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Greater anterior knee laxity (AKL) is known to be a significant predictor of anterior cruciate ligament (ACL) injury. Individuals with high AKL are known to have a proprioception deficit and exhibit compensatory movement patterns. The potential altered sensory information and associated movement strategies may lead to decreased functional stability, contributing to a higher risk of ACL injury. The brain has an essential role in integrating and processing sensory information in the course of stabilizing the joint. Our brain also has the ability to reorganize its function and structure (neuroplasticity) in response to sensory changes. However, it is still unknown how sensory information, associated with ACL loading in high AKL individuals, may affect brain function and structure. Decreased proprioception influenced by high knee laxity may also negatively impact postural stability. Postural stability is impacted by visual, vestibular, somatosensory input. It is broadly understood that individuals who are ACL deficient as well as hypermobile individuals joints have poor proprioception and postural control. It is suggested that poor proprioception negatively impacts postural control. Decreased proprioception due to greater knee laxity may thus diminish postural stability. However, the influence of greater AKL on postural control is not yet understood. Therefore, the primary purpose of this study is to determine the impact of high and low knee laxity on brain function and structure as well as dynamic postural stability.

Healthy and physically active female college students volunteered for this study. Anterior knee laxity was measured to assign participants to either high (N=15) or low knee laxity (N=12) groups. Functional and structural brain data were obtained through magnetic resonance imaging (MRI). Functional MRI data were analyzed in order to compare brain activation differences during anterior knee joint loading between the two groups. Structural brain data were analyzed to

identify differences in gray matter volume between the groups. Time to stabilization testing following a single-leg jump landing task was recorded in order to quantify dynamic postural stability. Independent t-tests contrasted dynamic postural stability between high and low to average laxity groups. fMRI data revealed that those with high knee laxity had significantly less activation in the left superior parietal lobe and right premotor cortex, and greater activation in the right cerebellum (Crus I and II) during anterior knee joint loading. The results suggest that individuals with greater knee laxity might experience a different awareness of their body's position and may face challenges in preplanning and preprogramming potential movements. We also observed that the high knee laxity group had a nearly significant larger gray matter volume in BA6 (premotor cortex and supplementary motor area). We suggest that the larger gray matter volume in BA6 may be a response to the challenges in preplanning movements as a compensatory strategy. However, the time to stabilization test did not reveal any differences between the high and low to average laxity group. An advanced postural control test that separated the influence of somatosensation from other sensory input (visual and vestibular) may be recommended in order to identify the differences in dynamic postural control between groups. Our study reveals valuable information concerning possible functional and structural neuroplasticity associated with knee laxity. These results may help researchers better understand the influence of knee laxity on the sensorimotor system, especially the central integration and processing components, in individuals who are at increased risk of ACL injury.

THE IMPACT OF DIFFERENTIAL KNEE LAXITY ON BRAIN FUNCTION/STRUCTURE AND POSTURAL CONTROL

by

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CHAPTER I

INTRODUCTION

Statement of Problem

Anterior cruciate ligament (ACL) injury is one of the most common traumatic knee injuries to occur during sports and physical activity (Prodromos et al. 2007). Over 200,000 ACL injuries are estimated to occur annually in the US with a corresponding 80,000 to 100,000 ACL surgical reconstructions (Prodromos et al. 2007). Beyond the loss of physical activity (Ardern et al. 2011; D. Y. H. Lee, Karim, and Chang 2008), the initial ACL injury likely results in the early onset of osteoarthritis (A. R. Brown and Rose 1966; Dare and Rodeo 2014; Vad and Bhat 2000) as well as increases in incidences of a second ACL injury (Paterno et al. 2014; Schilaty et al. 2017). Even with rehabilitation programs focused on ACL injury treatment (Sugimoto et al. 2016; Voskanian 2013), the secondary injury rate for athletes younger than 25 years who return to their sport was reported to be 23% (Wiggins et al. 2016). While multiple risk factors of primary ACL injury such as knee geometry, BMI, sex hormones, neuromuscular control, and joint laxity have been reported (Shultz et al. 2015; H. C. Smith et al. 2012b, 2012a), anterior knee laxity (AKL) is known as one of the strongest independent predictors of ACL injury (Uhorchak et al. 2003; Vacek et al. 2016; Woodford-Rogers, Cyphert, and Denegar 1994).

AKL is the product of loading multiple anatomical structures including ligaments, joint capsular structures, and muscles/tendons. The ACL is the primary structure resisting AKL loading that mechanically restrains about 80% of anterior translation of the tibia related to the femur (Butler, Noyes, and Grood 1980; Ellison and Berg 1985). Beyond its mechanical restraint role, the ACL also has a sensory role through ligamentous mechanoreceptors that provide

proprioceptive information to the central nervous system (CNS) (H. Johansson, Sjolander, and Sojka 1991; P Sjolander et al. 1989; Per Sjolander, Johansson, and Djupsjobacka 2002). It has been demonstrated that greater AKL has a negative relationship with proprioception, which is the sensory information arising from the peripheral area (Rozzi et al. 1999). Rozzi et al. demonstrated that healthy females had significantly greater AKL and longer time to detect joint motion compared to males (Rozzi et al. 1999). They suggested that excessive joint laxity in females may contribute to poorer joint proprioception. Their results are supported by Laudner et al. who reported that greater shoulder anterior joint laxity was associated with lesser shoulder proprioception (Laudner et al. 2012). Although this study examined the shoulder as opposed to the knee joint, it supports the concept of a negative relationship between joint laxity and proprioception.

While the previous studies demonstrated potentially poorer sensory information being accompanied by greater AKL (Ageberg et al. 2005; Roberts, Andersson, and Friden 2004; Rozzi et al. 1999), the reasons or mechanisms behind this relationship are largely unknown. One hypothesis may be that individuals with greater AKL may have less ligament tension than low laxity individuals which results in less afferent information from sensory structures within the ligament. The negative relationship between ligament tension and laxity has been understood; however, the evidence is primarily seen in ACL reconstruction patients (Yasuda et al. 1997). Individuals who had lower graft tension during a surgical procedure had greater anterior knee laxity two years following reconstruction (Yasuda et al. 1997). Since mechanoreceptors respond to tension (Zimny, Schutte, and Dabezies 1986), decreased ligament tension may lead to a longer time to sufficiently stimulate the mechanoreceptors. In addition, there may also need to be greater ligamentous displacement to fire the mechanoreceptors. Golgi tendon organ-like endings, as an example of mechanoreceptors which are located in the ACL, are stimulated most efficiently at the

extreme of the movement range when tension in the ligament is increased (Andrew 1954; Freeman and Wyke 1967; SKOGLUND 1956). Thus, at a fixed displacement, a high knee laxity knee may not as frequently reach the threshold to stimulate the Gogi tendon organ-like endings compared to a lower laxity knee. Therefore, when the same force of the mechanical load is applied to the joint of high and low laxity knees, a potentially smaller number of mechanoreceptors may be stimulated in the high laxity knee. This may be why individuals with greater AKL may have poorer sensory information resulting in reduced clinical proprioceptive measurements.

Knee laxity may also be related to how individuals control and load their lower extremities. Individuals with high knee laxity demonstrated a longer delay time in hamstring muscle reflex following a perturbation (Shultz, Carcia, and Perrin 2004). Individuals with greater knee laxity also demonstrated increased knee work absorption during drop jump landing (Shultz et al. 2010). Moreover, high laxity individuals had greater hamstring muscle activation during jumping (Rozzi et al. 1999) and following a perturbation (Shultz et al. 2006). The observed different movement strategies and muscle activation patterns in individuals with high knee laxity may be due to poor sensory input. Given the above hypothesis that high laxity individuals may have less ligamentous tension at fixed displacements, it can be seen that stimulating a lower number of mechanoreceptors and/or taking a longer time to fire the mechanoreceptors may result in altered muscle activation and movement patterns.

The potentially decreased sensory input and altered movement pattern in the greater knee laxity individuals may lead to a decrease in joint stability during a physical movement, which is known as functional stability (Riemann and Lephart 2002a). Functional stability is maintained by the sensorimotor system, which encompasses all the sensory, motor, and central integration and processing components. In this process, the brain has important roles (Peter Grigg 1994; Riemann

and Lephart 2002a). The brain integrates and processes the sensory information arising from a peripheral area in order to generate neuromuscular control solutions to meet the task demands as well as stabilizing the joint (Kandel, Schwartz, and Jessell 1991). Moreover, the brain has the unique ability to modify neuronal circuits depending on interaction with an environment, it is known neuroplasticity or brain reorganization (Daphne Bavelier and Neville 2002; B. B. Johansson 2004).

Since the brain has an essential role in joint stabilization during locomotion, there is a need to understand central mechanism differences and how they may be related to an injury. Several studies examined brain function while performing movements and loading of the knee joint in ACL deficient (ACLD) (Kapreli et al. 2009) and ACL reconstructed (ACLR) individuals (Gokeler et al. 2019; Grooms et al. 2017; Alan R Needle, Lepley, and Grooms 2017). The ACLR patients had significantly higher cortical activation associated with the somatosensory area during knee joint loading compared to the non-injured limb and matched limb of the control group (An et al. 2019). The increased cortical activation was positively correlated with knee laxity. This finding is similar to other studies identifying increased brain activation, including the somatosensory cortex, during knee extension-flexion movements in ACLD (Kapreli et al. 2009) and ACLR patients (Grooms et al. 2017). The results showed evidence of possible functional brain reorganization due to altered sensory perception resulting from ACL injury; this may be related to the degree of knee joint laxity.

While brain reorganization associated with ligament injury has been demonstrated, the reason behind observed functional neuroplastic changes is unclear. One reason may be that deafferentation may unmask other preexisting connections between the somatosensory cortex and sensory input (Ziemann, Hallett, and Cohen 1998). The loss of dominant input by the injury increases the efficacy of other pre-existing connections and results in brain functional

reorganization (Cusick et al. 1990; Merzenich et al. 1983; Rasmusson 1982). Likewise, it can be assumed that the ACL is involved in providing information of joint position sense and movement to the somatosensory cortex. The ACL injury may impair sensory transmission due to mechanoreceptor damage. This deafferentation may unmask other pre-existing connections to provide sensory information to the somatosensory cortex. This may be why the ACL injury patients have higher activity in the somatosensory cortex.

Deafferentation has also been demonstrated to influence structural neuroplasticity. Structural neuroplasticity includes changes in gray matter and white matter properties. It may be caused by the formation and elimination of axon and dendritic spines in brain cells. It has been revealed that dendritic spines and axons can appear and disappear in response to hormonal changes, environmental factors, and sensory stimulation (Trachtenberg et al. 2002). Previous studies have shown that individuals with somatosensory deficits such as nerve transection (K. S. Taylor, Anastakis, and Davis 2009), vestibular failure (Gottlich et al. 2016), and carpal tunnel syndrome (Maeda et al. 2013) have less gray matter volume of various regions compared to the healthy control groups. Taylor, Anastakis, and Davis reported that individuals with the median and ulnar nerve transection and corresponding surgical repairs had less gray matter thickness of the brain regions encompassing the somatosensory cortex (K. S. Taylor, Anastakis, and Davis 2009). Gray matter reduction is also shown in patients with lower or upper limb amputation (Draganski et al. 2006; Di Vita et al. 2018). Patients with lower limb amputation not using prostheses had reduced gray matter volume in the bilateral cerebellum when compared with healthy individuals (Di Vita et al. 2018). The results showed evidence of the structural neuroplasticity influenced by deafferentation and corresponding sensory loss.

The altered sensory system in high knee laxity individuals may not only result in neuroplastic changes, but it may also have an impact on the functional movement through

alterations in the somatosensory system. Postural control measurements are commonly obtained in clinical and laboratory settings when assessing the integrity of the somatosensory system (Howells, Ardern, and Webster 2011; Negahban et al. 2014). While postural control requires multiple inter-related systems including sensory, motor, and cognition (Shumway-Cook and Woollacott 1995); poor afferent information following by a joint injury has largely contributed to postural control deficit in sports medicine literature (Riemann and Lephart 2002a). It is well understood that ACLD and ACLR patients have decreased postural control compared to healthy individuals (Howells, Ardern, and Webster 2011; Negahban et al. 2014). This may indicate that impaired afferent information arising from mechanoreceptors innervated in ACL may negatively contribute to postural control. Likewise, potentially altered sensory information in high anterior knee laxity individuals may also negatively impact postural control. Ageberg et al. reported a negative relationship between knee laxity and postural control in ACLD patients (Ageberg et al. 2005). The patients with greater anterior-posterior knee laxity had greater postural sway and lower average center of pressure speed during single-leg stance tasks, which indicated decreased postural control (Ageberg et al. 2005). Similar results are observed in individuals with greater general joint laxity. Those individuals demonstrated significantly higher postural sway during a static balance test (Aydin et al. 2017). The negative relationship between laxity and postural control is also found in the ankle joint as well. Individuals with perceived ankle instability and mechanical laxity demonstrated impaired dynamic postural control during a single-leg jump landing (C. N. Brown et al. 2015). The above studies collectively provide evidence that individuals with greater joint laxity have a postural control deficit.

Through a review of the previous literature, we have understood how greater knee laxity negatively influences sensory and motor system performance. In addition, we also acknowledged the essential role of brain function in the sensorimotor system in maintaining functional stability.

While the evidence to connect high knee laxity with altered sensory and motor system functionality has been reported, the connection between laxity and brain function/structure is still unknown. In addition, the impact of potential poor sensory input on postural control in individuals with high AKL is not yet known. Understanding the differences in brain function/structure and its connection to postural control in individuals with various knee laxity will help us to more fully understand sensorimotor system functionality relationship to joint stability and subsequent injury risk. It will also help us to inform further research and strategies to prevent ACL injury.

Objective and Hypotheses

The primary objective of this study is to determine the impact of degree of knee laxity on brain function/structure and postural control.

Aim 1: To determine the context to which the magnitude of AKL impacts brain activation during knee joint loading designed to elicit sensory information from ACL mechanoreceptors.

Hypothesis 1: High AKL individuals will demonstrate significantly higher brain activation of the somatosensory cortex compared to individuals with low AKL during joint loading.

Aim 2: To determine the impact of high and low AKL on brain structure.

Hypothesis 2: High AKL individuals will reveal significantly less gray matter volume of the somatosensory cortex than individuals with lower AKL.

Aim 3: To determine the impact of high and low knee laxity on dynamic postural stability.

Hypothesis 3: High AKL individuals will demonstrate a longer time to control the dynamic postural stability compared to lower knee laxity individuals.

Limitations and Assumptions

1. Participants' knee laxity value will remain their assigned group range (HL> 9.5mm, LL<8.5mm) all components of the study.
2. Participants have not practiced the balance task before the measurement.
3. Participants who are using an oral contraceptive pill will have similar effect between different type of pills.
4. The sampling frequency of 200 Hz for the dynamic postural control measurements will be accurately tracked and calculated the ground reaction force (GRF) in the anterior-posterior (AP) and medial-lateral (ML) direction.
5. fMRI will obtain the brain activity resulting from loading the joint in a manner which the ACL provides primary restraint.
6. Participants remain still while inside the MRI scanner.
7. fMRI indirectly measures brain activation, however, still sensitively measures changes in regional blood flow by neuronal activity.

Delimitations

1. Only female participants will be recruited who are aged between 18 to 30 years old.
2. Participants will be right-handed and footed.
3. Participants will be physically active who are participating in physical activity per the Marx scale (Marx et al. 2001) at least once a month and a minimum score of 3 on the Tegner scale (Briggs et al. 2009).
4. Participants between groups will be matched based on their activity level using Tegner (Briggs et al. 2009) and Marx scale (Marx et al. 2001).

5. Participants will be excluded if they have: 1) previous history of significant lower leg injuries; 2) any neurologic disorders; 3) currently undergoing a neuromuscular training program; 4) contradictions to MRI assessment (any metal or implanted medical device in the body or claustrophobic etc.).

Operational Definitions

Anterior Knee Joint Laxity: Amount of anterior displacement of the tibia relative to the femur as assessed at 130 N of load.

Functional Stability: Ability to maintain and control the joint from external forces during physical movement (Lephart SM 2000).

Sensorimotor system: The sensory, motor, and central integration and processing components that relate to maintenance of functional joint stability (Lephart SM 2000).

Proprioception: Afferent information arising from internal peripheral areas of the body that relates to postural control, joint stability, and several conscious sensations (Riemann and Lephart 2002a).

fMRI (functional Magnetic Resonance Images): A neuroimaging technique that uses a standard MRI scanner to investigate changes in brain function (BOLD response) over time.

Net Magnetization: The sum of the magnetic moments of all spins within a spin system (Scott, Allen, and McCarthy 2014).

Longitudinal Relaxation: The recovery of the net magnetization within the longitudinal direction as spins return to the parallel state (Scott, Allen, and McCarthy 2014).

Transverse Relaxation: The loss of net magnetization along the transverse plane as a result of the loss of phase coherence of the spins (Scott, Allen, and McCarthy 2014).

T_1: The time constant that describes the recovery of the longitudinal component of net magnetization over time (Scott, Allen, and McCarthy 2014).

T_1_weighted: Images that obtain information about the relative T_1 value of tissue (Scott, Allen, and McCarthy 2014).

T2*: The time constant that describes the decay of the transverse component of net magnetization due to both accumulated phase differences and local magnetic field in homogeneities (Scott, Allen, and McCarthy 2014).

T2*_weighted: (T2*_dependent) Images that provide information about the relative T2* values of tissue (Scott, Allen, and McCarthy 2014).

BOLD: Bold The difference in signal on T2*_weight images as a function of the amount of deoxygenated hemoglobin (Scott, Allen, and McCarthy 2014).

MPRAGE (Magnetization Prepared Rapid Gradient Echo): A fast 3D gradient echo pulse sequence designed for rapid acquisition with T_1 weighted dominance (Brant-Zawadzki, Gillan, and Nitz 1992).

Neuroplasticity: An ability of the brain to adopt any changes in cortical properties either morphological or functional (Daphne Bavelier and Neville 2002; B. B. Johansson 2004).

Postural control: Maintaining the overall body position and orientation in space during any static and dynamic activity (Kandel, Schwartz, and Jessell 1991).

Variables

Independent Variable

Group: Participants will be assigned into either greater AKL group (≥8mm) or lower AKL group (≤5mm).

Oral Contraceptive Users: While not a part of any specific hypotheses we will attempt to recruit participants, who use and do not use contraceptives evenly between each laxity laxity group.

Dependent Variables

BOLD (Blood Oxygen Level Dependence) signal: The differences in BOLD signals during anterior knee joint loading compared to the resting period. This data will be collected using fMRI and analyzed using FSL software package. It is described in full detail in chapter 3.

Gray matter volume: Gray matter volume in the somatosensory cortex (Broadman areas 1, 2, and 3). These data will be collected using MRI and analyzed using FreeSurfer (Bruce Fischl 2012). It is described in full detail in chapter 3.

Time To Stabilization: The time that takes for the initial component of GRF to become similar to the components of the GRF of the optimal stability during jump landing single-leg stance (S. Ross and Guskiewicz 2003). AP and ML components of GRF will be separately obtained. This data will be collected using a force plate and described in full detail in chapter 3.

CHAPTER II

REVIEW OF THE LITERATURE

Knee Laxity and Neuromuscular Control

Knee joint laxity is the amount of joint displacement of the tibia related to the femur at a fixed load. Knee laxity can be assessed in the sagittal, frontal, and transverse planes when loads are applied to the joint. The sagittal plane assessments include anterior-posterior knee laxity, the genu recurvatum, and general joint laxity. The frontal plane and transverse plane knee laxity can be evaluated using valgus-varus and internal-external rotation knee laxity measurement, respectively. It has been understood that high joint laxity negatively influences sensory input, and it may also lead to decrease joint stability, thus increase risk factors of the knee injury (Laudner et al. 2012; Rozzi et al. 1999). This section will discuss the role of knee laxity in injury risk and its relationship to functional stability of the joint.

Laxity as a Risk Factor of ACL Injury

Anterior knee joint laxity is well known as one of the most influential independent risk factors for ACL injury. Uhorchak et al. (Uhorchak et al. 2003) prospectively examined 859 new cadets from the United States Military Academy (USMA) in 1995 and tracked them for 4 years to identify risk factors of non-contact ACL injury. There was a total of 29 complete ACL tears sustained during their four years of tenure at USMA. They reported that greater anterior knee laxity (AKL) was a significant risk factor for ACL injury; in addition to narrower notch width, greater generalized joint laxity, and increased BMI in females. Woodford-Roger et al. (1994) retrospectively examined ACL injured high school and college athletes, and compared them with

matched uninjured athletes. They stated that AKL was a significant predictor of ACL injury group classification in addition to navicular drop. Mouton et al. (Mouton et al. 2015) also studied the knee laxity of ACL injured patients compared to healthy control participants. They measured the anterior knee laxity and the rotational knee laxity on 171 healthy contralateral knees on ACL injured patients and 104 healthy knees of control participants. The ACL injury group revealed greater anterior and internal rotation displacement in their uninjured knee compared to the control group. A multivariate analysis study also reported greater anterior-posterior knee laxity as one of the most important risk factors for ACL injury among multiple risk factors (Vacek et al. 2016). Vacek et al. found the diverse combination of risk factors among the five categories: demographic characteristics (family history, race, weight, height, BMI, hours of practice, number of years participating in sport, use of braces, use medication and injury history), joint laxity (knee, ankle, and generalized), lower extremity alignment, strength (trunk, hip, knee, and ankle), and personal characteristics (evaluated with the Temperament and Character Inventory). Females who have the combination of increased anterior-posterior knee laxity, increased BMI, and having a parent who had suffered an ACL injury were involved with increased risk of noncontact ACL injury. For males, the combined effect of increased anterior-posterior knee laxity, posterior knee stiffness, and navicular drop and decreased standing quadriceps angle predicted ACL injury. While a combination of multiple risk factors influences an ACL injury, greater knee laxity was the important predictive factor for both female and male. The previous prospective and retrospective research reveals greater AKL as a significant risk factor for ACL injury.

Passive and Dynamic Contributions to Knee Laxity

Knee laxity is a function of both static and dynamic contributors. The static contributors include ligaments, joint capsule, meniscus, and bone geometry (Jansson et al. 2004; Riemann and Lephart 2002a). The primary role of the static contributors is to mechanically stabilize the joint.

The ACL contributes about 85% of the passive resistant to anterior translation of the tibia relative to the femur (Butler, Noyes, and Grood 1980; Ellison and Berg 1985). The ACL also guides knee axial rotation of the tibiofemoral joint and provides significant resistance to internal tibial rotation(Andersen and Dyhre-Poulsen 1997). The medial collateral ligament (MCL) is the main structure to stabilize the valgus and internal rotation as well as contributing anterior-posterior knee laxity with posterior capsule (Markolf, Mensch, and Amstutz 1976).

The dynamic stabilizers are controlled through both feedforward and feedback mechanisms (Grillner 1972; Lephart SM 2000). The muscles that cross the tibiofemoral joint can be considered dynamic contributors to knee joint stabilization. At the knee, the hamstrings, quadriceps, and gastrocnemius are the primary muscle group that provides dynamic stabilization of the knee joint (Cashaback and Potvin 2012; Swanik et al. 1997a). When ACL is fully stretched in knee valgus with internal rotation near knee full extension, the hamstring muscle groups are reflexively contracted to stabilize the anterior translation of tibia related to the femur (Li et al. 1999). It has been known that hamstring muscles are highly activated in ACL deficient patients (Hagood et al. 1990; Solomonow et al. 1987; Walla et al. 1985) as well as individuals with greater AKL to compensate the knee joint instability (Rozzi et al. 1999; Shultz, Carcia, and Perrin 2004). Thus, mechanoreceptors innervated in an ACL may regulate muscles coordination to stabilize the knee joint ultimately affecting the measurement of laxity.

While the muscular system's contributions are obvious to dynamic stability, the ligamentous structures may also affect dynamic stabilization by regulating muscle contraction around the joint. The mechanoreceptors that innervate the ligaments provide information of joint position and movement to the CNS and also influence muscle contraction through muscle spindle system (H. Johansson, Sjolander, and Sojka 1990; Per Sjolander, Johansson, and Djupsjobacka 2002). Johansson and colleagues demonstrated that stretching the cruciate ligament changes the

response of the spindle afferent from the posterior biceps and semitendinosus and gastrocnemius (H. Johansson et al. 1989, 1990). The author suggested that it may due to the action of stretch/tension sensitive afferent receptors innervated in the ACL. Stretching ACL may increase the dynamic sensitivity of spindle afferent and induce reflex activation primarily on fusimotor neurons projecting to posterior biceps and semitendinosus and gastrocnemius muscles. Thus, afferent receptors in ACL may contribute to stabilizing the joint via regulating muscle contraction.

The above literature demonstrated that both skeletal muscle/tendons crossing the joint and ligamentous structures contribute to dynamic stability through γ-motor spindle system. The following sub-sections will in detail discuss innervation of the knee and the role of such structures when loaded.

Innervation of the Knee

Mechanoreceptors are responsible for conducting the sensory signals associated with joint position sense and movements to the CNS (Peter Grigg 1994; H. Johansson 1991; H. Johansson et al. 1990; H. Johansson, Sjolander, and Sojka 1990; Tran et al. 2018). These mechanoreceptors have been found in the skin, muscle, fascia, ligament, tendon, and joint capsule (GARDNER 1948; Gomez-Barrena, Martinez-Moreno, and Munuera 1996; Peter Grigg 1994; H. Johansson, Sjolander, and Sojka 1991). Generally speaking, these mechanoreceptors are stimulated when the knee joint is deformed or loaded and transmit the action potential by afferent neurons to the spinal cord, brain stem, and cerebral cortex (Peter Grigg 1994). In this section, we will mainly focus on sensory innervation in the joint capsule, muscle, and cruciate ligament structures.

Sensory Structures Found in Joint Capsules

In the joint capsule, there are two kinds of sensory receptors: Ruffini Afferents and Paciniform afferents (Ralphs and Benjamin 1994). Ruffini afferents are Group II afferents nerve fibers, which are slow adapting to stimulation and also have a low mechanical threshold and moderate conduction velocity (Andrew 1954; W R Ferrell 1980). Ruffini afferents were only found in the posterior side of the knee joint capsule (P Grigg and Hoffman 1982; Strasmann and Halata 1988). In the knee joint, Ruffini afferents will likely be stimulated only during extreme knee extension when the posterior side of the knee is stretched (Hoffman and Grigg 1989). Therefore, they may be able to play a role in proprioception to detect the limit of the joint movement in extension (Peter Grigg 1994). Ruffini endings are also sensitive to both static and dynamic mechanical movements, thus they transmit signals of static joint position, intra-articular pressure, and amplitude and velocity of movement (EKLUND and SKOGLUND 1960; P Grigg and Hoffman 1982).

Pacinian Corpuscles are also Group II afferent nerve fibers, which rapidly adapt to stimulation and have a low threshold (H. Johansson 1991). They are extremely sensitive to small changes in a distortion of the capsule when mechanical pressure is applied to the joint (Solomonow and Krogsgaard 2001). Pacinian Corpuscles are located in the deeper layers of knee joint capsules, ligament meniscus, and articular fat pad (Strasmann and Halata 1988; Zimny 1988).

Sensory Structures Found in Skeletal Muscle

Sensory organs are also found in the skeletal muscles (Peter Grigg 1994; Kandel, Schwartz, and Jessell 1991). Muscle spindles are the most predominant sensory organ in skeletal muscle (Ellaway, Taylor, and Durbaba 2015). Muscle spindles are responsible for conducting information regarding muscle length and velocity (Kandel, Schwartz, and Jessell 1991), and are

also implicated in reflex control (Houk 1976; Sinkjaer et al. 1988). Muscle spindles consist of both sensory and motor neuron fibers in series with extrafusal muscle fibers (Barker 1974; Ellaway, Taylor, and Durbaba 2015). Muscle spindle afferents transmit the information of muscle length and velocity to the CNS via afferent nerve fibers (Wolf and Segal 1990) and are also involved with regulating muscle contraction by the changing muscle spindle sensitivity responding to muscle length and velocity via ɣ-motoneuron (Latash 2007). When a muscle lengthens, the muscle spindle is stretched and discharges afferent signals to produce muscle contraction, this is called stretch reflex (H. Johansson, Sjolander, and Sojka 1986; Kandel, Schwartz, and Jessell 1991; Wolf and Segal 1990). The sensitivity of muscle spindle is raised by increased signals from the gamma motor neuron (H. Johansson, Sjolander, and Sojka 1986). Increase spindle sensitivity may enhance muscle reflex excitability as well as muscle stiffness. It has been known that greater muscle stiffness positively correlates to functional stability (McNair, Wood, and Marshall 1992).

Golgi tendon organs (GTOs) are contraction-sensitive mechanoreceptors and located in the musculotendinous junctions or junctions or muscle-aponeurosis junctions (Jami 1992). These structures are innervated by fast-conducting Ib afferent fibers, and collagen fibers in the tendon organ attach to the muscle fibers and divide into fine fascicles that form a braided structure (Kandel, Schwartz, and Jessell 1991). The organs present a high threshold and low dynamic sensitivity and provide muscle tension information to CNS (Jami 1992). The GTOs are sensitive to detect the active tension that the force developed by contraction (Jami 1992). When the muscle contracts, the tendon organs are stretched, and it straightens the collagen fibers and compresses afferent axon (Kandel, Schwartz, and Jessell 1991). The compression and elongation of the nerve endings trigger GTOs to fire. The sensory signals from GTOs are useful in a variety of motor acts

such as maintaining muscle contraction (e.g. a steady grip on an object) or decreasing levels of muscle tension (Kandel, Schwartz, and Jessell 1991).

Sensory Structures Found in the ACL

Mechanoreceptors such as Golgi tendon organ-like, Pacinian corpuscles, Ruffini endings, and free nerve endings are found in the ligamentous structures including ACL (H. Johansson 1991; H. Johansson, Sjolander, and Sojka 1990; P Sjolander et al. 1989; Per Sjolander, Johansson, and Djupsjobacka 2002). This section will specifically deal with the sensory structures associated with the intra-articular ACL. Johansson and Solomonow et al. addressed the sensory role of the anterior cruciate ligament in several investigations. (H. Johansson 1991; H. Johansson, Sjolander, and Sojka 1990; Solomonow et al. 1987). Using a cat model to explore whether ACL strain may influence muscle reflexes (H. Johansson, Sjolander, and Sojka 1990), it was demonstrated that during ACL stretch, the dynamic sensitivity of the muscle spindles from lateral gastrocnemius and plantaris-soleus (GS), and posterior biceps and semitendinosus (PBSt) were increased. These results showed that the ACL is not only transmitting afferent information but also involved with reflex control to a degree that may change the muscle spindle activity. The authors suggested that the ACL may regulate the stretch reflex and muscle stiffness, thereby also contribute to knee joint stability.

Solomonow et al. (Solomonow et al. 1987) also observed activation of the quadriceps and hamstring muscles during knee loading and ACL stretching in humans and animal models, respectively. They observed the mean absolute value of the EMG in the hamstring and quadriceps during knee joint loading (a maximal voluntary contraction of extension/flexion) in human healthy subjects and ACL deficient patients (Solomonow et al. 1987). Patients with ACLD showed that the EMG activity was increased in the hamstring, and decreased in the quadriceps at about 46 degrees of flexion (Solomonow et al. 1987). Whereas, healthy subjects showed no

irregular EMG activity. During the animal experiment, they also observed EMG in the hamstring and quadriceps while directly stretching the ACL in the adults cat. EMG activity in the hamstring was also increased, while the quadriceps muscle had a short and lower level EMG activity and then became silent. The increased hamstring activation was only found in the high level of ACL loading, not during the low to moderate loads. They suggested that the results demonstrated the existence of reflex arc from mechanoreceptors in the ACL to the hamstring. Moreover, a second reflex arc existed from mechanoreceptors in muscle or joint capsule to provide hamstring activation upon knee instability. Both studies demonstrated that the ACL has a sensory role in influencing the muscle spindle reflex effect, especially in the hamstring muscles.

Sensory Pathways during Joint Loading

When the stimulation is not present to the joint, only a few channels in a mechanoreceptor are open. However, when the joint is mechanically loaded (e.g. pressure, tension, etc.), the mechanical stimulation deforms the membrane and causes a change in the physical characteristics of the cell membrane of mechanoreceptors (Kandel, Schwartz, and Jessell 1991). As a result, more mechanoreceptor channels open and more Na+ and K+ ions flow through the membrane. The influx of Na+ and K+ cause receptor terminals to depolarize and results in the generation of a receptor potential. When the receptor potential reaches the threshold of the cell's trigger zone, an action potential is produced (Kandel, Schwartz, and Jessell 1991). This action potential, which can be considered a signal, is transmitted to the spinal cord by afferent nerve fibers and subsequently to the cerebral cortex to provide information of joint position sense and movement (Kandel, Schwartz, and Jessell 1991). The sensory signals arising from peripheral areas that relate to limb position sense and kinesthesia (sense of limb movement) are conveyed along the dorsal column-medial lemniscal system or spinocerebellar tracts (Kandel, Schwartz, and Jessell 1991; Riemann and Lephart 2002a). The dorsal column-medial lemniscal

system transmits information of tactile sensation and proprioception to the somatosensory cortex. The axon of the dorsal columns ascend to the caudal medulla, the thalamus via the medial lemniscus, brain stem, and then to the cerebral cortex (Kandel, Schwartz, and Jessell 1991).

Neuromuscular Control

Neuromuscular control can be defined as the efferent (motor) response to sensory information (Swanik et al. 1997b). Feed-forward and feedback motor control mechanisms are involved with interpreting afferent information and regulating efferent responses to generate preferred movement and maintain functional stability (Dunn et al. 1986; Kandel, Schwartz, and Jessell 1991). The feedforward mechanism is known as the anticipatory action occurring prior to the sensory detection of the stimulus (R. Johansson and Magnusson 1991). The muscle activation pattern is preprogrammed, usually from previous experience (Dietz, Noth, and Schmidtbleicher 1981). The feedback mechanism of motor control is characterized by numerous reflex pathway continuously processing the afferent information (Dunn et al. 1986; Riemann, Myers, and Lephart 2002). Maintaining and/or modulating variables such as position or force uses the feedback mechanism (Kandel, Schwartz, and Jessell 1991). Because the time it takes to process afferent information is long relative to the time of potentially harmful environmental perturbations, the feedback mechanism is limited to slow and repetitive movements (Kandel, Schwartz, and Jessell 1991). Therefore, it is impossible to only rely on a feedback mechanism to catch a ball or stabilize the joint. Thus, in such movements of catching a ball, stabilizing a joint, or rapidly moving an object, the feedforward mechanism must interpret sensory information correctly to anticipate muscle contraction and to set the position feedback correctly (Kandel, Schwartz, and Jessell 1991).

During the feedforward and feedback mechanism, the neurologic and mechanical components of a joint must work together in order to generate favorable movement and stabilize

the joint (Freeman and Wyke 1967; H. Johansson 1991). This neuromechanical coupling can enhance muscle stiffness (Nielsen et al. 1994; Sinkjaer et al. 1988). In addition, the greater muscle stiffness enables the joint to absorb load and store elastic energy to stabilize the joint better during movements (A R Needle et al. 2014). Thus, enhanced muscle stiffness by neuromechanical coupling may positively influence functional stability (McNair, Wood, and Marshall 1992).

Somatosensation

Somatosensation is described as the processes that encompass all the sensory information from the mechanoreceptive, thermoreceptive, and pain arising from the periphery areas (Riemann and Lephart 2002a). This section will address the role of greater AKL potentially having a negative effect on proprioception components and movement patterns.

Proprioception

Proprioception is defined as sensory information arising from internal peripheral areas of the body that contribute to postural control, joint stability, and several conscious sensations (Riemann and Lephart 2002a). Proprioceptive outcomes have been commonly used to assess the somatosensory system. There are three sub-modalities used to commonly measure proprioception: Kinesthesia, joint position sense (JPS), and sense of tension(Lephart SM 2000). Kinesthesia is commonly assessed as a threshold to detection of passive motion (TTDPM) which is one's ability to not only detect motion but also detect in which direction the motion is occurring (Lephart et al. 1994). JPS assesses the ability to replicate the joint position accurately. It can be performed actively and passively in both open and closed kinetic chain positions (Lephart et al. 1994). The sense of tension is examining the ability to replicate torque magnitude produced by the muscle (Lephart et al. 1994).

It has been known that in knee injuries such as ACL injury, the disrupted ligament or joint capsule may damage mechanoreceptors, which in turn diminish the proprioception (Barrack et al. 1983; Harter, Osternig, and Singer 1992; Kennedy, Alexander, and Hayes 1982; MacDonald et al. 1996; Roberts, Andersson, and Friden 2004). Moreover, individuals with ACL deficient and reconstruction are also known to have greater knee laxity (Mouton et al. 2015; Vacek et al. 2016). Since there is a lack of literature observed the proprioception outcomes associated with the knee joint laxity in healthy participants, this section will also examine in ACL deficient and ACL reconstructed individuals.

The Relationship Between Laxity and Proprioception

The following section will focus on the relationship between knee laxity and proprioceptive outcomes. It is broken down into Healthy, ACLD, and ACLR populations.

Proprioception and Knee Laxity in Healthy Group

Rozzi et al. reported on the relationship between the knee joint laxity and proprioception in 34 healthy individuals (Rozzi et al. 1999). Specifically, they examined sex differences in anterior knee laxity (AKL) and neuromuscular function including kinesthesia, balance, the amount of time required to generate a peak torque of the knee flexor and extensor muscles. Additional they performed an electromyography assessment of lower extremity muscles' activity in response to a landing task. Kinesthesia was measured by threshold detection of passive motion (TTDPM) into knee flexion and extension in a seated position with the inflated boot for both feet, with eyes blindfolded, and with a headset in order to remove the cutaneous, visual, and auditory cues. They reported that females had significantly higher AKL, longer time to detect joint motion, and greater EMG peak amplitude on hamstring muscle during landing compared to males. They suggested that the excessive joint laxity in females may contribute to diminished joint proprioception, and it might lead to having a compensatory muscle activation pattern. The Rozzi

et al. study suggests that congenital greater joint laxity is associated with lesser joint proprioception. Thus, there is a potential that greater laxity may have a resultant somatosensory influence on dynamic knee stabilization. Their finding is similar to the result of Laudner et al. (2012)(Laudner et al. 2012). Laudner measured proprioception (active joint position sense) and anterior glenohumeral (GH) laxity in 30 collegiate baseball players. The results showed that the shoulder proprioception decreased as anterior glenohumeral (GH) laxity increased in the healthy group ($r = 0.56$, $P = 0.001$). Even though the study by Laudner et al. observed shoulder joints, it still gives us valuable evidence of the significant relationship between greater joint laxity and poor proprioception in healthy individuals.

Proprioception and Knee Laxity in ACLD Patients

Several researchers have investigated the relationship between the knee laxity and proprioception in ACL deficient (ACLD) individuals. Roberts et al. examined knee joint proprioception, laxity, and age in the ACLD group (Roberts, Andersson, and Friden 2004). Subjects included a total of 54 patients with an ACL injury, and all of the patients had a complete ACL rupture diagnosed by the arthroscopy. Proprioception was assessed by measuring TTDPM of the knee (toward knee extension and flexion) at a mean of 2.7 years after arthroscopy. They reported a significant correlation between higher TTDPM (greater threshold to detect) and greater anterior knee laxity. They suggested the correlation may be due to the fact that the receptors innervated in the knee joint may be adapted to a looser tension of the structures such as joint capsule and ligament, and it may increase the threshold to detect motion. However, this study measured the AKL by manual Lachman test (graded 0 to 3: 0=no increase in laxity, 1=slight increase in laxity, 2=obvious increase in laxity, 3=increase in laxity), which can be biased and not objective. Thus, the limitation needs to be considered when interpreting the results. Similarly Barrack et al. measured knee laxity using KT-1000 and assessed proprioception via TTDPM in

ACL deficient patients 3 months after injury (Barrack, Skinner, and Buckley 1989). Barrack and his coworkers reported negative correlation between joint position sense and knee laxity ($r=0.465$, $p=0.029$). They suggested that decreased proprioception may be a result of increased joint laxity. The loss of proprioception due to damage of mechanoreceptors in ACL possibly contribute to increasing instability over time by loss of dynamic stabilizing reflexes. The results show evidence of a negative relationship between proprioception and knee laxity in ACL deficient individuals.

Proprioception and Knee Laxity in ACLR Patients

Various proprioception outcomes, as well as laxity measures, have been assessed in studies of ACLR patient. MacDonald et al. examined proprioception, patient satisfaction scores, and knee laxity in ACLD patients, ACLR patients, and healthy control individuals (MacDonald et al. 1996). Proprioception was assessed by the threshold for perception of passive knee movement (flexion or extension). Laxity testing was performed by using the KT-1000 for both of ACLD and ACLR groups. The results revealed a significant difference in TPPM between the involved and noninvolved knee in ACLD ($p=0.0041$) and ACLR groups. Those individuals with ACLD and ACLR showed a significant increase in threshold to detection of change of joint position of the knee, which represents decreased proprioception. However, the ACLR and ACLD group had no significant correlation between TPPM and knee laxity. This result is inconsistent compared to the previous discussion of ACLD populations (Barrack, Skinner, and Buckley 1989; Roberts, Andersson, and Friden 2004), which reported negative correlation between proprioception and laxity in ACLD individuals. The inconsistency results may be due to the different period of time after injury. MacDonald et al. reported average 5.5 years since injury, whereas, it was 2.7 by Robert et al. and 1.7 years in Barrack et al.'s study. The time between injury and testing was much longer in the study by MacDonald et al. (5.5 years) compared to Barrack et al. (1.7 years)

and Roberts et al. (2.7 years). It may indicate that ACLD individuals may compensate to receive sensory information over time. Moreover, MacDonald et al. also showed no correlation between proprioception and laxity in ACLR individuals. It may indicate that ACL reconstruction may improve the mechanical stability of the knee joint, which may decrease anterior-posterior knee laxity. However, individuals with ACLR still shows a significantly reduced proprioception in the injured limb compared to the uninvolved limb. It may indicate that patients with ligament impairment may not be able to enhance their proprioception even with mechanical stability improvement. Thus, it would be difficult to show a negative correlation between proprioception and laxity. Harter et al. also demonstrated no correlation between proprioception outcome and laxity (Harter, Osternig, and Singer 1992). They examined ACLR patients at an average of months after surgery. They measured the joint position sense and knee laxity. Knee joint laxity of the reconstructed limb was assessed using both subjective and objective measures. The modified anterior drawer test was used to conduct the subjective assessment and a KT-1000 was employed to evaluate knee laxity objectively. The results showed no significant differences in knee joint position sense between the ACLR knees and contralateral normal knees ($p>0.05$). There was no significant correlation between joint position sense and laxity tests (KT-2000 and anterior drawer) either ($p>0.13$). This result was in disagreement with MacDonald et al. who found a statistically decreased proprioception in ACLD and ACLR individuals' injured limb. These inconsistent results could be due to the different methodologies applied to assess propriopcetion. Harter and his coworkers failed to account for cutaneous and auditory input during the proprioception testing, whereas the study from MacDonald et al. eradicated cutaneous and auditory cues. Thus, participants in the Harter et al. study may have employed compensatory strategies to receive proprioceptive information from the other sensory resources such as cutaneous receptors. In addition, the time interval from the surgery to the proprioceptive examination was not consistent

between the two studies. The average time interval by MacDonald et al. was 27.5 months, whereas 49.2 months by Harter et al. Even though the above two studies show different results of proprioception in ACLR patients, both studies showed no significant correlation between proprioception and knee laxity in ACLR patients. This is might because sensory receptors related to joint stability may compensate to receive proprioceptive information, it possible due to the rehabilitation after surgical procedure. In addition, the improvement of the mechanical stability after ACL reconstruciton may influnece the relationship between laxity and proprioception.

According to the studies from Rozzi et al. and Laudner et al., higher joint laxity related to diminished proprioception in healthy individuals. There was also a correlation between knee laxity and proprioception in the ACLD group, based on the results from Roberts et al. and Barrack et al. It may indicate that individuals with greater knee laxity caused by injury or inherent may have diminished sensory information arising from peripheral areas. Although there was no correlation between laxity and proprioception after operative reconstruction, the relationships between greater knee laxity and the poorer proprioception in the healthy and ACLD group were observed.

The Mechanism Behind Reduced Proprioception in Individuals with Greater Knee Laxity

Individuals with greater joint laxity have been suggested to have poor sensory input to the CNS in stabilizing the joint during physical movement (functional stability) (Laudner et al. 2012; Rozzi et al. 1999). One of the reasons behind the sensory deficit may be due to the fact that individuals with greater AKL have less tension in the anterior cruciate ligament at a given deformation. Previous research has shown the negative relationship between ligament laxity and tension (Fleming et al. 2001; Yasuda et al. 1997). Since the mechanoreceptors are stimulated by tension (Zimny, Schutte, and Dabezies 1986), the low tension in greater AKL knee may

negatively influence the firing rate of the mechanoreceptors innervated in ACL. Thus, individuals with greater AKL may have a diminished number of stimulated mechanoreceptors and/or take more time to stimulate them to transmit the sensory signals to the CNS. Therefore, individuals with AKL may have poor sensory information related to joint position sense and movement.

Previous research supports the above hypothesis. While limited in scope, there is a small collection of research to help understand the relationship of AKL and somatosensation. Rozzi et al. examined sex differences in the knee joint laxity and neuromuscular function including proprioception (threshold to detect passive motion) (Rozzi et al., 1999). Females had significantly greater AKL and longer time to detect joint motion moving into the knee extension. They suggested that inherent excessive joint laxity in females may contribute to decreasing joint proprioception, which may result in the neuromuscular system being less sensitive to potentially damaging forces. These results are evidence that greater laxity knee needs more time or may need to be displaced further to stimulate the mechanoreceptor in order to detect the joint motion. Shultz, Carcia & Perrin observed muscle activation patterns including reflex time between greater (KT>7mm) and lower AKL (KT<5mm) individuals during a lower extremity perturbation (forward and either internal or external rotation of the trunk during single-leg stance) (Shultz, Carcia, and Perrin 2004). The individuals with greater anterior knee laxity showed a 16ms delay in reflex time in biceps femoris following lower extremity perturbation. The results provide evidence that the knee with greater laxity needs longer time or needs to be stretched further to stimulate the mechanoreceptors to regulate muscle coordination in order to stabilize the joint from perturbation. The greater reflex time and longer time to detect joint motion in individuals with greater knee laxity may be due to the lower tension of the ligament. This may lead to poor sensory input or taking more time to stabilize the knee joint, thus, individuals with greater knee laxity may be less able to stabilize the joint from the potential damaging force.

In addition, greater knee joint laxity may also lead to diminishing muscle stiffness. Muscle stiffness refers to the ratio of change in force to change in length (k=Δ Force/ Δ Length) (Blackburn, Norcross, and Padua 2011). When the joint undergoes a given displacement, a higher AKL knee will have less tension of the ligament. This may result in lower mechanoreceptor firing and a resultant lack of afferent input to the CNS in individuals with greater AKL. Those individuals may have diminished sensory signals to the gamma motor neuron; thus, it may lead to a decrease in Ɣ-muscle spindle reflex system and results in decreased muscle stiffness. In support of this premise, individuals with high knee laxity have been reported to have decreased muscle stiffness compared to the lower laxity individuals (Blackburn, Norcross, and Padua 2011; Shultz et al. 2012). Blackburn, Norcross, and Padua observed the anterior tibial translation by calculating the difference between the anterior displacement of the thigh and shank segments during perturbation to the posterior proximal shank when subjects lay down in prone position with 30 degrees of hip and knee flexion. They also measured hamstring muscle stiffness by quantifying the damping effect of the hamstring oscillatory knee flexion/extension (Blackburn, Norcross, and Padua 2011). They found a significant negative correlation between anterior tibial translation and muscle stiffness ($r=-0.538$, $p=0.002$). Shultz et al also demonstrated that females showed a greater laxity (varus-valgus laxity (degrees): female=11.3±2.9, male=6.7±2.3, $p<.05$; internal-external laxity (degrees): female= 27.8±7.6, male= 22.6±4.8, $p<.05$) and less incremental stiffness in the frontal and transverse plane, but not in the sagittal plane compared to males (Shultz et al. 2012). The above evidence demonstrated that individuals with greater knee laxity may have less muscle stiffness (Blackburn, Norcross, and Padua 2011; Shultz et al. 2012).

This diminished muscle stiffness may decrease the sensitivity of pre-activation and reactivation of the muscle, and it may result in decreased functional stability in individuals with greater knee laxity. McNair measured hamstring muscle stiffness in three different maximal

voluntary efforts (30%, 45%, 60%) and functional stability using the Noyes questionnaire, which provides subjective information of the subject's knee condition, in patients who had complete ACL rupture. The questionnaire includes the categories related to return to sports activity, specific tasks in daily activities, sports that cause symptoms, and the patient's attitude to their knee joint. The results revealed a significant and positive correlation between hamstring muscle stiffness and perceived functional stability in all three different maximal voluntary effort ($r=0.71$, 0.72, 0.62, $p<0.05$). This diminished muscle stiffness may, thus, decrease the ability of the joint to stabilize from the potential damaging force.

The Relationship Between Knee Laxity and Movement Function

Since greater knee laxity has been reported as one of the strongest predictors of an ACL injury (Loudon, Jenkins, and Loudon 1996; Uhorchak et al. 2003; Vacek et al. 2016; Woodford-Rogers, Cyphert, and Denegar 1994), the relationship between knee laxity and mechanical movements of the lower extremities has also been studied. Shultz et al examined AKL, genu recurvatum (GR), and general joint laxity (GJL) during a drop jump landing in healthy males and females (Shultz et al. 2010). All of these three laxity valuables showed significant relationships with greater knee work absorption and knee stiffness and lower ankle stiffness in females. They also reported that females with above-average AKL (8.6mm), GJL (3.6) and average GR (3.5) were more likely to have greater knee work absorption ($R^2=.43$), knee stiffness ($R^2=.18$), and lower ankle stiffness ($R^2=.13$) compare to females with average AKL (6.6mm), GJL (1.9), and GR (3.5). This may be due to a protective strategy in order to reduce the workload to the knee joint. The author also suggested that this landing strategy may also contribute to decreasing athletic performance, thus, it may result in a decreased ability to stabilize the joint when a potential damage force is applied to the joint.

Shultz, Carcia, and Perrin (Shultz, Carcia, and Perrin 2004) also examined the effect of AKL on muscle activation patterns prior to and following a perturbation. They included healthy college female athletes; below-average AKL (<5mm) and above-average AKL (>7mm). The muscle activity of the vastus medialis and vastus lateralis, medial hamstring and biceps femoris, and medial and lateral gastrocnemius were measured by electromyogram (EMG). The EMG signals were recorded prior to the perturbation during maximal voluntary isometric contraction of each muscle, and also during the perturbation trials. The reflex time was also measured by recording the time delay between the onset of the perturbation and quadriceps, or hamstring and gastrocnemius. The results showed that the biceps femoris had a 16ms greater delay in above-average AKL group than below-average AKL group. The above-average AKL group also had a higher biceps femoris activation during the perturbation. However, the above-average AKL group had a significantly less magnitude of change from the pre to the post-perturbation in the medial and the lateral gastrocnemius compared to the below-average AKL group. This was due to higher levels of muscle activity on medial gastrocnemius prior to the perturbation in the above-average AKL group, but not for the lateral gastrocnemius. The researchers suggested that the greater delay of biceps femoris could indicate a proprioceptive deficit in individuals with greater AKL. They also suggested that a greater pre-activity of medial gastrocnemius and greater muscle activation of the biceps femoris would imply a compensatory strategy in the above-average AKL group to aid in joint stabilization. The above studies demonstrate knee laxity may negatively influence sensory pathway, through mechanoreceptors innervated around the joint, to have a proprioceptive deficit. The diminished sensory information from the peripheral area to the CNS in individuals with greater knee laxity may lead to having compensatory movement patterns such as greater hamstring muscle activation or stiff landing mechanics.

Both poor proprioception and mechanical weakness may contribute to decreased functional joint stability in individuals with greater AKL. It may explain to us why an individual with a greater knee laxity has a higher risk of ACL injury. The studies related to greater knee laxity and the sensory system and motor system showed us that greater knee laxity has a negative influence on the sensory system and motor system.

In order to maintain functional stability, the sensorimotor system, including central integration and processing components (Lephart SM 2000), performs a complex system of functions to stabilize the joint and generate the desired motion. While research has been conducted on sensory and motor system's role in joint stabilization, the role of the CNS, especially the brain's role, is comparatively far less understood. Therefore, identifying the brain's function in joint stability will help us fully understand the sensorimotor system as it relates to joint stability.

Neuroplasticity

Neuroplasticity, or brain reorganization, is the unique ability of the human brain to modify neuronal circuits depending on interaction with an environment (Daphne Bavelier and Neville 2002; B. B. Johansson 2004). Neuroplasticity can be occur both functionally and morphologically, and can be caused by sensory deprivation (Liepert, Tegenthoff, and Malin 1995), experience (Maguire et al. 2000), peripheral lesions (Dettmers et al. 1999), and/or CNS injury (Sabbah et al. 2002). Functional cerebral reorganization can be thought as a different pattern of cerebral activation. For example, it is known that deaf signers and hearing subjects activate different brain regions during visual motion processing (D Bavelier et al. 2001). Morphological neuroplasticity can be defined as brain physical structure changes. For example, long-term experienced taxi drivers show larger volume of gray matter in the hippocampus area, which plays a primary role in spatial navigation, compared to the non-taxi drivers (Maguire et al.

2000). Our brain is constantly changing throughout our lifetime and it is important to adopt continuous changes during aging, learning, experiences, and injuries.

Functional Neuroplasticity Caused by Sensory Deprivation

While experience, peripheral lesions, and CNS injury (among numerous other things) may result in neuroplasticity, this document will focus on neuroplasticity associated with sensory deprivation. The alteration of sensory input resulting from joint immobilization (Liepert, Tegenthoff, and Malin 1995) and ACL injury are understood to result in neuroplastic changes (Kapreli et al. 2009; Alan R Needle, Lepley, and Grooms 2017). Liepert et al. observed the motor cortex areas of tibial anterior muscles in patients with unilateral immobilization of ankle and healthy control groups using the transcranial magnetic stimulation (TMS) (Liepert, Tegenthoff, and Malin 1995). Patients with immobilization had complicated fractures in distal parts of the tibia or talus, and the mean duration of immobilization was 16 weeks, ranging from 0-60 weeks (several subjects were examined within 24 hours after immobilization). Researchers applied motor evoked potentials for both groups and measured the surface area ratio (areas of the injured leg/ area of the unaffected leg). Immobilization group showed that there were no significant differences in the motor cortex size within the first days of immobilization, however, there was a significant reduction of the motor cortex area representing the anterior tibialis after 4-6 weeks of immobilization compared to the control group ($p<0.01$). Moreover, the reduction of the motor cortex area was positively correlated with the duration of immobilization ($r=0.66$, $p<0.01$), which means motor cortex size decreases further with longer term of immobilization. The results show functional neuroplasticity occurs during immobilization and the associated changes in sensation that accompany typical immobilization. The author suggests that it may due to deafferentation, which is a reduced afferent input from muscle spindle and mechanoreceptors innervated in the joint and skin as the reduction of tibialis anterior activity. This finding indicates

the possible functional neuroplasticity influenced by impaired sensory input due to lower limb injury and immobilization.

Functional Neuroplasticity Associated with an ACL Injury and Reconstruction

There are several reports in the literature of assessing brain activation in ACL injured patients using neuroimaging techniques. Although the current investigation will be focused on healthy individuals who have high or low knee laxity, previous research in ACL injury patients provide evidence that lack of sensory input due to ACL impairments may influence to alter cortical activation. Similar to individuals with high knee laxity, it is well known that ACLD and ACLR individuals have decreased proprioception (MacDonald et al. 1996; Roberts, Andersson, and Friden 2004) as well as increased knee laxity (Barrack, Skinner, and Buckley 1989; Roberts, Andersson, and Friden 2004; Vacek et al. 2016). In this section, I will review the studies that used functional magnetic resonance image (fMRI) (Grooms et al. 2017; Kapreli et al. 2009) and electroencephalogram (EEG) (An et al. 2019; Baumeister, Reinecke, and Weiss 2008) paradigms to understand the brain's role in motor function in patients with ACLD and ACLR.

ACL Deficient Patients

fMRI Approach

ACLD patients can help us to understand the role of sensory alterations to the brain. Kapreli et al investigated the brain activity patterns during knee extension-flexion movement in chronic ACLD patients and healthy control individuals to identify the possible brain reorganization due to the peripheral injury (Kapreli et al. 2009). While measuring fMRI data, the patients were asked to perform a unilateral extension-flexion movement of the involved or matched control knee. The movement was triggered by auditory command, and metronome was used to provide a cue to flex or extend the knee. They found that ACLD patients had increased brain activation in the contralateral pre-supplementary motor area (pre-SMA; preparation of

movement), contralateral posterior secondary somatosensory area (SIIp; tactile representation), and ipsilateral posterior inferior temporal gyrus (pITG; visual process). These findings indicate that the deafferentation caused by ACL injury (MacDonald et al. 1996; Roberts, Andersson, and Friden 2004) may influence a functional reorganization of the brain. The main findings of this study were that individuals with ACLD demand more cortical resources to process visual information and to prepare the movement during a simple motor task. This may be due to chronically altered sensory input caused by an ACL injury (see the previous section for a detailed review of the pertinent literature on ACL receptors).

EEG Approach

Miao et al investigated the EEG signals in ACL deficient patients and healthy control individuals while performing various lower extremity movements (walking, jogging, and landing) to identify cortical activation changes influenced by ACL injury (Miao et al. 2017). Sixteen subjects with unilateral ACL injury (10 right side injuries and 6 left side injuries) were tested prior to the reconstruction surgery, and fifteen healthy subjects were tested as a control group. The participants performed the following three different movement tasks: walking, walked 20 meters naturally; jogging, jogged 20 meters; and landing from 25 cm high step. All three movement tasks were performed while wearing a Cognionics EEG 32 channel amplifier with sampling at 1000Hz. The results showed that all EEG band powers (Delta, Theta, Alpha, Beta) in ACL deficient (ACLD) patients were significantly higher compared to the control group. The author suggested that the increased in those band powers could be additional noise in the system due to lack of sensory signals from the ACL. Increased alpha power could be related to the suppression of a process (Allen, Coan, and Nazarian 2004), especially suppressing unrelated information (von Stein and Sarnthein 2000). Moreover, greater alpha power may reflect increased attention (Babiloni et al. 2010; Del Percio et al. 2011). Thus, the author suggested that individuals

with ACLD need more cognitive resources to perform the tasks. Moreover, the power of EEG signals in the frontal-parietal lobe became significantly stronger and asymmetric during jogging, walking and landing in the ACLD group. The frontal lobe is involved with attention and information storage, and the parietal lobes are associated with feed-forward signals, proprioceptive information, and fine motor movements of lateral limbs (Aziz-Zadeh et al. 2002). Thus, increased EEG signals on the frontal-parietal lobes in ACLD individuals may indicate that ACL injury may negatively influence the proprioceptive input and feed-forward process, thus those individuals require further sensor information related to it. However, this EEG study has a limitation of potentially excessive noise from the movement tasks (walking, jogging, and landing). Although EEG techniques are more practical to use during physical movements compared to the fMRI, the research approach is challenged to reduce noise that accompanies movements.

ACL Reconstruction Patients

fMRI Approach

Grooms et al. measured brain activation in patients who have undergone ACL reconstruction and matched healthy control individuals during a simple lower extremity motor task (Grooms et al. 2017). Their movement task was similar to Kapreli et al. (Kapreli et al. 2009), which asked patients to perform knee extension-flexion, however, they used the visual prompt instead auditory command to trigger the movement while using a metronome to pace the movement to impose a constant timing. Their results showed that ACLR patients had diminished activation of the ipsilateral motor cortex and cerebellum compared to the control group. In addition, ACLR patients had higher cortical activation in the contralateral primary motor cortex, ipsilateral lingual gyrus (visual process), and ipsilateral secondary somatosensory cortex (tactile representation). The findings demonstrate that ACL injury and subsequent ACLR may alter the

cortical activation in the brain regions associated with sensory, motor, and visual processing. The authors suggested that increased cortical activation of motor cortex may be associated with the biomechanical insufficiencies (strength, range of motion) after ACL injury and reconstruction. Individuals with ACLR have developed altered motor control strategies to compensate their insufficiencies to perform even simple movements. ACLR individuals also demonstrated higher activation on the somatosensory cortex, which is responsible for the somatosensory process and painful stimuli (Chen et al. 2008). It may indicate a functional cortical reorganization processing sensory information following knee injury and treatment. Moreover, ACLR individuals showed increased ipsilateral lingual gyrus activity, which is involved with visual feedback and navigation (James et al. 2002; Macaluso, Frith, and Driver 2000). The visual cortex is also known to adapt to altered sensory information (Baumeister, Reinecke, and Weiss 2008), and also have a connection with the sensorimotor cortex to control motor movements (Bracci and Peelen 2013). Thus, the authors suggested that the increased lingual gyrus activation may be associated with the adapted sensory feedback due to the loss of ACL mechanoreceptors. The above results demonstrate possible functional neuroplasticity followed by ACL injury and surgical procedures compensating for the loss of sensory input to perform the movement.

EEG Approach

Several studies have observed electrophysiological changes in ACLR patients during joint loading, force control, and joint position sense tests (An et al. 2019; Baumeister et al. 2011; Baumeister, Reinecke, and Weiss 2008). An et al compared 17 ACLR patients' brain activity and 17 healthy control individuals using EEG while participants are performing anterior-posterior knee joint loading using KT-2000 (An et al. 2019). The ACLR group had a reconstruction within the last 10 years (3.48±2.06 years) and had been cleared to return to previous activity level. The results showed that ACLR patients had higher cortical activation in the somatosensory cortex

during knee joint loading compared to the healthy control matched knee ($p=0.013$) and uninjured knee ($p=0.001$). Moreover, the positive relationship was shown between cortical activation and joint loading ($r=0.501$), while no relationship was found in a healthy control group. The increased neural demand in the somatosensory cortex coupled with greater joint laxity in ACLR patients may indicate the compensatory protective neuroplasticity for the increased anterior knee displacement during loading.

Cortical activity during force reproduction in ACLR patients has also been studied (Baumeister et al. 2011). Baumeister et al. measured EMG and EEG signals during the force reproduction tasks as they performed a 50% maximal voluntary isometric contraction (Baumeister et al., 2011). No significant difference was found in task accuracy and neuromuscular activity between groups. However, EEG analyses demonstrated that ACLR patients show a significantly higher frontal Theta power. The frontal Theta activity has been known as a major role in working memory function (M. E. Smith, McEvoy, and Gevins 1999). The increased activity on the frontal Theta power may be interpreted that although ACLR patients can perform the force reproduction tasks equal to the healthy individuals, they need to use more neurocognitive resources in order to perform the task. A similar finding was also demonstrated in another study by Baumeister (Baumeister, Reinecke, and Weiss 2008). They measured EEG in ACLR patients and a healthy control group while performing joint position sense test. The participants were asked to reproduce a given knee angle of 40° after the visual feedback was withdrawn. The result showed that ACL patients had significantly more error when reproducing the target angle compared with the control group ($p<0.05$). ACL patients also revealed significantly more power at frontal Theta power and significantly less Alpha-2 power during the joint position reproduction test. The frontal Theta plays an important role in the human attentional system (LaBerge and Buchsbaum 1990; Vogt, Finch, and Olson 1992). Moreover, the Alpha

activity is known to have an inverse relationship with the neuronal activation during cognitive and motor process (Gevins et al. 1997). Thus, it may indicate that ACLR patients require more neuronal activation and more focused attention (cognition) during the complex performance.

While acknowledging the retrospective nature of the above studies, they reflect a possible brain functional reorganization influenced by ACL injury and reconstructive surgical procedure. The EEG studies show greater cortical activation in the somatosensory cortex and frontal cortex region during sensory stimulus tasks (J Baumeister et al., 2008; J Baumeister et al., 2011). The studies using fMRI indicate the different brain activation patterns during knee extension-flexion exercise in ACLD (Kapreli et al. 2009) and ACLR (Grooms et al. 2017) individuals. Both studies reported significantly higher activation including the somatosensory cortex and visual cortex. It may emphasize that impaired sensory input may alter the cortical level of information processing. An increased cortical activation during a performance in ACLD and ACLR patients also reflects that individuals with compromised sensory input may require more central resources to compensate for their sensory deficit.

The Potential for Functional Neuroplasticity Resulting from High Knee Laxity

To the best our knowledge we are unaware of investigations of laxity on neuroplastic changes. Given the above discussed findings of increases in cortical activation in ACLR and ACLD patients, it can be theorized that individuals with high knee laxity may have greater cortical activation in the somatosensory cortex compared to the lower knee laxity individuals. As mentioned before, this is due to the fact that those individuals may have decreased sensory input resulting from low tension of the anterior cruciate ligament and lower resultant mechanoreceptor firing rate. Impaired sensory information may increase connection from pre-existing sensory resources to the CNS, it may lead to functional neuroplasticity.

It is known that an alteration to sensory input, such as amputation or nerve transection, may increase the efficacy of the pre-existing connection from other the peripheral sensory resources to the cortex to transmit the impaired sensory information (Cusick et al. 1990; Rasmusson 1982; Ziemann, Hallett, and Cohen 1998). Cusick et al. observed the somatosensory cortical hind paw area in rats after the sciatic nerve transection for 7-9 months. Prior to the sciatic nerve transection, 15% of the cortical area was dominantly activated by low threshold tactile input from the saphenous nerve, and 85% were from the sciatic afferent. After the sciatic nerve transection, the saphenous nerve representation area in the somatosensory cortex was gradually expanded from day 1 to 9 month. At 7-9 months, the saphenous area in the somatosensory cortex was not significantly different than the normal total hindpaw representation (normal saphenous + sciatic). This finding supports that loss of the primary sensory input may unmask the pre-existing connections to the CNS. This might occur due to the fact that most of the sensory modalities are transmitted by more than one serial pathway (Kandel, Schwartz, and Jessell 1991). The separate pathways that transmit sensory information from the peripheral area to the CNS are known as parallel pathways. The parallel pathways connect the remaining pathways to transmit the aspect of altered sensation after damaging one sensory pathway (Kandel, Schwartz, and Jessell 1991). Thus, the altered sensory information from the primary sensory resource may increase the sensory transmission from other pre-existing connections to the CNS by increasing neuronal membrane excitability and synaptic efficacy and removal of local inhibition (Rossini and Pauri 2000; Ziemann, Hallett, and Cohen 1998). Thus, it is possible that if individuals with high laxity knee had reduced sensory input to the CNS that it may increase the efficacy of other sensory resources, such as cutaneous receptors, to transmit the afferent signals to the brain to compensate for a lack of sensory information.

Morphological Neuroplasticity Influenced by Deafferentation

Deafferentation not only leads to functional neuroplasticity but also leads to morphological brain reorganization in brain gray matter. Studies have observed structural brain reorganization in individuals with deafferentation influenced by pain (May 2008; Metz et al. 2009), nerve transection (K. S. Taylor, Anastakis, and Davis 2009), vestibular failure (Gottlich et al. 2016; Hufner et al. 2009), and carpal tunnel syndrome (Maeda et al. 2013).

Maeda et al. measured brain gray matter and white matter using MRI when comparing the patients with carpal tunnel syndrome versus healthy controls (Maeda et al. 2013). T1-weighted structural MRI was measured to identify brain gray matter. The results revealed that carpal tunnel syndrome patients had significantly reduced gray matter volume in the primary somatosensory cortex, thalamus, and frontal pole. The gray matter volume in the primary somatosensory area was also positively correlated to nerve conduction velocity ($r=0.45$, $p<0.01$). The author suggested that this structure neuroplasticity may be triggered by peripheral nerve pathology and altered somatosensory afference. However, this study did not control the patient's rehabilitation status. Since it is known that rehabilitation may restore the anatomical structures of the brain, the gray matter thickness was increased 6 months after treatment of chronic low back pain (Seminowicz et al. 2011). Thus, controlling activity levels would be critical in fully understanding morphologic changes following injury. However, these works still provide evidence to support structural changes of brain influenced by deafferentation.

Taylor, Anastakis, and Davis also used MRI to measure brain functional and morphological plasticity in patients with nerve transection and surgical repair in the median and ulnar nerve (minimum 1.5 years prior to the study enrolment, recovery time 1.5 -8 years) (K. S. Taylor, Anastakis, and Davis 2009). They measured vibration detection, mechanical detection, and nerve conduction velocity as well. The results demonstrated that patients have less activation

in the primary and somatosensory cortex. Moreover, patients had 13-22% less gray matter thickness of the primary and secondary somatosensory cortex compared to the control group. The cortical reduction also revealed a negative correlation with vibration and mechanical detection threshold on the primary and secondary somatosensory cortex (vibration: $p<0.001$, $r= -.80$ (primary), $r=-.91$ (secondary); mechanical: $p<0.001$, $r=-.83$ (primary), $r=-.85$ (secondary), which means poor detection of vibration and mechanical loading (increased threshold) was associated with less gray matter thickness. These results indicate that the nerve transection may negatively influence proprioceptive functions, and the somatosensory deficit may contribute to reducing cortical activation and gray matter thickness.

Gray matter reduction is also shown in patients with chronic pain (Metz et al. 2009), vestibular nerve failure (Gottlich et al. 2016; Hufner et al. 2009), and amputation (Draganski et al. 2006; Di Vita et al. 2018). Lower limb amputees not using prostheses had a decreased gray matter volume in the bilateral cerebellum compared with healthy control individuals (Di Vita et al. 2018). A similar result was found in upper and lower limb amputees (Draganski et al. 2006). Individuals with upper or lower limb amputation had a reduced gray matter volume in the bilateral thalamus (Draganski et al. 2006). The inconsistency of brain regions may be due to the different part of amputated body and different time frame from amputation. It still, however, provide evidence of gray matter volume reduction following amputation, which has an associated loss of somatosensation from the amputated body region.

The above studies revealed that deafferentation can modify not only functional brain reorganization but also structural adaptation. This may have related to atrophy and/or loss of neurons or glia, or loss of dendritic spine density (May 2008; Metz et al. 2009). The detailed mechanism behind structural neuroplasticity will be mentioned next session.

The Potential for Morphological Neuroplasticity Resulting from High Knee Laxity

Similar to the gray matter reduction influenced by deafferentation and associated decrease in sensory input, it may be hypothesized that individuals with high knee laxity may also have structural neuroplasticity caused by a lack of sensory input. As mentioned above, individuals with high knee laxity potentially have poor sensory input, and it may result in reduced gray matter volume in the somatosensory area. While the precise physiology of structural neuroplasticity is not fully understood yet, one view suggests the plasticity is a growth/elimination of axonal and dendritic spines (Darian-Smith and Gilbert 1994; Florence, Taub, and Kaas 1998). The axon plays a primary role in transmitting an electrical impulse from the cell body to the synapse, and it is located in white matter (Scott, Allen, and McCarthy 2014). Dendrites receive signals from other cells and play an integrative function, and are located in gray matter (Scott, Allen, and McCarthy 2014). Dendrites in the brain contain spines, which are the tiny protrusions on the dendrites (Purves et al. 2017). These dendritic spines are known as primary sites of synaptic plasticity (Calverley and Jones 1990). It has been known that the dendritic spines have appeared and disappeared over a period of days to weeks, although the number of dendric branches is stable (Trachtenberg et al. 2002). Trachtenberg et al. observed dendrites on a daily manner in rats over periods of 8-10 days and less frequently thereafter. They found that about 20% of dendrites disappeared between test sessions from one day to the next day. The disappeared spines were balanced by the formation of new spines.

The number of dendritic spines can change in response to hormonal changes (Yankova, Hart, and Woolley 2001), sensory stimulation (Calverley and Jones 1990), and environmental factors (B. B. Johansson and Belichenko 2002). Johansson and Belichenko compared the dendrite and spine morphology of pyramidal cells (a type of multipolar neuron found in the brain) of the somatosensory cortex between rats housed in a standard environment and an enriched

environment (B. Johansson 2003; B. B. Johansson and Belichenko 2002). The results demonstrated that the number of dendrite branches and spines in the cortical cortex is increased in the enriched environmental rats than the standard environmental rats. The results indicate that the density of dendric branches and spine can be changed responding to the environment.

Sprouting axon densities can also change following changes to sensory input. Darian-Smith and Galibert observed the cortex in young adult cats following retinal lesion (Darian-Smith and Gilbert 1994). They observed that cortical scotoma was recovered visually after 3-9 months of retinal lesion, which represented functional neuroplasticity. Then, they compared the axon densities between the cortex that underwent neuroplastic changes and the normal cortex (un-lesioned animal). There were 57-88% greater axon densities in the cat with retinal lesion than the control group. The formation of sprouting axons was also found in rats with sciatic nerve transection (Fitzgerald, Woolf, and Shortland 1990) and laminectomy (McMahon and Kett-White 1991), and also in monkey with spinal cord transection (Florence et al. 1993) and peripheral injury (Florence, Taub, and Kaas 1998).

The above results explain the possible reason behind structural plasticity through the formation and elimination of axon and dendrites spines in the brain cell. It is assumed that the number of dendrites and dendritic spine changes may affect the gray matter volume and changes of axon densities may influence the white matter volume (Purves et al. 2017). Likewise, individuals with greater knee laxity may have a dendritic spine reduction due to altered sensory input, and it may result in less gray matter volume in the somatosensory cortex, which is associated with receiving sensory information, compared to individuals with low laxity knee individuals. This sprouting and retraction of the dendritic spines are also accompanied with synapse formation and elimination (Trachtenberg et al. 2002). Thus, changes number of the axon

and dendritic spines may also change synaptic efficacy and may subsequently influence functional plasticity as well.

Identifying functional and morphological neuroplasticity associated with known risk factors of ACL injury will help us to better understand the sensorimotor system in individuals who at high risk of the injury. Pinpointing differences in sensorimotor system functions in individuals with a high risk of ACL injury is the first step towards furthering research to prevent ACL injuries. Moreover, determining the brain's role in individuals with high knee laxity may impact injury prevention programs. If we can understand the mechanism of the processing of the cortical information as well as the structural differences in high laxity individuals compared to low laxity, it may help us to develop a brain-based intervention program that would optimize sensorimotor function. Brain-based rehabilitation activities may help those individuals to increase the efficacy of facilitating sensory information. The increased afferent system may also improve the reflex excitability as well as muscle stiffness and functional stability (McNair, Wood, and Marshall 1992). Improved ability to stabilize the joint during physical movements (functional stability) may help individuals who are at high risk of ACL injury to prevent the injury.

Neuroimaging Techniques

Various neuroimaging techniques have been used to measure human brain structure and activation in research and clinical settings. Neuroimaging techniques allow us to non-invasively measure the human's brain. There are two primary types of techniques. The first measures brain metabolism including blood oxygen level and glucose level (Rossini and Pauri 2000; Scott, Allen, and McCarthy 2014). This technique is used in functional Magnetic Resonance Imaging (fMRI) and positron emission tomography (PET). The second obtains electrical and magnetic activity generated inside of the brain. This technique is used in electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS) (Rossini and Pauri

2000; Scott, Allen, and McCarthy 2014). In this section, I will review how fMRI works to measure human brain activity.

Functional Magnetic Resonance Imaging (fMRI)

fMRI is a neuroimaging technique that uses a standard MRI scanner to measure active brain function over time in both clinical and research setting (Scott, Allen, and McCarthy 2014). It is made sensitive to measure the increase in regional blood flow by local neural activity associated with sensory, motor, and cognitive process, which is called functional hyperemia (Matthews and Jezzard 2004). During functional hyperemia, oxygen is delivered to the brain at a rate above its consumption to prevent oxygen depletion. Oxygen in the blood is bound to the hemoglobin molecules. The hemoglobin molecules have different magnetic properties depending on whether they are bound with an oxygen molecule. Oxygenated hemoglobin is diamagnetic, which has little effect on the magnetic field, has no unpaired electrons, and zero magnetic moments. Deoxygenated hemoglobin is paramagnetic, which concentrates magnetic field lines, and are also unpaired electrons, and are a significant magnetic moment. Because paramagnetic substances distort the surrounding magnetic field, they precess at different frequencies and result in rapid decay of transverse magnetization (a shorter T2*). Thus, increased oxygenated hemoglobin due to neural activity shows increased MR signal intensity on T2*- weighted images, whereas increased deoxygenated hemoglobin shows less MR signal intensity. Thus, T2* is used to measure blood oxygenated dependent level (BOLD) signals. The changes in blood flow or blood properties by local neuronal activity are called hemodynamic response (HDR). Therefore, BOLD contrast describes the differences in MR signals on T2*-weighted images that accompany HDR.

fMRI has a greater special resolution (the ability to distinguish different locations within an image) compared to other neuroimaging techniques such as EEG, which is the measurement of

the electrical potential of the brain through electrodes located on the surface of the scalp (Scott, Allen, and McCarthy 2014). However, fMRI has a much slower temporal resolution, which is the ability to distinguish changes in signals across a time when compared to techniques measuring electrical activity (Scott, Allen, and McCarthy 2014). The sampling rate of fMRI is often one brain volume every one or two seconds. It is much faster than PET, which measures the brain metabolism every few minutes to many ten minutes, but much slower than EEG, usually on the order of milliseconds (Scott, Allen, and McCarthy 2014). Moreover, fMRI indirectly measures brain activation, whereas EEG directly measures neuronal activity (Scott, Allen, and McCarthy 2014). fMRI studies must lie down on the table with the head still, whereas EEG can be measured in physically dynamic situations. However, motion-related noise remains a challenge for EEG studies (Enders and Nigg 2016). EEG also has the limitation that signals can be distorted en route to the scalp as well as poor spatial resolution.

Strength and Weakness of Using fMRI While Joint Loading

In the current proposed study, fMRI will be used in order to understand how the brain activates in individuals with various level of knee laxity. Using fMRI would facilitate identifying specific brain regions that are highly activated or less activated during an experimental task, which anterior knee joint loading will be used in this study. Thus, it may tell us what cortical resources are needed in high knee laxity individuals to receive a sensory signal when stretching ACL. However, there a limited method to perform knee joint loading inside of MRI due to space and material constraints. Any ferromagnetic materials strongly influence the magnetic field. A projectile effect can happen because of ferromagnetic objects which result in the translation and movement toward the scanner bore (Scott, Allen, and McCarthy 2014). The movement of those materials will be dramatically accelerated near the scanner bore, and severe projectile injuries can occur. Thus, the only non-ferromagnetic object made by such as plastic, wood, rubber, nonferrous

metals, etc. can be used inside of MRI. Aluminum, tin, and titanium are examples of non-ferromagnetic materials; however, it has to be considered that objects are rarely made by single materials. Thus, there is a limitation as to methods to physically manipulate knee joint loading in the MRI environment. Moreover, head motion is another limitation in the measurement of brain activation during anterior knee joint loading. Although anterior knee joint loading and laxity assessment do not involve voluntary movement, it can generate subtle head motion through the application of external forces causing problems with fMRI data acquisition. Head motion can lead to loss of data at the edges of the imaging volume (Scott, Allen, and McCarthy 2014). For example, excessive head motion can cause a given voxel to contain signals from two very different types of brain tissue, such as gray matter and ventricle, thus it can cause obvious changes in raw signal over time due to changing tissue type rather than actual changes in the BOLD signal due to blood flow changes in a given voxel. Head movement can also possibly interact with image artifacts to create complex and difficult-to-remove patterns of unwanted signal (Scott, Allen, and McCarthy 2014). However, the issues by created head motion can be prevented or minimized. Various head restraint systems (e.g., bite bar, vacuum pack, and thermoplastic masks mold) have been used to immobilize the head during fMRI scan (Scott, Allen, and McCarthy 2014). A bite bar is attached to the top of the head coil, and the subjects clench their teeth on a custom-made dental mold. It can largely restrict the excessive head motion; however, some participants can dislike this system due to discomfort. A thermoplastic mold can create a mask around the subject's head and is anchored to the static support. This system can largely limit the excessive head motion; however, some participants may feel claustrophobic due to a high degree of immobilization. Vacuum packs contain a large number of soft beads within a flexible plastic casing. When the subject is positioned, the air is pumped out to

form a shell around the subject's head. This system has good motion prevention potential as well as likely being more comfortable for the patient.

Although head motion may occur during anterior knee joint loading, measures can be taken to help minimize head motion artifact without severely immobilizing patient comfort. Thus, those extreme head restraint system may not be needed for this current proposed study. To assess the feasibility of joint loading and associated head motion, we performed a pilot study of knee joint loading while scanning fMRI. A variety of blocking pads and straps were used in the pilot study to minimize the head motion. Sandbags were located the top of the head and in front of the forehead. Multiple foam pads were filled into the space between the subject's head and head coil. This arrangement minimized head motion during anterior joint loading with resultant absolute head motion being 0.33±0.1 mm. The complete description of the validation study is described below.

Validation Test of the MR Compatible Anterior Knee Joint Loading Device

Due to the lack of a commercially MR-safe device that would allow joint loading, there was a need for the research team to develop an MR compatible anterior knee joint loading device that is designed to apply a load similar to the KT 2000. The current iteration of the device can be seen in Figure 2.1. It is constructed to perform passive anterior translation of the tibia by inflating an air-cuff located posterior to the participants' calf. Non-ferromagnetic materials such as wood, plastic, and latex tube were used in this device. The examiner inflates and deflates the air-cuff located underneath the participant's calf using the air-pump through the latex tube in the adjacent operator room.

To ensure that force equivalent to the 133N used in AKL testing, load validation was performed with the air cuff and an external dynamometer to determine the desired cuff inflation pressure. Loading the cuff at multiple inflation pressures while simultaneously assessed

dynamometer load it was determined that 187 mmHg equated to 133 N of force (y=0.672x + 7.147, R^2=0.98).

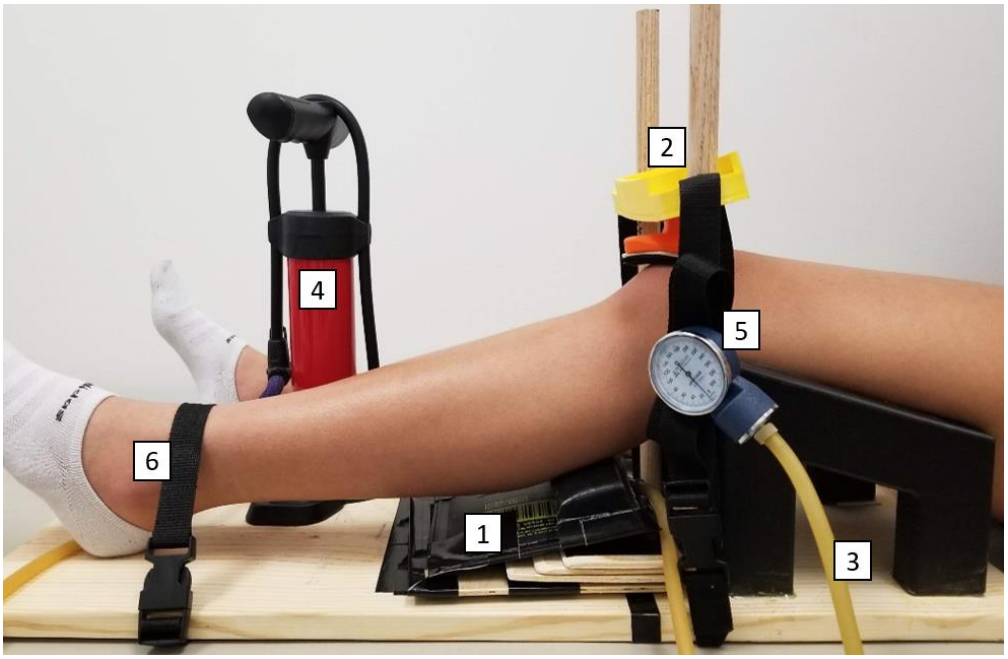

Figure 2.1 MR Compatible Anterior Knee Joint Loading Device. (1) Air-cuff, (2) patellar stabilizer, (3) latex tube, (4) bicycle pump, (5) air-pressure gauge, (6) ankle strap. The Air cuff (1) located underneath the participant's calf will produce a force (arrow) to translate the tibia relative to the femur while stabilizing the patella (2) and ankle (6). The Air cuff (1) is connected with latex tubing (3), and air pressure is provided by a manual pump(4) inflating the air-cuff via latex tubing. 189 mmHg air-pressure will be used to translate the tibia (equivalent to 133N), and it will be measured by air gauge (5).

Next, it was necessary to validate the loading device in the MR scanner to ensure that the joint loading device translates the tibia relative to the femur. Sixteen healthy and physically active female participants who were MR safe volunteered for this validation study. First, anterior knee laxity using KT-2000 was obtained using the same methods that will be described in chapter 3. Next, MR knee images were obtained during joint loading. The participants were placed supine position inside the scanner with their leg on the MR compatible anterior knee joint loading device (Figure 2.2). The air cuff has placed underneath the participant's calf, and the patella and thigh

were firmly stabilized (Figure 2.1). The air cuff is connected with latex tube which is passed through a small hole in the wall between MR scanning room and the operator room. The latex tube was also connected to manual pump located the adjacent operator room to inflate and deflate the air-cuff. Once completion of patient setup with the MR compatible joint loading device, a 36-channel large body coil (Siemens Trim Tri; Erlangen, Germany) was used to obtain the knee image (Figure 2.2).

Figure 2.2 Participant Setup with MR Compatible Anterior Knee Joint Loading Device

A localizer image was taken to best prescribe the subsequent dynamic images to the central sagittal slice of the knee joint. The dynamic MR acquisition parameters followed the methods of Quick et al., which obtained an image every 363 ms for 36.3 seconds, resulted in a total of 100 images (repetition time= 363 ms; echo time= 160 ms, voxel size= 1.1 mm x 1.1 mm x 4.0 mm) (Quick et al. 2002). This result in an effective 2.8 Hz sampling frequency of a single sagittal window. During the MR scanning, the anterior knee joint loading was performed from beginning at 0 mmHg and rising up to 187 mmHg (130N) for a total of five load/relaxation cycles.

Next, anterior tibial translation (ATT) was measured from the knee MR images using the open-source software MIPAV (version 8.0.2 Medical Image Processing, Analysis and Visualization; Center for Information Technology, National Institutes of Health (http://www.mipav.cit.nih.gov). The tibial tuberosity (Figure 2.3_1) and the most anterior point of the femoral condyle (Figure 2.3_2) were tracked through all the 100 knee images. The distance from the peak point of the maximum joint displacement to the point of the unloading was measured (Figure 2.3_b). It was assumed that peak displacement occurred in conjunction with the peak physical load applied. Although we attempted to firmly stabilize the femur, there was a small amount anterior movement of the femur. Thus, we measured the anterior translation of tibia (ATT) value by subtracting the movement of the femoral condyle from the distance of tibial tuberosity displacement (Figure 2.3_b).

The ATT dataset is shown in Figure 2.4 as well as AKL value. The researcher also established intratester consistency and precision of the ATT measurement [$ICC_{3,1}$ (SEM) =0.95 (0.6mm)]. Results demonstrated a significant positive correlation between AKL and MRI obtained ATT values (R^2=0.31, p=0.025). Thus, it is suggested that the MR compatible anterior knee joint loading device anteriorly translates the tibia while stabilizing the femur in a manner relative to the KT 2000.

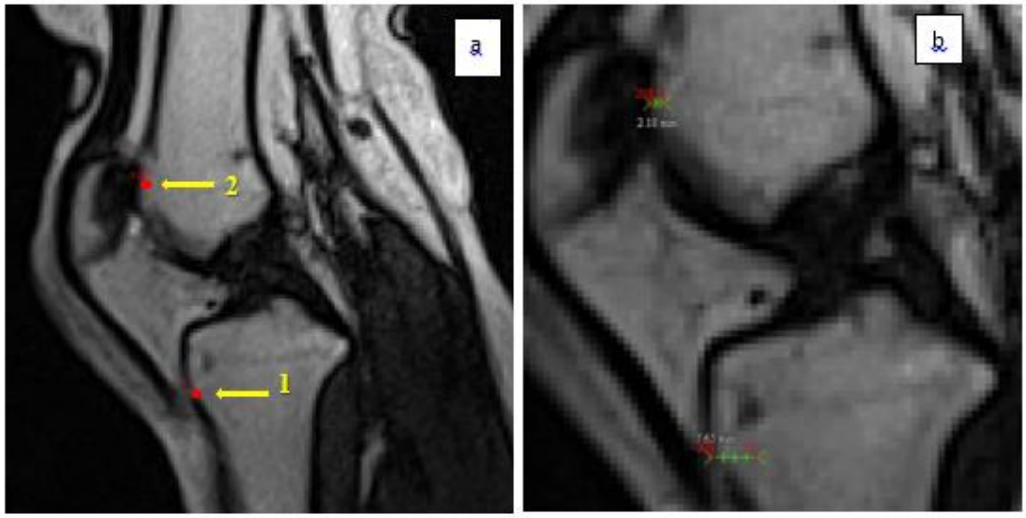

Figure 2.3 Measuring ATT Value Using MIPAV. (a) the frame without anterior joint loading, (b) the frame with maximum anterior joint loading, (1) the point of the tibial tuberosity, (2) the most anterior point of femoral condyle

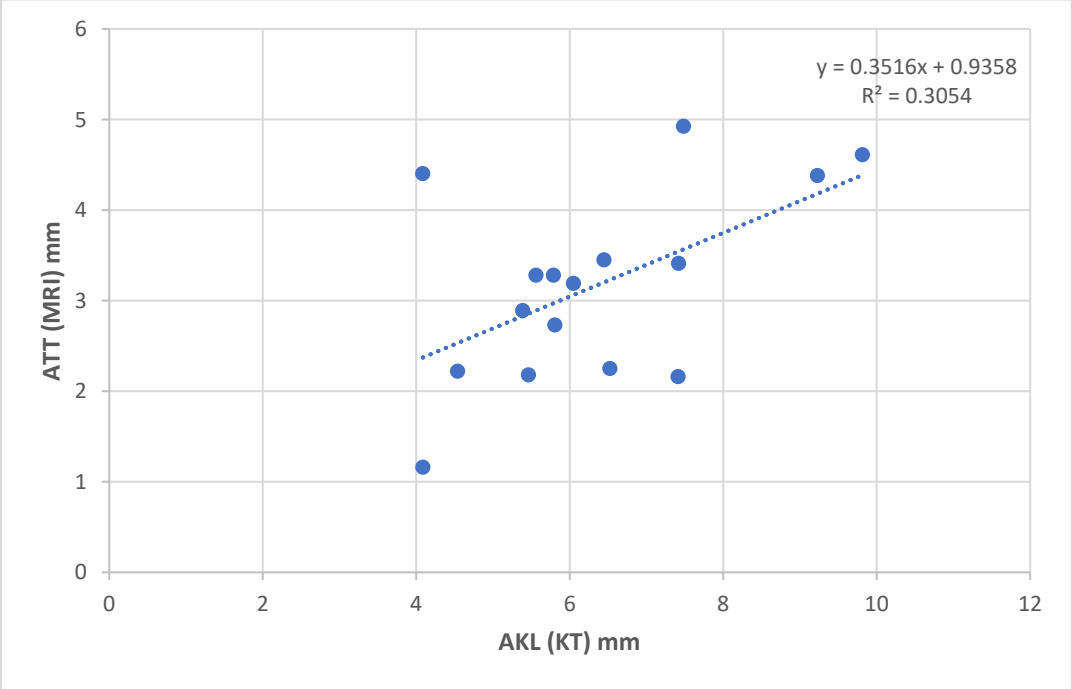

Figure 2.4 Scatter Plot of AKL and MRI Obtained ATT

fMRI Pilot Study Using the MR Compatible Anterior Knee Joint Loading Device

We also performed pilot fMRI acquisition during anterior knee joint loading using the same device in healthy female participants (Figure 2.5). Five healthy female college students who were right-handed/footed, recreationally active, and without a history of significant lower leg injury nor neurologic disorder volunteered to participate (aged 26.8±5, range 20-35 years old). The same fMRI data acquisition as outlined in the proposal (repetition time= 3000 ms; echo time = 28ms, phase encoding direction = anterior to posterior; matrix field of view = 220mm; voxel size = 2.5mm x 2.5mm x 2.5mm) was used with a block design (30 seconds of cyclical joint loading followed by 30 seconds of rest, total 4 joint loading and 5 rest period). The main effect of joint loading compared to the rest was analyzed. Details of the analyses can be found in chapter 3. The results showed that brain regions including the primary somatosensory cortex were highly activated during joint loading compared to during the rest (Figure 2.6, Table 2.1). This result supports our proposed study that the joint loading device performs the anterior translation and that it causes the brain activation to receive the sensory signal arising from receptors that would be fired during anterior knee joint loading. It is acknowledged that without peripheral nerve blocks it would be impossible to rule out sensory impulses from other cutaneous receptors. However, given the fMRI paradigm, such a technique could compare relative activations between different groups.

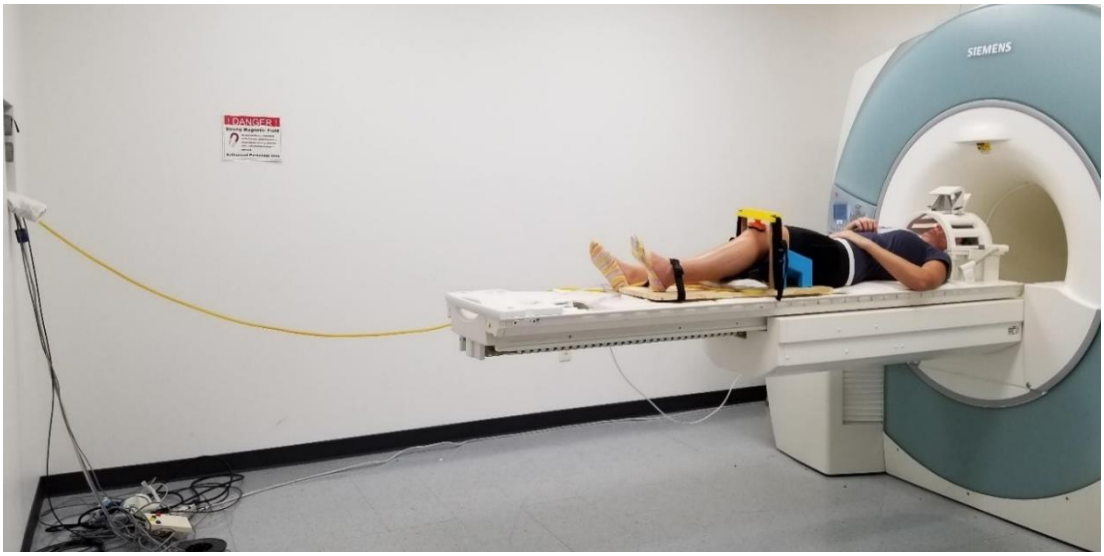

Figure 2.5 fMRI Scanning During Anterior Knee Joint Loading

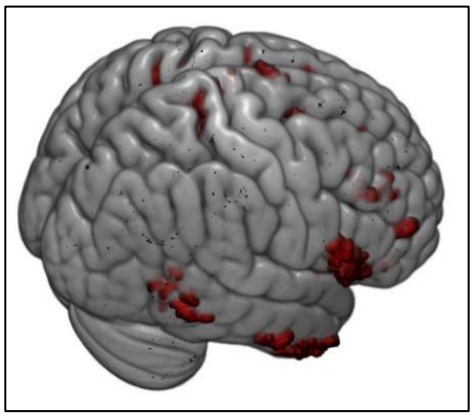

Figure 2.6 Brain Activation Joint Loading > Rest Contrast
The red areas represent significant activation clusters during joint loading

Table 2.1 Brain Regions Highly Activate During Joint Loading vs Rest

Regions	Size	P	Z-Max X (mm)	Z-Max Y (mm)	Z-Max z (mm)
R Primary somatosensory cortex	18614	<0.00	16	-38	68
L Frontal Pole	834	5.96e-08	-14	52	32
R Middle Frontal Gyrus	431	0.000169	48	32	28
R Subcallosal Cortex	385	0.000475	10	28	-20
R Inferior Frontal Gryrus	284	0.00533	56	20	-6

Postural Control

The above literature has supported my assumption that high knee laxity may negatively impact the sensory system, and it may also lead to neuroplastic changes. While the compensatory movement followed by impaired sensory information is also demonstrated, it is plausible that individuals with high knee laxity may also have postural control deficits. Postural control is known as the process of maintaining the overall body position and orientation in space during any static posture or dynamic activity (Kandel, Schwartz, and Jessell 1991). Maintaining postural control serves the following functions: 1) supporting the head and body against gravity and other external forces, 2) maintaining the center of the body mass (COM) aligned and balanced over the base of support on the ground, and 3) stabilizing supporting part of the body while others are being moved (Kandel, Schwartz, and Jessell 1991). Postural control can be classified as static or dynamic postural control. Static postural control is commonly understood as maintaining steadiness on a fixed, firm, unmoving base of support (Riemann, Caggiano, and Lephart 1999). Dynamic postural control is defined as a functional performance while stabilizing body (Wikstrom et al. 2007).

Strategies of Postural Control

Postural control requires multiple inter-related systems including sensory (vestibular, visual, and somatosensory), motor, and cognitive (Shumway-Cook and Woollacott 1995) systems. Postural adjustments are controlled by two mechanisms; 'reactive' (feedback) or 'predictive' (feedforward) (Kandel, Schwartz, and Jessell 1991). A reactive postural control strategy engages with movement or muscular contraction responding to unpredicted disturbance; whereas predictive strategy involves with voluntary movement or increase in muscle activity in anticipation of a predicted disturbance (Pollock et al. 2000). Reactive and predictive mechanisms have to work together in order to maintain postural stability. Traditionally, postural control has been thought of as reflex-like responses that are automatically evoked by a sensory stimulus (Pollock et al. 2000). However, it has been considered that postural control depends on the assessment and control of many variables by the CNS, especially involvement of the cerebral cortex (Horak, Henry, and Shumway-Cook 1997). It is known that postural responses are comprised of short-latency (SL), medium-latency (ML), and long-latency (LL) components (Jacobs and Horak 2007). Even though the initial postural response to perturbation occurs more quickly than voluntary muscle contraction, it occurs at longer latency than spinal stretch reflexes (Chan et al. 1979). Taube et al. observed the transcranial magnetic stimulation (TMS) induced H-reflex facilitation and motor evoked potentials (MEPs) facilitation during perturbation at the peaks of short- (SLR), medium- (MLR), and long-latency responses (LLR) (Taube et al. 2006). The participants stood on a treadmill, and the platform was accelerated in posterior direction while EMG was recorded from tibialis anterior, gastrocnemius, and soleus muscles. The perturbation evoked several reflex peaks in the soleus EMG. SLR was defined as the first deflection in the EMG, MLR was calculated from 50 ms to 85 ms, and LLR was defined exceeding 85 ms. During perturbation, the TMS to the left motor cortex and peripheral nerve

stimulation in the popliteal fossa were also individually adjusted, thus, the peaks of either MEPs and or H-reflex coincided with peaks of SLR, MLR, and LLR, respectively. The results demonstrate that both MEPs and H-reflex facilitation by a subthreshold TMS were significantly enhanced at the LLR peak compared to SLR and MLR. The TMS induced H-reflex facilitation at LLR suggests that increased cortical excitability contributes to enhancing the LLR peaks. It may indicate that the LLR in the soleus muscle is partially transcortical involved, and directly involved with corticospinal pathways. This finding provides evidence that postural control is also engaged with the higher level of the CNS.

Studies of animals and humans with cortical lesions that spared the brain stem showed abnormal postural control when exposed to perturbations (Chan et al. 1979; Geurts et al. 2005). The results also provide evidence of the involvement of cerebral cortex in postural control. The Cerebral cortex, specifically in the primary motor cortex (control and execution voluntary movement), supplementary motor area (control and prepare the movement), and prefrontal cortex (executive control) are commonly known to associate with postural control (Fujimoto et al. 2014; Mihara et al. 2008; Taube et al. 2006). Detailed information about the role of cerebral cortex in postural control will be discussed later in this document.

Postural Control Assessments

Postural control can be assessed objectively through measurement of postural sway. Force plates have commonly been used to measure the center of pressure (COP) over time. A single-leg stance on the force plate is a common assessment to measure static postural control (Ageberg et al. 2005; Negahban et al. 2014). However, it is suggested that a static measurement may not be functional and sufficient to observe postural control related to physical performance and lower leg injury (Colby et al. 1999). This may be due to the fact that the lower extremity ligament injury often occurs during physical movements such as foot strike during cutting and

jump landing (Bahr and Krosshaug 2005). Thus, dynamic postural control has been suggested for the measurement of neuromuscular deficits related to lower limb ligament injuries (Colby et al. 1999). Dynamic postural control is assessed following a perturbation of the support surface, a perturbation of the individual, or requesting individuals to maintain their balance following movement (i.e. single leg jump or landing) (Sell 2012). The single-Leg Hop-Stabilization test (Riemann, Caggiano, and Lephart 1999), star-excursion test (Kinzey and Armstrong 1998), Dynamic Postural Stability Index (Wikstrom et al. 2005), and Time to Stabilization test (S. Ross and Guskiewicz 2003) are commonly used to measure the dynamic postural control. In this review, I will focus on the time to stabilization test.

Time to Stabilization Test

Time to stabilization (TTS) is a quantitative force plate measurement for evaluating dynamic postural stability (S. Ross and Guskiewicz 2003). Unlikely the static postural control assessment such as single-leg static stance, TTS requires to subject to jump and then stabilize as quickly as they can ("stick landing"). During the test, participants will jump with both feet at 50% of their maximum vertical-jump height and land on one leg on a force plate. Then, participants are asked to remain as motionless as possible in a single-leg stance. TTS is calculated using the peak ground reaction force (GRF) of the jump landing. The components of the GRF has been used to determine the postural stability (Goldie, Bach, and Evans 1989). The components of the GRF with minimum variation during a single-leg stance indicates the optimal stability (S. Ross and Guskiewicz 2003). Thus, TTS observes the time that takes for the initial component of GRF of a jump landing to become similar to the components of the GRF of the optimal stability in a stabilized single-leg stance (S. Ross and Guskiewicz 2003). The greater time (slower) represents poor dynamic postural stability (Hirokawa et al. 1991). Since the sensory, motor, and cognitive

systems are required to maintain postural stability, identifying dynamic postural control deficit might help us to quantify neuromuscular deficit (Shumway-Cook and Woollacott 1995).

Postural Control Influenced by Deafferentation

While somatosensory, visual and vestibular sensory systems contribute to maintaining postural stability (Shumway-Cook and Woollacott 1995), deficits in somatosensory information are widely understood to be one of the biggest contributors in postural control deficits (Riemann, Myers, and Lephart 2002). Poor postural control with associated somatosensory impairment has been found in patients with spinal cord injuries (Wirz and van Hedel 2018), multiple sclerosis (Jamali et al. 2017), and ligament injuries (Gribble, Hertel, and Plisky 2012). In this section, I will focus on dynamic postural stability deficit influenced by ligamentous injury, especially ACL injury.

ACL Injury and Postural Stability

Impaired postural control has been reported in ACLD (Negahban et al. 2014) and ACLR patients (Howells, Ardern, and Webster 2011). This may be due to the ACL's role in stabilizing the knee joint. The ACL mechanically stabilizes a knee joint in multiple planes (Butler, Noyes, and Grood 1980; Ellison and Berg 1985), and it also stabilizes the knee joint by transmitting sensory information to the CNS and regulating muscle coordination via mechanoreceptors (H. Johansson et al. 1990). Thus, the damaged mechanoreceptors following ACL injury may lead to impaired somatosensation, and the impaired somatosensation may result in postural control deficit (Negahban et al. 2014).

Postural control deficits in ACLD and ACLR patients are commonly found using static balance assessment. However, dynamic measurements can also assess postural control deficits. It may be more appropriate to dynamically measure postural stability, rather than statically, in understanding the effects of ligamentous injury as injury occurs during physical movement

(Boden et al. 2000; Shimokochi and Shultz 2008). The study by Webster and Gribble observed TTS in ACLR patients and matched healthy female college athletes (Webster and Gribble 2010). The athletes with ACLR took longer time to stabilize (2.01 ± 0.15 seconds) compared to the matched control individuals (1.90 ± 0.07 seconds, p=0.05). The author suggested that this may be due to the participant's trying to decrease peak vertical forces as well as anterior tibial translation from landing. They also suggested that since proper muscular strength and firing rate/patterns are required for rapid stabilization, insufficient muscular strength and firing rate/patterns may also contribute to having dynamic stability deficits. Different neuromuscular kinetic and kinematic results such as increased valgus knee moments (Ristanis et al. 2005), increased anterior-posterior shear forces at tibia (Ortiz et al. 2008), and changes in muscle firing patterns (Ortiz et al. 2008; Vairo et al. 2008) have been demonstrated in ACLR patients. Moreover, deafferentation following ACLR may negatively affect dynamic postural control in addition to the kinematic and kinetic changes after ACL reconstruction. It is well understood that ACLR individuals still have poor proprioception outcomes even after the surgical procedure (Harter, Osternig, and Singer 1992; MacDonald et al. 1996).

Longer time to stabilize during dynamic tests in the ACL reconstructed limb compared to the uninjured limb has also been reported (Colby et al. 1999). Stabilization time based on the vertical force during single-leg step-down and single-leg hop task was measured. There was a significantly greater stabilization time in the injured limb during the step-down test compared to their uninjured limb in ACLR individuals. The author suggested that this might be due to a compensatory movement pattern influenced by increased knee laxity after the ACL injury. Colby et al. also observed TTS in ACLD participants, however, there were no significant differences between the injured limb and un-injured limb. Since it is well known that ACLD individuals have compensatory movement strategies such as asymmetric walking, weight-bearing, and muscle

strength (Hajizadeh et al. 2016; Markstrom, Tengman, and Hager 2018), an uninjured limb may be loaded in an manner differently than the contralateral limb of a healthy individual. Thus comparisons to a healthy, non-injured system are difficult to prove the differences in postural control between injured and non-injured limb. The study by Colby et al. still provides us evidence of dynamic postural stability deficits in the ACL reconstructed limb.

A slower stabilization time was also reported to be a predictor of ACL injury (DuPrey et al. 2016). DuPrey and his coworkers measured TTS during the single-legged jump landing tasks of backward, forward, medial, and lateral jumps in 278 college athletes. Nine participants had noncontact ACL ruptures. The athletes with ACL injury took a significantly longer time (0.49 seconds) to stabilize during baseline backward jumping compared to the uninjured athletes ($p=.0052$). The absolute mean time to forward, medial, and lateral jumping was slower in injured athletes, however, it was not statistically significant (forward TTS: 1.31±0.51 and 1.14±0.49 seconds, $p= 0.33$; medial TTS: 1.38±0.36 and 1.10±0.51 seconds, $p= 0.11$; and lateral TTS: 1.35±0.47 and 1.15±0.54 seconds, $p= 0.28$). The results indicate that individuals who are at high risk of an ACL injury may have postural dynamic control deficit.

A longer stabilization time during single-legged jump landing was found in individuals with ACLR vs healthy, ACL reconstructed limb vs uninjured limb, and baseline backward jumping of ACL injured athletes vs non-injured athletes. This collectively reveals that impaired postural stability may be associated with the ACL injury, and it may not be improved following a surgical procedure. This may be due to the fact that the ACL reconstruction may not capable of returning the sensory input lost due to the original injury. Thus, not only is mechanical weakness a contributing factor of postural stability deficit but also deafferentation may influence postural control.

High Knee Laxity and Postural Stability

As ACLR patients showed a postural control deficit likely influenced by deafferentation and knee instability, it may be hypothesized that individuals with high knee laxity may have poor postural control due to altered sensory information consequent to high knee laxity (See above section on laxity and proprioception). The negative relationship between laxity and postural control has been reported in ACLD patients. Ageberg et al. investigated the influence of knee laxity, proprioception, and muscle strength on balance (Ageberg et al. 2005). They measured KT-1000 for knee laxity assessment, the threshold to detection of passive motion (TTDPM) for proprioception test, and a single-leg stance for balance. They counted the number of movements exceeding 10 mm from the mean value of the center of pressure for balance assessment. They also observed the average speed of the center of pressure movements. There was a positive correlation between laxity and balance assessment. Specifically, when laxity increased by 2 mm, the number of exceeding COP movements increased in women ($b = 0.48$; $p = .05$). In men, there was negative correlation between laxity and average speed of COP movement, if laxity increased by 1 mm, the average speed was decreased by 1.2 mm/s ($b = -1.21$, $p = .02$). The results show evidence of negative correlation between laxity and postural control in ACLD individuals.

However, several other studies have demonstrated no correlation between laxity and postural control in ACL injured patients (Eastlack, Axe, and Snyder-Mackler 1999; H.-M. Lee, Cheng, and Liau 2009). There was no correlation between anterior knee laxity (KT-1000) and dynamic balance (H.-M. Lee, Cheng, and Liau 2009) in ACLD patients. It may be due to the different method of the postural control assessment and the time interval from injury to test in ACLD individuals. Ageberg et al. and Lee et al. both observed ACLD individuals, however, Ageberg et al. measured the static balance, whereas Lee et al. obtained dynamic postural control. In addition, the average time between injury to the test was 3.8 years (range 0.5-11 years) in a

study by Ageberg et al. and 12.8 months (range 9-24 month) by Lee et al. The different postural control method and the subjects' time interval to the test may contribute to having different results in ACLD patients. Moreover, a weak correlation between anterior knee laxity (KT-1000) and single-leg stance balance has been reported in ACL reconstructed individuals (Shiraishi et al. 1996). It may be due to improved mechanical stability following reconstructive procedure. Moreover, it may be possible that compensations from the visual and vestibular systems helped to maintain postural control as the participants with ACLR previously underwent to neuromuscular training programs. These rehabilitation programs and improved mechanical stability may lead to compensatory strategies to make up for the loss of somatosensation, and it may positively impact patients' ability to maintain posture. Therefore, individuals with high knee laxity who did not undergo any neuromuscular training programs may have poor postural control due to altered sensory input as well as mechanical weakness of the knee joint.

While we are unaware of research observing relationships between anterior knee laxity and postural control in a healthy population, postural control deficits were found in individuals with hypermobile joints (Aydin et al. 2017; Mebes et al. 2008). Aydin et al observed static postural control (double leg stance) in 8 different conditions (eye opens/close, firm/elastic surface, different head position) in individuals with normal mobility, moderately hypermobility and distinctly hypermobile (Aydin et al. 2017). The level of hypermobility was determined using the Beighton-Horan joint mobility index (hyperextension of the 5^{th} metacarpophalangeal, elbow and knee, oppose the thumb to the forearm, hands flat on the floor). Individuals with hypermobility demonstrated significantly higher postural sway during static balance with head backward tilt, eye closed, and firm surface (vestibular stress and elimination of the visual system) ($p=0.041$). It may indicate that when greater reliance on the somatosensory system is necessary to maintain postural control, individuals with hypermobility had more difficulty in sustaining

postural control compared to individuals without hypermobility and moderate hypermobile individuals. The result was similar to the finding by Iatridou et al. (Iatridou et al. 2014) in which they measured a static balance and dynamic balance using modified BESS test (counting error during multiple single leg hops) in hypermobile syndrome and control individuals. The joint hypermobile syndrome was diagnosed with the revised Beighton-Horan joint mobility index (BHJMI) (Grahame, Bird, and Child 2000). Hypermobile individuals had significantly greater mediolateral postural sway with eyes open ($p<0.01$), mediolateral and anteroposterior sway with eyes open and head extension ($p<0.05$), as well as a greater number of landing errors during dynamic postural control test ($p<0.05$). A similar finding was also reported in a study of chronic ankle instability (CAI) with greater laxity individuals (C. N. Brown et al. 2015). Those CAI with high ankle laxity individuals had significantly longer time to stabilize during single leg jump landing compared to coppers (history of ankle sprain without developing CAI) and CAI without increased laxity individuals ($p=0.05$). The work presented here suggests that greater laxity negatively influences both static and dynamic postural control.

Postural Control with Regard to Cortical Activation

Since potential cortical involvement in postural control has been suggested, animal studies provide direct evidence by measuring cortical neuron activation during perturbation. Neurons in the motor cortex were observed while cats (Beloozerova et al. 2005) and rabbits (Beloozerova et al. 2003) maintained their balance on the platform, and the platform was periodically tilted in the frontal plane. Both studies demonstrated that neurons in the motor cortex are strongly activated during postural correction. The results revealed direct involvement of cerebral cortex in maintaining postural control.

Multiple investigations have also studied human brains during postural control using neuroimaging techniques such as EEG, transcranial magnetic stimulation (TMS), and functional

near-infrared spectroscopy (fNIRS). Herold et al. used fNIRS during double-leg stance on the balance board in healthy adults (Herold et al. 2017). Participants required to stand still on the floor for the baseline test and then asked to step on the balance board and remain still with both feet. fNIRS, which measures oxygenated and deoxygenated hemoglobin levels, monitored the supplementary motor area (SMA), precentral gyrus (PrG), and postcentral gyrus (PoG) during the balance test, and then compared them between baseline and balance board conditions. The results revealed that oxygenated hemoglobin values were significantly increased from standing to balance in SMA (P=.005), PrG (p=0.005), and PoR (p=0.013). This finding provides evidence of cortical cortex involvement in maintaining postural stability. Herold et al. also observed the postural sway in the anterior-posterior and mediolateral direction while maintaining balance on the balance board. The results revealed that there was a strong negative correlation between mediolateral sway and mean oxygen hemoglobin changes in the supplementary motor area; specifically , the brain activity increases were larger with increase amplitude of mediolateral sway (r=-0.80, p=0.005) (Herold et al. 2017). This result may imply the involvement of the supplementary motor area in postural control in the medial-lateral direction.

Similar results were found in another study using EEG (Hülsdünker et al. 2015). The participants performed nine balance tasks while recording EEG. The tasks differed in difficulty by changing the factors of surface stability (solid surface, instability level 1, and instability level 2 x bilateral stance, dominant unilateral stance, and non-dominant unilateral stance). When balance tasks become more challenging, theta power increased in the frontal, central, and parietal regions ($P<0.001$). Increased theta power was also found during the transition from balancing on a stable surface to an unstable surface (Mierau et al. 2017). The frontal Theta is known to play an important role in the attentional system in human (LaBerge and Buchsbaum 1990). In addition, increased Theta activity in frontal-central regions is associated with error detection, processing,

and monitoring of postural stability (Adkin et al. 2006; Slobounov et al. 2009). Thus, increased Theta activity in the frontal-central and extended to the parietal region may reveal that when maintaining postural control becomes more challenging, resources from cerebral cortex associated with focused attention to detect error and monitor of the postural stability are required to maintain postural tasks.

Collectively this literature provides evidence of the involvement of cortical cortex in order to maintain postural control by measuring brain activation during balance tasks using neuroimaging techniques. While altered sensory input in individuals with high knee laxity possibly leads to functional and structural cortical plasticity, this neuroplasticity may also negatively influence postural control. Thus, identifying postural control ability in various laxity levels may help us to understand functional movements following the neuroplasticity influenced in part by knee laxity.

Summary

Greater anterior knee laxity (AKL) is known as one of the strongest independent predictors of ACL injuries (Mouton et al. 2015; Uhorchak et al. 2003; Vacek et al. 2016; Woodford-Rogers, Cyphert, and Denegar 1994). Knee laxity is determined by static (ligament, joint capsule, meniscus, etc.) and dynamic contributors (muscles across the joint) of joint stabilization. Among the multiple anatomic structures, the ACL plays an important role in stabilizing the knee joint with both systems. An ACL provides ~85% of the restraint to anterior translation of the tibia related to the femur (Butler, Noyes, and Grood 1980; Ellison and Berg 1985). Moreover, the ACL also has a role in a dynamic system via mechanoreceptors transmitting the afferent information to the CNS as well as regulating muscle coordination (H. Johansson et al. 1990). Thus, both the static and dynamic roles played by the ACL contribute to joint stability.

It is known that individuals with high joint laxity have poor proprioception (Laudner et al. 2012; Rozzi et al. 1999). Females showed higher AKL, longer time detecting joint motion, and greater EMG peak amplitude in hamstring muscles during landing when compared to males (Rozzi et al. 1999). It suggests that excessive joint laxity in females may contribute to diminishing joint proprioception, and it might lead to having a compensatory muscle activation pattern. Individuals with greater anterior shoulder laxity also showed poor proprioception (Laudner et al. 2012). The studies provide evidence of the negative influence of joint laxity on the sensory input and proprioception outcomes. This may be due to a reduced firing rate of mechanoreceptors caused by lower tension of the ligament. Greater AKL has also impacted motor outcomes. Individuals with high knee laxity showed higher activation in the hamstring muscle group during landing (Rozzi et al. 1999) and perturbation (Shultz, Carcia, and Perrin 2004), as well as higher knee work absorption and stiffness during landing (Shultz et al. 2010). ACL injury can be the result of this potentially decreased sensory input and compensatory movements, which is associated with diminished functional stability.

Functional stability is controlled by the sensorimotor system, which encompasses all the sensory, motor, and CNS (Riemann and Lephart 2002b). In the process of stabilizing the joint, the brain plays an important role in integrating and processing the sensory information. While researchers have focused on sensory and motor systems associated with knee laxity, the influences on the central processing component by knee laxity are not yet well understood.

The human brain has a unique ability to adapt any changes functionally and morphologically, this is called neuroplasticity (Bavelier & Neville, 2002; B. B. Johansson, 2004). Deafferentation due to facters such as joint immobilization (Liepert, Tegenthoff, & Malin, 1995; Zanette et al., 1997) and peripheral nerve lesion contributes to functional neuroplasticity (Eleni Kapreli & Athanasopoulos, 2006; Needle, Lepley, & Grooms, 2017). A significantly reduced

mean motor cortex size representing anterior tibialis was found in individuals with ankle immobilization when compared to the control group (Liepert, Tegenthoff, and Malin 1995). Individuals with ACLD and ACLR also demonstrated higher activation in the regions of the brain responsible for sensory processing, motor planning, and visual processing during lower limb movements (Grooms et al. 2017; Kapreli et al. 2009). Gray matter volume reduction was also found in individuals with nerve transection (K. S. Taylor, Anastakis, and Davis 2009), chronic pain (Metz et al. 2009), vestibular nerve failure (Gottlich et al. 2016; Hufner et al. 2009), and amputation (Draganski et al. 2006; Di Vita et al. 2018). These previous findings indicate the possible functional and morphological neuroplasticity influenced by deafferentation. Likewise, it is plausible that high knee laxity possibly leads to functional and structural neuroplasticity due to impaired sensory information. Identifying neuroplasticity related to variations in knee laxity levels will help us to better understand the potential sensorimotor system contributions to risk of ACL injury. Determining sensorimotor system differences between individuals with high and low laxity may be the first step towards developing further research to prevent ACL injury.

Altered sensory information due to high knee laxity may not only influence neuroplasticity, but it may also negatively impact postural control. In order to maintain postural control, the sensory, motor, and cognitive systems must operate in an integrated manner. Thus, impaired sensory information may lead to postural control deficit. It is well understood that individuals with ACL injury (Colby et al. 1999; Negahban et al. 2014) or ankle instability (C. N. Brown et al. 2015; J. H. Lee et al. 2018) have poorer static and dynamic postural control. A negative correlation between knee laxity and postural control was also found in ACLD patients (Ageberg et al. 2005). Correspondingly, healthy individuals with high AKL could be theorized to have postural control deficits due to impaired sensory information.

Historically, postural control has been considered a reflex-like response mainly involved with the brainstem and spinal circuits. However, the cerebral cortex, directly and indirectly, influences postural response via the corticospinal loop and communication with the brainstem, respectively (Bolton 2015). Animal studies showed strong activation of neurons in the motor cortex during perturbation (Beloozerova et al. 2003, 2005). Neuroimaging studies with humans also demonstrated a higher cortical activation while performing balance tasks (Mierau et al. 2017; Mihara et al. 2008; Taube et al. 2006). The results may reveal the involvement of the cortical cortex in the process of maintaining postural control. While altered sensory input in individuals with high AKL potentially leads to brain plasticity, the neuroplasticity may also impact on postural control. Thus, determining postural control in individuals of various laxity levels may help us to understand functional movements following neuroplasticity.

CHAPTER III

METHODS

Participants

Twenty-eight, physically active collegiate female students aged between 18 -35 years old, and who are right-handed and footed will be recruited. The number of subjects was determined following previous fMRI studies with ACL injured and reconstructed patients (Kapreli et al. 2009; Alan R Needle, Lepley, and Grooms 2017). Additionally, participants must have a normal menstrual cycles lasting 26-32 days for the past 6 months, consistent cycle length that varies no more than +1 day from month to month for the last 6 months, and no history of pregnancy or no planning to become pregnant (Shultz et al. 2010). Moreover, contraceptive users and non-users will be equally included in each laxity group. Participants' activity level will be matched as much as possible between groups using Tegner (Briggs et al. 2009) and Marx scales (Marx et al. 2001). Participants will be recruited if they have a minimum score of Tegner scale 3 and participate in activities listed on the Marx scale at least once a month.

Participants will be excluded if they have: 1) previous significant lower leg injuries, 2) any neurologic disorders, 3) anxiety, 4) claustrophobic, 5) over 30 BMI (falling into the category of obesity) (Nuttall 2015), 6) currently undergoing a neuromuscular training program, 7) currently participating in intercollegiate sports. Prior to participation in this study, all subjects will read and sign an informed consent form approved by the University's Institutional Review Board for the Protection of Human Subjects. Compensation ($75) will be offered for participants.

Procedures

General Overview

This study will require a participant to visit on 3 separate occasions. On the first visit, a participant will complete a knee laxity test and a MRI safety screening form. On the second visit, participants will complete a consent form and knee laxity test; the results of which will assign them to the high laxity (HL) and low laxity (LL) groups. Then, there will be a battery of dynamic postural stability tests. On the third visit, they will complete of series of neuroimaging scans as well as another knee laxity test. Figure 3.1 shows an overview of the procedure. A knee laxity test using KT-2000 will be performed on all three visits in order to ensure that the participants' laxity value remains in the assigned laxity group.

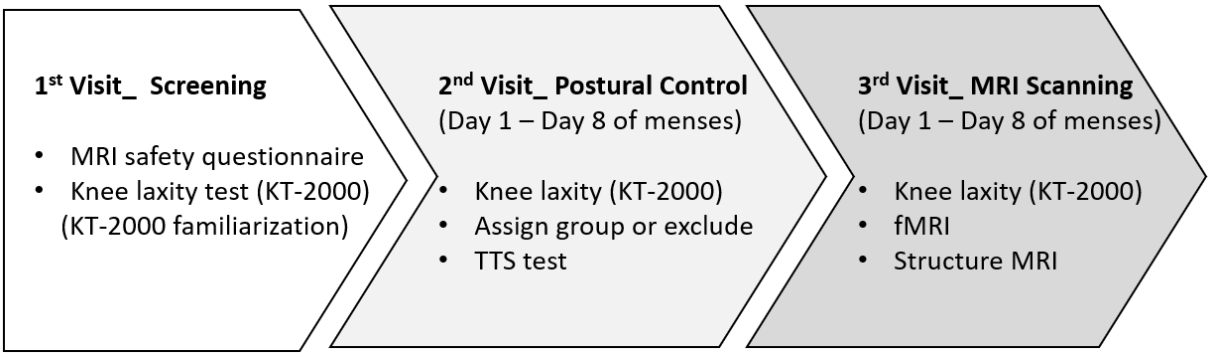

Figure 3.1 Overview of Procedure

1st Visit_ Screening Day

Participants will meet the researcher at the Applied Neuromechanics Lab in the Coleman building at UNC Greensboro campus. Participants will complete the short version of the MRI screening form (Appendix A) in order to determine if the participants are eligible/safe for MRI scanning. If a participant is MRI safe, they will be familiarized with the knee laxity test using KT-2000 knee arthrometer (MEDmetric, San Diego, CA).

Knee Laxity Test

The participants' anterior knee laxity (AKL), which is the amount of displacement of anterior tibial translation relative to the femur, will be assessed. Participants will be tested in the supine position with knee flexion to 25±5º. A Velcro strap will be placed around their thigh to control the hip external rotation. Then, the KT-2000 will be located on the participant's anterior aspect of the tibia, and the examiner will apply 89 N of force in the posterior direction and 133N of force in the anterior direction for three cycles. The investigator has previously established between day measurement consistency and precision [ICC (SEM) =0.97 (0.5mm)]. Potential subjects will be prescreened to obtain a distribution of high and low AKL (see details below). Participants will be asked to schedule the second and third visits between first and eighth day of their menstrual cycle. The menstrual cycle will be self-reported, and the researcher will check up on the participants to ensure her cycle and test dates.

2nd Visit_ Knee Laxity and Postural Stability Testing

The participants will visit the research team between first and eighth day of their menstrual cycle to complete knee laxity and postural stability tests. Participants will be instructed to avoid high-intensity activities 24 hours prior to testing. All measurements will be performed on the left knee. First, AKL value will be measured in order to assign the group. Previous research from the lab (Shultz et al. 2007) included average (M=5.6 ± 1.0 mm, F=8.1 ± 2.5 mm), above-

average (>1 SD; M=6.6mm, F=10.6mm), and below-average (<1 SD; (M=4.6mm, F=5.6mm) of AKL. The current study will have participants assigned into either the high laxity (HL) group (AKL> 9.5mm) or the low-average laxity (LL) group (AKL< 8.5mm). AKL will be measured bilaterally, however, the only left knee will be used to assign the group. Participants who fall into the average-high knee laxity (>8.5mm, <9.5mm) will be excluded.

Following assignment to either the HL or LL group, the participants will complete the physical activity questionnaires using the Tegner (Briggs et al. 2009) and Marx scales (Marx et al. 2001) (Appendix B).

Time to Stabilization Test

Upon completion of the physical activity questionnaires, participants will undergo Time to Stabilization (TTS) testing to assess dynamic postural stability. Participants will wear the same brand of lab shoes. First, the maximal vertical jumping heights of the participants will be established. Participants' standing-reach height will be measured by instructing them to stand below the Vertec and reach up to touch the highest tab possible with one hand without their heels leaving the ground. Then, participants will be asked to complete the maximal vertical jump, hitting the highest possible tab, while standing directly under the Vertec. The best trial among the 3 jumps will be recorded. Then, 50% of the maximal jump height will be set, which is the tab that measured halfway between the standing reach and maximal jump height.

Next, the ground reaction force (GRF) of the anterior-posterior (AP) and medial-lateral (ML) components will be sampled at 200 Hz (S. Ross and Guskiewicz 2003) with the MotionMonitor software from a force plate (Bertec NC 6 DOF force platform). Participants will be instructed to stand behind a mark on the floor, which is located 70 cm away from the center of the force plate (S. Ross and Guskiewicz 2003). Then, they will be asked to jump with 2 feet and hit the target on the Vertec (50% of maximal jump height) with their right hand, and then land on

the force plate on the left foot. Participants will be instructed to 'stick' the landing, stabilize as quickly as possible, and remain motionless for 20 seconds (Wikstrom et al. 2005) while keeping their eyes forward. They will be able to swing their arms during the jump but will be required to place their hands on their hips after landing. A total of 3 trials will be completed on left limb. Upon completion of the postural stability test, the researcher will schedule the third visit with participants within first and eighth day of their menstrual cycle.

3rd Visit_ MRI Examination

Participants will visit the research team within their first 8 days of the menstrual cycle to complete the neuroimaging session. Functional and structural brain images will be obtained on a 3.0 T MRI scanner using a 12-channel head coil (Siemens Trim Tri; Erlangen, Germany). They will meet the researcher at the front door of the Joint School of Nanoscience and Nanoengineering building. Participants will sign into the facility and be escorted to the MRI suite by the researcher, and then complete the UNC Greensboro MRI screening form to ensure the participant's eligibility for the MRI scanning (Appendix C). The researcher is trained to screen participants to identify the contraindications of MRI. Once a participant's eligibility is confirmed, they will be instructed to remove all jewelry, anything in the pockets, and shoes. The knee laxity test will be completed again to ensure that the participant remains in the assigned group. Then the participants were escorted to the MR scanning room. The participants will be asked to lay down in a supine position on the MR table. The MR compatible anterior knee joint loading device will then be located on their left knee. The air-cuff will be placed underneath their calf with slightly touching. The patella stabilizer will be strapped down on the patella using straps (Figure 2.1). Please see Chapter 2 for full details of the loading device.

When the joint loading device is set, the participants will be familiarized to the device by experiencing a few cycles of anterior knee joint loading. Once completed with the familiarization,

a variety of forms and sandbags will be placed around the subject's head to minimize head motion and then the head coil will be positioned (Figure 1.4). Participants will be given a safety squeeze ball and informed how to communicate with the researchers and remain as motionless as possible during the scanning. A mirror will be placed on the head coil so that the participant will be able to see the researchers who will be at the adjacent operator room. However, during anterior knee joint loading while obtaining functional images, participants will be asked to close their eyes to minimize visual information. Other than the functional image scan, participants will not be required to close their eyes, thus, they will freely decide to close or open their eyes. The entire MRI examination will take about 45 minutes including setting up and familiarization.

Functional Brain Imaging

The functional and structural MRI scans will largely follow the methodology of previous fMRI study by Raisbeck et al. (Raisbeck et al. 2018). Following a localizer scan to prescribe scan region, the functional MRI will be initially obtained (repetition time= 3000 ms; echo time = 28ms, phase encoding direction = anterior to posterior; matrix field of view = 220mm; voxel size = 2.5mm x 2.5mm x 2.5mm). A total of 93 full-brain datasets will be obtained, however, the first 3 images will be eliminated to account for scanner preparation and equilibration effect. It will measure 10 full-brain datasets per 30 seconds for anterior knee joint loading blocks (total 4 blocks, 40 full-brain activation maps) followed by 30 seconds resting blocks (5 blocks, 50 full-brain maps), beginning with the resting condition. The fMRI scanning will take about 4 minutes and 39 seconds. During the joint loading, the researcher will inflate and deflate the joint loading device (described above chapter 2) at a rate of 25 bpm in the adjacent operator room. The participants will experience 7 repetitions of anterior joint loading. During the fMRI imaging, the participants will be asked to close their eyes to control the brain activation processing of visual information. Upon completion of the functional imaging, the patella stabilizer and associated

straps will be loosed to avoid any participant's potential knee discomfort for ensuing structural imaging.

Structural Brain Imaging

Following functional imaging, a Localizer will again be attained. Then, T1-weighted MPRAGE structural images will be obtained (TR = 2000 ms; TE = 4.58ms, FOV = 256mm; voxel size = 1 × 1 × 1mm Scan Time = 6.5 mins). After completion of structural brain image scan, participants will be removed from the scanner and escorted out of the facility.

Data Pre-processing

fMRI

fMRI data will be analyzed using the fMRI of the brain (FMRIB) software library (FSL: The Oxford Centre for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom). Preprocessing will be completed for each subject's functional MRI data, and this process includes image format converting (DCM to NII), reorientation, and brain extraction (Scott, Allen, and McCarthy 2014). Then, FEAT (sub-component of the FSL software) will be used to perform preprocessing of ICA-AROMA. This process includes 4D mean intensity normalization, temporal filtering (90s), spatial smoothing at 5mm full width at half maximum (FWHM), interleaved slice timing correction, and FMRIB'S linear image registration tool for motion correction (MCFLIRT) (Jenkinson et al. 2002; S. M. Smith 2002; S. M. Smith et al. 2004). After completing the preprocessing for all subject data, independent component analysis-based automatic removal of motion artifacts (ICA-AROMA) will be used to remove motion-related noise (Pruim et al. 2015). ICA-AROMA decomposes the data and automatically finds and removes signals associated with head motion (Pruim et al. 2015). It has been revealed that ICA-AROMA is sensitive to motion artifacts while protecting

task-related signal, and it also increases sensitivity for the group-level of analysis (Pruim et al. 2015). The denoised data will be used for the first level of analysis.

Structural Brain Images

MPRAGE brain structural images will be analyzed in FreeSurfer software https://surfer.nmr.mgh.harvard.edu/) to identify gray matter volume from each subject's data. FreeSurfer is a software package to analyze structural brain data (T1 weighted images) to provide data regarding the structural properties of the brain as well as the functional and connectional properties (Bruce Fischl 2012). Prior to use FreeSurfer, high-resolution T1-weighted full brain data sets will be converted to NIFTI format and then reorganized. Then, the FreeSurfer analysis will be perform briefly including skull stripping (Ségonne et al. 2004), Talairach transformation, volumetric segmentation of subcortical white and gray matter structures (Bruce Fischl et al. 2002), intensity normalization, tessellation of white and gray matter boundaries, and topology correction (B Fischl, Liu, and Dale 2001). In addition, surface inflation and spherical atlas registration using individual folding patterns to match cortical geometry across subjects (Bruce Fischl, Sereno, and Dale 1999), and gyral based cortical parcellation (Desikan et al. 2006) will be processed. The cortical thickness will be calculated by measuring the distance between the gray/white matter boundary and gray/pial boundary at each vertex on the tessellated surface (B Fischl and Dale 2000). The robust within-subject template (Reuter and Fischl 2011) will be created between the two-time points of each participants using the longitudinal stream of FreeSurfer in order to minimize within-subject noise. Next, each participants' image data will be visually inspected to manually correct inaccuracy segmentation by the researcher. Upon completion of all processes of the brain structural analysis, structural properties including surface area, gray matter volume, and cortical thickness from the multiple brain regions will be provided.

Specific to the current study these regions will include the somatosensory cortex (Broadman area 1, 2, and 3).

Time to Stabilization Test

TTS analyses will largely follow the method of previous researches (S. E. Ross, Guskiewicz, and Yu 2005; S. Ross and Guskiewicz 2003). A second-order recursive low-pass Butterworth filter at 12 Hz will be applied to the GRF data (S. E. Ross, Guskiewicz, and Yu 2005). We will use the last 10 seconds of single-leg stance jump landing to record AP and ML GRF sway. The results of this procedure will be used to define dynamic postural stability. The AP and ML components of the GRF data will be separately analyzed by using a MATLAB software package (The MathWorks, Inc., USA).

We will observe two windows: one will be 10-15 seconds and the other one will be 15-20 seconds. After this observation, the highest peak of GRF for each window will be found. Among the two groups' peak GRFs, the smaller peak range will be selected as the optimal range-variation value. This indicates subjects' optimal postural stability (Figure 3.3). Average subject's range-variation will be calculated from 3 trials. The overall procedure will be repeated for each subject. Then group means range of variation and standard deviation (SD) will be determined for both HL and LL groups.

Next, we will compare the group mean of optimal range-variation between the high and low laxity groups using the unpaired t-test. We will perform this comparison prior to the process of calculating TTS in order to make a decision on whether to perform data normalization or not. This is because when one group definitely stabilizes better than another group (i.e., stable ankle group stabilize better than chronic ankle instability group (Simpson et al. 2019)), the better group's TTS can be slower due to smaller optimal range-variation values (Figure 3.2) (S. E. Ross, Guskiewicz, and Yu 2005). Thus, data normalization will be needed. However, we do not have

previous evidence supporting that healthy individuals with high knee laxity have significantly decreased postural control compared to lower laxity individuals. It will be difficult to tell if we need to perform the normalization without group comparison. Thus, if one group's optimal range-variation value is significantly higher than another ($p<0.05$), the normalization process will be performed.

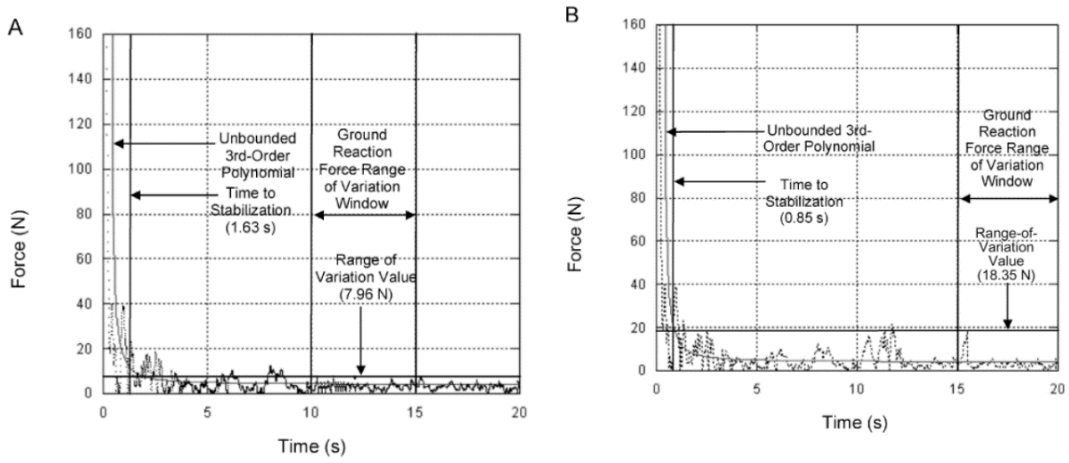

Figure 3.2_Time to Stabilization Data Processing with Normalization. (A) stable ankle, (B) unstable ankle. Even though individuals with stable ankle has better postural control, the TTS was slower (1.63s) than chronic ankle instability individual (0.85s) due to their smaller optimal range of variation value (7.96 N) than instability individuals (18.35 N). (S. E. Ross, Guskiewicz, and Yu 2005)

No Significant Differences in Optimal Range-Variation Between Groups

If the optimal range range-variation values between HL and LL group are not significantly different ($p>0.05$), we will not need to normalize the data. A range-variation of the AP and ML will be superimposed over the respective GRF data via horizontal lines (Figure 3.3). Then, an unbounded third-order polynomial curve-fit line will be applied to the 20 seconds of GRF data. The TTS will be when the unbounded polynomial is equal to or less than the range-variation (Figure 3.3).

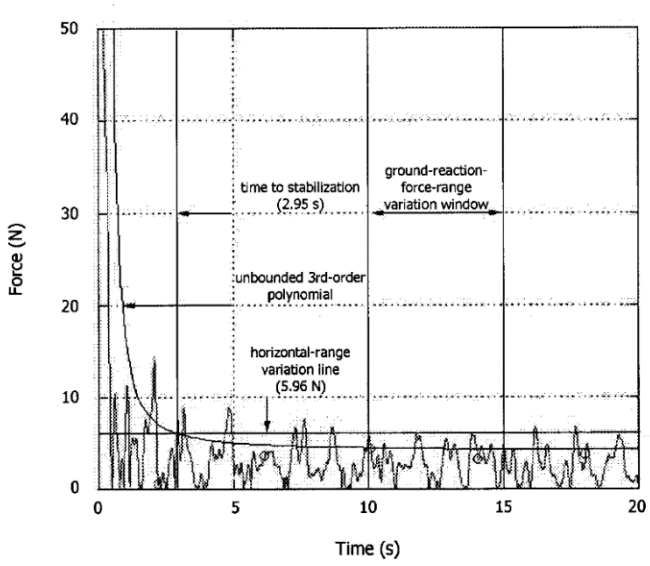

Figure 3.3 Time to Stabilization Data Processing without Normalization. TTS in a single trial of 1 subject from AP sway. The optimal range-variation value was selected in 10-15 windows (highest peak GRF: 10-15s < 15-20s). TTS was calculated from anterior/posterior GRF in 10-15 seconds window (S. Ross and Guskiewicz 2003)

Significant Differences in Optimal Range-Variation Between Groups

If it is found that one group's mean optimal range-variation value is significantly higher than another group ($p<0.05$), the data will be normalized. The higher functioning group's (smaller mean range-variation) AP and ML components will be used to determine the reference variable for further normalization process. All processes to normalize and calculate TTS will be performed separately for the AP and ML component. First, the optimal range-variation value will be calculated following the same method as described above. The smaller range of the highest peak GRF between two windows (10-15s and 15-20s) will be selected as the optimal range-variation value. Then, the range-variation value for a subject will be divided by her body weight in Newton. A mean range-variation will be calculated from 3 trials for a subject. The procedure will be repeated for each subject, and then an overall mean range of variation and standard deviation (SD) will be calculated. Next, three SDs will be added to overall range-variation mean to

determine the reference variable (reference variable= mean range of variation + 3*SDs). A subject's normalized range-variation value will be calculated by multiplying the subject's body weight (N) by the reference variable (normalized range-variation= reference variable x bodyweight). The normalized range-variation will be superimposed over the respective GRF data via a horizontal line. Then, an unbounded third-order polynomial line will be applied. Finally, TTS will be calculated by observing the time when the polynomial line is equal to or less than the normalized range-variation (horizontal line) (Figure 3.3).

Statistical Approach

fMRI Data

Hypothesis 1: *High AKL individuals will demonstrate significantly higher brain activation of the somatosensory cortex compared to individuals with low AKL during joint loading.*

In order to answer Hypothesis 1, we will use FSL_FEAT to conduct the first-level analysis and subsequent group level analysis. The foundation of statistical modeling of FSL is based on the General Linear Model, which assume that the data are composed of a linear combination of different model factors, along with uncorrelated noise (Scott, Allen, and McCarthy 2014). It assumes that even though adjacent voxels are very similar to each other, all voxels represent independent statistical tests (Scott, Allen, and McCarthy 2014). Thus, without correction for the multiple comparisons, there is a high rate to have Type I error, which is that a voxel is labeled as active when it is not. Therefore, we will conduct the cluster-based threshold, which adopts the minimum size for a cluster of active voxels to be labeled as significant (Scott, Allen, and McCarthy 2014), with z threshold at 3.1 and p threshold at 0.05 for each individuals' fMRI data. Then, we will conduct the group level of analysis using the two-sample unpaired t-test. This group analysis will provide us the contrast between groups (HL-LL & LL-HL). The group analysis will also be analyzed with z threshold at 3.1 and p threshold at 0.05. The group

variable (HL and LL) will be used as an independent variable and the BOLD signal will be used as a dependent variable.

Brain Structure Data

Hypothesis 2*: High AKL individuals will reveal significantly less gray matter volume of the somatosensory cortex than individuals with lower AKL.*

In order to answer Hypothesis 2, the FreeSurfer software will be used to identify gray matter volume from each subject's data. FreeSurfer is a powerful software package to analyze structural brain data (T1 weight image) to provide data regarding the structural properties of the brain (Bruce Fischl 2012). This analysis includes volumetric segmentation of the most visible brain structure, segmentation of the hippocampus, inter-subject alignment, segmentation of white matter, parcellation of cortical folding pattern, mapping of the thickness of cortical gray matter, and the construction of surface models of the human cerebral cortex (Bruce Fischl 2012; Bruce Fischl et al. 2002). After completion of the FreeSurfer analysis, it will provide us the structural quantities including gray matter volume, surface area, and cortical thickness from the multiple brain regions. Since it is hypothesized that individuals with higher knee laxity would have altered sensory information, the gray matter volumes from the somatosensory cortex (Broadman areas (BA) 1,2, and 3) will be assessed. To analyze the group differences, the independent t-test will be conducted with group variable (HL and LL) as an independent variable, and gray matter volume and thickness (GMV1, GMV2, GMV3) as dependent variables ($p<.05$). The analysis will be conducted using the Statistical Package for the Social Science (SPSS Inc, Chicago, Ill).

Time to Stabilization Data

Hypothesis 3*: High AKL individuals will demonstrate a longer time to control the dynamic postural stability compared to lower knee laxity individuals.*

In order to answer Hypothesis 3, the AP and ML direction's TTS value will be used. The Statistical Package for the Social Science (SPSS Inc, Chicago, Ill) will be used to perform the analysis. The average TTS value for each subject will be calculated using the 3 trials with the AP and ML components will be calculated separately. The comparison between HL and LL groups will be analyzed using the independent t-test ($p<0.05$). The TTS (seconds) will be used as a dependent variable, and the groups (HL and LL) will be used as an independent variable. Effect size and power for analysis of variance will be calculated using the Cohen effect size index (Cohen 1988) and power of F test tables for the group-by-direction interaction, the main effect for HL and LL groups, and the main effect for AP and ML direction.

CHAPTER IV

MANUSCRIPT I

Title

The Impact of Differential Knee Laxity on Brain Activation during Knee Joint Loading.

Abstract

Background: Although greater anterior knee laxity (AKL) is an established risk factor of ACL injury; underlying mechanisms are uncertain. Our brain receives sensory input from the joint and plays an essential role in the process of joint stabilization. The potential impact of greater laxity on brain function is not well understood.

Hypothesis: High AKL individuals will demonstrate significantly higher brain activation of the somatosensory cortex compared to individuals with low to average AKL during joint loading.

Study Design: Cross-sectional study

Methods: Twenty seven healthy and active female college students without any previous severe lower leg injuries volunteered for this study. Anterior knee laxity was measured to assign participants to a high laxity (N=15) or low to average laxity group (N=12). Functional magnetic resonance images were obtained during anterior knee joint loading in a task-based design using a 3T MRI scanner.

Results: High knee laxity individuals demonstrated diminished cortical activation in the left superior parietal lobe and right premotor cortex; and increased cerebellar activation in Crus I and II during anterior knee joint loading.

Conclusion: Altered brain activation in individuals with high knee laxity may indicate possible functional neuroplasticity influenced by knee laxity. These findings suggest that individuals with high knee laxity may have a different perception of their body's internal representation as well as altered strategies in preplanning and preprogramming potential movements when the knee joint is loaded.

Keywords: Functional neuroplasticity; functional brain reorganization; anterior knee laxity; ACL risk factors

Introduction

Anterior cruciate ligament (ACL) injury is one of the most common traumatic knee injuries to occur during sporting activities (Prodromos et al. 2007). This injury is highly associated with the development of early-onset osteoarthritis (Knoop et al. 2014; Vad and Bhat 2000) as it is reported that there is an 80% likelihood to have knee osteoarthritis within 15 years following the primary ACL injury (Dare and Rodeo 2014; Lohmander et al. 2004; Vad and Bhat 2000). Among the multiple reported risk factors of ACL injury, greater anterior knee laxity (AKL) is known as one of the strongest independent predictors of ACL injury (Uhorchak et al. 2003; Vacek et al. 2016; Woodford-Rogers, Cyphert, and Denegar 1994).

Greater knee laxity has been associated with diminished sensory input (Rozzi et al. 1999). This may be due in part to lower ligament tension in a high knee laxity joint. ACL reconstructed patients who had lower graft tension during a surgical procedure were reported to have greater AKL two years post reconstruction (Yasuda et al. 1997). Since mechanoreceptors in the ligaments respond to tension (Zimny 1988), decreased ligament tension may result in a

decreased firing rate of the mechanoreceptors when force is applied to the joint in a manner to engage the ligaments. Thus, individuals with high knee laxity may potentially have diminished sensory input. Impaired sensory information has been found in individuals with greater AKL as well as altered muscle activation and movement patterns (Rozzi et al. 1999; Shultz et al. 2006). The potentially impaired sensory input (Rozzi et al. 1999) along with reports of altered movement patterns (Shultz et al. 2010; Shultz, Carcia, and Perrin 2004) in high knee laxity individuals may collectively lead to a decreased ability stabilize the joint during physical movement (functional stability) (Riemann and Lephart 2002a); thus resulting in an increased risk of ACL injury.

Functional stability of the joint is maintained by the sensorimotor system, which encompasses all the sensory, motor, and central integration and processing components. In this process, the brain has various crucial roles (Peter Grigg 1994; Riemann and Lephart 2002a). The brain integrates and processes sensory information arising from a peripheral area to generate neuromuscular control solutions to meet the task demands as well as stabilizing the joint (Kandel, Schwartz, and Jessell 1991).

Since the brain has an essential role in integrating information to effectively stabilize the joint stabilization during locomotion, there is a need to understand central mechanisms associated with potential alterations in sensory input from the joint and how they may be related to an injury. Several studies examined brain function while performing movements or loading of the of the knee joint in ACL deficient (ACLD) (Kapreli et al. 2009) and ACL reconstructed (ACLR) individuals (An et al. 2019; Baumeister et al. 2011; Grooms et al. 2017). An et al demonstrated that ACL reconstructed patients had significantly higher cortical activation in the somatosensory area during anterior knee loading compared to healthy limbs, and was positively correlated with anterior knee laxity (An et al. 2019). The results showed evidence of possible functional

neuroplasticity due to altered sensory perception resulting from an ACL injury and associated disruption in mechanoreception from the ligament. The functional neuroplasticity may have occurred because diminished sensory input may increase the efficacy of pre-existing connections from other sensory resources to the cortex to transmit the impaired sensory information (Cusick et al. 1990; Rasmusson 1982; Ziemann, Hallett, and Cohen 1998). When the sciatic nerve, which is the dominant nerve transmitting tactile input, was transected; it unmasked saphenous nerve afferent pathways to transmit the impaired tactile information (Cusick et al. 1990). This altered sensory pathway may lead to functional neuroplasticity of the brain.

Potential functional neuroplastic adaptations related to high knee laxity in healthy individuals are still unknown. Identifying brain function while loading the knee joint in a manner designed to stress the ACL in those individuals may help us to fully understand sensorimotor system function associated with ACL injury. Thus, the purpose of this study is to identify the impact of knee laxity magnitude on brain activation during knee joint loading, designed to elicit sensory information from ACL mechanoreceptors. It was hypothesized that high AKL individuals would demonstrate significantly higher activation in regions of the brain associated with processing sensory information, compared to individuals with low to average AKL.

Methods

Participants

Physically active female students aged between 18 -35 years old, who were right-handed and footed were recruited from the University of North Carolina at Greensboro. Participants reported a normal menstrual cycle lasting 26-32 days for the past six months and no history of pregnancy or no planning to become pregnant. Participants were physically active, participating in moderate activity at least three times a week. Exclusion criteria included: 1) previous significant lower leg injuries; 2) any neurologic disorders; 3) anxiety; 4) claustrophobia; 5) over

30 BMI (falling into the category of obesity) (Nuttall 2015); 6) currently undergoing a neuromuscular training program; and 7) currently participating in intercollegiate sports. The group consisted of an equal number of participants where half used a hormonal contraceptive (i.e. contraceptive pill, IUD, and birth control patch) and the other half did not use these contraceptives. 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.

Prescreening

An MRI safety questionnaire and knee laxity test were performed during the prescreening day to make sure participants' eligibility in this study. A total of 103 potential participants were screened. Sixty-four potential participants were excluded because they did not meet the inclusion, or their knee laxity values did not fall into the desired range. A total of thirty-nine participants fit the inclusion criteria. Two participants dropped due to the change of their knee laxity values across screening/testing days, and ten others dropped due to MRI contraindication, previous history of surgery, or complicated schedule during the pre-screening. A total of twenty-seven participants were included in this study (age= 20.4±1.8 years; height= 166.05±6.8 cm, mass= 64. 5±8.2 kg).

The knee laxity test was performed using a KT-2000 knee arthrometer (Medmetric Corp) using previously established measures (Shultz et al. 2010). Participants were tested in the supine position with 25±5º of knee flexion. A Velcro strap was placed around their thigh to control the hip external rotation. Then, the KT-2000 was located on the participant's anterior aspect of the tibia, and the examiner applied 89 N of force in the posterior direction and 133N of force in the anterior direction for three cycles. The investigator had previously compared between day measurement consistency and precision [ICC (SEM) =0.97 (0.5mm)]. Participants who had AKL greater than 9.5 mm were assigned into the high laxity group (HL group; N=15). Participants who

had AKL lower than 8.5 mm were assigned into the low to average laxity group (LL group; N=12). The knee laxity test was performed during both the prescreening day and MRI scanning day to ensure that participants remained in their assigned group (high laxity or low-average laxity group).

MRI Scan

The functional magnetic resonance images (fMRI) were measured during the participants' first eight days of menstrual cycles or placebo pill week (self-reported). A 3.0 T MRI scanner with a 12-channel head coil (Siemens Trim Tri; Erlangen, Germany) was used to obtain fMRI data. In order to perform anterior knee joint loading while obtaining functional MR images, the MR compatible anterior knee joint loading device was built with non-ferromagnetic materials such as wood, plastic, and latex tube (Figure 4.1). Inflation of air cuff placed underneath to the participant's calf causes anterior translation of tibia while stabilizing the femur. A custom-designed MR compatible anterior knee joint loading device was placed underneath the participant's calf in the scanner room, and its familiarization was completed. Please see chapter III for full validation details. The task completed in the scanner was 30 sec of rest followed by 30 sec of passive anterior joint loading for a total of 4 cycles ending with a rest block. During the knee joint loading blocks, the MR compatible anterior knee joint loading device was inflated (130N) and deflated (0 N) manually at a rate of 20 beats per minute in the adjacent operator room. Participants experienced approximately 5 anterior knee joint loadings for each block (30 seconds), a total of 20 repetitions of knee joint loadings (4 cycles). During this time, a participants were asked to close their eyes to minimize visual confounds and remain awake.

The fMRI task-based imaging parameters largely followed the methodology of the previous fMRI study (Raisbeck et al. 2018). The initial localizer scan was completed followed by the functional MRI scan (repetition time= 3000 ms; echo time = 28ms, phase encoding direction

= anterior to posterior; matrix field of view = 220mm; voxel size = 2.5mm x 2.5mm x 2.5mm). A total of 90 full-brain datasets were obtained; this included 10 full-brain datasets per 30 seconds for resting blocks (total 5 blocks, 50 full-brain maps) followed by 30 seconds anterior knee joint loading blocks (total 4 blocks, 40 full-brain activation maps), and ending with the resting block. Following functional MRI scan, T1-weighted MPRAGE structural brain images were obtained (TR = 2000 ms; TE = 4.58ms, FOV = 256mm; voxel size = 1 × 1 × 1mm Scan Time = 6.5 mins).

Data Analyses

fMRI data analyses and statistical analyses were performed using the fMRI of the brain (FMRIB) software library (FSL: The Oxford Centre for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom). Preprocessing was completed using FEAT (sub-component of the FSL software); it included 4D mean intensity normalization, temporal filtering (90s), spatial smoothing at 6mm full width at half maximum (FWHM), interleaved slice timing correction, and FMRIB'S linear image registration tool for motion correction (MCFLIRT) (Jenkinson et al. 2002; S. M. Smith 2002; S. M. Smith et al. 2004). Upon completion of the preprocessing, each data was denoised with the independent component analysis-based automatic removal of motion artifacts (ICA-AROMA) pipeline (Pruim et al. 2015). ICA-AROMA decomposes the data and automatically finds and removes signals associated with head motion (Pruim et al. 2015). ICA-AROMA is found to be sensitive to motion artifacts while protecting task-related signals, and increases sensitivity for group-level analysis (Pruim et al. 2015). Then, the first-level GLM analysis was performed to determine each individual subject's contrast between conditions (rest vs. joint loading) using a cluster-based threshold with z threshold at 3.1 and p threshold at 0.05. Lastly, the higher level GLM analysis was performed with FLAME 1+2 using unpaired samples t-test to contrast between groups (HL> LL, LL>HL). The voxel-wise gray matter volumes were included as

covariates during the higher-level analysis to avoid possible differences in participants' brain structure between groups that may lead to misinterpretation of functional results (Oakes et al. 2007).

Results

Demographics of the high laxity and low to average laxity groups are presented in Table 4.1. There were no significant differences between high laxity and low to average laxity groups in Marx ($p=0.056$) and TEGNER ($p=0.91$) activity scales (Table 4.1). Additionally, there was no difference in absolute head motion ($p=.307$) and relative head motion ($p=0.146$) during the experimental tasks (Table 4.1).

During anterior knee joint loading, the low to average laxity group revealed greater activation in the left superior parietal ($p=0.00119$) and right premotor cortex ($p=0.0025$) when compared to the high laxity group (Figure 4.3). The high laxity group demonstrated significantly higher activation in the right cerebellar Crus I ($p=0.0109$) compared to the LL group (Figure 4.4). The fMRI comparison between groups during anterior knee joint loading is reported in Table 4.2.

Discussion

To the best of our knowledge, this is the first fMRI study of brain activation differences during anterior knee joint loading in healthy individuals with various degrees of AKL. We undertook this study to better understand central mechanisms associated with a known prospective risk factor of ACL injury. The following discussion will address our findings of differences in brain activation during passive loading designed to stress the ACL.

Current results revealed that high AKL individuals had significantly less activation in the left superior parietal lobe and right premotor cortex during anterior knee joint loading when compared with average to low to average AKL individuals. It is understood that the superior parietal lobe plays a primary role in maintaining attention to visual and tactile stimuli (Posner et

al. 1984), associating somatosensory, visual, auditory, and vestibular signals, in addition to generating a neuronal construct of the body (position and movement) (Purves et al. 2017). Wolpert and his colleagues observed a patient with a left superior parietal lesion (Wolpert, Goodbody, and Husain 1998). The patient demonstrated a profound tactile fading to constant stimuli and a concurrent inability to maintain a constant force output in the right hand. Moreover, the patient's perception of the location of her right arm drifted when it was outside of her vision. The patient also demonstrated motor errors when she was asked to make slow pointing movements to peripheral targets while fixating a central stimulus. Acknowledging this was a case report, the authors suggested that the superior parietal had an essential role in actively maintaining an internal presentation of the body's state. Thus, less activation of the superior parietal lobe in the high laxity individuals may indicate that those individuals may have a different perception of their body's internal representation compared to the low to average AKL individuals. The current findings may explain why individuals with greater AKL or hypermobile joints showed longer time to detect joint motion (Rozzi et al. 1999) or large amount of error during joint position sense test, respectively (Ituen et al. 2020; Sahin et al. 2008).

The premotor cortex plays an essential function in the planning or programming of voluntary movements. Neurons in the premotor cortex begin firing about 800ms prior to voluntary movement (Deecke, Scheid, and Kornhuber 1969). It has been reported that many neurons in the premotor cortex activate when receiving an instruction to move (Wise 1985). This indicates the function of the premotor cortex in the preparation of the voluntary movement. Furthermore, lesions of the premotor cortex showed severely impaired ability to develop an appropriate movement strategy (Moll and Kuypers 1977). It was observed that when primates with the premotor cortex lesions were presented with a food target that required a movement strategy through an opening rather than directly accessing the food target resulted in an inability

to execute a more complicated movement strategy (Moll and Kuypers 1977). This result provides evidence that the premotor cortex plays an essential role in planning complex movements that requires sequence-specific muscle contractions to execute a motor task (Kandel, Schwartz, and Jessell 1991). Thus, the current findings regarding the premotor cortex may indicate that individuals with high laxity may have challenges in planning proper movement strategies when their knee joint is loaded or deformed.

Previously, Grooms and his colleagues found higher activation of the premotor cortex in ACL reconstructed (ACLR) patients using fMRI task of active knee flexion/extension. They obtained fMRI data of the ACLR patient several days before secondary ACL injury of the contralateral reconstructed knee and compared the fMRI data to a matched healthy control participant (Grooms, Page, and Onate 2015). The ACLR patient had higher activation in several brain regions, including the contralateral premotor cortex, when compared to a matched healthy participant. The authors suggested that it may be due to the increased demand to engage higher-level cortical processing to plan movement in ACLR participants (Meister et al. 2005). This may occur due to the fact that ACLR patients may still experience impaired proprioception even with mechanical stability improvement (MacDonald et al. 1996; Relph, Herrington, and Tyson 2014).

However, our current finding revealed less activation of the premotor cortex in individuals with greater AKL who may have potentially impaired sensory input. Even though both groups (ACLR and high laxity individuals) may potentially have poor proprioception, the results showed different findings, which may be due to the differing experimental paradigms. The experimental task in the study by Grooms et al. required voluntary movements (knee extension/flexion), whereas the current study's task was a passive experience in which the participants were asked to be relaxed and they felt knee joint loadings. While direct comparisons are difficult, we suggest that when pre-planned voluntary movements are required, individuals

with poor proprioception may need more corticomotor strategies to plan a voluntary movement, whereas those individuals may have hindered strategies to plan for potential movement and joint stabilization when voluntary movements are not required.

Current findings also demonstrated individuals with high AKL demonstrated significantly higher activation of the right cerebellum, specifically in Crus I and II. The cerebellum consists of 10% of the total volume of the brain and it contains both sensory and motor components that indirectly adjusts movement and posture (Kandel, Schwartz, and Jessell 1991). Among the ten lobules in the cerebellum, lobule VII expands in the lateral hemisphere, forming Crus I and Crus II. Crus I and Crus II are the most prominent regions in the lateral aspects of the human cerebellum and are involved in cognitive function, including the planning and integration of the different processes (Larsell 1970; Stoodley and Schmahmann 2009). The cerebellum receives information related to the programming and execution of movement from the motor and premotor area of the cerebrum. It also receives information regarding motor performance from the periphery as well as all levels of the CNS (Kandel, Schwartz, and Jessell 1991). Then, the cerebellum projects signals to the descending motor systems (Kandel, Schwartz, and Jessell 1991). The cerebellum also plays a wide range of roles in language, spatial, and executive function in addition to the sensorimotor control (Stoodley and Schmahmann 2009). The greater activation of the Crus I and Crus II in individuals with higher AKL may indicate compensatory strategies in pre-programming of the execution of motor actions.

Our hypothesis was that individuals with higher AKL would have greater activation in the somatosensory areas. This was due to the possibility that higher AKL individuals may have compensatory strategies to receive impaired sensory signals. An et al. showed significantly higher cortical activation (as assessed with EEG) associated with the somatosensory area during anterior-posterior knee joint loading in ACLR patients compared to the uninjured limb and the

matched control group (An et al. 2019). The increased cortical activation was also positively correlated with knee laxity. The author suggested that their results may reveal different neural adaptation strategies in ACLR patients due to neuromechanical recoupling following an ACL injury and reconstructive surgery. Thus, ACLR patients might show the increased cortical activity in the somatosensory areas in order to compensate for their sensory input deficit (An et al. 2019).

However, the current findings showed no statistically different activation of the somatosensory areas between high laxity and low to average laxity groups. This was similar in result to a previous study by Needle et al. (Alan R Needle et al. 2014) that observed cortical activation via EEG during ankle joint loading in healthy control, coper, and unstable ankle individuals. Results demonstrated that cortical activation increased during load application to the ankle in all groups. However, there were no differences in the somatosensory areas between healthy, coper, and unstable ankles. The authors suggested that other mechanoreceptors such as cutaneous receptors or potentially increased anticipation in the sensory cortex might compensate and overcome the sensory deficit in individuals with an unstable ankle during joint loading. Similar to Needle et al.'s findings, our results may indicate that individuals with higher AKL may have compensatory strategies that do not result in changes in the somatosensory cortex. However, the impaired sensory input may result in activation alterations of the superior parietal lobe and premotor cortex.

Although the present study demonstrated differences in brain activation in individuals with high AKL compared to low to average AKL individuals, there are several factors that may limit the interpretation of the findings. The high laxity group had a greater mean height than the low to average laxity group (Table 4.1). However, mass or BMI did not differ between groups. Thus, although high laxity individuals were taller than the lower to average laxity individuals, BMI did not differ. Given the importance of BMI in ACL injury risk (Bojicic et al. 2017;

Uhorchak et al. 2003; Vacek et al. 2016) and not height, the group differences may not directly impact the observed outcomes. Furthermore, there was a near significant difference in the Marx scale ($p= 0.056$). However, the Tegner activity level scale did not show any significant differences between groups. While the Tegner scale measures the type of activity done, the Marx scale is more direct measure of activities that include cutting, deceleration, and pivoting. Thus, it may indicate that individuals in both groups participate a similar level of activity resulting in similar overall loading magnitudes, with individuals in the high laxity group performing more activities that including cutting, decelerating, and pivoting. Due to these limitations, we conducted secondary statistical analyses with height and Marx scale as covariates. There were the similar results as high knee laxity group still demonstrated less activation in the left superior parietal lobe and right premotor cortex compared to the low to average laxity group. However, there was no significantly greater activated region in high knee laxity group. It may indicate that height and Marx scale may not largely impact our outcomes with regard to cerebral findings.

Moreover, it is possible that the differences in brain activation during anterior knee joint loading were not only due to differences in stimulation of the ligamentous receptors but were also due to differences in stimulation of the cutaneous receptors surrounding the knee and calf via the air-cuff placed underneath participants' calf. However, even with the likely involvement cutaneous receptor stimulation, the validation test of the MR compatible joint loading device (included in Chapter VI) showed evidence of anterior translation of tibia related to the femur, which represents stretching of the ACL. Given that both groups received similar loading stimuli and the fMRI analyses are designed to account for similarities between groups, the difference observed in the current study may be attributed to the different stimuli of the mechanoreceptors innervated in ACL among the two groups. Therefore, our findings demonstrate the impact of differential knee laxity on brain activation.

The current study assessed fMRI data during anterior knee joint loading in individuals with high and low to average laxity. Results demonstrated that the high laxity group had significantly higher activation in the right cerebellum, and the low to average laxity group showed significantly higher activation in the right premotor and left superior parietal lobe. These findings suggest that individuals with high knee laxity may face challenges when planning potential movements. They may also have different perceptions of their body's internal representation when their knee joint is loaded. The current study demonstrated brain activation while receiving sensory signals during passive loading. However, little is known of brain function during voluntary movement in individuals who are at high risk of ACL injury. In the next steps to understanding the brain's role in the process of joint stabilization, more dynamic motor control tasks may be needed. If we can understand the brain's function during integrated sensorimotor function, it may help us to fully understand the brain's role in joint stabilization.

Figure 4.1 MR Compatible Anterior Knee Joint Loading Device

Figure 4.2 Participant Setup with MR Compatible Anterior Joint Loading Device

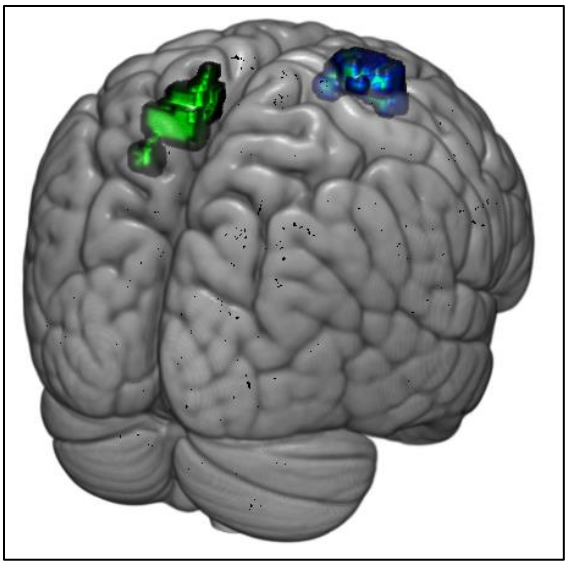

Figure 4.3 Regions with Greater Activation in Low to Average AKL Individuals.
The blue area represents the right premotor cortex, the green area represents the left superior parietal lobe.

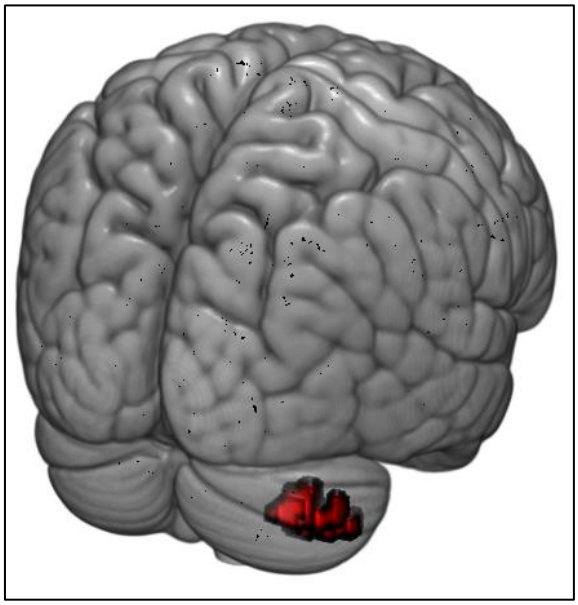

Figure 4.4 Regions with Greater Activation in Greater AKL Individuals.
The red area represents the Crus I and II.

Table 4.1 Participants Demographics, Physical Activity Rating Scale, and Head Motion. (mean± standard deviation)

Groups	High Laxity	Low-Average Laxity	p-value
Anterior Knee Laxity (mm)	12.3±2.6	6.5±1.6	.000
Age	19.9±1.7	20.9±1.9	0.163
Weight(kg)	66.8±7.3	61.5±8.7	0.099
Height(cm)	166.8±5.0	162.3±6.2	0.050
BMI	24.0±2.6	23.3±2.8	0.486
MARX	8.1±2.9	5.6±3.7	0.056
TEGNER	5.2±1.3	5.3±0.9	0.911
Absolute Head motion (mm)	0.17±0.08	0.14±0.05	0.307
Relative Head motion (mm)	0.06±0.03	0.07±0.02	0.146

Table 4.2 Statistically Significant Regions Contrast between HL Group and LL Group

	Regions	P	Peak MNI Coordinate (mm)			MRI Mean Signal Change (%)			
						High Laxity		Low-Average Laxity	
			x	y	z	mean	SD	mean	SD
HL>LL	R Crus I & II	0.011	40	-76	-38	0.08	0.13	-0.12	0.15
LL>HL	L Superior Parietal Lobe	0.001	-8	-56	66	-0.10	0.10	0.13	0.08
	R Premotor cortex	0.003	26	-8	72	-0.14	0.09	0.13	0.12

CHAPTER V

MANUSCRIPT II

Title

The Impact of Differential Knee Laxity on Brain Structure

Abstract

Background: Anterior knee laxity (AKL) is a risk factor of ACL injury associated with sensorimotor alterations. The brain plays a vital role in processing the sensory signals and executing a motor solution. Given the brain's ability to reorganize its structure in response to altered sensory input, laxity associated changes in proprioception may impact brain structure.

Hypothesis: High AKL individuals will reveal significantly less gray matter volume of the somatosensory cortex than individuals with lower AKL.

Study Design: Cross-sectional study

Methods: Twenty-seven female participants volunteered for this study (high laxity:15, low-average laxity:12). Anterior knee laxity was measured to assign participants either to the high knee laxity (AKL> 9.5 mm) or low to average laxity group (AKL<8.5 mm). Gray matter volumes were measured using T1-weighted magnetic resonance imaging.

Results: There were no significant structural differences in the somatosensory areas. However, there was a large effect size of the high anterior knee laxity group having a larger gray matter volume in Brodmann area 6 (BA6), compared to the low to average laxity group.

Conclusion: BA6 consists of the supplementary motor area and premotor cortex. Thus, larger BA6 gray matter volume in individuals with greater anterior knee laxity may represent morphological neuroplasticity influenced by knee laxity. Increased gray matter volume in BA6 may be a compensatory response to overcome challenges of high laxity individuals to initiate and direct the sequence of movements to stabilize the knee joint.

Keywords: Structural neuroplasticity; Brain structure; Structural reorganization; Anterior knee laxity; Knee injury

Introduction

Higher anterior knee laxity (AKL) is one of the strongest independent predictors of ACL injury (Uhorchak et al. 2003; Vacek et al. 2016; Woodford-Rogers, Cyphert, and Denegar 1994). Greater anterior knee laxity may be related to poor functional stability, which is the joint's ability to stabilize during physical movement (Riemann and Lephart 2002a). Beyond ligamentous mechanical deficiencies, it is suggested that the decreased functional stability is due to impaired sensory and motor systems. Previous studies demonstrated that individuals with higher AKL (Rozzi et al. 1999) and individuals with greater shoulder laxity showed impaired proprioception (Laudner et al. 2012). Diminished proprioception may also negatively influence motor patterns. Individuals with higher AKL had greater EMG activity of their hamstring muscles following a lower extremity perturbation (Shultz, Carcia, and Perrin 2004), and increased knee work absorption during jump landing tasks (Shultz et al. 2010) compared to low laxity individuals. This may indicate that individuals with higher AKL have adopted compensatory motor strategies in response to altered sensory input.

Reasons underlying the observed sensory deficit in individuals with greater AKL are not yet well known. One possible view may be due to less tension of the anterior cruciate ligament in higher anterior laxity knees. The negative relationship between ligament laxity and ligament

tension have been demonstrated in ACL reconstruction patients (Fleming et al. 2001; Yasuda et al. 1997). Patients who had lower graft tension during a surgical procedure had greater AKL two years following reconstruction (Yasuda et al. 1997). Since mechanoreceptors are stimulated by tension (Zimny, Schutte, and Dabezies 1986), fewer stimuli associated with mechanoreceptors in the anterior cruciate ligament may be present when a fixed deformation is applied to the knee joint. This may transmit less sensory information to the central nervous system (CNS).

The brain plays an essential role in the process of voluntarily stabilizing the knee joint. The brain integrates and processes the sensory information and transmits it to the motor system to execute the preferred movement and stabilize the joint (Kandel, Schwartz, and Jessell 1991). It is also known that the brain has the ability to structurally reorganize in response to altered sensation. For example, structural brain reorganization was observed in individuals influenced by pain (May 2008; Metz et al. 2009), nerve transection (K. S. Taylor, Anastakis, and Davis 2009), vestibular failure (Gottlich et al. 2016; Hufner et al. 2009), and carpal tunnel syndrome (Maeda et al. 2013). Patients with nerve transection and surgical repair in the median and ulnar nerve had 13-22% less gray matter thickness of the primary and secondary somatosensory cortex compared to healthy controls (K. S. Taylor, Anastakis, and Davis 2009). While the precise physiology of structural brain reorganization is not fully understood yet, one possible view is a growth and/or elimination of axonal and dendritic spines (Darian-Smith and Gilbert 1994; Florence, Taub, and Kaas 1998). The number of axons and dendritic spines can change in response to sensory stimulation (Calverley and Jones 1990), nerve transection (Fitzgerald, Woolf, and Shortland 1990; Florence et al. 1993), and environmental factors (B. B. Johansson and Belichenko 2002). The formation and elimination of axons and dendritic spines may influence both the white and gray matter volume (Purves et al. 2017).

Previous research demonstrated the importance of the brain's role in joint stabilization, and the brain's ability to reorganize its structure influenced by alterations in sensory input. Even with importance of the brain in voluntary movement control and response to external stimuli, structural brain reorganization is not well understood in individuals with established risk factors for ACL injury that may affect sensory input. We hypothesized that individuals with higher AKL may have a lower gray matter volume in the regions involved with somatosensory areas (Broadman area (BA) 1, 2, and 3) because of potentially impaired sensory input to higher brain centers.

Methods

Participants

Physically active female students aged between 18 -35 years old, who were right-handed and footed were recruited from the University of North Carolina at Greensboro. Participants reported a normal menstrual cycle lasting 26-32 days for the past six months and no history of pregnancy or no planning to become pregnant. Participants were physically active, participating in moderate activity at least three times a week. Exclusion criteria included: 1) previous significant lower leg injuries; 2) any neurologic disorders; 3) anxiety; 4) claustrophobia; 5) over 30 BMI (falling into the category of obesity) (Nuttall 2015); 6) currently undergoing a neuromuscular training program; and 7) currently participating in intercollegiate sports. The group consisted of an equal number of participants where half used a hormonal contraceptive (i.e. contraceptive pill, IUD, and birth control patch) and the other half did not use these contraceptives. 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.

Prescreening

An MRI safety questionnaire and knee laxity test were performed during the prescreening day to make sure participants' eligibility in this study. A total of 103 potential participants were screened. Sixty-four potential participants were excluded because they did not meet the inclusion, or their knee laxity values did not fall into the desired range. A total of thirty-nine participants fit the inclusion criteria. Two participants dropped due to the change of their knee laxity values across screening/testing days, and ten others dropped due to MRI contraindication, previous history of surgery, or complicated schedule during the pre-screening. A total of twenty-seven participants were included in this study (mean age= 20.4±1.8 years; mean height= 166.05±6.8 cm, mean mass= 64. 5±8.2 kg).

The knee laxity test was performed using a KT-2000 knee arthrometer (Medmetric Corp) using previously established measures (Shultz et al. 2010). Participants were tested in the supine position with 25±5º of knee flexion. A Velcro strap was placed around their thigh to control the hip external rotation. Then, the KT-2000 was located on the participant's anterior aspect of the tibia, and the examiner applied 89 N of force in the posterior direction and 133N of force in the anterior direction for three cycles. The investigator had previously compared between day measurement consistency and precision [ICC (SEM) =0.97 (0.5mm)]. Participants who had AKL greater than 9.5 mm were assigned into the high laxity group (HL group; N=15). Participants who had AKL lower than 8.5 mm were assigned into the low to average laxity group (LL group; N=12). The knee laxity test was performed during both the prescreening day and MRI scanning day to ensure that participants remained in their assigned group (high laxity or low-average laxity group).

Structural Brain Imaging

Structural brain imaging was performed during the participants' first 8 days of their menstrual cycle or placebo pill week (self-reported). A 3.0 T MRI scanner was used to measure the structural brain images with a 12-channel head coil (Siemens Trim Tri; Erlangen, Germany). The MRI acquisition technique mainly followed the previous fMRI study by Raisbeck et al. (Raisbeck et al. 2018). A localizer scan was obtained first with ensuing T1-weighted MPRAGE structural brain images (TR = 2000 ms; TE = 4.58ms, FOV = 256mm; voxel size = 1 × 1 × 1mm Scan Time = 6.5 mins).

Data Analyses

Processing of MPRAGE structural images and subsequent volumetric segmentation were performed using the neuroimaging package FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). Prior to using FreeSurfer, high-resolution T1-weighted full brain data sets were converted to NIFTI format and then reorganized. FreeSurfer analyses included skull stripping (Ségonne et al. 2004), Talairach transformation, volumetric segmentation of subcortical white and gray matter structures (Bruce Fischl et al. 2002), intensity normalization, tessellation of white and gray matter boundaries, and topology correction (B Fischl, Liu, and Dale 2001). In addition, surface inflation and spherical atlas registration using individual folding patterns to match cortical geometry across subjects (Bruce Fischl, Sereno, and Dale 1999) and gyral based cortical parcellation (Desikan et al. 2006) were processed. All images were visually inspected for motion blurring and gross segmentation errors.

Statistical Analyses

The somatosensory areas (Broadman area (BA)1, 2, and 3) were selected as regions of interest (ROIs) for gray matter volume because of their involvement in receiving sensory information (Arezzo, Schaumburg, and Spencer 1982). Additionally, due to Chapter IV

demonstrating premotor cortex activation differences between laxity groups, Broadmann area 6 (BA 6) volume was included as a secondary dependent variable. Independent t-tests were conducted to analyze the differences between HL and LL groups in gray matter volumes (BA1, BA2, BA3, and BA6) ($P<.05$). Cohen D effect sizes were calculated for all analyses. The analyses were conducted using the Statistical Package for Social Science (SPSS Inc, Chicago, Ill).

Results

Higher AKL and low to average AKL individuals did not differ in terms of age, weight, BMI, and activity rating scale (Table 5.1). Table 5.2 reports the gray matter volumes (mm^3) of HL and LL groups. Each of the somatosensory areas (BA1, 2, and 3) demonstrated no significant difference between groups ($p = 0.376 - 0.967$). However, the right BA6 (premotor cortex and supplementary motor area) neared statistical significance ($p=0.053$) between groups. There was a large effect size (Cohen's $d= 0.8$) in high laxity individuals (18269.3 ± 2049.9 mm^3) having a greater gray matter volume in BA 6 than low laxity individuals (16845.9 ± 1436.4 mm^3).

Discussion

The primary purpose of this study was to identify morphological neuroplasticity associated with knee laxity, a known risk factor of ACL injury. We were initially focused on the gray matter volume in the somatosensory areas (BA 1, 2, and 3) due to the potentially impaired sensory input in individuals with high knee laxity. Because of activation differences found in Chapter IV 1, BA 6 volume (includes premotor cortex and supplementary motor area) was secondarily investigated. To the best of our knowledge this is the first study examining differences in brain structures between groups sorted by magnitude of a known prospective risk factor for ACL injury (anterior knee laxity).

We demonstrated no significant differences in gray matter volume of somatosensory areas between groups. However, there was a large effect size in BA6 between groups with the

high knee laxity group having larger mean BA6 volume than the low to average laxity group. In Chapter IV, we demonstrated that individuals with high AKL had less activation in the premotor cortex during anterior knee joint loading compared to the low to average laxity individuals. The altered cortical activation in the premotor cortex may be related to the structural plasticity observed in BA 6.

BA 6 is located anterior to the primary motor cortex (Kandel, Schwartz, and Jessell 1991). The axons of neurons in this area send signals to the primary motor cortex, subcortical structures, and spinal cord (Penfield and Rasmussen 1950). The two principal areas of BA 6 are the supplementary motor area, which is located on the medial aspect of the hemisphere, and the premotor cortex, which is located on the lateral aspect of the hemisphere. Both of these areas are involved in planning, initiating, and directing voluntary sequence movements (Purves et al. 2017). The supplementary motor area plays an essential role in planning, rehearsing, programming, and initiating complex contralateral motor sequences, with the posterior part of the supplementary motor area mediating those functions for the lower limb (Shah et al. 2015). While the supplementary motor area and premotor cortex have many similar functions, the premotor cortex is more associated with sequential movements when visual information is available (Halsband et al. 1993), whereas the supplementary motor area is largely involved in internally remembered motor movements (Halsband 1987). The premotor cortex is also associated with mirroring movements of another individual performing the same or similar action (Kilner and Lemon 2013; Purves et al. 2017). Collectively the premotor cortex and supplementary motor area are critical in the development and subsequent execution of pre-planned motor actions.

We are not aware of other studies that observed brain structure in individuals with various degrees of knee joint laxity. However, previous studies of structural plasticity have investigated brain structural changes influenced by alterations in sensory input such as spinal cord

injury, pain, or nerve transection. Deafferentation typically results in reductions of gray matter volume. Patients who had upper limb peripheral nerve transaction and surgical repair demonstrated decreased gray matter thickness in several brain regions, including primary and secondary somatosensory areas, compared to healthy controls(K. S. Taylor, Anastakis, and Davis 2009). It has been hypothesized that the gray matter volume reduction may occur due to the elimination of axons, dendritic spine, or peripheral cell death and/or incomplete re-myelination caused by an impaired afferent system (Darian-Smith and Gilbert 1994; Florence, Taub, and Kaas 1998; May 2008). In accordance with the deafferentation literature, we initially hypothesized that individuals with high knee laxity would have reduced gray matter volume in the somatosensory areas due to their potentially impaired sensory input. However, current results demonstrated no significant differences in the gray matter volume of the somatosensory areas. Since our participants in the high knee laxity group were healthy and had no previous history of a severe lower leg injury, greater knee laxity may not have considerably affected the structure of regions in the brain associated with the somatosensory processing.

Our results demonstrated near statistical significance in BA6, which consist of supplementary motor area and premotor cortex between high and low to average groups. Individuals with high knee laxity had larger gray matter volumes in BA6. In Chapter IV, we suggested that our finding of decreased cortical activation in the premotor cortex during passive knee joint loading may correspond with challenges in preplanning and preprogramming potential movements in individuals with high knee laxity. These challenges may be related to the structure of BA6, which is associated with planning and programming motor activities. Individuals with greater knee laxity may require more cortical involvement in BA6 during actual physical movements to overcome their challenges to initiate and direct the sequence of movements. Increased gray matter volume is known to indicate augmented dendritic branching and/or

increased myelination (Draganski et al. 2011). Thus, individuals with greater knee laxity may have increased dendritic branching and/or heightened myelination in the BA6 regions as a compensatory strategy.

Increased volumes of gray matter are typically found in response to motor skill acquisition, such as physical activity training (Draganski et al. 2011; Erickson et al. 2011; Rogge et al. 2018; Weber et al. 2019). For example, unicycling training showed increased cortical thickness in the primary motor cortex compared to before training (Weber et al. 2019). Moreover, aerobic training (Erickson et al. 2011) and balance training (Rogge et al. 2018) also resulted in increased gray matter volumes which included premotor, frontal, and parietal regions of the brain. This increased gray matter volume followed by physical training may indicate a positive neural adaptation in the motor system. Likewise, increased gray matter volume in high knee laxity individuals might be associated with positive adaptation to protect them from ACL injury. However, it is not certain that increased gray matter is indicative of a positive adaptation to help them function or a negative adaptation associated with the risk of sustaining an ACL injury.

There are several factors that may limit the interpretation of the present findings. The high laxity group had a greater mean height than the low to average laxity group (Table 5.1). High laxity individuals were taller than the lower to average laxity individuals, but BMI did not differ. Given the importance of BMI to ACL injury risk (Bojicic et al. 2017; Uhorchak et al. 2003; Vacek et al. 2016) and not height, the group differences may not directly impact the observed outcomes. Furthermore, there was a near significant difference in the Marx scale ($p = 0.056$). However, the Tegner activity, which measures a type of work and recreational activities (Briggs et al. 2009), did not differ between groups. Thus, individuals in both groups reported a similar general level of activity resulting in similar overall loading magnitudes, but individuals in the high laxity group reported more activities that including cutting, decelerating, and pivoting. A

higher level of physical activity, which is determined by leisure time and commuting activity, is known to associate with larger gray matter volume in the prefrontal cortex and striatum (sub-gyral and inferior frontal gyri) (Rottensteiner et al. 2015). Therefore, future brain structural studies may need to consider more fully controlling participant's physical activity levels. In addition, we were not able to control other confounding factors that have been reported to change brain structure, such as experience with playing musical instruments (Munte, Altenmuller, and Jancke 2002; Schlaug 2015). Future brain structure studies will require controlling the confounding factors of experience with playing musical instruments as well as physical activity levels.

To our knowledge, the present study is the first investigation of brain structural differences between individuals with various degrees of anterior knee laxity. Our results demonstrated that there were no significant structural differences in the volumes of somatosensory areas between groups. However, there was a large effect size for greater BA 6 volume in high laxity individuals. BA 6 is inclusive of regions of the brain important to planning of voluntary motor actions. Increased gray matter volume in the BA6 of high laxity individuals may indicate morphological neuroplasticity influenced by greater knee laxity. This may be a compensatory response to the challenge to preplan and preprogram for the potential movement to stabilize the joint in individuals with greater knee laxity. Our results contribute to the identification of fundamental differences in individuals with greater knee laxity. This in turn may help with the understanding of approaching preventive interventions differently for individuals who are at a high risk of ACL injury.

Table 5.1 Participants' Demographics and Physical Activity Rating Scale. (mean± standard deviation)

	Laxity Group			
	High	**Low**	**p-value**	**Effect size (Cohen's d)**
Anterior Knee Laxity (mm)	12.3±2.6	6.5±1.6	.000	2.69
Age(year)	19.9±1.7	20.9±1.9	0.16	-0.55
Mass(kg)	66.8±7.3	61.5±8.7	0.10	0.66
Height(cm)	166.8±5.0	162.3±6.2	0.05	0.79
BMI(kg/m^2)	24.0±2.6	23.3±2.8	0.49	0.27
MARX	8.1±2.9	5.6±3.7	0.06	0.76
TEGNER	5.2±1.3	5.3±0.9	0.91	-0.04

Table 5.2 Gray Matter Volumes in mm^3. (mean± standard deviation)

	Brodmann Area	**Brain Structures**	**High Laxity (mm^3)**	**Low Laxity (mm^3)**	**p-value**	**(Effect size) Cohen's d**
Right	BA1	S1 (postcentral gyrus)	1725.3±256.0	1639.4±232.0	0.376	0.35
	BA2		4985.9±1282.3	4775.9±580.2	0.605	0.21
	BA3a		910.0±117.2	89235±89.3	0.669	0.17
	BA3b		2747.2±572.8	2613.7±309.1	0.475	0.29
	BA6	Premotor, SMA	18269.3±2049.9	16845.9±1436.4	0.053	0.8
Left	BA1	S1 (postcentral gyrus)	1902.1±326.0	1881.0±188.8	0.848	0.08
	BA2		6115.7±952.7	6094.4±807.8	0.951	0.02
	BA3a		860.3±85.5	856.4±84.4	0.908	0.05
	BA3b		3332.1±537.6	3339.3±259.4	0.967	0.02
	BA6	Premotor, SMA	21166.9±2135.6	20540.3±1909.3	0.435	0.31

CHAPTER VI

MANUSCRIPT III

Title

The Impact of Differential Knee Laxity on Dynamic Postural Control

Abstract

Background: While anterior knee laxity is demonstrated to be one of the strongest independent predictors of ACL injury, mechanisms by which laxity affect injury risk are not fully understood. Impaired proprioception associated with greater laxity may result in poor postural control. However, little is known about the impact of anterior knee laxity on postural control.

Hypothesis: High AKL individuals will demonstrate a longer time to stabilize following a dynamic task compared to lower knee laxity individuals.

Study Design: Cross-sectional study

Methods: Fifteen healthy female college students with greater anterior knee laxity and twelve females with low to average anterior knee laxity volunteered for this study. Participant's anterior knee laxity was measured, and dynamic postural control was assessed using the time to stabilization test (TTS) in anterior/posterior and medial/lateral directions following single-leg jump landing tasks. An Independent t-test was administered to identify the differences in TTS between groups.

Results: There were no significant differences in TTS in either anterior/posterior or medial/lateral directions between the two groups.

Conclusion: The time to stabilization measure did not reveal differences in dynamic postural control between groups. More advanced postural control tests that challenge the ACL and are able to separate the vestibular, visual, somatosensory contributions to postural control deficit may be required in order fully understand the influence of knee laxity on postural stability.

Keywords: Anterior knee laxity; Postural control; ACL risk factors; Knee injury

Introduction

Anterior cruciate ligament (ACL) injury is one of the most common traumatic knee injuries occurring during sporting activity (Prodromos et al. 2007). The initial ACL injury carries a high risk of secondary ACL injury, and accelerates the onset of osteoarthritis (Dare and Rodeo 2014; Knoop et al. 2014; Vad and Bhat 2000). This ACL injury incidence rates are 2-4 times higher in females than males (Beynnon et al. 2005; Scerpella, Stayer, and Makhuli 2005). Among the multiple risk factors of ACL injury in females, greater anterior knee joint laxity (AKL) is known as one of the strongest independent predictors of ACL injury (Uhorchak et al. 2003; Vacek et al. 2016; Woodford-Rogers, Cyphert, and Denegar 1994).

It has been suggested that individuals with higher AKL may have less joint stabilization ability when a potentially damaging force is applied to the joint (Rozzi et al. 1999). In addition to obvious connective tissue biomechanics that may put the ligament at risk, this may be attributed to altered proprioception in high laxity individuals. Females with higher AKL had greater errors in a limb repositioning task which suggested poor proprioception (Rozzi et al. 1999). This may be attributed to the lower tension of the ACL at fixed loads in individuals with higher anterior knee joint laxity. Higher knee laxity and low tension of ACL is well understood in patients with ACL reconstruction (Fleming et al. 2001; Yasuda et al. 1997). As mechanoreceptors in the ACL are

stimulated corresponding to tension (Zimny, Schutte, and Dabezies 1986), a greater load may be needed to elicit the firing of mechanoreceptors in the low tension ACL. This may explain why individuals with higher AKL have poor somatosensation.

Since postural control is controlled by sensory information (vestibular, visual, and somatosensory), motor action, and cognition (Shumway-Cook and Woollacott 1995); diminished proprioception in individuals with higher AKL may also lead to a decrease in postural control and associated joint stabilization. Somatosensory deficits are widely understood to be one of the biggest contributors to poor postural control (Riemann, Myers, and Lephart 2002). Postural control deficits have been reported in ACL deficient (ACLD) patients (Ageberg et al. 2005) as well as healthy individuals with general joint laxity (hypermobile syndrome) (Aydin et al. 2017; Mebes et al. 2008). Ageberg et al. demonstrated in female ACLD patients that increased laxity was correlated with greater center of pressure excursion in the frontal plane. Individuals with the hypermobile syndrome, diagnosed with the Beighton scale, also showed significantly higher postural sway compared to control individuals during static (Aydin et al. 2017) and dynamic postural control tests (Iatridou et al. 2014). The above work collectively supports the concept of greater joint laxity having a negative influence on postural control.

Postural control is most commonly assessed through the measurement of postural sway using static tasks. However, it is suggested that static measurement may not be sufficient to observe postural control demands involved with sports-related injuries (Colby et al. 1999) due to the fact that the lower extremity injuries often occur during dynamic activity (Bahr and Krosshaug 2005). Thus, dynamic postural control assessments have been suggested to measure postural instability related to lower limb injuries (Colby et al. 1999). Time to stabilization (TTS) is a dynamic postural control measurement that requires the subject to land and stabilize on a single limb as quickly as possible. It observes how quickly it takes for the initial component of

the ground reaction force (GRF) to become similar to the components of the GRF of the optimal stability in a stabilized single-leg stance (S. Ross and Guskiewicz 2003). Such a task may allow a more dynamic assessment of the ability to attain a stable posture.

Although there are a number of studies describing a postural stability deficit in individuals with hypermobile joint and ACLD patients, we are not aware of studies of postural stability that include knee laxity as a factor. Therefore, the purpose of this study is to determine the impact of differential anterior knee laxity on dynamic postural control. Since somatosensory information is one of the essential contributors to postural control (Shumway-Cook and Woollacott 1995), decreased somatosensory input in individuals with greater AKL may lead to poor postural stability. Thus, we hypothesized that individuals with higher AKL might have greater (slower) time to stabilize during a single-leg stance from a jump landing compared to the lower to average AKL individuals.

Methods

Participants

Physically active female students aged between 18 -35 years old, who were right-handed and footed were recruited from the University of North Carolina at Greensboro. The sample population was the same as Chapter IV and V, examining the impacts of different degrees of knee laxity on brain function and structures. Participants reported a normal menstrual cycle lasting 26-32 days for the past six months and no history of pregnancy or no planning to become pregnant. Participants were physically active, participating in moderate activity at least three times a week. Exclusion criteria included: 1) previous significant lower leg injuries; 2) any neurologic disorders; 3) anxiety; 4) claustrophobia; 5) over 30 BMI (falling into the category of obesity) (Nuttall 2015); 6) currently undergoing a neuromuscular training program; and 7) currently participating in intercollegiate sports. The group consisted of an equal number of participants

where half used a hormonal contraceptive (i.e. contraceptive pill, IUD, and birth control patch) and the other half did not use these contraceptives. 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.

Prescreening

Knee laxity testing and the MRI safety questionnaire (required for other component of study) were performed during the prescreening day to make sure participants' eligibility in this study. A total of 103 potential participants were screened. Sixty-four potential participants were excluded because they did not meet the inclusion, or their knee laxity values did not fall into the desired range. A total of thirty-nine participants fit the inclusion criteria. Two participants dropped due to the change of their knee laxity values across screening/testing days, and ten others dropped due to MRI contraindication, previous history of surgery, or complicated schedule during the pre-screening. A total of twenty-seven participants were included in this study (mean age= 20.4±1.8 years; mean height= 166.05±6.8 cm, mean mass= 64. 5±8.2 kg).

The knee laxity test was performed using a KT-2000 knee arthrometer (Medmetric Corp) using previously established measures (Shultz et al. 2010). Participants were tested in the supine position with 25±5º of knee flexion. A Velcro strap was placed around their thigh to control the hip external rotation. Then, the KT-2000 was located on the participant's anterior aspect of the tibia, and the examiner applied 89 N of force in the posterior direction and 133N of force in the anterior direction for three cycles. The investigator had previously compared between day measurement consistency and precision [ICC (SEM) =0.97 (0.5mm)]. Participants who had AKL greater than 9.5 mm were assigned into the high laxity group (HL group; N=15). Participants who had AKL lower than 8.5 mm were assigned into the low to average laxity group (LL group; N=12). The knee laxity test was performed during both the prescreening day and the time to

stabilization measurement day to ensure that participants remained in their assigned group (high laxity or low-average laxity group).

Time to Stabilization Test

To control for the effect menstrual cycle phase on knee laxity, time to stabilization testing occurred between participants' 1st and 8th day of their menstrual cycle or during the placebo phase of oral contraceptive regimen. Participants were initially assessed for their maximum vertical jump height as they jumped directly under a Vertec (Sports Imports, Columbus, OH). Participants were asked to jump as high as possible and hit the highest possible tab with either hand. The best trial among three jumps was recorded. For the time to stabilization task, participants stood 70 cm away from the center of the force plate. The vertical target on the Vertec corresponding to 50% of maximal jump height was placed 35 cm in front of the starting position. Participants were instructed to jump forward from two feet using their right hand to touch the vertical target on the Vertec and then land on the force plate with the left foot. Participants were asked to 'stick' the landing, stabilizing as quickly as possible, and return their arms to a resting position as soon as they maintained balance, and remain motionless for 20 seconds (Wikstrom et al. 2005) while keeping their eyes forward on a blank wall. Practice trials were performed approximately 3-4 times until participants were familiar with the task. Trials for the data collection were retested if the landing foot was not still, were unable to remain in single-leg stance, or failed to hit the vertical target. A total of three acceptable trials were acquired. For all stabilization trials, the ground reaction force (GRF) of the anterior-posterior (AP) and medial-lateral (ML) components were sampled at 200 Hz (S. Ross and Guskiewicz 2003) with the MotionMonitor software from a force plate (Bertec NC 6 DOF force platform) embedded in the floor.

Data Analyses

The AP and ML components of the GRF data were separately analyzed for the calculation of TTS in the AP and ML directions. All data were analyzed using the MATLAB software package (The MathWorks, Inc., Natick, MA). A second-order 12Hz recursive low-pass Butterworth filter was applied to the GRF data. The optimal range-of-variation was initially determined from the last 10 seconds of a single-leg stance (S. Ross and Guskiewicz 2003). We observed two windows, which were during10-15 seconds and 15-20 seconds of the stabilization period. The peak GRF for each of these windows was found. Among the two windows' peak GRFs, the smaller peak value was selected as the optimal range-of-variation value, which was representative of subjects' optimal postural stability (S. Ross and Guskiewicz 2003). The overall procedure was repeated for each trial, and mean optimal range-of-variation for the AP and ML component was found for each subject. Unpaired t-tests compared the group means of optimal range-of-variation values between high and low to average laxity groups using the Statistical Package for the Social Science (SPSS Inc, Chicago, Ill). There was no significant difference in the optimal range-of-variation between high and low to average laxity groups ($p>0.05$). Thus, data normalization was not needed (S. E. Ross, Guskiewicz, and Yu 2005).

The optimal range-of-variation was then superimposed over the respective GRF data. Then, an unbounded third-order polynomial curve-fit line was applied to the entire 20 seconds of GRF data (Figure 6.1). Finally, the TTS was observed when the unbounded third-order polynomial is equal to or less than the optimal range-of-variation. The calculation of TTS was repeated for each trial and for the AP and ML components (Figure1).

Statistical Analyses

SPSS software v.26 (SPSS Inc, Chicago, Ill) was used for all statistical analyses. The mean TTS value for each subject across the three trials was calculated for the e AP and ML

components. The comparison between high and low to average laxity groups was analyzed using the independent t-test. The AP and ML components of the TTS were used as a dependent variable, and the group (HL and LL) was used as an independent variable.

Results

There were no significant differences between high and low to average laxity groups in age (p=0.16), weight (p=0.099), BMI (p=0.49), Marx (0.056), and Tegner activity level scale (p=0.91) (Table 6.1). Table 6.2 displays the means ± SD associated with the time to stabilization and statistical differences between groups by direction. There was no statistical difference for anterior/posterior ($t(25)=-0.88$, $p=0.39$) or medial/lateral ($t(25)=-0.45$, $p=0.66$) time to stabilization between high and low to average laxity groups.

Discussion

We observed the time to stabilization from single-leg landing tasks in individuals with high and low to average knee laxity. We hypothesized that individuals with high knee laxity take longer to stabilize following a dynamic task due to their potentially impaired sensory input. However, the results demonstrated that there were no significant differences in the time to stabilization in both anterior/posterior and medial/lateral directions between the high and low to average laxity groups. These findings partially support the previous results of Lee et al. (H.-M. Lee, Cheng, and Liau 2009) in which no relationship was evident between anterior knee laxity and dynamic postural control in ACL deficient patients. The authors suggested that anterior knee joint laxity was not likely to serve as a predictor of postural control (H.-M. Lee, Cheng, and Liau 2009). However, the sample population in the study by Lee et al. was ACL deficient patients; thus, it may be difficult to compare their results to our current study's finding, which includes only a healthy population with intact ACLs.

While we are not aware of any previous postural control studies of knee laxity in healthy individuals, several studies demonstrated a negative impact of general joint laxity on the postural control in individuals with hypermobile joints (Iatridou et al. 2014; Mebes et al. 2008). Iatridou et al. revealed that females with the joint hypermobile syndrome, who were diagnosed with the revised Brighton criteria (diagnostic criteria for hypermobility syndrome) (Grahame, Bird, and Child 2000), had impaired static and dynamic postural control compared to females without hypermobile joints (Iatridou et al. 2014). They suggested that impaired postural control may be attributed to a proprioceptive deficit. Since both greater knee laxity (Rozzi et al. 1999) and hypermobile joints are known to have a proprioceptive deficit (William R Ferrell et al. 2004), the different findings may be due in part to different postural control tasks tested. Iatridou et al. performed multiple single-leg-hops tasks to assess a dynamic postural control and measured errors during the landing and balancing phases (using the Balance Error Scoring System). For the static postural control task, the single-leg static stance series was used (Iatridou et al. 2014). They reported significantly greater postural sway during eyes open and eyes open-head extension conditions in hypermobile groups compared to the control group. Mebes et al. also assessed the static balance of hypermobile individuals and controls using single-leg static tests, and demonstrated significantly higher mediolateral sway in hypermobile individuals (Mebes et al. 2008). Since postural stability is controlled by the visual, vestibular, and somatosensory systems, a postural control assessment focusing on contributions of each system, such as the Sensory Organization Test, may assist in finding differences in postural control influenced solely by the somatosensory deficit.

Current results did not support our hypothesis of decreased postural stability, as assessed by TTS in individuals with a greater magnitude of anterior knee laxity. The time to stabilization test may not be an optimal task for measuring differences in postural control differences in high

and low knee laxity groups. We chose the TTS test because ACL injuries commonly occur during physical activities, including landing from jumping (Alentorn-Geli et al. 2009). Thus, assessing the amount of time required to stabilize the body's posture following a jump landing task was thought to assist in identifying the differences between high and low to average laxity groups. Knee joint laxity was previously reported to have no correlation with functional outcomes as assessed by the Lysholm knee rating scale (Snyder-Mackler et al. 1997). The Lysholm is a patient-centered scoring system to examine knee symptoms, including instability, pain, and swelling (Lysholm and Gillquist 1982). However, greater multiplanar knee laxity was related to lower Knee Outcome Survey Activities of Daily Living and Sports Activities Scale (J. B. Taylor et al. 2015). Given the inconsistent findings of the impact of laxity on postural stability and perceived function, more advanced postural control measurements that target the ACL may be needed to fully understand potential postural control differences in individuals with various degrees of knee laxity.

We acknowledge that this study has limitations that may have impacted the findings. The small sample size (N=27) adversely affected statistical power. Furthermore, we were not able to fully control the participants' height and activity performance scale. Individuals in the high laxity group were taller than the lower laxity group ($p=0.05$) (Table 6.1). However, there were no significant differences in weight and BMI. Since BMI is reported as a risk factor of ACL injury (Bojicic et al. 2017; Uhorchak et al. 2003; Vacek et al. 2016) and not height, the group differences in height may not directly impact the observed outcome. In addition, even though the greater knee laxity group was significantly taller than the low to average group, there was no significant difference in TTS between groups. Thus, height might not be a confounding factor. Furthermore, there was a near significant difference in the Marx activity rating scale ($p=0.056$), which suggested that individuals with high knee laxity participate more in physical activities

involved with cutting, decelerating, and pivoting than lower laxity individuals. However, the Tegner activity level scale did not show any significant differences between groups. While the Tegner scale measures the level and type of activity done, the Marx scale is a more direct measure of activities that include cutting, deceleration, and pivoting. Given the importance of physical activity level to the postural control (Delfa-de-la-Morena et al. 2018), future studies may need to fully control participant's types and levels of physical activity.

We observed dynamic postural control between high and low to average laxity groups using the time to stabilization test. The results demonstrated that there were no significant differences in time to stabilization in the medial/lateral and anterior/posterior direction following single-leg jump-landing tasks. The results suggest that more advanced postural control measurements may be necessary to observe the differences in postural control in individuals with various degrees of knee laxity.

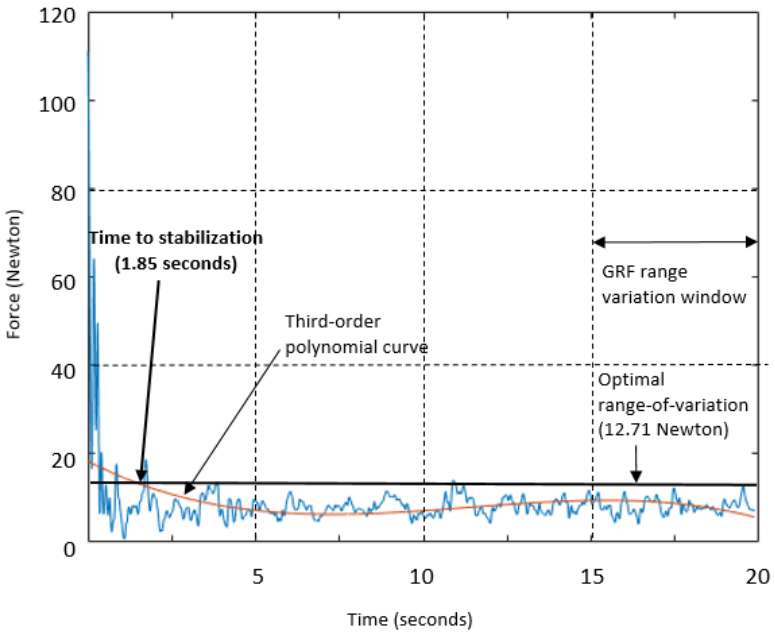

Figure 6.1 Time to Stabilization Calculation for a Single Trial. The 15 to 20 seconds window of was determined as the optimal ground reaction force range of variation used to calculate TTS. The optimal range of variation value for this 5 second window was 12.71 N. The horizontal line of this range-of-variation was superimposed the data as well as the unbounded third-order polynomial curve. TTS was calculated where the third-order polynomial transected the horizontal range of variation line.

Table 6.1 Participants Demographics, Physical Activity Rating Scale, and Head Motion

	Laxity Group			
	High	**Low**	**p-value**	**Effect size (Cohen's d)**
Anterior Knee Laxity (mm)	12.3±2.6	6.5±1.6	.000	2.69
Age(year)	19.9±1.7	20.9±1.9	0.16	-0.55
Mass(kg)	66.8±7.3	61.5±8.7	0.10	0.66
Height(cm)	166.8±5.0	162.3±6.2	0.05	0.79
BMI(kg/m^2)	24.0±2.6	23.3±2.8	0.49	0.27
MARX	8.1±2.9	5.6±3.7	0.06	0.76
TEGNER	5.2±1.3	5.3±0.9	0.91	-0.04

Table 6.2 Time to Stabilization. Means ± SDs for anterior/posterior and medial/lateral direction with High Laxity and Low-Average Laxity Groups

	High Laxity	**Low to Average Laxity**	**p-value**
anterior-posterior (s)	1.31±0.81	1.59±0.90	0.39
medial-lateral (s)	3.63±0.22	3.66±0.14	0.66

CHAPTER VII

EXECUTIVE SUMMARY

Anterior knee laxity (AKL) is known as an independent predictor of ACL injury in females (Uhorchak et al. 2003; Vacek et al. 2016). Individuals with greater knee laxity may have decreased ability to stabilize the knee joint during physical movements. Beyond ligamentous mechanical reasons, this in part may be attributed to potentially impaired sensory input (Rozzi et al. 1999) and altered movement patterns (Shultz et al. 2010). In the process of joint stabilization, the brain plays an essential role in receiving sensory signals from peripheral areas and transmitting those signals to the motor system (Kandel, Schwartz, and Jessell 1991). The brain also has the ability to reorganize its function and structure by experience, training, and sensory input (B. B. Johansson 2004). While impaired proprioception in individuals with greater knee laxity is understood, its influence on brain function and structure is not yet well known. Moreover, it is not well understood how impaired proprioception due to high laxity is related to postural control.

We observed brain activation during anterior joint loading, brain structure, and a measure of dynamic postural control in individuals with various degrees of anterior knee laxity. The results revealed that individuals with greater knee laxity had higher cortical activation in the right Crus I and Crus II in the cerebellum, and less activation in the left superior parietal lobe and right premotor cortex during intermittent joint loading. Such findings suggest that those individuals may have different perceptions of their body's internal representation, and also face challenges when planning potential movements in response to knee joint loading. Moreover, this result may

indicate a possible functional neuroplasticity adaptation due to greater knee laxity. This functional neuroplasticity may also be associated with structural changes in the brain as our structural brain study demonstrated that high knee laxity individuals had a large effect size of greater gray matter volume in the Brodmann area 6 (BA6) compared to low-average laxity individuals. The BA6 consists of the supplementary area and premotor cortex, and plays an essential role in planning, initiating, and directing voluntary sequence movements (Purves et al. 2017). We suggest that a larger gray matter volume in the BA6 in individuals with greater knee laxity may occur as a compensatory response due to their possible challenges to preplan and preprogram potential movements. Our measure of dynamic postural control, time to stabilization, did not reveal any significant differences in dynamic postural control between groups. An advanced postural control test that separates the influence of somatosensation from other sensory input might be required to identify the differences in dynamic postural control between high and low-average laxity groups in a healthy population. To further explore factors contributing to dynamic stabilization, we conducted a secondary stepwise regression analysis to identify the relationship between postural control and brain function and anterior knee laxity. The mean signal changes of the left superior parietal lobe, right premotor cortex, right Crust I&II, and anterior knee laxity were used as predictors, and times to stabilization were used as a dependent variables. Anterior/posterior and medial/lateral time to stabilization were separately analyzed. The stepwise regression analyses demonstrated that there were no significant different relationships between predictors and time to stabilization (Table 7.1, 7.2). Thus, the mean signal changes of superior parietal lobe, premotor cortex, and Crus I&II, and anterior knee laxity does not contribute to predict the time to stabilization values.

We theorized that individuals with greater knee laxity have low tension of the anterior cruciate ligament which may cause a decrease in somatosensation as well as mechanical

weakness of the joint (figure 1). The altered sensory input may also be a factor in the brain's function and structure in individuals with greater knee laxity. This, in turn, is theorized to result in alterations of the motor system with resultant decreases in functional stability of the knee joint (Figure 7.1). This may explain in part why individuals with greater knee laxity have a high risk of ACL injury. Previously, the evidence of impaired sensory input (Rozzi et al. 1999) and altered movement patterns (Shultz et al. 2010; Shultz, Carcia, and Perrin 2004) in those individuals were observed. Our results established initial cross-sectional evidence of functional and structural neuroplasticity in individuals with greater knee laxity. Even though our study did not show the differences in the postural stability between the various degrees of knee laxity groups, it still provides us valuable information on brain activation pattern and brain structure associated with knee laxity.

Our results contribute to a better understanding the role of the sensorimotor system and functional stability in individuals who are at high risk of ACL injury. The sensorimotor system is defined as all the sensory, motor, and central integration and processing components associated with maintaining joint stability during physical movement (functional stability) (Lephart SM 2000). While sensory and motor responses in greater knee laxity individuals have been demonstrated by previous researchers (Rozzi et al. 1999; Shultz et al. 2010; Shultz, Carcia, and Perrin 2004), the central integration and processing components have not yet observed. Our results contribute valuable information concerning potential functional and structural neuroplasticity influenced by knee laxity, which may help close the gap of unknown knowledge regarding the sensorimotor system. Through our findings, we suggest that the possibly impaired proprioception due to greater knee laxity may be enough of an influence to change cortical activation in the regions related to planning and programming voluntary movements as well as the perception of the body's internal representation. Thus, individuals with greater knee laxity

might have a different awareness of their body's position and face challenges to preplan and preprogram sequence of potential movements to stabilize the joint when a force applied to the joint. Because of these challenges, those with greater knee laxity may develop compensatory strategies, which demand more cortical involvement in planning and programming the movements during actual physical activities. Thus, it may lead them to have increased gray matter volume in BA6.

The findings may assist researchers in fully understanding the sensorimotor system in individuals who are at high risk of ACL injury. Understanding functional and structural neuroplasticity in individuals with high knee laxity may contribute to clinicians considering different approaches of therapeutic intervention for at-risk individuals. However, the current results only reveal the central integration and processing components associated with the sensory system, not the motor system. Therefore, future research needs to observe brain activation during voluntary movements that require joint stabilization. Dynamic movement tasks that mimic complex activities such as jumping, running, and pivoting may be beneficial to understanding how the brain integrates and processes the sensory signals during physical movements. This may due to the fact that ACL injuries commonly happen when the knee joint is loaded during a complex sequence of physical movements (Bahr and Krosshaug 2005). If we can fully understand the central components of the sensory and motor systems related to functional joint stability, it may help us develop therapeutic intervention programs for individuals who are at high risk of ACL injury.

In conclusion, our study demonstrated that individuals with high knee laxity had greater cortical activation in the right Crus I and II, and less cortical activation in the left superior parietal lobe and right premotor cortex during passive loading designed to elicit mechanoreception from the ACL. Our study also demonstrated that the high knee laxity individuals had a near

significantly large gray matter volume in the Brodmann area 6, which consists of the supplementary motor area and premotor cortex. The results may indicate possible functional and structural neuroplasticity associated with greater knee laxity.

Table 7.1 Medial/lateral Time to Stabilization Stepwise Regression Model Summary

Stepwise Model	Change Statistics		
	R Square	R Square Change	Sig. F Change
mean_PM	0.007	0.007	0.668
mean_PM, mean_SPL	0.018	0.011	0.616
mean_PM, mean_SPL, mean_Crus I&II	0.022	0.004	0.76

mean_PM= mean signal change in right premotor cortex; mean_SPL= mean signal change in left superior parietal lobe; mean_Crus I&II= mean signal change in right Crus I &II

Table 7.2 Anterior/posterior Time to Stabilization Stepwise Regression Model Summary

Stepwise Model	Change Statistics		
	R Square	R Square Change	Sig. F Change
mean_PM	0.025	0.025	0.43
mean_PM, mean_SPL	0.039	0.014	0.557
mean_PM, mean_SPL, mean_Crus	0.041	0.001	0.853
mean_PM, mean_SPL, mean_Crus, AKL	0.042	0.002	0.849

mean_PM= mean signal change in right premotor cortex; mean_SPL= mean signal change in left superior parietal lobe; mean_Crus I&II= mean signal change in right Crus I &II; AKL= anterior knee laxity

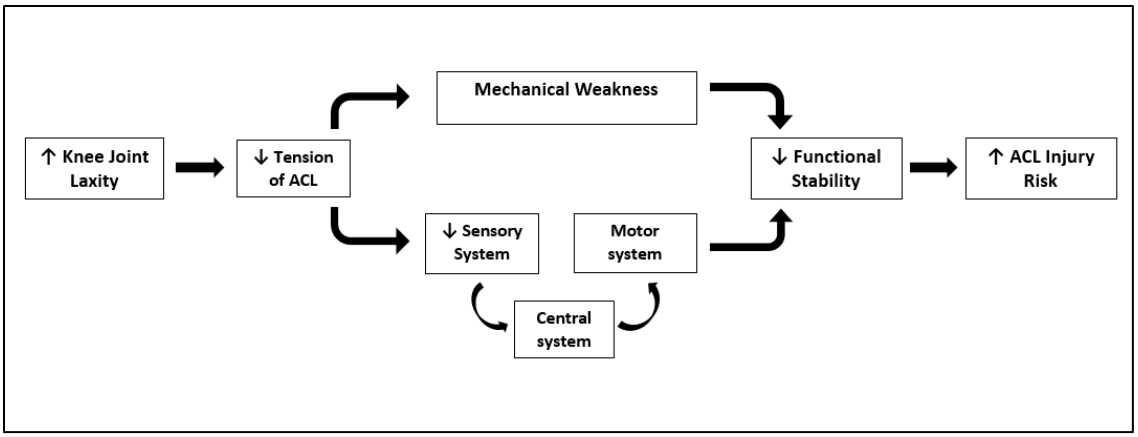

Figure 7.1 Theoretical Model

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APPENDIX A

SHORT VERSION OF THE MRI SCREENING FORM

Certify that there are no absolute contraindications to MRI

1.	☐ Yes	☐ No	Do you have a heart pacemaker?
2.	☐ Yes	☐ No	Is there a possibility of metal in your head? (e.g. aneurysm clips, metal ear tubes, etc.) Exclude dental work.
3.	☐ Yes	☐ No	Is there a possibility of metal in your eyes, have you ever needed an eyewash while working with metals, have you ever had an injury to the eye involving a metal object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)
4.	☐ Yes	☐ No	Do you have any implanted medical devices in your body?
5.	☐ Yes	☐ No	Do you have any implants held in by a magnet (dentures, posts, or crowns)?
6.	☐ Yes	☐ No	Have you had surgery **within the last 6 weeks**?
7.	☐ Yes	☐ No	Do you weigh more than 450 pounds (181 kg)? (Only ask if unsure)
8.	☐ Yes	☐ No	Are you pregnant or suspect you may be pregnant? (Obviously, females only)
9.	☐ Yes	☐ No	Do you have claustrophobic?

APPENDIX B

PHYSICAL ACTIVITY QUESTIONNAIRES

Subject Number: _____ **Date:** _____

Dominant Hand: Right / Left **Stance Leg**: Right / Left **Recreationally Active 3 x 1wk for 30 min**: Y / N

Sex		**Age**	
Height (cm)		**Mass (kg)**	

PHYSICAL ACTIVITY AND HEALTH HISTORY

Do you have any General Health Problems or Illnesses? (e.g. diabetes, respiratory disease)
Yes____ No____

Do you have any vestibular (inner ear) or balance disorders? Yes____ No____

Please list any medications you take regularly: _____

_____

Please list any previous injuries to your lower extremities. Please include a description of the injury (e.g. ligament sprain, muscle strain), severity of the injury, date of the injury, and whether it was on the left or right side.

Body Part	Description	Severity	Date of Injury	L or R
Hip				
Thigh				
Knee				
Lower Leg				
Ankle				
Foot				

THE MARX RATING SCALE

Please indicate how often you performed each activity in your healthiest and most active state, **in the past year.**

	Less than one time in a month	**One time in a month**	**One time in a week**	**2 or 3 times in a week**	**4 or more times in a week**
Running: running while playing a sport or jogging					
Cutting: Changing directions while running					
Decelerating: coming to a quick stop while running					
Pivoting: turning your body with your foot planted while playing a sport; For example: skiing, skating, kicking, throwing, hitting a ball (golf, tennis, squash), etc.					

Investigator Comments:

TEGNER ACTIVITY LEVEL SCALE

Please indicate in the space below the current level of activity in which you participate.

Level_____

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

APPENDIX C

MRI SCREENING FORM

Gateway MRI Screening Form

To be filled out by PI or Study Coordinator:

Acrostic for Last Name Field : _____

Participant ID : _____

Accession Number : _____

Date and Time : _____

Height: **Weight:** **Birth Year:** ☐ **Male** ☐ **Female**

⚠ MRI utilizes a very strong magnetic field, rapidly switching gradient magnetic fields and powerful radiofrequency transmissions. While having an **MRI is safe for most people, there are a number of instances when it can be dangerous (even fatal) for someone to have an MRI exam.** This screening form is used to identify which individuals can safely have an MRI exam.

Absolute Contraindications:

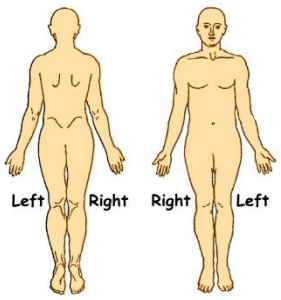
1.	☐ Yes	☐ No	Do you have a heart pacemaker?
2.	☐ Yes	☐ No	Is there a possibility of metal in your head? (e.g. aneurysm clips, metal ear tubes, etc.) for this question exclude dental work)
3.	☐ Yes	☐ No	Is there a possibility of metal in your eyes, have you ever needed an eyewash while working with metals, have you ever had an injury to the eye involving a metal object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)
4.	☐ Yes	☐ No	Do you have any implanted medical devices in your body? (cochlear implant, metal ear tubes, bone stimulator, neurostimulator, biostimulator, medication pump, automatic defibrillator, internal pacing wires, etc). Exclude orthopedic hardware and dental work
5.	☐ Yes	☐ No	Do you have any implants held in by a magnet (dentures, posts, or crowns)?
6.	☐ Yes	☐ No	Have you had any bone, tendon, spine, or dental surgery **within the last 6 weeks**?
7.	☐ Yes	☐ No	Do you weigh more than 450 pounds (181 kg)?
8.	☐ Yes	☐ No	Are you pregnant or suspect you may be pregnant?

If you checked **Yes** to any of the questions above you do not need to complete the rest of the form. **<u>You cannot enter the MRI Exam room under any circumstances</u>** until you are able to answer No to all of these questions.

Potential Contraindications:

9.	☐ Yes ☐ No	Do you have an IUD that may contain copper, or a contraceptive diaphragm?
10.	☐ Yes ☐ No	Have you had any stents, clips or surgery to any of any of your vessels (carotid artery vascular clamp, coronary stent, aortic clips, IVC filter, coils for blocked arteries)
11.	☐ Yes ☐ No	Do you have metal anywhere else in your body? (screws, pins, plates, spinal rods, dental work - not including fillings and caps, piercings, shrapnel, buckshot, bullets) – please
12.	☐ Yes ☐ No	Do you have a cerebrospinal fluid (CSF) shunt? (treatment for hydrocephalus or water on the brain)
13.	☐ Yes ☐	Do you have any piercings that can't be removed?
14.	☐ Yes ☐ No	Do you have a transdermal medicated patch? (nicotine patch, contraceptive patch, medicated pain relief patch)
15.	☐ Yes ☐ No	Have you had any medical condition that has prevented you completing an MRI exam in the past?
16.	☐ Yes ☐ No	Do you wear a prosthetic device?
17.	☐ Yes ☐ No	Have you had any previous surgery? (give details, and indicate where on your body using the diagram below)

Details:



If you have answered **Yes** to any of the questions 10 through 19 then we need additional information and documentation before you may have your MRI exam. If possible, the items resulting in a Yes answer should be removed before your MRI exam. If this is impossible, the Principle Investigator/Study Coordinator needs to provide additional information that your device is MRI safe before you enter the MRI exam room.

Notes:

Precautions:

18.	☐ Yes ☐ No	Do you have tattooed eyeliner, tattooed eyebrows or hair dye?
19.	☐ Yes ☐ No	Do you have any tattoos? If yes, where?
20.	☐ Yes ☐ No	Are you wearing a wig or hair extensions?
21.	☐ Yes ☐ No	Do you have any problems when you lie flat on your back? (breathing problems, back pain, nausea, etc.)
22.	☐ Yes ☐ No	Do you take beta blockers, sedatives, or diuretics?
23.	☐ Yes ☐ No	Do you have a fever?
24.	☐ Yes ☐ No	Are you wearing a hearing aid or dentures?
25.	☐ Yes ☐ No	Do you suffer from claustrophobia?

If you have answered **Yes** to questions 18-24 then you may have an MRI today but we want to take a moment to provide you with some additional instructions. Please remove your hearing aid and/or dentures (along with all other metal) before entering the MRI scanner. MRI uses radio waves to make a picture. These radio waves are perfectly safe but under certain circumstances may make you feel warm. This can occur locally, for example at the site of a tattoo, or over your entire body. If this happens please let the operator know immediately -- even if the MRI scanner is making a large knocking noise.

Before entering the MR environment or MR system room, you **must remove ALL metallic objects** including hearing aids, dentures, partial plates, keys, cell phones, eyeglasses, hairpins, barrettes, jewelry, body piercings, credit cards, clothing with metal fasteners, & clothing with metal or metallic threads. **Please consult the MRI Operator if you have any questions or concerns BEFORE you enter the MR Exam room.**

I attest that the above information is correct to the best of my knowledge. I have read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form: _____

Signature and Date

Form Completed By:

☐ Participant ☐ Other

_____

If other, print name and relationship to participant

Reviewed By MRI Operator: _____

Print name, signature, and date

To be filled out by MRI Operator:

MRI Operator Pre-Entry checklist …

If the subject entered **Yes** to any of the questions above **the participant cannot enter the MRI scanner under any circumstances**

1.	☐	Review screening form.
2.	☐	Do you have any questions or concerns about the questions on this form?
3.	☐	Do you have anything in your body that wasn't there when you were born?
4.	☐	Have you ever had an MRI before? Be careful with this question, many people don't know the difference between an MRI scan and a CT scan.

Certify that there are no absolute contraindications to MRI

1.	☐ Yes	☐ No	Do you have a heart pacemaker?
2.	☐ Yes	☐ No	Is there a possibility of metal in your head? (e.g. aneurysm clips, metal ear tubes, etc.) Exclude dental work.
3.	☐ Yes	☐ No	Is there a possibility of metal in your eyes, have you ever needed an eyewash while working with metals, have you ever had an injury to the eye involving a metal object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)
4.	☐ Yes	☐ No	Do you have any implanted medical devices in your body?
5.	☐ Yes	☐ No	Do you have any implants held in by a magnet (dentures, posts, or crowns)?
6.	☐ Yes	☐ No	Have you had surgery **within the last 6 weeks**?
7.	☐ Yes	☐ No	Do you weigh more than 450 pounds (181 kg)? (Only ask if unsure)
8.	☐ Yes	☐ No	Are you pregnant or suspect you may be pregnant? (Obviously, females only)

Last minute checks

☐ Use Restroom	☐ Cell phone / pager	☐ Hair pins/barrettes
☐ Pockets empty?	☐ Metal Buttons	☐ Wig/Hair extensions
☐ Keys / coins	☐ Clothing with metal	☐ Hearing aid
☐ Wallet / money clip	☐ Shoes with metal	☐ Removable dentures
☐ Watch / Jewelry	☐ Belt	☐ Nicotine or other patch
☐ Glasses	☐ Piercings	☐ Magnetic implants

MRI Operator Initials: _____

Operator final Prescan checklist …

- ☐ Hang MRI Use Sign on MRI Suite Door
- ☐ Earplugs in place and working
- ☐ Participant given call ball with instructions on how to use
- ☐ Confirm that participant is comfortable and can communicate via patient monitoring system.

MRI Operator Initials: _____

Operator final Post Exam checklist …

- ☐ Ask participant if there were any sensations of **tingling and/or heating** during the exam that were uncomfortable or caused him/her concern. **If yes, Operator must fill out these questions**

- ☐ Ask participant if there hands were clasped and/or feet crossed during when the tingling and/or heating occurred.

- ☐ PI, Acrostic, and Date completed on every page of screening form.
- ☐ PI, Acrostic, and Date completed on every page of Operator Check List form.

- ☐ Data has been archived (transferred to the UNCG PACS, burned to CD/DVD, copied to flash drive)
- ☐ Copy of images given to participant.
- ☐ Clean table, pads, headphones, and coil with disinfectant.
- ☐ Place head coil on table.
- ☐ Return table to home position
- ☐ Close out patient on system console.
- ☐ Remove MRI In Use sign from MRI Suite door.

MRI Operator Initials: _____

Notes on potential contraindications to MRI:

The UNCG Gateway screening form is broken up into three sets of questions.

- **Questions 1-8** are all absolute contraindications for having an MRI at Gateway. Participants that answer Yes to any of these questions may not have an MRI exam at Gateway.

- **Questions 9-17** are potential contraindications for having an MRI exam at Gateway. If a participant answers yes to any of these questions either additional information is needed before the participant may undergo an MRI exam at Gateway or the item in question must be removed before the participant enters the MRI Exam room. Implanted devices that cannot be removed must be looked up in the Shellock guide or the online list (http://www.mrisafety.com/list_search.asp). In order for a person to be scanned at Gateway with an implanted device three conditions must be met. **First**, the exact make, model, and manufacturer of the implanted device must be documented. **Second**, the exact make and model of the implanted device must be approved for scanning in a 3T magnetic field in either the Shellock guide or Shellock's online list. **Third**, the documentation of the device and approval by either the Shellock guide or online list must be reviewed and approved by a certified Gateway operator that is not involved in the study.

- **Questions 18-25** are intended to give the operator more information about the participant and how best to make the MRI a safe and as pleasant experience as possible. For example, questions concerning tattoos let the operator know that the participant should be informed of the potential heating issues with tattoos and the participant should let the operator know if he/she experiences any heat in the area of the tattoo.

Information about each specific question is below

Q3. Metal Fragments in Eyes

Metal fragments in the eye are a serious concern. Even if the magnetic fragments are small the main magnetic field can cause these metal fragments to move and cause permanent damage to the eye. For clinical MRIs, the standard of care is to order a high resolution CT or orbital X-rays to rule out the possibility of metal fragments in the eye. Since this is not possible for subjects undergoing an research MRI exam at Gateway, subjects with the potential of metal in their eye are excluded from participating in the study.

Q7. 450lb patient limit

The patient table has a limit of 550lbs. The 450lb limit is established to provide some margin of error when scanning larger participants. Even though the patient

table may support the weight of a larger person, the person may not fit in the scanner. Operators should be aware that there are special considerations when scanning larger participants. Larger patients require more RF power for MRI scanning and will experience higher Specific Absorption Rates then average sized participants. Protocols that are setup for average size participants may not function without modifications. Larger size patients may come in contact with the sides of the scanner bore. This increases the chance of burns so padding should be placed between the participant and the scanner bore to minimize this risk. Operators should also understand that in the event of a medical emergency it is important that the participant should be removed from the MRI exam room. If this is not possible, operators must control access to the MRI exam room when additional help arrives.

Q8. Pregnancy

MRIs are considered safe for pregnant women and the fetus but there are minor concerns with tissue heating due to exposure to radio waves. An MRI exam of a pregnant woman is prescribed when there is a direct benefit to either the mother or the fetus. In the research environment where there is no direct benefit to the participants pregnant women, as determined from self reporting, are excluded from all research studies at Gateway unless one has specific IRB approval to scan women who answer yes to this question.

Q9. Copper-containing IUD, or diaphragm

Older IUD contraceptives containing copper are safe at 1.5T but untested at 3T. **You must identify the exact device that the subject has and it must be listed as safe at http://www.mrisafety.com/.** Diaphragms containing a metal ring may get hot (remove before scan).

Q10. Metal associated with vessels

There is a potential danger of ferromagnetic hardware being displaced by the strong magnetic field. Coronary (heart) stents are MRI safe. Most carotid (neck) vascular clamps are safe at 1.5T (except Poppen-Blaylock clamp) but untested at 3T. Stents become firmly attached to tissues, and are unlikely to move beyond first few months. More details are needed before proceeding. **You must identify the exact device that the subject has and it must be listed as safe at http://www.mrisafety.com/**

Q11. Other metal in the body

Metal bullets/shot/shrapnel in the head or torso are a contraindication to MRI. The only exception to this is implanted dental work in place for more than 6 weeks. Longstanding immobile bullets/shot/shrapnel in bones in the limbs are not a contraindication. Spinal rods or intramedullary rods older than 6 weeks are not a

contraindication to MRI, but in these cases images quality may be significantly degraded depending on location. Piercings should be removed (or see below).

Q12. CSF shunts

Most are MRI safe – but some are programmed magnetically, and subjects will need the unit to be reprogrammed by their doctor after MRI. More details are needed before proceeding. **You must identify the exact device that the subject has and it must be listed as safe at http://www.mrisafety.com/**

Q13 Non-removable piercings

We recommend that subjects should not be scanned with piercings in place as there is a small risk of heating, vibration or discomfort. If not removable and non-magnetic (test with magnet in workshop) and it is deemed important to proceed with the MRI, scanning may be OK – but immobilize piercing with tape and insulate as much as possible from skin (at least 1cm insulation to prevent burns). Remain in close verbal and visual contact with subject. Warn subject about pain, heating, and possible vibration of piercing. Any unpleasant sensations / adverse reaction must be reported to IRB.

Q14. Transdermal delivery patch (e.g. nicotine, contraceptive or medicated pain relief patch)

These may cause local heating. Remove before MRI

Q15. Prior problems completing a MRI exam

This question is an opportunity to find out about potential medical problems or contraindications to MRI that subjects forgot to mention in earlier questions.

Q16. Prosthetic Devices

Prosthetic devices should be removed before entering the MRI exam room. Gateway does not have an MR compatible wheel chair. Operators will need to plan accordingly when helping the participant walk to the patient table.

Q17. Previous surgery.

This question is an opportunity to find out about metal in the body that subjects failed to mention in questions 10,11, or 12. Surgeries are not necessarily contraindications but subjects should wait at least six weeks if there is a possibility of an implanted device becoming dislodged. If no devices were implanted during the surgery then the participant is safe to be scanned. If the screener is unfamiliar with the surgery then additional questions should be asked before allowing the participant to be scanned.

Q18. Tattooed eyeliner, tattooed eyebrows or Bigen hair dye

May cause local heating and distortion of the MR images. Scanning may be unproblematic – but remain in close visual and verbal contact with subject Warn subject about pain, heating, tactile sensations in the tattoo (and complete a peripheral nerve stimulation form if tactile sensations are experienced). Any unpleasant sensations / adverse reaction must also be reported to IRB.

Q19. Tattoos

Participants may experience local heating. The further the tattoo is located outside the bore the less likely local heating will be a problem. Even though the risk of local heating is low remain in close visual and verbal contact with subject. Warn subject about pain, heating, tactile sensations in the tattoo (and complete a peripheral nerve stimulation form if tactile sensations are experienced).). Any unpleasant sensations / adverse reaction must also be reported to IRB.

Q20. Wigs and hair extensions

Q21. Difficulty lying supine

Subjects with medical conditions that are exacerbated when they lie flat are unlikely to be able to complete a MRI exam. If symptoms are severe enough to hamper communication (e.g. very breathless subject), then they should not undergo MRI. If symptoms are mild, then it is OK to proceed, but remain in close verbal and visual contact with the subject. Keeping the exam short will help.

Q22. Beta blockers, sedatives, and diuretics

These types of drugs may compromise a person's ability to regulate their body temperature during the exposure to the RF magnetic field. These types of medication are not a contraindication for MRI but we are asking that the operator verify with the participant that they are comfortable during the exam and are not over heating.

Q23. Fever

If a person has a fever then a person's ability to regulate their body temperature during the exposure to the RF magnetic field may be impaired. Scanning a person with a fever is not a contraindication but should the operator verify with the participant that they are comfortable during the exam and are not over heating.

Q24. Hearing aids & dentures (and removable bridge)
Remove before MRI. Hearing aids that are implanted and cannot be removed are a contraindication to MRI exam. There is a minor risk of injury as these objects are turned into projectiles. In addition, hearing aid may no longer function after exposure to main magnetic field. Dentures and removable bridges may experience local heating during the MRI exam and may create significant image artifacts that will render the data worthless.

Q25. Claustrophobia
Subjects with claustrophobia will require additional training and encouragement to complete their MRI exam. Keeping the exam very short will help. Claustrophobic subjects who have been unable to complete MRI exams in the past remain unlikely to complete them in the future.