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Over 200,000 anterior cruciate ligament (ACL) injuries occur each year. Noncontact mechanisms during sport account for ~70% of these injuries. Greater anterior knee laxity (AKL) is an established independent risk factor of ACL injuries in females. While the mechanical aspects of increased AKL have been studied, relatively little is known about the neural aspects of the ACL in regard to how relates to increased AKL. The purpose of this study is to investigate differences in somatosensory cortical activity between high and low knee laxity individuals. Electroencephalography (EEG) was used to measure contralateral somatosensory cortical activation during passive anterior tibial translations (ATT) in females with high and low knee laxity across 3 joint loading phases (LP) (LP1, 0-65N; LP2, 65-130N; LP3, 130N hold for 1 second). Results indicated no difference in cortical activation between females with high and low AKL during passive loading of the knee joint across the 3 loading phases. This suggests that despite mechanical differences at the knee, sensory information traveling from the knee joint to the somatosensory cortex is similar in females with high and low laxity. While there were no between group differences there was a trend ($p = .07$) in the decrease of cortical activation from LP1 to LP3 within groups. With more exploration of this decrease in activity this information could better help explain the roles of the mechanoreceptors in and round the knee joint during joint loading. This study represents a primary step taken to understand the neural role of the ACL during joint loading with a long-term vision of attempting to develop brain-based interventions in effort to reduce ACL injuries. To build upon this, this data should be further investigated to look at differences in the latency of the signal from the knee to the brain to see if there is a difference in how rapidly the signal travels to the somatosensory cortex between groups.

DIFFERENCES IN CORTICAL ACTIVATION DURING ANTERIOR TIBIAL TRANSLATION BETWEEN FEMALES WITH HIGH AND LOW LAXITY

by

Beth R. Bacon

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Dr. Randy Schmitz
Committee Chair

DEDICATION

This thesis is dedicated to everyone who supported me throughout this process. Most importantly this is dedicated to my family for their love, patience and understanding that helped me push through to the end!

APPROVAL PAGE

This thesis written by Beth R. Bacon has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair

Dr. Randy Schmitz

Committee Members

Dr. Sandra Shultz

Dr. Derek Monroe

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Date of Final Oral Examination

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I: INTRODUCTION

One of the most common traumatic knee injuries to occur during sporting activity is an anterior cruciate ligament (ACL) injury. Over 200,000 ACL injuries occur each year (Kim et al., 2011) with non-contact activities accounting for ~70% of these injuries (Boden & Sheehan, 2022; Griffin et al., 2000) and nearly 90% resulting in ACL surgical reconstruction (Cheng et al., 2022; Linko et al., 2005; Paterno et al., 2014). Females are 2-4 times more likely to sustain an ACL injury compared to similarly trained males with majority of ACL ruptures occurring between the ages of 14 - 18 years old (Beck et al., 2017; Parkkari et al., 2008; Shea et al., 2004). While an ACL injury may cause acute disability, there are also long term consequences, including increased risk of re-injury (Butler et al., 1980; Paterno et al., 2014; Schilaty et al., 2017) as well as early onset of post traumatic osteoarthritis (PTOA) which can arise as early as one year from the initial injury (Driban et al., 2014). It has been reported that as many as 50-60% of ACL injuries will result in PTOA (Luc et al., 2014). There is a need to better understand the risk factors of ACL injury to decrease the incidence of these traumatic injuries.

Multiple known concomitant risk factors for a 1st time ACL injury include bony knee geometry, body mass index (BMI), sex hormones, neuromuscular control, and joint laxity (Griffin et al., 2000; Hughes & Watkins, 2006; Shultz, Kirk, et al., 2004). However, a greater magnitude of anterior knee laxity (AKL) is one of the strongest independent predictors of ACL injury (Uhorchak et al., 2003; Vacek et al., 2016). AKL is commonly described as the anterior displacement of the tibia relative to the femur under a fixed, anteriorly directed load on the tibia. This measurement encompasses many different anatomical structures that comprise the knee joint including muscles/tendons, the joint capsule, and intrinsic ligaments. However, the ACL is

the primary static restraint to anterior tibial translation and provides approximately 80% of the restraint against this motion (Butler et al., 1980; Ellison & Berg, 1985) during joint loading.

In addition to mechanically restraining the tibia, the ACL provides afferent input via mechanoreceptors to the central nervous system (CNS) (Johansson, 1991; Johansson et al., 1991). This includes information traveling to and being processed at spinal and supraspinal levels. This afferent information is used in detecting the limb position and movement, tension and force, tissue elongation, as well as perceived effort during active/passive and static/dynamic motions (Gritsenko et al., 2007; Kawato et al., 1987; Nyland et al., 1994; Proske & Gandevia, 2012; Stroeve, 1997).

The concept of neuromuscular errors (NME) has been suggested to result in body mechanics that put the ACL at risk (Grooms & Onate 2016; London & Miller 2013). A NME may be defined as a discrepancy in motor control within the feedback and/or feedforward system in response to perceived mechanical demands on the system. (London & Miller). A NME may occur when the knee joint is loaded during movements such as a quick cut, rapid deceleration, or single leg landing. During these motions, the ACL deforms the embedded mechanoreceptors which send afferent information about the knee joint to the spine and brain (Gritsenko et al., 2007; Kawato et al., 1987; Nyland et al., 1994; Proske & Gandevia, 2012; Stroeve, 1997). The brain quickly compares this information with previously encoded joint information. If the information received matches, then the brain's response will signal an appropriate subsequent movement to keep the joint in a safe envelope of motion. If the information does not match, then a NME may occur (Grooms & Onate 2016; London & Miller 2013). If the mismatch in information is large enough it could lead to a possible ACL injury by producing a neuromuscular solution that does not adequately protect the joint.

It is plausible that greater AKL may contribute to an NME. At the peripheral level, greater AKL may lead to relatively less ligamentous tension when the ligament is loaded. This could possibly lead to lesser stimulation of the mechanoreceptors in and around the ACL (Dhillon et al., 2011; Yasuda et al., 2006). Greater AKL has been associated with decreased kinesthesia suggesting that diminished afferent information is propagating from the ACL to higher levels (Barrack et al., 1983; Rozzi et al., 1999). At the spinal level, greater AKL may cause an increase in the latency of the responding communication within the reflexive ACL mechanism that is thought to modulate joint stability, suggesting a decrease in sensory reception and reflex control at the knee joint (Shultz, Carcia, et al., 2004; Solomonow et al., 1987; Wojtys & Huston, 1994). At the supraspinal level, as previously mentioned, it has been theorized that an NME may cause an ACL injury. Moreover, greater AKL is one of the strongest independent risk factors for ACL injuries. Therefore, it is possible to speculate that greater AKL may lead to lesser mechanoreceptor firing which could cause a decrease in sensory information being sent to the brain, thus leading to an NME and a subsequent ACL injury.

Limited research has evaluated the effects of laxity on supraspinal activity during passive joint loading (An et al., 2019; Needle et al., 2014; Park-Braswell, 2020). Using electroencephalogram (EEG) one study compared ACL reconstructed (ACLR) participants to healthy controls and reported that the ACLR group exhibited increased somatosensory cortical activation compared to the healthy group during passive knee joint loading tasks (An et al., 2019). Another EEG study reported no differences in somatosensory cortical activation during a passive ankle joint manipulation between participants with previously injured stable ankles, previously injured unstable ankles, and uninjured healthy ankles (Needle et al., 2014). We were able to locate a single study investigating neural activity in a high laxity, healthy population

compared to a low laxity population during passive knee joint loading using functional magnetic resonance imaging (fMRI) (Park-Braswell, 2020). This study demonstrated no differences in activation in the somatosensory cortex between higher and lower knee laxity populations (Park-Braswell, 2020). Critically, the previous EEG studies measured somatosensory cortical activation using bidirectional loading of the joint across load phases. Since greater AKL is one of the strongest independent risk factors of ACL injuries, using an anterior-onlyl force measure is ideal to obtain a surrogate measure of the ACL via anterior knee joint loading. While the fMRI study used this type of joint loading to measure somatosensory cortical activity, they did not assess activity of various loading phases during the joint loading task to assess whether there were any sensory cortical activity differences in early joint loading compared to later. Furthermore, they were unable to simultaneously obtain knee joint laxity measurements in conjunction with fMRI data to ensure that the knee joint was adequately loaded. Therefore, this limited research demonstrates inconsistencies with results thus warranting further investigation.

Collectively, research suggests greater laxity can adversely affect sensory performance. Since AKL is one of the strongest independent predictors of ACL injuries it is important to understand the neural components that may be affected by AKL. EEG would be a useful tool to examine the differences in neuronal activation between low laxity individuals and high laxity individuals while simultaneously measuring knee joint laxity based on its temporal resolution. Comparing the cortical activity during different knee joint loading phases relative to tibial displacement in high and low laxity individuals could help develop a better understanding of the sensorimotor pathway and brain activity during passive joint loading. The purpose of this study is to investigate differences in somatosensory cortical activity between high and low knee laxity individuals. The specific aims follow.

Aim 1: To determine the effects of knee laxity on somatosensory cortical activity measured as measured by an EEG electrode located over the contralateral somatosensory cortex during phases of passive anterior tibial loading of the knee joint (load phase 1 = 0-65N; load phase 2 = 65-130N; load phase 3 = maintaining 130N).

Hypothesis 1: Low laxity group will have higher cortical activation in load phase 1 compared to High laxity group.

Hypothesis 2: Low laxity group will have higher cortical activation in load phase 2 compared to High laxity group.

Hypothesis 3: Low laxity group will have higher cortical activation in load phase 3 compared to High laxity group.

CHAPTER II: REVIEW OF THE LITERATURE

The understanding of what is specifically relative to anterior cruciate ligament (ACL) injuries is instrumental in developing ACL injury prevention strategies. There is a large body of literature that focuses on the proposed mechanisms and risk factors that can lead to these traumatic knee injuries which provides the basis for this study. This chapter will focus on the factors that build the case for the study's research question and research design.

Joint Laxity

Joint laxity is defined as the looseness of a joint. The more lax a joint is the looser and possibly less stable a joint may be. This section will focus on characteristics of joint laxity.

Generalized Joint Laxity

Generalized joint laxity is thought to be a condition or disorder that does not typically require any treatment (Saccomanno et al., 2013) but can lead to instability of the joint, general joint pain, and traumatic injuries such as ligament ruptures in joints (Johnson, 2010). It can be detected through multi-planar analyses that measure increased range of motion in the joint, typically by the Beighton and Horan Joint Mobility Index (Beighton et al., 1999). This can be characterized by the increase of rotation of the articular surfaces which is caused by increased ligament length and elasticity (Johnson, 2010; Saccomanno et al., 2013).

The increase in ligament length and elasticity can be found in one or more joints (Hately S., 2021) which can be linked to genetic disorders such as Joint Hypermobility Syndrome (JHS), Ehlers Danlos Syndrome (EDS) and other connective tissue disorders. Non-pathological causes can also be linked to an increase in joint laxity (Dubs & Gschwend, 1988) such as sex differences (Huston & Wojtys, 1996), hormonal effects (Shultz, Kirk, et al., 2004) and

repetitiveness or overuse of certain joints during training or competitions in athletes (Saccomanno et al., 2013).

Knee Joint Laxity

Knee joint laxity is colloquially often described as looseness of the knee joint. Knee joint laxity can be assessed by measuring the displacement of the tibia relative to the femur in 3 planes of motion when fixed loads are applied to the limb. There are four ligaments that provide restriction to the displacement of motion in the knee joint. In the sagittal plane, load is exerted to the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) to evaluate anterior and posterior knee laxity (Zantop et al., 2007). In the frontal plane, load is exerted to the lateral collateral ligament (LCL) and medial collateral ligament (MCL) for assessment of knee varus and knee valgus, respectively (Butler et al., 1980; Ellison & Berg, 1985; Markolf et al., 1984). In the transverse plane, several of these ligaments are assessed when load is applied through internal and external rotation (Zantop et al., 2007). Within the construct of knee laxity, anterior knee laxity (anterior/posterior translation of the tibia relative to the femur) is the most common clinical assessment of ACL function (Wang et al., 2016).

ACL Injury

An ACL injury is one of the most traumatic knee injuries that occurs in sporting activity. Each year over 200,000 ACL injuries occur in the United States (Kim et al., 2011). In sport, a tear or rupture of the ACL can occur by either contact (directly or indirectly hit) and noncontact (landing, cutting, and deceleration) mechanisms. Noncontact mechanisms are responsible for ~70% of these injuries (Boden & Sheehan, 2022; Griffin et al., 2000). Furthermore, females are 2-4 times more likely to sustain an ACL injury compared to similarly trained males with many of these ACL ruptures occurring between the ages of 13 - 16 years old (Beck et al., 2017; Parkkari

et al., 2008; Shea et al., 2004). To best decrease the risk of ACL injury it is critical to understand what factors may put an individual at an increased risk of injury.

Laxity as a Risk Factor for ACL Injuries

Although there are multiple factors that cause an individual to sustain a non-contact ACL injury, researchers have retrospectively and prospectively demonstrated that greater knee laxity is a risk factor of ACL injury. In a retrospective study, 66 female athletes were examined to help determine factors associated with ACL injuries (Kramer et al., 2007). Along with previous medical history of knees and ankle injuries, 16 lower extremity measurements were taken from 33 control participants and 33 previously ACL-injured participants. Measurements included generalized joint laxity, lower extremity malalignment, and lower extremity range of motion and flexibility. Overall, the authors stated that increased joint laxity, genu recurvatum, a tight iliotibial band with previous history of a lateral ankle sprain appeared to be retrospective predictors of an ipsilateral ACL injury. Another study examined athletes that had previously injured their ACLs (Woodford-Rogers et al., 1994). For the non-contact ACL injuries, 10 male football players and 8 female basketball players and gymnasts with an ACL injury were matched to controls based on sport and level of competition. When comparing anterior knee laxity and navicular drop from the non-injured limb of the injured athletes to the matched limb of the controls, data showed that ACL injured had greater anterior knee laxity along with subtalar pronation, (caused by a hypermobile foot (Beckett et al., 1992; Shultz et al., 2009; Woodford-Rogers et al., 1994). More specifically, discriminant analysis and a multiple regression analysis correctly predicted the athletes' injury statuses (females = 87.5%; overall = 70.5%) (Woodford-Rogers et al., 1994).

While retrospective studies can be informative of risk of injury, prospective studies may provide stronger evidence of injury risk. During a 4-year prospective study of first-time non-contact ACL injuries, Uhorchak et al. (2003) evaluated 859 (739 males, 120 females) West Point cadets. During the first 4 weeks of the study, cadets provided previous medical history and underwent a thorough physical examination, radiographic studies, and strength testing. The lifestyles of the cadets were vigorous with mandatory requirements of physical education, summer training and involvement in intramural or collegiate sports. During the 4-year evaluation a total of 29 cadets sustained first time ACL tears with 24 (16 males, 8 females) resulting from a non-contact injury. From this study the authors reported that anterior knee laxity was a significant prospective risk factor for ACL injuries among females along with a narrower femoral notch width, increased general laxity and increased BMI. Similar findings were reported in a cohort study that monitored 38 college and high school sports teams over the course of 4 years. During the 4 years 109 athletes suffered ACL injuries and were control matched to 227 athletes. Greater anterior/posterior knee laxity and greater BMI collectively were identified as prospective risk factors of ACL injury (Vacek et al., 2016). Collectively these large multivariate risk factor studies that increased anterior knee laxity is among the strongest independent predictors of ACL injury risk.

Joint Stability

Joint stability is the ability to maintain or control movement of the joint within the proper arthrokinematic and osteokinematic range of motions. There are three major contributors to joint stability: the musculotendinous units which provide dynamic joint support, the ligamentous restraints that provide passive support, and the congruity of the bony articular surfaces when a joint is loaded (Hertel, 2002). Control of joint movement is provided through opposing forces

that surround the joint via these musculoskeletal tissues. Various factors such as weakness of the musculoskeletal tissues and disruptions in neuromuscular communication can lead to instability of the joint (Matsuo et al., 2020; Tropp, 2002). Joint instability can thusly increase load on the ligamentous structure increase the risk of injury (Zhou et al., 2017). This section of the review will focus on stability at the knee joint.

Knee Joint Stability

The inherent stability of the knee joint comes from both passive and dynamic components (Zlotnicki et al., 2016). The knee joint is comprised of intrinsic ligaments, joint capsule, menisci, and bone geometry that contribute to mechanically stabilizing the joint in a passive manner (Johansson, 1991; Riemann & Lephart, 2002); whereas dynamic contributions consist of the muscles that cross the tibiofemoral joint. These passive and dynamic stabilizers are responsible for stability of the knee during functional movement that occurs in 6 degrees of freedom (knee flexion/extension, external/internal rotation, adduction/abduction, anterior/posterior translation, compression/distraction, and medial/lateral shift) (Abulhasan & Grey, 2017; Zlotnicki et al., 2016).

Passive Contributions to Knee Joint Stability

The passive stabilizers of the knee joint include the cruciate and collateral ligaments. Both the ACL and PCL provide guidance and restraint of the anteroposterior movement of the tibia relative to the femur when the knee is in a flexed position(Butler et al., 1980; Dargel J., 2007). When the knee is in a flexed between 30°- 90° the ACL provides more than 80% of anterior tibial restraint (Butler et al., 1980; Ellison & Berg, 1985; Markolf et al., 1984). It is not until the knee exceeds 90° of flexion that secondary stabilizers (medial joint capsule, iliotibial band, MCL and LCL) contribute to the anteroposterior stability (Butler et al., 1980; Ellison &

Berg, 1985; Markolf et al., 1984). Markolf et al. (1984) also reported that anterior tibial translation (ATT) relative to the femur was greatest between 20° and 45°of knee flexion. Moreover, least strain on the ACL occurs between 20° and 30° of knee flexion (Abulhasan & Grey, 2017). The ACL in tandem with the MCL also contributes to rotational stabilization by controlling internal axial rotation of the tibia relative to the femur (Moewis et al., 2016; Zantop et al., 2007). The MCL works in tandem with the ACL to control for this internal rotation. When medial and lateral stability of the knee is needed to control valgus and varus motion, the MCL and LCL, respectively, are the primary contributors (Zantop et al., 2007).

Dynamic Contributions to Knee Joint Stability

The dynamic stabilizers of the knee joint work in concert with the passive stabilizers during active movement (Zlotnicki et al., 2016) in effort to maintain joint congruency. The dynamic stabilizers are the muscles that cross the tibiofemoral joint. The primary function of these muscles is to produce and control movement within the 6 degrees of freedom (Abulhasan & Grey, 2017; Zlotnicki et al., 2016). The quadriceps (rectus femoris, vastus lateralis, vastus medialis and vastus intermedius) are the primary knee extensors and provide additional stabilizing support on the anterior aspect of the knee. The hamstrings (biceps femoris, semimembranosus and semitendinosus) function as the primary flexors of the lower extremity at the knee joint while providing stability to the posterior side of the knee in conjunction with the musculature of the distal portion of the leg. This includes the plantaris muscle and medial and lateral heads of the gastrocnemius which helps restrict anterior translation of the knee (Abulhasan & Grey, 2017; Zlotnicki et al., 2016). Additionally, the biceps femoris and semimembranosus aid in lateral knee rotation while the semitendinosus aids in medial rotation (Abulhasan & Grey, 2017; Zlotnicki et al., 2016).

The extensors and flexors of the knee joint provide opposing forces on the primary passive stabilizing ligaments. Thus, the strength of these muscles as well as stiffness can play an instrumental role in keeping the knee stable (Abulhasan & Grey, 2017; Zlotnicki et al., 2016). The hamstrings act as an agonist of the ACL thru stabilization of the tibia relative to the femur during the anterior translation (Li et al., 1999). During the contraction of the knee flexors the antagonist muscles, the quadriceps, demonstrate a concurrent low co-activation while lengthened to aid in regulation of joint stability (Baratta et al., 1988). The co-activation is important in maintaining joint stability as the antagonist inhibits excessive posterior forces on the tibia from the agonist. Together they also increase joint compression which increases joint congruency and knee stability (Baratta et al., 1988).

Potential Effects of Knee Laxity on Joint Stability

The ACL plays an integral role in both active and passive joint stability. Passive contributions are linked to ACL size (cross-sectional area, width and volume) (Grood et al., 1992; Nordin & Frankel, 2001; Wang et al., 2020; Wang et al., 2021; Wang et al., 2016). Increased cross-sectional area of the ACL and thus, the width, have been associated with less deformation at fixed loads (Grood et al., 1992; Nordin & Frankel, 2001; Wang et al., 2016). Wang and colleagues (2021)also established an inverse relationship between ACL volume and AKL using ACL contouring from sagittal slices from Magnetic Resonance Imaging (MRI). Collectively, research has established that a decrease in ACL size is indicative of an increase in AKL (Grood et al., 1992; Nordin & Frankel, 2001; Wang et al., 2020; Wang et al., 2021; Wang et al., 2016). The ACL also actively contributes to knee joint stability via sensory organs communicating information about joint position and joint movement back to the dynamic stabilizers as well as central nervous system (CNS) (Zimny & Wink, 1991). The following

section will detail the innervation of structures in and about the knee joint and these pathways of communication.

Sensory Structures of the Knee Joint

With high knee laxity being a risk factor for ACL injuries it is critical to look beyond the biomechanical nature of laxity and understand the role of connective tissues on neuromuscular function of the knee joint. Sensory organs, known as mechanoreceptors (Ruffini ends, and Pacinian corpuscles, free nerve endings, muscle spindles and Golgi tendon organs), of the knee joint are located within the muscles, tendons, joint capsules, and ligaments (Johansson, 1991; Johansson et al., 1991). These mechanosensory neurons enable communication about the body's awareness of position and movement between the knee joint and the CNS through neuromuscular control. These structures are present in both contractile and non-contractile tissues.

Sensory Structures of Skeletal Muscles

The communication between the sensory organs and motor units is instrumental in the reflexive pathways of the neuromuscular system. The best way to describe the sensory structures of the knee joint is to begin externally on the outside of the knee joint and move internally to the inside of the joint. The external components of the knee joint consist of the dynamic stabilizers (skeletal muscle and tendons). Muscle spindles are sensory organs that are composed of 6-8 specialized muscle fibers (nuclear chain fibers, static nuclear fibers, and dynamic nuclear fibers) that can be found deep in the skeletal muscle belly and are the primary sensory organs located in the muscle (Banks, 1994; Kröger & Watkins, 2021). These intrafusal muscle fibers get their name from their fusiform shape. The nuclei are arranged in a single row in the nuclear chain fibers and signal information about static length. The static nuclear fibers also signal information

about static length however they are a bundle of nuclei located in the middle of the fiber. Dynamic nuclear fibers are anatomically similar to static nuclear fibers however their primary role is to signal about the rate of change of the length of the muscle (Banks, 1994; Kröger & Watkins, 2021). Group Ia afferents (primary afferents) innervate all 3 types of intrafusal fibers and provide information about both muscle length and velocity. Group II afferents (secondary afferents) only innervate the ends of the nuclear chain fibers and static nuclear fibers meaning that the secondary afferents only provide information about the muscle length. While alpha motor neurons innervate extrafusal muscle fibers and cause a strong contraction, gamma motor neurons innervate the muscle spindle and have a small magnitude of contractile properties (Banks, 1994). This alpha-gamma coactivation allows for the gamma motor neuron to reduce any slack in the muscle spindle which allows it to maintain sensitivity to the various lengths of the extrafusal fiber (Manuel & Zytnicki, 2011). This type of coactivation is important for knee joint integrity and stability. In general, the role of the muscle spindle is to sense muscle length and velocity as well as play a significant part in reflex control and regulation of intrinsic muscular stiffness (Kandel et al., 1991).

Joint stability is also made possible by sensory organs embedded in the tendons of the skeletal muscle which are called Golgi tendon organs (GTOs). GTOs are considered contraction-sensitive mechanoreceptors that monitor gradations in muscle tension and movement. GTOs are innervated by fast conducting Ib afferent fibers which are attached to the tendon organ by collagen fibers. They are more sensitive to tension or load that is created by concentric activation compared to passive stretching or eccentric activation (Nyland et al., 1994). When a muscle contracts, the GTO stretches and straightens out the collagen fibers. This mechanical stimulation of the tendon organ elongates and compresses the afferent axon. The deformation of the afferent

axon triggers excitation of the GTO (Solomonow & Krogsgaard, 2001). These sensory signals are used for various contractile motor movements and create a preventative measure against joint injury which inhibits the muscle from generating force if muscle tension is too high.

Sensory Structures of the Joint Capsule and Ligaments

Deeper into the knee joint lies the internal passive structures that provide static stability. There are 4 primary types of mechanoreceptors (Ruffini, Pacinian, Golgi tendon-like organs and free nerve endings) that innervate the joint capsule and encapsulated ligaments (Nyland et al., 1994). The joint capsule and connective tissue contain Ruffini mechanoreceptors which have a low threshold, adapt slowly to changes in static joint position, intra-articular pressure changes and joint kinematics, and contribute to the preservation of muscle tone (Zimny & Wink, 1991). These mechanoreceptors fire continuously at various rates in response to different ligamentous or capsular tension. Pacinian mechanoreceptors are present in the joint capsule and ligaments. They also have a low threshold but adapt rapidly to changes in dynamic joint position. The firing of the Pacinian receptors is not continuous. However, they are considered to be the most sensitive type of sensory organ in the ACL during ligamentous tension changes and acceleration at both initiation and termination of movement (Nyland et al., 1994; Zimny & Wink, 1991). Golgi tendon-like organs are located predominantly in the collateral and cruciate ligaments near the insertion sites (Johansson, 1991; Johansson et al., 1991; Nyland et al., 1994; Zimny & Wink, 1991). They tend to discharge at extreme ranges of motions such as motions that could cause joint injury and provide agonistic muscular inhibition. Free nerve ending receptors are located in the fibrous joint capsule and transmit information about pain and inflammation to the brain which can be both mechanically and chemically activated (Gilman, 2002; Johansson, 1991;

Johansson et al., 1991; Nyland et al., 1994; Riemann & Lephart, 2002; Solomonow & Krogsgaard, 2001; Zimny & Wink, 1991).

Afferent Pathways During Passive Joint Loading

Deformation of mechanoreceptors occurs when the knee joint is mechanically loaded. When the membranes of these sensory receptors are deformed by mechanical stimulation, mechanically gated ion channels are opened which allow for the release of Na+ and K+ ions. The influx of these ions creates a receptor potential that is transformed into an action potential by voltage-gated ion channels (French & Torkkeli, 2009).

Spinal Pathways

The receptor generated action potential has encoded information about limb position sense and tension. The information then propagates through the peripheral afferent neurons (Ib) to the dorsal root ganglion. From here the action potential reaches the axon collateral where the neuron bifurcates which forms a polysynaptic reflex onto excitatory and inhibitory interneurons in gray matter on the ipsilateral side of the spinal cord (Johns, 2014). This action potential then sends a signal to contract the agnostic muscle and relax the antagonistic muscle (Johns, 2014)This reciprocal excitation in the autogenic inhibition reflex helps the dynamic stabilizers of the knee joint to work in synchrony in effort to stabilize the knee joint (Johns, 2014). The role of these signals in supraspinal level contributions to knee stability will be discussed below.

Supraspinal Pathways

In additional to spinal level activity, the receptor generated action potential is also propagated to the lateral dorsal column in the spinal cord (Gilman, 2002). This afferent neuron then synapses onto the first order afferent neuron which ascends the action potential up the spinal cord via the dorsal column-medial lemniscal pathway or spinocerebellar tracts (Riemann &

Lephart, 2002). The dorsal column-medial lemniscal pathway is the sensory pathway of the nervous system that conveys information about touch, vibration, and proprioception to the somatosensory cortex (Gilman, 2002). The first order afferent neuron then decussates in the medulla oblongata where it synapses onto the second order afferent neuron. The signal then travels up the medial lemniscus pathway through the brainstem to the thalamus where it synapses on the tertiary afferent neuron (Riemann & Lephart, 2002). This brings the action potential to the contralateral somatosensory cortex of the joint that was loaded.

Sensory Pathways in Pathological and Non-Pathological Laxity Knees

During ATT the Golgi tendon-like organs and Pacinian receptors are the primary sensory organs in the ACL that sense tension in the ligament (Nyland et al., 1994). During a study that investigated the relationship between ligamentous laxity and tension, Yasuda et al. (1997) compared ACL reconstructed (ACLR) graft types based on tension applied to the graft during a surgical procedure. The authors reported that 2 years after the surgical procedure individuals with lower graft tension had increased AKL compared to those who had higher graft tension during the procedure. This study suggests that the lesser tension in the ACL may be related to greater AKL. Since the role of the mechanoreceptors in the ACL is to sense tension when the tibia is anteriorly translating under a fixed load, the mechanoreceptors may not be stimulated as easily in an individual with decreased ligamentous tension (Yasuda et al., 1997).

An extensive amount of literature (Ekholm et al., 1960; Freeman M. A. R., 1967; Johansson et al., 1991; Sjölander et al., 1994) suggests that mechanoreceptors in joint capsules and ligaments contribute to dynamic joint stability and muscle stiffness via the gamma reflex loop. Johansson et al., (1986) used electrical stimulation to activate sensory organs in the posterior articular nerve of cat which elicited a response from flexor and knee extensors via

gamma-motoneuron reflex. In another cat study, Johansson et al., (1991) found that after securing the feline's femur and tibia to ensure there was no boney motion at the knee, stimulation of the ACL could also elicit a reciprocal excitatory and autogenic inhibition reflex response of the knee flexors and extensors, respectively. A reflex arc between the ACL mechanoreceptors and sensory receptors in the thigh muscles work synergistically to create stabilization in and around the knee (Tsuda et al., 2001). This reflex arc was demonstrated in humans by using electromyography (EMG) to measure muscle activity induced by direct stress via wire electrodes placed on the ACL using an arthroscopic technique in healthy controls. Under normal knee conditions this direct stress provoked moderate quadricep inhibition while exciting the hamstrings, whereas after intraarticular anesthesia there was no change in activation during stimulation (Tsuda et a., 2001). The reciprocal inhibition exhibited under normal knee conditions indicates that the Ruffini receptors in the joint capsule and the Golgi tendon-like organs as well as the Pacinian receptors in the ACL have an established neural pathway in relation to the muscle spindles and Golgi tendon organs during ACL stimulation (Solomonow et al., 1987; Tsuda et al., 2001). Solomonow and colleagues (1987) compared healthy controls to ACL deficient (ACLD) participants. The ACLD group demonstrated similar quadricep/hamstring activation as described by the reflex arc despite a possible decrease in sensory input from the ACL due to injury. However, the reflex arc that was found in the ACLD group demonstrated a lack of spindle excitatory regulators which increased latency of the action potential suggesting that the injury induced a secondary afferent pathway. These findings suggest that in the Tsuda (2001) study no acute neural adaptation was present in the anesthetic knee because no injury had occurred which would warrant the creation of a secondary afferent pathway or neuroplasticity.

Wojtys and Huston's (1994) research indicates that the above stated theory of neuroplasticity, neural adaptations occur due to [ACL] injury, could be correct. In a cross-sectional study, during a load bearing task the tibia was passively anteriorly translated by directing a 30-pound step force to the posterior aspect of the leg while electromyographic (EMG) sensors were donned on the load bearing limb in five locations to measure lower extremity functions in the ACLD groups that were considered acute (injury < 6 months) semi-acute (6 – 18 months) and chronic (injury > 18 months) and the control groups. The ACLD acute group displayed what was reported as relatively normal muscle activation (55% quadriceps; 30% hamstring; strength average by body weight - torque foot (lbs)/body weight (lbs)). As time of post injury increased to 6 months or more there was a decrease in quadricep activation and an increase in hamstring activation (65% hamstring; 20% quadriceps). Spinal cord and cortical level neural responses to ATT were slower in ACLD individuals, suggesting that with time a secondary pathway, possibly between the receptors in the joint capsule, muscle spindles and Golgi tendon organs, was established. Therefore, it can be speculated that functional neuroplasticity can take upwards to 6 months or more to rewire the sensorimotor network after an ACL injury.

Unlike ACLD individuals who demonstrate evidence of functional neuroplasticity greater than 6 months post injury, there is not a time component related to the onset of functional neuroplasticity for individuals that have greater amounts of AKL in a healthy/native knee. Shultz et al (2004) had comparable muscular activation results, as well, with non-pathological high AKL individuals during a similar weight bearing task as Wojtys and Huston (1994). These findings could imply that high laxity individuals may have an established secondary afferent pathway compared to healthy controls as indicated by the ACLD group.

Neuromuscular Control and Joint Laxity

Neuromuscular control is the body's ability to produce controlled movement in response to and in conjunction with communication from the peripheral sensory organs to the central nervous system. This communication allows for coordinated muscle activation due to the efferent response to the afferent input from the somatosensory system known as feedforward and feedback motor control. The following paragraphs will discuss neuromuscular control in more detail and its effects on joint laxity.

Neuromuscular Control

In general, feedforward components are developed over time from neural coding of system dynamics provided by previous sensory information (Soso and Fetz 1980). These types of mechanisms are controlled from a top-down hierarchy of the CNS that prepare the muscles for movement and joint loading (Kawato et al., 1987; Stroeve, 1997). Whereas feedback components are in direct response to sensory information. More specifically, mechanoreceptors sense limb position and movement, tension and force, as well as effort during active/passive and static/dynamic motion in all three planes (Gritsenko et al., 2007; Kawato et al., 1987; Proske & Gandevia, 2012; Stroeve, 1997). These feedback mechanisms supply reflex pathways from joint afferents to gamma motor neurons in musculotendinous units at the spinal cord level and supply various afferent neuronal pathways at the cortical level (Wojtys & Huston, 1994). The communication between the feedback and feedforward mechanisms allows the neuromuscular control system to quickly adapt to change and react to error (Kawato et al., 1987) to keep the knee joint safe.

Laxity Effects on Neuromuscular Control

Neuromuscular control has been evaluated in non-pathological high laxity and low laxity or healthy individuals. Shultz et al (2004) compared the muscle activation patterns prior to and following lower extremity perturbation in 42 healthy NCAA D1 intercollegiate female basketball players stratified into high anterior knee laxity (>7mm) and low anterior knee laxity (<5mm) groups. Participants were affixed with electromyography (EMG) surface electrodes on the muscles surrounding the knee joint. A custom-built lower extremity perturbation device was developed to produce an internal or external rotation of the trunk while the participant was strapped in the device, standing on their dominant leg with their knee at ~30 degrees flexion. Muscle activation was taken 50ms before perturbation and 150ms immediately post perturbation. This study found that the high laxity group demonstrating increased levels in muscle pre-activity as well as a delay in reflex timing with the greatest delay in activation of the biceps femoris (16ms) and a similar group difference was found in the medial hamstring (15ms). No differences were found between internal and external trunk rotation. These results suggest that increased pre-activation of the muscles are a compensatory strategy to aid in joint stabilization and the increased latency in activation suggests a proprioceptive deficit. Keizer et al. (2020) also investigated the effects of knee laxity in relation to knee flexion and muscle control for limiting ATT during landing in 21 healthy participants [males and females]. Passive ATT was assessed using a KT – 1000 arthrometer which measured the displacement of the tibia relative to the femur. Dynamic ATT and muscle activation were observed during a single leg landing using surface EMG and 3D motion capture. During 10 repetitions of a single leg hop for distance the higher laxity individuals exhibited less knee flexion, smaller dynamic ATT, and less knee flexor muscle activation when landing compared to lower laxity or lower passive ATT individuals

insinuating that this type of landing mechanism may be how healthy, high laxity individuals compensate to control their landings. While this type of dynamic loading of the tibia may be seen as an alternative control mechanism to landing for healthy higher lax individuals, this type of decrease in joint angle and muscle activation has been observed to increase strain on the ACL and increase risk of injury (Favre et al., 2016; Stettler et al., 2018) The landing strategy demonstrated by the high laxity individuals could be consequences of diminished sensory outputs from the knee flexors to the CNS.

Implications for Noncontact ACL Injury Mechanisms

Noncontact ACL injuries account for roughly 70% of ACL injuries (Boden et al., 2000). Noncontact sports such as soccer, handball, volleyball, and basketball involve maneuvers that can put excess stress on the ACL. These ACL injury mechanisms consist of rapid deceleration, plant and cut maneuvers, and landing/stopping on a single foot. During these types of fast pace athletic movements, the knee joint maybe compromised when the tibia is externally or internally rotated (5° - 15°) and the limb is close to fully extended and even hyperextended at the knee (5° - 25°) in an excessive knee valgus position (5° - 20°) (Boden et al., 2000; Krosshaug and Boden 2007). The combination of this potentially catastrophic motion is referred to as “the point of no return” (Ireland, 1999). In the frontal plane, it constrains the medial compartment of the knee joint causing the ligaments to become taut. Whereas the lateral compartment ligaments are loose causing the tibial plateau to shift anteriorly, in the sagittal plane, and externally or internally, in the transverse plane, putting increased strain on the (Boden et al., 2000; Boden et al., 2010; Ireland, 1999). The combination of the stressed ACL and compensatory contributions, or lack of contributions of the musculoskeletal tissues in and around the knee joint can be detrimental to ACL health.

Others have reported similar maneuvers at the time of ACL injury. Fifty-two National Championship level volleyball players (10 males, 42 females) who suffered non-contact ACL injuries during sport self-reported combinations of plant and cut, rapid deceleration and single foot landing and stopping maneuvers at the time of injury during a 10-year time span that possible led to the injuries (Ferretti et al., 1992). Additionally, Olsen and colleagues (Olsen et al., 2004) performed a systematic video analysis of 20 competitive handball players sustaining an ACL injury and compared these videos to the results of interviews from 32 additional handball athletes who injured their ACL during sport in a single season. There results suggest that a forceful valgus collapse with the knee close to full extension combined with external or internal rotation of the tibia leads to ACL injury during maneuvers, like the ones mentioned above. The "point of no return" could be a consequence of these movement patterns putting strain on the ACL, more so in high laxity individuals, which could have possibly caused from a delay in afferent signaling due to a secondary afferent pathway from the PNS to the CNS (Shultz, Carcia, et al., 2004; Solomonow et al., 1987; Wojtys & Huston, 1994).

Plausible Theories of Sensory Role in ACL Injury

The decrease in resistance of the tissue is thought to decrease the stability of the joint (Needle et al., 2014). Thus, an individual with greater AKL may exhibit this decrease in resistance to loading the ACL may result in the sensory mechanisms may not sufficiently signaling joint motion and joint position sense when the tibia is anteriorly translated. Communication from the ACL sensory organs are transmitted to the dynamic stabilizers via interneurons at the spinal and supraspinal level (Ochi et al., 2002; Shultz, Carcia, et al., 2004; Wojtys & Huston, 1994). The diminished sensory information could therefore influence the dynamic stability of the knee joint by not transmitting adequate kinesthetic information to the

spinal cord and brain to dynamically activate the musculature. This decrease in sensory signaling may cause a lack of voluntary and involuntary action on the muscles which could cause a negative influence on functional stability of the knee joint and cause the joint to move beyond normal range of motion (Matsuo et al., 2020; Tropp, 2002).

The strength of the reflex arc between afferent and motor neurons that is responsible for ligament to muscle communication of the knee joint at the spinal level is also influenced by top-down efferent signals which could cause disruption from efferent outputs of the motor cortex onto the interneurons (Baars & Gage, 2010). Knee joint mechanoreceptors could be negatively influenced by the efferent signals projecting down the spinal cord onto the reflex arc thus leading to possible functional instability and excessive range of motion. Collectively, miscommunication from the mechanoreceptors in the ACL whether it is from feedback or feedforward control could lead to neuromuscular error and consequently increase the risk of knee injuries (Baars & Gage, 2010; Mouton et al., 2016).

Methods of CNS Function Assessment

In order to investigate the afferent signal from peripheral level at the knee joint to the supraspinal level at the somatosensory cortex, a general understanding of the techniques use to measure these signals is warranted. The following section will focus on the neuroimaging techniques used in research to measure somatosensory cortical activity.

Neuroimaging Techniques

Various non-invasive neuroimaging techniques can be used to measure the human brain structure and perceived neuronal activity (Morita et al., 2016). There are two primary techniques used in research and clinical settings. The first technique provides information about the brain's metabolism through hemodynamic effects such as the blood oxygen level dependency (BOLD)

signal via functional magnetic resonance imaging (fMRI) (Logothetis, 2002) and positron emission tomography (PET) (Morita et al., 2016). The second technique provides information about electrical conduction and magnetic activity which can be measured from the scalp using instruments such as electroencephalography (EEG), magnetoencephalography (MEG), and transcranial magnetic stimulus (TMS) (Rossini & Pauri, 2000). This study will utilize EEG to measure electrical activity from the scalp thus the continuation of this literature review will focus on the measurement aspects of EEG.

Electroencephalography (EEG)

EEG is a neuroimaging tool to indirectly measure neuronal activity of the human brain from the scalp. This measurement is obtained from electrodes that are attached to a cap and placed on the surface of the scalp. The electrodes measure the electrical activity related to the post-synaptic potentials that arise from the pyramidal cells of the cortex (Biasiucci et al., 2019). The electrical signals form brainwaves are of varying frequencies. The frequencies of the obtained electrical signals measured through the EEG electrodes are referred to as frequency bands (Kumar & Bhuvaneswar, 2012).

EEG is often used in clinical settings to determine changes in brain activity relative to brain disorder or disease. Some of the advantages to using EEG are that it is cost-effective, non-invasive and has high temporal resolution. Whereas a limitation is the poor spatial resolution which makes it difficult to identify the areas of the brain that are generating the neuronal activity.

Frequency Bands

Frequency bands can be characterized as a fixed range of wave frequencies and amplitudes over a time scale (Kumar & Bhuvaneswar, 2012). As the amplitude of the brain waves increases the frequency decreases. There are four frequency bands that are commonly

utilized in human research: Beta (14-30 Hz), Alpha (8-13 Hz), Theta (4-7 Hz), and Delta (1-3 Hz) (Kumar & Bhuvaneswar, 2012). Each of these frequency bands have been identified as specific neural oscillations and has been related to specific human behaviors (Kumar & Bhuvaneswar, 2012). This study will focus on the alpha frequency band because it is inversely related to cortical activity.

Alpha Frequency Band

The alpha frequency band or rhythm is one of the most prominent frequency bands in the adult brain (Klimesch, 2012). The alpha rhythm can be identified by its frequency, spatial topography, behavioral correlates, and reactivity to stimuli (Pfurtscheller, 1991). Sensory stimulation and movement as well as working memory, attention and mental tasks are known to suppress alpha (Deiber et al., 2012). Research has demonstrated that the alpha frequency represents the inverse of cortical activity (Murta et al., 2015). There are two regions from where alpha is thought to originate. They are typically found over the lateral and posterior portions (occipital and parietal lobes) of the scalp when measured with EEG. However, a specific alpha frequency, known as the mu-alpha rhythm (10-12Hz), is often related to task-specific aspects and topographically restricted, being thought to arise from the somatosensory cortex of the human brain (Lemm et al., 2009). This rhythm is generated from the thalami-cortical system (Halgreen et al., 2019). It is typically observed from the scalp over the central and central-parietal region in humans. The mu-alpha frequency is fully present in healthy individuals when they are mentally inactive yet alert with eyes open. This is due to its association with somatosensory information and not visual information processed in the occipital lobe (Halgreen et al., 2019). The mu-alpha waves are sensitive to inhibiting signals and sensory-to-motor feedback due to the basal ganglia and sensorimotor function (Jenson et al., 2020). However, due to alpha frequencies varying from

person to person (Bazanova, 2011), measuring alpha across the entire frequency range (8-13Hz) while eyes are open will be most likely to suppress alpha related to the visual cortices while capturing all frequencies of interest.

Neural Correlates of Proprioception and Kinesthesia

The brain's perception of how the body senses its movement, action and location is known as proprioception. The afferent information that is transmitted through signals at the knee joint to the somatosensory cortex is kinesthesia (Reed & Ziat, 2018). The following information will discuss how loading and movement affects cortical activation in somatosensory cortex in both animal and human models.

Neural Correlates of Active and Passive Movement in Primates

Rhesus macaques are the most common nonhuman primate in biomedical research. They are utilized in much of the cognitive function research due to their long lifespans and ability to learn memory tasks compared to rodents (Stonebarger et al., 2021). Through surgically implanted microelectrodes into select sensory cortical neurons, various primate studies have established that neurons fire differently or inhibit firing during passive and active movements (London & Miller, 2013; Mountcastle & Powell, 1959; Soso & Fetz, 1980). Soso and Fetz (1980) trained awake rhesus macaques to alternately flex and extend their left elbow joint while wearing a cast on their forearm that restricted range of motion (between 45° and 100°). The cast was form-fitting and hinged with a potentiometer monitoring joint position. The monkeys were also trained to relax during passive motion and cutaneous manipulation. EMG was used to quantifiably detect muscle activation. Passive movement was recorded only if EMG was silent. During evaluation of response patterns during active movement deep cells, referring to joint and surrounding afferents, were activated by phasic movements in one direction and were inhibited

or unresponsive in the other direction. During passive movement, deep cells responded in either the opposite or the same direction as active movement.

Conversely, cutaneous cells were activated during both flexion and extension for both active and passive movement. For relative timing of postcentral cells and movement there was a difference in latency. Change in the somatosensory cell activity began, on average 61.4 ±17.8ms before onset of agonist muscles during active movement. Whereas passive movement usually evoked activity within the first 20ms after movement onset. Interestingly, active elbow movements exhibited reduced phasic response compared to passive movements. Previously encoded sensory information and central modulation input during active movement may contributed the differences in active and passive movement (Soso & Fetz, 1980). These findings are similar to Landon and Miller's (2013) results suggesting that sensory information via active movement may be modified by the motor system projecting its own previously encoded commands to the sensory system. This is known as efference copy. This efference copy information evokes activity, known as corollary discharge, when it reaches sensory areas (Crapse & Sommer, 2008). Thusly, passive movement may not induce activity from the motor system which potentially could inhibit neural activity that provides identical information movement information (London & Miller, 2013). Therefore, passive movement could elicit increased neural excitation from the sensory area compared to active movement.

Role of Increased Pathological and Non-Pathological Laxity on CNS Activity.

As previously discussed, the ACL has mechanoreceptors that enable it to potentially play a role in neuromuscular control. This section will focus on the previous work associating CNS activity to varying degrees of laxity.

Park-Brasswell and colleagues (2020) measured the hemodynamic response in the brain via functional magnetic resonance imaging (fMRI) during passive ATT in healthy high and low knee laxity individuals. The participants laid supine on the MR table with their left knee strapped to an MR safe anterior tibial translating device (Park-Brasswell et al., 2021) while intermittent anterior tibial loading was performed using a block design. No differences were found in cortical activation of the contralateral somatosensory cortex. However, there was a decrease in the blood oxygen level dependency (BOLD) signal in both left and right premotor cortices of the high laxity group compared to the low laxity group. These findings suggest that the CNS of healthy individuals with high laxity may interpret afferent signals during knee joint loading differently in preplanning and programming of movement compared to low laxity individuals.

While we have only been able to locate a single fMRI study to date that evaluates AKL and its effects on brain activity, there are several EEG studies that have explored the relationship between joint integrity/laxity and somatosensory cortical activation. During arthroscopic electrical and mechanical stimulation of the ACL, Ochi and colleagues (2002) used an electrical stimulation probe that sent an electric signal directly to the mechanoreceptors in the ACL and a mechanical stimulation probe that physically put tension on the ACL to produce somatosensory evoked potentials (SEP) measured by EEG. The authors compared the SEPs in 3 groups of participants; control (normal ACL), injured (ACL intact but not reconstructed) and ACLR. They reported that they were able to detect reproducible SEPs 36 out of 38 ALCR participants. Whereas out of 45 individuals in the injured group, 19 were unable to consistently reproduce somatosensory evoked potentials (SEP) during both electrical and mechanical stimulation while 12 of the 45 were able to demonstrate SEPs under electrical stimulation but not mechanical. The group with nonreproducible SEPs also demonstrated higher AKL values compared to the

reproducible SEP group. The mean voltage, when SEPs were detected, in all the groups were not statically significant between groups. However, the ACLR group did have the lowest SEP value (mean SEP values: injured = 1.30; ACLR = 1.27; Control = 1.42). The lack of SEPs in the injured group could indicate that AKL could contribute to a decrease in somatosensory cortical activity. This decrease could be due to damage to the mechanoreceptors during injury and/or the decrease in the ligamentous tension which could affect the firing rates of the sensory organs in the ACL.

Likewise, a study of ankle joint instability looked at cortical activation relative to joint loading measuring the ERD of the mu-alpha (10-12Hz) band using EEG (Needle et al., 2014). This study compared ankle translation of three groups (controls, copers, and unstable ankles) to the ERD measures produced from somatosensory cortical activation. Ankle translations and joint laxity were assessed using an instrumented ankle arthrometer while obtaining EEG data. Each testing block consisted of 1 minute of rest, 10 posterior/anterior translations, a 5 second rest between translations and was repeated 5 times. While the unstable group exhibited significantly higher ankle joint laxity than the control group, no significant differences in the quantity of somatosensory activation were found between groups (Needle et al., 2014). Interestingly, cortical activation increased similarly in all 3 groups through both loading phases. This finding could be similar to the rhesus macaques. Similar cortical activation could potentially be due to the affect that passive joint loading has on the somatosensory cortex where there is no motor control information to compare to the passive movement (London & Miller, 2013; Soso & Fetz, 1980). Perhaps any differences in the 3 groups are not noticeable in the afferent pathway alone but could be at different points during feedforward and feedback control. Another theory for not seeing a significant difference in cortical activation during the anterior ankle translations could

be due to the number of times the ankle was manipulated. Fifty anterior translations of a previously injured ankle could cause the muscles around the ankle joint to involuntarily become stiff and guard (Hanlon et al., 2016) which would create more afferent inputs due to the muscle guarding manipulating the sensory organs.

A similar block test study was performed comparing ERD in healthy and ACLR participants. An et al (2019) investigated proprioceptive inputs during knee joint loading and its effects on cortical activation in ACLR patients compared to healthy controls using EEG. The authors reported results contrary to the ankle study discussed above. The ACLR participants displayed higher cortical activation of the somatosensory cortex during ATT of their previously injured limb. These results suggest that greater laxity in the ACLR patients is associated with cortical activation that might be caused by increased neural demands of the somatosensory cortex, indicating an existence of possible neural adaptation.

Summary

Greater AKL is one of the strongest independent predictors of ACL injuries that affect females (Mouton et al., 2016; Vacek et al., 2016; Woodford-Rogers et al., 1994). Knee stability is a construct of static and dynamic anatomic structures that comprise the knee joint and can be measured in 3 planes of motion. When these components are working synergistically the joint is stable. The ACL plays an important role in both the static and dynamic systems to maintain this stability. The ACL is the primary ligamentous (static) restraint to anterior tibial translation relative to the femur (Butler et al., 1980; Ellison & Berg, 1985; Nordin & Frankel, 2001). Whereas, in the dynamic system the ACL communicates via mechanoreceptors with the CNS by transmitting afferent information about joint position and sense as well as regulation of muscle coordination (Johansson, 1991; Johansson et al., 1991).

Many ACL injury prevention studies focus on the mechanical influences of increased AKL whereas much less is understood about how increased laxity affects afferent outputs from mechanoreceptors. Greater AKL has been reported to have an inverse relationship with proprioception. When compared to males, females exhibited higher measurements of AKL, increased joint motion detection, decreased joint position sense and greater EMG peak amplitude. (Barrack et al., 1983; Barrack et al., 1984; Rozzi et al., 1999). These alterations in proprioception may be explained by deafferentation of the mechanoreceptors and/or the reduced ligamentous tension of the ACL which would decrease mechanoreceptor deformation during anterior tibial joint loading. The decrease in the sensory organ deformation could also reduce the signal propagated through a secondary ACL-hamstring reflex arc ((Johansson et al., 1986; Solomonow et al., 1987; Tsuda et al., 2001) causing an alternate muscular activation pattern in the dynamic stabilizers around the knee joint (Shultz, Carcia, et al., 2004; Solomonow et al., 1987; Wojtys & Huston, 1994). The lack of sensory input could also influence a secondary afferent pathway to the brain (Ochi et al., 2002; Wojtys & Huston, 1994).

To gain a better understanding of the changes occurring in the brain caused by increased AKL neuroimaging is necessary. Evidence of altered cortical brain activation during ATT in high AKL individuals compared to low AKL individuals has been demonstrated during an fMRI task-based exercise (Park-Braswell, 2020). However, there is only one study to date that has measured cortical brain activity on healthy high laxity individuals. All other studies have focused on injured populations (An et al., 2019; Needle et al., 2014; Ochi et al., 2002). While measuring the hemodynamic response to ATT is helpful spatially, a temporal measurement of somatosensory cortical activation during different ACL loading phases is needed to better understand the influence of increased AKL on the different mechanoreceptors and how it may

impact sensory and motor pathways. Using EEG will allow for simultaneous measurements of the neurophysiological aspects of joint loading as well as the mechanical measures of the ACL during joint loading. Understanding these pathways in high laxity populations is the initial step in developing brain-based rehabilitation interventions to prevent ACL injuries.

CHAPTER III: METHODS

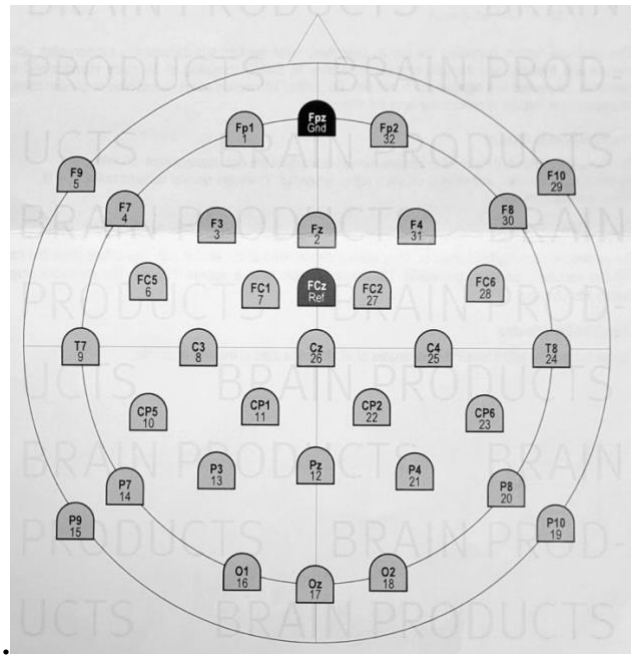
Participants

Twenty-eight recreationally active females were recruited from UNCG and surrounding areas with ages ranging from 18 to 29 years, right-handed and right-footed (dominant kicking limb). Exclusion criteria included lower extremity injuries within the past year and previous history of ACL injuries or injuries of other ligaments of the knee, as well as connective tissue disease or disorder, BMI > 30, and known neurological disorders. All participants were informed of the study process and signed a consent form approved by the Institution's Review Board for the Protection of Human Subjects. Data were collected over two separate laboratory visits.

Instrumentation

Cortical activation was measured at 500Hz using 32 Ag/AgCl electrodes (Fp1, Fz, F3, F7, F9, FC5, FC1, C3, T7, CP5, CP1, Pz, P3, P7, P9, O1, Oz, O2, P10, P8, CP2, CP6, T8, C4, Cz, FC2, FC6, F10, F8, F4, Fp2, FCz, FPz (Gnd)) using an international 10 – 20 system (Brain Products 32Ch Wet-Sponge R-net cap for LiveAmp; Brain Vision, Morrisville, NC). See Figure 1. Knee laxity for participant screening an group assignment was assessed using the KT2000 (Med Metric Corp, San Diego, California) The GMetric3D Knee Laxity arthrometer (Shultz et al., 2022) was used to apply anterior knee loading during EEG data collection. Specific to the arthrometer, load was assessed with an Interface WMC-100 load cell and displacement was assessed with an LRS-18 series of LVIT (Linear Variable Inductance Transducer) spring-loaded position sensor potentiometer. Force and displacement were collected simultaneously at 15Hz.

Figure 1. Electrode placement on scalp



Prescreening / Visit 1

During the 1st visit participants signed the informed consent form then underwent laxity measurement screening using the KT-2000 to determine laxity group. Anterior knee laxity was measured supine, with the knees flexed to 25° (± 5°) over a thigh bolster and recorded in millimeters (mm) as the amount of anterior displacement of the tibia relative to the femur while applying a 133 N anterior load to the posterior tibia (3 total repetitions). Both knee joints were measured to ensure no clinically significant differences (laxity difference > 3mm) in laxity between knees. The investigator has established between day measurement consistency and precision [ICC (SEM) =0.94 (0.62mm)]. To qualify for study inclusion, participants were divided into 2 groups determined by laxity measurements (low laxity group ≤ 5mm, high laxity group ≥ 7mm).

A total of 42 potential participants were screened, and 14 participants were initially excluded from this study during the recruitment process (1 due to BMI > 30; 1 experienced

anxiety during data collection; 3 did not return for 2nd visit; 9 due to their laxity value being between 5 mm – 7 mm). A total of 28 participants were included in this study.

Following enrollment, height, weight, and head circumference were recorded. While not a part of the immediate research question, questionnaires including Tegner Activity Level (Tegner & Lysholm, 1985), Marx Activity Scale (Marx, 2001), and the Tampa Scale of Kinesiophobia (Miller et al., 1991) were completed as secondary variables for future studies. General joint laxity was assessed using the Beighton score (Beighton et al., 1999). The participants were also familiarized to the GMetric3D arthrometer and data collection procedure (see full set up of arthrometer in Visit 2).

Visit 2

The second visit took place 3-5 days following the onset of the participant's menstrual cycle. Knee laxity was recorded again with the KT2000 using the same procedures as Visit 1 (see figure 2). A silicone EEG cap with 32 passive Ag/AgCl electrodes surrounded by sponges in a standard 10-20 arrangement (Brain Products GmbH, Germany) was prepared according to manufacturer instructions and then secured on the participant's head (see figure 3). The EEG cap was centered in the anterior-posterior and sagittal planes using the Cz electrode. Saline solution was added to sponges to reduce impedances below 50 kOhm in accordance with manufacturers recommendations. The participant laid supine on the exam table with their left leg placed in the GMetric3D. Their thigh rested in a thigh cradle which allowed for the knee to be flexed at 25° ± 5°. Bilateral clamps secured the thigh to limit femoral motion. Condylar clamps were placed on the femoral condyles to restrain the distal femur while a pad was placed on the anterior portion of the patella to provide a posteriorly directly force on the femur. A pressure sensor was placed on the patella pad to ensure equal resting patella load (70-75N) for all participants. A Velcro

strap connected to the load cell handle assembly was securely wrapped around the proximal shank. A potentiometer fixated to the patellar pad assembly was placed on the tibial tuberosity which was used to measure anterior tibial translation (mm) while the load cell measured the force (lbs) applied to the posterior aspect of the tibia. The leg was in neutral position (not externally or internally rotated) while the ankle was positioned at 90° in the footplate (see figure 4).

Figure 2. Participant positioned in KT2000

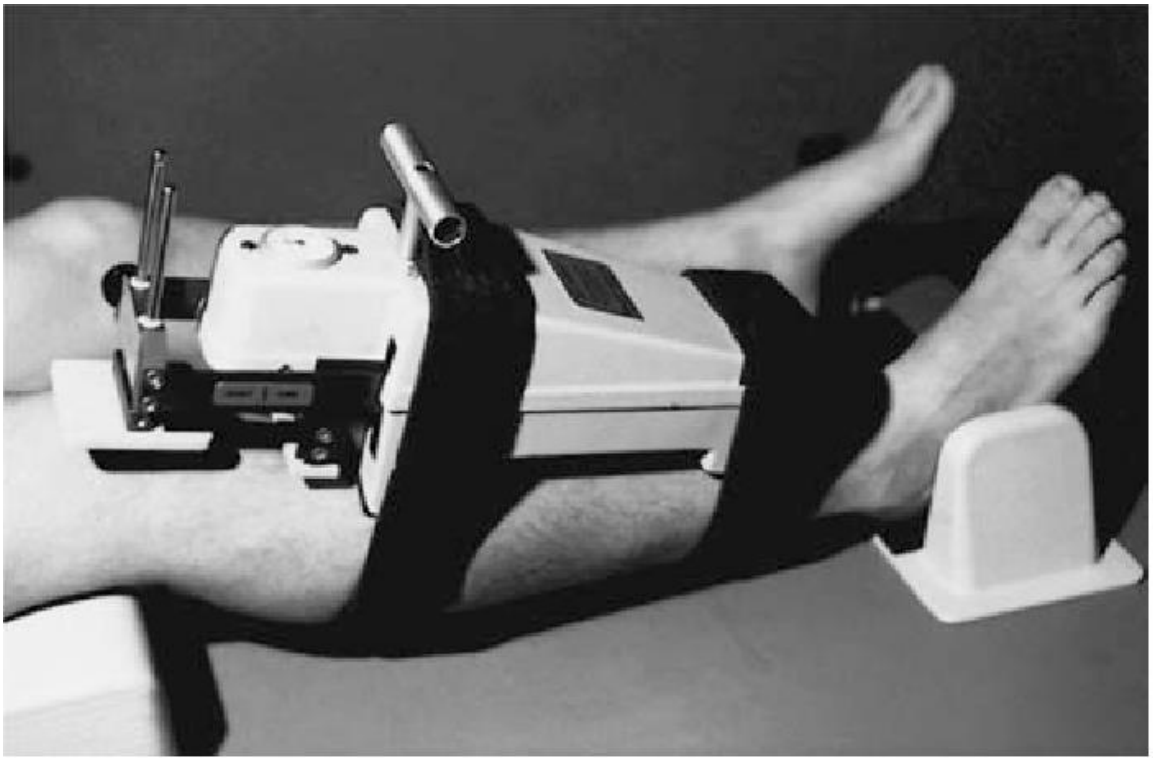


Figure 3. R-net saltwater-based electrode system

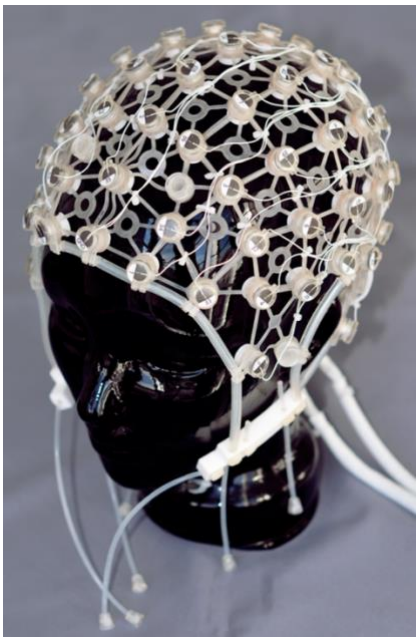
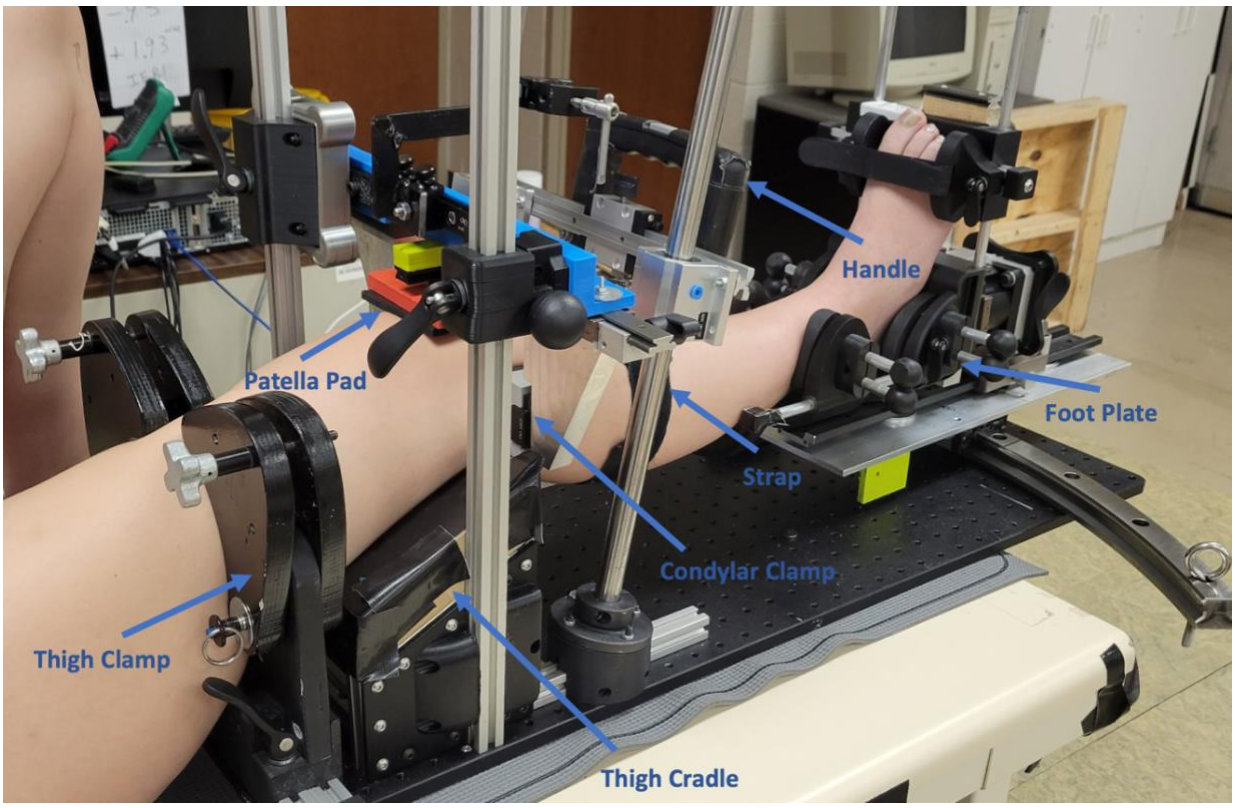
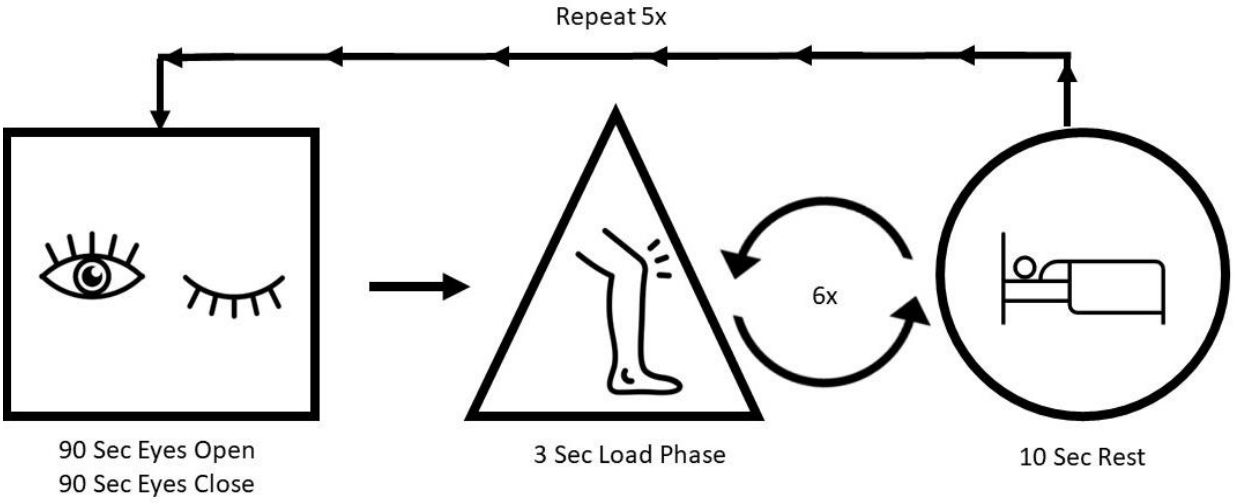


Figure 4. Participant in GMetric3D arthrometer



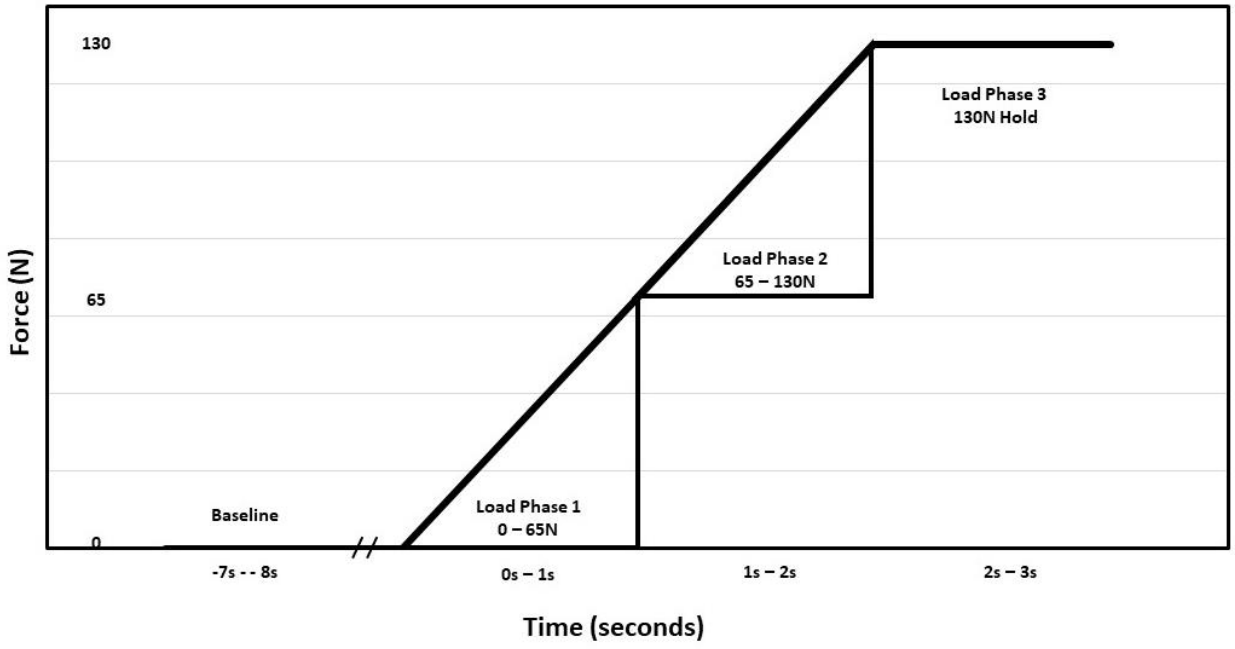
After positioning in the Gmetric3D EEG activity with intermittent anterior knee loading began. There were 5 blocks of ACL Loading with EEG data collection. Each block began in an unloaded condition in which there were 90 sec of an eyes open (EO) and 90 seconds eyes closed (EC) data collected. During the EO phase the participant was instructed to fixate their eye gaze on a cat poster on the ceiling to reduce eye movement. During the EC phase the participant was instructed to stay awake, relax, clear their mind, and stay as still as possible. After the EC rest participants were instructed to open their eyes. The loading phase of the block then commenced. This included six applications of an anteriorly directed force of 130N. Each load application was manually applied by a single investigator. The load application (See Figure 5) was designed to take 2 seconds to reach 130N with a sustained hold at 130 N for an additional 1 second followed by a 10 second unloaded rest condition. This load application was then repeated for a total of 6 repetitions within each testing block. The first block served as a conditioning block. The last 4 blocks were testing blocks used for data collection (see figure 5).

Figure 5. Testing block procedure for 2nd visit



Each loading trial was stratified into 3 load phases to measure joint displacement during cortical activation. Load phase 1 (LP1) was from 0-65N of the anterior pull cycle, load phase 2 (LP2) was from 65-130N and load phase 3 (LP3) was a 1 sec hold at 130N. A metronome as well as numerical visualization of load was used to keep time and force consistent as possible during manual loading. Neurophysiological data from the 10 sec rest intervals between translations (specifically 7,000ms - 8,000ms) were used as the rest trials. See figure 6.

Figure 6. Testing procedure for each load trial



Data Preprocessing

All EEG/loading data from blocks 2 though 5 with trials 2 through 5 were included. GMetric3D anterior Laxity values were calculated for load phase 2 and load phase 3. All Gmetric3D laxity data were processed using Excel (Microsoft Excel for Mac v. 16.7, 2023) Laxity was averaged for each load phase across trials 2-5 and then across blocks 2-5 per subject.

Block 1 was treated as a conditioning/familiarization block and loading trial 1 was treated as a conditioning/familiarization load.

EEG

Raw data were imported into Matlab for preprocessing (R2020b, Natick, Massachusetts: The MathWorks Inc.) using functions implemented in EEGlab (Delorme & Makeig, 2004), Fieldtrip (Oostenveld et al., 2011) and publicly available wrappers (https://github.com/BeMoBIL/bemobil-pipeline). Data were filtered between 1 and 50 Hz (*pop_eegfiltnew*). The data were subjected to independent component analysis (ICA) using an Adaptive Mixture ICA (AMICA; (Gorjan et al., 2022; Palmer et al., 2012)) (*runamica15)* and non-brain components were removed (median =30% of components; range = 8% - 56% of components) using ICLabel (Pion-Tonachini, 2019). Noisy segments were corrected using artifact subspace reconstruction (ASR; (Plechawska-Wojcik et al., 2019) with default setting and channels that were poorly correlated ($r<0.8$) with their robust prediction using neighboring channels were removed and subsequently interpolated using a spherical spline (*clean_rawdata*). A second ICA (with rank reduced to match the number of 'good' channels) was performed and non-brain artifacts were again removed (median = 27% of components; range = 7%-52% of components). Channel-wise data was re-referenced to the common average as a way to account for the effects of volume conduction (Hu et al., 2018). A series of multitapers was used to compute and visualize event-related changes by calculating time-frequency representations (TFRs) of power (Thomson, 1982). Power spectral density (PSD) was computed as the average power in the alpha frequency band (8-13 Hz) from the C4 electrode over 1000ms epochs representing the rest phase and each of the three load phases. Less than 2% of trials were interpolated at the C4 electrode. PSD at rest was subtracted from the PSD in each load phase.

Change in Alpha PSD within each load phase was then averaged across 4 trials (trials 2-5) and 4 blocks (blocks 2-5) for each participant and subsequently subjected to statistical analysis.

Statistical Analysis

Statistical analyses were completed using SPSS (SPSS Inc. v. 28.0.1.1, Chicago, Il.). A repeated measures ANOVA was used to analyze somatosensory cortical activation g between groups (2 levels (high/low laxity) and within load phase (3 levels (load phase 1, load phase 2, load phase 3)).

CHAPTER IV: RESULTS

Demographics of the high and low laxity groups are presented in Table 1. No statistical differences were found between groups regarding age, mass, height, and body mass index (BM), Marx Activity, Tegner Activity, and Beighton Laxity Score. As expected, the High Group laxity values measured by the KT2000 were significantly greater than the Low Group. ($p=<0.001$) GMetric3D values were obtained during data collection and are presented in Table 2. The High Group was significantly greater for LP1 ($p=0.008$) and LP3 ($p=0.02$). No difference was found between groups in LP2 laxity ($p=0.15$).

Table 1. Participants' Demographics, Physical Activity Rating Scale, and Knee Laxity

	Laxity Group			
N = 28	**High**	**Low**	**p-value**	**Effect size (Cohen's d)**
Age(year)	21.6±3.2	21.8±3.6	0.45	0.05
Mass(kg)	67.3±12.6	66.0±8.5	0.38	-0.12
Height(cm)	165.8±6.1	165.0±8.5	0.36	-0.14
BMI(kg/m^2)	24.3±3.7	24.3±2.9	0.48	-.022
Marx	8.4±3.8	9.5±3.7	0.21	0.30
Tegner	5.5±1.6	5.1±1.6	0.28	-0.23
Beighton	1.6±1.3	3.1±1.3	0.29	0.21
KT_AKL(mm)	7.8±0.9	4.2±0.7	<.001	-4.51

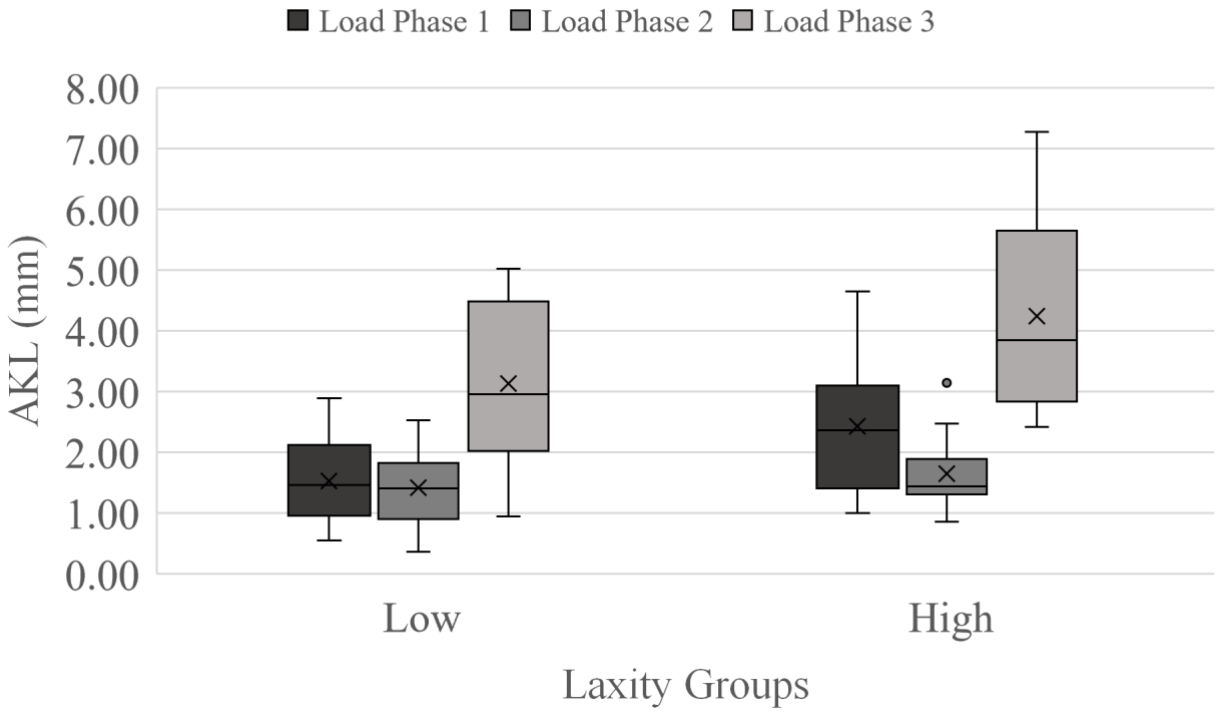
Anterior Knee Laxity Values. KT AKL = KT2000 laxity values (High Group < 7mm; Low Group > 5mm).

Table 2. Laxity Values from GMetric3D

	Laxity Group			
	High	**Low**	**p-value**	**Effect size (Cohen's d)**
AKL LP1(mm)	2.4±1.1	1.5±0.7	.008	-0.98
AKL LP2(mm)	1.6±0.6	1.4±0.6	0.15	-0.39
AKL LP3(mm)	4.2±1.5	3.1±1.3	0.02	-0.79

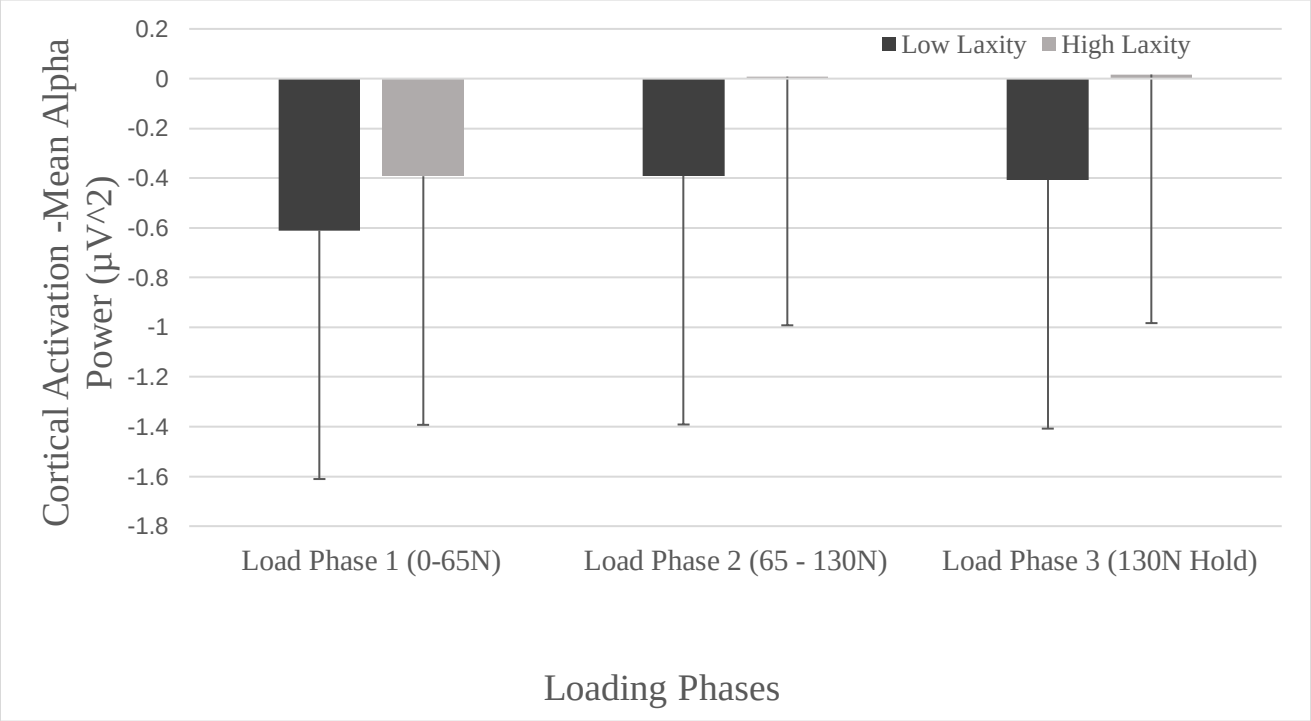
Loading phases. AKL LP1 = GMetric3D laxity obtained from 0-65N, AKL LP2 = Gmetric3D laxity obtained from 65N-130N, AKL LP3 = GMetric3D laxity obtained during 130N static hold.

Figure 7. Box plots of laxity values obtained during GMetric3D testing per load phase.



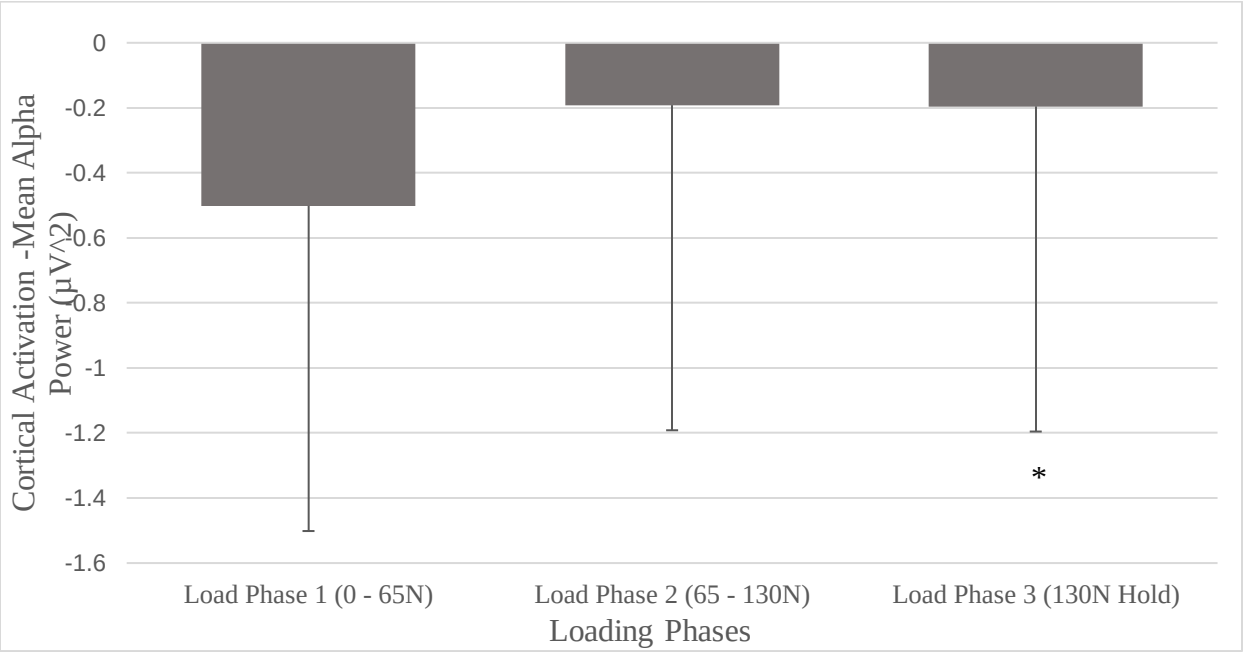
No significant interaction was found between laxity groups with loading phase (F (2,52) = 0.278, p = .758) or main effect for laxity group phase (F (1,26) = .623, p = .437; see Figure 7). Consequently, this study fails to reject the null hypotheses that there would be a decrease in cortical activation in the high laxity group compared to the low laxity group in LP1, LP2, and LP3 during passive anterior tibial translation.

Figure 8. Somatosensory cortical activation at C4 electrode between groups per load phase.



While there were no between group statical differences in cortical activation there was a near statistically significant main effect for phase (F (2,52) = 2.781, p = .071; see Figure 8). A pairwise comparison determined that an increase in alpha power was observed within groups from LP1 to LP3 suggesting a decrease in cortical activity from initial joint loading to terminal knee joint loading (p = .034; see table 2). This trend suggested that the difference in alpha power increased from LP1 to LP3, suggesting a decrease in cortical activity from early loading to static holding at 130N.

Figure 9. Somatosensory cortical activation per load phase.



* Trend (p = 0.71). for load phase with Load Phase 3 > Load Phase 1

Table 3. Pairwise Comparisons of Load Phases

Load Phase	Load Phase	Mean Difference	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	-.310	.193	.120	-.706	.086
	3	-.306*	.137	.034	-.588	-.024
2	1	.310	.193	.120	-.086	.706
	3	.004	.111	.972	-.224	.232
3	1	.306*	.137	.034	.024	.588
	2	-.004	.111	.972	-.232	.224

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

CHAPTER V: DISCUSSION

To the best of our knowledge, this study is the first EEG study of cortical activity associated with anterior knee joint loading in healthy population of higher and lower laxity individuals. This study was performed to better understand how central nervous system (CNS) function may be associated with an established prospective risk factor of ACL injury. Specifically, we observed cortical activation during passive anterior tibial translation between females with higher knee laxity and lower knee laxity. There is previous evidence of slower responses to stimuli of mechanoreceptors in the knee joint to activate hamstrings at the spinal level in the high laxity population (Shultz, Carcia, et al., 2004; Solomonow et al., 1987; Wojtys & Huston, 1994). Additionally, kinesthesia has been inversely related to knee joint laxity (Barrack et al., 1983; Rozzi et al., 1999). Thus, we expected the high laxity group to exhibit diminished afferent outputs from the knee joint measured at the supraspinal level. Specifically, we hypothesized that females with high knee laxity would have less cortical activation (increase in alpha power) compared to females with low knee laxity during knee joint loading. However, our hypothesis was not supported.

The current data provide evidence of no difference in supraspinal processing of mechanoreceptors in the knee joints of healthy high and low laxity female populations. More specifically, we identified there is no evidence of sensory information differences between groups during passive loading of the knee joint as measured by EEG over the contralateral sensory cortex. Current findings are in agreement with the previous work of Needle et al., (2014) and Park-Brasswell et al., (2020). Needle's (2014) study measured cortical activity using EEG while loading the ankle joint in unstable, coper, and control groups. Park-Brasswell (2020) observed cortical activation via fMRI in healthy higher and lower laxity groups during anterior

knee loading. Both studies reported no statistical differences in cortical activation of the contralateral somatosensory hemisphere between differential laxity groups during passive joint loading of the ankle joint and knee joint, respectively. Similarities in cortical activation between groups in the previously mentioned studies and our current study could indicate that even though there are functional (Needle et al., 2014) and/or mechanical (Park-Braswell, 2020) differences at the joints, these differences are not evident in the somatosensory cortex during passive joint loading. These findings do not consider information being processed at the spinal level or how the information is processed after it has traveled to the somatosensory cortex. Therefore, while there were no statistical differences in somatosensory cortical activation between laxity groups to support our hypotheses, this does not rule out other laxity specific neural activation patterns may exist throughout the sensory feedback and motor feedforward systems.

The similarity between groups in cortical activation of the sensory cortex during the loading phases despite laxity differences could imply that both healthy high and low laxity females transmit joint movement information similarly to the sensory cortex. While this study did not evaluate the premotor cortex, Park-Brasswell and colleagues (2020) did find that higher laxity healthy individuals have significantly lesser cortical activation during isolated anterior knee loading in both right and left premotor cortices as measured by fMRI as compared to lower laxity group. This previous study suggested different activation patterns may be established in response to long term anterior knee joint landing in healthy high laxity females. This difference in activation patterns could affect preplanning and preprogramming of movement. Cross sectional evidence supports the concept of neuroplastic changes in the brain following ligamentous injuries of the knee and ankle and joints (Kapreli et al., 2009; Pietrosimone, 2017; Swanik, 2015). Needle and colleagues (2017) theorized a ligamentous injury event paradigm that

links ligament injury to induced neuroplasticity and resulting sensorimotor function. This paradigm suggested that 4 key components (pain, inflammation, peripheral deafferentation, and laxity) lead to a continuous cycle of disrupted sensory feedback to altered motor output, to further degraded sensory feedback to continued flawed output, and then the cycle repeats. Although some perceived functional deficits have been reported in healthy high laxity populations, the results were correlated in individuals with higher posterior knee laxity and not AKL (Taylor et al., 2015). To our knowledge, our high laxity participants self-reported no instances of pain or inflammation at the knee. There is previous research that supports a decrease in afferent output at the knee joint in high laxity groups (Barrack et al., 1983; Rozzi et al., 1999; Shultz, Carcia, et al., 2004). Thusly, according to the ligamentous injury event paradigm proposed by Needle et al., (2017) the population of interest has the potential to display peripheral deafferentation and increased knee laxity which are 2 of the 4 key components that can lead to induced neuroplastic alterations in brain function. However, these potential laxity related activation differences were not observed in the current population.

No statistical differences were found in cortical activation of the somatosensory cortex between high and low laxity groups in the present study. However, there is previous evidence of differences in activation of the premotor cortices during anterior knee joint loading (Park-Braswell, 2020). Descending signals from the cortex can modulate the strength of reflex pathways in the spinal cord (Kandel et al., 1991). Thus, it is plausible that the observed decrease in premotor activity in high laxity individuals may result in descending signals from the brain that adversely affect processing of afferent information at the spinal level. This could be considered a discrepancy in communication within the feedforward system. This

miscommunication from the CNS to the periphery could lead to failure or neuromuscular error that could result in injury of the ACL during sport.

In a dynamic sense these findings can be compared/contrasted to athletes loading their knee joints during movements such as running, cutting, and single leg landings in sport. During these movements, it is important to note that many sensory signals (visual feedback, proprioception, and vestibular equilibrium, etc.) are being processed simultaneously in the CNS from the external environment and the athlete must adapt quickly to these environmental demands (Grooms & Onate, 2016). Possibly, similar initial loading information is reaching the sensory cortex during these rapid movements in both groups, but the input of information at the spinal level could be different or interpreted differently in high laxity individuals compared to low laxity individuals (Shultz, Carcia, et al., 2004). Thus, affecting the ability of the joint sensory information to initiate proper muscle activation at the spinal level in athletes with high laxity to effectively engage their dynamic joint stabilizers.

Although there is no evidence of differences between laxity groups our study did identify a trend toward differences in cortical activity measured over the contralateral somatosensory cortex. between loading phases. The overall findings by load phase (P=.07) suggested less alpha power during the initial loading phase (0-65N) than during the holding phase (130 N). Given the inverse relationship of alpha power to cortical activity, this suggests greater cortical activity as measured over the contralateral somatosensory cortex during the early phase of loading. By measuring post-synaptic potentials over the hemisphere contralateral to the loaded knee joint, this may indicate more afferent information is traveling to and being processed at the supraspinal level during the initial loading phase (LP1) of the knee joint compared to static joint loading (LP3). The concept of ACL mechanoreceptor firing during onset of load and subsequent action

potential propagation is supported by that of Johansson et al., (1991) which demonstrated a 40N force applied to the cat ACL was enough to elicit peripheral activity as measured by primary muscle spindle afferent activity. Moreover, it was shown at the supraspinal level intraoperatively while using EEG to measure somatosensory evoked potentials (SEPs) over the scalp (Ochi et al., 2002). During ACL and menisci surgeries, a low force mechanical stimulation (3.92N) elicited cortical activation from mechanoreceptors of the ACL in ACLD (intact, injured ACL), ACLR and control subjects (Ochi et al., 2002). Thus, our work is in accordance with other previous work providing evidence of the mechanoreceptor firing and resultant supraspinal processing during ACL loading.

The trend in decrease in activity from LP1 to LP3 may be explained in part by the specificity of mechanoreceptor type and function in and around the ACL and joint capsule. Pacinian and Ruffini sensory receptors both have a low firing threshold for mechanical distortion (Nyland et al., 1994; Zimny & Wink, 1991). However, Pacinian receptors adapt rapidly to initial changes in load (Nyland et al., 1994; Zimny & Wink, 1991) such as the forces used to passively translate the tibia from LP1 to LP3. Moreover, these receptors do not fire continuously and are most sensitive during change in ligamentous tension at both initiation and termination (Nyland et al., 1994; Zimny & Wink, 1991) of joint loading. Thus, firing of the Pacinian receptors may have diminished after initial joint loading and discontinued firing during a static hold where joint loading was maintained at 130N for 1 second. This could explain the increased cortical activation in LP1. Ruffini mechanoreceptors also have a low firing threshold but fire continuously at various rates in response to ligament deformation (Nyland et al., 1994; Zimny & Wink, 1991). These receptors adapt slowly to changes in static joint position, intra-articular pressure changes and joint kinematics, and contribute to the preservation of muscle tone (Nyland

et al., 1994; Zimny & Wink, 1991). The holding of 130 N towards the more likely end range of anterior tibial motion using the clinical measurement may not have applied enough tension on the ACL and surrounding structures to activate the Golgi tendon-like organs which activate during extreme end ranges such as motions that produce joint injury (Johansson, 1991; Johansson et al., 1991; Nyland et al., 1994; Zimny & Wink, 1991). This suggests that the Ruffini receptors may have been firing throughout the duration of all 3 load phases. The static hold created no changes in length or tension on the ACL meaning that only the Ruffini receptors were firing during LP3 whereas the Pacinian receptors firing rates would have diminished. Thus, a decrease in cortical activation from initial loading phase to holding phase based on the characteristics of the mechanoreceptors is plausible due to the reduced firing of Pacinian receptors. Collectively, while the current investigation is unable to discern the type of sensory receptor firing that may be responsible for the EEG signal changes measured at the cortex, it is likely that the established functionality of Pacinian and Ruffini sensory receptors may best explain our current findings.

Similar cortical activation of laxity groups during joint loading in LP1 to decreased activation in LP3 could be representative of the signals that are being processed at the spinal and supraspinal levels. While each load phase lasted ~1000ms, the initiation of joint loading mechanically stimulating mechanoreceptors would have taken less than one tenth of this time to reach the brain (Baars & Gage, 2010). This could imply that while the joint is still being loaded through LP1 and LP2 (0-2,000ms), the sensory information of the initial joint loading may contain the necessary information about the position of the knee joint and is able to interpret further joint motion based on previous joint loading encoding of the brain (Crapse & Sommer, 2008; London & Miller, 2013). The supraspinal information from Pacinian receptors during

initial joint loading may then transfer from the somatosensory cortex to the premotor cortex for preplanning of movement thus causing a decrease in cortical activation in subsequent loading phases. The information processed at the spinal level may contribute to joint position sense, reflexes, and stabilization of the knee joint (Zimny & Wink, 1991).

Contrary to the current findings, Needle and colleagues (2014) reported increased cortical activation at the sensory cortex as load increased across loading phases in unstable, coper and control subjects. Several factors may explain these differences in cortical activation during loading phases. Needle performed a posterior to anterior translation of the ankle during each loading phase (-30N – 130N) over a period of 2,000ms (two, 1,000ms loading phases). This bi-directional manipulation on the ankle may cause joint mechanoreceptors to fire at the onset of each direction when ligaments are being loaded. Thus, causing increased cortical activation as load increased per phase. Since our study was focused on a surrogate measurement of ACL loading and resultant mechanoreceptor activity, we performed only anterior translations of the knee joint (0 - 130N) over 2,000ms with a 1,000ms hold at 130N. Such a loading paradigm would only deform the mechanoreceptors in one direction and focused loading on structures involved in restraining anterior tibial motion. Another consideration is the number of trials performed in each study. Needle's study performed 50 total translations of the ankle joint whereas our study performed 30 translations of the knee joint. Excess manipulation of the joint could add excess stress to the joint and surrounding tissues causing the muscle to begin guarding to protect the joint, more so if the joint is previously injured (Hanlon et al., 2016). The induced muscle contractions from possible guarding may cause an increase in cortical activation via other mechanoreceptors such as free nerve endings which provide information about pain and inflammation to the brain (Gilman, 2002; Johansson, 1991). Taking the contrasts in methods

between the Needle study (2014) and our study into consideration and in combination with the overview of the characteristics of joint mechanoreceptors, our results of a trend decreasing cortical activation during passive joint loading across loading phases could be plausible.

Limitations

We acknowledge there are limitations that may have impacted these results. The number of subjects (N=28) adversely affected the statistical power. An a priori power analysis determined that 38 subjects would be needed to adequately power this study. Finding subjects within the desired laxity ranges during the recruitment period was difficult. Also, participants intermittently would describe feelings of paresthesia of the left lower extremity after blocks 2-3 of joint loading which could have caused the participants to be uncomfortable and unable to relax. To minimize this limitation, we did calculate the difference in loading phase with the respective rest phase obtained prior to loading block. It was decided a priori that only 20 out of the 30 recorded trials would be used to ensure clean, quality EEG data. Trial 1 was considered a conditioning trial whereas trial 6 was excluded due to inconsistencies in participants anticipating last trial and possibly activating muscles of the lower limb to get feeling back in their leg. However, while more trials may improve our ability to detect differences, we were concerned with guarding of the knee joint from too many anterior tibial translations. This could affect the EEG data due to the participant's discomfort and the tester's ability to successfully translate the tibia. Finally, we only used data extracted from the C4 electrode which lies over the sensory cortex. Given the poor spatial specificity of EEG, we cannot assume that the data we collected was directly or solely from the region of interest.

Summary

In summary, we hypothesized that females with high anterior knee laxity would exhibit decreased cortical activation during knee joint loading compared to females with low knee laxity across 3 load phases (0-65N, 65N-130N, 130N hold (1 second). Our current results did not support our hypotheses. Our results demonstrated no differences in how individual greater anterior knee laxity received passive joint loading information to the somatosensory cortex. Our findings are in agreement with those of Needle et al., (2014) and Park-Brasswell et al., (2020).

While our hypotheses were not supported with this study, additional findings indicate a decrease in cortical activation as more force is applied to the joint and through static joint hold within groups. This could suggest that pertinent joint loading information is being sent to the somatosensory cortex during initial joint loading. Future studies should focus on different aspects of afferent and efferent pathways to determine if neural activity related to passive joint loading is different between high and low laxity populations through various parts of the neuromuscular control system. They could also focus on measuring different regions of the scalp (frontal and parietal or whole head) with EEG versus one electrode as well as observe different brain rhythms to better understand and ascertain differences in processing and execution of movement. This study represents a primary step taken to understand the neural role of the ACL during joint loading with a long-term vision of attempting to develop brain-based interventions in effort to reduce ACL injuries.

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