors in the synovial lining of the ACL that contribute a great deal to afferent function.

The interaction between proprioceptive inputs, such as that from the ACL, and visual input plays a crucial role in providing overall afferent input to the CNS to regulate movement control feedback loops. The brain receives somatosensory information in the thalamus and primary somatosensory cortex (via Brodmann’s areas 3 to 1 to 2) then integrates that afferent information caudally in the posterior parietal cortex, areas 5 and 7. This is also where the temporal lobe processed vestibular and visual information integrates with somatosensation before transmitting to the premotor cortex (area 8) and finally to the motor cortex (area 6) to achieve motor drive.

Musculoskeletal injuries may alter this flow of somatosensory, vestibular, and visual processing in the CNS to sustain motor control. To
maintain neuromuscular integrity in the presence of joint injury the CNS may compensate with altered motor
Figure 2. Illustrating the sensorimotor control system with sensory-afferent components on the left and motor-efferent on the right with CNS integration in the middle; adopted and modified from Hertel (2008).
planning\textsuperscript{131}, regulation of integrated sensory information reaching the motor areas\textsuperscript{24,25}, increased reliance on visual feedback or memory\textsuperscript{25,222} and/or alter the cortical-spinal drive\textsuperscript{145,167}. This CNS functional reorganization is most likely due to the mechanoreceptors lost in the damaged tissue contributing to decreased afferent input.\textsuperscript{2,73} This diminished sensory function is present despite years after the injury and normalized strength of the surrounding musculature.\textsuperscript{3,244} This is a likely source of neuroplasticity post musculoskeletal injury, thus examining methods to address the sensory-visual-motor system along with the neuromuscular system in rehabilitation may improve patient function and decrease recurrent injury risk.

**Anterior Cruciate Ligament Specific Neurological Adaptations**

To better understand the rationale for how examining the brain may enhance ACL injury rehabilitation, a thorough understanding of the current evidence on neuroplastic changes associated with ACL injury is required. The overarching concept is that the CNS afferent input is disrupted due to the lost somatosensory signals from the ruptured ligament and increased nociceptor activity associated with pain, swelling, and inflammation. The disrupted sensory input and injury-associated joint instability, muscle atrophy, and movement compensations combine to induce motor control adaptations. The reconstruction process leads to further deafferentation of the joint, causing continued neuroplastic modifications that result in maladapted efferent neuromuscular output (figure 3).
Figure 3. Framework for neurological adaptations post ACL injury
In animal models, the ACL mechanoreceptor and afferent connections can be traced within the nervous system to the spinal cord, brain stem, and cerebral regions that contribute to proprioceptive, nociceptive, and reflex function.\textsuperscript{83,216} The initial sensorimotor neuroplasticity, after ACL injury, is likely caused by the abrupt loss of this connection that once provided the nervous system with continuous feedback.\textsuperscript{2,73,130,134,256,307} In human studies, the afferent loss is demonstrated by altered or absent somatosensory evoked potentials with stimulation of the common peroneal nerve\textsuperscript{48,50,285,286} or, in surgery, of the ACL directly.\textsuperscript{227} The loss of primary afferent information, combined with the pain and inflammatory responses, contribute to fundamentally alter the somatosensory feedback.\textsuperscript{39,122,131,154} The disrupted input, combined with mechanical changes and compensations\textsuperscript{200,247} (contralateral loading,\textsuperscript{20,218} hip or ankle strategies\textsuperscript{65,81}), facilitates the adaptations for motor control.\textsuperscript{68,129,130} On a foundational level, altered motor output is displayed by disrupted gamma motor neuron function\textsuperscript{140,142,143} and perturbation reflexes\textsuperscript{49,56} that play a key role in the ability to maintain neuromuscular integrity in a changing environment, requiring rapid and precise muscle stiffness or activation strategies.\textsuperscript{37,137,279} The lost ability to rely on reflex and gamma motor neuron drive to prepare alpha motor neuron function requires the CNS to engage in supplementary mechanisms such as increased utilization of visual feedback to maintain the required sensory input for motor control. As such, neuromuscular control after ACL injury may require enhanced visual feedback or memory reliance, depriving the CNS of resources once used for managing environmental interaction to maintain knee joint stability.
These deficits in neural function are not rectified with ACLR, as they may in fact become even more pronounced and/or present bilaterally.\textsuperscript{30,140,141,145,167,245,286} The bilateral motor control, reflex, and proprioceptive changes are theorized to be due to both spinal\textsuperscript{83,216} and supraspinal\textsuperscript{50,225} mechanisms.\textsuperscript{226} This ongoing neuroplasticity and altered mechanical and biological function of the joint combines to reduce proprioception acuity as measured by joint position sense,\textsuperscript{34,158} movement detection,\textsuperscript{34,74} and force sense.\textsuperscript{102} To investigate the neurologic adaptations of functional sensory loss, Baumeister et al (2008) used electroencephalography (EEG), during force and joint sense tasks, and found that those with ACLR had greater brain activation in attentional and sensory areas.\textsuperscript{24,25} The increased activation may be attributed to less neural efficiency, or increased neural load to complete the same task; interestingly, despite increased cortical activation, proprioceptive performance was still worse in those with ACLR as compared to controls.\textsuperscript{24,25} These results indicate the loss of the native ACL not only constitutes a mechanical instability but a degree of nervous system deafferentation that is not rectified with reconstructive surgery and rehabilitation.\textsuperscript{130} This partial deafferentation is further illustrated by investigations utilizing transcranial magnetic stimulation (TMS) to assess the CNS efferent pathway between the quadriceps and the brain.\textsuperscript{101,151,204,225} Heroux and Tremblay (2006) reported enhanced resting corticomotor excitability in those with ACL injury.\textsuperscript{101} A potential mechanism for increased resting motor cortex excitability may be the altered sensory feedback, as the brain attempts to maintain motor output with attenuated sensory input. This increase in excitability may increase potential feedforward
mechanisms, by decreasing the threshold for connections with motor planning areas, or allowing for increased input from other sensory sources (vision, vestibular)\textsuperscript{95,209,278,304}.

A recent neuroimaging investigation by Kapreli et al\textsuperscript{131} provides further evidence of the neuroplastic effects of ACL injury. They performed functional magnetic resonance imaging (fMRI) of the brain, during knee extension-flexion, and found those with an ACL injury had increased activation of the pre-supplementary motor area, posterior secondary somatosensory area, and the posterior inferior temporal gyrus (pITG), compared to matched controls.\textsuperscript{131} The pre-supplementary motor area is highly involved in complex motor planning\textsuperscript{17,201}, and despite the relative simplicity of the movement task (single joint movement of 40 degrees of knee extension-flexion while laying supine), those with an ACL injury needed to engage higher level motor control areas to a greater degree to execute the movement. This increased activation possibly indicates that on a neural-control-level, simple movements are more taxing to those with a previous ACL injury.\textsuperscript{182} The increase in posterior secondary somatosensory area provides further evidence of sensory-based neuroplasticity after injury, as this area is involved in regulating painful stimuli, but highly interconnected with the anterior secondary somatosensory area that integrates somatosensory inputs.\textsuperscript{43,68,279} Interestingly, the participants in the study did not report pain during the movement, conceivably indicating a sensory processing adaptation from the initial increase in nociceptive input from the traumatic nature of the injury and not an acute effect. Alternatively, the prolonged nature of the rehabilitation, chronic pain, or joint instability may continue to disrupt typical somatosensory system afferent integration. The pITG plays a role in many
cerebral functions\textsuperscript{31,35} but may primarily be involved with visual processing of movement.\textsuperscript{222} As such, increase in pITG activation during movement may indicate that in response to ACL injury there is an increased utilization of visual processing and motor-planning resources for movement concurrent with depression of somatosensory function.\textsuperscript{48,50,75,131,285,286}

**ACL Injury Induced Sensory-Visual-Motor Processing Compensations**

These neuroplastic observations, following ACL injury, are further supported by biomechanical evidence, suggesting that with increased task complexity, neuromuscular control is deteriorated in individuals with an ACL injury or reconstruction to a greater extent than controls, possibly due to overload of motor planning resources.\textsuperscript{119,202} The specific neuroplastic visual-motor control adaptation is observed during static balance as those with ACL injury have significantly diminished postural control when vision is obstructed (blindfold or eyes closed),\textsuperscript{206,207} but limited to no degradation in postural control with eyes open, as they are able to use vision to compensate and maintain balance.\textsuperscript{113,174} A more pronounced effect on neuromuscular control is observed when disrupting visual-motor processing, during complex landing and cutting maneuvers, that play an even greater role in injury risk.\textsuperscript{179,180,270} The simple addition of a target, during a jump landing task, increased injury risk mechanics\textsuperscript{72} and altered muscle activation, decreasing postural stability.\textsuperscript{291} The effects of forcing visual focus on the environment, during more complex cutting or direction change tasks, further degrades neuromuscular control capability in healthy athletes with the addition of a defender,\textsuperscript{179} a virtual soccer interface,\textsuperscript{47} or a level of unanticipated decision making during the task (selecting
direction). The effect of occupying the visual system with environmental cues, during landing or change of direction, has an even greater effect on those with ACL injury history. Furthermore, adding an anticipatory component that integrates visual processing and reaction time further demonstrates a reduction in knee neuromuscular control. The inclusion of short-term memory and online decision-making also demonstrates specific adaptations in the maintenance of joint-to-joint neuromuscular integrity during complex athletic maneuvers such as cutting or sidestepping. 

Recently, examination of injury risk, comparing ball-handling or offensive action (considered anticipatory and feedforward in nature) vs. defending (considered unanticipatory and responsive in nature), demonstrated a higher risk with defensive action. This large-scale epidemiological data further supports the possible increased injury risk movement strategies when unanticipated, rapid decision-making and/or visual-motor feedback is altered, during the laboratory biomechanical studies.

These findings, taken together, suggest that ACL injury may lead to a cascade of neuroplastic and neuromuscular alterations that increase reliance on visual feedback and cortical motor planning for the control of knee movement. The post injury disrupted sensory feedback, combined with the observed motor compensations, contributes to fundamentally alter the CNS mechanisms for motor control. In attempting to regulate neuromuscular control in the presence of decreased somatosensory input, the nervous system supplements with increased motor planning, conscious cortical involvement, and greater reliance on visual feedback. This ACL injury induced neuroplasticity can have consequences for function and further injury risk as the visual
feedback and motor planning neural mechanisms become overloaded in the athletic environment. Specific additions to current neuromuscular interventions, targeting these neuroplastic imbalances, may play a significant role to induce sensory-motor adaptations to decrease dependence on visual feedback, when transitioning to more demanding activities.

Neuroplasticity in Return to Sport Rehabilitation

The transition from rehabilitation to sport activity is challenged by complex environmental interactions that place high demand on cognitive and sensorimotor processes and, in turn, increase ACL re-injury risk. In a constantly changing environment, the primary afferent pathways (vestibular, visual, and somatosensory) interact to integrate and contextualize the feedback necessary for the efferent neuromuscular control system to maintain adequate stability and control. One area of sensorimotor function that may uniquely be affected by ACL injury is motor control requiring visual feedback. The visual system provides a fundamental mechanism for coordination, regulation, and control of movement while managing environmental interactions (external focus). The need for visual feedback is especially true in executing movement sequences and with increases in task complexity and variability. The interplay between vision and somatosensation is particularly vital to provide sufficient afferent input to the central nervous system (CNS) to regulate motor control and maintain neuromuscular integrity during action and environmental interaction. In this sensory-to-motor feedback loop, changes to visual or

19
sensory feedback lead to subsequent alterations in neuromuscular control during movement (closed-loop processing).\textsuperscript{29,168,253,276,290,293}

As an example, typical rehabilitative exercises are completed with an internal focus of control, meaning full attention is being directed to the internal aspects of the movement only (eg, avoidance of excessive knee valgus or increasing knee flexion).\textsuperscript{28,300,302} Such an internal focus can offer positive benefits early in rehabilitation, when the need to develop or restore a motor pattern or muscle contraction ability is vital. However, function in the athletic environment, or even activities of daily living, require constant interactions with the dynamic and constantly changing visual environment. Sport and activities of daily living, therefore, require an external focus of control, where attention is directed to the environment and the body relies on automatic motor control to maintain joint-to-joint integrity.\textsuperscript{16,53,243}

The need to challenge a broad spectrum of sensorimotor control is demonstrated by the noncontact ACL injury scenario itself: a failure to maintain knee neuromuscular control, while attending to an external focus of attention, involving highly complex dynamic visual stimuli, variable surfaces, movement planning, rapid decision-making, variable player positions and environment interactions, and unanticipated perturbations.\textsuperscript{33,111,139,147} The need to bridge the intense neurocognitive and motor control demands of sport during rehabilitation may, therefore, benefit from specific interventions that target these neurologic factors in addition to the biomechanical techniques that are already widely addressed.
Trauma to the ACL has been shown to modify how the nervous system processes the integration between vision and somatosensation. These findings elucidate a need to uncover the intricacies of the neurological processes associated with lower extremity movement control. By targeting injury-induced sensory-motor plasticity, a unique opportunity exists to improve the translation of neuromuscular system enhancements from the rehabilitation environment to the return to sport environment. Thus, our purpose is to highlight the contributions of nervous system function and reorganization after ACL injury, and specifically, better understand how nervous system plasticity alters neuromuscular control. The successful identification of brain activation changes after musculoskeletal injury will begin to bridge a critical missing gap and enhance understanding of the neuromuscular implications of injury. Attainment of this knowledge is critical to the development of targeted neuromuscular interventions. It is our expectation that the cerebral differences in injured individuals will allow the development of targeted motor control approaches that have yet to be elucidated with current methods.
Chapter 2: Neuroplasticity after Anterior Cruciate Ligament Reconstruction

Abstract

Context: Anterior cruciate ligament (ACL) injury may cause neuroplastic effects due to the lost mechanoreceptors of the native ACL and compensations in neuromuscular control. These alterations are not completely understood and may not be addressed in rehabilitation, as typical neuromuscular control assessments do not adequately measure neurological function. Assessing brain function more directly after injury with functional magnetic resonance imaging provides a means to address this gap in knowledge.

Purpose: To investigate brain activation differences during a knee extension-flexion movement task in those with ACLR (anterior cruciate ligament reconstruction) and matched healthy controls.

Methods: Participants were matched on height, mass, extremity dominance, history and current physical activity level. Fifteen left ACLR (21.71±2.68 years, 1.72±0.10 m, 70.43±15.83 kg, Tegner activity level 7.20 ± 1.26.0, 38.13±27.16 months post-surgery) and 15 matched healthy controls (23.15±3.48 years, 1.74±0.09 m 69.77±14.27 kg, Tegner activity level 6.76 ± 1.48) participated. The brain fMRI was collected during a unilateral knee motor task consisting of repeated cycles of extension and flexion while laying supine in the MRI scanner. The two groups were compared with a general linear model second-level fixed-effects analysis with a priori threshold at p <.05 corrected.
**Results:** Participants with ACLR had increased activation in the contralateral sensorimotor cortex ($z=12.46 \ p<.01$), lingual gyrus ($z=8.315 \ p<.01$), ipsilateral secondary somatosensory area ($11.27 \ p<.01$) and diminished activation in the ipsilateral sensorimotor cortex ($z=12.32, \ p<.01$), when compared to healthy matched controls.

**Conclusion:** Brain activation differences exist following ACLR and rehabilitation. An increase in lingual gyrus activation indicated utilization of visual processing to maintain motor control. The different motor and sensory area activations may be due to the extensive training on unilateral quadriceps control after surgery and the use of conscious cortical mechanisms to maintain knee stability. These findings shed light on the motor control differences that remain in ACL reconstructed individuals.
Introduction

Individuals who experience a primary anterior cruciate ligament (ACL) injury are at substantial increased risk to experience a second ACL injury, despite surgical reconstruction and rehabilitation. The contralateral ACL is at similar, if not increased, risk of rupture as the involved ACL, suggesting a possible systematic neurological response to injury in addition to the physiological and mechanical alterations of the reconstructed knee joint. Thus far, these neurologic changes have been found to include diminished central nervous system (CNS) afferent function, altered CNS efferent output and changes in brain activity for movement control. This altered brain function after injury has been theorized to be due to lost mechanoreceptors of the native ACL, which contributes to altered afferent information and influences the efferent response. This modified neural control is not normalized with reconstruction and rehabilitation even when functional performance is improved. Due to the underlying neurological alterations in motor control from the injury and subsequent compensations, standard rehabilitation methods may not address these neuroplastic factors.

The combined afferent neuroplasticity due to the lost mechanoreceptors of the ACL and efferent neuroplasticity due to arthrogenic muscle inhibition and disrupted gamma-motor neuron feedback loops may induce specific central nervous system compensations. We hypothesize that the central nervous system will increase reliance on visual-feedback to program motion. Despite the injury, the nervous system continues to sustain motor output in the presence of depressed proprioceptive input.
which may force increased use of visual related feedback (memory or directly) by the motor cortex. This may also be partially induced, during rehabilitation, as therapy is strongly targeted at increases quadriceps activation immediately after surgery with a constant focus of attention on the knee joint; thus, the nervous system may create this visual-motor link during recovery.

Minimal research has evaluated the neurological changes that occur, following ACL injury, reconstruction, and rehabilitation. The purpose of this work is to describe the brain activation for knee motor control measured after return to sport from ACL injury and reconstruction, contrasted with a matched healthy control group. It was hypothesized that the injury would induce neuroplastic changes, requiring increased motor planning and sensory compensations relative to the matched controls. This post injury neuroplasticity and/or predisposing neurologic function may help explain the underlying mechanisms contributing to prolonged deficits in neuromuscular control seen after ACL injury.

Methods

Participants

Participants consisted of fifteen ACLR individuals (7 males, 8 females, 21.71±2.68 years, 1.72±0.10 m, 70.43±15.83 kg, Tegner activity level 7.20 ± 1.26.0, 38.13±27.16 moths post-surgery) and 15 matched healthy controls (7 males, 8 females, 23.15±3.48 years, 1.74±0.09 m 69.77±14.27 kg, Tegner activity level 6.76 ± 1.48).
Data Collection

The Functional Magnetic Resonance Imaging (fMRI) data were collected on a 3.0-Tesla Siemens Magnetom scanner using a 12-channel array receiver only head coil. The session included 9-functional time series, consisting of 90 whole brain gradient-echo echo-planer scans, acquired every 3.0 seconds with anterior-posterior phase encoding direction (slice thickness 2.5 mm, 55 transversal slices). This equates to ten whole brain data sets per knee movement, so 40 whole brain activation maps for knee movement (4 sessions) contrasted with 50 whole brain maps for rest (5 session). After the functional runs, an anatomical 3-dimensional high-resolution T1-weighted image (repetition time: 2000 ms, echo time: 4.58 ms, field of view: 256 mm matrix, slice thickness 1 mm, 176 slices) was completed for registering the activation data, brain region identification and normalization to compare the ACL and matched participants.

The participant performed unilateral knee extension-flexion for 4 sets of 30 seconds (10 whole brain images), triggered by an auditory metronome at 1.2 Hz or 36 knee extension-flexion cycles per 30 second stimulus (figure 4). The subject was positioned supine in the scanner with legs on a custom cushion that limited knee flexion to 45°. Movement artifact was limited with padding and straps to 0.5 mm absolute and 0.30 mm relative displacement for all participants. An ankle-toe splint was used to restrict ankle and toe movement, and the participant was monitored for accessory motions. The movement condition was contrasted with a 30-second rest condition that preceded and followed each movement cycle. A mock scanner session was completed.
prior to the actual scanning session to ensure the participant was familiar with the movement.
Figure 4. Knee motor control task: Four sets of 30 seconds of rest followed by 30 seconds of 45° extension-flexion completed at 1.2 Hz.
Data Analysis

The fMRI technique measures the hemodynamic BOLD (blood oxygen level dependent) response in each voxel (cubic millimeter) under the indirect assumption that blood flow increases with neural activity.\textsuperscript{77,78} The response during a stimulus is contrasted with a rest condition to determine regions of change during the task, using a General Linear Model. The MRI is able to detect this change in blood flow due to the precise magnetic field alignment of protons at a predefined \textit{Larmor} frequency and the subsequent flip angle of the field to disrupt phase coherence; this causes a small amount of energy to be released that varies by tissue, as the transport of oxygen requires hemoglobin, and it is less magnetic; blood flow creates a different signal than less vascularized tissue.\textsuperscript{229} This key difference in the magnetic properties of the tissue and relative blood flow allows image analyses to be performed to determine the relative BOLD response during a task.

The fMRI image analyses and statistical analyses were performed using the Oxford Centre for functional MRI of the brain software package.\textsuperscript{261} This began with standard pre-statistic processing applied to individual data, including: non-brain removal, spatial smoothing using a Gaussian kernel of full width at 6 mm standard motion correction and realignment parameters (3 rotations and 3 translations) as covariates to limit confounding effects of head movement.\textsuperscript{127} High pass temporal filtering at 90 Hz and time-series statistical analyses were carried out using a linear model with local autocorrelation correction.\textsuperscript{296} Functional images were co-registered with the respective high resolution T1 image and standard MNI 152, 2mm space using linear image
registration. This registration process allows the data from the two subjects to be spatially aligned on a standardized brain template for comparison. First level analysis of functional knee movement relative to rest were carried out with $Z > 4.6$ and a (corrected) cluster significance threshold of $p = 0.001$. The cluster correction uses a variant of Gaussian Random Field theory to decrease type-I error in statistical parametric mapping of imaging data by not only evaluating the activation at each voxel but also the surrounding voxel cluster (as it is unlikely that the voxel tested and surrounding voxels are active above threshold due to chance).\textsuperscript{229,297} The contrast between the ACL reconstructed subject and matched control were then performed with group Z-statistic images set at $Z > 3.5$ threshold and a corrected cluster significance level of $p=0.05$. The atypically higher threshold and lower p value were selected to mitigate inter-subject variability and decrease probability of motion artifact in the data, as well as further decreasing the probability of type I error.\textsuperscript{229}

Results

The brain area activation reported as contralateral indicates activation on the opposite side of motion (or right side, as the movement was left knee extension) or ipsilateral, indicating on the same side of motion (or left). The results are presented as Z-score (activation level relative to baseline condition and the matched control activation) of the peak voxel of that activation cluster (region).

The ACLR group demonstrated increased activation of the contralateral primary sensorimotor cortex (peak voxel $z=12.46$, $p=0.0309$, figure 5), ipsilateral lingual gyrus (peak voxel $z=8.315$, $p=0.0086$, figure 6) and secondary somatosensory cortex (peak...
voxel $z=11.27$, $p<0.0001$, figure 7) and diminished activation of the ipsilateral sensorimotor cortex (peak voxel $z=12.32$, $p<0.0001$ figure 8) area compared to the matched control group.
Figure 5. Statistically significant region with HIGHER activation in the ACLR cohort during involved knee movement p<0.05 cluster corrected for multiple comparisons.

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Figure 6. Statistically significant region with HIGHER activation in the ACLR cohort during involved knee movement p<0.05 cluster corrected for multiple comparisons.
Figure 7. Statistically significant region with HIGHER activation in the ACLR cohort during involved knee movement p<0.05 cluster corrected for multiple comparisons.

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Figure 8. Statistically significant region with LOWER activation in the ACLR cohort during involved knee movement p<0.05 cluster corrected for multiple comparisons.

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<th>Area</th>
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<tr>
<td>Left Sensorimotor</td>
<td>-2 -36 68</td>
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Discussion

**ACL Knee Cerebrum Increased Activation**

Similar to a recent report of the same movement task in a cohort of ACL deficient individuals\(^\text{131}\), the ACLR group had increased activation of a visual-spatial area, in this case the lingual gyrus (named for anatomical shape, not a speech functional area), as well as sensorimotor cortex and the secondary somatosensory cortex. The lingual gyrus role in motor control is unclear, but it may be related to visual processing, specifically encoding images and memory related to motion or spatial attention.\(^\text{62,166,171,222}\) Increased visual-motor-related activation may be in response to the disrupted afferent input from the ACL injury and reconstruction process, inducing cortical reorganization to maintain motor function by reweighting sensory vs. visual input.\(^\text{25,286}\) This may be in response to the disrupted afferent input from the ACL injury and reconstruction process. This down regulation in somatosensory input likely plays a role in cortical reorganization, to maintain motor function, after the injury. The altered sensory input may necessitate an up regulation in use of visual processing resources in an attempt to maintain sufficient input information for motor control.\(^\text{254}\)

The secondary somatosensory area was also activated more in the ACL participants, during involved knee motion, similar to what Kapreli et al. (2009) reported in ACL deficient individuals. This area is responsible for a great deal of somatosensory processing with the anterior region integrating sensory stimuli and the posterior painful stimuli.\(^\text{279}\) The participants did not report any pain, when prompted during scanning or after the session; this may represent a functional cortical sensory processing
reorganization due to the knee trauma. Interestingly, it was on the ipsilateral side of movement, which may indicate a bilateral neuroplastic effect of the injury to induce adaptations in sensory processing. The contralateral side of the brain controls the ipsilateral leg, but the secondary somatosensory area functions bilaterally with little lateralization in activation due to unilateral stimuli. \(^{68, 69, 270}\) Thus, the increased ipsilateral secondary somatosensory activation after injury, reconstruction, and rehabilitation may be a functional reorganization of sensory processing in both hemispheres.\(^{45}\)

In addition to the lingual gyrus and secondary somatosensory area, the primary sensorimotor cortex had greater activation, which may be due to the increased need to engage higher-level cortical activation to control movement.\(^{182}\) The primary motor cortex had greater activation, during involved knee extension-flexion in the ACLR group, which may be due to the increased need for cortical drive to engage the quadriceps after injury and reconstruction.\(^ {17, 101, 153, 225}\) With the injury disrupting sensory input, the increase in sensory processing and visual-motor interaction likely combine to increase the processing demands on the motor cortex to maintain even simple motor control integrity.\(^ {182}\)

These altered brain region activations taken together indicate a functional brain reorganization to produce knee extension-flexion in the ACL reconstructed cohort.\(^ {132, 133}\) It is possible that the underlying neurological adaptions, requiring more cortical control for knee movement and utilizing increased visual processing to generate movement, were not rectified by ligament reconstruction and rehabilitation, indicating an increased need to motor plan and engage in descending control.\(^ {235, 277}\) Another possibility is that these neurologic differences are prospective in nature, contributing to injury risk. An
interesting note is that the activation of the inferior temporal region and lingual gyrus of the visual cortex has only been documented in ACL injured individuals\textsuperscript{131} and not reported in the study of healthy individuals.\textsuperscript{132,133} This may indicate that the injury or rehabilitation process could have induced these neurological differences.\textsuperscript{282}

**ACL Knee Cerebrum Decreased Activation**

The decreased ipsilateral motor cortex activation, during knee motion, may be due to the extensive unilateral therapy after surgical reconstruction. Motor control of the lower extremity tends to engage bilaterally, and the ipsilateral side may activate to inhibit contralateral or bimanual contraction during unilateral movement.\textsuperscript{273} Thus, it is possible that the ipsilateral sensorimotor area became more efficient and required less neural activation to execute unilateral movement due to the therapy targeting the involved knee.\textsuperscript{53} Alternately, cortical motor control may become less bilateral due to ipsilateral inhibition, from compensations after injury to increase reliance on the contralateral knee.\textsuperscript{303} While unilateral therapy is advised to address the significant asymmetries in strength and function after ACL injury and reconstruction, the bilaterally neurological effects are well documented ranging from local gamma-motor neuron dysfunction\textsuperscript{145} to cortical excitability\textsuperscript{153,224}, and this adds to the possibility of contralateral adaptions after this unilateral trauma.

Primary ACL injury causes a cascade of altered neuromuscular control and alterations to the central nervous system\textsuperscript{131,145,167,286}, resulting in dysfunction of the injured limb\textsuperscript{221} and increased risk of re-injury\textsuperscript{220,221}. The nature of the neurological difference between the ACLR group and expected activation from previous neuroimaging
reports as well as the matched control group indicate this maybe an opportunity for therapeutic intervention and future research.

Clinical Implications

These findings provide a unique opportunity to develop clinical and research constructs for further exploration; indicating that three primary systems may be over utilized in the ACL reconstructed patient: 1) increased cortical top-down control, 2) increased visual processing in knee movement and 3) adapted sensory processing.

The increased level of cortical control for movement in the ACLR group provides evidence of the neurological mechanism(s) to support the increased co-contraction and muscle guarding strategies in this population. This is consistent with an increase in internal focus of control, likely due to the increased conscious awareness of the injured joint and subsequent internal focus of training. This means that after a traumatic event, such as an ACL rupture and reconstruction, individuals are more likely to consciously think about their knee and its movement as opposed to the external environment. This is accentuated with typical rehabilitation guidelines that focus on explicit feedback (ex: contract quadriceps or keep knees over your toes) that might be accentuating the top-down cortical control of movement as opposed to autonomic control. The increased activation of the motor cortex for a simple knee joint movement is likely not desirable, as the demands of complex more dynamic motion may exceed the capability of the region to program optimal movement and contribute to second injury risk.
To rectify this increased reliance on cortical mechanisms for lower extremity control, clinicians should strive to advance patients to the autonomous stage of motor learning.\textsuperscript{168} In later stage rehabilitation, once basic movement patterns have been mastered, moving away from internally focused feedback such as: “knees over the toes” or “bend your knees”, will improve transfer to the athletic field, when conscious attention is being paid to the environment and not knee position. Advancing rehabilitative feedback to an external focus such as “land on the markers” or “touch the target as you land” should facilitate this transfer of motor control to sub-cortical regions and free cortical resources for programming more complex motor actions.\textsuperscript{82,238} This motor learning approach to neuromuscular training may decrease cortical activation, during motor tasks, and improve sub-cortical control.\textsuperscript{238}

The increased visual-motor activation in the ACLR group further suggests an adapted motor control strategy that may not be rectified with current rehabilitation methods. Advancing the neuromuscular control challenge during rehabilitation and prevention strategies can facilitate neuroplasticity not only for the motor regions but also improve sensory integration and, thereby, address the visual processing bias. The key to this training is to consider the focus of attention, task complexity, visual input and cognitive load during rehabilitation.\textsuperscript{36,231} Many mechanisms such as incorporating reaction time components\textsuperscript{231}, ball tracking, engaging other players\textsuperscript{179}, adding decision making\textsuperscript{36} or anticipatory aspects\textsuperscript{231} and having the patient dual task\textsuperscript{202}, by engaging the upper extremity, while doing lower extremity exercises, or simply occupy the mind with memory or related tasks, can all increase the neural demand of our neuromuscular
training strategies. Additionally, as eyes closed or blindfolded conditions have a greater effect on balance and movement performance in those with ACL injury, incorporating them during rehabilitation may address the visual-motor neuroplasticity.\textsuperscript{75,207} New technologies such as stroboscopic glasses provide a means to directly perturbate the visual-motor system under a variety of novel conditions that may help the transition back to the athletic environment, when visual attention is constantly distracted.\textsuperscript{9,10}

While the suggestions above provide a direct method to challenge the visual-motor system during high level dynamic movements, training the visual processing system in isolation may also have a beneficial effect on neuromuscular control. Swanik et al. provided prospective evidence for decreased visual processing speed as a risk factor for primary ACL injury.\textsuperscript{269} Visual training has been shown to improve reaction time and visual processing ability related to sport performance and may be worth considering as an aspect of neuromuscular reeducation.\textsuperscript{9}

The increased secondary somatosensory area activation further corroborates previous findings of increased activation of this area in those with a history of ACL injury.\textsuperscript{131} Adapted sensory processing has also been demonstrated with increased overall parietal lobe activation to reproduce joint positions in those with ACLR,\textsuperscript{25} and absent or depressed somatosensory evoked potentials after ACL injury that is not restored with reconstruction.\textsuperscript{286} It is possible that, due to the chronic pain and prolonged dysfunction associated with the injury, sensory processing for movement becomes altered with increased activation of higher-level sensory integration areas. The secondary somatosensory area also activates during painful stimuli.\textsuperscript{68,279} Our participants were well
beyond the acute stage of injury and did not report any discomfort during the fMRI, but sensory neuroplasticity may have occurred to increase nociceptive processing brain activation during any knee related movement.

**Study Limitations**

As the traditional rehabilitation approach highly encourages a focus of attention on the knee with increased visual and cognitive knee control during movement training, it is likely that the neuroplastic differences are partially due to the rehabilitation. However, without prospective data, inferring a cause and effect mechanism is not possible. We are not able to determine when these neurological changes occur, whether right after surgery or further out, due to prolonged changes in motor control strategies, nor can we determine an effect of reconstruction technique or rehabilitative care from the data. However, previous reports of altered neuromuscular control report continued neuromuscular changes after similar periods post ACL injury as in our study.\(^6\,^{157}\)

Neuroimaging does suffer from high variability; we included additional controls in the analysis to decrease this variability and present only the results passing higher than typical corrections and threshold.\(^{229}\) Additionally, each subject’s activation pattern was contrasted with a control, matched on many of the factors that generate this variability, including: gender, height, mass, actively level history, current actively level, education level, hand and leg dominance and previous and current sport participation.
Future Work

Future work should be completed longitudinally with control for the rehabilitation and surgical interventions to determine within subject changes due to injury, surgery and treatment. The next steps to quantify the musculoskeletal injury induced neuroplasticity will require more advanced motor control tasks such as force or position matching or multi-joint movements to improve the clinical applicability of these results. The integration of TMS and/or EEG with fMRI also presents an opportunity to quantify brain function with superior spatial and temporal resolution to further capture aspects of motor control that may be playing a role in the ACL injury risk profile.

Conclusion

This report presented the brain activation differences between those with a history of ACLR and matched healthy controls for knee movement. After ACL injury, reconstruction, rehabilitation and return to activity, engaging in knee movement requires increased sensorimotor, visual-motor and sensory area activation, indicating a neuroplastic effect of musculoskeletal trauma that is not normalized after treatment or even years after return to activity.
Chapter 3: Visual-Motor Control following Anterior Cruciate Ligament Reconstruction

Abstract

**Context:** Visual input is a crucial component in the control of human movement. Previous research, using vision obstruction (blindfold), demonstrates alterations in landing neuromuscular control that may increase injury risk. Due to the method of limiting vision, these investigations lacked generalizability and sport specificity as the tasks were simple single movements without environmental interaction. The development of stroboscopic glasses that disrupt vision without completely removing it now allows visual-motor assessment during dynamic movements and target acquisition tasks. No research has yet considered the effect of dynamic stroboscopic visual feedback disruption on knee landing mechanics.

**Purpose:** To investigate the effects of stroboscopic visual feedback disruption on drop vertical jump (DVJ) landing mechanics and if ACLR injury history alters these effects.

**Methods:** Participants consisted of fifteen ACL reconstructed individuals and fifteen healthy matched controls. Participants completed three normal DVJs, three wearing stroboscopic glasses at two settings (high and low), and finally, a blindfolded DVJ. Knee flexion, adduction angles, moments and vertical ground reaction forces were calculated, during the landing phase. A repeated measures ANOVA was used to assess the effects of
gender, ACL injury history, side and visual condition on landing mechanics. A one samples t-test was used to determine if the peak stroboscopic condition altered variables of interest greater than previously determined measurement error and a paired t-test to assess the change score of full vision to the peak change stroboscopic condition for the ACL vs. control groups.

**Results:** Disrupting vision, during landing, altered knee mechanics for all five variables of interest. Change scores from full vision to stroboscopic condition for knee flexion and adduction angle were higher than previously reported typical measurement error. There was a paired group difference for knee flexion with the ACLR cohort increasing knee flexion to a greater degree than the matched control group.

**Conclusion:** The effect of altered visual feedback during landing was variable across the groups with a non-uniform effect. Stroboscopic visual feedback disruption may have an individualized effect; future work may be able to differentiate individuals that are most dependent on visual feedback for motor control and those most likely to respond to visual-motor therapy.
Introduction

Anterior cruciate ligament (ACL) rupture is a common activity-related knee injury that usually requires surgical reconstruction to restore knee stability and function. The lifetime burden of ACL injury ranges from $7.6 to $17.7 billion/year in the United States. Despite surgical reconstruction and physical rehabilitation, injury of the ACL dramatically increases the risk for costly and long term disabling osteoarthritis, associated decreased lifelong physical activity, and decreased work productivity. Importantly, reconstruction and rehabilitation that rely primarily on traditional neuromuscular interventions have a failure rate up to 25% for re-rupture after return to sport. This high failure rate is further compounded due to a majority of individuals not returning to pre-injury levels of activity.

Although evidence supports neuromuscular training for effective injury prevention and rehabilitation, many of these approaches primarily target biomechanical factors such as muscle strength, balance, and plyometric function with less consideration for cognitive or neurological components. While rectifying the biomechanical profile and restoring muscle strength are vital components of the rehabilitation process, there may be potential to further improve function and decrease re-injury risk. Recent reports demonstrate unresolved neuroplastic alterations after injury, reconstruction, and rehabilitation that may be limiting function and the return to sports participation. By targeting neurologic factors, during neuromuscular rehabilitation progressions, it may be possible to improve the transfer of sensorimotor adaptations from the clinic to activity, and ultimately improve patient outcomes.
Previous investigations into the neuroplasticity after ACL injury have suggested a possible visual-motor control alteration after injury that goes unresolved with current therapy.\textsuperscript{75,92,93,131} Previous research using vision obstruction (blindfold) demonstrates alterations in landing neuromuscular control that may increase injury risk.\textsuperscript{271,272} Due to the method of limiting vision, these investigations lacked generalizability and sport specificity as the tasks were simple single movements without environmental interaction. The development of stroboscopic glasses that disrupt vision, without completely removing it, now allows visual-motor assessment during dynamic movements and target acquisition tasks. No research has yet considered the effect of dynamic stroboscopic visual feedback disruption on lower extremity landing kinematics.

The purpose of this study is to investigate the effects of stroboscopic visual feedback disruption on drop vertical jump (DVJ) landing mechanics and if ACLR history, side or gender alter these effects. It was hypothesized that visual feedback disruption would decrease landing knee flexion, increase landing knee abduction and increase landing ground reaction force, knee flexion moment and abduction moment across gender and injury history, with a more pronounced effect on those with a history of ACLR.

Methods

Participants

Participants consisted of fifteen ACLR individuals (7 males, 8 females, 21.41.5±2.60 years, 1.72±0.09 m, 69.24±15.24 kg, Tegner activity level 7.3 ± 1.3,
36.18±26.50 months post-surgery) and 15 matched healthy controls (7 males, 8 females, 23.15±3.48 years, 1.73±0.09 m, 69.98±14.83 kg, Tegner activity level 6.77 ± 1.48).

**Data Collection**

A three-dimensional passive motion capture system (Vicon, Los Angeles, CA) was used to assess jump-landing biomechanics. This system collects the precise locations of body segments during high speed dynamic tasks, using retro-reflective markers to establish rigid body anatomical and tracking coordinates for each segment (foot, shank, thigh, pelvis etc.) with the point cluster marker technique. The Vicon cameras capture the marker positions at 300 frames per second and transmit their positions to the computer software. This digitization creates a highly accurate spatiotemporal kinematic model so that joint angles, velocity, and acceleration can be quantified. Six 40x60cm force plates (Bertec, Columbus OH) measure ground reaction forces. In conjunction with 3D kinematics, a kinetic analysis was performed, using standard inverse dynamics.

The drop vertical jump assessment involves the subject falling forward from a 30 cm box and, then, immediately performing a maximum vertical jump with a target set at 90% of their maximum jump height. Subjects are instructed to fall directly off the box and immediately perform a maximum vertical jump, raising both arms as if they were jumping for a basketball rebound. A Vertec (Power Systems, Knoxville, TN) jump target was placed at 90% of their maximum drop vertical jump height to provide an in-air target.
The utilization of the 3D motion capture to quantify the drop vertical jump in this investigation serves as a standard method to determine biomechanical impairments and lower extremity injury risk (figure 9). The primary biomechanical outcomes are sagittal and frontal plane knee excursion and peak moment during landing, which are typical standard analyses for knee control and predictors for primary and secondary ACL injury risk.\textsuperscript{104,106,109,194,234} These metrics are highly reliable with inter-class correlation coefficients greater than 0.93.\textsuperscript{70,109,194}

The drop vertical jump was completed under four conditions: normal vision, vision disruption low, vision disruption high and vision obstructed. Three trials under each condition were completed and averaged for each participant. For the disruption condition, individuals completed at least 5 minutes to get accustomed to the stroboscopic glasses. If any discomfort arose, the protocol was discontinued. The standard warm up protocol consists of one minute of tossing a small ball, followed by five minutes of tossing with the rate of visual disruption increasing after each set of five successful catches.\textsuperscript{9,10} This allows the individual to get accustomed to the strobe glasses and to limit any effect on movement performance due to their novelty. No participant had an issue tolerating the visual disruption.
Figure 9. Frame of analysis with 2D video, Vicon model, Visual 3D model respectively.
**Normal Vision:** Participants will complete the DVJ assessment under normal conditions.

**Disrupted Vision:** The Nike SPARQ Vapor Strobe goggles (figure 10) were worn to impose a visual disruption. These glasses do not block vision continuously, but instead, strobe in a manner to block vision for milliseconds at a time. The length and frequency of these periods of “lost” versus “intact” vision can be customized to eight different levels, with a constant 100ms transparent vs. 50ms-900ms opaque period, depending on the setting. For the purposes of this investigation, we utilized two levels of disruption (low (100ms opaque\100ms transparent) and high (250ms opaque\100ms transparent). The higher levels equate to increased intervals of “lost” vs “intact” vision. In pilot testing, we found visual disruption levels higher than 250ms opaque to result in complete loss of vision, during the entire DVJ, and a maximum of 250 ms opaque to be ideal for maximum visual feedback disruption but not complete obstruction. The acquisition of the in air target was also complicated by increased visual disruption beyond 250ms opaque. In the future, longer temporal resolution maneuvers may be completed to explore a higher level of stroboscopic visual disruption. These glasses have been utilized to improve reaction time, agility, hand-eye coordination, and quickness, while performing athletic tasks such as running, cutting, jump landing, and other sport specific movements such as catching, throwing, or shooting a ball.\textsuperscript{9,10}
Figure 10. Stroboscopic visual disruption experience
**Obstructed Vision:** The visual obstructed condition uses a blindfold to completely remove vision and provides perspective data on the absolute contribution of vision to neuromuscular control in this population. This is the first study to our knowledge to examine landing mechanic alterations with visual perturbations in an ACLR cohort. The inclusion of this condition will allow for comparison to previous literature along with our control cohort. As well as allowing an aspect of scaling in the data analysis as we will have a full vision, vision knock down (disruption) and vision knock out assessment of landing kinematics. The target was removed for safety during this vision-obstructed condition.

**Data Analysis**

Data analysis was performed in Visual3D (Version 5.0, C-Motion, Inc, Germantown Maryland) and MATLAB (R2013B, The Mathworks, Inc., Natick, Massachusetts). Initial contact of each limb was defined when the vertical ground-reaction force first exceeded 20 N. The landing phase was defined from initial contact to the peak knee flexion (figure 9). Lower extremity kinematics and kinetics were calculated, during this phase, and variables of interest extracted. The mean of three trials for each condition was used for statistical analysis.

Marker trajectories were filtered with a low-pass Butterworth filter at cutoff frequency of 15 Hz. Hip joint centers were estimated, using a previously described method, to improve joint center approximation. The midpoint between the medial and lateral knee and ankle joint markers defined the joint centers for the knee and ankle, respectively. Knee flexion and adduction were described as positive values. Peak knee
flexion and the change in adduction from initial contact to peak knee flexion were extracted for analysis.

Inverse dynamics were used to calculate sagittal and frontal plane knee moments from the kinematic and force plate data. Force data were filtered through a low-pass Butterworth filter at a matched cutoff frequency of 15 Hz. External (force acting on the body) knee flexion and abduction moments were described as positive values. Peak external knee flexion and abduction moments were calculated for each landing. Moments are presented as absolute and body weight normalized. Ground reaction force is presented as body weight normalized.

Change scores were computed for the involved knee (ACLR cohort) and matched knee (control cohort), using the subtracted average of the normal landings from the stroboscopic landings. A peak stroboscopic effect score was calculated as the mean of the full vision trials contrasted with the peak mean of the low or high stroboscopic conditions.

**Statistical Analysis**

A repeated measures ANOVA with 4x2 within subject factors: visual condition (full vision, low stroboscopic vision, high stroboscopic vision and blind vison) and side (left or right) and 2x2 between subject factors: ACL injury (yes, no) and gender (male and female) was used to evaluate the effect of vision, side, injury and gender on landing mechanics. Covariates were mass and height for kinetic analysis. Confidence intervals were calculated and displayed graphically with the method described by Loftus for within
subject designs using the mean square of error and degrees of freedom error terms from the ANOVA.\textsuperscript{159,172}

To determine if the stroboscopic condition altered knee mechanics beyond previously established within-session typical error, a one-sample t-test was used on the absolute change scores for the involved and matched knee with the threshold set at the respective error for the respective measure. The stroboscopic change score for knee flexion was tested for an effect greater than a previously determined measure of error of $3.2^\circ$ and knee adduction greater than previously determined measure of error of 0.9.\textsuperscript{70} The stroboscopic change score for knee flexion moment was tested for an effect greater than a previously determined measure of error of 0.15Nm/kg and knee abduction moment greater than previously determined measure of error of 0.12 Nm/Kg.\textsuperscript{70} In addition, a paired t-test was completed to evaluate individual change scores computed between the full vision condition and the peak stroboscopic condition for the involved ACLR knee and the matched control knee.

\textbf{Results}

Biomechanical variables of interest mean and standard deviation for each visual condition are presented in table 1.
<table>
<thead>
<tr>
<th>Variable</th>
<th>FV</th>
<th>SV-Low</th>
<th>SV-High</th>
<th>BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Peak Knee Flexion Angle (degrees)</td>
<td>78.24(10.16)</td>
<td>78.86(11.85)</td>
<td>79.68(11.73)</td>
<td>81.34(12.87)</td>
</tr>
<tr>
<td>Left Peak Knee Flexion Angle (degrees)</td>
<td>78.08(9.84)</td>
<td>78.65(11.16)</td>
<td>79.36(10.98)</td>
<td>81.04(12.29)</td>
</tr>
<tr>
<td>Right Knee Adduction (degrees)*</td>
<td>-3.01(5.06)</td>
<td>-3.82(4.81)</td>
<td>-3.38(5.36)</td>
<td>-2.37(5.42)</td>
</tr>
<tr>
<td>Left Knee Adduction (degrees)*</td>
<td>-3.28(5.85)</td>
<td>-4.29(5.82)</td>
<td>-3.89(5.60)</td>
<td>-2.9(5.98)</td>
</tr>
<tr>
<td>Right Peak External Knee Flexion Moment</td>
<td>117.23(41.06)</td>
<td>125.51(47.78)</td>
<td>123.86(45.15)</td>
<td>115.95(45.53)</td>
</tr>
<tr>
<td>Right Peak External Knee Flexion Moment</td>
<td>0.95(0.23)</td>
<td>1.01(0.26)</td>
<td>0.99(0.26)</td>
<td>0.92(0.23)</td>
</tr>
<tr>
<td>Left Peak External Knee Flexion Moment</td>
<td>96.97(39.59)</td>
<td>108.23(45.25)</td>
<td>104.44(40.73)</td>
<td>99.15(40.67)</td>
</tr>
<tr>
<td>Left Peak External Knee Flexion Moment</td>
<td>0.77(0.19)</td>
<td>0.85(0.23)</td>
<td>0.82(0.19)</td>
<td>0.78(0.22)</td>
</tr>
<tr>
<td>Right Peak External Knee Abduction Moment</td>
<td>11.3(11.26)</td>
<td>12.51(11.18)</td>
<td>12.99(13.03)</td>
<td>10.25(9.43)</td>
</tr>
<tr>
<td>Left Peak External Knee Abduction Moment</td>
<td>13.17(9.47)</td>
<td>3.78(10.97)</td>
<td>114.61(10.58)</td>
<td>12.47(10.13)</td>
</tr>
<tr>
<td>Right Peak Ground Reaction Force (Body mass)</td>
<td>1.95(0.46)</td>
<td>2.11(0.58)</td>
<td>2.01(0.48)</td>
<td>1.90(0.54)</td>
</tr>
<tr>
<td>Left Peak Ground Reaction force (Body mass)</td>
<td>1.91(0.35)</td>
<td>1.94(0.56)</td>
<td>1.77(0.46)</td>
<td>1.94(0.49)</td>
</tr>
</tbody>
</table>

Table 1. Data across all participants by visual condition *Knee adduction angle is degree change from initial contact to peak flexion. Peak vertical ground reaction forces are expressed relative to body weight.
Kinematic – Sagittal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak knee flexion angle (F (1.831, 36.621) = 4.842, p = 0.014, figure 11). Post hoc tests revealed that visual condition elicited a slight increase in knee flexion that corresponded with the level of visual feedback. Full vision to low stroboscopic vision did not significantly increase knee flexion (0.924±0.529, p =0.092). Full vision to high stroboscopic vison significantly increased knee flexion (1.495±0.671, p=0.035), and full vision to blind vision significantly increased knee flexion (3.289±1.161, p=0.009). There was no main effect for side, gender or injury history. There was also a significant difference between the ACLR and control group in the paired t-test of peak knee flexion angle change from full vision to stroboscopic vision (ACL: 3.12±3.76, CON: -0.84±4.45, p=0.001, figure 12). A one-sample t-test against the typical error of 3.2 degrees for knee flexion⁷⁰ was also significant with an overall absolute mean change of 4.038±2.2, p=0.048, indicating the change was higher than within session assessment error.
Figure 11. Mean peak knee flexion under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition
Figure 12. Mean knee flexion degree change under stroboscopic condition compared to full vision.
Kinematic – Frontal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for adduction angle change between initial contact to peak knee flexion (F(1.756, 37.050)= 5.063, p = 0.013, figure 13). The mean frontal plane knee excursion from initial contact to peak knee flexion was toward abduction for all conditions. Post hoc tests revealed that visual condition elicited an increase in knee abduction initially, but returned closer to baseline with increased level of visual disruption. Full vision to low stroboscopic vision significantly increased knee abduction (0.799±0.269, p =0.006), but there was no change compared to high stroboscopic and blind vision. The blind visual condition significantly decreased knee abduction compared to low stroboscopic vision (1.436±0.491, p=0.007) and high stroboscopic vision (1.089±0.491, p=.035). There was no main effect for side, gender or injury history. There was no significant change in knee adduction angle in the paired analysis (ACL: -1.574±2.719, Con: -1.046±1.419, p=0.429, figure 14). A one-sample t-test against the typical error of 0.9 degrees for knee adduction\textsuperscript{70} was significant across the entire cohort with an overall absolute mean change of 1.978±1.530, p=0.001, indicating the change was higher than within session assessment error.
Figure 13. Mean peak knee adduction angle under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition.
Figure 14. Mean knee adduction degree change under stroboscopic condition compared to full vision.
Kinetic – Ground Reaction Force

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak ground reaction force (F (2.725, 65.395) = 3.892, p = 0.012, figure 15). Post hoc tests revealed that visual disruption or obstruction elicited no difference from the full vision condition. However, stroboscopic-low increased ground reaction force (0.172±0.045, p =0.005) compared to stroboscopic-high. No other pair-wise differences were significant. There was no main effect for side, gender or injury history. There was no significant difference in ground reaction force change induced by the stroboscopic condition in the paired analysis (ACL: 0.021±0.500, Con: -0.137±0.445, p=0.395, figure 16). A one-sample t-test was significant with an overall absolute mean change across the entire cohort of 0.387±0.2663, p<0.001 for the peak stroboscopic effect.
Figure 15. Mean peak ground reaction force under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition.
Figure 16. Mean peak ground reaction force change under stroboscopic condition compared to full vision.
Kinetic – Sagittal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak external knee flexion moment (F (2.085, 54.208) = 11.502, p < 0.001, figure 17). Post hoc tests revealed that visual condition elicited an increase in peak external knee flexion moment during landing that corresponded with the level of visual disruption except blind vision decreased the peak moment, compared to full vision levels. Full vision to low stroboscopic vision significantly increased knee flexion moment (10.404±2.727, p =0.005). Full vision to high stroboscopic vison also significantly increased knee flexion moment (6.962±2.085, p=0.015), but there was no change from full vision to blind vision. There was no main effect for side, gender or injury history. There was no significant change in knee flexion moment in the paired analysis (ACL: 11.66±12.78, Con: 12.18±15.27, p=0.875, figure 18 & 19). The mass normalized knee flexion moment change score from full vision to peak stroboscopic condition one-sample t-test was not significantly higher than the previously established typical within session error of 0.15 Nm/kg (0.186±0.133, p=0.143), indicating no change across the cohort beyond within session measure error.
Figure 17. Mean peak knee flexion moment under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition.
Figure 18. Mean peak knee flexion moment change under stroboscopic condition compared to full vision.
Figure 19. Mean peak knee flexion moment change under stroboscopic condition compared to full vision. (mass normalized)
Kinetic – Frontal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak external knee abduction moment (F (1.951, 50.719) = 4.525, p =0.016, figure 20). Post hoc tests revealed that visual condition elicited an increase in peak external knee abduction moment during landing that corresponded with the level of visual disruption except for blind vision, which decreased the peak moment to close to full vision levels. Full vision to high stroboscopic vision significantly increased knee abduction moment (1.522±0.440, p =0.002). Full vision to low stroboscopic vision and blindfold resulted in no change. The blind condition had significantly lowered peak knee abduction moment compared to stroboscopic-low (1.560±0.693, p=0.033) and stroboscopic-high (2.195±0.887, p=0.020) but not full vision. There was no main effect for side, gender or injury history. There was no significant change in knee abduction moment in the paired analysis (ACL: 3.174±3.776, Con: 1.954±2.10, p=0.314, figure 21) and body weight normalized (ACL: 0.044±0.0463, Con: 0.0289±0.0337, p=0.341, figure 22). The mass normalized knee abduction moment change one-sample t-test was significantly lower than the previously established typical within session error of 0.12 Nm/kg (0.041±0.0359, p<0.001), indicating no change across the cohort.
Figure 20. Mean peak knee abduction moment under FV (full vision), SV-low (stroboscopic low setting), SV-High (stroboscopic high setting) and BV (blind vision). * indicates significant difference from FV condition.
Figure 21. Mean peak knee abduction moment change under stroboscopic condition compared to full vision.
Figure 22. Mean peak knee abduction moment change under stroboscopic condition compared to full vision. (mass normalized)
Discussion

The purpose of this study was to evaluate the effects of various levels of reduced visual feedback on landing kinematics and kinetics. Results indicated that stroboscopic visual disruption and complete removal of vision affects drop landing knee mechanics across knee sagittal and frontal plane angle and moment that was independent of injury history, gender or side. While the relative overall group changes in biomechanics were slight in some cases, the stroboscopic condition created a varied response in motor control. These results suggest that even a mild disruption to visual-motor processing can influence bilateral landing mechanics. Only peak knee flexion demonstrated a group pair-wise effect for increased knee flexion in the ACL group. Knee frontal plane angle, moment, and knee sagittal plane moment did not demonstrate a similar pair-wise injury condition effect.

Sagittal

As visual feedback decreased with stroboscopic conditions and blind vision, peak knee flexion also increased. The peak stroboscopic change scores also demonstrate a greater knee flexion effect in the ACL group. Increased knee flexion with visual perturbation is counter to what has been previously reported in healthy controls subjects when vision is fully removed. However, in our study in the combined cohort analysis, when vision was disrupted, the participants increased knee flexion, with the greatest increase during the blind vision condition. The control group did demonstrate an overall effect of decreased knee flexion under the peak stroboscopic condition in the pairwise analysis, but the group average was less than a degree. Other key
methodological differences between previous reports of visual restricted landing in healthy subjects includes no vertical jump component after landing\textsuperscript{253}, increased drop height (our study was set at 30.5 cm., where as other reports used 50 cm.\textsuperscript{46,253}) or variable heights, ranging from 20 cm. to 80 cm.\textsuperscript{276}, and comparing only full vision to blind vision conditions with no middle component of decreased visual input via stroboscopic glasses, as done in our study or any other means.\textsuperscript{46,253} This scaling effect may have allowed our participants to prepare gradually for the loss of visual-feedback and not undergo a stiffening strategy, when vision was completely removed.

The pair-wise increase in knee flexion for the ACLR cohort may indicate a specific visual-motor adaption in those individuals compared to the controls. However, it is interesting to note that some individuals in the control group, demonstrated an ACLR like adaptation in motor control by also increasing knee flexion. Eight of the 15 ACLR participants increased knee flexion above minimal detectable threshold of 3.2°, whereas only four of the control participants experienced a similar change in flexion kinematics. While such a small change in knee flexion, (absolute mean change of 4°) may seem clinically insignificant; it is on a similar level as an in-flight perturbation with a 3.1° change in knee flexion due to a 15% body mass lateral perturbation, during the drop phase before ground contact. It is also in line with neuromuscular injury prevention training program effects with changes in knee flexion of 3.1°\textsuperscript{232}, plyometric jump training program effects with a change of 3.0°\textsuperscript{110}, and the immediate effects of self-feedback interventions of 3.5°\textsuperscript{66}. The immediate altering of knee flexion kinematics with modification of visual feedback on similar levels as these previous three examples
indicates that visual-motor control may influence lower extremity function on a clinically significant level.

While there was an effect on knee sagittal plane peak moment with visual condition in the repeated measures ANOVA, the effect of stroboscopic visual disruption was not significantly greater than previously reported measurement error, and there was no difference in the peak stroboscopic effect between the ACLR and control cohorts. The changes, while statistically significant in the repeated measures model, may not be clinically significant. Interestingly, while on the whole there was no significant change in knee flexion moment on the one sample t-test for the absolute stroboscopic effect, 16 individuals experienced a change in knee flexion moment above typical error with an almost even split between those with ACLR(8) and controls(7). This may warrant further investigation to discover the neuromuscular factors that caused these individual to respond to a greater degree to visual feedback disruption than those that did not.

**Frontal**

Knee frontal plane angle changed with visual condition only with no group, side or gender effect. The effect on knee adduction angle was more consistent regardless of group with the majority of participants going into more abduction (more knee valgus) during landing due to disrupted visual feedback. Seven of the 15 ACLR participants increased knee abduction beyond minimal detectable threshold of 0.9° while only four of the 15 matched controls experience a similar increase in knee abduction. The 1.978° change in knee abduction angle due to disrupted visual feedback is also in line with previous reports for the effect of a multi-week neuromuscular training program: 1.7°
change\textsuperscript{232}, a self-feedback intervention: 0.96° change\textsuperscript{66}, and an in-flight perturbation: 2.31° change\textsuperscript{301}.

While there was an effect on knee frontal plane peak moment with visual condition in the repeated measures ANOVA, the effect of stroboscopic visual disruption was not significantly greater than previously reported measurement error, and there was no difference in the peak stroboscopic effect between the ACLR and control cohorts. The changes, while statistically significant in the repeated measures model, may not be clinically significant. Only one ACLR participant changed knee abduction moment greater than typical error, and no control participants did. This indicates that stroboscopic visual feedback disruption has little impact on knee abduction moment.

**Clinical Implications**

The alterations in knee mechanics under varied visual feedback conditions indicate that lower extremity landing and injury risk maybe influenced by the amount of visual feedback during landing. While the stroboscopic conditions increased knee abduction angle and abduction moment, the complete removal of visual feedback caused the opposite effects with decreased knee abduction and moment. It would seem that a threshold might exist whereby the neuromuscular control system responds to protect the lower extremity when sufficient visual feedback is removed by further increasing knee flexion and decreasing peak ground reaction force, moments, and abduction angle. However, if only a mild or moderate visual feedback disruption is present, only knee flexion increases to accommodate the increased demand on the neuromuscular control system due to the depressed visual feedback. At the stroboscopic visual disruption level,
the concurrent increase in ground reaction force, knee abduction angle, knee abduction moment, and knee flexion moment indicate from a neuromuscular control perspective the effect of immediate visual disruption is to increase knee loading and possible injury risk that is not mitigated by increasing knee flexion.

Visual-motor control may be a key aspect of the multifactor overlapping subspecialty nature of noncontact ACL injury. A possibly overlooked factor in ACL injury prevention and rehabilitation design is visual-motor control associated with maintaining neuromuscular joint-to-joint integrity while engaging in the complex athletic environment.\textsuperscript{147,292} As physical activity and athletic participation require high demand on the visual-motor system to maintain environmental interaction as well as neuromuscular integrity, visual disruption in rehabilitation may be a promising tool to more closely mimic sport demands. The ability to sustain motor control in the variable sport environment demands a complex central nervous system (CNS) integration of a constantly changing profile of sensory inputs including visual feedback, proprioception, and vestibular equilibrium to maintain neuromuscular control.\textsuperscript{168,293}

Swanik et al.\textsuperscript{269} prospectively reported decreased aspects of neurocognitive function increased the risk of experiencing a non-contact ACL injury. Specifically, reaction time, visual processing and memory, measured via a computerized concussion baseline assessment (IMPACT), were significantly lower than matched controls.\textsuperscript{269} The role of visual-motor function and reaction time to facilitate preparation of the neuromuscular system in anticipation of high-risk situations, maneuvers or incoming players provides the theorized mechanism for neurocognition to influence
musculoskeletal injury risk. Faster reaction time or processing speed may increase the potential to prepare for incoming perturbations or cognitively manage the complex athletic environment, while maintaining neuromuscular control. Our data support a role for visual-motor function affecting neuromuscular control during landing. Both the ACLR cohort and the control cohort experienced similar changes with visual disruption, with ACLR having increased knee flexion, indicating a possible influence of the rehabilitation program or that visual feedback may be providing a larger input to sustain neuromuscular control after ACL injury.

If visual-motor processing ability is suboptimal, this may decrease the ability to compensate for external stimuli and/or attenuate the rapid and sometimes, unanticipated maneuvers that depend on quick visual-motor interaction. Visual-motor processing is imperative to successful sport function whereby complex sensory and visual feedback must be handled with minimal preparation time. Visual memory ability may also assist in motor planning during activity as the constantly changing environment (player or ball positions) must be kept in short-term visual memory, when planning movement sequences. While limited connections exist, relating biomechanical, visual-motor function and changes induced by ACL injury, previous reports indicate altered neuromuscular control during visual-motor environmental interaction that may influence injury risk mechanics in healthy active participants. The results of this study further add to the implications of visual-motor function in lower extremity neuromuscular control and specifically in exploring the effects in an ACLR cohort.
A promising aspect of the influence of visual-motor function on neuromuscular control is that it is highly trainable.\textsuperscript{186,262} The consideration of visual-motor approaches, during injury prevention and rehabilitation programs, may provide a means to further improve intervention effectiveness. These approaches can be paired with foundational neuromuscular techniques for optimizing strength, multi-planar knee and trunk control, and movement asymmetries.\textsuperscript{57} The use of a direct visual disruption technology such as stroboscopic glasses provides an opportunity to supplement traditional interventions.\textsuperscript{186,202} The clinician can add another training area that may decrease injury risk by targeting visual-motor processing along with the traditional neuromuscular, strength and movement dysfunctions. The cognitive approximation of the demands involved in higher intensity athletic activity under the supervision of a well-trained clinician may further decrease musculoskeletal injury risk. Recognition of the visual-motor implications for maintaining neuromuscular control and injury avoidance may help to mitigate injury risk.

**Limitations**

The ACLR cohort was heterogeneous relative to sport, mechanism of injury, and time from surgery. However, this would only strengthen the ACLR specific effects relative to the matched controls, in that regardless of this cohort’s demographic variability the response to visual disruption was still unique in some ways in the ACLR group. The lack of longitudinal data limits our ability to determine if these individuals had this visual-motor control difference before injury or if it was partially induced by the trauma, surgery and rehabilitation. The study design to scale the visual disruption from
none, to stroboscopic then blind vision may also play a role in the results. The lack of a cross-over or counter-balanced design was selected apriori to limit any effects of task novelty from the visual disrupted conditions. By always doing practice trials and the full vision test trials first, we ensured as much familiarity with the task as possible before disrupting vision to limit the effect of task novelty on performance as much as possible. Simply wearing the stroboscopic glasses or trying to move while blindfolded is a sufficient challenge to the neuromuscular control system, and we wanted to avoid having a combined challenge of a new task and visual disruption. In addition, the selection of progressive difficulty was made to mimic how this technology may be used clinically.

The goal of this work is to provide an evidence base for rehabilitation, and we expect that clinicians will typical use these tools in a similar scaling way and wanted to examine the effects of stepping up the difficulty incrementally.

It is possible that some individuals engaged in visual-motor training or underwent specialized rehabilitation that influenced the results. To control for this, we used rehabilitation and training survey in this study to determine if anyone had undergone any specialized training with regard to visual-motor function. No one in the study reported engaging in any specific visual-motor training in rehabilitation or for sports performance.

Future work

The high variability in the response to visual disruption indicates this maybe an area of future analysis to examine the changes in movement variability due to depressed visual feedback, as the mean peak angles and moments may not change to a great degree, but the inter-trial variability maybe modified. The variability in the mean individual
responses also may indicate that some participants have a relative visual-motor processing bias compared with sensory-motor. Capturing other metrics of function such as proprioception, strength or psychological factors may also help answer why some participants responded to a greater degree to stroboscopic visual disruption.

The goal of this investigation was to determine if visual feedback disruption altered landing mechanics and to investigate the effects of visual feedback on landing mechanics after ACLR. More complex and/or unilateral tasks may also be more adaptable to detect variations in visual-motor control after ACL injury. Due to the bilateral nature of the drop vertical jump, the repeated measures ANOVA did not detect an effect for side in any variable across all four conditions. As vision is not known to play a unique unilateral role in motor programming in the lower extremity, we did expect a side effect with visual disruption in this task.

It is possible with specialized visual-motor training the adaptations to disrupting visual feedback can be enhanced, to improve neuromuscular function and decrease injury risk when vision is disrupted. Intervention studies with traditional neuromuscular control training and visual-motor focused neuromuscular training may provide a mechanistic understanding of how altering visual-motor processing ability influences landing mechanics.

Conclusion

Visual feedback disruption via stroboscopic glasses alters bilateral landing mechanics to a similar degree across injury history and gender. The stroboscopic effect on knee flexion is higher in those with ACLR history. Dynamic visual disruption maybe
a worthwhile addition to rehabilitation as it alters neuromuscular function and may simulate athletic exposure.
Chapter 4: The Brain-Behavior relationship after Anterior Cruciate Ligament Reconstruction

Abstract

Context: Anterior cruciate ligament (ACL) injury may induce brain neuroplastic adaptations that are unresolved with reconstruction and rehabilitation. Visual-motor function appears to be a key driver of this neuroplasticity. The relationship between the neuroplasticity after ACLR (anterior cruciate ligament reconstruction) and visually perturbated neuromuscular control is unknown.

Purpose: To determine: 1) if a relationship exists between brain activation during knee movement and visually perturbated drop landing neuromuscular control and 2) if ACLR alters this relationship.

Methods: Participants consisted of 26 recreationally active individuals from the local university community (13 ACL, 13 control matched on height, mass, extremity dominance, education level, history and current physical activity level). A drop vertical jump was completed to assess knee kinematics as a measure of functional neuromuscular control ability (knee flexion and adduction). Stroboscopic eyewear provided a visually perturbed condition. The effect of disrupting visual feedback was calculated with a mean change score form the full vision to the disrupted condition. A brain fMRI was collected during a unilateral knee motor task of the involved or matched knee consisted of repeated cycles of extension-flexion. The percent signal change of apriori regions of interest
(motor cortex, lingual gyrus) were calculated and correlated against the stroboscopic effect on knee flexion and adduction.

**Results:** Lingual gyrus activation was correlated with the stroboscopic effect on knee flexion for the entire cohort and the ACLR and control cohorts specifically. Motor cortex activation was correlated with the stroboscopic effect on knee adduction for only the ACLR cohort.

**Conclusion:** The neuroplasticity after ACL injury, reconstruction, rehabilitation and return to activity to engage in knee motor control is moderately related to visually perturbated drop landing neuromuscular control. These finding indicate visual-motor control maybe a driving factor behind neuromuscular control changes after ACL injury and a possible contributing mechanism to the continued poor neuromuscular control despite current therapy. Additional attention to the sensory-motor and visual-motor interaction and adaptations after injury and during therapy may provide a means to improve neuromuscular therapy.
Introduction

Anterior cruciate ligament (ACL) injury and reconstruction may induce brain motor control adaptations that influence neuromuscular function and potentially, future injury risk.\textsuperscript{152,153,221,224,225,286} These adaptations are likely due to a combination of response to the disrupted afferent pathway\textsuperscript{130,285,286} and developed motor compensations\textsuperscript{130,167,219}. The fundamental CNS alterations after injury likely extend from the localized mechanoreceptor disruption\textsuperscript{2} and decrease in local muscle activation potential\textsuperscript{44} to global remodeling of the CNS\textsuperscript{131,183}. The sensory system is impaired with a decrease or absence of the P27 somatosensory potential in the primary sensory cortex with stimulation the common peroneal nerve\textsuperscript{285} or the ACL directly\textsuperscript{227}. This afferent adaptation contributes to decreased proprioception and dynamic stability that influence rehabilitative outcomes.\textsuperscript{48,50} More recent and functional work with EEG has demonstrated that, after ACLR (anterior cruciate ligament reconstruction) to control knee position and force generation, the brain must increase somatosensory cortex (afferent processing) and anterior cingulate cortex (attention procession) activation.\textsuperscript{24,25}

The neuroplastic implications of ACL injury further extend beyond adapted sensory processing. The motor system is altered with increased corticomotor excitability\textsuperscript{101} of the quadriceps but decreased spinal reflex excitability\textsuperscript{281,282} and gamma motor neuron drive\textsuperscript{140,144}. These results are theorized to be due to the increased need for motor planning and cortical drive in the absence of expected sensory input inducing presynaptic inhibition.\textsuperscript{215,226} The connectivity between spinal reflexes and cortical voluntary control, assessed via trans-cortical long latency response to knee perturbation,
is also inhibited, indicating a CNS systematic wide adaptation to the injury.\textsuperscript{167} The need to sustain motor function in the presence of disrupted sensory input and processing may cause the motor system to utilize alternative sources of feedback such as visual or vestibular inputs. Kapreli et al. in the first neuroimaging study of knee motion after ACL injury found increased activation of visual areas that process biological motion during knee movement in those with ACL deficiency.\textsuperscript{131}

These findings indicate a neurophysiologic change due to ACL trauma, but it is unknown how this injury-induced neuroplasticity relates to neuromuscular control during complex action. We theorize motor control after ACLR to become more dependent on visual feedback,\textsuperscript{91-93} but the absence of both neurological and biomechanical measures in the same subjects has not allowed the neural correlates for motor control after ACL injury to be targeted in rehabilitation. The combination of functional magnetic resonance imaging (fMRI) to provide a detailed method to assess brain changes and 3-dimensional biomechanics to quantity movement function provide mechanisms to bridge this gap in knowledge. The purpose of this work is to determine the relationship between biomechanically measured neuromuscular control, during visually perturbed drop landing, and brain activation, during a knee motor control task in those with ACLR and matched controls. We hypothesize that the change in knee sagittal and frontal plane kinematics during a visually disrupted landing condition will be related to lingual gyrus and motor cortex activation with a stronger effect in the ACLR cohort.
Methods

Participants

Participants were matched on height, mass, extremity dominance, education level, history and current physical activity level. Thirteen left ACL reconstructed (ACLR) (21.46±2.81 years, 1.7±0.11 m, 70.80±17.04 kg, Tegner activity level 7.38 ± 1.5, 36.16±27.48 months post-surgery) and 13 matched healthy controls (23.15±3.48 years, 1.74±0.09 m, 69.77±14.27 kg, Tegner activity level 6.77 ± 1.48) participated.

Neuroimaging - Data Collection

The Functional Magnetic Resonance Imaging (fMRI) data were collected on a 3.0-Tesla Siemens Magnetom scanner using a 12-channel array receive only head coil. The session included 9-functional time series, consisting of 90 whole brain gradient-echo echoplaner scans acquired every 3.0 seconds with anterior-posterior phase encoding direction (slice thickness 2.5 mm, 55 transversal slices). This equates to ten whole brain data sets per knee movement, so 40 whole brain activation maps for knee movement(4 sessions) contrasted with 50 whole brain maps for rest (5 session). After the functional runs, an anatomical 3-diminsional high-resolution T1-weighted image (repetition time: 2000 ms, echo time: 4.58 ms, field of view: 256 mm matrix, slice thickness 1 mm, 176 slices) was completed for registering the activation data, brain region identification and normalization to compare the ACL and matched participants.

The participant performed unilateral knee extension-flexion for 4 sets of 30 seconds (10 whole brain images), triggered by an auditory metronome at1.2 Hz or 36
knee extension-flexion cycles per 30 second stimulus (figure 4). The participant was positioned supine in the scanner with legs on a custom cushion that limited knee flexion to 45°. Movement artifact was limited with padding and straps to a maximum of 0.5 mm absolute and 0.30 mm relative displacement for all participants. An ankle-toe splint was used to restrict ankle or toe movement and the participant was monitored for accessory motions. The movement condition was contrasted with a 30 second rest condition that preceded and followed each movement cycle. A mock scanner session was completed prior to the actual scanning session to ensure the participant was familiar with the movement.

Neuroimaging - Data Analysis

The fMRI image analyses and statistical analyses were performed using the Oxford Centre for functional MRI of the brain software package. This began with standard pre-statistic processing applied to individual data, including: non-brain removal, spatial smoothing using a Gaussian kernel of full width at 6 mm standard motion correction and realignment parameters (3 rotations and 3 translations) as covariates to limit confounding effects of head movement. High pass temporal filtering at 90 Hz and time-series statistical analyses were carried out using a linear model with local autocorrelation correction. Functional images were co-registered with the respective high resolution T1 image and standard MNI 152, 2mm space using linear image registration. This registration process allows the data from the two groups to be spatially aligned on a standardized brain template for comparison. First level analysis of functional knee movement relative to rest were carried out with Z>4.6 and a (corrected) cluster
significance threshold of $p = 0.001$. The cluster correction uses a variant of Gaussian Random Field theory to decrease type-I error in statistical parametric mapping of imaging data by not only evaluating the activation at each voxel, but also the surrounding voxel cluster (as it is unlikely that the voxel tested and surrounding voxels are active above threshold due to chance). The contrast between the ACL reconstructed subject and matched control were then performed with group Z-statistic images set at $Z>3.5$ threshold and a corrected cluster significance level of $p=0.01$. The atypically higher threshold and lower p value were selected to mitigate inter-subject variability and decrease probability of motion artifact in the data, as well as further decreasing the probability of type I error.

**Neuroimaging - Region of Interest Analysis**

We selected the motor cortex (right side; all ACLRs were left side and the movement was completed with the left knee) and lingual gyrus (bilateral mask, peak voxel was right side) as *apriori* regions of interest based on previous analysis that these areas activated higher in the ACLR cohort, during involved knee movement. The structural-anatomical masks from the Harvard-Oxford Atlas (implemented in FSL view version 5.0) for the pre-central gyrus and lingual gyrus were used to define anatomical regions. To limit the mask to knee motor specific regions within the anatomical region, the anatomical mask was binarized and combined with the group contrast mask for knee movement. FSL region of interest analysis was carried out on the subject level with featquery, and the percent signal change of knee movement contrast with baseline was
calculated. The mean region signal change and peak voxel signal change was selected for analysis.

**Biomechanics - Data Collection**

A three-dimensional passive motion capture system (Vicon, Los Angeles, CA) was used to assess jump-landing biomechanics. This system collects the precise locations of body segments during high speed dynamic tasks using retro-reflective markers to establish rigid body anatomical and tracking coordinates for each segment (foot, shank, thigh, pelvis etc.) using the point cluster marker technique. The Vicon cameras capture the marker positions at 300 frames per second and transmit their positions to the computer software. This digitization creates a highly accurate spatiotemporal kinematic model so that joint angles, velocity, and acceleration can be quantified.

A drop vertical jump task was completed to assess functional neuromuscular control. The drop vertical jump assessment involves the subject falling forward from a 30.5 cm box and then immediately performing a maximum vertical jump with a target set at 90% of their maximum jump height. Subjects are instructed to fall directly off the box and immediately perform a maximum vertical jump, raising both arms as if they were jumping for a basketball rebound. A Vertec (Power Systems, Knoxville, TN) jump target was placed at 90% of their maximum drop vertical jump height to provide an in-air target.

The utilization of the 3D motion capture to quantify the drop vertical jump in this investigation serves as a standard method to determine biomechanical impairments and lower extremity injury risk. The biomechanical variables of interest are sagittal and
frontal plane knee excursion during landing, which are typical standard analyses for knee control and predictors for primary and secondary ACL injury risk. These metrics are highly reliable with inter-class correlation coefficients greater than 0.93.

The drop vertical jump was completed under two conditions: normal vision and vision disruption. Three trials under each condition were completed and averaged for each participant. For the disruption condition, individuals were allowed at least 5 minutes to get accustomed to the stroboscopic glasses. The standard warm up protocol consists of one minute of tossing a small ball, followed by five minutes of tossing as the rate of visual disruption is increased after each set of five successful catches. This allows the individual to get accustomed to the stroboscopic glasses and to limit any effect on movement performance due to their novelty.

Biomechanics - Data Analysis

Data analysis was performed in Visual3D (Version 5.0, C-Motion, Inc., Germantown Maryland) and MATLAB (R2013B, the Mathworks, Inc., Natick, Massachusetts). Initial contact of each limb was defined when the vertical ground-reaction force first exceeded 20 N. The landing phase was defined from initial contact to the peak knee flexion. Lower extremity kinematics were calculated during this phase and the mean of the three trials for each condition were used for statistical analysis.

Marker trajectories were filtered with a low-pass Butterworth filter at cutoff frequency of 15 Hz. Hip joint centers were estimated using a previously described method to improve joint center approximation. Knee and ankle joint centers were
defined as the midpoint between the respective medial and lateral knee and ankle joint markers. Knee flexion and adduction were described as positive values.

Change scores were computed for the involved knee (ACLR cohort) and matched knee (control cohort) using the subtracted average of the normal landings from the stroboscopic landings. A stroboscopic effect score was calculated as the mean of the full vision trials contrasted with the peak mean of the low or high stroboscopic conditions.

**Statistical Analysis**

A Pearson correlation was completed on the relationship between motor cortex and lingual gyrus activation during knee extension-flexion and knee flexion and adduction angle during landing.

**Results**

The mean and peak percent signal change for the lingual gyrus and motor cortex and the stroboscopic mean change scores are presented by group in table 2.

Lingual gyrus brain activation (figure 23) across all participants was significantly correlated with the knee flexion change from the full vision to the stroboscopic visual condition \((r=0.654, p<0.001, \text{figure } 24)\). There was also a relationship within each group, ACLR \((r=0.582, p=0.037)\) and controls \((r=0.688, p=0.009)\). There was no relationship between knee frontal plane angle and lingual gyrus activation \((r=0.023, p=0.912)\).

Across all participants, motor cortex activation (figure 25) was not correlated with knee sagittal \((r=0.042, p=0.840)\) or frontal plane angle \((r=0.183, p=0.370)\). In the control group, there was no correlation between knee kinematics and motor cortex brain
activation (frontal: $r=0.032$, $p=0.916$; sagittal: $r=0.023$, $p=0.913$). In the ACL cohort, there was a significant correlation between the stroboscopic effect on knee frontal plane angle and motor cortex activation ($r=0.683$, $p=0.005$, figure 26). There was no relationship between motor cortex activation and sagittal plane kinematics ($r=-0.268$, $p=0.333$).
<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Motor Cortex Activation (% signal change)</th>
<th>Strobe effect Knee Adduction</th>
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</thead>
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<tr>
<td></td>
<td>Peak</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>ACL</td>
<td>10.12±2.28</td>
<td>2.468±0.373</td>
<td>-1.07±2.45</td>
</tr>
<tr>
<td>Control</td>
<td>8.11±4.53</td>
<td>1.823 ± 0.693</td>
<td>-0.50±2.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Lingual Gyrus Activation (% signal change)</th>
<th>Strobe effect Knee Flexion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>ACL</td>
<td>4.64±1.82</td>
<td>0.556±0.493</td>
<td>1.51±3.34</td>
</tr>
<tr>
<td>Control</td>
<td>3.14±1.72</td>
<td>0.174±0.450</td>
<td>-0.46±4.82</td>
</tr>
</tbody>
</table>

Table 2. Mean of region and peak voxel within region respective and standard deviations for motor cortex activation (percent signal change) and lingual gyrus (percent signal change) in columns 2 and 3. Mean stroboscopic effect on knee flexion and knee adduction (degrees) for each group in column 4.
Figure 23. Typical lingual gyrus area brain activation for left knee movement.

Figure 24. Scatter plot of lingual gyrus activation and change score from full vision to stroboscopic vision for knee flexion. 0 – black circle are controls \( (r=0.688, \ p=0.009) \); 1 – red squares are ACLR \( (r=0.582, \ p=0.037) \)
Figure 25. Typical sensorimotor brain activation for left knee movement.

Figure 26. Scatter plot of motor cortex activation and change score from full vision to stroboscopic vision for knee adduction. 0 – black circle are controls (r=0.032, p=0.916); 1 – red squares are ACLR (r=0.683, p=0.005)
Discussion

The entire group and each cohort had a moderate positive correlation between lingual gyrus activation and change in knee flexion during stroboscopic landing, specifically increased knee flexion was associated with increased lingual gyrus activation and decreased knee flexion was associated with decreased lingual gyrus activation. This indicates that as visual-motor brain regions are engaged to complete knee movement the relative amount of knee flexion during landing increases. This indicates that increased activation of the lingual gyrus may play a role in adopting a “safer” control strategy, when visual feedback is reduced, by concurrently increasing knee flexion.

The ACL reconstructed cohort had a moderate positive correlation between motor cortex activation and change in knee adduction, during stroboscopic landing, specifically increased knee adduction (more knee varus position) was associated with increased motor cortex activation, and decreased knee adduction (more knee valgus position) was associated with decreased motor cortex activation. This suggests that, as drive from the motor cortex increases to complete knee movement, the relative amount of knee adduction during landing increased.

The lack of a relationship in the control group between motor cortex activation and knee kinematics may indicate that the fMRI task does not offer sufficient physical demand for controls. The relative activation level of the motor cortex in the ACLR cohort was higher than the controls. This corroborates previous work that indicated greater motor planning, and sensory area activation in those with ACL injury, possibly indicating that the task is neurologically more challenging in this cohort. It may be that, in a
healthy population, a more challenging motor control task, during fMRI, is required to be related to the more functional drop landing.

Knee flexion and adduction were selected as they are common metrics of neuromuscular control during drop landing, with more knee flexion and less knee valgus indicating increased ability to control the landing and decreased joint loading.\textsuperscript{197,234} In contrast, a landing with decreased knee flexion and increased knee valgus is associated with increased injury risk\textsuperscript{109}, poorer neuromuscular control\textsuperscript{193} and increased respective plane moments\textsuperscript{196,234}. The association of motor cortex activation indicates there is likely a relationship between how the brain generates knee motor control and the neuromuscular control displayed during visually perturbated drop landing after ACLR. The association of lingual gyrus activation suggests that there is likely a relationship between visual-motor processing and knee neuromuscular control during landing regardless of ACL injury history.

**Cortical Excitability**

Recently, investigators using TMS showed that at six months after ACLR quadriceps cortical excitability was decreased, and this was especially pronounced in those with poorer knee function and lower strength.\textsuperscript{153,224} There are very few investigations comparing cortical excitability and cortical activation during similar tasks. What few studies do exist are commonly done on changes after a treatment, are in the upper extremity and involved pathologic populations such as stroke or spinal cord injury. However, with this limited data, it would seem that decreased cortical excitability may be associated with increased motor cortex activation.\textsuperscript{95,163} Therefore our results may seem
counter to the previous literature, in that those with higher activation tended to land with less knee valgus or adopt a more knee neutral frontal plane landing profile, indicating improved landing neuromuscular function under the visually disrupted condition. It is possible that those with higher activation are simply overcoming the depressed cortical excitability described by Lepley et al. (2015)\textsuperscript{153} and have adapted cerebral processing to improve neuromuscular function. A direct comparison to previous TMS work is difficult as they measure different aspects of the nervous system and the tasks are fundamentally different: active knee extension during fMRI vs. isometric knee extension during TMS. More research is needed to better understand the cortical excitability and activation relationship with fMRI and TMS along with behavioral assessment of neuromuscular control in the same subjects.

**Clinical Implications**

The training, and even restoration, of primarily biomechanical factors relative to ACL injury risk\textsuperscript{109,251} may not be addressing all the physiologic consequences of the injury, as even years post injury, patient-reported dysfunction and poor movement control persist.\textsuperscript{13,198,218,244,247,303} The impaired physical performance and patient reported dysfunction might in part have a neurologic origin.\textsuperscript{131,141,225} The capacity for neuroplasticity, after injury and during therapy, presents an avenue to close a gap between rehabilitation and activity by targeting a broader spectrum of sensorimotor function during neuromuscular training.\textsuperscript{82,100,198,199} Alternative approaches and adjunct therapies may help to address the neurological system functions associated with the faulty movement patterns underlying ACL re-injury risk.\textsuperscript{25,145,167,221}
The visual-motor processing and landing neuromuscular control connection across groups may indicate this is a component of neurological function that should be considered for primary injury prevention as well as rehabilitation. Swanik and Wilkerson independently found a relationship between visual-motor processing speed and ACL or lower extremity injury risk respectively. However, no study to our knowledge has yet to examine prospective visual-motor control during lower extremity landing or other dynamic tasks to consider a combination of visual processing and neuromuscular control on injury risk. While the relationship between lingual gyrus activation and the stroboscopic effect on knee flexion was similar across groups, the ACLR cohort’s relationship is shifted upward, with both increased lingual gyrus activation and knee flexion. This may indicate that the injury simply induces a greater dependence on visual-motor processing and concurrently an increased effect of disrupting visual processing during landing. Clinicians may consider incorporating visual-motor training as a part of rehabilitation and prevention alongside standard neuromuscular training approaches.

The increased motor cortex activation decreasing knee valgus in the ACLR cohort may indicate unique insights into the motor control adaptations associated with the injury and recovery process. The increased activation, during knee extension-flexion in the ACLR cohort, may indicate increased connectivity with the rest of the brain as the adapted sensory processing after the injury may increase use of alternative feedback to program motion. This may increase overall activation of the motor cortex, as these alternative input sources have to be integrated with established motor planning to
generate motor control.\textsuperscript{11,79,249} Thus, the increased motor cortex activation may be a positive adaption that allows those with ACLR to not experience an increase in valgus motion during visually disrupted drop landing.

**Limitations**

It is unknown if these relationships were present prior to the injury and may have played a role in the initial loss of neuromuscular control associated with the ACL injury mechanism or developed due to the injury. In addition, the intensive unilateral rehabilitative therapy after injury may induce a greater visual-motor relationship after ACL injury. The great deal of training to restore muscular function post injury may also increase the level of cortical vs. sub-cortical or spinal cord contribution to knee neuromuscular control.\textsuperscript{217}

The DVJ is a vastly different motor task than unilateral knee extension-flexion. The DVJ involves greater ranges of motion, increased muscle production, is bilateral in nature and is not completed in a supine position. Thus, the inability to do such a functional task during fMRI due to excessive head motion, limits any direct relationship between the neural activation and biomechanics of the two tasks. However, as our apriori hypothesis was that visual-motor control was a key area of neuroplasticity after ACL injury we included a disrupted visual landing condition so that a visual processing effect on landing kinematics could be calculated and correlated with the neuroplasticity after injury.

The within group heterogeneity regarding time from ACL injury may also have played a role in the findings. It is very likely that the neuroplasticity closer to injury is
different from the adaptations made chronically over many years living with an ACLR knee. This does strengthen the results that despite this heterogeneity, a clear brain activation difference exists to simply generate knee movement and this activation relates to visually disrupted neuromuscular control. We lack the sample size to investigate at this time whether the effects are being driven by those closer to reconstruction\injury or further out, but it appears that including visual-motor and motor learning approaching in rehabilitation may have implications across the recovery cycle and is not limited to early treatment or return to sport progression.

**Future Work**

Future investigation may consider adopt a multimodality approach to measuring the neuroplasticity after musculoskeletal trauma, incorporating TMS, EEG, and fMRI and along with biomechanical and neuromuscular measures of behavior. This multifaceted approach will allow the strengths of each technique to compensate for the respective inherent weaknesses of each technique. For instance, fMRI has excellent spatial resolution but lacks the temporal resolution of EEG and both of these are correlational in nature, while magnetic stimulation allows for causation as the experimenter generates the impulses. This combination can allow a scaling of function in the neurological data, from very basic knee movement, to knee force\position control with EEG\TMS and even functional measures of walking\postural control with EEG.

A longitudinal investigation would also address many of the new questions generated by this work, including how does time, injury, surgery, immediate and long-term recovery change how the brain maintains knee motor control. A within subject
design would also allow for a much greater causation statement regarding brain activation changes, as in it is unknown how much if any of these results are present prior to injury.

**Conclusion**

ACLR may induce specific neuroplastic adaptations in motor control within the brain that translate into neuromuscular control, during visually perturbed landing. Specifically motor cortex activation is associated with decreasing knee valgus during landing and lingual gyrus activation is associated with increasing knee flexion. Motor learning and visual-motor intervention may be able to influence this relationship and improve neuromuscular control after ACL injury by targeting these neural correlates.
This work highlights a conceptual and data driven framework for the integration of neuroscience measures and principles in the approach to musculoskeletal medicine. The application of neuroplastic constructs during neuromuscular rehabilitation to optimize musculoskeletal therapy interventions is a new frontier for orthopedic care. The objective of this research was to investigate how musculoskeletal injury, specifically knee anterior cruciate ligament injury, may influence the nervous system to maintain or adapt motor function. A strength of these findings is that they can provide the evidence base for adjunct strategies along with foundational neuromuscular techniques for optimizing strength, multi-planar knee and trunk control, and other impairments. The opportunity to supplement traditional interventions by further targeting neuroplastic, cognitive, and visual-motor capabilities is an exciting time for research and clinical practice. These new approaches allow clinicians to approximate the neurocognitive demands of higher intensity athletic activity in a safe, controlled, and most importantly feedback rich environment before reintegration into sport. Recognition of the visual-motor implications in neuromuscular control, injury recovery and prevention, combined with new technologies, may help to mitigate post-injury movement dysfunction and decrease injury risk when returning to activity.
The data collected herein expands the current state of neuroimaging paradigms for lower extremity motor function, exploring the relationship between knee biomechanics and the brain. The implications for this brain-behavior relationship in lower extremity function have the potential to influence the clinical approach to other musculoskeletal disorders. While the finding of this specific investigation are focused on orthopedic musculoskeletal injury of the ACL, the general progression of fMRI paradigms to assess lower extremity motor control will contribute to the understanding of the neurologic implications for vital life functions such as gait to improve treatment for lower extremity orthopedic and neurological impairments.\textsuperscript{60,165,289}

A key question surrounding the neuroimaging literature regarding group analysis is what does higher or lower task based brain activation actually mean.\textsuperscript{228} The competing hypothesis of neural efficiency\textsuperscript{53} (improved performance\textbackslash learning\textbackslash ability equating with decreased activation), and neuroplasticity associated with learning, engaging more synapses\textbackslash networks, increasing cortical representation and enhancing excitability, equating with increased activation\textsuperscript{146,182,280} make for a difficult interpretation. Our investigation (chapter 4) indicates that increased activation of visual-motor and primary motor regions may be a positive adaptation to improve knee neuromuscular control after injury. Courtney et al.\textsuperscript{48-50} in a series of works demonstrated that ACL deficient individuals that went on to become copers (positive outcome without surgery) and adapted their movement strategy with increased hamstring activation to compensate for the instability had absent somatosensory evoked potentials in the brain from the ACL. This was in opposition to non-copers or those that needed surgery or had a poor outcome
having intact somatosensory evoked potentials and no adaptation in motor control strategy. This work indicates that, if the brain does not receive the disrupted or absent afferent signal from a damaged ACL, no motor adaptation will occur. Any peripheral or spinal adaptations that mitigate the loss of the somatosensory evoked potential at the brain actually resulted in a poorer outcome. Therefore, the increased activation in those that optimally adapted their motor control strategy, in this study, may indicate that increasing lingual gyrus and motor cortex activation during knee motor control is a positive adaption (or the in those that had the most change in brain activation after injury compared to controls had the greater optimization of landing neuromuscular control).

Somewhat counter to our initial intuition, the more the injury affects the nervous system the better the resulting neuromuscular control profile. This is further supported by recent work of Pietrosimone and colleges that, after ACLR, those that have the lowest quadriceps activation failure, highest strength and best reported outcomes have the greatest increase in cortical excitability. This corroborates our hypothesis that cortical mechanisms may underpin recovery from injury and increased top-down and feed forward mechanisms can compensate to a degree the resulting instability and depressed afferent feedback form the injury.

**Future Work**

Future investigation into the neuroplastic effects of musculoskeletal trauma and treatment may allow the targeting of factors not currently considered in rehabilitation to improve patient outcomes. The current state of neuroimaging technology greatly limits the lower extremity motor control tasks that are viable during fMRI. This is primarily due
to the fact that any head motion, during brain imaging, causes significant artifact due to spin history effects (slices no longer lining up appropriately due to head translation) and head motion associated blood flow changes convoluting the desired signal. This work (chapter 2) used a simple knee motor task, and while this was one of the first times reported in the scientific literature of using neuroimaging to successfully quantify brain activity during knee movement, it was still rather simplistic. As motion correction, methods continue to progress for both data collection and analysis, more externally valid forms of movement may become possible, during neuroimaging. Innovations such as prospective acquisition correction, whereby the data capture location shifts with head motion to ensure slice alignment\textsuperscript{19}, automated\textsuperscript{240} and motion correlated\textsuperscript{156} independent component analysis to remove motion correlated noise and preserve stimulus signal, and other techniques such as scrubbing\textsuperscript{237} (removal of high motion acquisition) may allow future investigators to utilize more externally valid tasks such as simulated gait, postural control or adding force or joint position parameters. These new approaches may allow the development and use of non-ferrous (MRI safe) load cells, goniometers or other movement capture devices to allow a combined neural and motor quantification of a more sophisticated movement paradigm.

This work utilized a cross sectional design and, thus, was unable to draw causation from the neuroplastic and biomechanical findings. A longitudinal design would provide a measure of change within subjects and may allow a more definite statement to be made, regarding how injury and therapy interact to change the nervous system. Acquiring data prior to injury may not be feasible, but doing so just after injury, before
surgery, after surgery and at time of recovery would allow for a distinction between the
europlasticity induced by rehabilitation vs. injury. However, this post-injury design,
while answering how therapy/surgery modify neural control, would not be able to answer
whether these neurologic motor control differences existed prior to injury at baseline
testing. ACL injury has a high second injury rate (up to 30% for active cohorts\textsuperscript{221}) but a
low initial injury incident (5% for active cohorts\textsuperscript{239}); therefore, following a cohort after
ACL injury may provide a means to evaluate neurologic risk factors for second injury
that may help inform both primary and secondary injury prevention methods.

Research into possible neurological factors that influence primary injury may
allow injury prevention programs to account for the random and complex nature of the
sport injury scenario and provide the means for the continued advance of injury
preventive neuromuscular therapy. The continued examination of the neuroplastic effects
of musculoskeletal injury may allow the development of additional therapeutic targets
ranging from brain stimulation to modalities that improve visual-motor function or future
yet unexplored avenues. One such technique we evaluated in this work was stroboscopic
glasses (chapter 4). This technology allows the patient to engage in neuromuscular
training under depressed visual feedback and increased cognitive load in a safe clinical
environment. This ability to train under a visually disrupted or knockdown stress may
provide a means to target unique neuroplastic factors in rehabilitation. The relationship
between visual-motor brain activation and movement-induced changes by the
stroboscopic eyewear indicate that those who increase motor cortex and lingual gyrus
activation adopt a safer landing movement pattern. This may indicate that training with
This or related technology to improve visual-motor control may allow for improved neuromuscular control when vision is disrupted in athletic activity.

This work provides a platform to examine novel treatment approaches after musculoskeletal injury, targeting the specific neural systems susceptible to injury-induced modifications but not addressed during standard of care rehabilitation. We have discovered that brain activation is altered to simply engage in knee motor control after injury. This neuroplasticity includes adapted sensory system processing and increased visual-motor activation. The considerations of cognitive load, visual-motor function, dual tasking, mental practice, motor learning and feedback adaptation all have a place in musculoskeletal rehabilitation.

The clinical translation of this work is vital for improving the care of those that sustain musculoskeletal trauma. The use of neuroimaging as a research tool has great potential, but without primary clinical tests or approaches to find those that may have maladapted neuromotor control strategies, this work will lack clinical impact. Future research investigating neural correlates, such as behavioral measures of visual-motor processing or adapted sensory input that have high correlation with the brains motor control activation strategy, may help to translate this work into clinical practice. The use of dual tasking, neurocognitive testing or movement assessment under visual disruption may provide a means to detect those with an associated visual-motor dominant controls strategy. The development of primary low cost tests may allow the identification of those with visual feedback reliance for motor control and allow the further personalization of musculoskeletal therapy beyond targeted muscle or joint dysfunctions.
References


298. Wright RW, Dunn WR, et al. Risk of tearing the intact anterior cruciate ligament in the contralateral knee and rupturing the anterior cruciate ligament graft during the first 2...


Appendix A: Alternative Chapter 4 Statistical Analysis

Introduction

To decrease multiple condition comparisons and in light of the high dependency of the stroboscopic conditions and overall high group wise variability, included below is an additional analysis with the average of the two stroboscopic conditions instead of separate high and low conditions. To illustrate the degree of co-linearity between the stroboscopic change scores; the correlations of the change score from full vision to the stroboscopic low and high conditions for kinematics and kinetics are presented below (table 3).

<table>
<thead>
<tr>
<th>Variable (right knee)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee flexion angle</td>
<td>r=0.474; p=0.008</td>
</tr>
<tr>
<td>Knee adduction angle</td>
<td>r=0.612; p=.0001</td>
</tr>
<tr>
<td>Knee flexion moment</td>
<td>r=0.500; p=0.005</td>
</tr>
<tr>
<td>Knee abduction moment</td>
<td>r=0.834; p=0.0001</td>
</tr>
</tbody>
</table>

Table 3 Bivariate Pearson correlation between change score from full vision to low stroboscopic visual condition and change score of full vision to high stroboscopic condition.

Only the results for knee flexion angle and ground reaction force are altered with the use of a Bonferroni or modified Bonferroni correction. The use of either correction mitigates the effect of either stroboscopic condition, and only a pair-wise difference exists from full vision to blind vision for knee flexion and no pair-wise effect for ground reaction force. All other variables sustain their result regardless of correction. The use of
even a modified Bonferroni correction on the pair-wise comparison p-values, however, is debated and is considered overly conservative in a repeated measures design. Loftus advocates that using the repeated measuring confidence intervals may be a superior practice as it is less conservative and takes into consideration the within subject error as opposed to between subject error.\textsuperscript{159} This largely depends on the research question, however, if a between or within subject effect is to be investigated. In this work, our primary goal was to determine how visual feedback alters neuromuscular within a subject. Additionally, this study is exploratory (first to our knowledge to assess stroboscopic dynamic visual feedback disruption) and not confirmatory, thus not adjusting for multiple comparisons maybe reasonable to ensure a possible effect is not missed for future research.\textsuperscript{27} Regardless, we have conducted an additional analysis to reduce the multiple comparison problems and provide further confirmation of the reported results in chapter 3.

**Kinematic – Sagittal**

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak knee flexion angle (F(1.249, 32.471)= 6.589, p = 0.011, figure 27). Post hoc tests revealed that visual condition elicited an increase in knee flexion that corresponded with the level of visual feedback. Full vision to average stroboscopic vision significantly increased knee flexion (1.210±0.482, p =0.019). Full vision to blind vision significantly increased knee flexion (3.289±1.161, p=0.009). There was no main effect for side, gender or injury history.
Figure 27 Mean peak knee flexion under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition.
Kinematic – Frontal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for adduction angle change between initial contact to peak knee flexion between visual conditions (F(1.348, 35.059) = 4.541, p = 0.030, figure 28). The mean frontal plane knee excursion from initial contact to peak knee flexion was toward abduction for all conditions. Post hoc tests revealed that visual condition elicited an increase in knee abduction initially and then closer to neutral as visual condition was increased. Full vision to average stroboscopic vision significantly increased knee abduction (0.625±0.232, p =0.012), but there was no change compared to blind vision. The blind visual condition significantly decreased knee abduction compared to average stroboscopic vision (1.263±0.478, p=0.014). No other pair-wise differences were significant. There was no main effect for side, gender or injury history.
Figure 28  Mean knee adduction change from initial contact (IC) to peak knee flexion (PKF) under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition.
Kinetic – Ground Reaction Force

The repeated measures ANOVA with a Greenhouse-Geisser correction determined no main effect for visual condition for peak ground reaction force between (F(1.721, 43.018) = 0.221, p = 0.769, figure 15). Post hoc tests revealed that visual disruption or obstruction elicited no difference from the full vision condition. No other pair-wise differences were significant. There was no main effect for side, gender or injury history.
Figure 29 Mean peak vertical ground reaction force under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision).
Kinetic – Sagittal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak external knee flexion moment between visual conditions (F(1.509, 39.244) = 10.116, p < 0.001, figure 30). Post hoc tests revealed that visual condition elicited an increase in peak external knee flexion moment during landing that corresponded with the level of visual disruption except blind vision decreasing peak moment to full vision levels. Full vision to average stroboscopic vision significantly increased knee flexion moment (8.683±2.293, p=0.001), but there was no change from full vision to blind vision. The blind condition had significantly lower peak knee flexion moment compared to stroboscopic average (7.877±1.426, p=0.001) but not full vision. There was no main effect for side, gender or injury history.
Figure 30  Mean peak external knee flexion moment under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition.
Kinetic – Frontal

The repeated measures ANOVA with a Greenhouse-Geisser correction determined a main effect for visual condition for peak external knee abduction moment between visual conditions (F(1.442,37.492)= 4.556, p =0.027, figure 31). Post hoc tests revealed that visual condition elicited an increase in peak external knee abduction moment during landing that corresponded with the level of visual disrupted except blind vision decreasing peak moment to close to full vision levels. Full vision to average stroboscopic vision significantly increased knee abduction moment (1.205±0.395, p =0.005). Full vision to average stroboscopic vison and blind resulted in no change. The blind condition had significantly lower peak knee abduction moment compared to stroboscopic average (1.877±0.751, p=0.019) but not full vision. There was no main effect for side, gender or injury history.
Figure 31 Mean peak knee abduction moment under FV (full vision), SV-AVG (stroboscopic average effect) and BV (blind vision). * indicates significant difference from FV condition.