NEUROMECHANICAL LINKS BETWEEN COGNITION, FEAR AND JOINT INSTABILITY

by

Yong Woo An

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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ABSTRACT

Functional joint instability following an anterior cruciate ligament (ACL) sprain can lead to a secondary ipsilateral or contralateral ACL rupture and untimely knee osteoarthritis, despite surgical repair. Previous research has examined neuromuscular control (NMC) interventions to address functional joint stability; however, clinical outcomes have varied. Recent neuroimaging studies suggest an ACL injury not only damages static restraints and peripheral mechanoreceptors, but also alters neural networks in the brain (neuroplasticity). These neural adaptations are responsible for perceiving and integrating sensory input, as well as executing the appropriate motor responses necessary for dynamic restraint. Additionally, ACL patients who have higher fear of re-injury/movement seem to have diminished knee function compared to those with relatively less fear perception. Emotion regulatory neural circuits in the brain demand greater cognitive processing to manage increased attentional resources, which suggests that greater fear interrupts executive functions related to neuromuscular control. This coordination is necessary for maintaining functional joint stability by optimizing muscle stiffness surrounding the knee. However, minimal data exists on how the brain perceives sensory information emanating from the knee, how fear may disrupt NMC, or how enhanced executive-function skills can improve fear-regulation and muscle stiffening strategies following ACL rupture. The results of this study demonstrate that: 1) the brain increases cortical activation in response to joint loading following an ACL injury; 2) general and specific situation-related fearful stimuli result in greater alterations in heart rate and

neural processing in the brain, as well as joint stiffness regulation strategies; 3) a cognitive-based online training intervention improves executive-function skills, neurophysiological emotional responses, and joint stiffness regulation strategies in ACL patients. These findings suggest that measure of electrocortical signals can detect instantaneous neuromechanical coupling between joint load and brain activity and that ACL injured patients have altered somatosensory networks following ACL injury. This altered neural circuits in ACL patients may be insufficient to regulate feed-forward and feedback dynamic restraint mechanisms, when unanticipated negative events occur during high velocity physical activity. However, we can enhance executive functioning skills and emotional regulation which may help with functional joint stability. These findings offer that we can better assess instantaneous neuromechanical coupling and test individualized brain plasticity among various patient population to determine neurocognitive intervention strategies that may enhance patient outcomes.

Chapter 1

ROLE OF THE BRAIN IN MAINTAINING FUNCTIONAL JOINT STABILITY FOLLOWING ACL INJURY

Introduction

The maintenance of functional joint stability is essential not only for activities of daily living and the prevention of recurrent injury, but also for the recovery and clearance to return to pre-injury level of physical performance following an unintentional ligamentous sprain(Gobbi & Francisco, 2006; Riemann & Lephart, 2002b; Charles Buz Swanik, Lephart, Swanik, Stone, & Fu, 2004). Appropriate pairing between ligamentous and neurological constituents of a joint (neuromechanical coupling) and the cognitive processing abilities of motor planning for muscle coordination, can optimize modulation of muscle stiffness necessary for maintaining functional joint stability during physical activity(Bonnard, Camus, de Graaf, & Pailhous, 2003; Freeman & Wyke, 1967; H. Johansson, Sjölander, & Sojka, 1991a; Sinkjaer, Toft, Andreassen, & Hornemann, 1988; Charles Buz Swanik, Covassin, Stearne, & Schatz, 2007). Therefore, the CNS plays an important role in the regulation of neuromuscular control, and it must appropriately remodel existing neural networks in the brain to adapt after musculoskeletal injury because the neuromechanical links between joint tissue and the CNS may be uncoupled(Campbell & Ehlert, 2012; B. B. Johansson, 2004; Alan R Needle, Palmer, Kesar, Binder-macleod, & Swanik, 2013). Moreover, it has been suggested that several frontal cortical regions related to cognitive processing for voluntary movements, are also highly associated with the

regulation of emotion(LeDoux & Damasio, 2013). An unpleasant emotional state such as fear, increases cortical activity in these frontal areas of the brain to regulate emotional responses, by projecting significant information to other brain regions responsible for sensorimotor control(Horn & Swanson, 2013; Morris & Dolan, 2004). It has been shown that unconscious "fight-or-flight" behaviors, in response to unanticipated events, will alter muscle contraction patterns necessary for joint stability(Haegler et al., 2010; Okada, Hirakawa, Takada, & Kinoshita, 2001). Given this fact, emotional dysregulation as a result of negative emotional stimuli may interrupt a normal cascade of neurocognitive processes associated with the muscle coordination to protect joints (dynamic restraint) and maximize patients' functional outcomes(Kapreli et al., 2009; Okada et al., 2001; C. Buz Swanik, Lephart, Giannantonio, & Fu, 1997). The purpose of this article is to identify the neural mechanisms underlying functional joint stability, cognitive and emotional regulation processes, assess the interrelationships that exist between joint stiffness regulation, cognition and emotion, and to discuss potential neural adaptations within the CNS that occurs after an anterior cruciate ligament (ACL) injury that creates barriers to patient's full function.

Functional Joint Stability

Role the Sensorimotor System in Joint Stability

The sensorimotor system maintains joint integrity during physical activity, referred to as functional stability, through complex neurophysiological events involving series and parallel networks(Riemann & Lephart, 2002a). The sensorimotor system is responsible for perceiving external and/or internal stimuli, processing and integrating the information, and executing the appropriate motor behaviors in

response. Therefore, the CNS and peripheral nervous system (PNS) must work cooperatively in order to maximize movement performance while maintaining joint stability(David G. Amaral & Strick, 2013; J. Baumeister, 2013; Riemann & Lephart, 2002a). Neurological responses underlying the maintenance of functional joint stability generally begin in the PNS, by detecting joint proprioceptive information and conveying its associated neural signals to the higher cortical levels via the spinal cord (SC). The SC interconnects the PNS and brain bilaterally through several ascending and descending neural pathways. The brain integrates the information and establishes the significance of the peripheral proprioceptive information (perception). Various regions then organize and execute appropriate muscular responses to maintain functional joint stability by modulating activation of motor neurons for targeted muscles through efferent descending pathways(David G. Amaral & Strick, 2013; Horn & Swanson, 2013; H. Johansson, 1991) (Figure 1).

Role of Static and Dynamic Restraint Systems in Functional Joint Stability

It is well known that the knee joint is secured mechanically and functionally by static and dynamic restraint systems, respectively(Riemann & Lephart, 2002b; C. Buz Swanik et al., 1997). In a healthy knee, the static restraint system provides mechanical stability through anatomical structures such as the knee capsule and ligaments. As the primary static stabilizer of the knee, the anterior cruciate ligament (ACL) prevents excessive anterior displacement of the tibiofemoral joint in response to an external loading. The ACL also conveys critical knee proprioceptive information to the CNS such that appropriate neuromuscular control strategies can facilitate dynamic restraint(Riemann & Lephart, 2002a, 2002b; C. Buz Swanik et al., 1997). This dynamic restraint system contributes to functional joint stability by stiffening muscles

surrounding the joint based on integrated and coordinated efferent motor commands from the CNS(C. Buz Swanik et al., 1997; Wolpert, Pearson, & Ghez, 2013). In order to provide optimal stiffness, this dynamic restraint system must not only be compliant enough to stretch muscles, absorb and store elastic energy for maximal performance, but also rigid enough to stress-shield static structures from excessive loads during physical activity(Riemann & Lephart, 2002b). The level of muscle stiffness must also be able to change rapidly in order to accommodate the large variety of movement types and high-velocity tasks(Horita, Komi, Nicol, & Kyröläinen, 2002).

The neuromuscular control system regulates dynamic restraint by two neural mechanisms. The reflexive feedback mechanism is continuously modulating reactive muscular contraction based on the proprioceptive feedback from a joint to the CNS(H. Johansson, 1991; C. Buz Swanik et al., 1997). This neuromechanical coupling between ligamentous mechanoreceptors in the knee and the CNS delivers proprioceptive sensory responses to the fusimotor-muscle-spindle system in the targeted muscles surrounding the knee joint. The muscle spindle system then controls the level of muscle tone by adjusting for the length and tension of the muscles, as well as the anticipated stiffness needed for each motor task(H. Johansson, 1991). Direct measures of sensory neural conveyance, through a microneurography technique recording traffic in peripheral nerves, have demonstrated positive correlations between ankles joint force, ligamentous laxity, and afferent sensory traffic transmitted from muscle spindles to the CNS(Alan R Needle, Charles B Buz, et al., 2013). This suggests that the dynamic feedback mechanism underlying neuromuscular control, which modulates the stiffness of the knee muscles responding to joint loading, is dependent upon neuromechanical coupling(H. Johansson, 1991). The involvement of

muscle spindles in this feedback process is important because their sensitivity can be modulated by the brain, which affects muscle tone, and they remain intact after a joint injury. Muscle spindles can also excite the fastest motor responses through monosynaptic reflexes. As the dynamic feedback mechanism generates reflexive muscle activity, in response to a sudden perturbation, there is often a latency period in the reactive muscular contraction(Lacroix, 1981; Shultz et al., 2001). The delayed reactive muscle contractions can be compensated for by anticipating future loads through the dynamic feed-forward neuromuscular control mechanism(Klous, Mikulic, & Latash, 2011).

The preparatory feed-forward mechanism involves preprogrammed muscle activation, dependent on the sensory information from previous experiences of proprioceptive and kinesthetic sensations such as joint position, motion, acceleration and/or loading, but not from current movements(C. Buz Swanik et al., 1997; Charles Buz Swanik et al., 2007). As a result, it initiates early muscle activation prior to anticipated joint perturbations(H. Johansson, 1991; C. Buz Swanik et al., 1997). These preactivated muscle patterns are regulated directly by cognitive processing through preprogrammed recruitment strategies by which muscles' excitation and inhibition surrounding the knee can be quickly activated(Santello, 2005; C. Buz Swanik et al., 1997; Charles Buz Swanik et al., 2004). This suggests that the preparatory feed-forward mechanism plays a critical role in regulating appropriate, task dependent level of muscle stiffness. Taken together, interactions between the static and dynamic restraint components are critical to providing appropriate neuromechanical coupling and muscle coordination needed for maintaining functional knee stability during physical activity(Riemann & Lephart, 2002a; Charles Buz Swanik et al., 2007, 2004).

Therefore, the recovery of both the mechanical properties and proprioception of the knee joint would allow for the restoration of knee function after ACL sprains, but despite this, between 44% and 56% of these patients still suffer persistent knee dysfunctions even with surgical reconstruction and extensive rehabilitation(Ageberg, Thomeé, Neeter, Silbernagel, & Roos, 2008; Dhillon, Bali, & Prabhakar, 2011).

Challenges In Current Research

Functional joint instability, which is defined as repetitive episodes of a joint "giving way" or "buckling" during physical activity, has received great attention in numerous peripheral joint pathologies such as sprains of the ankle or ACL, and shoulder subluxations(Brophy & Marx, 2005; Golditz et al., 2014; J. M. Hootman & Albohm, 2012; Lohmander, Englund, Dahl, & Roos, 2007; Wright, Magnussen, Dunn, & Spindler, 2011). This increased attention is due to serious pathological complications following these injuries, including recurrent ligamentous injuries, early development of post-traumatic osteoarthritis and disability. In fact, almost 30% of ACL patients have a second ACL rupture within 10 years(Pinczewski et al., 2007), and approximately 50% of ACL patients develop early knee osteoarthritis and experience a diminished health-related quality of life(J. M. Hootman & Albohm, 2012). Therefore, many researchers have attempted to examine possible mechanisms contributing to functional joint instability in this population. It has been suggested that factors leading to a failure in neuromuscular control, such as altered neuromechanical coupling and muscle stiffness strategies, may put individuals at risk of having unpleasant knee-giving-way episodes and subsequent disability, or even recurrent peripheral knee injury(Borsa, Lephart, Irrgang, Safran, & Fu, 1997; Dhillon et al., 2011; Riemann & Lephart, 2002a, 2002b; C. Buz Swanik et al., 1997; Charles Buz

Swanik et al., 2007). However, there are several remaining questions underlying predisposing factors for functional joint instability in ACL patients.

Joint Laxity and Neuromechanical Decoupling

Following an ACL injury excessive ligamentous laxity is thought to be the primary contributing factor to neuromechanical decoupling and subsequent neuromuscular control deficits, which leads to repetitive episodes of a knee giving way(Denti, Monteleone, Berardi, & Panni, 1994; Freeman, 1965; Roberts, Andersson, & Fridén, 2004). At the moment of an ACL rupture, an extreme anterior tibial translation, beyond its mechanical limit, causes damage to capsuloligamentous structures, including deafferentation of mechanoreceptors in the knee(Denti et al., 1994; Shimizu et al., 1999). These mechanoreceptors in the ACL such as Ruffini and Pacini corpuscles transmit signals coding joint position and kinematic movement, respectively(Hogervorst & Brand, 1998). Moreover, the fusimotor-muscle-spindle system is highly sensitive to ACL receptors' afferent information related to the changes in ligamentous length and tension, which can alter spindle sensitivity through gamma-motor neurons(H. Johansson, Sjölander, & Sojka, 1990, 1991b; H. Johansson, 1991). Following an ACL injury, excessive ACL laxity corresponding to knee movement may project altered proprioceptive inputs from all of the receptors, compared to the healthy knee. The changes in arthrokinematics, combined with deafferentation may create the perception of neuromechanical decoupling within the CNS and brain(Hogervorst & Brand, 1998; H. Johansson, 1991). As a result, it is possible that the knee dynamic restraint system can be compromised for both the preparatory and reactive muscle contraction mechanisms, thus the altered muscle stiffness is no longer capable of protecting joint structures(J. C. Kennedy, Alexander,

& Hayes, 1982; Rozzi, Lephart, Gear, & Fu, 1999; Shultz et al., 2001; C. Buz Swanik et al., 1997; Charles Buz Swanik et al., 2004; Wojtys & Huston, 1994).

For this reason, animal and in vivo human studies have suggested that ACL reconstruction can not only recover mechanical stability but also regenerate mechanoreceptors in the graft, which may allow restoration of proprioception as well as improvement of knee function(Denti et al., 1994; Georgoulis et al., 2001; B. I. Lee et al., 2009; Ochi, Uchio, Adachi, & Sumen, 1999; Shimizu et al., 1999). Hence, the combined surgical ACL repair and proprioception based rehabilitation program are considered to be the gold standard treatment option(Zech et al., 2009). In fact, more than 200,000 cases annually undergo ACL reconstruction (ACLR) by using the patella or hamstring tendon graft techniques after an ACL rupture, at an approximate cost of three billion dollars(Gobbi, Bathan, & Boldrini, 2009; Kaplan, 2011). However, recent studies showed that some ACL-deficient (ACLD) patients, who choose not to have surgical reconstruction, are also able to conservatively restore knee function, through completion of an intensive neuromuscular control training program(Chmielewski et al., 2005; Fitzgerald, Axe, & Snyder-Mackler, 2000a; Moksnes, Snyder-Mackler, & Risberg, 2008). Indeed, both surgical and conservative treatments have showed successfully enhanced muscle contraction patterns and improved knee function outcomes, without having additional episodes of their knee "giving way" (copers)(Grindem et al., 2011; Grindem, Eitzen, Moksnes, Snyder-Mackler, & Risberg, 2012). Nonetheless, some in the ACLI population, which includes both ACLD and ACLR patients, still suffer persistent functional joint instability (noncopers), regardless of type of post-ligamentous injury treatment(Ageberg et al., 2008; Gobbi & Francisco, 2006; Tripp, Stanish, Ebel-Lam, Brewer, & Birchard,

2007). In fact, up to 35% of ACLR and almost 60% of ACLD patients still experience functional instability and fail to return to their pre-injury level of physical activity(Dhillon et al., 2011; Fitzgerald et al., 2000a; Grindem et al., 2012; Herrington & Fowler, 2006; D. Y. H. Lee, Karim, & Chang, 2008). Moreover, ACL copers and noncopers have shown dissimilar neuromuscular control responses. Some ACLD copers with relatively greater joint laxity appear to have neuromuscular control strategies similar to healthy controls, i.e. unchanged, while other ACLD noncopers with less joint laxity show limited knee functioning(Eastlack, Axe, & Snyder-Mackler, 1999; Fitzgerald et al., 2000a; Snyder-Mackler, Fitzgerald, Bartolozzi, & Ciccotti, 1997). Similarly, ACLR noncopers, who have surgically restored mechanical stability and may sprout new mechanoreceptors after a reconstruction(Denti et al., 1994; Georgoulis et al., 2001), reveal attenuated knee muscles' strength, as well as worse functional outcomes such as lower scores of hopping tasks(E. H. Hartigan, Axe, & Snyder-Mackler, 2010; E. Hartigan, Zeni, Di Stasi, Axe, & Snyder-Mackler, 2012; Risberg & Holm, 2009; Zech et al., 2009). Some research have shown that excessive laxity is a risk factor leading to functional joint instability(Moksnes et al., 2008; Roberts et al., 2004), but many have also shown that it is not a reliable predictor for the dynamic stability(Eastlack et al., 1999; Snyder-Mackler et al., 1997). Overall, these contradictory clinical outcomes in ACLI patients may indicate that joint laxity alone does dictate proprioception or functional ability after an ACL injury, but some other factors are influencing neuromechanical coupling(Eastlack et al., 1999; Moksnes et al., 2008).

An ACL injury may change existing neural networks in the CNS, and therefore ACLI individuals have varying cortical adaptations in the brain responsible for

awareness of sensory inputs from multimodal sources. As a result, the CNS reorganization, which is referred to as neuroplasticity, may differ in proprioceptive feedback and neuromuscular control among ACLI patients(Kapreli & Athanasopoulos, 2006). However, limited data exists on the CNS's role in perceiving mechanical loading and laxity in the ACLI population. This is critical as several regions of the brain that depend on this information for neuromuscular control and maintenance of dynamic joint stability are also associated with cognitive motor planning and emotional regulation processing(J Baumeister, Reinecke, & Weiss, 2008; LeDoux & Damasio, 2013). The lack of understanding surrounding the CNS's role has created a barrier to determining why neuromechanical coupling differs among ACLI patients.

Cognition, Fear of re-injury/movement and Neuromuscular Control

The cognitive management strategy for motor planning is also a critical factor to providing early preparatory and continuous reactive muscle contractions needed for maintaining functional joint stability(Riemann & Lephart, 2002b; Charles Buz Swanik et al., 2007, 2004). Therefore, any brief failure in coordination or judgment can temporarily interrupt muscle stiffness regulatory strategies intended to protect the joint(Kirkendall & Garrett, 2000; Olsen, 2004). This would leave static restraints such as the ACL vulnerable to excessive loads, regardless of laxity, because the entire dynamic restraint mechanism would be compromised.

Sudden unanticipated events often result in a universal unconscious startle response in extremities(Maslovat, Kennedy, Forgaard, Chua, & Franks, 2012). This brief, and involuntary startle response, may be a result of increased errors in motor planning processes because the brain's cognitive network is not sufficient to simultaneously prepare for the overabundant environmental cues(DeAngelis et al.,

2014). Using a randomly timed acoustic stimulus to simulate realistic, sudden unintentional events during physical activity, is one of the most commonly employed research models(Carlsen, Almeida, & Franks, 2012; Maslovat et al., 2012; Queralt et al., 2008). Altered joint stiffness regulation strategies have been shown when an unexpected acoustic stimulus is delivered prior to a knee perturbation(DeAngelis et al., 2014). Particularly, the findings revealed higher short-range stiffness (0-4°), indicating spinal reflexive responses through the CNS, with early quadriceps contraction prior to joint loading and both attenuated long-range stiffness (0-40°) and muscle activation during and after the knee loading. It has been suggested that early activation of the quadriceps, before the unanticipated knee perturbation, results in knee extensor moments and increased anterior tibial translation, which would exacerbate ACL loading(DeMorat, Weinhold, Blackburn, Chudik, & Garrett, 2004). Moreover, decreased muscle activation during and after the knee movement implies insufficient energy absorption by muscles surrounding the knee, which ultimately impairs dynamic restraint capabilities(Hewett, Zazulak, Myer, & Ford, 2005; Charles Buz Swanik et al., 2004). This may indicate that the cognitive processing needed for anticipation of joint sensation is interrupted during an unexpected, startling event, thus resulting in altered preparatory (feed-forward) and reactive (feedback) muscle contractions that are incompatible with optimal joint stiffness and maintenance functional stability(A. L. Bryant, Newton, & Steele, 2009; Charles Buz Swanik et al., 2004).

It has been suggested that ACLI noncopers, regardless of having surgical or conservative treatment, have altered muscular contraction patterns when compared to ACLI copers(E. Hartigan et al., 2012; Charles Buz Swanik et al., 2004). ACLI individuals who suffer long-term disabilities also have significantly greater fear of

participating in intense physical activity, whereas others who successfully returned to pre-injury levels of physical activity show less fear of re-injury/movement, and better muscle activation patterns(Clare L Ardern, Taylor, Feller, & Webster, 2012; Gignac et al., 2015; D. Y. H. Lee et al., 2008). Moreover, ACLI noncopers with relatively higher fear, demonstrate lower knee function during activities of daily living when compared to other ACLI noncopers who have less fear of re-injury/movement(Kvist, Ek, Sporrstedt, & Good, 2005; Ross, 2010). It is still unknown how fear and function are linked sequentially, but according to Morrey et al.(Morrey, Stuart, Smith, & Wiese-Bjornstal, 1999), ACL patients show progressively improved emotional responses throughout the rehabilitation process. They express heightened arousal levels both immediately following the ACL injury and at clearance to physical activity participation even after completion of an extensive rehabilitation program. Given this fact, the direct correlations between reduced subjective knee function scores and augmented fear of re-injury/movement in ACLI noncopers may suggest that negative feelings can alter dynamic muscle contraction mechanisms(Chmielewski et al., 2008; Lentz et al., 2015).

Previous research models have consistently demonstrated that frightening stimuli can significantly influence functional performance(Noteboom, Fleshner, & Enoka, 2001; Yoon et al., 2009). In response to a sudden life-threatening event, for instance, a person is likely to exhibit a defensive behavior to either escape from or resist the situation. This "fight or flight" response has been observed in patients with numerous musculoskeletal injuries, such as a chronic low back pain (CLBP) and ACL injury(Flanigan, Everhart, Pedroza, Smith, & Kaeding, 2013; E. H. Hartigan, Lynch, Logerstedt, Chmielewski, & Snyder-Mackler, 2013; Vlaeyen, Kole-Snijders, Boeren,

& van Eek, 1995). According to these studies, CLBP and ACL patients tend to avoid intense physical activities that are associated with previously experienced pain or injurious situations because of the expectancy of having a relapse of pain or re-injury. Moreover, these patients reported significant development of subjective fear and diminished functional abilities over the long term. It has been suggested that advanced neural activity related to cognitive processes in the brain can suppress fear responses(Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). As executive-function skills can control these negative feelings, ACLI individuals with greater fear of re-injury/movement may need enhanced cognitive management skills of muscle stiffness regulatory strategies in order to prevent unpleasant experiences of knee "giving way," when they confront intensive knee functional tasks(LeDoux & Damasio, 2013; Charles Buz Swanik et al., 2007). However, it is unclear how negative emotions, particularly a fear of re-injury/movement, alters the neuromuscular control system. Moreover, determining how negative emotions can be regulated in ACLI patients and its effect on functional joint instability has not yet been investigated.

Manifestations Of Neuroplasticity In Neuromuscular Control

Recent studies have suggested that continuous neuromuscular deficits following a peripheral joint injury are a result of insufficient adaptation of the CNS(Kapreli & Athanasopoulos, 2006; Kapreli et al., 2009; Ward et al., 2015). This persistent change or re-organization of the CNS (neuroplasticity or plasticity) is an alteration in the chemical synaptic connections between neurons, particularly the modification of neural networks in the brain in response to internal and/or external stimuli(B. B. Johansson, 2004; Kapreli & Athanasopoulos, 2006; Kapreli et al., 2009). The somatosensory system, which is composed of various types of receptors, neuronal

ascending pathways and neurons at the cerebral cortex, evaluates the quantity and quality of incoming sensory information to provide fine and gross motor behavioral responses(D.G. Amaral, 2013; Riemann & Lephart, 2002b). For example, proprioceptors in the knee provide conscious awareness of joint position sense to the somatosensory cortex through the posterior column-medial lemniscus and thalamocortical pathways. Afterwards, the somatosensory cortex projects the peripheral proprioceptive information to the adjacent motor cortex, at which point sensory signals trigger motor neurons in order to optimize muscle contraction patterns to protect the knee joint through spinal efferent pathways(Ward et al., 2015). However, this simple unimodal sensorimotor control process rarely occurs during physical activity as complex and simultaneous neural interactions between several cerebral cortex areas are desired(Mizelle, Forrester, Hallett, & Wheaton, 2010b; Wheaton et al., 2007).

Contribution of Cortical Interactions to Neuromuscular Control

Coordinated neural activity within the cerebral cortex is important for neuromuscular control. The cerebral cortex is responsible for integrating sensory inputs transmitted from multisensory modalities, and neurocognitive processing needed for preparatory motor program, as well as continuous modulation of reflexive muscle tone during physical activities(David G. Amaral & Strick, 2013; Charles Buz Swanik et al., 2007). Internal and external stimuli simultaneously change cortical responses by controlling excitation and inhibition of existing neural networks across the cerebral cortex, including the four topographically classified major lobes—the frontal, temporal, parietal, and occipital—along with two additional deep regions, the cingulate and insular cortices(D.G. Amaral, 2013; David G. Amaral & Strick, 2013).

Generally, the frontal lobe is responsible for planning of movement; the parietal lobe integrates somatosensory information and executes motor commands. The temporal lobe plays an important role in mediating the auditory senses, and the occipital lobe is responsible for visual procession. Both the cingulate and insular cortices are also concerned with the regulation of cognition(David G. Amaral & Strick, 2013; Ohman, 2005). It has been suggested that the somatosensory cortex projects perceived sensory outputs to other cortical areas responsible for recognition and planning of desired movements(Cohen, Cross, Tunik, Grafton, & Culham, 2009; Olson & Colby, 2013; Sedda & Scarpina, 2012). This cortical activation occurs in series and parallel pathways with the subcortical structures, in order to provide optimal situational awareness, as well as neuromuscular coordination(Kalaska & Rizzolatti, 2013; Rizzolatti & Kalaska, 2012).

The subcortical structures, such as thalamus and basal ganglia, have been linked to muscle coordination and control(Noteboom et al., 2001; Ward et al., 2015; Wichmann & DeLong, 2013). The thalamus acts as gateway for sensory integration, complex motor planning, and emotion regulation, as it transmits information to the brain, not only about limb and joint proprioception but also related multimodal senses including pain, touch, vision and auditory(D.G. Amaral, 2013; David G. Amaral & Strick, 2013; Haegler et al., 2010). Each discrete sensory modality enters a specific part of the thalamus, such that distinct sensory information is sent to a targeted area in the cerebral cortex(D.G. Amaral, 2013). For instance, the anterior and medial nuclei of the thalamus link cognition-, memory-, or emotion-related information to the frontal cortex. The ventral posterior nucleus projects somatic sensory information to the somatosensory cortex. Lastly, the posterior portion of the thalamus conveys aural

information to the auditory cortex(D.G. Amaral, 2013). The thalamus arbitrates between sensory receptors and the cerebral cortex by unconsciously prioritizing the conveyance of specific sensory information to dedicated regions of the cerebral cortex(D.G. Amaral, 2013). Consciously integrated information in the prefrontal cortex, responsible for cognitive management processes, can influence the filtering of information at the thalamus(Paus, 2001). Moreover, the thalamus receives significant motor feedback outputs, not only from the premotor cortex, but also from the cerebellum and basal ganglia, which are connected to the brainstem and primary motor cortex, respectively, in order to consciously execute appropriate motor responses to targeted muscles(D.G. Amaral, 2013; Ward et al., 2015; Wichmann & DeLong, 2013). Both the basal ganglia and cerebellum are known to influence the control of complex movements, as these structures are involved in executive function for motor planning processes. Due to the multifaceted, neural interconnectivity of the CNS, ACL rupture may alter a normal cascade of neurophysiological events within both the somatosensory and motor cortices, decoupling the joints mechanical events with the anticipated neural inputs, which could ultimately disrupt specific pathways necessary for the development of precise neuromuscular control strategies and dynamic restraint during physical activities(Kapreli & Athanasopoulos, 2006). Clinical outcome differences between copers and noncopers in returning to pre-injury level of physical activity may suggest that these networks undergo plastic changes after ACL injury.

Evidence of Neuroplasticity in ACL patients

The neuromuscular control contributing to maintenance of functional joint stability is regulated by the integration of significant proprioceptive information and cognitive learning processing based on the previous physical performance(Riemann &

Lephart, 2002b; Charles Buz Swanik et al., 2004). This may be an indication of continuous cortical adaptation of existing neural networks at different levels of the CNS(Churchland, Cunningham, Kaufman, Ryu, & Shenoy, 2010; Cramer et al., 2011; Héroux & Tremblay, 2006). Recent evidence has linked reorganization of the CNS (neuroplasticity) to ACL injury, therefore possibly explaining why some patients that suffer repetitive functional instability have recurrent knee sprains and/or contralateral injuries, and fail to return to pre-injury level of physical activity, even though mechanical laxity is restored(Courtney & Rine, 2006; Courtney, Rine, & Kroll, 2005; Kapreli & Athanasopoulos, 2006). Following an ACL injury, dissimilar neuromuscular control responses such as altered proprioception and muscle stiffness regulation strategies have been observed among ACLI patients(Ageberg, Björkman, Rosén, & Roos, 2012; Ageberg et al., 2008; Gobbi & Francisco, 2006). Beard et al.(D. Beard, Kyberd, Fergusson, & Dodd, 1993) reposted the timing of reflex hamstring contraction latency (RHCL) as an indirect measure of knee proprioception in ACLD patients. The author found that ACLD individuals showed 46.1ms slower RHCL in the injured limb than the uninjured limb, when compared to the interlimb difference in healthy controls (4.2ms). These patients also reported higher frequency of "giving-way" episodes regardless of joint laxity. This ligament-muscle reflex latency changes observed in these patients may be indication of alteration in afferent integration processes from the muscle spindle system, which may change muscle inhibitory or excitatory strategies implicated in the neuromuscular control(Friemert et al., 2005; H. Johansson et al., 1991a). Furthermore, a number of studies have also reported conflicting results on joint position sense awareness in ACLR patients who are expected to have restoration of mechanical stability, with the re-innervation of

ligament mechanoreceptors providing sufficient knee joint proprioceptive information to the CNS. Angoules et al.(Angoules et al., 2011) and Mir et al.(Mir, Hadian, Talebian, & Nasseri, 2008) demonstrated that ACL reconstruction restored the ability to detect passive joint position during flexion and extension of the reconstructed knee. However, diminished sensation of active joint position reproduction and detection of passive knee motion was also observed when comparing ACLR patients to healthy controls(Bonfim, Jansen Paccola, & Barela, 2003). These proprioceptive deficits are also observed in the opposite intact limb in ACLI patients(Arockiaraj et al., 2013). Some ACLI noncopers have developed bilateral knee dysfunction and suffered a secondary rupture of their ACL, not only in the ipsilateral knee but also the contralateral side(Arockiaraj et al., 2013; Grindem et al., 2012; Paterno, Rauh, Schmitt, Ford, & Hewett, 2012, 2014; Webster, Feller, Leigh, & Richmond, 2014). Arockiaraj et al.(Arockiaraj et al., 2013) reported diminished balancing ability in both the injured and uninjured knees and increased errors of the threshold detection of passive movement (TDPM). This may indicate that the occurrence of ACL rupture would result in permanent modification of cortical networks (CNS reorganization) implicated in proprioceptive feedback mechanisms, thus interrupting its consequent on the dynamic restraint system(Kapreli & Athanasopoulos, 2006; Ward et al., 2015).

Following an ACL injury, ACLD patients have shown quadriceps inhibition following knee perturbations(Di Fabio, Graf, Badke, Breunig, & Jensen, 1992; Rice & McNair, 2010). Swanik et al.(C B Swanik, Lephart, Giraldo, Demont, & Fu, 1999) demonstrated that ACLD group revealed attenuated quadriceps, and exhibited hamstrings reactive activation in response to joint loading during high velocity movement tasks (landing and running), when compared to healthy controls. The

author also found this neuromuscular control deficit occurred in both deficient and healthy knees. As the hamstrings and quadriceps muscles reciprocally inhibit each other(Begalle, DiStefano, Blackburn, & Padua, 2012), this may indicate that the CNS reorganizes the neuromuscular control system to sustain functional stability by recruiting more knee flexors activity and decreasing extensor responses, thus minimizing excessive anterior shear forces and joint translation. This hamstrings exhibition is also observed for preparatory muscle activation process.

Swanik et al.(Charles Buz Swanik et al., 2004) reported that ACLD patients had enhanced preparatory activity of the hamstring muscles, which act as a restraint to anterior displacement of the ACL, during landing tasks. Although each patient had varied anterior joint laxity, reactive muscle patterns and functional performance did not differ between ACLD patients and healthy controls. Increased hamstring preparatory activity was also observed in ACLD individuals with better knee function during dynamic deceleration of the knee muscles when completing the landing motion of a single-leg hop(A. L. Bryant et al., 2009). Conversely, other studies have reported that ACLI patients with long-term disability showing no significant differences in the preparatory muscle activation patterns, i.e. quadriceps inhibition, between injured and non-injured knees or compared with healthy controls during a landing task(Gauffin & Tropp, 1992; McNair & Marshall, 1994). This implies that ACLI copers compensate for neuromechanical decoupling between the knee and CNS, regardless of joint laxity, thereby optimizing muscle contraction strategies to maintain functional joint stability during a complex physical activity known to stress the ACL, whereas ACLI noncopers do not(DeAngelis et al., 2014; Kaplan, 2011; Riemann & Lephart, 2002b; Charles Buz Swanik et al., 2004).

Moreover, several subsequent ACL injury studies have reported that once ACLI patients are cleared to return to normal activity without functional limitations, the incidence rate of a second ACL rupture after a reconstruction increases from 6% within 2 years(Wright et al., 2007), to 12% within 5 years(Salmon, Russell, Musgrove, Pinczewski, & Refshauge, 2005), and almost 30% within 10 years(Pinczewski et al., 2007). It has also been reported that the risk of a subsequent ACL rupture to the opposite limb is greater than the ipsilateral limb after the reconstruction, particularly in younger patients or with intensive activities(Salmon et al., 2005; Webster et al., 2014; Wright et al., 2011). Evidence of the development of proprioceptive and neuromuscular control deficits leading to secondary ACL sprains to the contralateral side may be indicative persistent neural maladaptation in the cerebral cortex, which can diminish neuromuscular control system over time(J Baumeister et al., 2008; Bonfim et al., 2003; Hiemstra, Webber, MacDonald, & Kriellaars, 2007; Kuenze et al., 2015). However, most of these findings are speculative, based on either indirect measure of the CNS's responses using proprioceptive tasks or clinical outcomes from prospective cohort studies. Therefore, direct observation of cortical activity in the brain will offer better insight into the manifestation of neuroplasticity in ACLI patients after an ACL injury.

Evaluation of Neuroplasticity in ACLI patients

In the past, researchers have attempted to investigate cortical remodeling in the brain through many experimental animal studies. These studies examined how artificially manipulated brain lesions and molecular processing resulted in neuroplasticity between cortical areas and subsequent motor behaviors(Johnston & Duty, 2003; Padberg et al., 2010). These studies often required a surgical operation to

open the skull, an invasive maneuver that cannot examine neuroplasticity in this human model of ACLs. However, the evolution of versatile functional neuroimaging techniques has allowed for the non-invasive exploration of cortical activation after injury(Rossini & Pauri, 2000).

Techniques that are most often used for in-vivo human brain studies can be classified into two types according to their methodological approach. The first type of functional neuroimaging techniques measures neuronal metabolic changes in the cortical and/or subcortical regions, including positron emission tomography (PET), function magnetic resonance imaging (fMRI) and near infrared spectroscopy (NIRS) techniques(Banaji, Mallet, Elwell, Nicholls, & Cooper, 2008; Crosson et al., 2010; S. H. Kennedy et al., 2001; Rossini & Pauri, 2000; Yamada et al., 1997). When specific areas in the brain are activated, in response to sensory inputs, neurons in those areas require greater supplies of glucose and oxygen through the cerebral circulatory system to meet the neurons' increased energy demands. Therefore, an indirect measure of metabolic changes in those areas reflects the level of neural excitability or inhibition, by measuring hemodynamic responses or cerebral blood flow (CBF). Although PET and fMRI techniques can examine neuronal events both in the cerebral cortex and subcortical region of the brain, the NIRS technique is able to measure only the superficial CBF of the brain(Crosson et al., 2010). Moreover, due to the requirement of injecting a radionuclide for tracking, the PET technique carries slightly more risk relative to fMRI and NIRS. For this reason, an fMRI technique has been used to examine neural adaptation following an ACL injury.

Kapreli et al.(Kapreli et al., 2009) found changes in cortical activation patterns in the CNS during a simple knee flexion/extension task among ACLD patients with

prolonged functional disability. In comparison with healthy controls, the ACLD individuals revealed reduced cortical activation in several cerebral and subcortical areas, including somatosensory and premotor cortices and thalamus, which are regions associated with regulation of sensory perception and motor outputs. On the contrary, these patients showed higher activation in some other cortical regions including the visual and primary motor cortices, which are proposed to be critical for preparatory feed-forward mechanism(D.G. Amaral, 2013; Neuper & Pfurtscheller, 2001). The author suggested that the increased neural demand of visual perception could compensate diminished proprioception in ACLD patients by enhancing recognition of significant visual cues for early planning of movement(Kapreli et al., 2009). This fMRI technique provides better spatial resolution, which is the accuracy in the location and dimension of brain activity(Crosson et al., 2010; Mamata et al., 2002). However, observing metabolic changes in cortical neurons requires a few seconds of temporal resolution, which refers to the accuracy in real time of the cascade of cortical activation within and between areas in the brain(Crosson et al., 2010; B. B. Johansson, 2004; Sabatinelli, Bradley, Lang, Costa, & Versace, 2007). Because ACL injuries can occur in less than 70ms and the neuromuscular control system can regulate muscle stiffness strategies in less than 50ms, the fMRI's temporal resolution is too slow for accurately measuring cortical events within the injury timeline of interest(Crosson et al., 2010; Mrachacz-Kersting & Sinkjaer, 2003; Sinkjaer et al., 1988). Therefore, it may not offer observation of critical neural mechanism underlying neuromuscular control during unanticipated events in physical activity that lead to functional instability episodes(Crosson et al., 2010; B. B. Johansson, 2004; Sabatinelli, Bradley, et al., 2007).

The second group of measurement techniques for brain activity is growing in popularity, including transcranial magnetic stimulation (TMS), electroencephalography (EEG) and magnetoencephalography (MEG) techniques(Crosson et al., 2010; Pfurtscheller, Lopes da Silva, & Lopes, 1999). These techniques provide excellent temporal resolution in milliseconds, and allow for the measurement of simultaneous cortical responses at the brain's raw "speed of thought"(Crosson et al., 2010; B. B. Johansson, 2004; Sabatinelli, Bradley, et al., 2007). When cortical neurons are activated, postsynaptic potentials produce small, fluctuating electrical ionic currents, as well as small magnetic field oscillations. The strength of these electrical currents imply the level of cortical activation. The TMS technique, more precisely, generates artificial electrical currents, which modifies the neurons' output excitability, by delivering a magnetic pulse into specific areas of the cerebral cortex(Héroux & Tremblay, 2006). Kuenze et al.(Kuenze et al., 2015) used the TMS technique to examine motor-evoked potentials (MEPs) of the primary motor cortex during isometric knee extension contraction at 5% of MVICs. In comparison with uninjured knees, reconstructed knees of ACLI patients revealed greater MEPs, but they did not differ from the bilateral knees of healthy controls. It is known that greater MEP indicate less cortical excitability and facilitation of muscle contraction(Bonnard et al., 2003). Given this fact, the results of this study may indicate that an ACL injury caused long-term muscle weakness in the reconstructed knee because the motor cortex was providing insufficient stimulus during physical activity(Howells, Ardern, & Webster, 2011; Pietrosimone, Lepley, Ericksen, Gribble, & Levine, 2013). Contralateral cortical excitability patterns were also observed by Heroux and Tremblay(Héroux & Tremblay, 2006) and Pietrosimone et

al.(Pietrosimone et al., 2013). These studies found that ACLR patients had greater excitability in their reconstructed knee compared to their uninvolved knee. From these combined results, the asymmetric corticospinal excitability over the primary motor cortex may imply that changes in neurophysiological networks at the cortex level would interfere with both the reconstructed and contralateral limbs' dynamic restraint needed for the maintenance of functional joint stability following ACL injury(Dayan & Cohen, 2011). However, this TMS technique is an indirect measure of the relationship between detection of proprioceptive inputs at the somatosensory cortex and an efferent neuronal excitability at the corticomotor level, only reflecting reactive muscle activity through the proprioceptive feedback mechanism(Héroux & Tremblay, 2006). It may not be a proper technique to investigate how the brain detects external and internal stimuli and controls preparation of bodily movement in advance.

Substantial advantages of EEG and MEG over other noninvasive functional neuroimaging of the brain, such as fMRI and PET, are their level of temporal resolution in the order of milliseconds, as well as direct record for the cascade of neuronal electrical currents of the entire cerebral cortex(Crosson et al., 2010; B. B. Johansson, 2004; Sabatinelli, Lang, Keil, & Bradley, 2007). Furthermore, EEG is portable, relatively cheap, and does not require a large space for the test setting, in contrast to stationary PET, fMRI and MEG, which are large and can cost millions(Crosson et al., 2010). Thus, high temporal resolution and observation of concurrent neural activation across cortical areas with EEG may provide the opportunity for the examination of highly transient brain source activities implicated in perception, motor planning, and execution of motor control after an ACL injury(Crosson et al., 2010; Pfurtscheller & Klimesch, 1991).

EEG recordings have shown a variety of frequency bands such as Delta (< 4 Hz), Theta (4 – 8 Hz), Alpha-1 (8 – 10 Hz), Alpha-2 (10 – 12 Hz), Beta (16-31), Gamma (> 32), and Mu (8-12) in the human's brain(Balconi & Lucchiari, 2006; Balconi & Pozzoli, 2009; Pfurtscheller, Brunner, Schlögl, & Lopes da Silva, 2006). With regards to neuromuscular control, the fast Alpha-2 frequency band in the parietal brain regions is concerned with sensorimotor neurons' excitation and inhibition during a motor task, while the Theta frequency band in the frontal brain areas is associated with task-related cognitive processing as well as emotional regulation(J. Baumeister, 2013; Pfurtscheller, Stancák, & Neuper, 1996; Tolegenova, Kustubayeva, & Matthews, 2014). Baumeister et al.(J Baumeister et al., 2008; Jochen Baumeister, Reinecke, Schubert, & Weiss, 2011) demonstrated in EEG studies that ACLR patients had dissimilar cortical activation in the frontal and parietal cortex during force and/or joint position reproduction tasks, when compared to healthy controls. When ACLR patients performed force or joint reproduction tasks, they had increased frontal theta frequency power, reflecting augmented cortical activation in the anterior cingulate cortex (ACC) responsible for cognitive motor processing(Paus, 2001), and thus supporting the findings reported by Kapreli et al.(Kapreli et al., 2009). Furthermore, during the joint reproduction task, ACLR patients revealed significant reduction in Alpha-2 parietal (P3, P4) frequency powers, indicating higher cortical activation in the parietal sensorimotor cortex responsible for perceiving proprioceptive inputs. Moreover, cortical connectivity between the frontal and parietal cortex is known as a neural network for working memory, which relates to short-term memory abilities of monitoring, maintaining and modulating information for goal-directed behaviors(Schweizer et al., 2013). Enhanced neural activity occurring simultaneously

in these cortices reflects heightened neurocognitive processing(J Baumeister et al., 2008; Mizelle, Forrester, Hallett, & Wheaton, 2010a). As a result, these findings may support the notion that the modified CNS after injury, must recruit more neural resources in the planning of movement to compensate for diminished sensory feedback information through neurocognitive processing(Mizelle et al., 2010b; Charles Buz Swanik et al., 2004). However, the CNS reorganization, as a result of an ACL rupture, may not provide enough neural resources in response to sudden knee perturbation in conjunction with emotional stimuli, as brain regions for task-related cognitive processing are also critical for emotion regulation. Therefore, it may interrupt both neuromuscular control and emotion regulation. For this reason, an individual's executive function capabilities may be linked to ACL injury proneness, and have a substantial role in restoration and maintenance of functional joint stability following an ACL injury(Cappellino et al., 2012; Charles Buz Swanik et al., 2007).

Contribution Of Negative Emotion To Neuromuscular Control

Swanik et al.(Charles Buz Swanik et al., 2007) attempted to link a noncontact ACL injury and neurocognitive characteristics in intercollegiate athletes by using a computerized neurocognitive test battery (ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing). The executive functioning baseline measurements of non-injured athletes compared to ACLI athletes revealed slower reaction time and processing speed, as well as diminished visual and verbal memory scores. These components are thought to represent cerebral performance associated with working memory and goal-directed decision making processing necessary for neuromuscular control(Consiglio, Driscoll, Witte, & Berg, 2003; Ebersbach, Dimitrijevic, & Poewe, 1995; Lamm, Windischberger, Moser, & Bauer, 2007; Macciocchi, Barth, Alves,

Rimel, & Jane, 1996; Maroon et al., 2000; Moser, Schatz, & Jordan, 2005). However, very limited studies have attempted to examine the effects of neurocognitive intervention in ACLI patients. Cappellino et al.(Cappellino et al., 2012) utilized neurocognitive exercises as an alternative rehabilitation approach following an ACL rupture. These exercises required using an ACLI patient's recognition of joint positions, various patterns of body movements and joint angles, and transition of joint load in addition to traditional proprioceptive and perceptive neuromuscular control programs. It was reported that ACLI patients who performed the neurocognitive exercises showed improved muscle coordination and decreased pain and edema at six months after a reconstruction compared to others who underwent a common physical therapy program. These findings suggest that use of an individual's attention during proprioceptive and perceptive rehabilitation may facilitate and attune existing affective control networks(Bonnard et al., 2003; Bonnard, de Graaf, & Pailhous, 2004). As a result, precise cognitive awareness and enhanced neuromechanical coupling can offer better muscle stiffness regulation strategies to protect the knee in response to an unanticipated event(A. R. Needle et al., 2014; Charles Buz Swanik et al., 2007). However, a negative feeling and its subsequent neural responses can instantly interfere with cognition and motor planning needed for coordination and the avoidance of unintentional injuries as several cortical and subcortical areas are responsible for both the regulation of emotion and cognition(David G. Amaral & Strick, 2013; Ohman, 2005). Although it has been suggested that executive-function skills are associated with ACL injury proneness and knee function, it remains unknown the direct relationships between cognition, fear, and joint stiffness regulation strategies that may exist in ACLI patients with long-term disability, as well as higher fear of re-

injury/movement(Cappellino et al., 2012; Gignac et al., 2015; Lentz et al., 2015; Charles Buz Swanik et al., 2007). Therefore, understanding neural mechanisms underlying fear and its neurophysiological reactions will offer better insight into the role of executive-function skills for fear of re-injury/movement, its effects on functional joint instability, and best practices to improve each patient's functional outcome following an ACL injury.

Negative Emotion: fear and its neurophysiological reactions

Human emotional response is a natural physiological homeostatic process regulated by the CNS(LeDoux & Damasio, 2013). Fear is an unconscious emotional awareness responding to an unanticipated frightening stimulus, whereas the feeling of fear is a conscious behavioral and cognitive response. In order to examine fear responses, many researchers have reproduced fearful situations by using visuospatial stimuli such as emotionally provocative pictures or films(Barke, Stahl, & Kröner-Herwig, 2012; M. Bradley & Lang, 2006; Chen, Katdare, & Lucas, 2006; Sehlmeyer et al., 2009). In several psychological studies on emotion, researchers have observed different neurophysiological reactions corresponding to either unconscious or conscious fear regulation processes in subjects responding to fear-related pictures(Ax, 1953; M. Bradley & Lang, 2006; Horn & Swanson, 2013; P. Lang & Bradley, 2007). The CNS influences these changes that are mediated by the peripheral nervous system, particularly, by either independent activation of the parasympathetic or sympathetic nervous systems, or through reciprocal regulation between them(M. Bradley & Lang, 2006; P. Lang & Bradley, 2007). It is well known that the parasympathetic nervous system is responsible for quick activation in target organs, by releasing rapidly dissipating acetylcholine neurotransmitters along a short length of post-ganglionic

fibers. Conversely, the sympathetic nervous system is responsible for slower, but longer lasting activation in target organs, by releasing slowly dissipating noradrenaline neurotransmitters through relatively lengthy post-ganglionic fibers. Activation of the parasympathetic branches decreases heart rate and blood pressure, whereas the sympathetic branches often increases heart rate and blood pressure.

One of most predominant neurophysiological responses associated with a fear-related stimulus is a cardiovascular reaction. Originally, it was proposed that a negative emotional stimulus triggers the sympathetic system to accelerate defensive behaviors by increasing heart rate(Ax, 1953; Graham & Clifton, 1966; Schneirla, 1959). However, many recent studies employing negative emotional stimulus showed initially decelerated heart rate followed by accelerated heart rate(Adenauer, Catani, Keil, Aichinger, & Neuner, 2010; M. M. Bradley, Hamby, Löw, & Lang, 2007; Smith, Bradley, & Lang, 2005). Furthermore, a more arousing negative stimulus induced greater cardiac deceleration and delayed and longer activation of the subsequent cardiac acceleration. This initial cardiac deceleration elicited by the parasympathetic nervous system indicates increased sensory intakes by the brain, which reflects initial unconscious awareness of the fearful stimulus. On the contrary, the heart rate acceleration that follows is a result of the sympathetic dominance, indicative of the internal cognitive processing for recognition and preparation for an appropriate "fight or flight" behavior(M. Bradley & Lang, 2006; Libby, Lacey, & Lacey, 1973).

Unlike normal fear-related cardiac responses, people who are emotionally vulnerable have shown somewhat different heart rate reactions(Adenauer et al., 2010; Globisch, Hamm, Esteves, & Ohman, 1999; Ohman, 2005). Particularly, patients with emotional disorders, such as spider or snake phobias, showed a relatively large or

early onset of the heart rate acceleration in response to high-fear-related stimuli compared to neutral stimuli and control subjects who display normal cardiac responses(Globisch et al., 1999; Wendt, Lotze, Weike, Hosten, & Hamm, 2008). Negative stimuli in patients with posttraumatic stress disorder (PTSD), who typically report difficulty in controlling emotions, also revealed similar cardiac responses to animal phobic individuals compared to both neutral stimuli and other non-PTSD groups(Adenauer et al., 2010). These findings may suggest that minimal fear-related sensory information in these patients can very quickly activate the conscious affective control processing, which means that they fail to recognize important environmental cues for successful anticipation of movement during a sudden high velocity physical activity(A. L. Bryant et al., 2009; R. a. Bryant et al., 2008). The prolonged recognition and appraisal processes may also interrupt cognitive neural networks related to muscle coordination because these neurophysiological reactions are a product of the CNS, particularly the simultaneous modulation of neural interconnections between subcortical and cortical regions of the brain(Horn & Swanson, 2013). These findings may infer that the fear network in the brain have a substantial role in regulation of negative feeling, as well as maintenance of functional joint stability.

Negative Emotion: Fear and its Neurophysiological Reaction

The amygdala, which is one of the limbic system structures, is interconnected with other cortical areas associated with fear-related perception, cognition and motor planning through multiple afferent and efferent pathways. Therefore, it is thought to be the center of the fear responses and subsequent motor behaviors(David G. Amaral & Strick, 2013; Ledoux, 2000). Fear-related neural processes begin with activation of the amygdala, which simultaneously projects the fear-related sensory inputs to the

hypothalamus and brainstem, as well as to the cerebral cortex(LeDoux & Damasio, 2013; Ohman, 2005). This early activation of the amygdala to the hypothalamus and brainstem is an indication of unconscious, automatic detection of fear-related stimulus, whereas the continuous cortical feedback between amygdala and the cerebral cortex is concerned with increased cognitive processing in the fear network for conscious regulation of negative emotional responses(Delgado, Olsson, & Phelps, 2006; Liddell et al., 2005).

A number of neuroimaging techniques have enabled the examination of neural interconnections between these subcortical and cortical areas during fear responses. Functional MRI (fMRI) studies showed increased amygdala activation and its neural functional connectivity with the dorsal anterior cingulate cortex (dACC) and the orbitofrontal cortex (OFC) during presentation of fear-related facial pictures(Morris & Dolan, 2004; Morris, Ohman, & Dolan, 1999; Williams et al., 2006). These cortical areas are thought to heighten cognitive awareness of the body in order to prepare voluntary movements(D.G. Amaral, 2013; Clark, Mahato, Nakazawa, Law, & Thomas, 2014; Ward et al., 2015). It is possible that feelings of fear can increase neural recruitment demands in these areas, and subsequently alter cognitive motor planning during unanticipated events(Cohen et al., 2009; Dayan & Cohen, 2011; Olson & Colby, 2013; Sedda & Scarpina, 2012; Charles Buz Swanik et al., 2007). Although these findings demonstrate that prefrontal areas are important for regulating both emotion and neuromuscular control, fMRI techniques cannot offer concurrent neural interactions in real time that may exist between them, but EEG technique provides an excellent temporal resolution(Crosson et al., 2010).

Direct observation of electrophysiological signal changes in the brain areas corresponding to a specific event or stimulus, which is referred to event-related potential (ERP), has provided a cascade of sequential neural responses in the cerebral cortex to external stimuli(Sur & Sinha, 2009). The brain shows different ERP components such as latency and amplitude corresponding with the type of neural events. In general, early latency and peak ERPs are concerned with perceptive processing, while late latency and peak ERPs are considered as neurocognitive processing. Several emotion studies utilizing EEG also showed different ERP components responses to emotional stimuli(M. M. Bradley, 2009; Krolak-Salmon, Hénaff, Vighetto, Bertrand, & Mauguière, 2004). Affective stimuli showed an early deflecting peak potential at about 200ms (N2) and positive peak potential around 300ms (P3) after the onset of stimuli, which have implied unconscious automatic detection of emotional stimuli. Additionally, a late negative peak potential at about 430ms (N4) and positive peak potential within a range of 300 to 1000ms (P3b) are also observed. These late ERP components are known to represent cognitive integration during conscious emotional responses(M. Bradley & Lang, 2006; M. M. Bradley et al., 2007; Codispoti, Ferrari, & Bradley, 2007; Liddell, Williams, Rathjen, Shevrin, & Gordon, 2004). Interestingly, the brain has showed difference ERP component responses according to a variety of arousal levels. A fearful stimulus, which provokes greater arousal than a neutral stimulus, induces a greater and early onset of N2 and P3a over the frontal and centroparietal sites and, in turn, elicits larger and later onset of P3b at the centroparietal and posteroparietal areas. The time course of the cerebral performances indicates that fearful stimuli can delay the beginning of cognitive processes in the fear network and require longer time for regulation of the

frightening situation. These altered cerebral functions are more predominant in individuals who are emotionally susceptible to a negative stimulus(Ohman, 2005).

Neuroimaging studies showed that individuals with an animal phobia have increased activity in subcortical and cortical areas, responding to fear-related stimuli(Carlsson et al., 2004; Wendt et al., 2008). This population also demonstrated enhanced P3a and P3b relative to non-phobic controls(Kolassa, Musial, Mohr, Trippe, & Miltner, 2005; Leutgeb, Schäfer, & Schienle, 2009; Miltner et al., 2005; Mühlberger, Wiedemann, Herrmann, & Pauli, 2006; Schienle, Schäfer, Stark, & Vaitl, 2009). Moreover, patients with military and civilian related post-traumatic stress disorder (PTSD) have also shown dissimilar ERPs than non-PTSD individuals such as larger increased N2, altered P3a, and extended period of P3b when exposed to trauma-related stimuli(Attias, Bleich, Furman, & Zinger, 1996; Attias, Bleich, & Gilat, 1996; Metzger, Orr, Lasko, McNally, & Pitman). A large early positive ERP implies rapid detection of the dangerous stimulus as a result of the enhanced afferent subcortical conveyance by the amygdala. This is thought to be the location of memories from previous fear-related experiences, so the positive ERP suggests the memories are being transmitted to the prefrontal cortex(Liddell et al., 2005; Morris & Dolan, 2004; Williams et al., 2006). The early induction of, and extent of late positive ERP may indicate increased cortical activation demands related to cognitive regulation processing in fear network.

It is suggested that emotion-related motor behavior is a result of affective control of emotional responses through a cortical pathway between the frontal and parietal cortices(Olson & Colby, 2013). This fear network begins from the OFC, to the premotor cortex through the dorsolateral prefrontal cortex (DLPFC), and from there to

the primary motor cortex (M1). Although it is unidentified how negative emotions alter neuromuscular control in ACLI patients, it is known that the frontoparietal neural network is highly associated with cognitive control of working memory and regulation of emotion(Schweizer et al., 2013). Irregular cortical activation in the prefrontal and somatosensory cortices in response to a fearful stimulus may imply abnormal neuroplasticity(Javanbakht, Liberzon, Amirsadri, Gjini, & Boutros, 2011; Mahan & Ressler, 2012). Therefore, it is possible that high fear of re-injury/movement may interfere not only with the affective regulatory neural network, but also with the cognitive motor planning network needed for neuromuscular control in ACLI patients. For this reason, it is suggested that improving executive-function skills can aid to mediate negative emotion, as well as quickly suppress emotion-related behaviors due to high neural connectivity between fear and cognition networks(Adolph, Meister, & Pause, 2013; Campbell & Ehlert, 2012; Gyurak et al., 2009; Gyurak, Goodkind, Kramer, Miller, & Levenson, 2012; Gyurak, Gross, & Etkin, 2011).

Emotional Regulation: Executive Functioning Training

Emotional regulation is an integrated cognitive behavioral process related to perceiving, evaluating, analyzing, and modulating the emotional state(Gyurak et al., 2009). Therefore, it is important that several brain regions temporarily work together for optimal neurocognitive processing. Neuroimaging studies have shown that neurocognitive function skills can contribute to improving fear network responsible for cognitive emotion regulatory processing. Desbordes et al.(Desbordes et al., 2012) demonstrated in fMRI study that healthy controls had inhibited cortical activity in the amygdala in response to emotion-related images after 8-week mindful-attention training (MAT), which aims to down-regulate emotional response by cultivating

internal and external awareness such as one's breathing, mental events, or even the training. Moreover, an intentional cognitive rethinking, referring to reappraisal, has known to be associated with working memory processes, and it showed increased cortical activity in the prefrontal areas but decreased activity in the limbic system, such as the amygdala and insula, in response to negative emotional stimuli(Goldin, McRae, Ramel, & Gross, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002). These findings may suggest that the enhanced prefrontal functioning is a cognitive neural compensation in the fear network utilized in an attempt to quickly inhibit fear-related reactivity in the limbic system(Ochsner et al., 2002). Although many types of neurocognitive components have been engaged in emotion regulation, executive functions may play a key role in the augmentation of affective control implicated in neuromuscular control(Gyurak et al., 2012, 2011; Schweizer et al., 2013).

Increased neural demands in the cortical areas during emotional regulation can disrupt neuromuscular control because the preparatory motor planning needed for feed-forward muscle contraction strategies also relies on high cognitive processing in the cerebral cortex(Noteboom et al., 2001; Okada et al., 2001; Riemann & Lephart, 2002a). Executive-function skills are associated with goal-directed motor behaviors because the cognitive processes include recognition, preparation, implementation and evaluation of an external stimulus(Zelazo & Cunningham, 2007). Attention, working memory, reaction time and decisional accuracy may be particularly critical components in the control of emotion regulation and muscle coordination as these cognitive characteristics are highly associated with neural activation in the frontoparietal areas as well as unintentional musculoskeletal injuries(Goldin et al., 2008; Schweizer et al., 2013; Charles Buz Swanik et al., 2007). Schweizer et

al.(Schweizer et al., 2013) utilized an emotional dual *n*-back task, matching a word via verbal cue with an emotional face paired with the word of *n* trials back, in order to improve working memory capacity. The results revealed improved executive functions and emotional regulation. In comparison to pre-training of working memory, individuals had decreased cortical activation in the frontoparietal networks during executive functioning task. These findings may suggest that decreased cortical activation provides evidence for improved neural productivity(Kelly & Garavan, 2005). Therefore, enhanced neural efficiency in cognitive control networks through executive function training may help ACLI patients to regulate high fear of re-injury/movement and dynamic restraint systems to maintain functional joint stability during intense physical activity.

Clinical Relevance

Following an ACL injury, regardless of the treatment option followed, some ACLI patients have shown altered joint stiffness regulatory strategies for preparatory and/or reactive muscle contraction patterns, diminished proprioception, and worse knee outcomes with heightened apprehension during functional tasks. This insufficient neuromuscular control and intense anxiety about re-injury may underscore the idea that persistent functional joint instability is an indication not only of the peripheral deafferentation input and its neuromechanical decoupling with the CNS, but also of interrupted cognitive processing as a result of neuroplasticity in addition to neuropsychological factors, rather than being due to mechanical laxity(Kapreli & Athanasopoulos, 2006; Valeriani et al., 1999). Although findings from neuroimaging studies on ACL injuries corroborate re-organized cortical activation in ACLI patients, it is unknown weather mechanical loading and laxity modifies the brain's function in

the somatosensory cortex as well. Moreover, it remains unclear whether injury-related negative stimuli interrupt neurocognitive processes and joint stiffness regulation strategies, as well as whether cortical adaptations represent enhanced compensatory neuromuscular control responses or neuromuscular control deficits and potential recurrent knee sprains.

ACL-injured individuals who have failed to resume pre-injury levels of physical activity report higher fear of re-injury/movement and suffer repetitive functional joint instability, when compared to others who are able to cope with physical activity without functional limitations(Clare L Ardern, Taylor, Feller, Whitehead, & Webster, 2013; D. Y. H. Lee et al., 2008). Evidence of neuroplasticity in emotionally vulnerable individuals such as animal phobic and PTSD patients, in response to particular animals or traumatic stimuli respectively, suggest that increased cortical activation in the fear network can interfere with goal-directed cognitive motor planning processes. As the PNS and CNS both are critical in the voluntary movements and emotion regulation, it is not surprising that emotional regulation also involves greater cortical activation to compensate for the increased fear-related sensory inputs to the CNS(Krolak-Salmon et al., 2004). However, researchers have observed a greater reduction in accuracy and reaction time in the general population in response to fear-related stimuli compared with neutral or happy facial expressions(Calvo & Lundqvist, 2008). This finding may suggest that increased cognitive neural processing demands in the prefrontal cortex as a result of frightening stimuli during an unanticipated physical activity may not be indicative of better planning of movement or anticipation for a joint perturbation, but may merely alter the cognitive processing for the neuromuscular control system necessary for maintaining dynamic joint

stability(Carlsson et al., 2004). Therefore, it is possible that ACL patients with ACL injury-related sports images may unconsciously activate and extremely increase neural activation in motor planning network in response to an unexpected event such as an acoustic startle stimulus, due to increased sensory resources for both the feed-forward and feedback muscle contraction mechanisms in addition to fear regulation. However, the neurophysiological mechanisms into direct interrelations between fear of re-injury/movement and dynamic muscle stiffness regulation strategies in these patients has not yet been investigated. Moreover, executive function is thought to provide cognitive regulation of negative emotions so that augmentation of ACLI individual's cognitive capacity may also improve affective control and muscle coordination, thus maintaining functional knee stability(Chen et al., 2006; Goldin et al., 2008; Gyurak et al., 2011; P. J. Lang, Bradley, & Cuthbert, 2008; Ohman, 2005).

Studying neural activity and its connectivity within the brain is an emerging area that may provide evidence of CNS adaptation underlying functional joint instability following a peripheral joint injury. This may provide valuable insight into the neuromechanical links between cognition, fear, and joint instability, and help improving patient outcome, minimizing functional disability, returning to one's chosen physical activity in ACL patients, as well as the results may apply to any other joint instability(Carlsson et al., 2004).

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Chapter 2

DIFFERENT BRAIN RESPONSES TO KNEE LOADING AFTER INJURY

Introduction

Ligaments contain numerous mechanoreceptors responsible for the sense of position, movement, and force at the joint, which help to maintain neuromuscular control via the sensorimotor system(M. A. Freeman & Wyke, 1966; M. a Freeman, 1965; Riemann & Lephart, 2002a, 2002b). A ligament tear may damage mechanoreceptors and ultimately lead to proprioceptive deficits and subsequent loss of joint function. Although many studies have examined proprioceptive deficits following peripheral ligamentous injuries at the ankle, knee, and shoulder(Clayton & Court-Brown, 2008; Munn, Sullivan, & Schneiders, 2010; Murray, Ahmed, White, & Robinson, 2013), the mechanisms underlying functional deficits still remain unclear because limited data exists demonstrating the brains role(J Baumeister, Reinecke, & Weiss, 2008; Kapreli et al., 2009).

It is known that the anterior cruciate ligament (ACL) acts to restrict excessive mechanical anterior translation and provides critical proprioceptive information to the sensorimotor system, such that the regulation of muscle stiffness can provide dynamic knee stability(C. Buz Swanik, Lephart, Giannantonio, & Fu, 1997). This neuromechanical coupling is critical to maintaining functional joint stability(Arockiaraj et al., 2013; Chmielewski et al., 2005). For this reason, it has been suggested that excessive anterior joint laxity and/or deafferentation of ACL mechanoreceptors in the knee cause episodes of "giving way," referred to as

functional joint instability. Diminished proprioception and altered neuromuscular control would result in inappropriate preparatory and reactive muscle contractions necessary for functional joint stability(Rozzi, Lephart, Gear, & Fu, 1999; C. Buz Swanik et al., 1997). Poor neuromuscular control increases the risk for long-term pathological sequelae such as secondary ACL ruptures, to either the ipsilateral or contralateral knee, as well as premature osteoarthritis(Hootman & Albohm, 2012; Hurd, Axe, & Snyder-Mackler, 2008; Lohmander, Englund, Dahl, & Roos, 2007; Paterno, Rauh, Schmitt, Ford, & Hewett, 2012).

Over recent decades, many interventions have been explored to improve functional joint stability in the ACL population. Research suggests that both surgical and conservative treatments following an ACL injury are advantageous in the restoration of joint function(Linko, Harilainen, Malmivaara, & Seitsalo, 2005). However, despite these efforts, up to 35% of ACL reconstruction (ACLR) patients and almost 60% of ACL deficient (ACLD) patients are still unable to protect their knees during physical activity through dynamic restraints alone(Clare L Ardern, Webster, Taylor, & Feller, 2011; Fitzgerald, Axe, & Snyder-Mackler, 2000a; Gobbi, Bathan, & Boldrini, 2009; Gobbi & Francisco, 2006; Grindem, Eitzen, Moksnes, Snyder-Mackler, & Risberg, 2012; D. Y. H. Lee, Karim, & Chang, 2008; Moksnes, Snyder-Mackler, & Risberg, 2008). Moreover, multiple follow-up studies now show inconsistent correlations between mechanical joint laxity and functional instability(Herrington & Fowler, 2006; Kaplan, 2011; Moksnes et al., 2008). Some ACLR patients complain of persistent giving-way episodes, while other ACL deficient (ACLD) patients that have relatively greater joint laxity are able to restore normal knee function, presumable through better neuromuscular coordination(Clare L Ardern

et al., 2011; Fitzgerald, Axe, & Snyder-Mackler, 2000b; Grindem et al., 2012; Moksnes et al., 2008). This may indicate that joint laxity measures alone do not reliably evaluate an unequivocal link between mechanical stability, alteration of proprioception or neuromuscular control, and functional joint instability(Eastlack, Axe, & Snyder-Mackler, 1999; Gokeler et al., 2012; H. M. Lee, Cheng, & Liau, 2009). As a result, ACL patient outcomes may vary greatly, and those who are unable to cope with functional tasks may be experiencing a neuromechanical decoupling between the knee and central nervous system (CNS)(Dhillon, Bali, & Prabhakar, 2011).

Recent research has suggested that brain plasticity may be the primary source for variation in patient outcomes and ability to maintain functional joint stability and physical activity after an ACL injury(J Baumeister et al., 2008; Kapreli & Athanasopoulos, 2006; Kapreli et al., 2009). Damage to articular receptors in the knee appears to cause adaptations in the CNS responsible for binding sensory feedback from the joint, to mechanical events such as loading and laxity. There is early evidence of plastic changes to higher level executive functions associated with neuromuscular control(Jochen Baumeister, Reinecke, Schubert, Schade, & Weiss, 2012; Kapreli et al., 2009). Neuroimaging research may lead to greater understanding of these potential neural adaptations between the musculoskeletal and nervous systems following ACL injury, and may reveal sources of variation that are responsible for unpredictable patient outcomes.

Neuroimaging research using electroencephalography (EEG) and functional Magnetic Resonance Imaging (fMRI) has suggested altered EEG activity in the frontal and parietal cortices of ACL patients, as well as diminished sensorimotor brain

activation (fMRI)(J. Baumeister, 2013; Kapreli et al., 2009). The frontal areas of the brain are responsible for the planning of movement, by monitoring and integrating internal/external changes, whereas the parietal areas regulate perception of sensory information, as well as execution of motor responses(J. Baumeister, 2013). These findings may indicate that CNS reorganization after joint injuries is a protective mechanism, associated with the altered proprioception, in order to enhance sensorimotor system responses and compensate for neuromechanical decoupling between joint afferents and the CNS(Kapreli et al., 2009; Needle et al., 2014). However, very limited data exist on the CNS's role in perceiving mechanical loading and laxity in either an ACL population or healthy controls.

Several psychological factors have also been shown to contribute to the restoration of knee function following ACL injury(Clare L Ardern, Taylor, Feller, Whitehead, & Webster, 2013). ACL patients who did not return to their previous injury level of physical activity reported higher subjective fear perception than ACL patients that regained normal knee function(Chmielewski et al., 2008; Hartigan, Lynch, Logerstedt, Chmielewski, & Snyder-Mackler, 2013). Improved knee function outcomes following neuromuscular interventions in these studies revealed decreased fear of re-injury among those with with higher return-to-play rates. It is possible that appropriate CNS reorganization, as a result of neuromuscular training, may have a positive effect on functional knee outcomes, as well as patient's levels of fear of returning to participation. However, it remains unclear how the potential neural adaptation in the somatosensory cortex following an ACL injury is associated with knee function or the level of fear perception.

One measure known to reflect cortical activation in the somatosensory cortex of the brain is event-related desynchronization (ERD) in the alpha-2 frequency band (10-12 Hz) at the parietal cortex. This is the regions responsible for perceiving sensory information from the ACL in order to prepare motor behaviors through dynamic restraints(J Baumeister et al., 2008; Martínez-Jauand et al., 2012; Pineda, 2005). A comparison of direct cortical activity measures over the somatosensory cortex in ACL patients and healthy controls could lead to an enhanced understanding of how the brain perceives sensory information during joint loading, and may provide some insight as to why some ACL patients suffer from long-term disability. Since the CNS may require protective compensatory neural adaptations for neuromechanical decoupling following an ACL rupture, we hypothesized that increased somatosensory cortex activation may be observed in the previously injured knee (reconstructed or deficient limb). Additionally, ACL patients with greater increases in cortical activity may have better knee functional outcomes and less fear of re-injury. Therefore, the purpose of this study was to examine somatosensory cortex activity during joint loading using EEG, to investigate the relationship between joint laxity, brain activity and knee functional outcomes, as well as fear of re-injury/movement commonly observed in ACL patients with long-term disabilities (Clare L Ardern, Taylor, Feller, & Webster, 2013).

Methods

Experimental design

This study utilized a case control design with a healthy control group. The independent variables included group (healthy controls, ACLR patients, ACLD patients), time of anterior loading (0-1000 ms, 1000-2000 ms, 2000-3000 ms), and

side. The dependent variables included measures of joint laxity (mm), passive stiffness (N/mm), knee functional assessment outcomes, fear of re-injury/movement scores, and electroencephalography (EEG) event-related power (log μV^2) compared to the resting condition in the Alpha-2 frequency band (10-12Hz).

Participants

Forty volunteers (17 healthy controls, 17 ACLR patients, 4 ACLD) between the ages of 18-45 years old were recruited for participation in this study (Table 1). All participants were matched on age range and gender between groups. Participants within the healthy control group were physically active at least three days per week and had no history of ACL injury. Participants with a history of ACL reconstruction (within the last10 years) had a unilateral cruciate ligament rupture confirmed with magnetic resonance imaging (MRI), and had been cleared to return to pre-injury level of physical activity. ACLD patients had a history of a unilateral cruciate ligament rupture confirmed with magnetic resonance imaging (MRI), resolved edema, full range of motion, and absence of surgical repair at the time of testing. Participants were excluded if they had history of lower extremity fracture or surgery within the last 6 months, due to the potential influence on knee functional assessment outcomes. Additionally, participants were excluded if they had history of neurological problems or a metal implant in their head, face, or jaw, which could result in poor quality of EEG signal. All participants were provided and signed the approved informed consent prior to a single testing session.

Instrumentations

Knee functional assessment outcomes were assessed using subjective questionnaires, including the Knee Outcome Survey-Activities of Daily Living (KOS-

ADL), the global rating of knee function via visual analog scale (VAS), the number of giving way episodes, as well as a single-legged hop for distance test (Appendix C)(Collins, Misra, Felson, Crossley, & Roos, 2011; Herrington & Fowler, 2006; Moksnes et al., 2008). The KOS-ADL is a 14-item self-report instrument designed to measure symptoms and functional limitation experiences during activities of daily living associated with knee injuries(Moksnes et al., 2008). The global rating of knee function is a self-report of knee function on a 10 centimeters long VAS ranging from 0 to 100 points. Zero indicates functionally unable to perform any daily activities and 100 represent the level of knee function prior to injury(Moksnes et al., 2008). An episode of giving way is a feeling of knee subluxation accompanied with pain and effusion. The number of experiences of giving way since the injury in ACLD patients, reconstruction in ACLR participants, number of episodes for healthy controls in the past 10 years will be used for analysis(Moksnes et al., 2008). The single-legged hop for distance, which is a measurement of the distance between the great toes at a standing and landing, is used to predict knee functional performance after ACL injuries(Noyes, Barber, & Mangine, 1991; Reid, Birmingham, Stratford, Alcock, & Giffin, 2007). This battery of knee functional outcome tests has been reported as a valid and reliable tool to evaluate the level of knee function following ACL rupture(Collins et al., 2011; Fitzgerald et al., 2000a).

The TSK-11, which is an 11-item of shortened version of the Tampa Scale for Kinesiophobia, was used to evaluate a person's fear of re-injury/movement at the moment of testing (Appendix C). It is a reliable tool that utilizes 4-point Likert scale ranging from 1 = strongly disagree to 4 = strongly agree. Higher score indicates

greater fear of re-injury/movement(Clare L Ardern, Taylor, Feller, Whitehead, et al., 2013; Woby, Roach, Urmston, & Watson, 2005).

Knee laxity and stiffness were assessed using a KT-2000 knee arthrometer (MedMetric, San Diego, CA) designed to measure anterior-posterior joint displacement during a pull-push cycle, by recording the relative motion of anterior force-tibial translation between the patellar and tibial sensor pads(Daniel et al., 1994). Raw analog force (maximum 134N for anteriorly and 89N for posteriorly) and displacement data were collected and stored to a laptop using custom LabVIEW software through an A/D board (DAQ 9215, National Instruments, Austin, TX).

Cerebral cortical activity was measured using 30 Ag/AgCL electrodes (FP1, FP2, F7, F3, Fz, F4, F8, FT7, FC3, FCZ, FC4, FT8, T7, C3, CZ, C4, T8, TP7, CP3, CPZ, CP4, TP8, P7, P3, PZ, P4, P6, O1, OZ, O2) inserted in an elastic cap (QuikCap^{TM}, Compumedics Neuroscan, Charlotte, NC) in compliance with the international 10:20 system. Electrodes were placed at the mid-forehead and average of mastoid processes [(A1+A2)/2] to represent a ground and an average reference respectively(Nunez & Srinivasan, 2006). EEG data with a sufficient signal-to-noise ratio (<5kΩ) was recorded at 1024 Hz using a NuAmps amplifier system and stored using Scan 4.5 Software (Compumedics Neuroscan, Charlotte, NC). Digital triggers from the knee arthrometer were sent to Scan4.5 software to appropriately synchronize the joint laxity data with brain activation.

Procedures

After completion of Knee functional assessment outcomes and the short version of the Tampa Sale of Kinesiophobia (TSK-11), all participants were fitted for an electro-cap (QuikCap^{TM}). Four additional electrodes were attached above and

below the left eyebrow and both mastoid processes to detect movements of the eye and jaw muscles (Figure 2). Conductive electrolyte solution was inserted into each electrode of the QuikCap^{TM} and a sufficient signal-to-noise ratio (<5kΩ) was confirmed with an impedance test.

Participants were then positioned supine on a padded treatment table, with the knee flexed between approximately 20 and 35 degrees, which was verified by a goniometer. Hands remained relaxed at the side of the body and participants were directed to position their eyes towards the target marker on the ceiling. The thigh and foot support platforms of the KT-2000 were placed under both legs at a proximal to the popliteal space and feet at a distal to the lateral malleolus. The arthrometer was positioned at the anterior aspect of the tibia aligned with the knee joint line and secured using Velcro straps to minimize an excessive hip external rotation (Figure 3).

Baseline brain activity was measured for one-minute with the eyes open and one-minute with the eyes closed prior to each testing block. A total of 5 testing blocks were performed to collect and record continuous brain activity using Scan 4.5 Software (Compumedics Neuroscan, Charlotte, NC) at 1024Hz/32 bit. Each testing block was composed of 10 standard pull-push cycles (anterior-posterior translation) at a consistent velocity (45N/sec) with 10 seconds of rest between each trial. Continuous force and ligamentous displacement data was collected and synchronized with EEG data via a custom LABVIEW program (National Instruments Co., Austin, TX). Integrated visual feedback was used to ensure a constant force (45N/sec) during loading both anteriorly (134N) and posteriorly (89N)(Van Thiel & Bach, 2010). Participants were instructed to keep their eyes open, while blinking comfortably throughout the entire testing. Participants were encouraged to minimize body or facial

muscle movements to limit impedance and artifacts and the signal was monitored during data collection. The same examiner performed all knee anteroposterior translations and testing order of limbs was counterbalanced.

Data Reduction

Joint laxity was reported as displacement (mm) of total laxity (LAXT) for all participants, as well as laxity for the first 1000ms (LAX1), the second 1000ms (LAX2), the third 1000ms (LAX3), and total anterior laxity (LAXA) during the anterior-posterior translation. Additionally, joint stiffness was reported as the change in load divided by the change in displacement (N/mm) for total joint stiffness (STFT), the first 1000ms (STF1), the second 1000ms (STF2), the third 1000ms (STF3), and the total anterior stiffness (STFA) (Figure 4). Inter-limb differences for joint laxity (mm) and stiffness (N/mm) were also calculated by subtracting value of the non-injured limb in ACL patients (or matched side in healthy controls) from the injured or matched limb.

Scan4.5 software (Compumedics Neuroscan, Charlotte, NC) was used for EEG data analysis. Initially, raw EEG signals were clarified using a band-pass filter from 1 to 30Hz. Ocular artifact reduction then was performed to visually remove eye movement artifacts (blinking) from EEG signals that were observed as measured through two electrodes, one above and one below the left eye (VEOU; Vertical Electro Oculogram Up, VEOL; Vertical Electro Oculogram Low). Synchronized EEG data with the knee arthrometer at the start of each translation were cut into 6000ms epochs: from 2000ms prior to start of the translation, to 4000ms after the start of the anterior translation. Averaged event-related desynchronization (ERD) in alpha-2 (10-12Hz) at baseline (BASE, -2000 to -1000ms prior to loading), the first 1000ms of loading

(ERD1, 0-1000ms from the start of loading), the second 1000ms of loading (ERD2, 1000-2000ms from the start of loading), and third 1000ms of loading (ERD3, 2000-3000ms from the start of loading) were calculated for selected electrodes of the contralateral somatosensory (CP3 for the right knee, CP4 for the left knee). Higher alpha-2 ERD that expresses as a percentage of activity decrease relative to the baseline has suggested as increased somatosensory cortex activation (Figure 4)(Pineda, 2005). An absolute percentage difference of cortical activity between limbs for each loading was also calculated to examine relationships with knee functional outcomes and an individual fear perception.

For the evaluation of the Knee Functional Outcome Assessment, a percentage value was calculated for the KOS-ADL and global rating of knee function. Hop limb symmetry index (LSI) for the single legged hop for distance test was calculated as a percentage of the injured limb to the non-injured limb for the ACLD and ACLR participants. Conversely, LSI for the healthy controls was calculated as a percentage of the matched injured limb to the matched non-injured limb. The number of "giving way" episodes was reported for further analysis. Fear of re-injury/movement (TKS-11) was calculated into a percentage by adding the score of each item and dividing by 44, the total possible maximum score, and multiplying by 100(Moksnes et al., 2008).

Statistical Analysis

Joint laxity, stiffness and cortical activation during each second of joint loading was assessed using separate 2-way ANOVAs with one within-subject factor (Side, 2 levels) and one between-subject factor (Group, 3 levels). The Knee Functional Outcome Assessment and fear of re-injury/movement (TSK-11), were compared using separate one-way analysis of variances (ANOVAs) between groups (3 levels). Post

hoc analysis was performed using *Tukey's post hoc* and pairwise comparisons. Descriptive analysis was used to identify any outliers or irregularities in the distribution. A probability alpha level was set a *prior* at 0.05.

Pearson product-moment correlation coefficients were used to assess the relationship between joint laxity and cortical response values within each group. Relationships among knee functional outcomes, fear of re-injury/movement, and cortical activation side-to-side difference were also assessed with Pearson product-moment correlation coefficients within each group.

Results

Joint Laxity

Table 2 presents means and standard deviations for joint laxity of each group. Significant side by group interaction effects were observed for LAXA ($F_{[2,34]}$= 5.176, p=0.011) and LAX3 ($F_{[2,32]}$ = 9.037, p=0.001) (Figure 5). Tukey's post-hoc tests revealed that ACLR group had significantly greater total anterior laxity (LAXA) in the reconstructed knee than the healthy limb (p=0.003). Additionally, both the ACLD (p=0.021) and ACLR (p<0.001) groups had significantly greater laxity in the injured-limbs during late loading (LAX3: 2000-3000ms) than the control group's matched limb, while no significant differences were observed between ACL patients' non-injured knees and healthy controls' matched knee (p>0.05). No group by side interaction effects were observed for LAX2 ($F_{[2,35]}$=2.736, p=0.079) and LAXT ($F_{[2,35]}$=0.754, p=0.478), but main effects for side revealed greater joint laxity in the injured (or matched) limbs than the other healthy limbs (respectively, $F_{[1,35]}$=7.131, p=0.011, $F_{[1,35]}$=9.084, p=0.005). Alternatively, neither the main effect for side or the

side-by-group interaction were significant for LAX1 (respectively, $F_{[1,31]}$=1.431, p=0.241, $F_{[2,31]}$=2.912, p=0.069).

Joint Stiffness

Joint stiffness values during loading are also presented in the Table 2. A significant side-by-group interaction effect was observed for STIF3 ($F_{[2,33]}$=3.803, p=0.033) (Figure 6). Tukey's post hoc test showed that ACLR group had significantly less mechanical stiffness in the reconstructed knee than the matched limb in CONT group during late loading (p<0.001). Although no side by group interaction effect was observed for STIFA ($F_{[2,35]}$=2.008, p=0.149), a significant main effect for group was found ($F_{[2,35]}$=3.655, p=0.036). Pairwise comparisons revealed significantly greater total anterior mechanical stiffness in the CONT group than the ACLR group (p=0.028), while the ACLD group was not significantly difference from either group (p>0.05).

Cortical Activation

Contralateral somatosensory cortex activation between sides across groups and times were displayed in Table 3. Significant side by group interaction effect was observed for ERD1 ($F_{[2,35]}$=11.239, p<0.001) (Figure 7). Tukey's post hoc comparisons revealed that ACLR group had higher ERD1 in the involved limb than the matched limb in the CONT group (p=.041), while ACLD group was not significantly different from either group (p>0.05). Additionally, the ACLR group showed greater increased ERD1 in the reconstructed limb when compared to the non-involved limb (p=0.001). However, both the CONT and ACLD groups had no statistically different ERD1 between limbs (p>0.05). Although no significant side by group interaction effect was observed for ERD3 ($F_{[2,32]}$=1.772, p=0.186), main effect

for group was significant ($F_{[2,32]}$=6.896, p=0.003). Pairwise comparisons found that ACLR group had significantly greater ERD3 activity than both the CONT (p=0.012) and ACLD (p=0.016). However, there was no significant difference in ERD3 between CONT and ACLD groups (p>0.05). There was no significant interaction or main effects for ERD2 (p>0.05).

Knee Functional Outcomes and Fear of Re-Injury/Movement

Means and standard deviations for the three groups on the dependent variables of the Knee functional outcomes and TSK-11 values are presented in Table 4. Preliminary comparisons revealed that the homogeneity assumption underlying ANOVAs were violated for KOS-ADL (Levene statistic = 11.099, df[2,35], p<0.001), GRFK (Levene statistic = 3.851, df[2,35], p=0.031), TSK-11 (Levene statistic = 3.743, df[3,35], p=0.034) and LSI (Levene statistic = 4.637, df[2,33], p=0.017). Therefore, post hoc comparisons were apportioned using the Games-Howell adjustment. The overall ANOVAs only showed statistically significant difference between groups in TSK-11 ($F_{[2,22.411]}$=20.919, p<0.001) and LSI ($F_{[2,8.822]}$=8.605, p=0.008) (Figure 8). Post hoc analyses demonstrated that the ACLD group reported significantly less fear (TSK-11) than both the CONT (p<0.001) and ACLR groups (p=0.001). Furthermore, the ACLR group had significantly less LSI percentage scores than CONT group (p=0.007), while the ACLD group was not statistically different from either group (p>0.05).

Correlations between Laxity and Cortical Activation

Pearson correlation coefficients between laxity and cortication activation values are presented in Table 5. Higher ERD2 activity in the reconstructed limb of the ACLR group positively correlated with LAX1 (r=0.530), LAX2 (r=0.506), LAXA

(r=0.543) and LAXT (r=0.501), while non-injured limbs in the ACLR group revealed negative correlations between LAXA and ERD1 (r= -0.534) as well as between LAX2 and ERD2 (r= -0.565) (Figure 9). Greater LAX1 in the deficient knee of the ACLD group was also positively correlated with higher ERD2 (r=0.981) and ERD3 (r=0.983). Increased LAX1 in the non-injury matched limb in the CONT group correlated with greater ERD3(r=0.515). There were no significant correlations between laxity and cortical activity in the injury matched limb for the CONT group and non-injured limb for the ACLD group.

Correlations between Cortical Activation, knee function and TSK-11

Pearson correlation coefficients between ERD activity, knee function outcomes, and TSK-11 are displayed in Table 6. Greater ERD1 side-to-side differences negatively correlated with TSK-11 for the ACLR group only (r= -0.523) (Figure 10). ACLD revealed negative correlation between KOS-ADL (%) and ERD1 interlimb differences (r= -0.971). Alternatively, the CONT group did not show any significant correlations between cortical activity, knee functional outcomes, and fear of re-injury/movement (TSK-11).

Discussion

This study is the first to examine somatosensory cortex activation in response to knee joint loading. The primary findings identified that different cortical activation patterns exist between the healthy controls, ACLR and ACLD patients during discrete phases of joint loading, regardless of changes in joint laxity or stiffness. Furthermore, dissimilar joint laxity and cortical activation correlations were observed between groups, where the ACLR group exhibited opposite laxity-cortex correlations between limbs, while healthy controls showed no correlations. The ACLR group, with

relatively less fear of re-injury/movement, also showed increased cortical activation in the reconstructed limb compared to the healthy knee. These may imply that increased somatosensory cortex activity during the involved joint loading is evidence of neuroplasticity, presumably to mitigate neuromechanical decoupling between the ACL and CNS following an ACL injury.

Joint Laxity and Stiffness

Regardless of surgical repair following an ACL rupture, our results indicate that both the ACLR and ACLD groups had significantly higher mechanical laxity than non-involved limb during anterior translation, while the healthy controls had no significant interlimb differences. Although the overall joint laxity in both the ACLR and ACLD group were less than 3 mm between limbs, which is not considered to be a clinically significant mechanical deficit(Hartigan, Axe, & Snyder-Mackler, 2010), it is apparently important to the brain. It has been theorized that diminished function of articular mechanoreceptors are associated with increased variation in the sense of joint position. This can result in the altered neuromuscular control leading to functional joint instability(Rozzi et al., 1999). Therefore, increased joint laxity, regardless of surgical or conservative treatments, may contribute to recurrent experiences of joint "giving way". However, recent research has shown a lack of evidence in the link between joint laxity and functional instability(Eastlack et al., 1999; Kaplan, 2011; Moksnes et al., 2008). Eastlack et al.(Eastlack et al., 1999) investigated the relationship between joint laxity, muscle strength, and knee functional tasks in ACLD patients between those who restored normal knee function and those who required a surgical repair to restore function, and suggested that both groups had no differences in laxity. Conversely, Moksnes et al.(Moksnes et al., 2008) demonstrated that ACL

patients who returned to pre-injury level of competition (copers) have significantly less side-to-side laxity differences when compared to other ACL patients who suffered persistent functional joint instability (noncopers). However, both studies demonstrated that ACL patients who returned to pre-injury level of physical activity had improved knee muscle strength or knee functional performance such as dynamic hop tasks. Results in these studies may suggest that mechanical stability, as an inherent factor, could present in either ACL copers or noncopers, however, it may not reflect neuromechanical coupling between the ACL and CNS(Dhillon et al., 2011).

Furthermore, our stiffness results show that the ACLR group had lower mechanical stiffness in the reconstructed limb during late anterior joint loading when compared to those healthy limbs or control group. This later phase of joint stiffness implicates mechanical resistance mostly from the ACL and contractile components of the muscle, which are crucial for the static restraint to maintain joint stability(Maitland, Bell, Mohtadi, & Herzog, 1995). Several studies conducted mechanical stiffness tests using knee arthrometers in females, at different phases of menstrual cycle(Eiling, Bryant, Petersen, Murphy, & Hohmann, 2007; Schmitz & Shultz, 2013). Results in these studies showed that female subjects with higher sex hormones had decreased joint stiffness during loading. Schmitz and Shultz (Schmitz & Shultz, 2013) suggested that relatively diminished mechanical stiffness may alter articular mechanoreceptors sensitivity during functional activity, thereby predisposing females' ACL to more vulnerable position than those in males. Our decreased mechanical stiffness in the ACLR group compared to the healthy control group may indicate that ACL mechanoreceptors following an ACL injury, respond differently to external loading. As the ACL conveys significant sensory information related to

changes in joint position, movement, and force at the knee to the CNS via afferent nerve tracts(C. Buz Swanik et al., 1997), these sensory inputs must be precisely processed and integrated at higher cortical areas. Furthermore, damage to joint structures may alter not only sensory afferent traffic to the CNS (deafferentation), but also sensibility of neurons' excitation and inhibition in the somatosensory cortex and other brain regions (Kapreli et al., 2009; Ward et al., 2015). Therefore, the differences in mechanical stiffness observed in our subjects may also alter critical proprioception information necessary for the brain to negotiate joint loading and protective dynamic restraint mechanisms necessary for maintaining functional stability(Rozzi et al., 1999; C. Buz Swanik et al., 1997). The investigation of somatosensory cortex activity in response to joint loading in the present study may provide neurophysiological evidence underlying neural adaptation (neuroplasticity) following an ACL injury.

Cortical Activation

Our electrocortical activation data, as measured through electroencephalograph (EEG), show increased event-related desynchronization (ERD) in the upper alpha frequency band (α-2; 10-12Hz) at CP4 and CP3 electrodes during joint loading to the left and right knee respectively, when compared to the baseline cortical responses during non-joint loading phase. EEG studies have suggested the suppressed electrocortical activity in the α-2 frequency band power is associated with increased cerebral cortex areas, particularly somatosensory and motor cortices related to the neuromuscular control(Martínez-Jauand et al., 2012; Needle et al., 2014; Pineda, 2005). Furthermore, the CP4 and CP3 electrodes reflect the right and left somatosensory cortex regions, respectively. Needle et al.(Needle et al., 2014) investigated cortical activation during ankle joint loading and demonstrated that event-

related desynchronization (ERD) in the upper alpha frequency at the somatosensory cortex increased as joint was loaded. Our findings of increased ERD data during joint loading are consistent with those of Needle et al.(Needle et al., 2014). The somatosensory cortex in the brain is known to perceive sensory inputs from the lower extremities. Therefore, the increased ERD with respect to joint loading may be an indication of the brain's heightened activity to process and integrate what proprioceptive information there is being transmitted from the injured knee, and then to project the encompassed proprioception to adjacent motor cortex for further muscle coordination(Sedda & Scarpina, 2012; Ward et al., 2015). This is the first study to identify instantaneous changes in cortical activity as a result of joint loading, and that activity is different in ACL injured patients despite surgical reconstruction.

One of the important findings in this study is that different cortical responses existed between groups, as well as within groups, regardless of mechanical laxity differences during joint loading. These findings were not consistent with the previous results at the ankle. Needle et al. (Needle et al., 2014) found that no somatosensory cortex response differences, but mechanical deficits existed between healthy controls and unstable ankles during joint loading. It was suggested that the different responses between cortical activation and joint laxity reflect the existence of the advanced neural adaptation, as a small amount of cortical activation may identify greater magnitude of joint laxity in the unstable ankles. Conversely, our results revealed that the ACLR group had increased cortical activity (ERD1) in the reconstructed limb during early loading, when compared to the non-involved limb and the matched limb in the healthy controls. No early joint laxity (LAX1) differences existed between groups and within each subset. Furthermore, greater somatosensory cortex activity (ERD3), but no

interlimb ERD differences, were observed in the ACLR group during late joint loading, compared to both the healthy controls and ACLD patients, while all ACL patients' involved limbs' joint laxity were greater than healthy controls' matched limb. These findings may imply that ACL patients have different neural adaptation strategies to neuromechanical re-coupling following an ACL injury. ACLR patients might have the increased somatosensory cortex capacity to compensate for the altered peripheral inputs from the joint, whereas ACLD patients might need to have more efficient neural processing schemes (Needle et al., 2014; Pfurtscheller, Lopes da Silva, & Lopes, 1999).

Our cortical activation results in the ACLR group also support previous EEG studies that investigated cortical responses during proprioception tasks(J Baumeister et al., 2008; Jochen Baumeister, Reinecke, Schubert, & Weiss, 2011). These studies showed ACLR patients had not only increased cortical activation, reflecting enhanced neuromechanical re-coupling strategies in the somatosensory cortex, but also higher executive-function related frontal cortex activation, while actively detecting joint position or reproducing targeted force. The fronto-parietal network is considered to be responsible for cognitive processing of goal-directed decision making related to neuromuscular control(J. Baumeister, 2013), but these results were not able to implicate the evidence of neuromechanical re-coupling between the CNS and articular mechanoreceptors within the ACL. However, our results may explain why ACLR patients display increased cortical activation in both the frontal and somatosensory cortices. As the somatosensory cortex project neural signals related to proprioception to the frontal area(J. Baumeister, 2013), the enhanced fronto-parietal network may be a protective compensatory neural adaptation to provide sufficient regulation of

dynamic restraints necessary for maintaining functional joint stability. Thus, our data suggest that an ACL rupture causes the CNS reorganization responsible for perceiving significance of sensory afferent inputs from the damaged ACL, and such neural adaptation may be not only the enhanced neuromechanical re-coupling strategies, but also the evidence of increased cognitive action-planning processing with respect to proprioception(Jochen Baumeister et al., 2011).

Correlations between Joint Laxity and Cortical Activation

Our ACL patients showed dissimilar cortical activation patterns compared to healthy controls. These laxity-cortex correlations could provide further insights into mechanisms underlying different neural adaptation strategies in the somatosensory cortex associated with perceiving proprioceptive inputs from the knee joint. Our data revealed that higher mid-cortical activity in the involved knee of ACLR patients was correlated with higher early, mid, anterior and total joint laxity. These correlations may suggest that increased neural demands in the somatosensory cortex are compliant with greater joint laxity, which is the compensatory protective neuroplasticity for the increased joint laxity during early loading(Pineda, 2005). Therefore, other cortex areas could facilitate sensory processing of somatic afferent information in order to appropriately regulate motor planning and optimize muscle contractions surrounding the knee joint(Charles Buz Swanik, 2015). This possible protective cortical reorganization was also observed between the early joint laxity and late cortical activity in the healthy matched limb in the control group, as well as in the ACLD patients, of whose deficient limbs' early laxity positively correlated with mid and late cortical activity.

Conversely, ACLR patients showed negative correlations between joint laxity and cortical activation in the healthy limb during mid phase of joint loading, as well as between total anterior laxity and early somatosensory cortex activity. For instance, if a patient had greater joint laxity, less cortical activation was observed. This may imply that better efficient neural adaptation associated with sensory perception in the healthy limb exists in the CNS(Needle et al., 2014). As the reconstructed knee demands higher somatosensory cortex activity with respect to greater mechanical laxity(Martínez-Jauand et al., 2012; Pineda, 2005), the inverse association in the healthy limbs may be compensatory neuroplasticity. After injury, therefore, the brain have increased neural sensitivity associated with the non-injured limb, as reflected by EEG. This facilitated neural sensitivity in the somatosensory cortex may allow precise detection of changes in joint position and loading. However, this reciprocal neural adaptation between sides was not observed in the ACLD patients, which may indicate existence of different sensory perception strategies between ACLD and ACLR patients(Kapreli & Athanasopoulos, 2006; Kapreli et al., 2009) Overall, laxity-cortex correlations in the present study suggest that different neuromechanical coupling strategies exist between ACLR and ACLD patients, therefore, the brain's function in perceiving sensory inputs with respect to joint loading must be considered when determining the proprioception following an ACL rupture.

Knee Function and Fear of Re-Injury/Movement, and its correlation with cortical activation

Several studies have suggested that ACL patients with long-term disabilities tend to have poor knee function outcomes, as well as higher subjective fear perception to re-injury or pre-injury level of physical activities(Clare L Ardern, Taylor, Feller, &

Webster, 2014; Fitzgerald et al., 2000a; Moksnes et al., 2008). These studies demonstrated that higher fear of re-injury could be either a symptom or risk factor associated with persistent functional joint instability. Our data showed that ACLD patients displayed no differences in knee function assessment outcomes compared to the control group and less fear of re-injury/movement. This may support previous studies as ACLD patients with significantly less fear perception had no differences in single-legged hop performance(Chmielewski et al., 2008; Hartigan et al., 2013). Although our ACLR patients had lower functional performance in the reconstructed limb for the single legged-hop for distance, they had similar fear perception and self-reported knee function outcomes to the control group, which is inconsistent with previous studies. However, both ACLR and control groups had higher kinesiophobia scores than the ACLD group, and it may be either an inherent personality trait or a result of the ACL rupture. It is possible that a disruption to muscle coordination in ACLR patients with altered sensorimotor system may occur, while healthy controls can overcome negative emotional influence on neural processing related to neuromuscular control(Charles Buz Swanik, 2015).

Although research has suggested psychological factors may contribute to functional joint instability following a ligamentous injury in the knee(C. L. Ardern et al., 2014), no studies have investigated the relationship between individual sensitivity to fear of re-injury and cortical activation yet. This is the first study to examine the correlation between kinesiophobia and cortical responses between ACL patients and healthy controls. Fear-cortex correlations in the present study revealed that less fear of re-injury in the ACLR patients was associated with greater interlimb cortical activation differences during early joint loading. This greater reciprocal neural

adaptation in the somatosensory cortex may serve as the advanced neuromechanical re-coupling strategy to appropriately perceive knee loading and maintain neuromuscular control. As a result, the improved ACLR individual's knee function may result in decreased fear of re-injury/movement.

Limitations

Although the present study suggests different neuroplasticity strategies may exist in ACLR and ACLD patients following ACL injury compared to healthy controls, there are several limitations. An equal number of ACLR and healthy control subjects were recruited and matched for gender and testing limbs to minimize covariate effects, but few ACLD subjects fulfilled the inclusion criteria prior to surgical intervention. Due to small sample size of the ACLD group, there were greater variations in dependent variables' outcomes within the subset. Furthermore, research has suggested that up to 50% of ACL patients develop long-term pathological complications, not only to the ipsilateral, but also to the contralateral limb within 10 years(Hootman & Albohm, 2012; Hurd et al., 2008; Lohmander et al., 2007; Paterno et al., 2012) Although all ACL patients had a history of ACL injury or a surgical repair within 10 years, we were not able to observe how the CNS has been reorganized since the initial injury or reconstruction, or whether the existing neural adaptation would lead to development of functional deficits. Thus, future research with longitudinal prospective cohort studies may be needed to establish the link between neuromechanical decoupling, neuroplasticity, and neuromuscular control among ACL copers and noncopers as well as healthy controls.

Conclusions

This is the first study that observed instantaneous cortical activity changes in the brain with respect to joint loading at the knee. Although the ACLD group showed significantly lower subjective fear of re-injury/movement than other groups, ACL patients (ACLR and ACLD) in the present study appear to have no clinical joint laxity differences or knee functional deficits when compared to healthy controls. However, greater cortical activation exists as the knee is loaded in the reconstructed limb when compared to the opposite, healthy knee or the control's matched limb. Furthermore, ACL patients have different sensory perception strategies in response to their mechanical laxity between limbs. While the reconstructed limb in the ACLR group showed positive correlations between cortical activation and joint laxity, the opposite limb in this population exhibited the inverse correlation. The ACLD patients' deficient knees also showed positive correlation between somatosensory cortex activation and joint laxity, whereas their healthy knees showed no correlation. Additionally, ACLR patients with less fear, tend to have greater cortical activation in the reconstructed limb compared to the healthy limb during joint loading. These findings indicate that knee injuries may change the brain's neural networks responsible for perceiving sensory inputs. The increased somatosensory cortex activity corresponding to joint loading may be evidence of enhanced neuromechanical coupling strategies between altered mechanoreceptor function in the knee and the CNS. This neuroplasticity may be critical to optimize neuromuscular control and patients knee function outcomes following ACL rupture.

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Chapter 3

NEGATIVE EMOTION ALTERS JOINT STIFFNESS REGULATION STRATEGIES

Introduction

Following an anterior cruciate ligament (ACL) injury, surgical repair has been considered the gold standard treatment, which may allow not only for restoration of mechanical stability and proprioception, but also improvement of neuromuscular control (NMC) and knee function (Denti, Monteleone, Berardi, & Panni, 1994; Georgoulis et al., 2001; B. I. Lee et al., 2009; Ochi, Uchio, Adachi, & Sumen, 1999; Shimizu et al., 1999). However, approximately 35% of ACL reconstruction (ACLR) patients suffer persistent functional knee instability, which is defined as recurring experiences of knee giving-way, with varied clinical knee functional outcomes (Clare L Ardern, Webster, Taylor, & Feller, 2011). These persistent symptoms can lead to a secondary ipsilateral or contralateral ACL rupture and untimely knee osteoarthritis (Hootman & Albohm, 2012; Pinczewski et al., 2007). Many researchers have suggested that altered neural networks related to muscle coordination may contribute to neuromuscular deficits and subsequent functional joint instability after ACL injury(Ageberg, Björkman, Rosén, Lundborg, & Roos, 2009; Kapreli et al., 2009; Charles Buz Swanik, 2015; Ward et al., 2015). Furthermore, several psychological factors, such as higher fear of movement to re-tear the injured-ACL, are thought to be greatly associated with diminished knee function and a failure in returning to pre-injury level of physical activity.(Clare L Ardern, Taylor, Feller, Whitehead, &

Webster, 2013; Ross, 2010; Charles Buz Swanik, 2015). In fact, it is known that the anterior cingulate cortex (ACC) and prefrontal cortex are responsible for executive-function skills, including the preparation of voluntary movements and emotional regulation(LeDoux & Damasio, 2013; Paus, 2001). This may suggest that emotion and muscle coordination are linked, however, it remains unclear how negative emotional stimuli may alter critical neural processing in the brain, which may predispose ACLR patients to experience persistent functional joint instability.

As many as 80% of ACL tears are non-contact injuries that result from failures in muscle coordination during unanticipated events(Bollen, 2000). Appropriate neuromuscular control is critical to provide muscle stiffness regulation and prevent an sudden episodes of the joint "giving way"(Johansson, 1991; Klous, Mikulic, & Latash, 2011; C. Buz Swanik, Lephart, Giannantonio, & Fu, 1997). In order to optimize neuromuscular control, the CNS must be able to simultaneously and precisely prepare for and react to a sudden events. These preparatory feed-forward and reactive feedback mechanisms for the dynamic restraint system can contribute to functional joint stability by optimizing muscle stiffness strategies during high velocity physical maneuvers(C. Buz Swanik et al., 1997; Wolpert, Pearson, & Ghez, 2013). The regulation of muscles' excitation and inhibition through both feed-forward and feedback dynamic mechanisms are highly associated with cognitive processing in the brain, related to previous and present proprioceptive information, which may be altered following an ACL rupture(Riemann & Lephart, 2002b; Santello, McDonagh, & Challis, 2001; Charles Buz Swanik, Lephart, Swanik, Stone, & Fu, 2004). Therefore, advanced neural processing in the brain may be necessary to provide appropriate muscle coordination needed for maintaining functional knee

stability(Grooms, Appelbaum, & Onate, 2015; Charles Buz Swanik, 2015; Ward et al., 2015). Thus, any factors that limit cognitive processing related to sensory integration, judgment of external stimuli or muscle coordination may lead to compromised joint stiffness regulation strategies, contributing to functional joint instability(Charles Buz Swanik, Covassin, Stearne, & Schatz, 2007; Charles Buz Swanik et al., 2004).

Recent epidemiologic research has suggested that negative emotions, particularly fear of re-injury, may have a profound impact on predicting functional joint stability, as well as determining return to pre-injury levels of physical activity following ACL injury(Clare L Ardern, Taylor, Feller, & Webster, 2013; Gobbi, Bathan, & Boldrini, 2009; D. Y. H. Lee, Karim, & Chang, 2008). Anterior cruciate ligament injured patients who complain of repeated episodes of "giving way," with poor knee function, have reported greater fear of re-injury/movement compared to those that were able to cope with pre-injury levels of physical activity(C. L. Ardern et al., 2014; Clare L Ardern, Taylor, Feller, Whitehead, et al., 2013; Kvist, Ek, Sporrstedt, & Good, 2005). Visual fear-evoking stimuli can increase cortical activation in several frontal regions in the brain as a part of fear regulation(LeDoux & Damasio, 2013; Paus, 2001). Cognitive processing in these frontal regions are also highly linked to other brain areas responsible for maintaining sensorimotor system(D.G. Amaral, 2013; David G. Amaral & Strick, 2013). EEG research has shown that ACLR patients have higher theta power in the frontal cortex during knee proprioceptive tasks, indicating that increased attentional resources are needed to compensate for the loss of joint sensation following ACL rupture(J Baumeister, Reinecke, & Weiss, 2008; Jochen Baumeister, Reinecke, Schubert, & Weiss, 2011). Moreover, acoustic stimuli, which are commonly used as probes to simulate unanticipated events in a controlled

research setting, can cause a universal startle response, such that increased errors in situational awareness result in altered preparatory and reactive muscle stiffness strategies(DeAngelis et al., 2014). This implies that various sensory and emotional factors can interrupt cognitive processing, and thus interfere with the neuromuscular control needed to maintain coordination and functional joint stability(Chmielewski et al., 2008; Lentz et al., 2015). In fact, diminished muscle activation patterns and functional performances have shown direct correlations with long-term heightened fear of re-injury/movement in patients with ACL rupture(Flanigan, Everhart, Pedroza, Smith, & Kaeding, 2013; Hartigan, Lynch, Logerstedt, Chmielewski, & Snyder-Mackler, 2013; Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995).

Since fear is a potent cognitive and emotional response to a perceived threat or noxious stimuli, emotion regulatory neural circuits in the brain demand greater cognitive processing to manage increased attentional resources(Campbell & Ehlert, 2012). Prolonged fear responses provoke greater cortex activity in frontal areas, such that higher executive functions (EF) can provide cognitive regulation of negative emotions needed for heightened caution and vigilance(Campbell & Ehlert, 2012; Chen, Katdare, & Lucas, 2006; Goldin, McRae, Ramel, & Gross, 2008; Gyurak, Gross, & Etkin, 2011; Ohman, 2005). Therefore, increased neuronal processing demands in the frontal areas of the brain, due to higher fear of re-injury/movement during physical activity following ACL injury, may disrupt neurocognitive strategies necessary for the very motor coordination needed to maintain knee stiffness and stability. (C. Buz Swanik et al., 1997; Charles Buz Swanik et al., 2007, 2004). Coordination is necessary for maintaining functional joint stability by optimizing muscle stiffness regulation surrounding the knee; however, no data exists exploring

how fear, after ACL injury, alters brain activity related to cognitive processing or muscle stiffness regulation strategies,. As higher fear of re-injury/movement can interrupt goal directed decision making cognitive processing related to muscle coordination, we hypothesized that increased frontoparietal cortex activation in theta frequency band (4-8 Hz) and greater alteration in joint stiffness regulation strategies in response to general fearful and/or sport knee-injury related pictures may be observed when compared to the neutral emotional stimuli. Therefore, the aim of the present study was to compare how cortical activation and joint stiffness regulation strategies may differ in response to general and/or specific situation-related fearful visual stimuli between ACLR patients and healthy controls.

Methods

Experimental Design

This study utilized a case control design with a healthy control group used for comparison. The independent variables included group (ACLR patients, healthy controls), emotional picture category (neutral, fear-related, injury-related), and condition (acoustic startle, non-acoustic startle). The dependent variables included knee functional outcomes, fear of re-injury/movement scores, electroencephalography (EEG) event-related power (log μV^2, %) compared to the resting condition in the Theta (4-8Hz) frequency band, neurophysiological emotion response (HR, change in bpm), the Self-Assessment Manikin (SAM), self-reported level of fear (a 9-point Likert scale), normalized knee stiffness (Nm/°/kg), and electromyography (EMG) muscle activity (timing [sec] and amplitude).

Participants

Forty volunteers (20 ACLR patients, 20 healthy controls) between the ages of 18-45 years old were recruited (Table 7). ACLR patients had one or more unilateral ACL ruptures with reconstruction and cleared to return to participate in pre-injury level of physical activities. Healthy controls were physical active with no history of an ACL rupture. Participants were excluded if they had a history of lower extremity fracture or surgery for 6 months or a medical condition that can interfere with ECG and EEG data acquisition, such as metal implants in the head, face or chest, or neurological problems. Additionally, participants were excluded if they had a history of hearing impairment due to use of an acoustic-startle stiffness condition. Institutional approved informed consent form was provided prior to a single testing session.

Instrumentations

Knee functional outcomes were assessed using a battery of self-reported surveys, including the Knee Outcome Survey-Activities of Daily Living (KOS-ADL), the global rating of knee function, and number of giving way episodes since a reconstruction, as well as the single-legged hop for distance test on both knees(Collins, Misra, Felson, Crossley, & Roos, 2011; Herrington & Fowler, 2006; Moksnes, Snyder-Mackler, & Risberg, 2008) (Appendix C). Subjective perception to fear of re-injury/movement was assessed using an 11-items of shorted version of the Tampa Scale for Kinesiophobia (TSK-11)(Clare L Ardern, Taylor, Feller, Whitehead, et al., 2013; Woby, Roach, Urmston, & Watson, 2005) (Appendix C).

In order to induce targeted neutral and fearful emotions, sixty-two neutral and 60 fear-related pictures were preselected from the International Affective Picture System (IAPS) (Appendix D), which was developed to provoke a variety of emotions regarding judgments on two major dimensions of the Self-Assessment Manikin

(SAM): affective valence and arousal(P. J. Lang, Bradley, & Cuthbert, 2008) (Figure 11). The neutral pictures, which consist of neutral objects such as plants, office supplies, or neutral human images, were chosen from the range of valence (4.03-5.20) and arousal (1.72-3.46), while the fear-related pictures such as severely injured animals or humans, attacks by animals, threaten images of other people, or accident-related pictures, were chosen from the range of valence values (1.31-4.32) and arousal (5.9-7.15). These valence and arousal ranges for both neutral and fear-related pictures were based on standard protocols that have been used in scientific literature(Barke, Baudewig, Schmidt-Samoa, Dechent, & Kröner-Herwig, 2012; Barke, Stahl, & Kröner-Herwig, 2012). Additionally, 60 knee injury-related pictures searched from online were added to determine the effects on neurophysiological responses, SAM scores, level of fear, brain activity, and joint stiffness regulation strategies compared to the selected pictures from IAPS (Figure 11) (Appendix D). The knee injury-related pictures included if pictures were sports-related, and contained either noncontact or contact mechanisms of ACL injuries such as pivoting or twisting movements. The criteria of sport selection was categorized into 9 types according to the ACL incident rate: basketball, cycling, football, gymnastic, handball, soccer, ski, tennis, and wresting(Prodromos, Han, Rogowski, Joyce, & Shi, 2007). A picture was excluded if a resolution of the picture was lower than 1024 X 768 pixels. Six presentation blocks were constructed and equally distributed such that each block had randomly distributed condition of 10-picture for each neutral and fear-related regarding type and the ranges of the valence and arousal domains in addition to 10 knee injury-related pictures.

Emotion responses were evaluated through measure of heart rate, cortical activation, and the SAM as well as level of fear using 9-point Likert scales. A custom-build single channel surface electrocardiography (ECG) was utilized in the analysis of heart rate differences between rest and picture presentation periods for determination of the neurophysiological fear response. Cortical activation related to each targeted emotion response was measured using a 32-channel EEG in compliance with the international 10:20 system. Average of mastoid processes [(A1+A2)/2] was used for an average reference signal while an electrode at the mid-forehead was measured for a ground signal(Nunez & Srinivasan, 2006) EEG data confirmed with a sufficient signal-to-noise ratio (<5kΩ) was recorded at 1024 Hz using a NuAmps amplifier system (Compumedics Neuroscan, Charlotte, NC). Digital triggers from a custom IAPS LabVIEW program (National Instruments, Austin, TX) was sent to Scan4.5 software (Compumedics Neuroscan, Charlotte, NC) to appropriately synchronize both picture onset and heart rate data with brain activation. Subjective fear perception was evaluated using the SAM, which consists of a 9-point rating scale, represents 1 as a low rating and 9 as a high rating on each valence and arousal dimension. The valence dimension is a ranging from 1 = vary unhappy to 9 = very happy, whereas the arousal dimension ranges from 1 = vary calm to 9 = very aroused. Additionally, a participant's level of fear to each emotionally evocative picture was evaluated by using a 9-point Likert scale ranging from 1 = not at all fearful to 9 = very fearful (Figure 12).

Joint stiffness and muscle contraction were measured using a custom-built Stiffness and Proprioception Assessment Device (SPAD), which is a modified isokinetic dynamometer (Figure 13). A servomotor that is fit into a gear box attached to an adaptor arm and adjustable chair can control a rapid and specific range of motion

through a custom LABVIEW SPAD control program. Analog torque values from a torque reaction sensor (Model #T5400, Futek Advanced Sensor Technology, Irvine, CA) and position changes were synchronized with electromyography data and stored in a custom LABVIEW SPAD collection program. The real-time of surface electromyography (EMG) was recorded from the vastus medialis (VM), vastus lateralis (VL), medial hamstrings (MH), and lateral hamstrings (LH) in addition to the orbicularis oculi (OM) to visually confirm a startle response (TrignoTM Wireless System 8138A-DST01, Delsys Inc., Boston, MA, USA). Electrode placement followed standard site identification and preparation protocols(Chittaro & Sioni, 2013; Heller, Greischar, Honor, Anderle, & Davidson, 2011; Rainoldi, Melchiorri, & Caruso, 2004).

Procedures

Each participant reported to the laboratory for a single testing session. After reviewing and signing the informed consent form approved by the University's Institutional Review Board, demographic and Physical Activity Readiness Questionnaires were completed to review any past or current health conditions that would exclude participants from this study. The Knee Functional Assessment and self-report of the TSK-11 were also completed (Appendix C).

Participants then worn the QuikCap™ and sit on a chair while a conductive electrolyte solution was inserted into each electrode of the EEG cap. Following confirmation of a sufficient signal-to-noise ratio (<5kΩ) with an impedance test, Ag/ACI bipolar self-adhesive ECG electrodes were attached to both sides of shoulders with hip as a reference location for the recording HR. A total of 3 testing blocks were performed to collect and record continuous brain activity in Scan 4.5 Software

(Compumedics Neuroscan, Charlotte, NC) at 1024Hz/32 bit. Each testing block was composed of randomly ordered 30 trials and each trial included a 6-sec black screen prior to picture onset (baseline), a 6-sec picture presentation, a 3-sec black screen (post baseline), and 12-sec emotional rating interval in which the picture was not displayed (Figure 14). Participants rated valence, arousal, and level of fear regarding the selected picture, which was presented on a minimum size of 17-inch LCD monitor (38 X 21 cm), approximately 100 cm from the participants(Marchewka, Zurawski, Jednoróg, & Grabowska, 2014; Smith, Bradley, & Lang, 2005). Participants had practice trials with two neutral pictures prior to the first testing block. Baseline brain activity was measured for 1-min eyes open and eyes closed prior to the first testing block as after last testing block. Continuous heart rate (HR) was collected during baseline, a picture presentation, and post baseline and synchronized with EEG data via a custom LABVIEW program while emotional rating scores were separately reported for each trial. Participants were asked to keep eyes open, but blinking comfortably, and look at the screen during testing. Participants were monitored and encouraged to minimize body or facial muscle movements to limit impedance and artifacts. The order of presentation between blocks were counterbalanced using *Latin Square* and pictures within each block were randomized across participants.

After measures of emotional responses were completed, the EEG cap and HR sensors were disconnected from participants and then EMG sensors were attached to the selected muscles to measure joint stiffness and muscle activity (VM: Vastus Medialis, VL: Vastus Lateralis, MH: semimembranosus/semitendinosus, LH: biceps femoris, OM: orbicularis oculi). Participants then seated on the SPAD with the trunk and thigh secured, the back supported, and the hip in 90 degrees of flexion. The axis of

rotation of the adaptor arm attached to the servomotor was aligned with the lateral joint line of the reconstructed knee for ACLR patients and the matching limb for controls. A pad projecting from the adaptor arm was used to apply pressure over the distal lower limb to stabilize the segment, while another pad projected off of the chair to stabilize the upper limb, applying pressure to the thigh. A vacuum splint was also placed over the distal two-thirds of the leg and ankle to mechanically secure the limb and adapter arm, and to minimizing the absorption of loads by soft tissues from the leg (Figure 15). The weight of the limb was measured in the relaxed state with the knee flexed to 30 degrees to correct for gravity. A measure of maximum voluntary isometric contraction (MVIC) was used to assess quadriceps and hamstrings strength. Participants were instructed to "Kick out," and produce maximal effort, by verbal encouragement, for a period of 10 seconds. Strength testing was repeated for three trials, which was averaged to achieve a maximal activation value. One picture presentation block, which was not utilized during the measures of cortical activity, and a perturbation was then applied to stiffness trials for assessment of overall knee stiffness and muscle activity. The perturbation consisted of a 1000°/s^2 acceleration to a velocity of 100°/s through a 40° flexion arc, and stiffness trials included two conditions: a control trial and an acoustic startle trial. The control trial has a picture presentation for 800ms prior to the perturbation, whereas the acoustic startle trial was used with a startle noise >100dB for a 10ms period supplied through headphones, and occurred 100ms before the perturbation via the customized LABVIEW program. One additional wireless EMG sensor was placed over the superior portion of orbicularis oculi (OM), to assess the time of onset of the acoustic startle response (ASR) and the headphones was provided during the entire testing that supplied the elicitation of the

acoustic startle stimulus, along with attenuating background noise. Participants were asked to remain completely relaxed and then respond with maximal effort to the perturbation during each stiffness trial. Participants had two control trials and one acoustic startle trial for each category of the selected block, while other pictures were displayed for a 6-sec without the perturbation. A minimum of 30-second rest periods were provided in between each of the trials and conditions to avoid fatigue. The order of stiffness trials and picture selections were randomized to provide variance in results and avoidance of a learning effect. However, participants were instructed that an acoustic startle or "loud sound" would happen randomly throughout testing.

Data Reduction

A percentage value for the KOS-ADL, global rating of knee function, and hip limb symmetry index (LSI) of the single legged hop for distance between the injured limb and non-injured limb in ACLR patients or between matched limbs in healthy controls was assessed for the Knee Functional Outcome Assessment outcomes. The number of experiences of "giving way" was reported for further analysis. Additionally, subjective fear of re-injury/movement (TKS-11) was calculated a percentage value to compare between healthy controls and ACLR patients.(Moksnes et al., 2008)

For the cerebral cortex fear responses, following ocular artifact reduction, only artifact-free EEG trials synchronized with picture onset and heart rate were cut into 4000ms epochs from 2000ms before to 2000ms after picture onset. Averaged event-related desynchronization/synchronization (ERD/ERS) in theta frequency band (4-8 Hz) at the first 1000ms of picture presentation (EEG, 0-1000ms from the picture presentation) compared to the baseline (BASE, -2000 to -1000ms prior to picture

onset) was calculated for selected electrodes of the frontal (F3, Fz, F3) and parietal (P3, Pz, P4) cortices. Positive values reflect decreased % of theta power (ERD), indicating less attention, while negative values represent increased % of theta power (ERS), indicating more mental effort (Figure 16).

For neurophysiological fear responses during emotionally evocative pictures, inter-beat R-wave intervals were detected to the nearest millisecond and 500-ms intervals were calculated for heart rate in beat per minute (bpm) according to a previous literature(Smith et al., 2005). The maximum heart rate deceleration (MHRD) was calculated as a heart rate difference between the minimum heart rate during the first 3-sec of picture presentation and the average heart ate of the 3-sec baseline (HRB, -3000 to 0ms prior to picture onset)(M. M. Bradley, Codispoti, Cuthbert, & Lang, 2001). The score of valence, arousal, and the level of fear to each picture were used for determination of the level of subjective fear perception of the picture(M. Bradley & Lang, 2006) (Figure 16).

For joint stiffness and muscle EMG activity, raw torque, position, and EMG signals were band-pass filtered at 20-400Hz, rectified and low-pass filtered at 5Hz. Stiffness values were calculated as the Δ Torque (Newton · meter) / Δ displacement (degrees) and normalized to body mass (Nm/°/kg). Normalized joint stiffness values were also corrected for gravity and calculated at the position of 0-4° (short-range), 0-20° (mid-range), and 0-40° (long range) during knee flexion perturbations. Normalized muscle activity to the maximum voluntary isometric contraction (MVICs) of the quadriceps and hamstrings were averaged over successful trials for each category (control, neutral, fear-related, and injury-related) and condition (non-startle and acoustic startle). Each muscle contraction pattern was analyzed for a time to peak

EMG (TTP, sec) and area under curve (AUC) for a window of 150ms prior to perturbation to 500ms following the perturbation as recommended by previous study(DeAngelis et al., 2014) (Figure 17).

Statistical Analysis

To determine group differences in the Knee Functional Outcome Assessment outcomes and subjective fear of re-injury/movement, separate independent sample *t*-tests were utilized. The effects of specific emotion type on subjective (valence, arousal, level of fear), neurophysiological (MHRD), and cortical (ERD/ERS) emotional responses were assessed by using separate 2-way repeated measures of ANOVAs with one within-subject factor (category, 3 levels) and one between-subject factor (group, 2 levels). Effects of emotion types on stiffness and muscle EMG activity between groups were assessed by conducting separate repeated measures of 2-way ANOVAs with one within-subject factor (type, 3 levels) and one between-subject factor (Group, 2 levels) for each stiffness condition. Additionally, effects of specific emotion type and condition on stiffness and muscle contraction were assessed using separate repeated measures of 2-way ANOVAs with two within-subject factors (category, 3 levels; condition, 2 levels) for each group. A probability alpha level was set a *priori* at 0.05.

Results

Knee Functions and Fear Perception

Table 8 presents group means and standard deviations for the knee function outcomes and kinesiophobia (TSK-11). Results showed that ACLR patients had significant poorer knee function outcomes with lower KOS-ADL ($t_{[38]} = 3.328$, p=0.004) and LSI ($t_{[38]} = 2.739$, p=0.009) as well as more episodes of number of

giving-way ($t_{[38]} = 3.328$, p=0.004), when compared to those in healthy controls (Figure 18). Although higher TSK-11 scores were observed in the ACLR group compared to the control group, it was not statistically significant ($t_{[38]} = -1.933$, p=0.061). There was no significant difference in GRKF between groups ($p > 0.05$).

Electrocortical Emotion Responses

Event-related desynchronization/synchronization (ERD/ERS) at the Theta frequency band (4-8 Hz) in both the frontal (F3, Fz, F4) and parietal (P3, Pz, P4) cortex areas during the first second of picture presentation between groups are presented in Table 9. Significant type main effects were found for the F3 ($F_{[2,76]} = 3.762$, p=0.028), Fz ($F_{[1.625,61.763]} = 3.470$, p=0.046), P3 ($F_{[1.674,63.622]} = 23.975$, p<0.001), Pz ($F_{[1.826,69.383]} = 24.043$, p<0.001), and the P4 ($F_{[1.532,58.228]} = 26.662$, p<0.001), although no significant type-by-group interaction effects were observed for any of the above frontal and parietal cortices. Pairwise comparisons revealed significantly greater theta ERS with fearful pictures than neutral for F3 (p=0.005), Fz (p=0.002), P3 (p=0.011), and Pz (p=0.024) (Figure 19). Specific knee injury-related pictures showed greater theta ERS than both the neutral and fearful pictures for P3 (p<0.001), Pz (p<0.001), and P4 (p<0.001) (Figure 19).

Neurophysiological Emotion Responses

Means and standard deviation for maximum heart rate deceleration (MHRD) during first 3-second between groups in response to each type of picture are displayed in Table 10. A significant type-by-group interaction effect was observed ($F_{[2,236]} = 3.236$, p=0.028). Post hoc comparisons showed that the control group had greater MHRD with fearful picture than neutral (p<0.001), while the ACLR group decreased

heart rate more with both the fearful (p<0.001) and injury-related (p<0.001) pictures compared to neutral pictures (Figure 20).

Self-reported Emotion Responses

The evaluation of valence, arousal and level of fear scores for each picture type is displayed for in Table 11. Significant type by group interaction effects were observed for the arousal dimension ($F_{[1.631,197.325]} = 4.991$, p=0.012) and level of fear ($F_{[1.732,209.590]} = 6.353$, p=0.003) (Figure 21). Post hoc pairwise comparisons revealed that ACLR group had significantly higher arousal (p=0.028) and level of fear (p=0.004) scores in response to injury-related pictures than of those in the control group. There were also significant type main effects for the valence ($F_{[1.846,223.341]} =$ 490.772, p<0.001), arousal ($F_{[1.631,197.325]} = 368.135$, p<0.001), and the level of fear ($F_{[1.732,209.590]} = 360.603$, p<0.001) components. Tukey's post hoc analysis showed neutral type of pictures resulted in higher valence scores than both the fearful and injury-related picture types (p<0.001). Injury-related pictures also revealed higher valence scores than fearful pictures (p<0.001). Conversely, both arousal dimension and level of fear showed significant differences among all emotion types (p<0.001) with fearful pictures producing the greatest score and neutral pictures producing the lowest score.

Joint Stiffness

Means and standard deviation for body mass normalized short-range (0-4°), mid-range (0-20°) and long-range (0-40°) stiffness values after each image type and stiffness condition between ACLR and control groups are displayed in Table 12. The ACLR group showed significant type by condition interaction effects for mid ($F_{[2,34]} =$ 6.659, p=0.004) and long ($F_{[2,34]} = 6.659$, p=0.004) range stiffness (Figure 22). Post hoc

pairwise comparisons revealed that fearful (p=0.024, p=0.014, respectively) and injury-related (p=0.017, p=0.031, respectively) pictures created significantly greater mid and long range stiffness values than neutral pictures, when an acoustic noise was delivered prior to the perturbation in the ACLR group, but no difference between fearful and injury-related pictures (p>0.05). However, the control group showed no interaction effects for mid or long range stiffness variables (p>0.05).

Our results also showed a main effect for condition with respect to normalized stiffness variables. While both groups displayed greater mid range stiffness values for all emotion types in response to startle condition than non-startle condition (CONT: $F_{[1,16]}$ = 43.874, p<0.001; ACLR: $F_{[1,17]}$ = 19.517, p<0.001) (Figure 22), only healthy controls showed increased stiffness for short ($F_{[1,15]}$ = 7.949, p=0.013) and long ($F_{[1,16]}$ = 12.576, p=0.003) ranges during the startle condition regardless of emotion types. Our data showed no group differences for all stiffness dependent variables for each emotion type or condition (p>0.05).

Muscle EMG Activation

Table 13 presents time to peak (TTP) EMG activation of the quadriceps and hamstrings between ACLR and control groups in response to neutral, fearful and injury-related pictures for each stiffness condition. A significant type by condition interaction effect for TTP for ACLR group was observed for VM only ($F_{[2,34]}$ = 6.659, p=0.004), and pairwise comparisons revealed ACLR patients had faster TTP EMG activation in response to injury-related picture during startle condition compared to non-startle condition (p=0.008), but no differences between conditions for either neutral or fearful pictures (p>0.05) (Figure 23). Our findings showed that healthy control subjects had significant condition main effects for lateral quadriceps ($F_{[1,11]}$ =

8.972, p=0.012) and both medial ($F_{[1,14]}$ = 16.123, p=0.001) and lateral ($F_{[1,12]}$ = 9.112, p=0.011) hamstrings muscles, although no significant main or interaction effects for or between type and group (p>0.05). Pairwise comparisons revealed that startle condition quickly produced peak EMG regardless of emotion types when compared to non-startle condition.

Quadriceps and hamstring EMG activity for the area under the curve (AUC) for 250ms prior to (PRE) and after (POST1) as well as between 250ms and 500ms after the perturbation (POST2) in response to each emotion type and condition between groups are displayed in Table 14. Significant main effects for group were observed for PRE of the lateral quadriceps (VL), and control subjects produced greater VL activity regardless of emotion types during both the startle ($F_{[1,26]}$ = 4.369, p=0.047) and non-startle ($F_{[1,35]}$ = 8.431, p=0.006) conditions when compared to ACLR patients (Figure 24). For POST1 EMG activity, the ACL group showed significant type by condition interaction effects for VM ($F_{[2,30]}$ = 6.945, p=0.003), VL ($F_{[2,24]}$ = 5.109, p=0.014), and MH ($F_{[2,32]}$ = 5.197, p=0.011). Post hoc pairwise comparisons revealed both fearful and injury-related pictures produced greater EMG activation than neutral pictures for VM (p=0.013, p=0.017, respectively), VL (p=0.009, p=0.045, respectively), and MH (p=0.031, p=0.044, respectively), when an acoustic startle was provided prior to the perturbation (Figure 25). However, the control group showed only a significant condition main effect for POST1 VM ($F_{[1,15]}$ = 18.871, p=0.041), VL ($F_{[1,15]}$ = 22.428, p<0.001), MH ($F_{[1,13]}$ = 13.404, p=0.003), and LH ($F_{[1,16]}$ = 31.983, p<0.001), and the startle condition produced greater EMG activity than non-startle condition, but no EMG activity differences among emotion types (p>0.05). Significant type by condition interaction effects were observed for

POST2 in the control group for VM ($F_{[2,34]} = 3.417, p=0.044$) and ACLR groups for LH ($F_{[2,32]} = 3.937, p=0.030$) (Figure 26). Post hoc analysis showed healthy controls had greater VM EMG activity in response to fearful pictures than neutral pictures ($p=0.017$) during the startle condition as well as when compared to non-startle condition ($p=0.049$). The ACLR group showed that startle condition produced greater POST2 LH EMG activity in response to fearful pictures than non-startle condition ($p=0.042$). Additionally, while the startle condition showed that fearful pictures induced greater LH EMG activity than neutral pictures ($p=0.028$), the non-startle condition revealed significantly lower POST2 LH muscle activity in response to fearful pictures than neutral pictures ($p=0.040$).

Discussion

The primary findings of this study were that the employed emotional stimuli provoked different electrocortical and neurophysiological activation and fear perceptions among neutral, fearful, and injury-related pictures. Furthermore, negative emotional pictures (fearful and/or knee injury-related pictures) altered joint stiffness and muscle EMG activity in both groups compared to neutral pictures, particularly when an unanticipated acoustic stimuli was delivered prior to 40-degree knee flexion perturbation. The effects of negative stimuli on joint stiffness regulation strategies were even greater in ACLR patients, who also showed lower knee function outcomes compared to healthy controls. This is the first study to provide a definitive evidence of neuromechanical coupling between emotions like fear, and muscle stiffness regulation strategies that are critical to dynamic restraint and functional joint stability. Results in the current study indicate that altered cognitive cortical processing resulting from negative emotion may further interfere with sudden, unanticipated events to modify

dynamic restraint mechanisms required to appropriately maintain functional joint stability.

Knee Functions and Fear Perception

Assessment of knee functional outcomes via subjective surveys or a battery of hop tasks in addition to fear of re-injury following ACL rupture have been used to predict whether ACLR patients are able to return to pre-injury level of physical activity or suffer persistent functional joint instability(Clare L Ardern, Taylor, Feller, & Webster, 2012; Grindem, Eitzen, Moksnes, Snyder-Mackler, & Risberg, 2012; Reid, Birmingham, Stratford, Alcock, & Giffin, 2007). Grindem et al.(Grindem et al., 2012) showed that ACLR copers who restored normal knee function have means (standard deviation) of 91.0 (7.7) % of KOS-ADL scores and 90.5 (14.0) % of the LSI for the single-legged hop for distance test. The ACLR patients in our study also showed no different KOS-ADL (Mean ± SD: 93.50 ± 8.41, %) and LSI scores (Mean ± SD: 94.08 ± 8.18, %) compared to the previous study. Furthermore, our ACLR patients did not have significantly different fear perception than healthy controls. These findings may suggest that ACLR patients in the present study were turned out to be fairly good to return to normal physical activities. However, our data revealed that ACLR patients had significantly lower knee function than the healthy controls, as well as a higher fear of re-injury than those of ACLR copers in previous research(Hartigan et al., 2013). This indicates that improved knee function and fear perception are still crucial factors in the prevention of a secondary ligamentous rupture, as it could limit a full return to sport activity levels(Clare L Ardern et al., 2012; Tripp, Stanish, Ebel-Lam, Brewer, & Birchard, 2007). Therefore, understanding emotional responses, particularly fear, and its effects on neuromuscular control may explain how negative

emotion predisposes some ACLR patients to have functional joint instability and a possible long-term disability such as re-tear of their either ipsilateral or contralateral ACL.

Emotion Responses: Subjective, Neurophysiological, and Electrocortical responses

The IAPS is one of most commonly used tools to induce a variety of emotional responses through the use of visual stimuli such as neutral, unpleasant or pleasant pictures(P. J. Lang et al., 2008). Different types of emotions, using the IAPS, have been evaluated by two subjective domains, valence and arousal(M. Bradley & Lang, 2006). Our results demonstrated that fearful and injury-related pictures resulted in lower valence (more sadness) and higher arousal values in addition to significantly increased fear than neutral type of pictures, with a greater impact on ACLR patients. These findings support previous research that individuals produce even greater negative aggressive feelings in response to not only fearful, but also specific traumatic knee injury-related pictures(P. Lang & Bradley, 2007).

Emotional stimuli, in general, alter cardiovascular reaction and cerebral cortical activation in the brain. These physiological and neurological responses are known to be a homeostatic emotion regulation occurring in the CNS(LeDoux & Damasio, 2013). Numerous studies that employed the IAPS have suggested that unpleasant pictures provoke greater, early heart rate deceleration and electrocortical activation in the frontal and parietal cortex areas when compared to neutral stimuli(Adenauer, Catani, Keil, Aichinger, & Neuner, 2010; Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2002; Balconi & Pozzoli, 2009; M. M. Bradley, Hamby, Löw, & Lang, 2007). The initially decreased heart rate is primarily associated with the parasympathetic nervous system, which quickly suppresses the targeted cardiac

outputs(Adenauer et al., 2010; Smith et al., 2005). This neurophysiological inhibition is concerned with early defensive behavior by promoting neural processing of aversive visual stimuli(M. M. Bradley et al., 2001). Fearful pictures in this study also caused greater heart rate deceleration than neutral pictures during early picture presentation and it support previous studies.

This neurophysiological emotional response is also associated with neural activation in both the subcortical and cortical areas, as the parasympathetic nervous system increases sensory input related to emotional cardiac responses to the brain(Carlsson et al., 2004; Ohman, 2005). The amygdala is the center of emotion regulation, by simultaneously interacting with other regions in the brain(LeDoux & Damasio, 2013; Ohman, 2005). Fearful stimuli can accelerate early activation in the amygdala and influence on prefrontal cortex areas. Neuroimaging studies have shown the neural connectivity between these areas in response to fearful pictures, and suggest that the early amygdala activation is an indication of quicker detection of negative stimuli, while the heightened prefrontal cortex activity implies increased cognitive processing required to sufficiently regulate fearful stimuli(Morris & Dolan, 2004; Williams et al., 2006). Our EEG data showed that fearful pictures increased theta frequency band power in the frontal and parietal regions during the first second of picture presentation when compared to neutral pictures. Injury-related pictures also increased theta power in the parietal cortex regions compared to neutral as well as fearful pictures. While the theta power in the frontal areas are known to be concerned with cognitive fear regulation processing, parietal theta activation is thought to be associated with situational awareness of visual cues(Morris & Dolan, 2004; Ohman, 2005; Olson & Colby, 2013; Williams et al., 2006). Moreover, sports knee injury-

related pictures induced greater heart rate deceleration and parietal theta power in the ACLR patients compared to general fear-related pictures. This population specific response to unpleasant visual scenes, related to previous traumatic experiences, could possibly exacerbate emotional responses, as vigorous negative stimulus can facilitate defensive behavior processing through the parasympathetic nervous system as well as cortical activation related to cognitive emotion regulatory management(Adenauer et al., 2010; Attias, Bleich, Furman, & Zinger, 1996; Schienle, Schäfer, Stark, & Vaitl, 2009; Wendt, Lotze, Weike, Hosten, & Hamm, 2008) These data imply that both general and specific situational fearful stimuli may elicit potent cortical activation in the frontal and parietal cortex areas, in addition to greater heart rate deceleration, which may be an indication of increased internal cognitive processing demands in the fear network(M. Bradley & Lang, 2006; Bryant et al., 2008). Because the frontal and parietal cortex areas are also crucial for cognitive processing related to task-specific muscle coordination(J. Baumeister, 2013; Horn & Swanson, 2013), certain visual cues, such as fearful pictures, simply disrupt a person's situational awareness because it grab his/her attention, which may occupy important cognitive resources or delay reactions to other critical events. Therefore, vigorous negative emotional stimuli during dynamic movements may disrupt normal cognitive motor planning processing needed for sufficient regulation of neuromuscular control in ACLR patients.

Fear and Joint Stiffness Regulation Strategies

An appropriate neuromuscular control strategy is critical to protect the knee during a rapid and intense physical activities, since passive joint structures alone may not be able to sufficiently maintain joint stability(Johansson, 1991; Klous et al., 2011; C. Buz Swanik et al., 1997). Furthermore, as non-contact mechanisms account for up

to 80% of all ACL injuries, failure to anticipate sudden perturbations or inadequate muscle coordination can lead to damage to the ACL(Bollen, 2000). Therefore, ACLR patients must be able to appropriately prepare for and react to an external loading by regulating muscle contractions surrounding the knee in order to absorb high forces and prevent excessive strain to the ACL(Riemann & Lephart, 2002b; C. Buz Swanik et al., 1997). These preparatory (feed-forward) and reactive (feedback) joint stiffness regulatory strategies are controlled by the CNS, as the brain simultaneously predicts oncoming loads and monitors afferent proprioceptive inputs to optimize the task-specific level of joint stiffness(Riemann & Lephart, 2002a; C. Buz Swanik et al., 1997; Wolpert et al., 2013). The measurement of joint stiffness regulation strategies, in response to a rapid joint loading, has been employed to neuromechanical coupling and observe how an altered dynamic restraint mechanisms may predispose individuals at a risk of peripheral ligamentous injury(DeAngelis et al., 2014; Charles Buz Swanik et al., 2004). Our previous research found a strong acoustic stimulus, which was delivered for a brief preparatory period prior to knee perturbations, alters joint stiffness and muscle contraction patterns(DeAngelis et al., 2014). As the startle condition was used to replicate an unanticipated event, which is the most common mechanism of non-contact ACL ruptures, this may imply that a sudden incident during high velocity of athletic maneuvers can diminish knee stiffness regulation strategies resulting from disturbing cognitive motor planning processing in several regions of the brain, which are also critical sites to mediate emotional responses(DeAngelis et al., 2014; LeDoux & Damasio, 2013; Paus, 2001). However, no research has investigated effects of negative emotion on knee stiffness regulation strategies.

Our results show that the startle condition increased mid- and long-range stiffness in both the ACLR patients and healthy controls, while short-range stiffness values were increased in healthy controls only, regardless of the type of emotional stimuli. Short-range stiffness is, in general, concerned with passive mechanical resistance, mainly provided by involuntary reversal of existing cross-bridges within muscle fibers in a brief period after the onset of loads. Long range stiffness is suggested as continuous voluntary eccentric contraction of the muscles, throughout a longer range of motion during knee perturbations(Sinkjaer, Toft, Andreassen, & Hornemann, 1988). As an increased internal tension to the ACL between nearly full extension and 45-degree of knee flexion can damage ligamentous tissues(Yu & Garrett, 2007), we also employed mid-range stiffness (from 30° to 50° of knee flexion), which may include not only passive contractile components but also reflexive and reactive muscular contractions(Mrachacz-Kersting & Sinkjaer, 2003; Sinkjaer et al., 1988). Our increased stiffness values, with respect to the acoustic startle, support findings from previous research that suggest an unanticipated event can disturb neuromuscular control, possibly due to the sudden attentional demand. This may compromise the cognitive processing associated with both feed-forward and feedback neural circuits in the brain(DeAngelis et al., 2014; Charles Buz Swanik, 2015).

The CNS can quickly detect negative stimuli that initiate early and strong, but prolonged cortical activation in the fear network between the prefrontal and parietal cortices(Liddell et al., 2005). Recent research suggested that an ACL rupture may cause neural adaptations in the CNS responsible for perceiving proprioceptive inputs as well as goal-directed motor behavior(J Baumeister et al., 2008; Jochen Baumeister et al., 2011; Kapreli & Athanasopoulos, 2006; Kapreli et al., 2009; Charles Buz

Swanik, 2015). This may indicate that the increased cerebral cortex activity, as a result of fearful stimulus, may limit available neural resources needed for optimal joint stiffness regulation strategies. Our data show that ACLR patients had increased mid- and long-range stiffness during an unanticipated startle condition in response to both fearful and injury-related pictures, with greatly increased cortical activation in the frontal and parietal cortices. Although both fearful and injury-related pictures also increased fronto-parietal cortical activation in the healthy controls, no significant stiffness differences were observed among three picture types. Because emotion-related pictures were presented 700 ms prior to the acoustic stimulus, our data may suggest that healthy controls were able to stiffen the knee joint regardless of picture types. However, the combined negative stimuli, and possibly reorganized sensorimotor system following an ACL injury, may exceed neural capability of goal-directed motor behavior in the ACLR patients. The increased neural demands produced by noxious visual cues may impair preparatory and reactive dynamic restraint mechanisms and ultimately lead to functional joint instability(Olson & Colby, 2013; Charles Buz Swanik, 2015). Moreover, muscle activity was observed to determine how alterations in stiffness may indicate biomechanical implications for ACL rupture(DeAngelis et al., 2014; Charles Buz Swanik et al., 2004).

Our data found that the acoustic startle quickly produced peak EMG activity for both quadriceps and hamstrings in the healthy controls regardless of emotional picture types, but ACLR patients only produced early quadriceps peak force in response to injury-related pictures. Furthermore, the control group was able to generate early quadriceps EMG activity prior to the perturbation compared to the ACLR group. Quadriceps and hamstrings EMG activation patterns before and after the

perturbation in response to unpleasant stimuli may explain further insights on why psychological factors have linked between ACLR patients and functional joint instability, leading to re-injury of their ACL. Specifically, the increased quadriceps EMG activation before the knee is forced to flexion motion following the startle can increase anterior shearing force to the ACL, leaving it vulnerable to excess strain(Chappell, Creighton, Giuliani, Yu, & Garrett, 2007; DeAngelis et al., 2014). However, healthy participants in the current study also increased preparatory hamstring co-contraction which may also prevent excessive anterior translation of the ACL as the knee is loaded(Hewett et al., 2005; Charles Buz Swanik et al., 2004). Therefore, both increased quadriceps and hamstrings preparatory muscle contraction, in concert with the increased short-range stiffness, may imply negative emotions actually enhanced feed-forward dynamic mechanisms in healthy controls, to prepare for the perturbation. Conversely, the unpleasant pictures appeared to delay initiation of the cognitive motor planning prior to the onset of the movement in ACLR patients because of prolonged emotional regulatory mental processing.

While the joint was being loaded, the startle increased early reactive quadriceps and hamstrings EMG activation in both groups, but greater hamstring effect on the ACLR patients with fearful and injury-related pictures. Furthermore, fearful pictures resulted in greater late reactive EMG activity for the medial quadriceps muscle (VM) in healthy controls during startle condition, but greater lateral hamstrings (LH) activation in the ACLR patients regardless of conditions. These unbalanced muscles activation patterns between the quadriceps and hamstrings has been suggested to be a risk factor for neuromuscular deficits, as well as ACL injury(Chappell et al., 2007; Hewett et al., 2005). Increased mid- and long-range

stiffness were observed in both groups in response to the startle condition, therefore an unanticipated event can disrupt normal reactive feedback muscle contraction as well, but negative emotional stimuli can cause even greater adverse effects on joint stiffness regulation strategies in ACLR patients. This may explain why some ACLR patients, with relatively greater fear of re-injury, fail to return to pre-injury level of physical activity and are susceptible to a secondary ligamentous rupture.

Limitations

In this study, we utilized the IAPS that commonly used in psychological literature in order to induce a variety of emotions, which are evaluated by using two subjective valence and arousal domains in addition to 9-point Likert scale, heart rate changes, and electrocortical responses as measured through EEG. While 60 pictures for each neutral and fearful category were included based on previous norm value ranges of valence and arousal domains, 60 sports knee injury-related pictures were chosen from online. Although our data show specific sports-injury pictures revealed significant negative effects compared to neutral pictures, they were not as strong as general fearful pictures. Furthermore, neurophysiological and electrocortical emotion responses were not directly accessed during joint stiffness regulation testing due to movement and wire artifacts, which could alter heart rate and EEG data. Future research may investigate real time measure of these emotional responses during measure of joint stiffness regulation testing. Additionally, the order of emotion types and stiffness condition were randomized in order to reduce practice effects, the picture presentation and acoustic startle were provided at 800 ms and 100 ms prior to the perturbation, respectively. This may allow participants to anticipate occurrences of

these events. Future studies may randomly provide a picture onset and timing of acoustic startle to minimize subject's anticipation.

Conclusions

Neuropsychological aspects may have a great impact on development of long-term knee functional disability and recurrent ACL sprains after an initial tear(Clare L Ardern, Taylor, Feller, Whitehead, et al., 2013). The brain's executive functioning is important to provide not only emotion regulation but also sufficient neuromuscular control in order to maintain functional joint stability. This study demonstrates that our ACLR patients have diminished knee functional outcomes and seem to have no different fear of re-injury/movement when compared to healthy controls, but greater than other ACLR patients who returned to normal in previous studies. However, our ACLR patients had a stronger adverse reaction than healthy controls in response to fearful and/or specific injury-related stimuli. These unpleasant contents showed more subjective fear responses than visually neutral contents and increased neurophysiological cardiac reaction (greater heart rate deceleration) and neural recruitments in the fronto-parietal cortices, which are crucial for the cognitive fear-regulation as well as muscle coordination. Furthermore, when a sudden event (i.e. acoustic startle) disrupts anticipation of joint loading, adverse visual stimuli may amplify the brain's difficulty with processing instantaneous environmental changes and cause neuromechanical de-coupling. This sequence of fear regulatory events could interfere with the goal-directed cognitive motor planning strategies, such that disrupted neurocognitive processing may be insufficient to prepare for and react to an unanticipated, high-velocity movement tasks. Therefore, the diminished knee stiffness regulation strategies would fail to maintain functional joint stability, thereby placing

the ACL in a vulnerable state. The adverse effects of fear on neuromuscular control may emphasize that psychological intervention must be incorporated with neuromuscular control exercise programs following ACL injury to minimize functional deficits and optimize patient outcomes.

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Chapter 4

EXECUTIVE FUNCTION TRAINING IMPROVES EMOTION AND JOINT STIFFNESS REGULATION STRATEGIES

Introduction

Anterior cruciate ligament (ACL) ruptures are the most common knee injury related to physical activity. Damage to the ACL can lead to neuromuscular control deficits, and longer periods of time loss with increased medical costs(J. Hootman, Dick, & Agel, 2007; J. M. Hootman & Albohm, 2012). During the rapid and sudden movements in physical activity, coordination failures in predicting knee loading and regulating optimal joint stiffness can predispose ACL patients to a secondary rupture(Charles Buz Swanik, Lephart, Swanik, Stone, & Fu, 2004). Several psychological factors, particularly fear of re-injury, have been suggested to be highly associated with diminished functional stability in ACL patients(Chmielewski et al., 2008; Lentz et al., 2015). The brain's executive-function skills are crucial to the simultaneous mediation of these negative feelings and muscle coordination(Gyurak, Goodkind, Kramer, Miller, & Levenson, 2013; Charles Buz Swanik, 2015). Furthermore, several components of the executive-function skills such as reaction time and working memory have been related to functional joint instability and injury proneness(Charles Buz Swanik, Covassin, Stearne, & Schatz, 2007), yet limited prospective research exists exploring whether executive function training can enhance emotion regulation and joint stiffness regulation strategies.

Many researchers have emphasized that the restoration of mechanical properties and proprioception of the knee joint is important to maintain functional joint stability in ACL population(Bryant, Newton, & Steele, 2009; Kuenze et al., 2015; Risberg, Holm, Myklebust, & Engebretsen, 2007). For this reason, a surgical ACL reconstruction (ACLR), in conjunction with a neuromuscular training program, is considered the gold standard of care. In fact, more than 200,000 US patients undergo ACLR annually following an ACL rupture, at an approximate cost of three billion dollars(Gobbi, Bathan, & Boldrini, 2009; Kaplan, 2011). Although neuromuscular training interventions have shown improved proprioception, muscle contraction patterns, and knee function in ACLR patients(Beard, Dodd, Trundle, & Simpson, 1994; Fitzgerald, Axe, & Snyder-Mackler, 2000; Hewett, Lindenfeld, Riccobene, & Noyes, 1999; Risberg et al., 2007; Risberg & Holm, 2009), the incidence of ACL injury has increased annually by 1.3%, while other musculoskeletal injuries have observed a decline(J. Hootman et al., 2007). Moreover, up to 50% of ACL patients experience a secondary rupture to either the ipsilateral or contralateral knee, and persistent knee dysfunction often leads to the development of early knee osteoarthritis within 10 years following the injury(Ageberg, Thomeé, Neeter, Silbernagel, & Roos, 2008; Dhillon, Bali, & Prabhakar, 2011; J. M. Hootman & Albohm, 2012). Based on this information, it can be concluded that barriers still exist within ACL injury rehabilitation programs that may prevent optimal patient outcomes. Additional prospective data is needed to compliment current prevention and rehabilitation strategies to foster improved patient function.

Growing evidence demonstrates that psychological factors such as fear of re-injury/movement, confidence, self-efficacy, locus of control, and self-esteem level are

highly associated with knee function and success rates of return to pre-injury level of physical activity(Christino, Fleming, Machan, & Shalvoy, 2016; Gobbi & Francisco, 2006). As negative emotions may alter existing neural action-planning networks in the CNS(Hofmann, 2008), advanced cognitive management strategies may be needed to maintain appropriate motor control and protect joint, when a sudden unanticipated event occurs(Gyurak et al., 2009; Charles Buz Swanik et al., 2007). It has been well documented that executive-function skills play an important role in maintaining muscle coordination, by monitoring environmental cues and simultaneously modulating the planning of movement(Consiglio, Driscoll, Witte, & Berg, 2003; Lamm, Windischberger, Moser, & Bauer, 2007; Moser, Schatz, & Jordan, 2005). One prospective study by Swanik et al.(Charles Buz Swanik et al., 2007) found that a group of collegiate athletes who had lower performance on neurocognitive tests, including slower processing speed and reaction, and poorer memory and visual-spatial abilities, also went on to suffer noncontact ACL sprains. These executive-function deficits are also correlated with defensive avoidance and hyperarousal behaviors(Mahan & Ressler, 2012). Since unintentional noncontact ACL injuries can occur very quickly(Mrachacz-Kersting & Sinkjaer, 2003; Yasuda, Erickson, Beynnon, Johnson, & Pope, 1993), these combined findings may suggest that superior executive-function skills could provide sufficient anticipatory motor programming and subsequent reactive muscle stiffness regulation to protect the knee during high velocity athletic maneuvers(Charles Buz Swanik et al., 2007). However, there is limited prospective data assessing the neuromechanical link between executive functioning intervention and enhanced dynamic joint stability.

Neuropsychological literature has established that training of executive functions can improve proficiency of neural processing in the frontal areas(Bomyea & Amir, 2011; Goldin, McRae, Ramel, & Gross, 2008; Gyurak et al., 2009), such that enhanced cognitive processing may quickly suppress cortical responses in the fear networks. This fear networks in the prefrontal cortex is highly associated with cognitive action-planning circuit so that enhanced executive-function skills may also simultaneously maintain the necessary motor control for muscle stiffness regulation and functional joint stability(Bomyea & Amir, 2011; Goldin et al., 2008; Gyurak et al., 2009). Although ACLR patients with less fear of re-injury have shown better clinical knee functional outcomes(Christino et al., 2016), limited research exists for evaluating the effect of a cognitive-based intervention program on emotion regulation and subsequent muscle stiffness regulation strategies following ligamentous injury. The absence of these data has created a barrier to our understanding of joint instability in ACL patients, as well as future best practices to maximize each patient's functional outcomes. We hypothesized that emotion regulatory executive function (EREF) training may improve executive function skills such that enhanced cognitive management will help regulate emotional responses and joint stiffness regulation strategies, as well as improve knee functional outcomes and fear perception. Therefore, the purpose of this study was to investigate the therapeutic effects of EREF training on fear regulation and joint stiffness regulation strategies between ACLR patients and healthy controls, and to explore the relationships between executive function skills, knee function, and fear.

Methods

Experimental Design

This study utilized a pretest-posttest design. The independent variable included group (ACLR patients, healthy controls), time (pre-training, post-training), and emotional picture category (neutral, fear-related, injury-related). The dependent variables included executive function assessment scores, knee functional outcomes, fear of re-injury/movement scores, neurophysiological fear response (HR [change in bpm]), subjective fear perception, normalized knee stiffness (Nm/°/kg), and muscle activity (timing [sec] and amplitude).

Participants

Forty volunteers (20 ACLR patients, 20 healthy controls) between the ages of 18 and 45 years were recruited in this study (Table 15). All participants had no history of lower extremity injury or surgery within the past 6 months, neurological problems, or hearing impairments that could limit executive function skill assessment, knee functional tasks, and/or joint stiffness and muscle activation measures. ACLR participants were included if they had one or more surgical repairs for unilateral ACL ruptures, but cleared to return to physical activity. Healthy controls regularly maintained moderate physical activity level at least 3 days/week. Following a pretest session, all participants were assigned to a 4-week emotional regulatory executive-function (EREF) training program. Participants were excluded if they did not complete the minimum of 10 hours of the EREF training(Ball, Ross, Roth, & Edwards, 2013), had a new lower extremity injury during the EREF training, or did not present for the posttest session. As a result, 3 healthy controls and 4 ACLR patients were excluded because of incomplete EREF training (Table 15). All participants were provided and signed an institutional approved informed consent form prior to the pretest session.

Instrumentations

The Brain Training for High Achievers course from the BrainHQ website("Brain Exercises, Brain Fitness, Brain Games - BrainHQ from Posit Science.," n.d.) was employed to examine the effects of EREF training program on executive function of the brain, perception of fear of re-injury/movement, functional knee outcomes and joint stiffness regulation strategies. The EREF training included 12 computational brain exercise games that focused on executive function, including attention, brain speed, working memory, fluid intelligence, and social cognition. Executive function performance was measured using the executive function assessment tool provided by the National Institutes of Health Toolbox (NIH-TB). The NIH-TB executive function assessment tool consisted of two computer-based tests: the *Dimensional Change Card Sort* (DCCS) and *Flanker Inhibitory Control and Attention* (FICA) tests (Figure 27). These tests are substantially equivalent to the paper-and-pencil cognition tests that are commonly administered in clinical and research settings(Heaton et al., 2014).

Participant knee function was examined utilizing three subjective surveys that include self-reported questionnaires of the Knee Outcome Survey-Activities of Daily Living (LOS-ADL), a visual analog scale of the global rating of knee function, and number of giving way episodes (Appendix C). These surveys are designed to measure symptoms and functional deficits related to knee injuries(Collins, Misra, Felson, Crossley, & Roos, 2011; Herrington & Fowler, 2006; Moksnes, Snyder-Mackler, & Risberg, 2008). The single-legged hop for distance was also performed to predict knee functional asymmetry between limbs(Reid, Birmingham, Stratford, Alcock, & Giffin, 2007) (Appendix C). Additionally, a short version of the Tampa Scale for

Kinesiophobia (TSK-11) questionnaire was used to evaluate each individual's fear of re-injury/movement(Ardern, Taylor, Feller, Whitehead, & Webster, 2013; Woby, Roach, Urmston, & Watson, 2005) (Appendix C).

We used 62 preselected neutral (valence: 4.03-5.20, arousal: 1.72-3.46) and 60 fear-related (valence: 1.31-4.32, arousal: 5.9-7.15) pictures from the International Affective Picture System (IAPS) to induce the targeted emotion(P. J. Lang, Bradley, & Cuthbert, 2008) (Appendix D). The neutral pictures were general objects such as flowers or office supplies, whereas fearful pictures were related to fear-evoking, such as threatening pictures by humans, animals, or accident. We also included 60 knee injury-related pictures associated with either contact or non-contact ACL mechanisms to determine if sports specific stimuli evoke the emotion of fear (Figure 11) (Appendix D). Sports type images were selected based on the highest ACL incidence rates: basketball, cycling, football, gymnastic, handball, soccer, ski, tennis, and wresting(Prodromos, Han, Rogowski, Joyce, & Shi, 2007). Prior to use for the present study, sixty collegiate volunteers with no history of knee injury viewed and rated valence and arousal values with respect to all of preselected pictures and these participants were excluded from the current study. Preliminary data showed valence scores ranging from 3.20 to 4.30 and arousal scores ranging from 5.17 to 6.31, and both domains' values fall on the scales of moderate levels to fear inducing pictures when compared to those in normative value ranges.

In order to evaluate emotional responses to pictures, a custom-built electrocardiograph (ECG) circuit, subjective self-report of the Self-Assessment Manikin (SAM)(P. Lang & Bradley, 2007), and level of fear were used to examine neurophysiological responses and subjective emotional perception, respectively. The

ECG circuit was utilized to measure heart rate changes by detecting R-peak waves(Wendt, Lotze, Weike, Hosten, & Hamm, 2008). The SAM was used to rate pictures regarding two dimensions: valence (range from 1 = very unhappy to 9 = very happy) and arousal (range from 1 = very calm to 9 = very aroused)(P. Lang & Bradley, 2007). The level of fear was also assessed by rating subjective fear perception to pictures on a Likert scale ranging from 1 = not at all fearful to 9 = very fearful (Figure 12).

Joint stiffness regulation strategies were assessed using a custom-built Stiffness and Proprioception Assessment Device (SPAD) and wireless electromyography (EMG) system (TrignoTM Wireless System 8138A-DST01, Delsys Inc., Boston, MA, USA) (Figure 13). A servomotor of the SPAD is connected to an adaptor arm and adjustable chair so that it allows a rapid and precise specific range of motion at the knee, controlled through a custom LABVIEW control program(DeAngelis et al., 2014). Analog torque and position values from the SPAD were also synchronized with knee muscles EMG data and saved via a custom LABVIEW collection program. Real-time surface EMG activity was collected for the medial and lateral quadriceps (VM: vastus medialis, VL: vastus lateralis) and hamstrings (MH: semimembranosus/semitendinosus, LH: biceps femoris). The corrugator supercilii (CS), eye muscle, was also recorded to visually detect a startle response(DeAngelis et al., 2014). Electrodes were placed on the selected muscles according to the standard site identification and preparation protocols(Chittaro & Sioni, 2013; Heller, Greischar, Honor, Anderle, & Davidson, 2011; Rainoldi, Melchiorri, & Caruso, 2004). Both SPAD and EMG data were collected at 2,400 sample rate.

Procedures

After agreement and screening of eligibility in this study, participants attended 2 separate testing sessions. During the first testing session (pre-training), the participants completed the Knee Functional Assessment and TSK-11 followed by the computational NIH executive function assessment to examine baseline executive function skill, which was presented on a 17-inch CLD monitor (38 X 21 cm), approximately 100 cm from the participant. For the DCCS test, participants matched a series of or switched between bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures as accurately and quickly as possible(Weintraub et al., 2013). For the *Flanker Inhibitory Control and Attention* (FICA) test, participants focused and chose the direction of a center-positioned arrow as accurately and quickly as possible, regardless of the direction of surrounding arrows(Weintraub et al., 2013). The participants were given oral instructions by the investigator and practice trials were provided prior to each executive function-skill testing; however, the number of practice trials was varied. The order between these two tests were randomized.

Ag/ACI bipolar self-adhesive ECG electrodes were then placed to the participants' both sides of shoulders with the right anterior superior iliac spine (ASIS) as a reference location for the recording HR. The participants were seated in a comfortable armchair and watched a total of 3 randomly chosen picture sets presented on a minimum size of 17-inch CLD monitor (38 X 21 cm), approximately 100 cm from the participants(Marchewka, Zurawski, Jednoróg, & Grabowska, 2014; Smith, Bradley, & Lang, 2005) (Figure 14). Each randomized picture set contained an equal distribution of 30 neutral, fearful, and injury-related pictures. A single trial was composed of a 6-sec of the initial black screen, a 6-sec picture presentation, a 3-sec

black screen, and evaluation of the picture for 12-sec according to valence, arousal, and level of fear. Synchronized heart rate data with the picture onset was recorded throughout the first 15-sec trial period and stored in a computer using a custom LABVIEW program. Participants were familiarized with the experiment by having two samples of neutral pictures prior to the first testing block(Bradley, Codispoti, Sabatinelli, & Lang, 2001).

After measurement of emotional responses, ECG electrodes were removed from the participants and EMG sensors were placed on the targeted eye and knee muscles as recommended by previous study(DeAngelis et al., 2014). The participants were then seated on the SPAD with the reconstructed limb for ACLR patients or the matched side for healthy controls at a 30-degree knee flexion angle, and the axis of rotational adaptor arm was aligned to the lateral knee joint line. In order to ensure torque production resulting from the knee muscles only, rather than from the trunk, hip and lower extremity, participants were secured with the back supported, 90-degree hip flexion and the ankle in a neutral position by using a seat belt, thigh pad, and a vacuum splint, respectively (Figure 15). The participants' weight and length of the testing limb were measured prior to the stiffness testing for further stiffness analysis.

Joint stiffness testing had the following sequence: a measure of three maximum voluntary isometric contractions (MVIC) for both the quadriceps and hamstrings, and followed by maximum knee extension resistance to a rapid perturbation (a 100°/s velocity and 1000°/s^2 acceleration) towards the 70-degree knee flexion position (40-degree flexion arc). An acoustic startle stimulus for each type of emotion was applied to the participants during presentation of one picture set that was not used in the measure of emotional responses. Randomly ordered pictures were

displayed on the monitor 800 ms prior to the perturbation and the acoustic startle was applied 100 ms prior to the perturbation with a high-pitched (1000 Hz) noise >100dB sound pressure level, and lasting 10 ms through headphones(DeAngelis et al., 2014). Other pictures for non-stiffness trials were played for 6-sec without perturbation and all participants were unaware of the order and number of trials.

After the pre-training testing, participants performed the online emotional regulatory executive function (EREF) training provided from the brainHQ using their computer or mobile device to complete at least 10 hours in a 4-week period at their own pace(Ball et al., 2013). An anonymous user ID and password were provided to each participant as well as a written instruction and a live flash demonstration. The investigator monitored each participant's logged-in playing time (hours) and performance.

Four-weeks after the pre-training testing session, participants who completed the minimum 10 hours of the EREF reported for the post-training test. The same procedures of the pre-training test were used in the following sequence: completion of the Knee Functional Outcome Assessment and TSK-11, the NIH executive function assessment, measure of emotional responses, followed by joint stiffness and muscle activity measurements. Two picture presentation sets, which had not yet been presented to participants were employed for each measure of emotion responses and joint stiffness regulation strategies.

Data Reduction

To evaluate the effects of the EREF training on knee function and subjective fear perception, percentage value differences between pre-training and post-training were calculated for each dependent variable. A percentage value for each of the self-

reported scores was calculated by dividing by maximum score, and then multiplying by 100 for the KOS-ADL, global rating of knee function, and TSK-11. For the single-legged hop for distance, a percentage of the reconstructed knee relative to the healthy limb in ACLR patients or the matched injured limb to the other limb in healthy controls was calculated as the hip limb symmetry index (LSI). The number of new "giving-way" episodes between the pre-training and post-training was only reported for further analysis(Moksnes et al., 2008).

Progression of executive function-skills was assessed by comparing the computed scores from 0 to 10 between pre-training and post-training for each *DCCS* and *FICA* test.(Heaton et al., 2014). Heart rate (HR) as a neurophysiological emotional response was calculated by detecting inter-beat R-wave intervals to the nearest millisecond. The HR differences were calculated by subtracting the averaged 3-sec HR prior to the picture onset from the minimum HR during the first 3-sec of picture presentation and compared between the pre-training and post-training(Bradley, Codispoti, Cuthbert, & Lang, 2001). The self-reported score differences in valence, arousal, and the level of fear were also reported (Figure 16).

Raw torque and position from the SPAD and knee muscles EMG signals were preprocessed by band-pass filtering at 20-400Hz, rectifying, and followed by low-pass filtering at 5Hz. The smoothed torque and position data were used to calculate joint stiffness value by dividing the Δ Torque (Newton $\cdot$ meter) / Δ displacement (degrees) and then corrected for gravity and normalized to each participant's body weight (Nm/°/kg). The short- (0-4°), mid- (0-20°), and long-range (0-40°) stiffness values throughout the knee flexion perturbations were reported for further analysis. The quadriceps and hamstrings EMG signals were normalized to the MVICs and the area

of EMG activity for prior to the perturbation (PRE: -150 ms to 0 ms) and after the perturbation (POST1: 0 ms to 250 ms, POST2: 250 ms to 500ms) were calculated(DeAngelis et al., 2014).

Statistical Analysis

Executive function-skills, knee functional outcomes, and the fear of re-injury/movement were compared with separate 2-way repeated measures of ANOVAs with one within-subject factor (time, 2 levels) and one between-subject factor (group, 2 levels) to determine between and within group differences. Emotional responses including heart rate and valence, arousal, and level of fear scores were compared using separate 3-way repeated ANOVAs with two within-subject factors (time: 2 levels, type: 3 levels) and one between-subject factor (group, 2 levels). Stiffness and muscle EMG activity between picture types was assessed using separate 3-way repeated measures ANOVAs with two within-subject factors (type: 3 levels, time: 2 levels) and one between-subject factor (group, 2 levels) for each dependent variable. Additionally, separate 2-way repeated ANOVAs with two within-subject factors (time; 2 levels, type; 3 levels) were used to determine within group differences for stiffness and muscle EMG variables. Post hoc analysis was performed using *Tukey's post hoc* and pairwise comparisons when a significant interaction effect was observed. Descriptive analysis was used to identify any outliers or irregularities in the distribution. Pearson coefficient correlations were also assessed to evaluate relationships between executive function skills, knee functional outcomes, and fear of re-injury (TSK-11) to examine overall and within group relationships. Statistical significance was set an alpha level of 0.05.

Results

EREF training effects on Executive Function Skills, Knee Functional outcomes and Kinesiophobia

Means and standard deviations for NIH executive function assessment, knee functional outcomes and fear of re-injury/movement before and after the EREF training are displayed in Table 16. Results showed a significant group main effect for DCCS ($F_{[1,30]} = 6.139, p = 0.019$) and time main effect for FICA ($F_{[1,31]} = 9.228, p = 0.005$) tests. Pairwise comparisons showed the ACLR group had better DCCS scores than the control group regardless of the EREF training. Both groups improved executive functioning scores for the FICA test following the EREF training (Figure 28).

A significant time by group interaction effect for the LSI was observed ($F_{[1,27]} = 4.319, p = 0.047$). Post hoc analysis revealed that ACL group had significantly lower functional performance in the injured-knee than the other limb when compared to those in healthy controls regardless of the EREF training ($p = 0.004, p = 0.024$, respectively). However, ACLR patients improved the involved limb's hop distance after the EREF training ($p = 0.024$), while healthy group showed no LSI differences between before and after the EREF training ($p > 0.05$) (Figure 29). Although other knee functional assessment variables did not show time by group interaction effects ($p > 0.05$), significant main effect for group was observed for GRKF ($F_{[1,26]} = 5.712, p = 0.024$), KOS-ADL ($F_{[1,29]} = 8.634, p = 0.006$), and number of giving-way episodes ($F_{[1,28]} = 16.049, p < 0.00$). Pairwise comparisons revealed that the ACLR group had lower GRKF and KOS-ADL scores and a higher number of knee giving-way episodes than the control group regardless of the EREF training. There were no main or interaction effects for the fear of re-injury/movement (TSK-11) ($p > 0.05$).

We also assessed the potential correlations between executive function skills, knee function, and fear of re-injury/movement outcomes. Pearson correlation coefficients between executive function outcomes and knee function or fear of re-injury are presented in Table 17. The FICA values only showed significant correlation in the ACLR group. ACLR patients who had better single legged-hop performance in the reconstructed knee positively correlated with greater improvement of the executive function skills before and after the EREF training program (r=0.534. r=0.519, respectively) (Figure 30), while the DCCS results were not correlated with any of knee function outcomes or TSK-11 values. Table 18 also displays correlation coefficients between knee function outcomes and fear of re-injury for overall and within each group. The fear of re-injury (TSK-11) was negatively correlated with self-reported knee function scores before (KOS-ADL; r= -0.441) and after (GRKF; r= -0.480, KOS-ADL; r= -0.384) the EREF training. While the ACLR group with relatively greater fear showed lower KOS-ADL scores before the brain training (r= -0.475) and GRFK after the training (r= -0.730) (Figure 31), the control groups revealed no correlations between knee function outcomes and subjective fear values.

EREF training effects on Fear regulation

Table 19 presents means and standard deviation for valence, arousal, and level of fear with respect to each emotion type between before and after the EREF training for overall and within each group. A significant main effect for type was observed for the valence domain ($F_{[1.657,24.854]} = 82.035, p < 0.001$) (Figure 32). Pairwise comparisons revealed that both groups had lower valence scores in response to fearful and injury-related pictures compared to neutral pictures ($p = 0.001$), as well as lower valence score with fearful pictures in comparison to injury-related pictures ($p <$

0.001). Significant time by type interaction effects were observed for arousal domain ($F_{[1.674,40.188]} = 4.027, p = 0.032$) and level of fear ($F_{[2,50]} = 5.806, p = 0.005$) (Figure 32). Post hoc analysis revealed that arousal values decreased in response to neutral ($p = 0.003$), fearful ($p = 0.008$), and injury-related pictures ($p = 0.027$) following the EREF training. Self-reported level of fear also decreased in response to neutral ($p = 0.007$), fearful ($p = 0.001$), and injury-related pictures pictures ($p = 0.038$) after the EREF training. Additionally, both arousal and level of fear values were significantly different between all emotion types, with fearful pictures producing the highest values and neutral pictures producing lowest values ($p < 0.001$) (Figure 32).

Neurophysiological emotional responses among emotion types were assessed by comparing heart rate differences. Table 20 displays means and standard deviation for initial heart rate deceleration among emotion types between before and after the EREF training within each group. Our HR data showed a significant time by type by group interaction effect ($F_{[20,58]} = 3.655, p = 0.032$) (Figure 33). Post hoc analysis revealed that the control group had decreased heart rate deceleration in response to all emotion types after the EREF training ($p = 0.032$), while neutral pictures resulted in less heart rate deceleration than both fearful and injury-related pictures regardless of the training ($p = 0.003$, $p = 0.003$, respectively). The ACLR group also exhibited decreased heart rate deceleration with respect to both negative emotion types after the training (FEAR: $p = 0.010$, INJ: $p = 0.011$). While the ACLR group had greater heart rate deceleration in response to fearful and injury-related pictures than neutral type before the EREF training ($p < 0.001$), no heart rate differences among emotion types were observed in participants with ACLR following the executive functioning intervention ($p > 0.05$).

EREF training effects on Regulation of Dynamic Restraint mechanisms to Joint Perturbation

Table 21 displays means and standard deviation for short-, mid-, and long-range stiffness values among emotion types between before and after the EREF training within each group. A significant group by type interaction effect was observed for short-range stiffness ($F_{[1.732,38.110]} = 5.536, p = 0.010$). Post hoc analysis revealed that the control group produced greater short-range stiffness in response to fearful ($p = 0.012$) and injury-related ($p = 0.031$) pictures compared to the ACLR group. For mid-range stiffness, a significant main effect for type was observed ($F_{[2,50]} = 6.503, p = 0.003$). Pairwise comparisons revealed greater stiffness in response to fearful pictures than neutral pictures ($p = 0.003$). Additionally, a significant time by type interaction effect for mid-range (0 to 20°) was observed in the ACLR group ($F_{[1.415,16.986]} = 4.908$, $p = 0.030$), but not in the control group ($p > 0.05$). Post hoc analysis revealed that the ACLR group produced greater mid-range stiffness in response to fearful and injury-related pictures than neutral pictures before the EREF training ($p = 0.024, p = 0.017$, respectively), while there were no stiffness differences among emotion types after the EREF training ($p > 0.05$) (Figure 34). No significant main or interaction effects for short- and long-range stiffness were observed ($p > 0.05$).

Mean and standard deviation for time-to-peak (TTP) EMG among emotion types between before and after the EREF training within each group are displayed in Table 22. A significant time main effect for TTP was observed for only the lateral quadriceps (VL) in the control group, and they quickly produced peak EMG before the EREF training during the 40-degree flexion perturbation compared to after the EREF training ($F_{[1,11]} = 4.909, p = 0.049$) (Figure 35).

Table 23 presents medial and lateral quadriceps and hamstrings EMG activity prior to (PRE: -150 to 0 ms) and after the perturbation (POST1: 0 to 250 ms, POST2: 250 to 500 ms) with respect to each emotion type between before and after the EREF training within each group. A significant time by group interaction effect for PRE EMG was observed for the lateral quadriceps (VL) ($F_{[1,17]} = 5.992, p = 0.026$). Post hoc analysis revealed that the ACLR group produced greater quadriceps activation following the EREF training ($p = 0.021$), while the control group showed no different EMG activity in the lateral quadriceps between before and after the EREF training ($p > 0.05$) (Figure 36).

For the first 250ms (POST1) during the knee flexion movement, significant type main effects were observed for the medial (VM) ($F_{[2,48]} = 6.526, p = 0.003$) and lateral quadriceps (VL) ($F_{[2,38]} = 3.145, p = 0.043$). Pairwise comparisons revealed greater EMG activation in the medial quadriceps in response to both fearful ($p = 0.013$) and injury-related pictures ($p = 0.012$) than neutral pictures, while fearful pictures only revealed greater EMG activation in the lateral quadriceps when compared to neutral pictures ($p = 0.015$) (Figure 37). Furthermore, a significant time-by-type-by-group interaction for POST1 was observed for the medial hamstrings (MH) ($F_{[2,44]} = 5.689, p = 0.006$) (Figure 37). Post hoc analysis revealed the control group increased medial hamstrings EMG activation in response to both fearful and injury-related pictures following the EREF training when compared to neutral pictures ($p = 0.019, p = 0.008$, respectively). Conversely, the ACLR group had greater medial hamstring EMG activation in response to both fearful and injury-related picture compared to neutral pictures before the EREF training ($p = 0.031, p = 0.044$,

respectively), but no differences in EMG activation existed among emotion types after the EREF training ($p > 0.05$)

During the late phase of knee perturbation (POST2), a significant time by type interaction effect was observed for the medial quadriceps (VM) in the control group ($F_{[2,26]} = 4.734, p = 0.018$). Post hoc analysis showed fearful pictures provoked greater medial quadriceps EMG activation than neutral pictures before the EREF training ($p = 0.017$), while no differences in EMG activation existed among emotion types following the training ($p > 0.05$) (Figure 38). A significant time by group interaction effect for POST2 was observed for the lateral quadriceps (VL) ($F_{[1,26]} = 6.340, p = 0.018$). Post hoc analysis revealed that the control group produced less quadriceps EMG activation after the EREF training ($p = 0.001$), although the ACLR group revealed no differences in the lateral quadriceps EMG activation between before and after the EREF training ($p > 0.05$) (Figure 38). There were no main or interaction effects for hamstring EMG for the POST2 ($p > 0.05$).

Discussion

The objective of this study was to examine effects of executive function training on emotion regulation and joint stiffening strategies in response to a sudden knee perturbation, with a general and/or specific fear-related stimuli. We utilized an online brain exercise program as a training tool for executive functioning skills, which may play an important role in regulating emotion and avoiding neuromechanical decoupling involved with knee injuries(Gyurak et al., 2013; Charles Buz Swanik, 2015). The primary findings identified that the ACLR group improved executive functioning skills, knee functions, and emotional neurophysiological responses, as well as joint stiffness and muscle contraction strategies following Emotional

Regulatory Executive Function (EREF) training. It may be implied that enhanced cognitive processing in the brain is important to simultaneously regulate emotion and neuromuscular control in order to protect the joint during unanticipated events.

EREF training effects on Executive Function Skills, and Knee Function

Overall, our results reveal that both the healthy control and ACLR groups improved executive functioning skills following the online emotional regulatory executive function (EREF) training. The NIH-TB executive function assessment, which consists of the Dimensional Change Card Sort (DCCS) and Flanker Inhibitory Control and Attention (FICA) tests, is designed to evaluate the ability to quickly and correctly identify continuously changing visual information in the surrounding environment, and it has been shown to be a reliable tool for the measurement of executive functioning skills when compared to standard pen-and-pencil standard tests(Heaton et al., 2014; Weintraub et al., 2014). Ball et al(Ball et al., 2002) investigated effects of cognitive training on mental healthy and daily living functioning and 87% of participants with computer-based speed-of-processing training showed better cognitive skills, such as visually identifying targeted information more accurately and quickly. Additionally, Jobe et al.(Jobe et al., 2001) demonstrated that the speed of processing training intervention maintained cognitive, physical, and daily living functional abilities over time in older population who typically present significant loss of mobility or impairments during cognitively demanding tasks. Our NIH-TB executive function assessment results support these findings that cognitive computer training can enhance executive functioning skills.

Regardless of the EREF training, ACLR patients showed poor self-reported knee function and greater single-legged hop for distance differences between limbs

when compared to healthy controls. However, the ACLR group not only improved knee functional performance in the reconstructed limb, but also showed a positive correlation between progression of executive functioning skills and improvement of the functional hop performance following the EREF training program. For instance, ACLR patients who increased more executive function scores (FICA) following the EREF training, also demonstrated less asymmetric hop distance between limbs. Although no studies have evaluated the effects of cognitive training intervention on knee function recovery after ACLR, it has been suggested that training of executive function can help improve motor control(Ball, Edwards, Ross, & McGwin, 2010; O'Connor, Hudak, & Edwards, 2011). One recent study implied that computerized speed-of-processing training can improve cognitive deficits following a traumatic brain injury (TBI), presumably through reinforcement of neural adaptation in the working memory network(Lebowitz, Dams-O'Connor, & Cantor, 2012). Our data may indicate that improvement of executive functioning skills, as a result of the brain training, facilitates cognitive processing related to not only emotion regulation, but also motor coordination.

EREF training effects on Fear Regulation

Our results showed there is no group differences in fear of re-injury, but no research, to our knowledge, had examined how patients with ACL injury perceive fear to movement differently due to a secondary rupture, when compared healthy individuals who never had knee injury. However, there were very important correlations with the fear of re-injury. The ACLR patients' knee function was strongly associated with the level of fear perception. Higher levels of fear for re-injury or intense physical activity in the ACLR group correlated with lower self-reported knee

function scores before and after the EREF training. Tripp et al.(Tripp, Stanish, Ebel-Lam, Brewer, & Birchard, 2007) found that ACL patients, who significantly reduced negative feelings one year after surgical repair, recovered normal knee function and had higher self-confidence to participate in pre-injury level of physical activity. The correlations we examined support that ACL patients with higher fear may have persistent knee functional deficits(Christino et al., 2016; Flanigan, Everhart, Pedroza, Smith, & Kaeding, 2013; Ross, 2010), which may lead to the development of long-term pathological sequelae such as re-tear of their ACL or early knee osteoarthritis(Ardern, Webster, Taylor, & Feller, 2011) However, caution should be used because fear perception to the likelihood of re-injury was not different between healthy controls and ACLR patients, but apparently there are individualized levels of fear in some ACLR patients that likely influence this strong correlation. Therefore, we would agree with some researchers who have emphasized psychological interventions must be considered after ACL injury(Ardern et al., 2011; Kvist, Ek, Sporrstedt, & Good, 2005). However, there are no studies, to our knowledge, that directly examined whether emotional regulatory executive function training can improve subjective fear of re-injury after reconstruction. Although our results showing that ACLR patients with lower fear for physical activity have better knee function were consistent with those in Tripp et al.(Tripp et al., 2007), the progress of executive function skills did not directly impact improvement of subjective fear perception of getting a re-injury in the ACLR group, despite having better knee function following the EREF training. This discrepancy between studies may be due to the fact that we reevaluated subjective fear of re-injury one month following baseline measures, while Tripp et al. conducted follow-up testing one year after the initial assessment. However,

diminished neurophysiological fear responses after only 1 month of the EREF training may be evidence of better emotion regulation, as subsequent advanced neural processing in the CNS may unconsciously improve knee functions.

Conversely, following the EREF training, both the control and ACLR groups showed better emotional responses when negative pictures were provided. Before the EREF training, both fearful and sports knee injury-related pictures produced lower valence and higher arousal domain scores as well as higher level of fear when compared to neutral pictures. Furthermore, these unpleasant pictures initially resulted in greater heart rate deceleration than neutral pictures, which agrees with previous literature(P. Lang & Bradley, 2007). Although both groups showed similar differences in the self-reported emotional responses among all emotion types following the EREF training, the arousal and level of fear scores decreased in both groups when compared to before the EREF training. Furthermore, the control group also decreased heart rate deceleration in response to all emotion types after the EREF training, while the ACLR had significantly decreased heart rate deceleration in response to both fearful and injury-related pictures.

Bradley et al.(Bradley, Codispoti, Cuthbert, et al., 2001) found that those exposed to negative emotional contents rated lower valence (happiness), higher arousal level, and greater early heart rate deceleration compared to when presented with neutral contents. These self-reported valence and arousal values reflect magnitude of adverse feeling that an individual perceives in response to external stimulus(P. Lang & Bradley, 2007), while the suppressed cardiac reactions are neurophysiological emotional responses, primarily derived by potent parasympathetic nervous system dominance, indicating increased sensory inputs to the fear network in

the CNS(Adenauer, Catani, Keil, Aichinger, & Neuner, 2010; Carlsson et al., 2004; Smith et al., 2005). Several studies also examined electrocortical responses in the brain using EEG, in addition to cardiac reaction, while observing responses to emotionally arousing pictures(Bradley, Hamby, Löw, & Lang, 2007; Codispoti, Ferrari, & Bradley, 2007; Ferrari, Bradley, Codispoti, & Lang, 2011). Results in these studies demonstrated negative pictures not only induce early heart rate deceleration, but also elicit greater cortical potentiation in the frontal and parietal cortices. It was suggested that the altered electrocortical activation may reflect increased cognitive processing demands in order to prepare for and react to unpleasant visual cues(Bradley et al., 2007). Our results of subjective and neurophysiological responses support many previous findings that fearful visual contents can adversely alter neural processing in the CNS(Bradley, Codispoti, Sabatinelli, et al., 2001; P. Lang & Bradley, 2007), but specific sports-related pictures may also negatively influence on emotional regulation. Furthermore, less self-reported fear perception and heart rate deceleration, responding to both fearful and specific sports pictures, may be indicative of better emotion regulatory strategies following the cognitive executive functioning intervention program(Gyurak et al., 2013).

Cognitive training may help regulate emotional responses by enhancing brain's fear network to quickly and accurately identify a negative stimulus or threat in the environment(Delgado, Olsson, & Phelps, 2006). Several brain imaging studies have shown enhanced neural processing in the subcortical limbic system and cerebral cortex areas with emotion regulation interventions. Desbordes et al.(Desbordes et al., 2012) demonstrated that a cognitive mental training program has a positive impact on decreasing negative emotions. Furthermore, participants with greater reductions in

self-reported depression scores following the mental training revealed increased neural activation in the amygdala, when negative pictures were presented. This subcortical structure is known to be the center of emotion regulation(Ohman, 2005). Direct measurement of electrocortical activation using EEG also showed that cognitive emotion regulation strategies, such as reappraising or suppressing negative stimulus, elevated frontal theta power in response to fearful contents(Tolegenova, Kustubayeva, & Matthews, 2014). This means executive function skills are highly associated with cortical activation in the frontal areas, and such increased neural processing in those regions are critical to regulate fear sufficiently(Delgado et al., 2006). One recent study by Schweizer et al.(Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013) used working memory training, which is one essential component executive functioning, to examine emotional regulation. Their results demonstrated that executive functioning training improved not only efficiency of cognitive neural processing in the fronto-parietal working memory network, but also negative emotion responses. Our results were consistent with many previous findings, and together these results support the hypothesis that EREF training can augment efficacy of cognitive processing speed in the fear network. Therefore, enhanced executive functioning skills may help to quickly identify and inhibit negative emotional stimuli, thereby sufficiently reducing fear responses. Furthermore, although the ACLR group in the present study did not show differences in the fear of re-injury between before and after the EREF training, but the self-reported emotion rating scores and neurophysiological cardiac responses in response to negative stimuli, as well as knee functional performance, were improved after the EREF training. These may indicate that training of the executive functioning

skills enhance not only emotional regulation, but also neural strategies for motor planning to optimize muscle coordination after ACL injury.

EREF training effects on Regulation of Dynamic Restraint mechanisms to Joint Perturbation

In the present study, an acoustic startle event was employed prior to a 40-degree of knee flexion perturbation to simulate sudden, unanticipated joint loading(DeAngelis et al., 2014), which during physical activity is the most common noncontact ACL injury mechanism(Charles Buz Swanik et al., 2004). A study by DeAngelis et al. (DeAngelis et al., 2014) showed altered joint stiffness values, as well as muscle activation patterns following a startle in healthy individuals. The altered joint stiffness regulation strategies reflect a compromised preparatory and reactive dynamic restraint mechanism, thereby exposing joint structures to excessive loads. This series of events is suggested to represent neuromechanical de-coupling between joint structure and the CNS, indicating insufficient neuromuscular control(DeAngelis et al., 2014).

Several studies found that fear of re-injury following ACL rupture is greatly associated with knee functional deficits(Chmielewski et al., 2008; Kvist et al., 2005; Ross, 2010), but no research, to our knowledge, is available with an unpleasant emotional stimuli linked to joint stiffness regulation strategy. As an appropriate motor planning cognitive management is crucial for dynamic restraint mechanisms in order to maintain functional joint stability(Charles Buz Swanik et al., 2007), the influence of unpleasant emotion and emotional regulatory executive function training on joint stiffness regulation strategies will advance our understanding of the proposed mechanisms underlying the link between fear of re-injury and functional joint

instability following ACL injury(Charles Buz Swanik, 2015). Our data showed that the cognitive executive function training intervention did not effect short-range stiffness, on either the ACLR or control groups. However, the ACLR patients produced less short-range stiffness values than those in the healthy controls when both general fearful and specific injury-related pictures were provided prior to the knee perturbation with the startle. Short-range stiffness reflects the resistance to sudden joint perturbations that is provided by the passive visco-elastic connective tissue properties, combined with the reverse pivoting and existing actin-myosin cross-bridges within muscle(Sinkjaer, Toft, Andreassen, & Hornemann, 1988). This involuntary muscle resistance is thought to be greatly associated by the fusimotor muscle spindle system, which determines the amount of resting muscle stiffness or tone(Needle et al., 2014). Potent negative emotional responses could lead to sudden changes in muscle tone(Leeuw et al., 2007), because parasympathetic dominant neurophysiological emotional responses may increase sensitivity of the muscle spindle system(Radovanovic, Peikert, Lindstrom, & Domellof, 2015). Decreased short-range stiffness in our patients with ACLR may be indicative of the altered neuromechanical coupling strategy between joint structures and the CNS, possibly due to diminished neural sensitivity within the muscle spindle system following ligamentous injury(Needle et al., 2014). Therefore, ACLR patients might be difficult to initially stiffen the knee joint structure through the fusimotor spindle system in response to sudden fearful stimuli, so that better dynamic restraint mechanisms would be needed to compensate involuntary muscle stiffness deficits to maintain functional joint stability.

Our results found that the EREF training results in better mid-range joint stiffness regulation strategies in the ACLR group, responding to negative emotional stimuli, during a sudden knee perturbation with the startle. Fearful stimuli could even more adversely affect the ability to optimize the stiffness behavior during functional tasks because several regions in the brain for emotion regulation are highly involved in cognitive processing for movement anticipation(Gyurak et al., 2009; Lamm et al., 2007). The mid-range stiffness represents the combined passive and dynamic restraint components of the muscles surrounding the knee(Mrachacz-Kersting & Sinkjaer, 2003; Sinkjaer et al., 1988). While the knee is loaded, the CNS must precisely interpret sensory feedback from the thigh muscles with respect to instantaneous changes in force ,length, and joint position, in order to continuously regulate optimal joint stiffness(Charles Buz Swanik et al., 2004). A study by Schmitz and Shultz(Schmitz & Shultz, 2010) investigated joint stiffness and muscle absorption during a drop jumping. They found that lower joint stiffness throughout the entire landing period was negatively correlated with greater force absorption in the knee muscles. Swanik et al.(Charles Buz Swanik et al., 2004) also found that ACL patients who demonstrated relatively normal knee function compared to healthy controls, had less muscle stiffness with enhanced hamstring muscle activation. Lower stiffness during dynamic movement may be evidence of better stiffness regulation strategy as muscles surrounding the joint can sufficiently absorb external force to during loading and stress-shield articular structures(Lephart & Henry, 1996; Rudolph, Axe, Buchanan, Scholz, & Snyder-Mackler, 2001). ACLR patients in the present study showed greater mid-range stiffness in response to both general and specific sport-injury related pictures before the EREF training. However, these patients decreased

mid-range stiffness with negative stimuli, but not differ from the neutral pictures after the executive functioning intervention. This means that ACLR patients were negatively effected by emotional stimuli before the EREF training, but at the end of the study there was not a significant different mid-range stiffness values between picture types. This supports many previous findings(Rudolph et al., 2001; Schmitz & Shultz, 2010; Charles Buz Swanik et al., 2004), and may imply that training of the executive function skills can improve preparatory and reactive dynamic restraint mechanisms following ACL injuries, presumably through better cognitive sensory integration and motor planning in the CNS.

In terms of EMG activation patterns, the EREF training altered preparatory and reactive muscle contractions. Previous studies suggested that timing and amount of muscle activation prior to and after the initiation of joint loading are critical factors potentially contributing to the maintenance of functional joint stability in ACL patients(DeAngelis et al., 2014; Charles Buz Swanik et al., 2004). Our data showed that healthy controls had slower time to produce peak EMG for the medial quadriceps following the executive functioning intervention, but no differences in the hamstrings. This was consistent with previous findings by DeAngelis et al.(DeAngelis et al., 2014) who found that the acoustic startle events resulted in early quadriceps activation when compared to a non-startle stiffness condition. If the quadriceps are too quickly activated while the hamstring antagonists activity is relatively slower, greater force absorption occurs at more extended knee position and increased tension can be placed on the ACL leading to injurious pathomechanics(Chappell, Creighton, Giuliani, Yu, & Garrett, 2007). Although the results of the current study did not reveal significant differences for the timing of peak EMG activity in the ACLR group between pre- and

post-training session, quadriceps dominant EMG activity in participants with ACLR was observed before the testing knee was loaded. The amount of muscle activation prior to the perturbation is the result of feed-forward motor control, and crucial for accurately anticipating joint loading(Chappell et al., 2007; Charles Buz Swanik et al., 2004). Chappell et al.(Chappell et al., 2007) suggested that increased quadriceps and decreased hamstring activation before the joint is loaded could be risk factors for higher incidence rates of ACL injuries. Another study by Swanik et al.(Charles Buz Swanik et al., 2004) showed that ACL patients with better knee performance had normal preparatory quadriceps activation, but greater hamstring activation. Our preparatory EMG data in conjunction with findings of the lower short-range stiffness in the ACLR patients suggests that fear can significantly disturb pre-programmed muscle activation necessary for the optimal stiffness regulation strategy. However, ACLR patients showed no mid-range stiffness differences among emotion types after the EREF training. This may imply the EREF training program help to quickly identify fear-evoking visual cues so that ACLR patients appear to have better control of their emotional responses, which may enable them to modify a sufficient magnitude of muscle contraction throughout the knee movement.

In response to the perturbation, both the control and ACLR groups showed greater reactive quadriceps activation with respect to fearful and/or injury-related pictures compared to neutral emotion type pictures when subjects did not have the EREF training. This quadriceps dominance may result in increased anterior shearing force to the knee, thereby biomechanically placing the ACL into more vulnerable position (Hewett, Ford, Hoogenboom, & Myer, 2010). Our results again indicate that negative emotional stimuli interrupt feedback dynamic restraint mechanism to

appropriately modulate reactive muscle contraction. However, following EREF training the control group also had greater early reactive hamstrings activation, but less late reactive quadriceps when negative pictures were provided. Moreover, the ACLR showed greater early reactive hamstrings activation in response to fearful and sports knee injurious pictures before the EREF training compared to neutral pictures, but no difference in late reactive quadriceps activation among emotion types existed after the EREF training. These results were also consistent with previous finding in Swanik et al.(C B Swanik, Lephart, Giraldo, Demont, & Fu, 1999) and Chappell et al.(Chappell et al., 2007). It is possible that quadriceps inhibition and/or compensatory antigravity hamstring activation exhibited in both the control and ACLR groups after improvement of executive functioning skills may be indicative of the augmented joint stiffness regulation strategies through the feed-forward and feedback dynamic restraint mechanisms(C B Swanik et al., 1999; Charles Buz Swanik et al., 2004).

Limitations

In the present study, we utilized the NIH-TB executive function assessment, including the DCCS and FICA tests, in order to evaluate the progress of executive functioning skills after the online brain exercise intervention program. Although these two tests provide excellent reliabilities compared to standard pen-and-pencil tests, they focus on measurement of the ability of attention and cognitive identification of the targeted objects among different visual cues. Other components of executive functioning, such as brain speed, working memory, and intelligence may be also critical for cognitive management strategies in order to maximize dynamic restraint mechanisms. Furthermore, executive functioning skills are highly associated with age and education level, but we only compared the overall computed scores. Although

there was no significant age difference between groups, education levels were varied between and within each group. Future study may consider how these potential covariant factors influence the progress of executive functioning skills as well as emotion and joint stiffness regulation strategies. These executive functioning skills may not result in permeant neuroplasticity in the brain, which may continuously alter the existing cognitive neural network. Although cognitive speed of processing training could maintain cognitive function associated with activities of daily living in older population over time(Jobe et al., 2001), it is unclear whether similar outcomes will be appeared in physical active population. Moreover, four ACLR patients (out of 20) and 3 healthy controls (out of 20) were excluded for the current study due to incomplete EREF training before the follow up testing, which resulted in underpowered statistical results for some of joint stiffness and EMG variables. These underpowered results were not reported in the present study. Future studies with more subjects should be conducted to fully explore potential effects of fear and executive functioning intervention on dynamic restraint mechanism.

Conclusions

This study is the first to examine the effect of executive function skills on, fear, emotional regulation and dynamic restraint mechanisms by using knee outcomes, self-reported surveys and assessing neurophysiological and neuromechanical de-coupling characteristics of ACLR patients compared to healthy controls. Participants with ACLR showed better executive function, fear responses and knee function outcomes following 4-weeks of cognitive-based brain training. After the EREF intervention, ACLR group also had decreased mid-range stiffness in response to general fearful and

specific injury-related pictures, as well as compensatory quadriceps inhibition and/or hamstrings excitation throughout the entire of knee movement.

Improved executive functioning skills and knee function outcomes, in conjunction with findings of decreased self-reported and heart rate deceleration in response to fearful and injury-related visual stimuli, suggest that the cognitive brain training intervention may provide better emotional and joint stiffness regulation strategies, thereby enhancing muscle coordination and maintaining functional joint stability. Future research may explore how neuromuscular control rehabilitation programs used in conjunction with executive function training contribute to the dynamic restraint system.

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Chapter 5

DISCUSSIONS & CONCLUSIONS: EVIDENCE OF NEUROPLASTICITY FOLLOWING ACL RUPTURES AND IMPORTANCE OF NEUROCOGNITIVE FUNCTION SKILLS IN FUNCTIONAL JOINT STABILITY

Discussions

Neuroplasticity, which is defined as the ability of the brain to reorganize its functional cortical activation, has recently received great attention in ACL research as a means of exploring mechanisms underlying functional joint instability following a ligamentous rupture of the knee(J Baumeister, Reinecke, & Weiss, 2008; Jochen Baumeister, Reinecke, Schubert, & Weiss, 2011; D. Grooms, Appelbaum, & Onate, 2015; D. R. Grooms, Page, & Onate, 2015; Kapreli & Athanasopoulos, 2006; Kapreli et al., 2009; Ward et al., 2015). It has been suggested that peripheral musculoskeletal injuries could cause neural adaptations in the CNS, as damaged mechanoreceptors embedded within ligamentous structures may result in an altered quantity and quality of afferent sensory input to the CNS (deafferentation)(Kapreli et al., 2009). Therefore, failure in returning to pre-injury level of physical activity with diminished proprioception and long-term functional deficits, despite surgical repair to regain mechanical stability and extensive neuromuscular control (NMC) training to restore functional joint stability, are speculated to be evidence of neuroplasticity following ACL rupture(D. Grooms et al., 2015). Furthermore, several brain regions including the frontal and parietal cortices are crucial for emotion regulation, particularly fear(LeDoux & Damasio, 2013), which has been recognized as a risk factor leading to

persistent knee disability in ACL patients(Clare L Ardern, Taylor, Feller, Whitehead, & Webster, 2013). These brain areas are also involved in action-planning networks for muscle coordination, which are critical to maintain functional joint stability, and negative emotions can temporarily alter cortical responses within the fronto-parietal network. Increased neurocognitive processing in response to fear or threat during a sudden movement could negatively influence NMC strategies(Amaral & Strick, 2013), but limited research exists on neuromechanical links between cognition, fear, and joint instability following ACL rupture. Therefore, the purpose of this dissertation was to examine if an ACL injury causes neuroplasticity with respect to sensory perception at the somatosensory cortex during joint loading, to explore how fear may interfere with neural processing in the brain and subsequent dynamic restraint mechanisms, and to assess how cognitive-based brain training helps regulate fear and NMC following ACL injury.

Neuromechanical Links between Laxity and the Brain following ACL injury

The use of a direct measure of electrocortical activity, electroencephalography (EEG), during joint loading at the knee allowed us to examine how the brain perceives critical proprioceptive input originating from the knee. ACL patients in our study had restored mechanical stability at a clinically significant level, but demonstrated greater somatosensory cortex activity as the injured limb was loaded compared to the opposite limb and healthy controls. This may imply that damaged mechanoreceptors embedded within the ACL have a diminished quantity or quality of sensory traffic to the CNS, and that neuromechanical de-coupling may result in lasting neuroplasticity in the somatosensory cortex following an ACL rupture. Because our ACL participants had lower knee function, which could lead to further functional joint instability, the neural

adaptations occurring in the brain areas responsible for sensory perception may reflect compensatory protective mechanisms by recruiting more neural resources to detect changes in joint position. However, a negative correlation was also observed between cortical activity and joint laxity in the healthy knee of the patients with ACLR. For instance, ACLR patients with greater joint laxity had less cortical activation. This reserve cortex-laxity correlation in the healthy limb may also reflect a compensatory neural adaptation by enhancing neural efficiency, as a small amount of neural excitation in the somatosensory cortex can detect and perceive more sensory information during joint loading. This is the first study that directly observed neuromechanical coupling between ligamentous properties and the CNS, and results suggests that damage to the ACL causes CNS reorganization for sensory perception(Kapreli & Athanasopoulos, 2006), but different neuromechanical re-coupling strategies exist between limbs following the ACL injury.

Neuromechanical Links between Fear, Cognition and Dynamic Restraint mechanisms

The findings of neuroplasticity with respect to the increased somatosensory cortex activity, representing neuromechanical coupling between the damaged ACL and CNS, may imply that better feed-forward and feedback strategies are needed to appropriately prepare for and react to a sudden movement at the knee in order to maintain joint stability(Swanik, 2015). In general, fear is a strong and unconscious emotional awareness corresponding to an unexpected threatening stimulus that elicits greater defensive cardiac reaction (heart rate deceleration) as well as increased cortical excitation in the frontal and parietal areas(Bradley, Hamby, Löw, & Lang, 2007; Ledoux, 2000). These fear responses are regulated through cognitive processing in the

prefrontal and parietal cortices. During unanticipated high-velocity athletic maneuvers, such as twisting or pivoting of the knee, instantaneous increases in neural demands within these brain regions may interrupt cognitive action-planning strategies needed for sufficient NMC. Since this study was the first to examine the effect of fear-related visual stimuli on dynamic restraint mechanisms, the results pertaining joint stiffness and muscle EMG activity patterns may provide evidence of neuromechanical decoupling, caused by fear, to the NMC system. Increased mid and long range stiffness values were observed in ACLR patients when negative visual stimulus were provided. These could place the knee in a more extended position during joint loading. Moreover, greater pre-programed quadriceps activation prior to and imbalanced reactive quadriceps-hamstrings activity after a sudden knee perturbation were observed in response to unpleasant visual contents. Combined with the increased mid and long range stiffness values, such altered muscle contraction patterns could increase shearing forces applied to the knee, thereby increasing incidence of a secondary ACL rupture. These altered dynamic restraint mechanisms may signify that fear disturbs neurocognitive processing needed for appropriate NMC, so that the brain fails to simultaneously predict and monitor joint position sense to modify the task-specific optimal level of joint stiffness.

The adverse effects of fear on joint stiffness regulation strategies in ACLR group may underline the importance of executive function skills needed to prevent persistent functional joint instability and to optimize patient outcomes following ACL injury(Swanik, Covassin, Stearne, & Schatz, 2007). Following completion of an easily accessible cognitive-based online executive functioning training intervention, we observed, improved neurophysiological fear responses in company with better knee

functions in ACLR patients. Furthermore, the ability to stiffen the knee joint in the ACLR patients was not affected by negative stimuli after the training. These findings demonstrate that an executive function training intervention improves neural processing in the brain, such that enhanced cognitive sensory integration and motor planning in the CNS could sufficiently detect and suppress the fear-provoking stimuli even during a sudden event, thereby enabling ACLR patients to secure the knee.

Conclusions

The results of this study support that neuroplasticity occurs in ACL patients following a ligamentous injury. These neural adaptations may represent protective compensatory neuromechanical re-coupling strategies in the CNS, which are necessary to simultaneously detect and perceive critical proprioceptive inputs from the joint to optimize specific-task related joint stiffness level. However, fear-provoking stimuli elicit neural excitation in the prefrontal and parietal areas as a part of emotion regulation, such that increased neural processing demands may interrupt cognitive action planning for motor coordination in ACLR patients. As a result, compromised preparatory feed-forward and reactive feedback dynamic mechanisms may be insufficient to maintain functional joint stability during a sudden event in company with a fearful or threatening stimulus. However, our results suggest that training of the executive function skills can improve the brain's neurocognitive ability, emotional responses, and joint stiffness regulation strategies.

Research Implications

This study was the first to investigate mechanisms underlying neuromechanical links between fear, cognition, and joint stability; however, there are several considerations for future research. Although the instrument (EEG) used in this study

has shown instantaneous electrocortical activity changes in the brain in response to joint loading or negative emotional stimuli, it has revealed limitation to show those originated brain regions precisely. Furthermore, in general, neuroimaging research settings pose a restriction on the investigation of the brain's function with respect to dynamic movement tasks due to signal artifact. Therefore, future studies should consider ways that will allow for monitoring of the brain's function during dynamic movement tasks, while maintaining excellent temporal and spatial resolutions. Additionally, ACLR patients in the current study were functionally stable when compared to other ACLR patients with long-term knee disabilities in previous studies. Investigation of a population who suffers from persistent functional joint instability, despite having surgical repair and/or rehabilitation process, may provide a better understanding of different neuroplasticity strategies that may aid in the identification of neuromechanical de-coupling. Furthermore, prospective research should be employed to examine in ACLR population if neuroplasticity and NMC strategies change over time, as we are unable to conclude whether existing neural adaptations represent better functional joint stability, or could be modified with rehabilitation. Finally, effects of specific-task related neuromuscular control rehabilitation programs used in conjunction with executive-function skills on maintaining of functional joint stability should be determined. Overall, future studies with the aforementioned considerations may provide future insights into not only the etiology of functional joint instability, but also the development of the best prevention and rehabilitation strategies following ACL injury.

Clinical Implications

The results of the present study support that both a neuropsychological and neurocognitive approach must be incorporated into existing neuromuscular control rehabilitation programs following ACL injury(C. L. Ardern et al., 2014). For instance, a combination of psychological emotional support, training of attention and brain speed, and specific task-related neuromuscular control rehabilitation program utilizing cognitive judgment may prevent functional joint instability and maximize patient outcomes following ACL injury. Furthermore, there are many executive function training programs available, which are easily accessible on computers and mobile devices at relatively low cost. This is one potential area that could possibly be beneficial in the reduction medical expenses associated with ACL injuries.

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Appendix A

TABLES

	CON	ACLR	ACLD
N	17	17	4
Age (yrs)	26.9 ± 5.6	22.3 ± 3.8	25.5 ± 8.7
Height (cm)	166.3 ± 7.7	164.5 ± 10.4	166.4 ± 7.9
Mass (kg)	62.7 ± 12.0	67.8 ± 18.7	69.5 ± 16.2

Table 1 Subjects' demographic information for EEG during joint laxity testing.

		Joint Laxity (mm)					Joint Stiffness (N/mm)				
		LAXT	LAXA	LAX1	LAX2	LAX3	STFT	STFA	STF1	STF2	STF3
CONT	Injury Matched limb	6.67 ± 2.67	4.90 ± 2.33	0.86 ± 0.42	2.46 ± 1.50	1.12 ± 0.40	38.77 ± 15.70	34.19 ± 17.60	56.70 ± 28.20	19.15 ± 8.88	38.73 ± 16.57
	Non-Injury Matched limb	6.58 ± 2.81	5.01 ± 2.52	0.91 ± 0.33	2.38 ± 1.62	1.18 ± 0.49	39.89 ± 17.05	33.79 ± 16.98	48.79 ± 17.34	26.31 ± 17.28	34.79 ± 15.70
	Limb Differences	*1.05 ± 0.71*	*0.82 ± 0.47*	*0.37 ± 0.26*	*0.49 ± 0.29*	*0.31 ± 0.24*	*6.60 ± 6.53*	*9.05 ± 8.61*	*26.39 ± 20.28*	*7.85 ± 8.73*	*11.81 ± 8.65*
ACLR	Injured Limb	9.04 ± 2.50	**7.39 ± 2.26***	1.27 ± 0.73	3.47 ± 1.58	**2.43 ± 0.86†**	26.16 ± 6.89	**19.20 ± 6.14a**	39.25 ± 15.74	13.56 ± 6.46	**18.09 ± 6.97†**
	Non-Injured Limb	7.47 ± 2.19	5.32 ± 1.51	0.74 ± 0.36	2.58 ± 1.09	1.51 ± 0.43	31.85 ± 8.56	**26.20 ± 7.76a**	46.20 ± 20.59	16.64 ± 5.36	28.20 ± 10.20
	Limb Differences	*1.65 ± 0.95*	*2.16 ± 1.50*	*0.47 ± 0.40*	*1.15 ± 0.96*	*1.02 ± 0.79*	*7.33 ± 4.96*	*8.30 ± 6.06*	*19.45 ± 18.19*	*5.66 ± 4.39*	*8.31 ± 6.99*
ACLD	Injured Limb	8.72 ± 5.30	7.22 ± 5.51	1.19 ± 0.69	2.23 ± 3.05	**2.45 ± 1.82†**	32.72 ± 17.04	26.68 ± 15.48	60.12 ± 58.90	26.33 ± 25.71	27.76 ± 22.91
	Non-Injured Limb	6.75 ± 3.18	5.44 ± 3.39	1.14 ± 0.51	2.53 ± 2.12	1.53 ± 0.93	37.40 ± 13.54	30.69 ± 13.73	46.70 ± 25.45	25.30 ± 15.09	33.65 ± 16.97
	Limb Differences	*2.61 ± 2.29*	*2.49 ± 2.12*	*0.44 ± 0.17*	*1.09 ± 0.82*	*1.06 ± 0.88*	*9.51 ± 8.97*	*9.77 ± 9.54*	*26.00 ± 26.68*	*11.73 ± 10.26*	*15.08 ± 13.69*

Table 2 Joint Laxity (mm) and Mechanical Stiffness (N/mm) across sides, groups, and times of loading.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. LAXT: total laxity. LAXA: total anterior laxity. LAX1: laxity during early loading (0-1000ms). LAX2: laxity during mid loading (1000-2000ms). LAX3: laxity during late loading (2000-3000ms). STFT: total stiffness. STFA: total anterior stiffness. STF1: stiffness during early loading (0-1000ms). STF2: stiffness during mid loading (1000-2000ms). STF3: stiffness during late loading (2000-3000ms). ± indicates standard deviation. *Significant differences between limbs within group; †Significant difference from CONT's matched limb; [a]Significant group difference from CONT. A probability α level was set a *prior* at 0.05.

		α-2 ERD (%) in Contralateral Somatosensory Cortex (CP3, CP4)		
		ERD1	ERD2	ERD3
CONT	Injury Matched limb	25.26 ± 13.24	32.12 ± 17.35	31.03 ± 22.65
	Non-Injury Matched limb	28.03 ± 11.53	34.27 ± 18.08	38.43 ± 14.92
ACLR	Injured Limb	**36.42 ± 11.49*†**	40.64 ± 21.03	**51.12 ± 16.45ª**
	Non-Injured Limb	25.05 ± 14.19	38.64 ± 13.86	**42.05 ± 18.76ª**
ACLD	Injured Limb	34.17 ± 16.94	37.72 ± 10.96	29.01 ± 26.41
	Non-Injured Limb	-6.78 ± 32.52	--6.21 ± 38.40	24.64 ± 13.30

Table 3 Group differences in somatosensory cortex activity during joint loading between sides and times.

± indicates standard deviation. CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. α-2: Upper Alpha frequency band (10-12 Hz). ERD: Event-related desynchronization (% decreased power relative to non-loading baseline). ERD1: cortical activation during early loading (0-1000ms). ERD2: cortical activation during mid loading (1000-2000ms). ERD3: cortical activation during late loading (2000-3000ms). CP3 and CP4: Left and Right centro-parietal electrode reflecting the left and Right somatosensory cortex, respectively. Increased α-2 ERD (%) indicates increased somatosensory cortex activity. *Significant differences between limbs within group; †Significant difference from CONT's matched limb; ªSignificant group differences from both CONT and ACLD groups. A probability α level was set a *prior* at 0.05.

	Knee Function Outcomes & TSK-11				
	GRKF (%)	KOS-ADL (%)	# of Giving-way	TSK-11 (%)	LSI (%)
CONT	98.29 ± 4.90	99.50 ± 1.75	0.00	44.79 ± 13.15	100.55 ± 4.57
ACLR	92.82 ± 8.76	92.52 ± 9.93	15.06 ± 32.41	44.25 ± 13.69	**92.46 ± 8.69***
ACLD	90.00 ± 8.16	97.50 ± 5.00	4.00 ± 4.90	**28.98 ± 1.14†**	90.74 ± 5.45

Table 4 Group differences in the Knee Functional Outcomes and TSK-11.

± indicates standard deviation. CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. TSK-11: Short-version of the Tampa Scale for Kinesiophobia. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). *Significant group difference from the CONT group; †Significant difference from both CONT and ACLR groups. A probability α level was set a *prior* at 0.05.

		Injured (Matched) Limb					Non-Injured (Matched) Limb				
	ERD	LAX1	LAX2	LAX3	LAXA	LAXT	LAX1	LAX2	LAX3	LAXA	LAXT
CONT	ERD1	.383	.407	.442	.445	.411	.412	.081	-.003	.120	.205
	ERD2	.321	.259	.194	.383	.336	.234	-.094	.011	-.072	-.004
	ERD3	.458	.273	.352	.382	.333	.515*	.217	.083	.225	.217
ACLR	ERD1	.126	.220	.211	.254	.175	.129	-.352	-.479	-.534*	-.473
	ERD2	.530*	.506*	.231	.543*	.501*	.153	-.565*	-.284	-.453	-.268
	ERD3	.028	.485	.142	.343	.274	.429	-.108	-.256	-.071	-.032
ACLD	ERD1	.891	.538	.240	.494	.574	-.425	.226	.421	.210	.204
	ERD2	.981*	.843	.563	.793	.831	-.094	.567	.882	.613	.568
	ERD3	.983*	.775	.494	.730	.783	-.389	.103	.199	.070	.079

Table 5 Correlation coefficients between joint laxity and cortical activation across times within each group.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. LAXT: total laxity. LAXA: total anterior laxity. LAX1: laxity during early loading (0-1000ms). LAX2: laxity during mid loading (1000-2000ms). LAX3: laxity during late loading (2000-3000ms). ERD: Event-related desynchronization (% decreased power relative to non-loading baseline). ERD1: cortical activation during early loading (0-1000ms). ERD2: cortical activation during mid loading (1000-2000ms). ERD3: cortical activation during late loading (2000-3000ms). *Significant correlation between laxity and cortical activation. A probability α level was set a *prior* at 0.05.

		Knee Function Outcomes & TSK-11			
	ERD	GRKF (%)	KOS-ADL (%)	TSK-11 (%)	LSI (%)
CONT	ERD1 Diff.	-.242	-.136	.016	.289
	ERD2 Diff.	-.065	-.119	.185	.130
	ERD3 Diff.	-.125	.103	.334	.229
ACLR	ERD1 Diff.	.027	.016	**-.523***	.345
	ERD2 Diff.	-.469	-.457	-.089	-.179
	ERD3 Diff.	-.309	-.320	.303	-.069
ACLD	ERD1 Diff.	-.923	**-.971***	.155	-.271
	ERD2 Diff.	-.712	-.490	-.650	-.147
	ERD3 Diff.	-.889	-.514	.011	-.891

Table 6 Correlation coefficients between side-to-side cortical activation differences and Knee Functional Outcomes and TSK-11 within each group.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. TSK-11: Short-version of the Tampa Scale for Kinesiophobia. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). *Significant correlation (p<0.05).

	CON	ACLR
N	20	20
Age (yrs)	23.9 ± 4.8	21.9 ± 3.5
Height (cm)	166.6 ± 9.2	165.9 ± 10.4
Mass (kg)	62.5 ± 12.5	71.8 ± 25.2

Table 7 Subjects' demographic information for emotion response and joint stiffness Testing

	Knee Function Outcomes & TSK-11				
	GRKF (%)	KOS-ADL (%)	# of Giving-way	TSK-11 (%)	LSI (%)
CONT	98.10 ± 4.90	99.64 ± 1.30	0.00	35.23 ± 10.85	100.16 ± 5.61
ACLR	95.10 ± 7.25	**93.50 ± 8.41***	**14.65 ± 30.14***	42.61 ± 13.21	**94.08 ± 8.18***

Table 8 Knee Functional outcomes and Kinesiophobia (TSK-11) between groups.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. TSK-11: Short-version of the Tampa Scale for Kinesiophobia. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). *Significant difference between groups (p<0.05).

		Theta (4-8 Hz) ERD/ERS (%)					
		Frontal Cortex Area			Parietal Cortex Area		
Group	Type	F3	Fz	F4	P3	Pz	P4
CONT	NEU	-25.47 ± 30.82	-27.36 ± 30.62	-33.25 ± 30.27	-29.91 ± 31.49	-62.87 ± 63.51	-56.00 ± 48.86
	FEAR	**-34.39 ± 27.15†**	**-37.25 ± 29.74†**	-30.76 ± 24.71	**-38.09 ± 34.96†**	**-70.17 ± 72.62†**	-54.77 ± 50.41
	INJ	-27.00 ± 26.00	-33.04 ± 30.87	-31.69 ± 29.20	**-75.40 ± 50.34†***	**-111.82 ± 95.61†***	**-107.96 ± 75.65†***
ACLR	NEU	-22.64 ± 26.78	-22.16 ± 29.30	-27.37 ± 31.57	-35.32 ± 43.33	-65.45 ± 45.95	-63.64 ± 39.92
	FEAR	**-39.99 ± 37.91†**	**-34.58 ± 29.79†**	-37.38 ± 37.95	**-56.46 ± 41.28†**	**-92.67 ± 60.12†**	-83.25 ± 42.21
	INJ	-29.64 ± 19.14	-35.06 ± 16.04	-42.79 ± 40.63	**-82.20 ± 72.84†***	**-116.96 ± 83.45†***	**-139.46 ± 95.51†***

Table 9 Fronto-parietal Event-Related Desynchronization/Synchronization (ERD/ERS) in the Theta frequency (4-8 Hz) across emotion types and groups during 1st second of picture presentation.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. ERD: Event-Related Desynchronization (% decreased power relative to non-loading baseline, positive [+]). ERS: Event-Related Synchronization (% increased power relative to non-loading baseline, negative [-]). *Significantly greater theta ERS than FEAR (p<0.05). †Significantly greater theta ERS than NEU (p<0.05).

	Heart Rate Deceleration (bpm)		
GROUP \ TYPE	NEU	FEAR	INJ
CONT	-3.64 ± 1.27	**-4.60 ± 1.41***	-4.17 ± 1.37
ACLR	-3.37 ± 1.36	**-4.58 ± 1.31***	**-4.43 ± 1.46***

Table 10 Means and standard deviation for heart rate deceleration between Groups across emotion types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. *Significantly greater heart rate deceleration than NEU (p<0.05).

		SAM & Level of Fear (9-point Likert Scale)		
TYPE	**GROUP**	**Valence**	**Arousal**	**Lv. of Fear**
NEU	**CONT**	4.99 ± 0.22	1.49 ± 0.99	1.14 ± 0.28
	ACLR	5.07 ± 0.35	1.31 ± 0.46	1.23 ± 0.38
	TOTAL	*5.03 ± 0.29*	*1.40 ± 0.78*	*1.18 ± 0.33*
	U.S. Norm Range	***4.03 - 5.2***	***1.72 - 3.46***	
FEAR	**CONT**	2.36 ± 0.94	5.63 ± 1.96	5.83 ± 1.92
	ACLR	2.55 ± 1.13	5.50 ± 2.23	5.63 ± 2.48
	TOTAL	***2.46 ± 1.04*[a]***	***5.57 ± 2.12*[a]***	***5.73 ± 2.20*[a]***
	U.S. Norm Range	***1.31 – 4.32***	***5.9 – 7.15***	
INJ	**CONT**	4.00 ± 0.69	3.29 ± 1.48	2.92 ± 1.51
	ACLR	3.85 ± 0.92	**3.97 ± 1.93†**	**3.83 ± 1.93†**
	TOTAL	***3.93 ± 0.81****	***3.62 ± 1.74****	***3.37 ± 1.78****

Table 11 Mean and standard deviation for SAM & Level of Fear between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. SAM: the Self-Assessment Manikin; including two valence and arousal domains. Valence: level of happiness ranging from 1 = very unhappy to 9 = very happy. Arousal: arousal level ranging from 1 = very calm to 9 = very arousal. Lv. of Fear: ranges from 1 = not fearful at all to 9 = very fearful. *Significant difference from NEU (p<0.05). †Significant difference between groups (p<0.05). [a]Significant difference from INJ (p<0.05).

Group	Picture Type	Condition	Normalized Stiffness (Nm/°/kg) Short Range (0-4°)	Mid Range (0-20°)	Long Range (0-40°)
CONT	NEU	Non-Startle	0.054 ± 0.006	0.008 ± 0.004	0.041 ± 0.010
		Startle	**0.057 ± 0.010†**	**0.022 ± 0.012†**	**0.048 ± 0.010†**
	FEAR	Non-Startle	0.052 ± 0.006	0.009 ± 0.006	0.039 ± 0.013
		Startle	**0.055 ± 0.009†**	**0.031 ± 0.022†**	**0.049 ± 0.016†**
	INJ	Non-Startle	0.052 ± 0.006	0.009 ± 0.005	0.040 ± 0.011
		Startle	**0.058 ± 0.012†**	**0.025 ± 0.019†**	**0.045 ± 0.013†**
ACLR	NEU	Non-Startle	0.049 ± 0.009	0.009 ± 0.008	0.045 ± 0.014
		Startle	0.054 ± 0.014	**0.017 ± 0.014†**	0.043 ± 0.016
	FEAR	Non-Startle	0.049 ± 0.010	0.008 ± 0.006	0.039 ± 0.016
		Startle	0.048 ± 0.011	**0.027 ± 0.020*†**	**0.050 ± 0.016***
	INJ	Non-Startle	0.050 ± 0.010	0.007 ± 0.007	0.040 ± 0.015
		Startle	0.052 ± 0.014	**0.028 ± 0.024*†**	**0.046 ± 0.019***

Table 12 Mean and standard deviation for normalized short (0-4°), mid (0-20°), and long (0-40°) range stiffness values between groups by emotion types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. *Significant difference from NEU (p<0.05). †Significant difference between stiffness conditions (p<0.05).

			TTP EMG (sec)			
Group	Picture Type	Condition	VM	VL	MH	LH
CONT	NEU	Non-Startle	0.383 ± 0.082	0.538 ± 0.189	0.387 ± 0.068	0.451 ± 0.109
		Startle	0.363 ± 0.158	**0.376 ± 0.104[a]**	**0.334 ± 0.084[a]**	**0.365 ± 0.106[a]**
	FEAR	Non-Startle	0.443 ± 0.151	0.511 ± 0.170	0.582 ± 0.396	0.532 ± 0.204
		Startle	0.367 ± 0.183	**0.344 ± 0.151[a]**	**0.316 ± 0.125[a]**	**0.373 ± 0.126[a]**
	INJ	Non-Startle	0.386 ± 0.085	0.421 ± 0.094	0.401 ± 0.147	0.411 ± 0.067
		Startle	0.429 ± 0.189	**0.404 ± 0.172[a]**	**0.305 ± 0.139[a]**	**0.365 ± 0.155[a]**
ACLR	NEU	Non-Startle	0.460 ± 0.191	0.503 ± 0.210	0.365 ± 0.124	0.393 ± 0.131
		Startle	0.430 ± 0.133	0.464 ± 0.141	0.404 ± 0.153	0.437 ± 0.134
	FEAR	Non-Startle	0.470 ± 0.142	0.512 ± 0.199	0.375 ± 0.137	0.461 ± 0.249
		Startle	0.374 ± 0.134	0.369 ± 0.129	0.379 ± 0.217	0.332 ± 0.100
	INJ	Non-Startle	0.507 ± 0.219	0.527 ± 0.231	0.387 ± 0.148	0.448 ± 0.143
		Startle	**0.373 ± 0.092***	0.407 ± 0.089	0.319 ± 0.192	0.385 ± 0.135

Table 13 Means and standard deviation for Time-To-Peak (TTP, [sec]) EMG for the quadriceps and hamstrings between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. *Significant difference from NEU (p<0.05). [a]Significant difference between stiffness conditions (p<0.05).

			PRE EMG Area (-250 ~ 0 ms)				POST-1 EMG Area (0 ~ 250 ms)				POST-2 EMG Area (250 ~ 500 ms)			
Group	Picture Type	Condition	VM	VL	MH	LH	VM	VL	MH	LH	VM	VL	MH	LH
CONT	NEU	Non-Startle	0.732 ± 0.502	0.431 ± 0.276	0.130 ± 0.064	0.197 ± 0.093	3.382 ± 2.312	2.96 ± 1.64	0.632 ± 0.396	0.814 ± 0.455	7.380 ± 4.939	5.755 ± 2.295	0.881 ± 0.552	1.343 ± 0.757
		Startle	0.699 ± 0.567	0.531 ± 0.491	0.129 ± 0.071	0.232 ± 0.139	6.42 ± 5.506[b]	4.98 ± 2.778[b]	1.028 ± 0.682[b]	1.609 ± 0.888[b]	6.892 ± 3.749	6.43 ± 3.283	0.875 ± 0.476	1.374 ± 0.773
	FEAR	Non-Startle	0.709 ± 0.512	0.425 ± 0.298	0.133 ± 0.061	0.203 ± 0.100	2.812 ± 1.539	2.47 ± 1.301	0.661 ± 0.449	0.886 ± 0.508	6.920 ± 3.583	5.647 ± 2.498	0.832 ± 0.524	1.116 ± 0.499
		Startle	0.741 ± 0.627	0.488 ± 0.511	0.165 ± 0.144	0.240 ± 0.217	9.307 ± 7.46[b]	7.041 ± 4.298[b]	1.128 ± 0.832[b]	1.927 ± 1.377[b]	8.684 ± 5.743[ab]	6.716 ± 4.086	0.870 ± 0.495	1.415 ± 1.013
	INJ	Non-Startle	0.770 ± 0.559	0.467 ± 0.280	0.133 ± 0.064	0.208 ± 0.112	3.71 ± 2.791	3.311 ± 2.166	0.654 ± 0.386	1.061 ± 0.807	7.934 ± 5.250	6.290 ± 3.025	0.960 ± 0.481	1.432 ± 0.949
		Startle	1.020 ± 0.835	0.525 ± 0.297	0.172 ± 0.106	0.238 ± 0.163	7.715 ± 5.639[b]	5.331 ± 3.501[b]	1.051 ± 0.66[b]	2.06 ± 1.393[b]	6.964 ± 3.418	6.897 ± 2.816	0.813 ± 0.495	1.459 ± 0.846
ACLR	NEU	Non-Startle	0.478 ± 0.288	0.238 ± 0.103*	0.152 ± 0.072	0.218 ± 0.111	3.254 ± 1.756	2.428 ± 1.704	1.004 ± 0.716	0.978 ± 0.678	6.893 ± 2.480	6.085 ± 3.008	1.003 ± 0.537	1.674 ± 1.214
		Startle	0.488 ± 0.364	0.269 ± 0.258*	0.171 ± 0.076	0.235 ± 0.142	3.475 ± 2.712	3.243 ± 2.439	0.794 ± 0.384	1.095 ± 0.608	5.936 ± 3.718	5.080 ± 3.266	0.952 ± 0.446	1.297 ± 0.750
	FEAR	Non-Startle	0.457 ± 0.303	0.245 ± 0.114*	0.139 ± 0.069	0.218 ± 0.099	2.64 ± 1.572	1.766 ± 1.055	0.919 ± 0.748	0.851 ± 0.549	5.429 ± 1.722	4.910 ± 2.546	0.859 ± 0.466	1.366 ± 0.899[a]
		Startle	0.466 ± 0.398	0.276 ± 0.203*	0.161 ± 0.127	0.208 ± 0.107	7.224 ± 6.296[a]	5.011 ± 4.337[a]	1.599 ± 1.553[a]	1.418 ± 1.074	6.831 ± 3.998	5.976 ± 3.621	1.153 ± 0.917	1.737 ± 1.312[ab]
	INJ	Non-Startle	0.480 ± 0.314	0.230 ± 0.115*	0.144 ± 0.072	0.203 ± 0.092	2.78 ± 1.633	1.901 ± 1.305	0.777 ± 0.511	0.951 ± 0.801	5.979 ± 1.641	5.048 ± 2.731	0.845 ± 0.476	1.367 ± 1.047
		Startle	0.540 ± 0.484	0.305 ± 0.254*	0.155 ± 0.093	0.261 ± 0.136	6.561 ± 4.67[a]	5.103 ± 3.944[a]	1.449 ± 1.269[a]	1.602 ± 1.141	6.817 ± 3.886	5.991 ± 2.928	1.016 ± 0.714	1.571 ± 1.05

Table 14 Means and standard deviation for the quadriceps and hamstrings EMG activation area prior to and after the perturbation between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings *Significant group differences (p<0.05). [a]Significant difference from NEU (p<0.05). [b]Significant difference between stiffness conditions (p<0.05).

	CON	ACLR
N	20 (17)	20 (16)
Age (yrs)	24.5 ± 4.9	22.2 ± 3.9
Height (cm)	166.0 ± 8.8	166.2 ± 10.8
Mass (kg)	62.5 ± 12.6	74.4 ± 27.5

Table 15 Subjects' demographic information for Emotional Regulatory Executive Function (EREF) training effects on Emotion Regulation and Joint Stiffness Testing.

N: Subjects recruited and participated in the pretest session (number of subjects participated in the posttest session).

		NIH Executive Function, Knee Function, & Kinesiophobia Outcomes						
		NIH Toolbox		Knee Function Outcomes				TSK-11 (%)
		DCCS	FICA	GRKF (%)	KOS-ADL (%)	# of Giving-way	LSI (%)	
PRE	CONT	9.44 ± 0.49	9.57 ± 0.32	100 ± 0	100 ± 0	0 ± 0	100.61 ± 4.49	36.50 ± 11.32
	ACLR	**9.80 ± 0.22[a]**	9.60 ± 0.27	**95.12 ± 7.96[a]**	**93.05 ± 9.66[a]**	**2.85 ± 3.29[a]**	**93.44 ± 6.49[a]**	41.90 ± 12.96
POST	CONT	9.59 ± 0.47	**9.72 ± 0.24***	100 ± 0	100 ± 0	0 ± 0	100.42 ± 2.17	36.77 ± 14.02
	ACLR	**9.83 ± 0.20[a]**	**9.71 ± 0.22***	**94.19 ± 8.42[a]**	**95.81 ± 5.75[a]**	**1.54 ± 1.941[a]**	**96.49 ± 5.27[a]***	39.77 ± 12.83

Table 16 Means and standard deviation for the NIH executive function and knee function assessment and fear of re-injury/movement outcomes Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. PRE: before the EREF training. POST: after the EREF training. DCCS: Dimensional Change Card Sort test. FICA: Flanker Inhibitory Control and Attention test. GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). TSK-11: Short-version of the Tampa Scale for Kinesiophobia. *Significant pre-post time differences (p<0.05). [a]Significant group differences (p<0.05).

		Correlations between executive function, knee functional outcomes and Fear of Re-injury									
		PRE					POST				
		GRKF (%)	KOS-ADL (%)	# of Giving-Way	TSK-11 (%)	LSI (%)	GRKF (%)	KOS-ADL (%)	# of Giving-Way	TSK-11 (%)	LSI (%)
DCCS DIFF	CONT				-.234	.019				-.224	-.296
	ACLR	.200	-.217	-.218	-.042	.179	.070	.014	-.053	-.276	.155
	TOTAL	.282	.198	.152	-.192	.090	.198	.226	-.133	-.260	.107
FICA DIFF	CONT				.079	-.007				.228	-0.536
	ACLR	.163	.142	.313	-.050	.534*	.281	-.202	.401	-.001	.519*
	TOTAL	.150	.117	.122	-.004	.292	.187	-.063	.157	.124	.200

Table 17 Overall and within group correlations between the executive function and knee function assessments and TSK-11 values before and after the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. PRE: before the EREF training. POST: after the EREF training. DCCS DIFF: Dimensional Change Card Sort value differences between before and after the EREF training (Post-training value – Pre-training value). FICA DIFF: Flanker Inhibitory Control and Attention value differences between before and after the EREF training (Post-training value – Pre-training value). GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). TSK-11: Short-version of the Tampa Scale for Kinesiophobia. *Significant correlation. A probability α level was set a *prior* at 0.05.

		Correlations between knee functional outcomes and TSK-11		
TSK-11 (%)		GRKF (%)	KOS-ADL (%)	LSI (%)
PRE	CONT	.054	.215	-.242
	ACLR	-.252	-.475*	-.341
	TOTAL	-.291	-.441**	-.318
POST	CONT	.143	.216	.143
	ACLR	-.730**	-.471	-.207
	TOTAL	-.480**	-.384*	-.116

Table 18 Overall and within group correlations between knee function assessments and TSK-11 values before and after the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. PRE: before the EREF training. POST: after the EREF training. GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). TSK-11: Short-version of the Tampa Scale for Kinesiophobia. *Significant correlation. A probability α level was set a *prior* at 0.05.

		SAM & Level of Fear (9-point Likert Scale)					
		Valence		Arousal		Lv. of Fear	
TYPE	GROUP	PRE	POST	PRE	POST	PRE	POST
NEU	CONT	5.00 ± 0.02	5.00 ± 0.00	1.10 ± 0.14	1.04 ± 0.07	1.08 ± 0.10	1.04 ± 0.06
	ACLR	5.01 ± 0.02	5.00 ± 0.00	1.21 ± 0.24	1.00 ± 0.00	1.11 ± 0.16	1.00 ± 0.00
	TOTAL	*5.01 ± 0.02*	*5.00 ± 0.00*	*1.15 ± 0.20*	***1.02 ± 0.05[a]***	*1.09 ± 0.13*	***1.02 ± 0.05[a]***
FEAR	CONT	2.54 ± 0.98	2.61 ± 0.87	5.39 ± 1.94	4.50 ± 1.83	5.88 ± 1.95	4.72 ± 1.67
	ACLR	2.98 ± 1.19	3.18 ± 0.92	5.14 ± 2.24	4.33 ± 2.58	4.93 ± 2.15	4.25 ± 2.23
	TOTAL	***2.75 ± 1.07[*] [†]***	***2.88 ± 0.91[*] [†]***	***5.26 ± 2.05[*] [†]***	***4.42 ± 2.19[a*] [†]***	***5.42 ± 2.06[*] [†]***	***4.5.0 ± 1.94[a*] [†]***
INJ	CONT	4.13 ± 0.63	4.06 ± 0.81	2.80 ± 1.02	2.55 ± 1.24	2.66 ± 1.18	2.36 ± 1.24
	ACLR	4.31 ± 0.82	4.44 ± 0.62	3.73 ± 2.00	2.92 ± 1.66	3.34 ± 1.74	2.61 ± 1.00
	TOTAL	***4.22 ± 0.71[*]***	***4.24 ± 0.73[*]***	***3.27 ± 1.62[*]***	***2.73 ± 1.45[a*]***	***2.99 ± 1.49[*]***	***2.48 ± 1.12[a*]***

Table 19 Effects of the EREF training on subjective emotional responses of all subjects among emotion types.

NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. PRE: before the EREF training. POST: after the EREF training. SAM: the Self-Assessment Manikin; including two valence and arousal domains. Valence: level of happiness ranging from 1 = very unhappy to 9 = very happy. Arousal: arousal level ranging from 1 = very calm to 9 = very arousal. Lv. of Fear: ranges from 1 = not fearful at all to 9 = very fearful. [*]Significant difference from NEU (p<0.05). [†]Significant difference from INJ (p<0.05). [a]Significant pre-post time differences (p<0.05).

		Heart Rate Deceleration (bpm)		
TIME	GROUP	NEU	FEAR	INJ
PRE	CONT	-3.75 ± 1.15	**-4.65 ± 1.15***	**-4.23 ± 0.95***
	ACLR	-3.41 ± 1.01	**-4.52 ± 0.83***	**-4.47 ± 1.01***
POST	CONT	**-3.24 ± 1.18[a]**	**-3.96 ± 1.51[a]***	**-4.01 ± 1.17[a]***
	ACLR	-3.45 ± 1.28	**-3.57 ± 1.14[a]**	**-3.51 ± 0.97[a]**

Table 20 Effects of the EREF training on changes in heart rate (HR) deceleration between Groups by Emotion Types.

NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. PRE: before the EREF training. POST: after the EREF training. *Significant difference from NEU (p<0.05). [a]Significant pre-post time differences (p<0.05).

Group	Picture Type	Normalized Stiffness (Nm/°/kg)					
		Short Range (0-4°)		Mid Range (0-20°)		Long Range (0-40°)	
		PRE	POST	PRE	POST	PRE	POST
CONT	NEU	0.053 ± 0.007	0.052 ± 0.009	0.020 ± 0.010	0.019 ± 0.009	0.048 ± 0.009	0.052 ± 0.014
	FEAR	0.053 ± 0.009	0.055 ± 0.011	0.031 ± 0.020	0.027 ± 0.019	0.047 ± 0.016	0.054 ± 0.013
	INJ	0.059 ± 0.012	0.054 ± 0.012	0.027 ± 0.016	0.023 ± 0.013	0.046 ± 0.014	0.054 ± 0.018
ACLR	NEU	0.051 ± 0.016	0.051 ± 0.007	0.016 ± 0.013	0.018 ± 0.016	0.04 ± 0.016	0.05 ± 0.013
	FEAR	0.046 ± 0.012[b]	0.049 ± 0.007[b]	0.028 ± 0.021[*]	0.022 ± 0.013	0.05 ± 0.015	0.049 ± 0.018
	INJ	0.047 ± 0.012[b]	0.047 ± 0.008[b]	0.031 ± 0.025[*]	0.017 ± 0.011	0.046 ± 0.018	0.052 ± 0.015

Table 21 Mean and standard deviation for Normalized Short (0-4°), Mid (0-20°), and long (0-40°) range stiffness values between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. PRE: before the EREF training. POST: after the EREF training. [*]Significant difference from NEU (p<0.05). [b]Significant group difference (p<0.05).

			TTP EMG (sec)			
GROUP	TIME	PICTURE TYPE	VM	VL	MH	LH
CONT	PRE	NEU	0.379 ± 0.134	0.352 ± 0.107	0.308 ± 0.064	0.365 ± 0.108
		FEAR	0.352 ± 0.187	0.29 ± 0.121	0.287 ± 0.142	0.35 ± 0.135
		INJ	0.478 ± 0.162	0.378 ± 0.184	0.316 ± 0.16	0.363 ± 0.178
	POST	NEU	0.352 ± 0.099	**0.527 ± 0.323[a]**	0.325 ± 0.168	0.372 ± 0.134
		FEAR	0.357 ± 0.104	**0.391 ± 0.171[a]**	0.388 ± 0.2	0.374 ± 0.157
		INJ	0.389 ± 0.123	**0.426 ± 0.174[a]**	0.317 ± 0.16	0.331 ± 0.18
ACLR	PRE	NEU	0.461 ± 0.145	0.475 ± 0.147	0.414 ± 0.161	0.47 ± 0.146
		FEAR	0.404 ± 0.146	0.393 ± 0.14	0.368 ± 0.239	0.333 ± 0.109
		INJ	0.365 ± 0.105	0.392 ± 0.081	0.281 ± 0.203	0.381 ± 0.121
	POST	NEU	0.439 ± 0.157	0.528 ± 0.222	0.434 ± 0.216	0.421 ± 0.204
		FEAR	0.383 ± 0.128	0.406 ± 0.183	0.548 ± 0.278	0.36 ± 0.103
		INJ	0.581 ± 0.466	0.488 ± 0.298	0.343 ± 0.211	0.353 ± 0.093

Table 22 Means and standard deviation for Time-To-Peak (TTP, [sec]) EMG for the quadriceps and hamstrings between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. PRE: before the EREF training. POST: after the EREF training. [a]Significant pre-post time difference (p<0.05).

			PRE EMG (-150 ~ 0ms)				POST1 EMG (0 ~ 250ms)				POST2 EMG (250 ~ 500ms)			
GROUP	TIME	PICTURE TYPE	VM	VL	MH	LH	VM	VL	MH	LH	VM	VL	MH	LH
CONT	PRE	NEU	0.487 ± 0.338	0.136 ± 0.070	0.205 ± 0.107	0.365 ± 0.108	6.045 ± 4.702	5.307 ± 2.844	1.100 ± 0.760	1.659 ± 0.949	7.584 ± 3.60	7.332 ± 2.907	0.912 ± 0.505	1.468 ± 0.799
		FEAR	0.562 ± 0.558	0.172 ± 0.143	0.185 ± 0.122	0.350 ± 0.135	**7.945 ± 4.815***	**6.763 ± 3.728***	1.195 ± 0.925	1.880 ± 1.375	**9.447 ± 5.447***	7.381 ± 3.854	0.918 ± 0.470	1.536 ± 1.024
		INJ	0.521 ± 0.341	0.144 ± 0.093	0.201 ± 0.115	0.363 ± 0.178	**7.895 ± 6.197***	6.078 ± 3.880	1.131 ± 0.731	1.961 ± 1.385	6.979 ± 3.399	7.248 ± 3.011	0.922 ± 0.511	1.494 ± 0.799
	POST	NEU	0.419 ± 0.247	0.207 ± 0.207	0.136 ± 0.054	0.372 ± 0.134	5.735 ± 3.302	3.853 ± 1.729	1.196 ± 0.627	1.082 ± 0.635	6.602 ± 2.802	**5.342 ± 2.172[a]**	1.170 ± 0.600	1.228 ± 0.655
		FEAR	0.471 ± 0.369	0.212 ± 0.177	0.163 ± 0.055	0.374 ± 0.157	**5.870 ± 2.972***	**5.081 ± 4.145***	**1.469 ± 0.907***	1.246 ± 0.824	6.740 ± 1.803	**5.695 ± 1.600[a]**	1.222 ± 0.476	1.423 ± 0.963
		INJ	0.383 ± 0.315	0.198 ± 0.190	0.137 ± 0.084	0.331 ± 0.180	**7.289 ± 4.660***	5.215 ± 3.046	**2.028 ± 1.302***	1.485 ± 1.104	7.656 ± 2.436	**6.180 ± 2.560[a]**	1.238 ± 0.570	1.362 ± 0.833
ACLR	PRE	NEU	0.335 ± 0.293	0.179 ± 0.088	0.261 ± 0.157	0.470 ± 0.146	3.33 ± 2.263	2.858 ± 2.460	0.625 ± 0.298	1.016 ± 0.442	5.731 ± 3.880	4.387 ± 3.194	0.810 ± 0.349	1.222 ± 0.683
		FEAR	0.315 ± 0.233	0.164 ± 0.150	0.220 ± 0.087	0.333 ± 0.109	**7.388 ± 6.388***	**5.018 ± 5.145***	**1.177 ± 1.247***	1.449 ± 1.131	6.625 ± 3.740	5.598 ± 3.934	1.072 ± 0.959	1.653 ± 1.317
		INJ	0.307 ± 0.253	0.147 ± 0.107	0.289 ± 0.155	0.381 ± 0.121	**7.343 ± 4.954***	5.355 ± 4.159	**1.489 ± 1.397***	1.753 ± 1.115	6.953 ± 3.384	5.933 ± 2.629	1.018 ± 0.760	1.562 ± 0.973
	POST	NEU	0.686 ± 0.357	**0.238 ± 0.153[a]**	0.187 ± 0.077	0.421 ± 0.204	5.921 ± 4.069	3.692 ± 2.342	1.026 ± 0.783	1.854 ± 2.036	7.609 ± 2.852	5.921 ± 2.167	1.029 ± 0.588	1.423 ± 1.082
		FEAR	0.591 ± 0.339	**0.206 ± 0.140[a]**	0.242 ± 0.180	0.360 ± 0.103	**8.783 ± 5.444***	**5.412 ± 3.566***	1.000 ± 0.673	1.416 ± 1.085	8.372 ± 4.989	6.437 ± 3.217	0.881 ± 0.559	1.255 ± 0.982
		INJ	0.573 ± 0.344	**0.217 ± 0.169[a]**	0.170 ± 0.069	0.353 ± 0.093	**6.993 ± 4.821***	3.444 ± 2.617	0.965 ± 0.455	2.176 ± 2.351	8.983 ± 4.917	6.217 ± 2.160	1.178 ± 0.658	1.721 ± 1.268

Table 23 Means and standard deviation for the quadriceps and hamstrings EMG activation area prior to and after the perturbation between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. PRE: before the EREF training. POST: after the EREF training. [a]Significant pre-post time difference (p<0.05). [*]Significant difference from NEU (p<0.05).

Appendix B

FIGURES

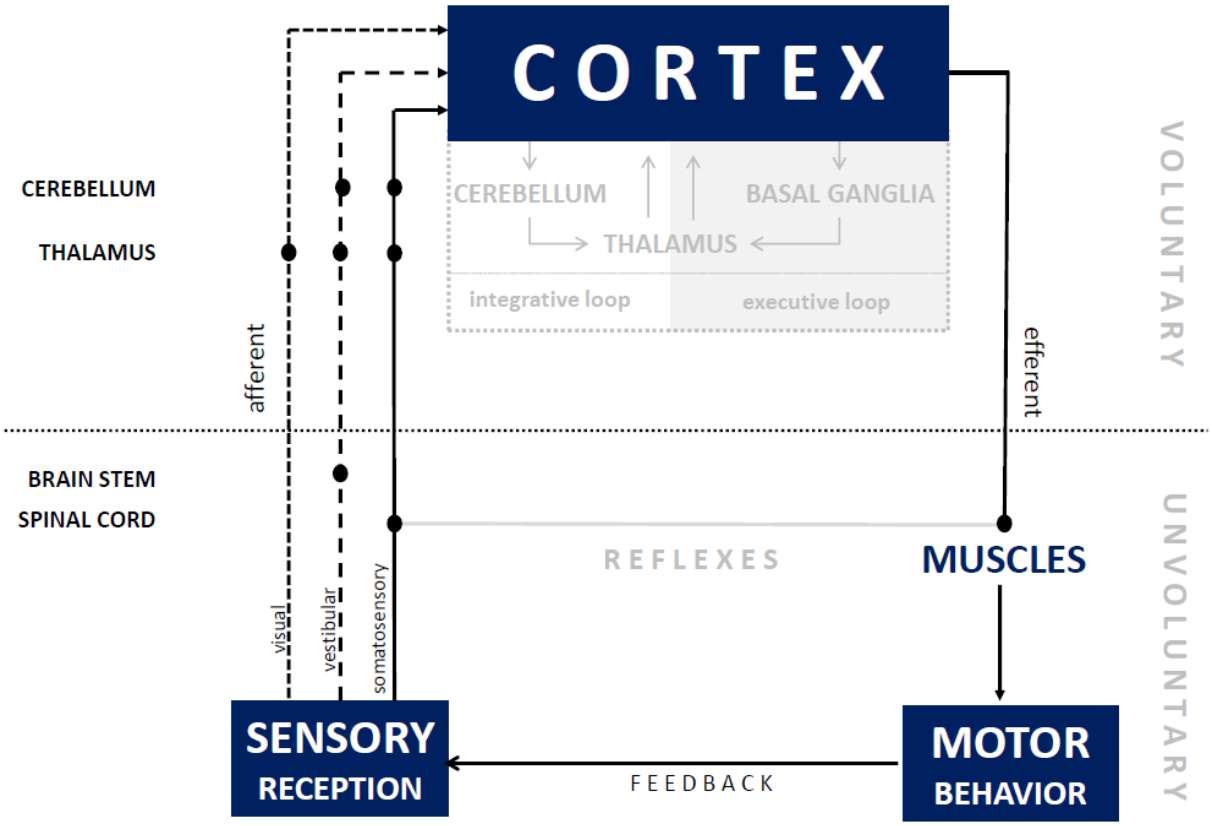


Figure 1 Model of sensorimotor control and its different levels of information processing (Baumeister, 2013)

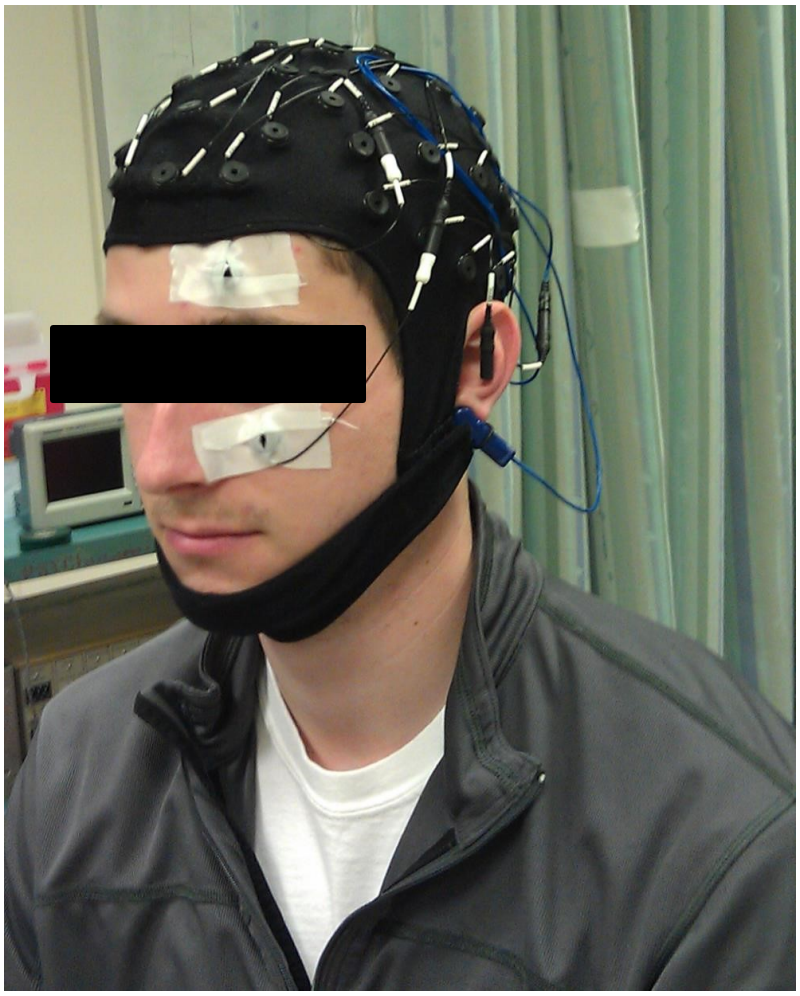


Figure 2 Fitting of brain activity (EEG) cap, with electrodes above and below the left eye.

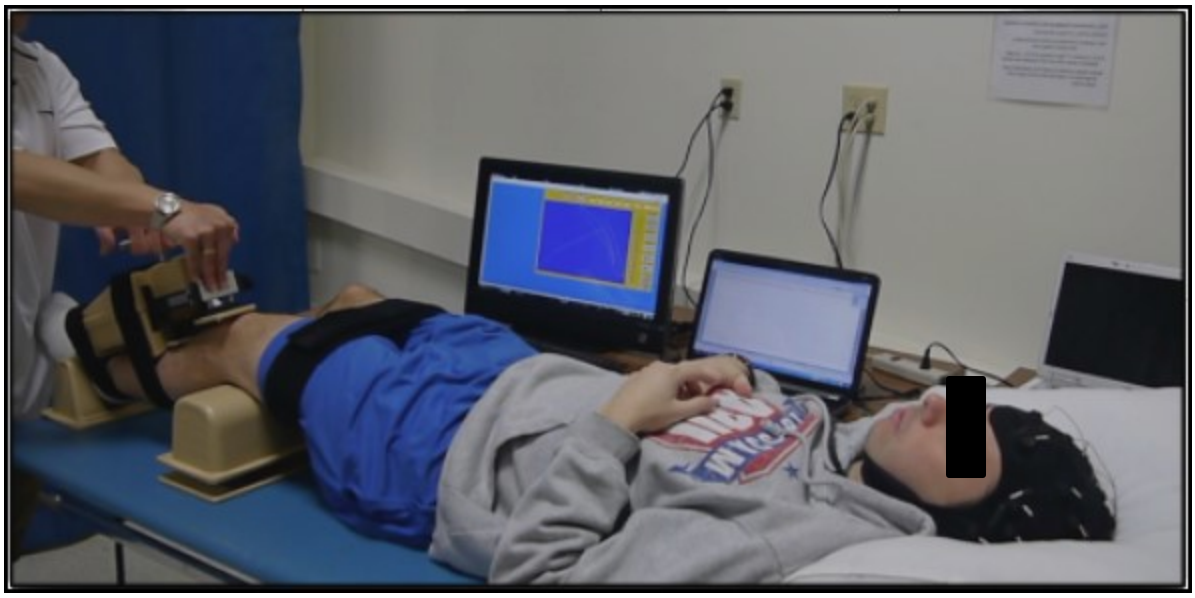


Figure 3 Instrumented knee arthrometer and set-up for brain activity during joint loading testing

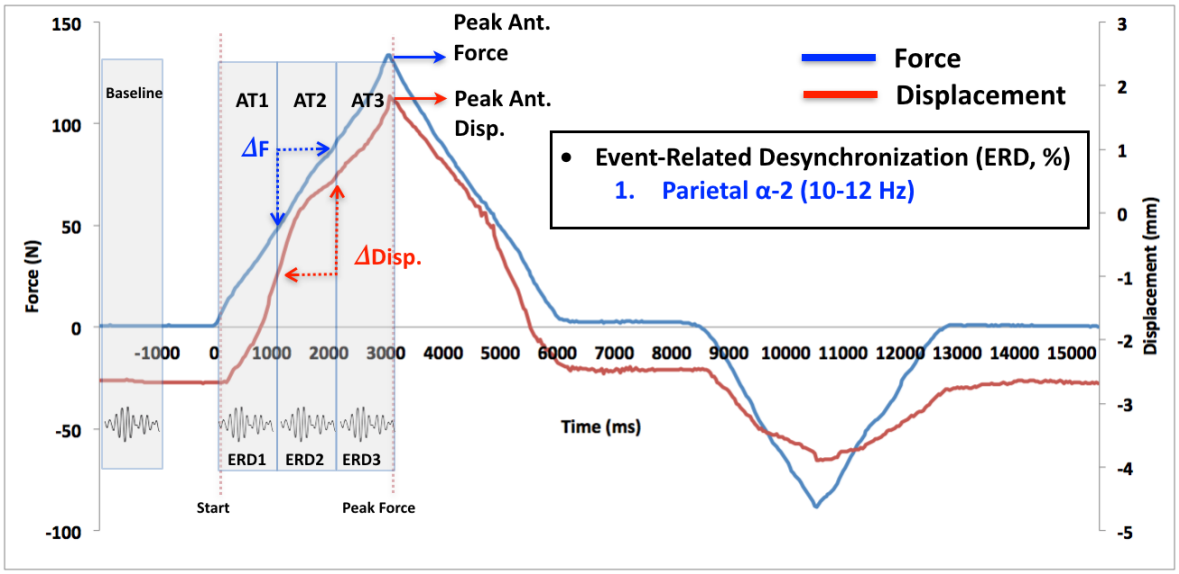


Figure 4 Data analysis scheme for brain activity during joint loading testing

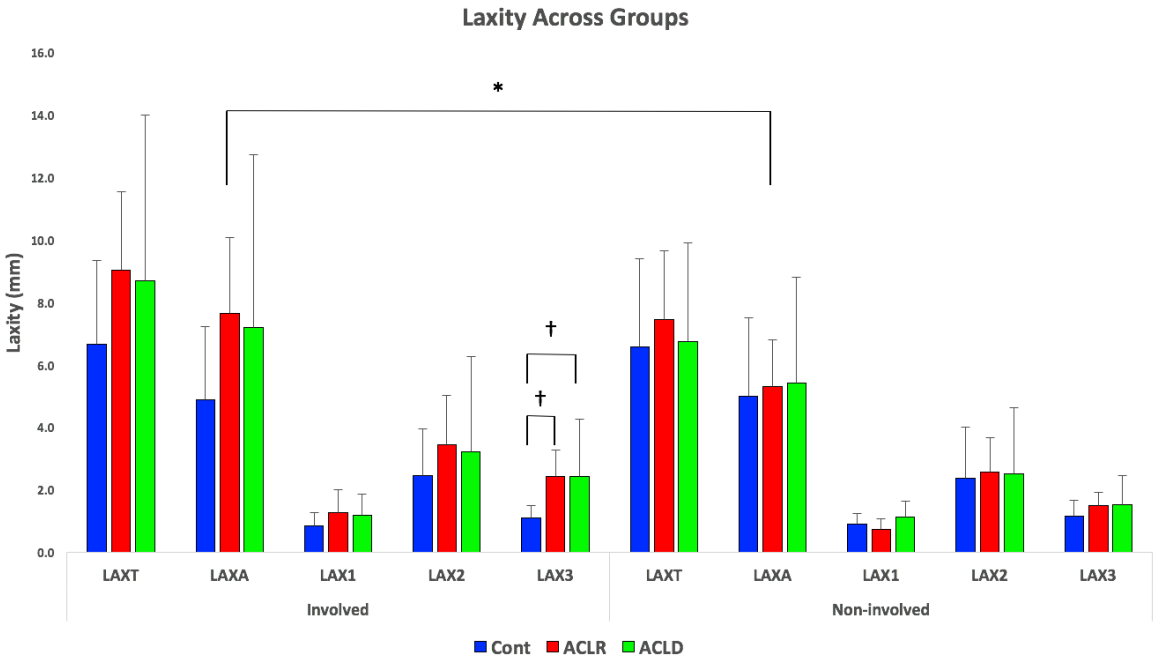


Figure 5 Joint laxity differences between limbs across groups and times of loading.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. LAXT: total laxity. LAXA: total anterior laxity. LAX1: laxity during early loading (0-1000ms). LAX2: laxity during mid loading (1000-2000ms). LAX3: laxity during late loading (2000-3000ms). Error bars represent standard deviation. *Significant LAXA differences between limbs in ACLR group (p=0.003); †Significant LAX3 differences from CONT's matched limb (ACLR: p<0.001, ACLD: p=0.021). A probability α level was set a *prior* at 0.05.

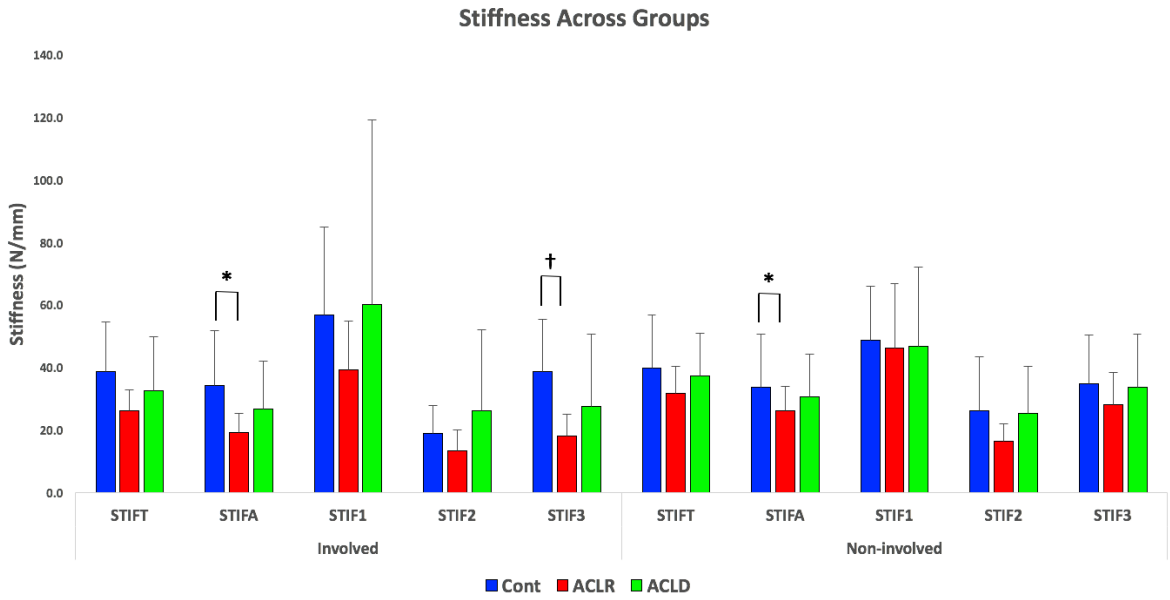


Figure 6 Mechanical stiffness differences between limbs across groups and times of loading.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. ACLD: ACL Deficient patients. STIFT: total stiffness. STIFA: total anterior stiffness. STIF1: stiffness during early loading (0-1000ms). STIF2: stiffness during mid loading (1000-2000ms). STIF3: stiffness during late loading (2000-3000ms). Error bars represent standard deviation. *Significant group difference between ACLR and CONT groups (p=0.028); †Significant stiffness differences between ACLR injured limb and the matched limb in CONT group (p<0.001). A probability α level was set a *prior* at 0.05.

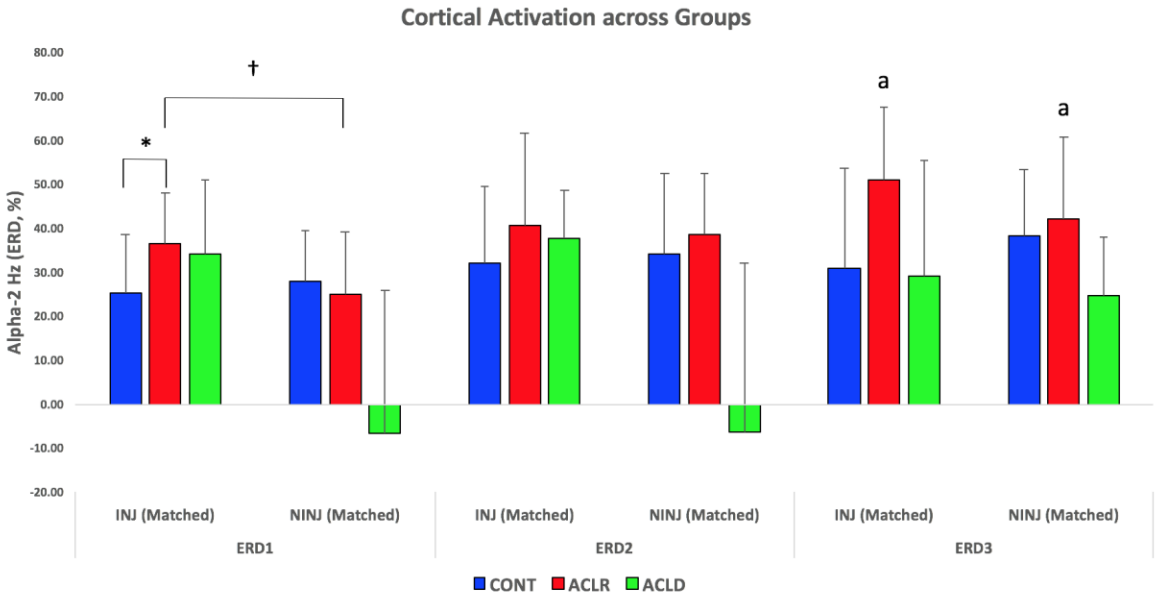


Figure 7 Cortical activation between limbs, across groups and times during joint loading.

CONT: Healthy Controls. ACLR: ACL-Reconstructed patients. ACLD: ACL-Deficient patients. ERD: Event-Related Desynchronization (% decreased power relative to non-loading baseline). Error bars represent standard deviation. *Significant difference from CONT's matched limb (p=0.041); †Significant side-to-side difference in ACLR (p<0.001); [a] Significantly greater ERD3 in ACLR group than both the CONT (p=0.012) and ACLD (p=0.016). A probability α level was set a *prior* at 0.05.

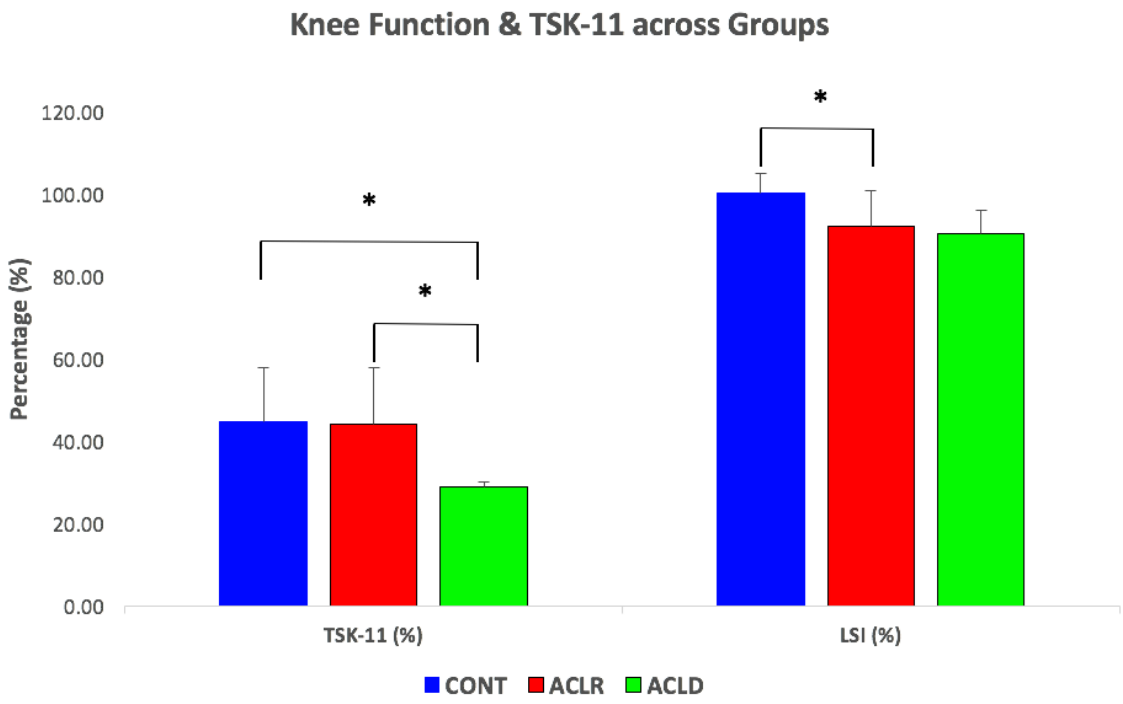


Figure 8 Group differences in Knee Function and Fear of re-injury/movement.

LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). TSK-11: Short-version of the Tampa Scale for Kinesiophobia. Error bars represent standard deviation. *Significant group difference (p<0.05).

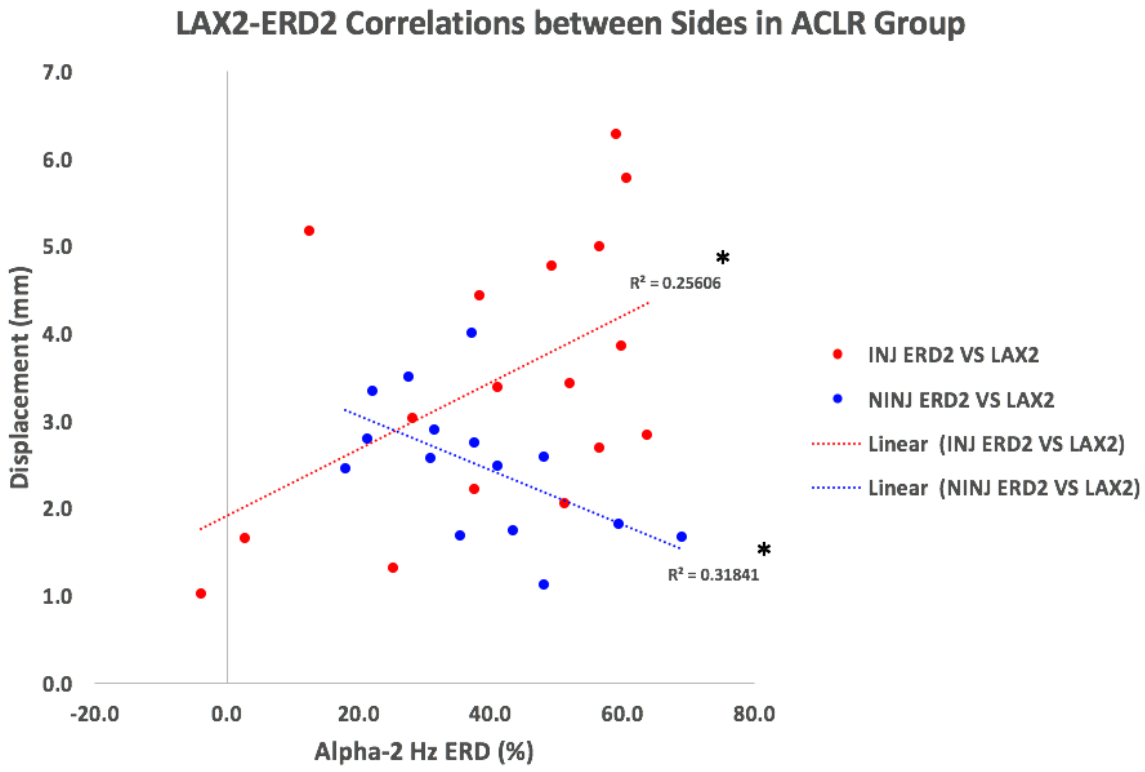


Figure 9 Relationships between joint laxity (mm) and cortical activation (ERD, %) during mid loading (1000-2000ms) in ACLR group.

*Significant correlation (p<0.05).

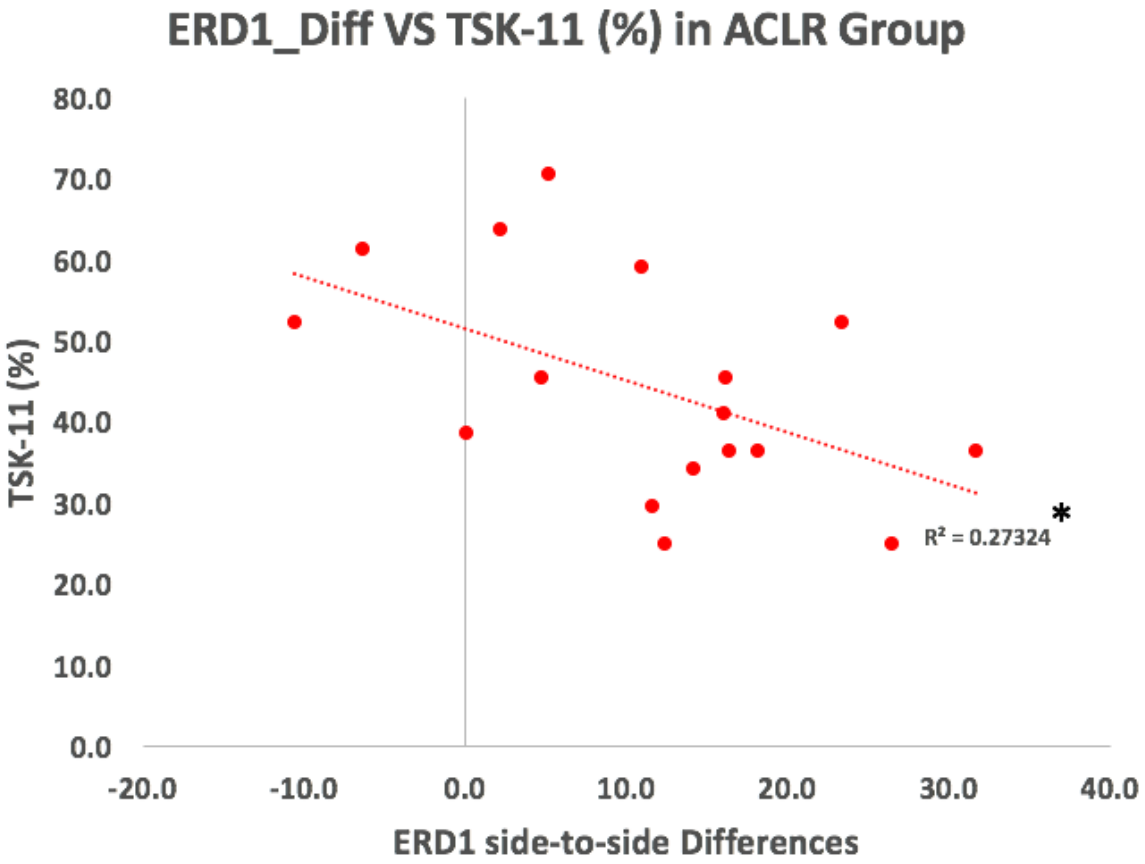


Figure 10 Relationships between cortical activation interlimb differences (ERD, %) and fear of re-injury/movement (TSK-11) in ACLR group.

*Significant correlation (p<0.05).

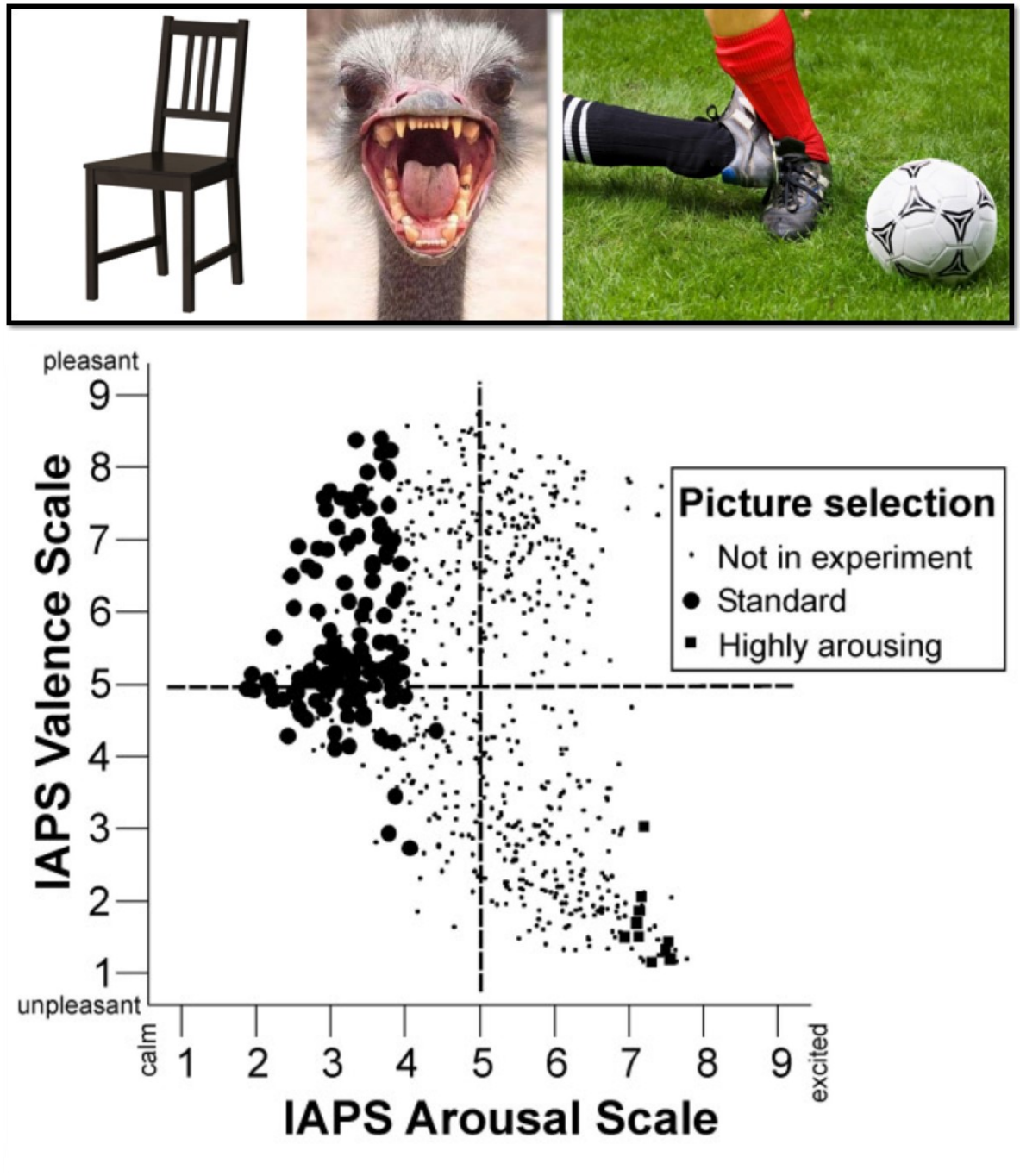


Figure 11 Examples of emotional evocative pictures.

Top Left: neutral, ***Top Middle***: Fear-related, ***Top Right***: Sport Injury-related
Bottom: IAPS Valence and Arousal scale

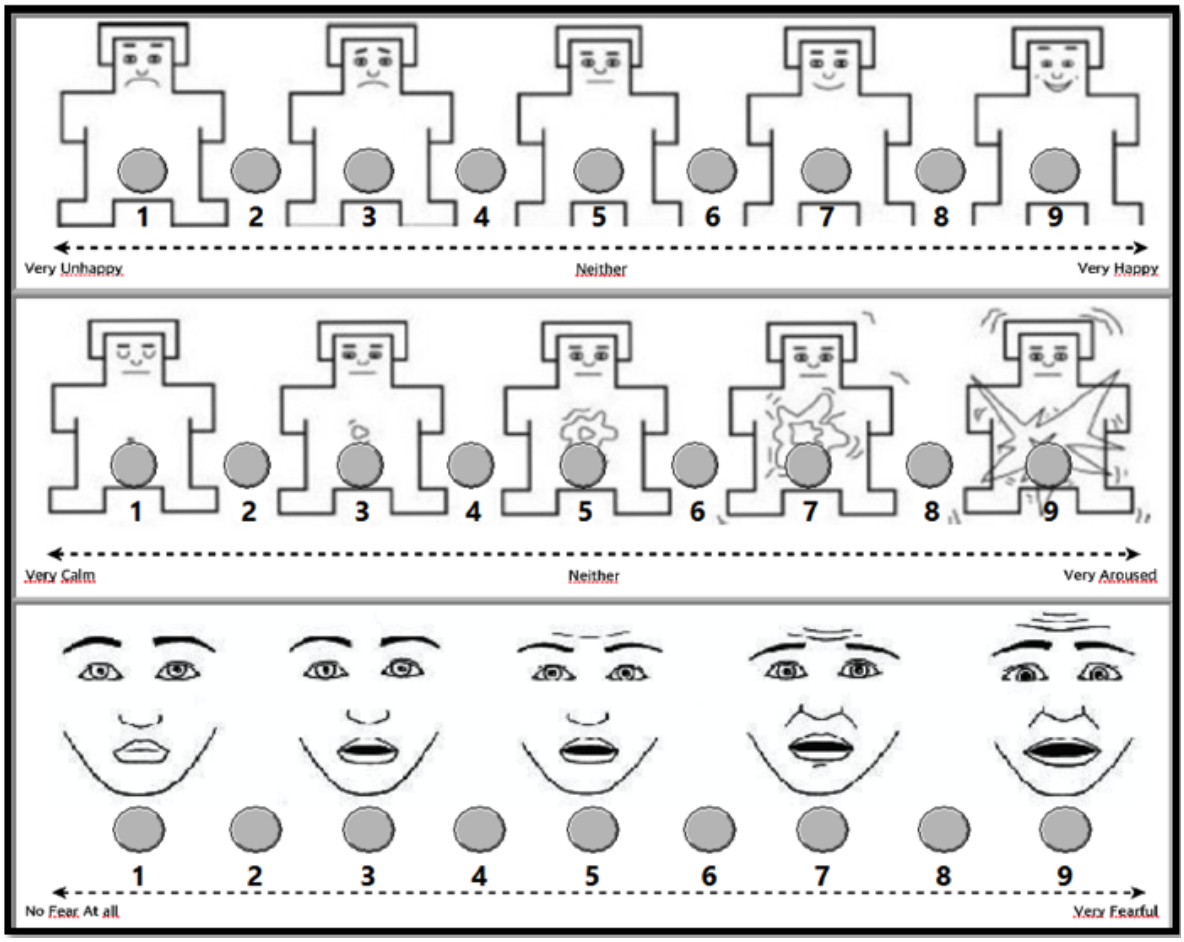
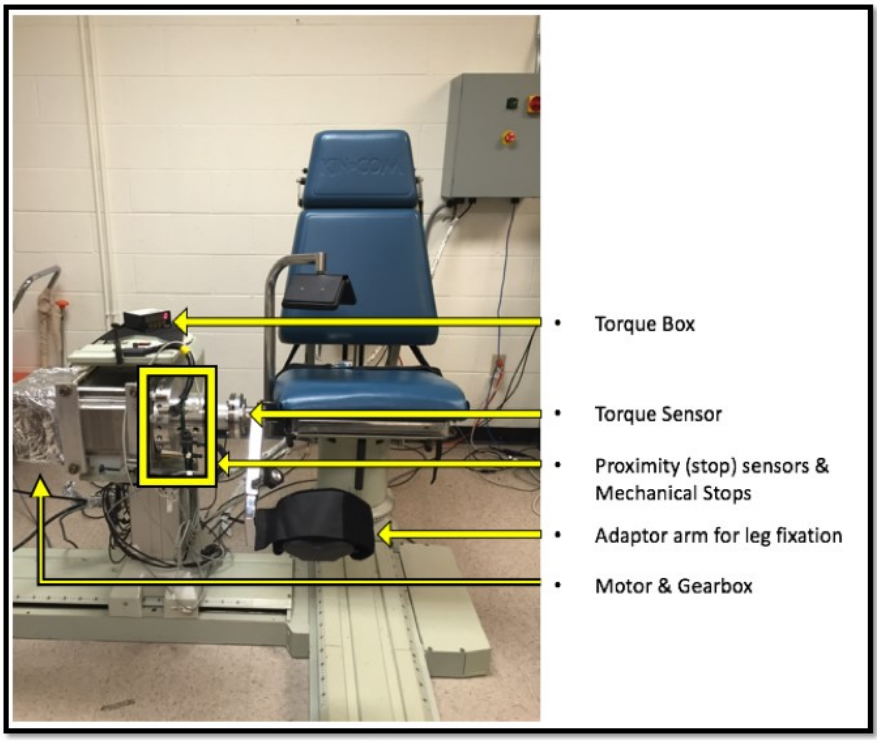


Figure 12 Emotion Rating Scales: SAM & Level of Fear.

(Top: Valence, Middle: Arousal, Bottom: Level of Fear)



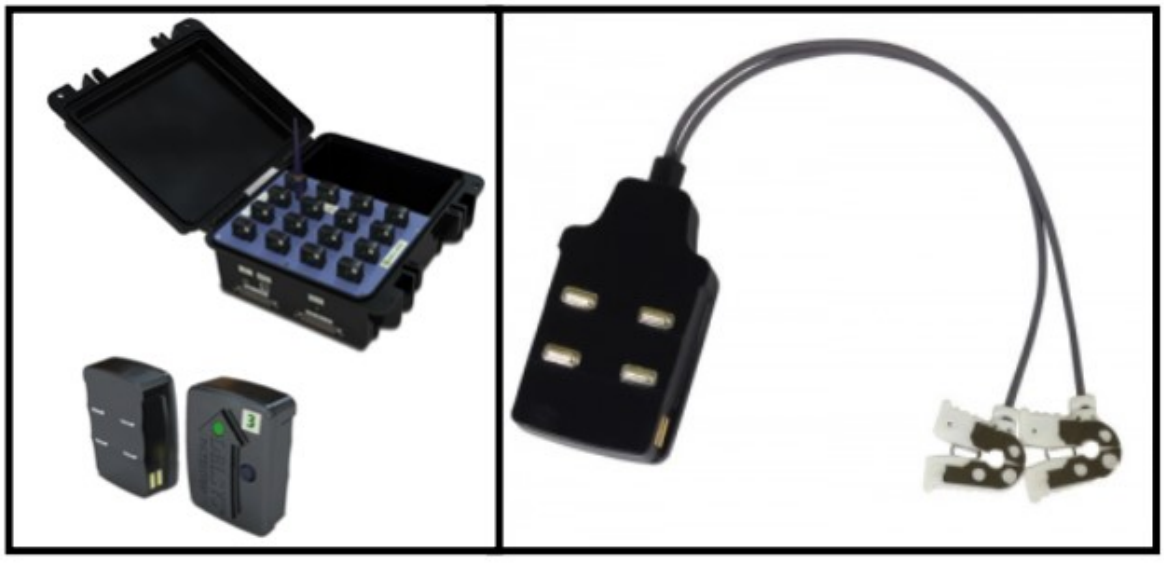


Figure 13 Stiffness and Proprioception Assessment Device (SPAD) & EMG system

Top: SPAD.

Bottom: Trigno™ Wireless EMG System (Delsys Inc., Boston, MA)

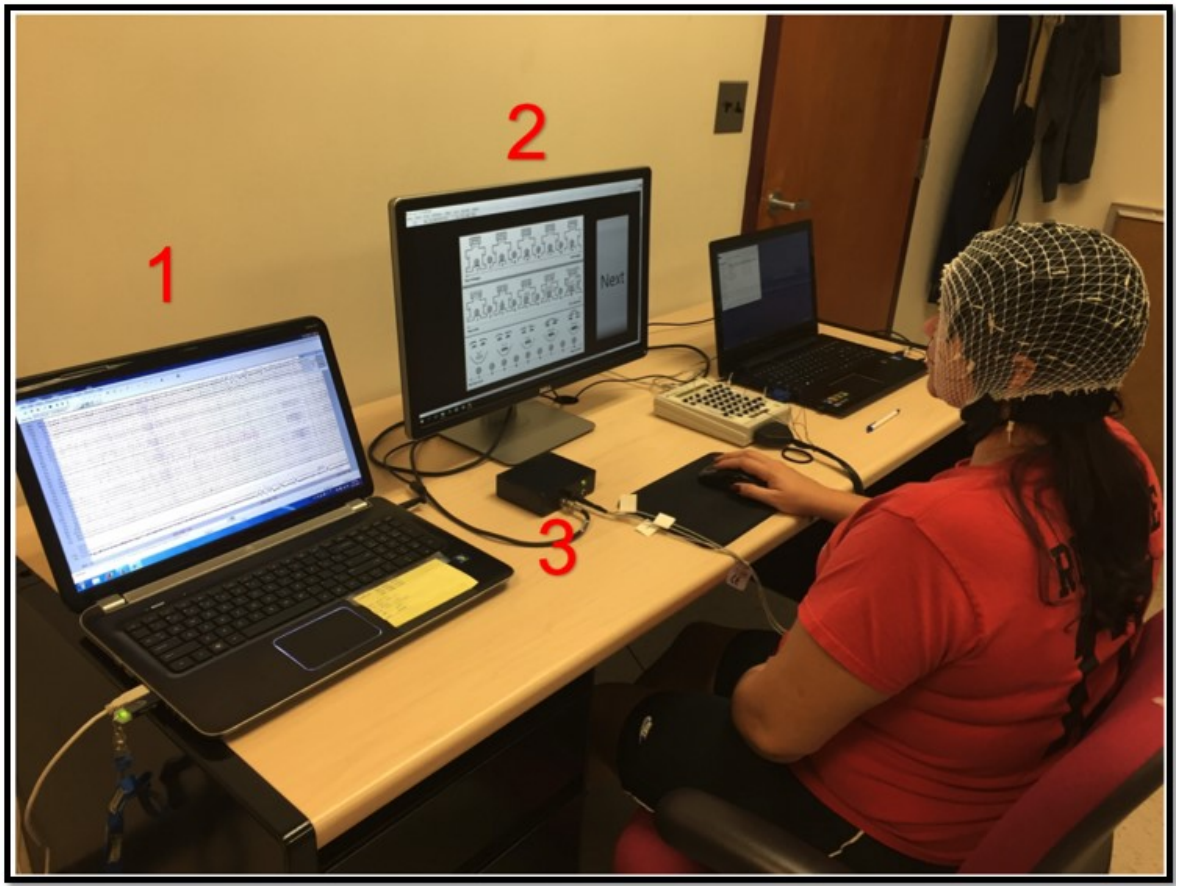


Figure 14 Set-up for Emotional Response testing.

(1: EEG, 2: IAPS, 3: ECG)

**EEG, IAPS, and ECG were used for Aim 2.*
**IAPS and ECG were only used for Aim 3.*

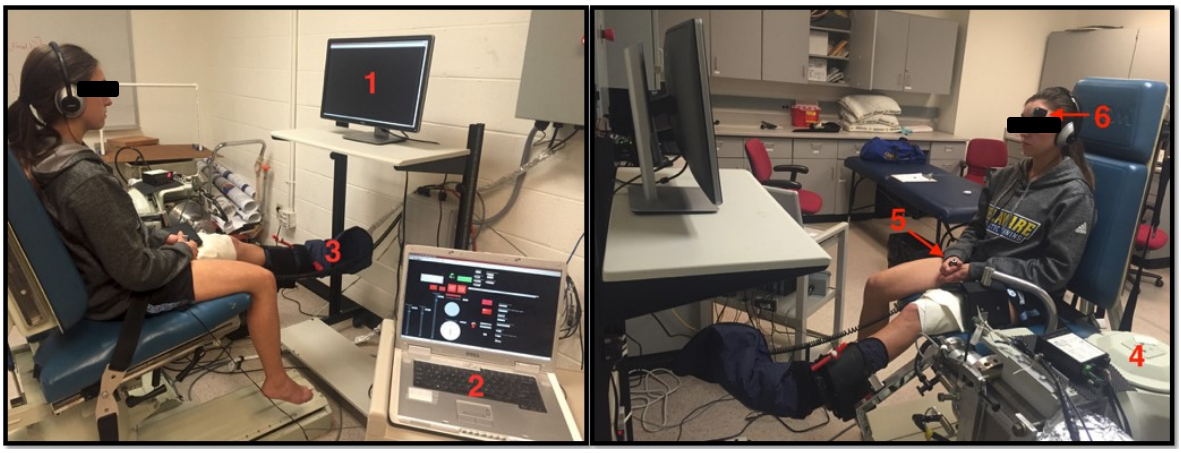


Figure 15 Set-up for stiffness and muscle contraction testing in response to emotional evocative pictures.

Left: Picture presentation (1), SPAD control computer (2), Vacuum splint (3). ***Right***: SPAD machine (4), Safety Switch (5), Eye EMG electrode (6). EMG electrodes for knee muscles are not visible on these figures.

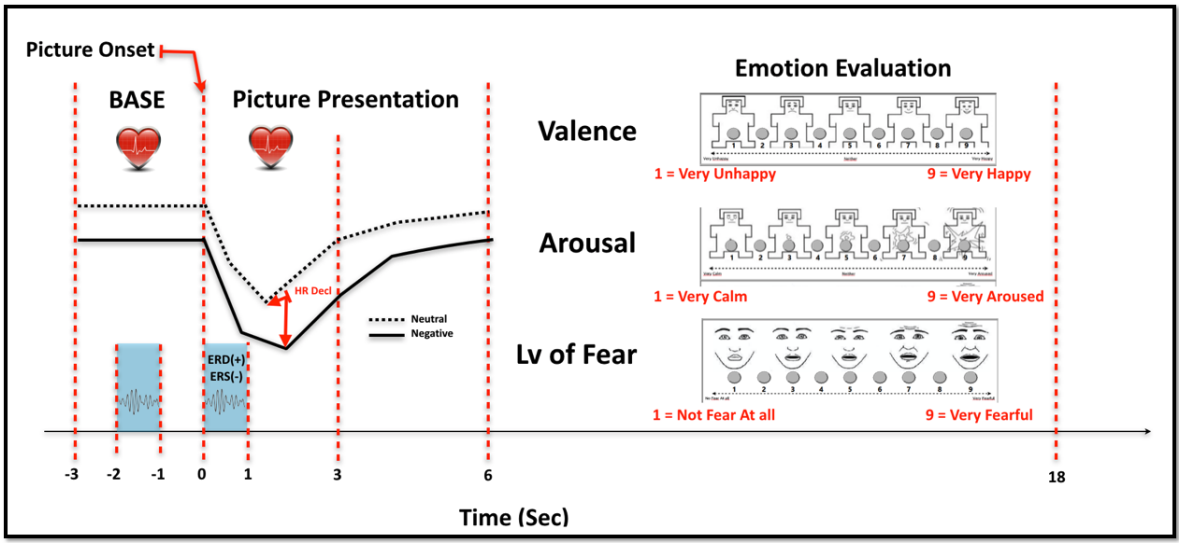


Figure 16 Data Analysis scheme for Emotion Responses including electrocortical and heart rate changes and subjective SAM and level of Fear scores.

** Electrocortical EEG data were not included for Aim 3.*

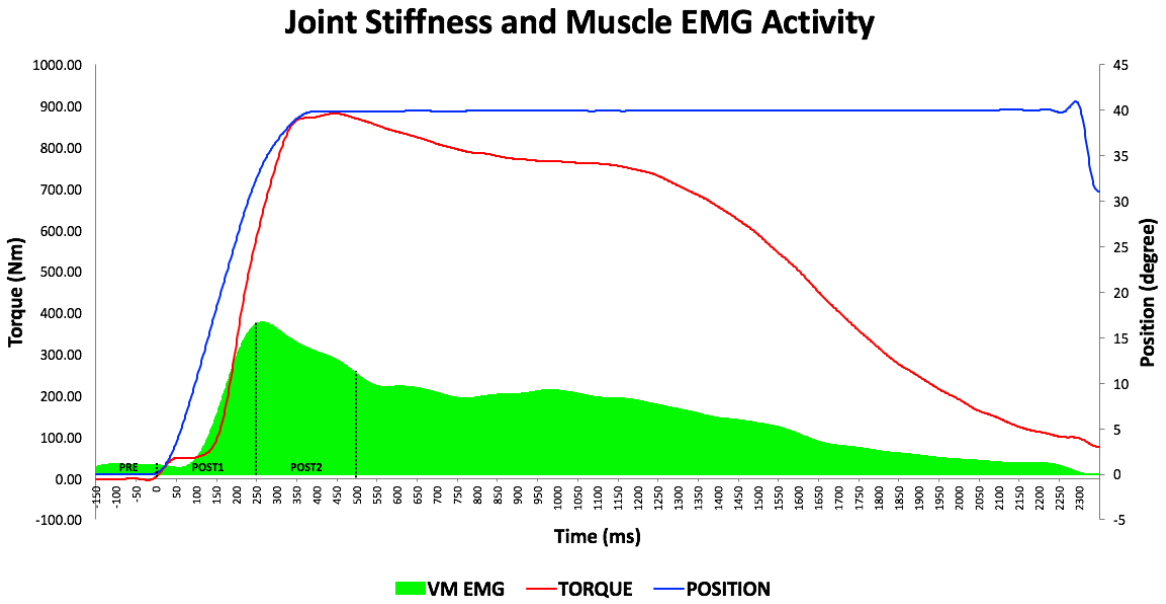


Figure 17 Data Analysis scheme for joint stiffness and EMG (AUC) muscle activation.

Joint stiffness was normalized to body mass ((Nm/°/kg). EMG muscle activation was normalized to MVIC. Figure displays an example of the medial quadriceps (VM) activation under the curve (AUC) before (PRE: -150 to 0 ms) and after the perturbation (POST1: 0 to 250 ms, POST2: 250 to 500 ms).

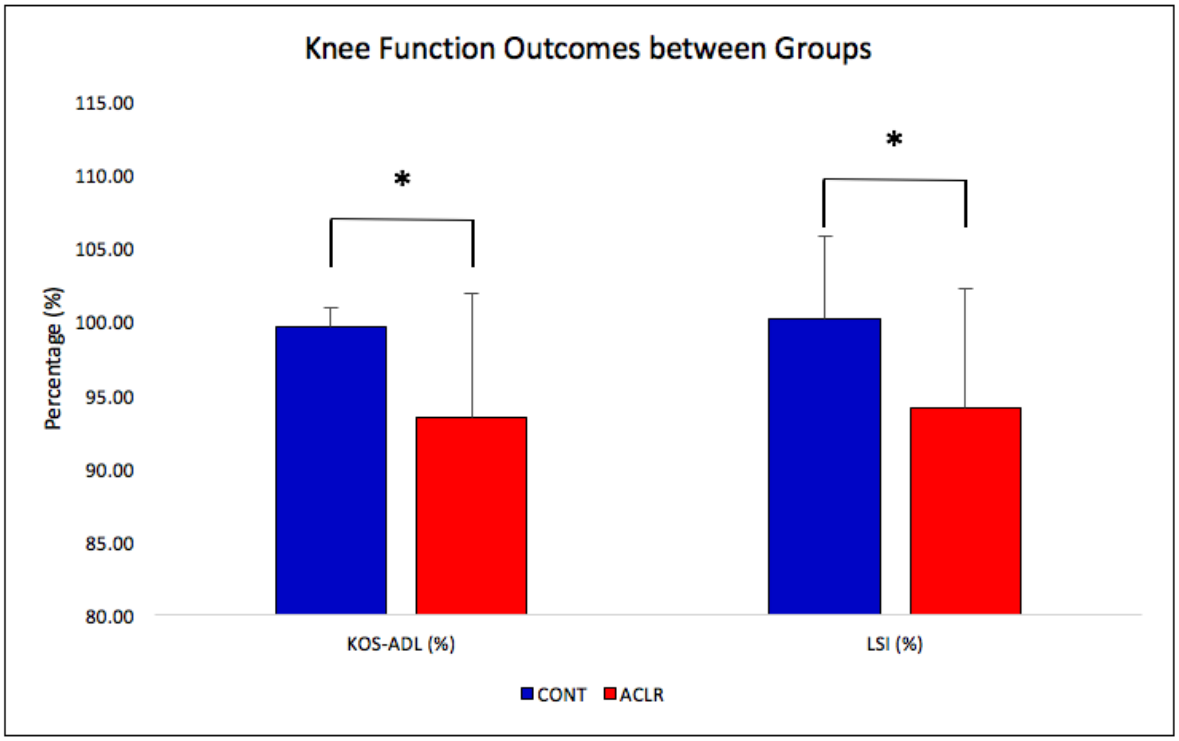


Figure 18 Knee Function outcomes between groups.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). *Significant correlation (p<0.05).

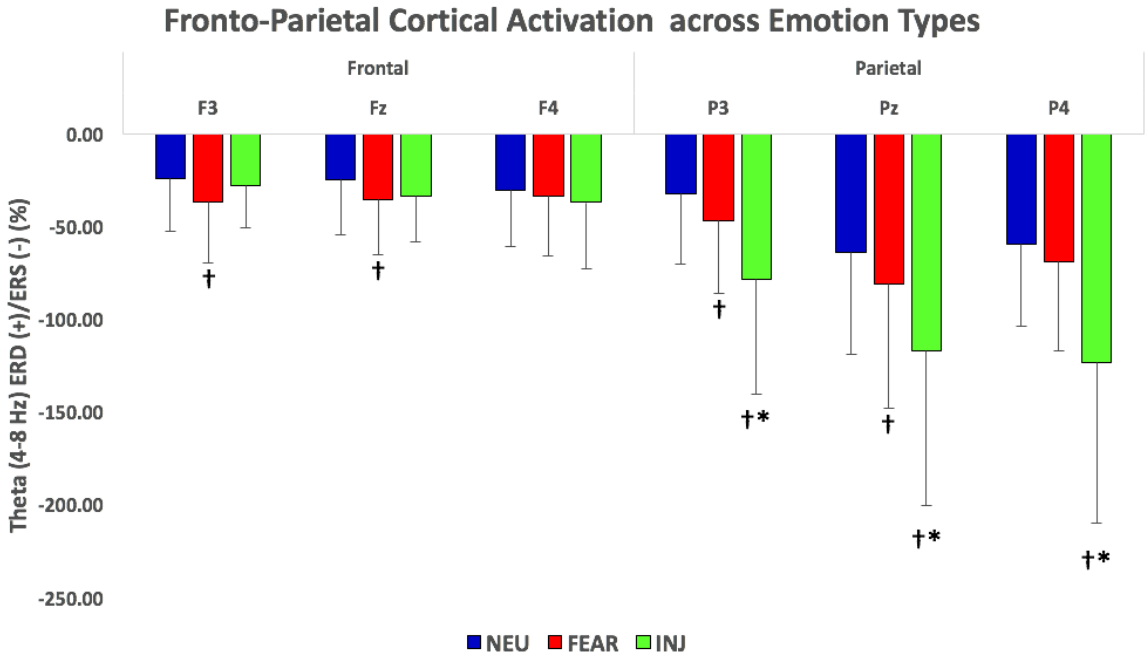


Figure 19 Fronto-parietal Event-Related Desynchronization/Synchronization (ERD/ERS) in the Theta frequency (4-8 Hz) across emotion types and groups during 1st second of picture presentation.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. ERD: Event-Related Desynchronization (% decreased power relative to non-loading baseline, positive [+]). ERS: Event-Related Synchronization (% increased power relative to non-loading baseline, negative [-]). *Significantly greater theta ERS than FEAR (p<0.05). †Significantly greater theta ERS than NEU (p<0.05).

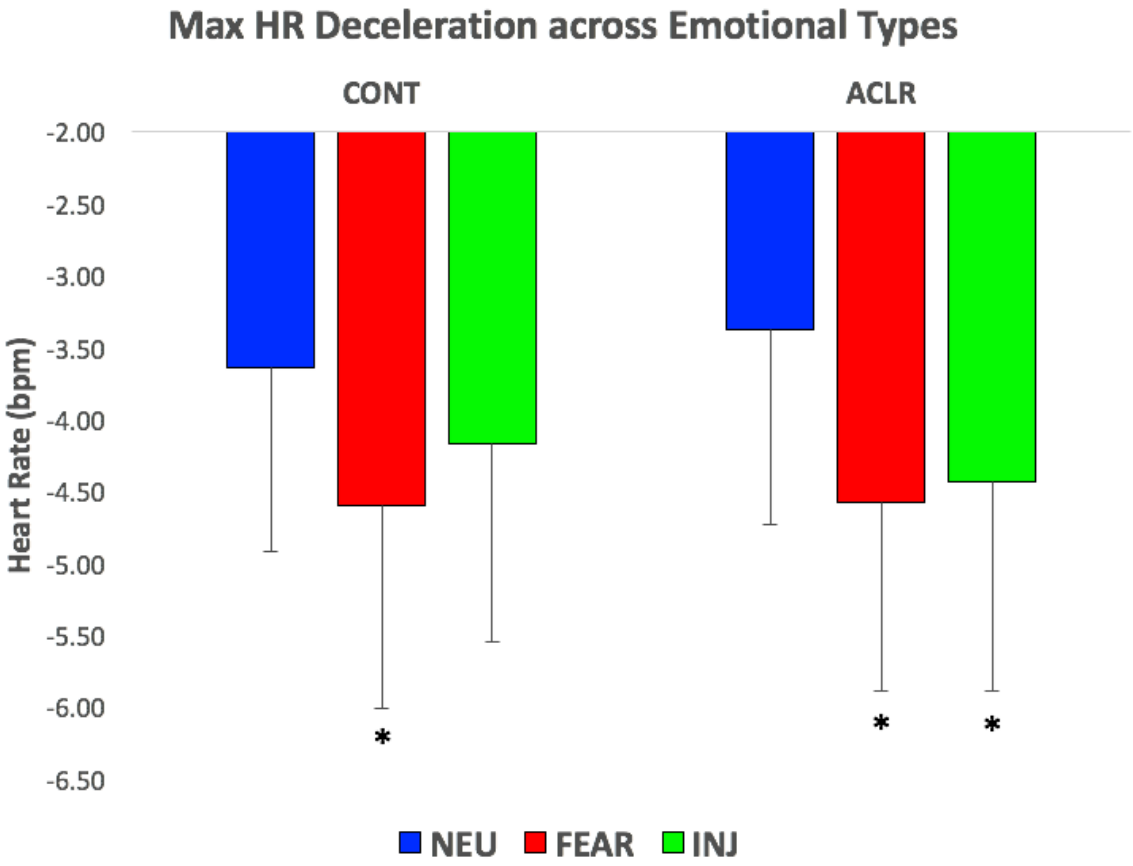


Figure 20 Maximum heart rate deceleration between Groups across emotion types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. *Significantly greater heart rate deceleration than NEU (p<0.05).

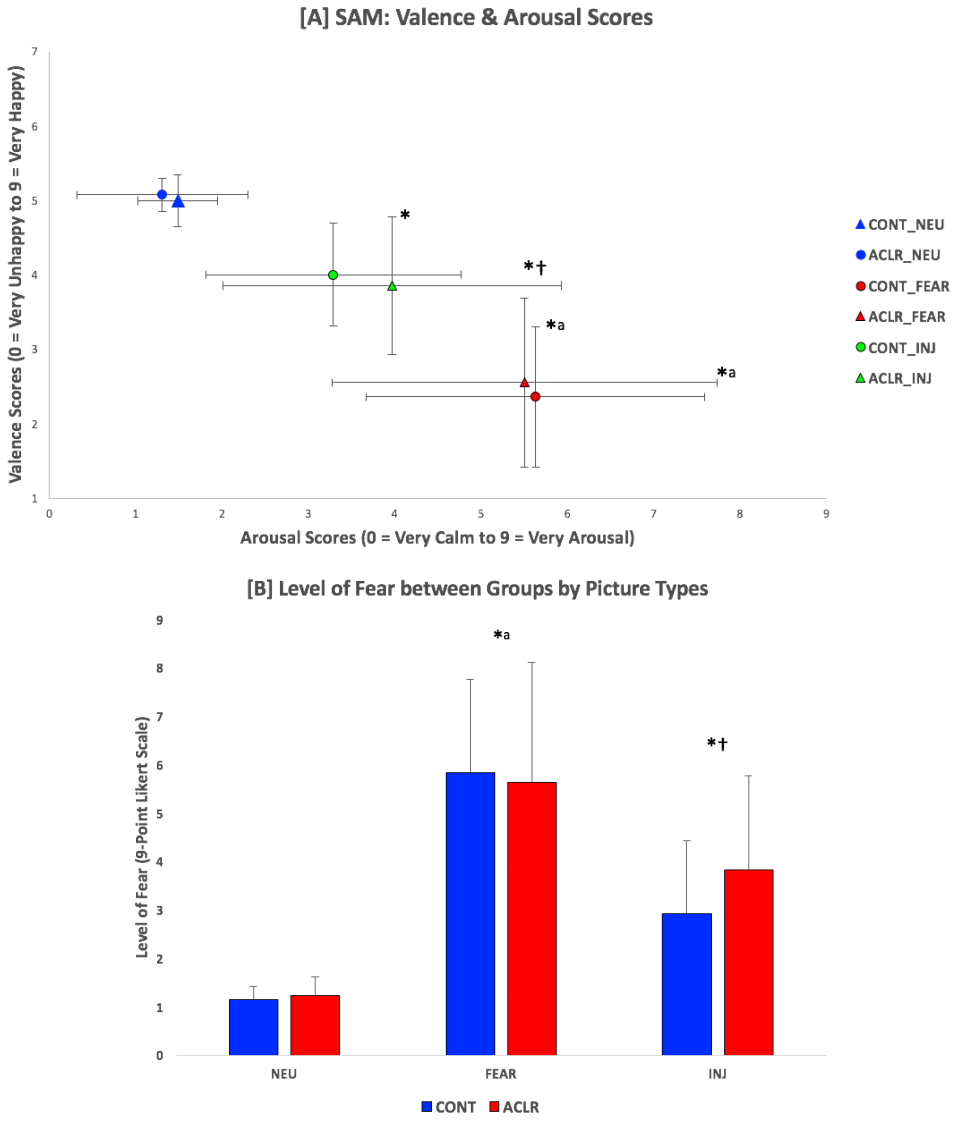


Figure 21 Subjective emotion rating scores: [A] SAM & [B] Level of Fear between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. SAM: Self-Assessment Manikin; including two valence and arousal domains. Valence: level of happiness ranging from 1 = very unhappy to 9 = very happy. Arousal: arousal level ranging from 1 = very calm to 9 = very arousal. Lv. of Fear: ranges from 1 = not fearful at all to 9 = very fearful. *Significant difference from NEU (p<0.05). †Significant difference between groups (p<0.05). [a]Significant difference from INJ (p<0.05).

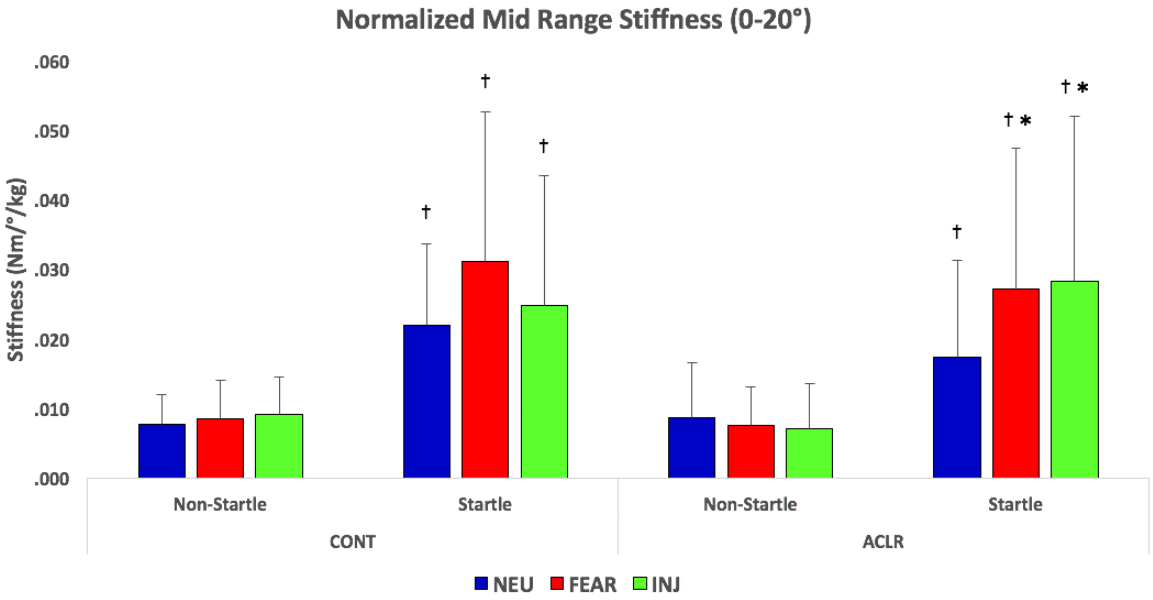


Figure 22 Normalized mid-range stiffness (0-20°) between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. *Significant difference from NEU (p<0.05). †Significant difference between stiffness conditions (p<0.05).

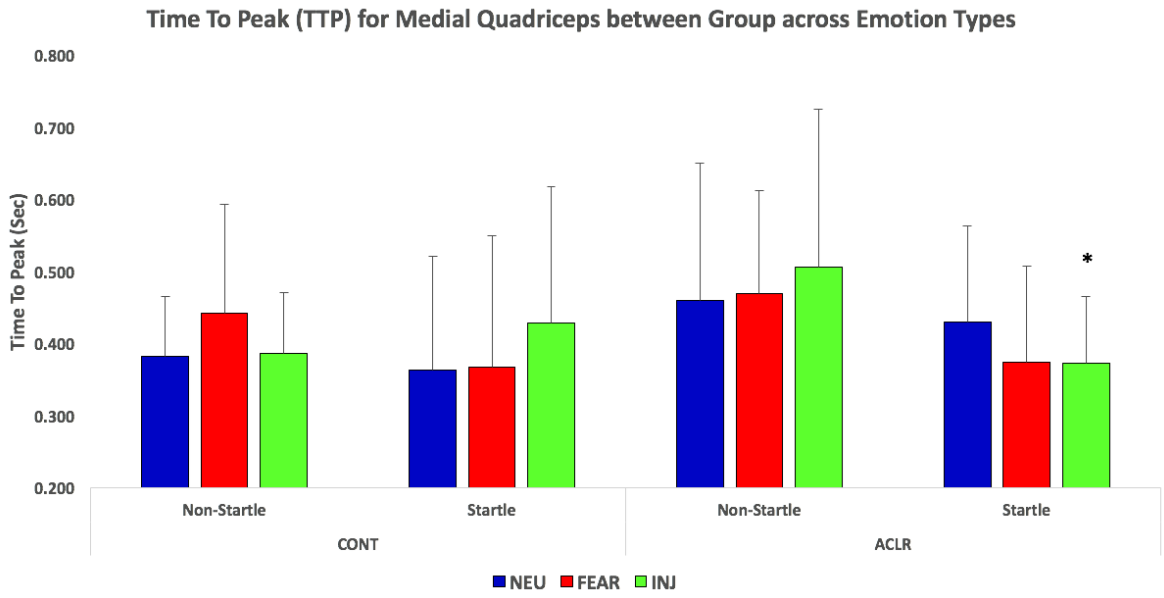


Figure 23 Time-To-Peak (TTP) EMG for medial quadriceps between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. *Significant difference from NEU (p<0.05).

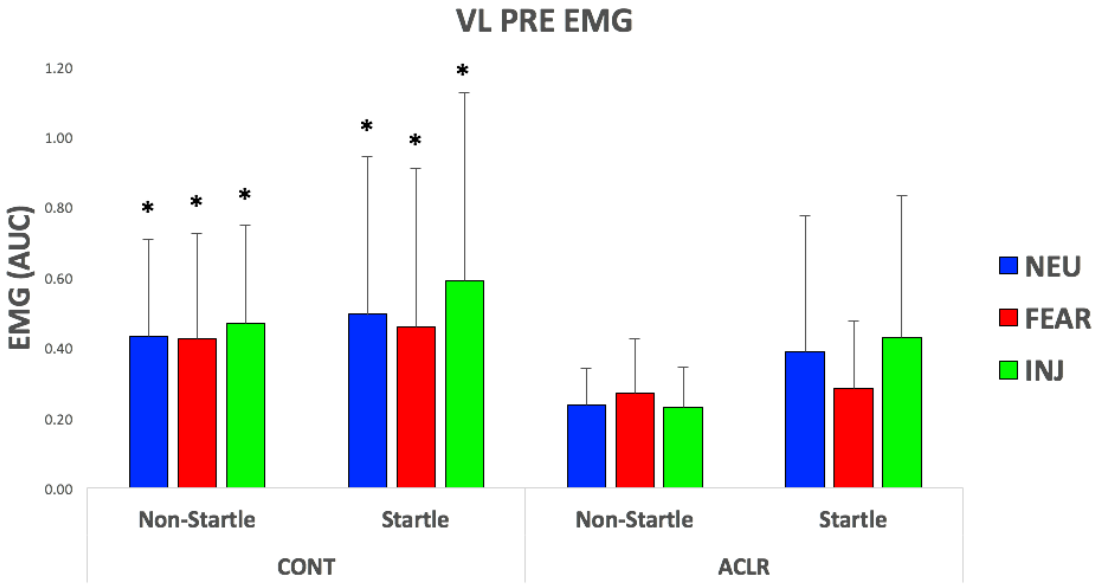


Figure 24 Lateral quadriceps (VL) EMG activation prior to the perturbation (PRE: -150 ~ 0ms) between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. *Significant group differences (p<0.05).

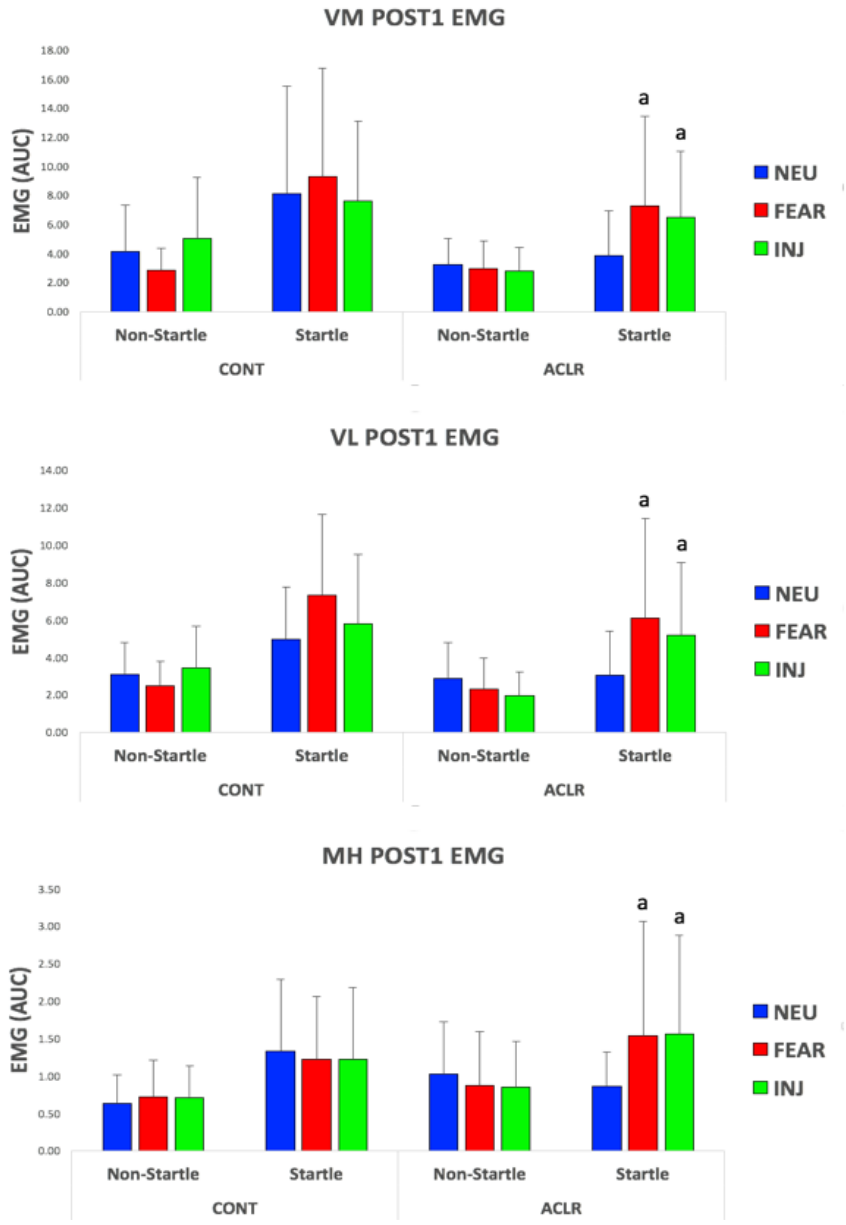


Figure 25 Quadriceps and Hamstrings EMG activation after the perturbation (POST1: 0 ~ 250ms) between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms

prior to the perturbation. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. [a]Significant difference from NEU ($p<0.05$).

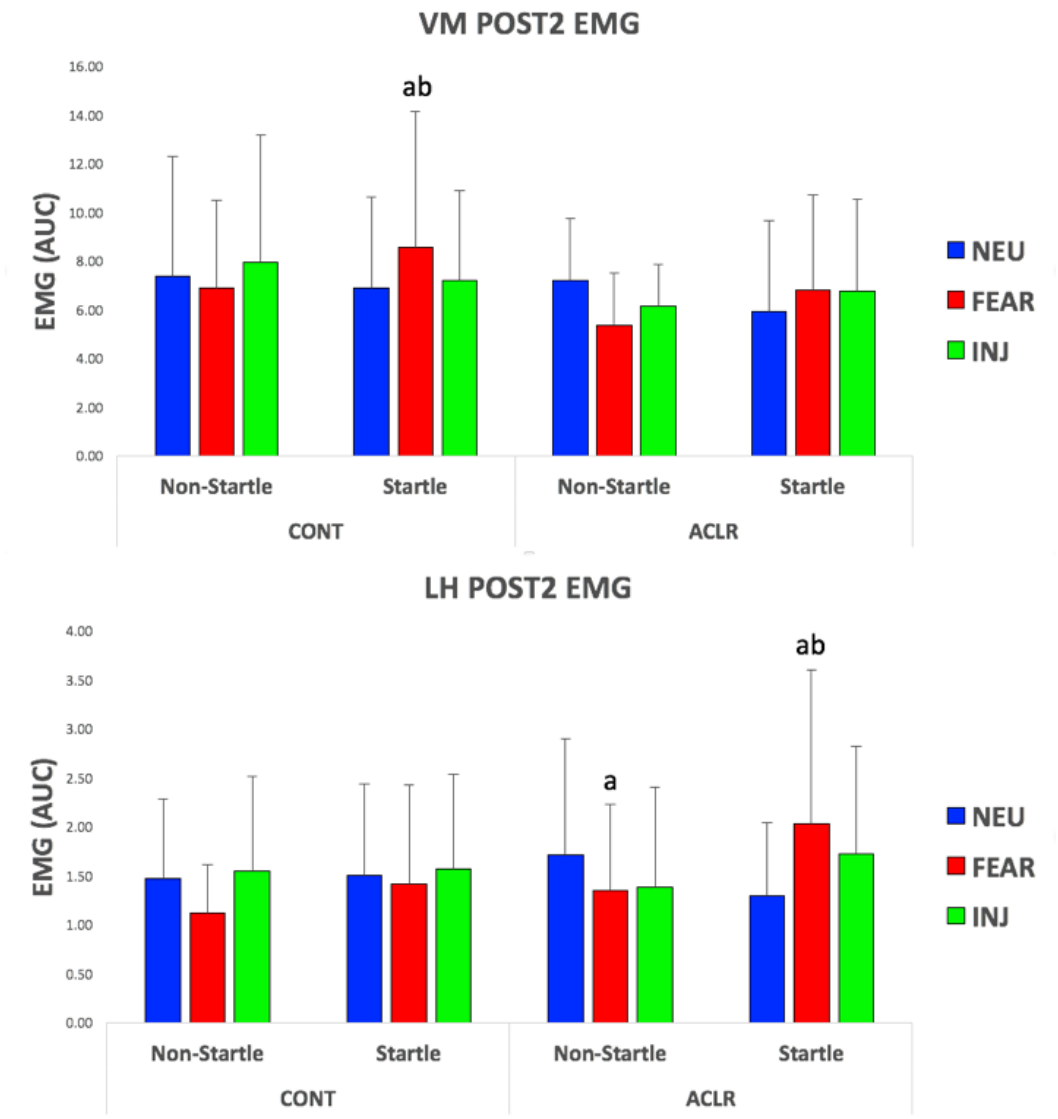
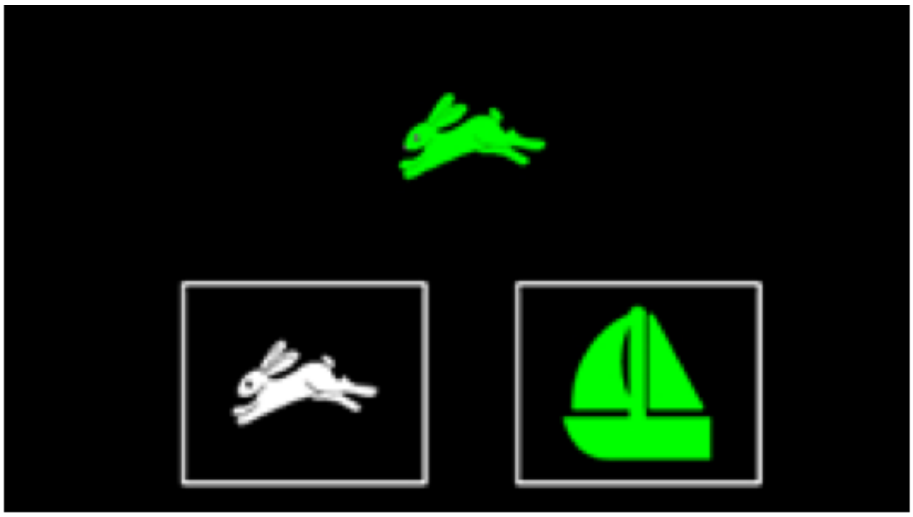
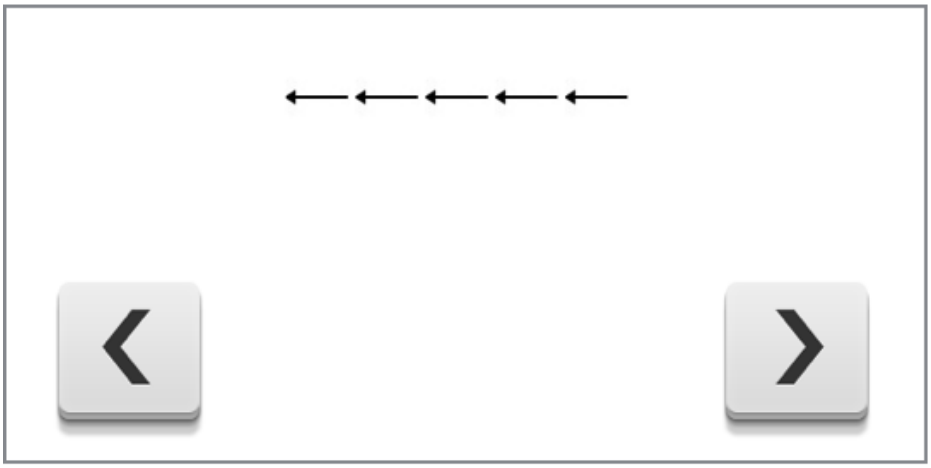


Figure 26 Quadriceps and Hamstrings EMG activation after the perturbation (POST2: 250 ~ 500ms) between Groups by Emotion Types.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. Non-startle: A 40° knee-flexion perturbation at 800ms after picture presentation. Startle: An acoustic sound at 100ms prior to the perturbation. VM: Vastus Medialis. LH: Lateral Hamstrings. [a]Significant difference from NEU (p<0.05). [b]Significant difference between stiffness conditions (p<0.05).



http://www.nihtoolbox.org/Resources/Sampleimages/Sample%20images/DCCS.png



http://www.nihtoolbox.org/Resources/Sampleimages/Sample%20images/Flanker.png

Figure 27 NIH Toolbox Executive Function Assessment tests.

Top: The *Dimensional Change Card Sort* (DCCS) test. Bottom: The *Flanker Inhibitory Control and Attention* (FICA) test.

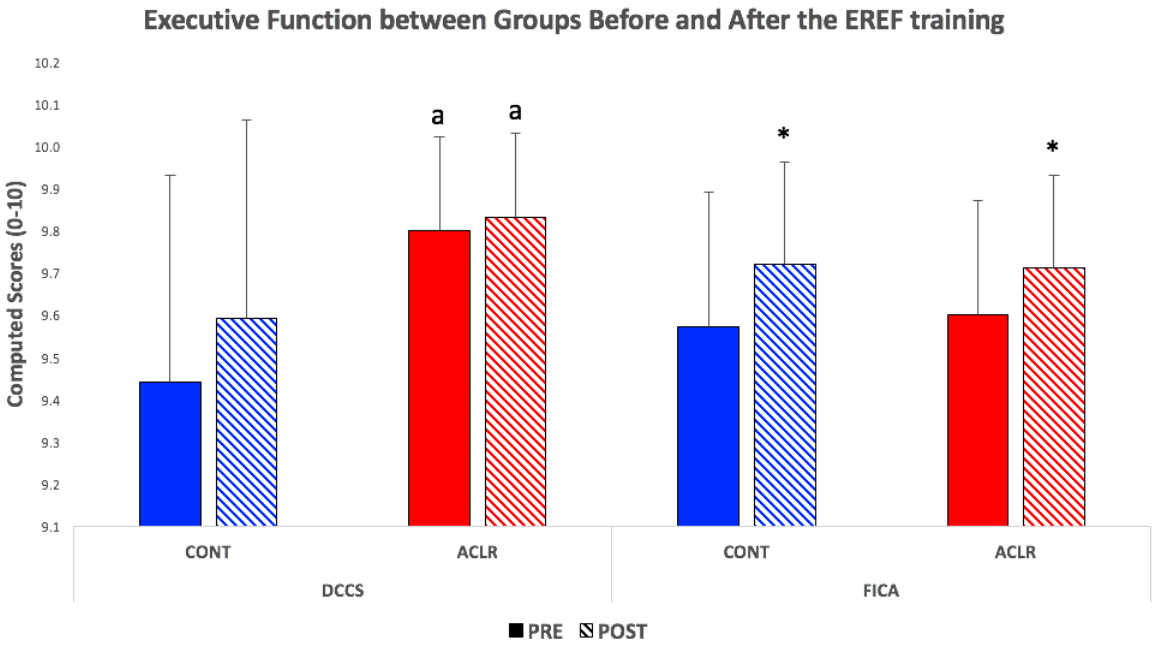


Figure 28 NIH-TB Executive Function Assessment Outcomes between Groups Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. EREF: Emotion Regulatory Executive Function training. PRE: before the EREF training. POST: after the EREF training. Higher computed scores reflect better executive function skills. *Significant pre-post time differences (p<0.05). [a]Significant group differences (p<0.05).

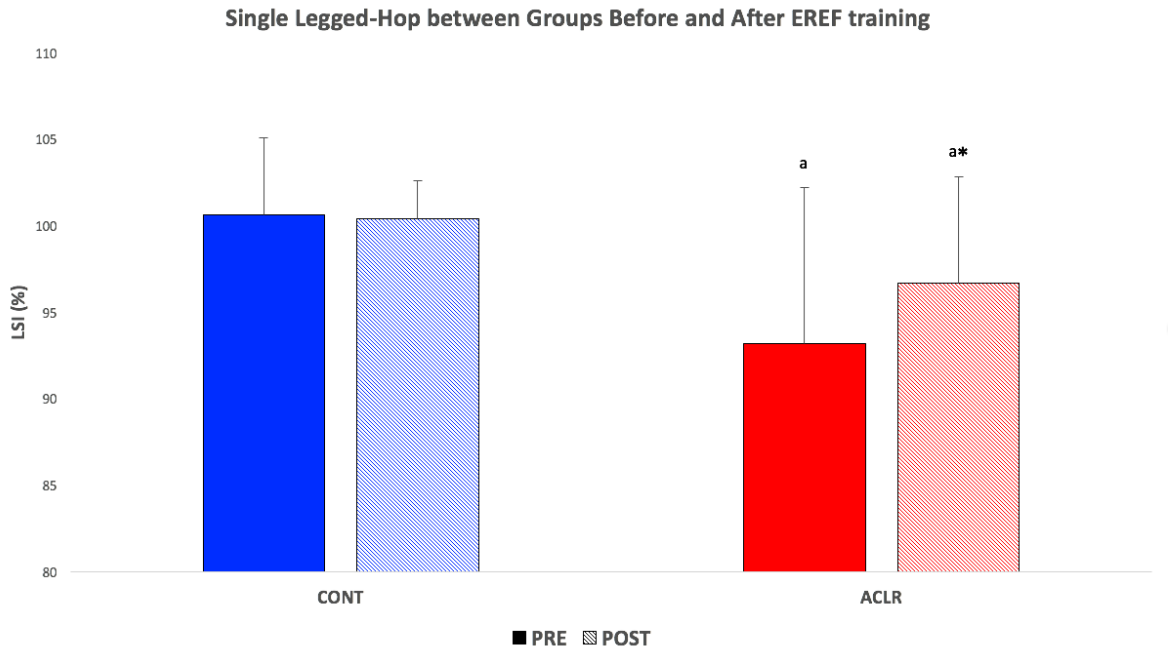


Figure 29 Single legged-hop for distance differences between between healthy control and ACLR groups Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. EREF: Emotion Regulatory Executive Function training. PRE: before the EREF training. POST: after the EREF training. LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). *Significant pre-post time differences (p<0.05). [a]Significant group differences (p<0.05).

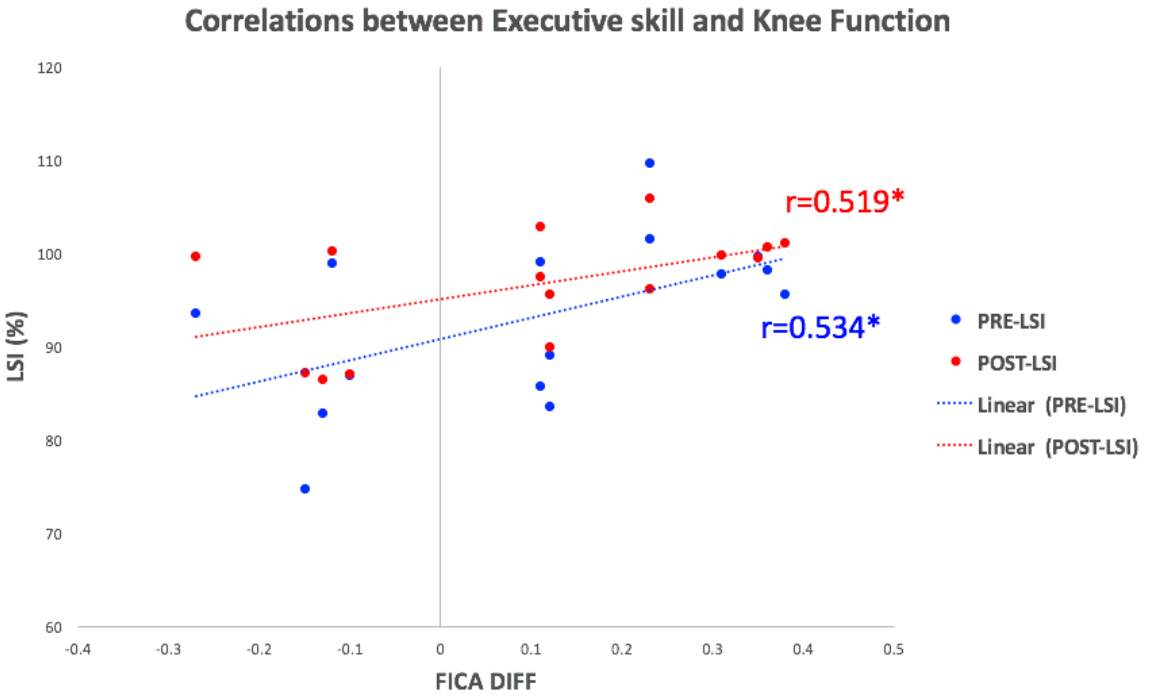


Figure 30 Correlations between improvement of executive function and single legged-hop for distance in ACLR group Before and After the EREF training.

FICA DIFF: Flanker Inhibitory Control and Attention value differences between before and after the EREF training (Post-training value – Pre-training value). LSI: Hop Limb Symmetry Index (% of involved limb's distance to non-involved limb's distance). PRE-LSI: LSI value before the EREF training. POST-LSI: LSI value after the EREF training. *Significant correlation (p<0.05).

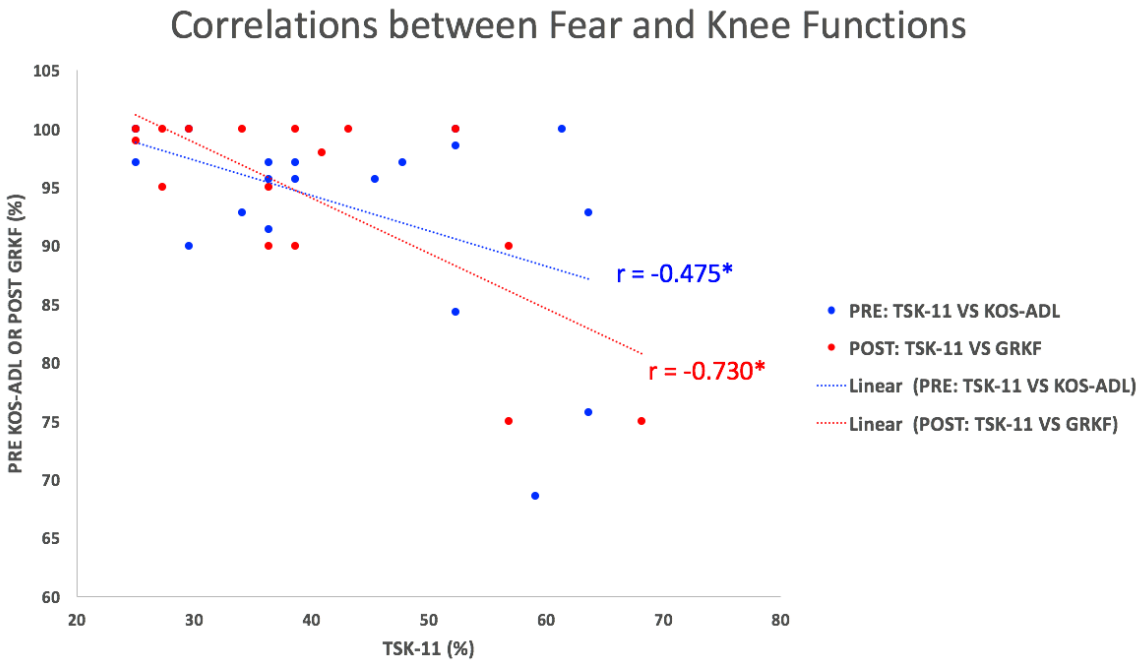


Figure 31 Correlations between Fear and Knee Functions Before and After the EREF training.

GRKF: Global Rating of Knee Function. KOS-ADL: Knee Outcome Survey-Activities of Daily Living. TSK-11: Short-version of the Tampa Scale for Kinesiophobia. *Significant correlation (p<0.05).

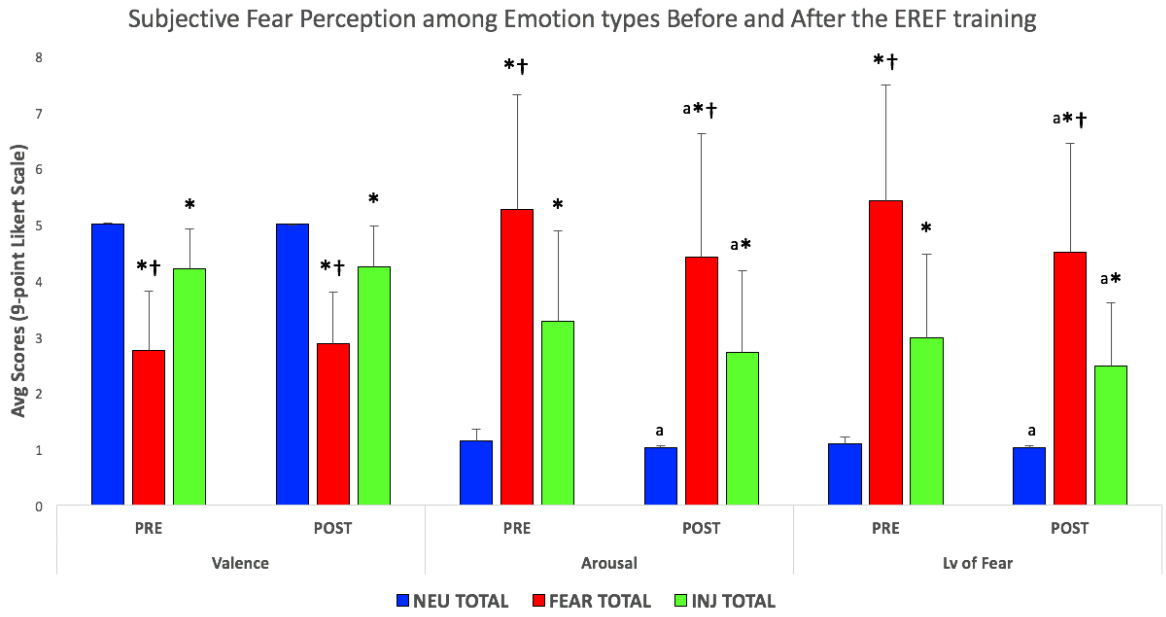


Figure 32 Effects of the EREF training on subjective emotional responses of all subjects among emotion types.

NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. PRE: before the EREF training. POST: after the EREF training. *Significant difference from NEU (p<0.05). †Significant difference from INJ (p<0.05). [a]Significant pre-post time differences (p<0.05).

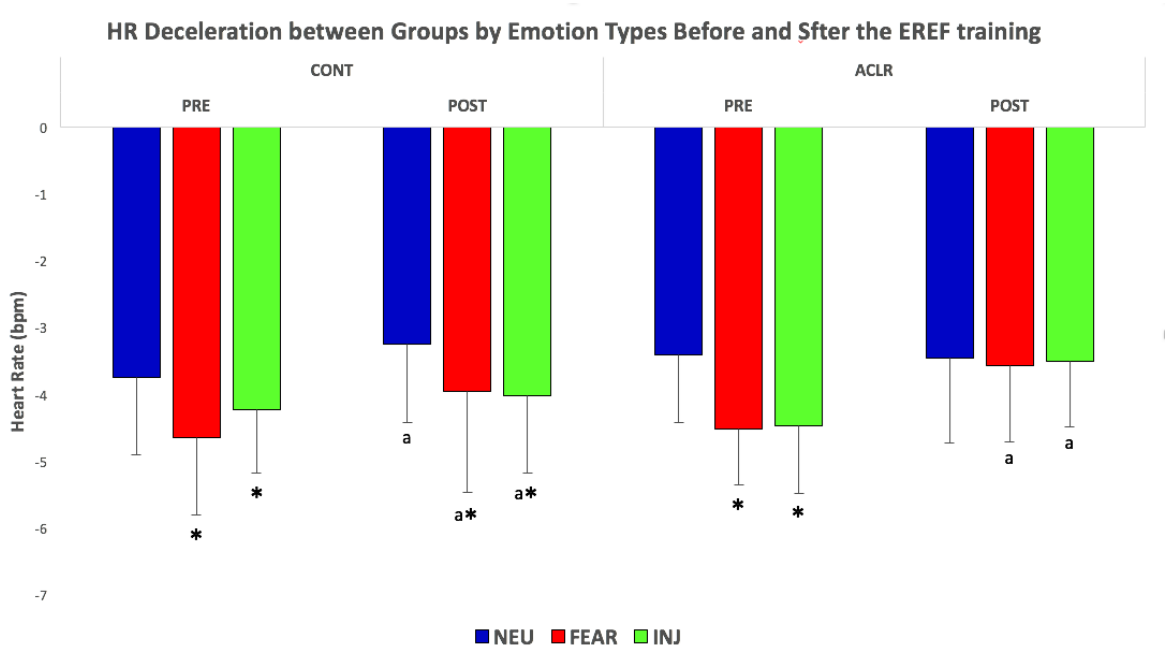


Figure 33 Effects of the EREF training on neurophysiological heart rate (HR) deceleration of all subjects among emotion types.

NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. PRE: before the EREF training. POST: after the EREF training. *Significant difference from NEU (p<0.05). [a]Significant pre-post time differences (p<0.05).

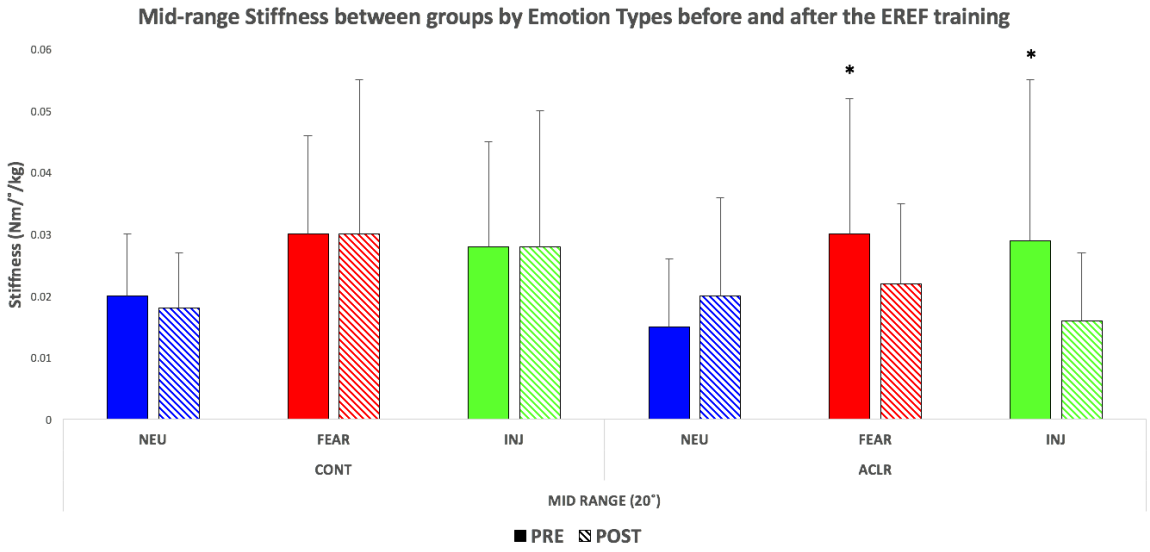


Figure 34 Normalized mid-range stiffness (0-20°) between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. PRE: before the EREF training. POST: after the EREF training. *Significant difference from NEU (p<0.05).

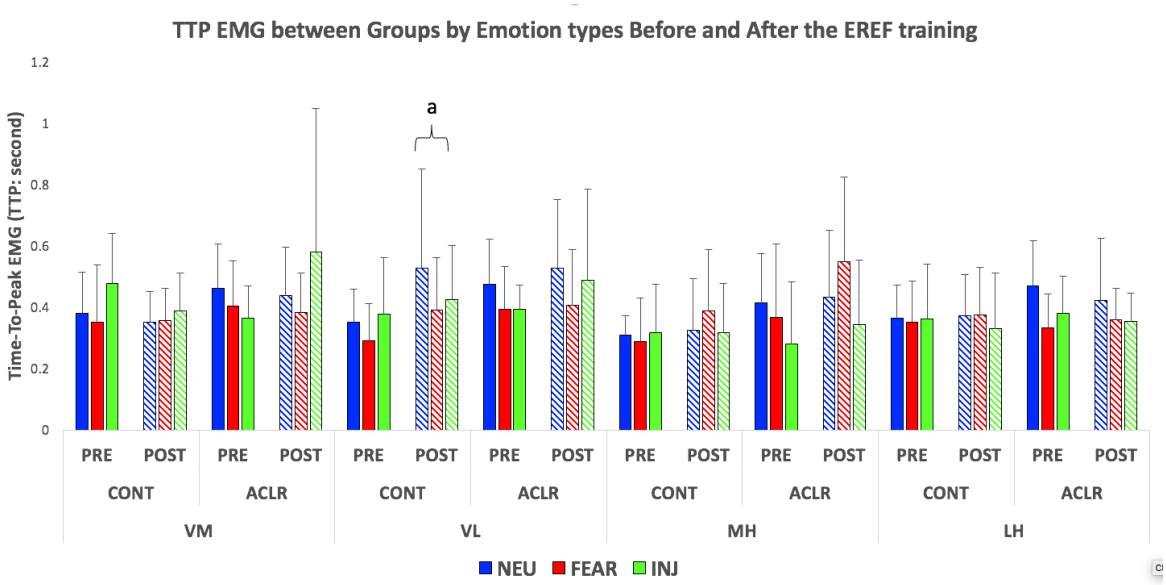


Figure 35 Time-To-Peak (TTP) EMG for the quadriceps and hamstrings between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. PRE: before the EREF training. POST: after the EREF training. [a]Significant pre-post time difference (p<0.05).

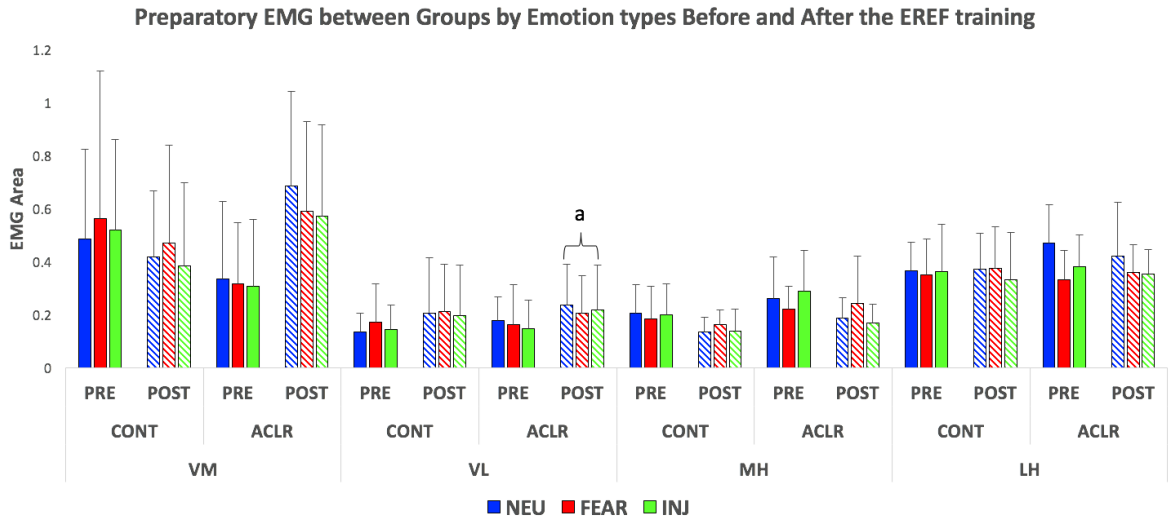


Figure 36 Preparatory quadriceps and hamstrings EMG activity (PRE: -150 ~ 0ms) between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. PRE: before the EREF training. POST: after the EREF training. [a]Significant pre-post time difference (p<0.05).

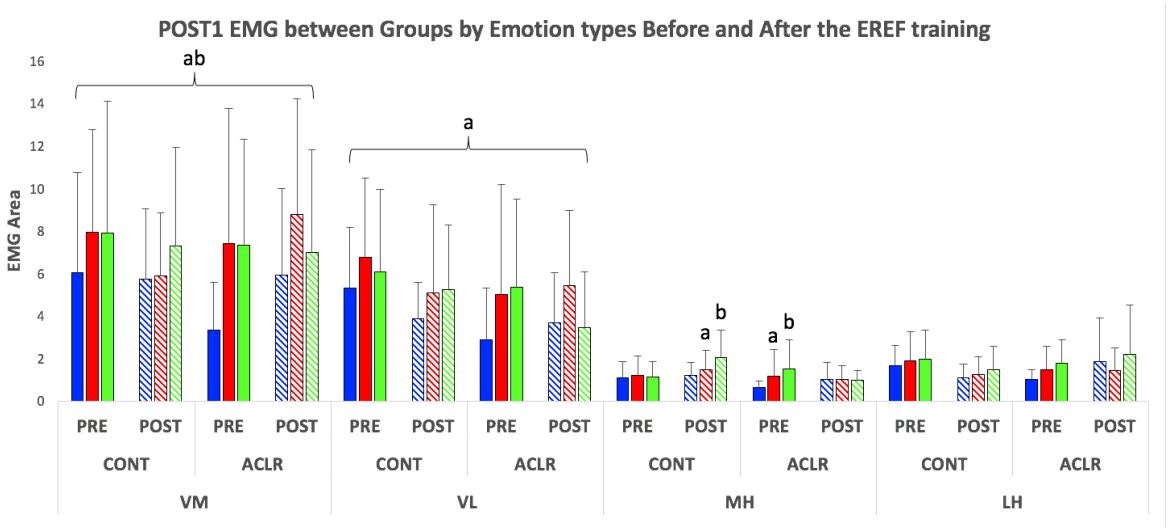


Figure 37 Early reactive quadriceps and hamstrings EMG activity (POST1: 0 ~ 250ms) between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. PRE: before the EREF training. POST: after the EREF training. [a]Significant differences between NEU and FEAR (p<0.05). [b]Significant differences between NEU and INJ (p<0.05).

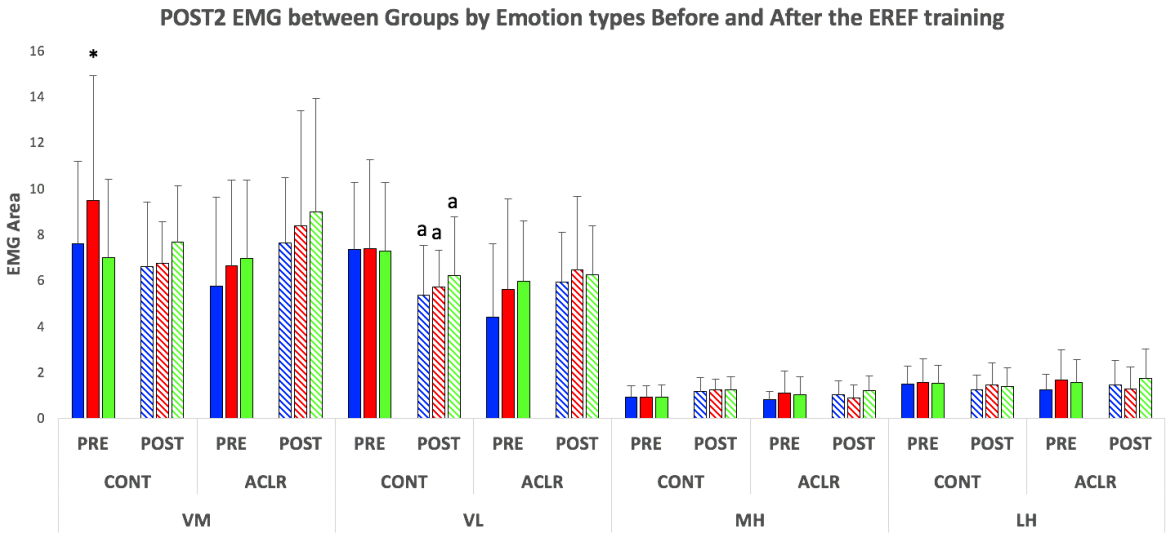


Figure 38 Late reactive quadriceps and hamstrings EMG activity (POST2: 0 ~ 250ms) between Groups by Emotion Types between Before and After the EREF training.

CONT: Healthy Controls. ACLR: ACL Reconstructed patients. NEU: Neutral pictures. FEAR: Fearful pictures. INJ: Sports Knee injury-related pictures. VM: Vastus Medialis. VL: Vastus Lateralis. MH: Medial Hamstrings. LH: Lateral Hamstrings. PRE: before the EREF training. POST: after the EREF training. [a]Significant pre-post time difference (p<0.05). [*]Significant difference from NEU (p<0.05).

Appendix C

SURVEYS: KNEE FUNCTION ASSESSMENT AND TSK-11

Knee Outcome Survey
Activities of Daily Living Scale

The following questionnaire is designed to determine the symptoms and limitations that you experience because of your knee while you perform your usual daily activities. Please answer each question by **checking the one statement that best describes you over the last 1 to 2 days**. For a given question, more than one statement may describe you, but please mark **only** the statement, which best describes you during your usual daily activities.

Symptoms

To what degree do each of the following symptoms affect your level of daily activity? Check one answer for each symptom.

	I do not have the symptom	I have the symptom but it does not affect my activity	The symptom affects my activity slightly	The symptom affects my activity moderately	The symptom affects my activity severely	The symptom prevents me from all daily activities
Pain						
Stiffness						
Swelling						
Giving way, buckling, or shifting of the knee						
Weakness						
Limping						

Functional Limitations with Activities of Daily Living

How does your knee affect your ability to perform each of the following tasks? Check one answer per task.

	Activity is not difficult	Activity is minimally difficult	Activity is somewhat difficult	Activity is fairly difficult	Activity is very difficult	I am unable to do the activity
Walk						
Go up stairs						
Go down stairs						
Stand						
Kneel on the front of your knee						
Squat						
Sit with your knee bent						
Rise from a chair						

Global Rating of Knee Function

How would you rate the current function of your knee during your usual daily activities on a scale from 0 to 100 with 100 being your level of function prior to your injury and 0 being the inability to perform any of your usual activities?

0 **50** **100**

1. Please mark on the scale above and write the number here _____

2. How would you rate the overall function of your knee during your usual daily activities?

_____ normal _____ nearly normal _____ abnormal _____ severely abnormal

3. As a result of your knee injury, how would you rate your current level of daily activity?

_____ normal _____ nearly normal _____ abnormal _____ severely abnormal

Incidences of Giving-way

How many times have you experienced your knee "giving way" or "buckling" since the initial injury? _____

Single Legged Hop for Distance

Uninjured (Dominant)	Practice Trial 1	Practice Trial 2	Trial #1	Trial #2	Trial #3
Single-Hop for Distance					
Injured (Non-dominant)	Practice Trial 1	Practice Trial 2	Trial #1	Trial #2	Trial #3
Single-Hop for Distance					

The Tampa Scale of Kinesiophobia (TSK-11).

This is a lost of phrases which other patients have used to express how the view their condition. Please circle the number that best describes how you feel about each statement.

	Strongly Disagree	Somewhat Disagree	Somewhat Agree	Strongly Agree
1. I'm afraid I might injure myself if I exercise.	1	2	3	4
2. If I were to try to overcome it, my pain would increase.	1	2	3	4
3. My body is telling me I have something dangerously wrong.	1	2	3	4
4. People aren't taking my medical condition serious enough.	1	2	3	4
5. My accident/problem has put my body at risk for the rest of my life.	1	2	3	4
6. Pain always means I have injured my body.	1	2	3	4
7. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening.	1	2	3	4
8. I wouldn't have this much pain if there wasn't something potentially dangerous going on in my body.	1	2	3	4
9. Pain lets me know when to stop exercising so that I don't injure myself.	1	2	3	4
10. I can't do all the things normal people do because it's too easy for me to get injured.	1	2	3	4
11. No one should have to exercise when he/she is in pain.	1	2	3	4

Source: Woby et al. (2005), Psychometric properties of the TSK-11: A shortened version of the Tampa Scale for Kinesiophobia. Pain, 117, 137-144.

Appendix D

IAPS PICTURE USED

IAPS Neutral: 2002, 2026, 2038, 2102, 2104, 2214, 2215, 2383, 2393, 2396, 2397, 2411, 2440, 2480, 2493, 2570, 2890, 5130, 5534, 7002, 7003, 7004, 7006, 7009, 7012, 7016, 7019, 7020, 7025, 7031, 7032, 7034, 7035, 7036, 7038, 7041, 7045, 7055, 7056, 7059, 7110, 760, 7161, 7175, 7179, 7180, 7185, 7187, 7217, 7224, 7233, 7234, 7235, 7255, 7491, 7705, 7950, 9260, 9360, 9700.

IAPS Fear: 1033, 1052, 1201, 1304, 1321, 1525, 1931, 1932, 2352.2, 2683, 2811, 3001, 3005.1, 3053, 3059, 3063, 3064, 3068, 3069, 3102, 3131, 3195, 3212, 3213, 3266, 3550.1, 4664.2, 5971, 5972, 6022, 6211, 6231, 6250.1, 6263, 6312, 6313, 6315, 6415, 6520, 6563, 6570.1, 6821, 6830, 6834, 8485, 9163, 9183, 9187, 9252, 9405, 9412, 9413, 9414, 9620, 9622, 9635.1, 9904, 9908, 9921, 9940.

Sport Injury-Related: I001, I002, I003, I004, I005, I006, I007, I008, I009, I010, I011, I012, I013, I014, I015, I016, I017, I018, I019, I020, I021, I022, I023, I024, I025, I026, I027, I028, I029, I030, I031, I032, I033, I034, I035, I036, I037, I038, I039, I040, I041, I042, I043, I044, I045, I046, I047, I048, I049, I050, I051, I052, I053, I054, I055, I056, I057, I058, I059, I060

Appendix E

AIM1: INFORMED CONSENT FORM

Title of Project: Brain Activity during Knee Joint Loading

Principal Investigator (s): Yong Woo An, MS, ATC

Other Investigators: C. Buz Swanik, PhD, ATC, FNATA; Aaron Struminger, MS, ATC; Andrea DiTrani, MS, ATC; Pactrick Fava, BS, ATC

You are being asked to participate in a research study. This form tells you about the study including its purpose, what you will do if you decide to participate, and any risks and benefits of being in the study. Please read the information below and ask the research team questions about anything we have not made clear before you decide whether to participate. Your participation is voluntary and you can refuse to participate or withdraw at anytime without penalty or loss of benefits to which you are otherwise entitled. If you decide to participate, you will be asked to sign this form and a copy will be given to you to keep for your reference.

WHAT IS THE PURPOSE OF THIS STUDY?
The purpose of this research is to investigate why some people complain that their knees continue to "give way" following a knee ligament injury, while others do not complain of their knees "giving-way". We will examine brain activity while measuring how loose knees are in patients who have injured knee ligaments (ACLD, ACLR or PCL) and compare them to healthy knees. In addition, we will examine direct relationships between fear of movement or re-injury, brain activity and knee looseness.

You are being asked to take part in this study because you are:

- between the age 18 and 45 years
- are physically active at least three days per week with no history of knee injury to the
  ACL or PCL ligaments OR
- have an ACL or PCL injury to one knee without a surgical repair OR
- have a reconstruction after an ACL injury

You are not eligible to take part in this study because you are (have):

1. Multi-ligamentous knee injuries other than isolated to the ACL or PCL
2. History of ACL rupture or reconstruction to both knees

3. History of fracture or surgery on lower extremity within the past 6 months
4. Any symptoms including pain, swelling, decreased range of motion
5. An implanted cardiac pacemaker
6. Metal implants in the head or face
7. Skull abnormalities or fractures
8. Problem at the joint of the jaw
9. History of neurologic disease or surgery
10. History of recurring or severe headaches/migraine
11. History of a concussion within the last 6 months
12. History of heart or brain surgery
13. History of seizures or epilepsy
14. Currently pregnant
15. Currently undergoing medical treatment for any psychiatric disorders

WHAT WILL YOU BE ASKED TO DO?

If you participate in this study, we will have one test session lasting 3 hours. The test will be in the Neuromechanics Laboratory at the Fred Rust Ice Arena on the South campus at the University of Delaware.

Following completion of this consent, you will be asked to complete 2 questionnaires and 4 surveys assessing your history of knee injury and function and fear of re-injury/movement. You will then be asked to perform a single legged hop on both limbs for maximum distance. You will have two practice trials followed by three real trials. If you are one of ACLD participants, you will be asked if you think you can hop on your injured leg. If you do not think you are able to perform single legged hop for distance, then you will not perform the hop testing. If you think you are able to do the hop test, you will perform on the non-injured limb followed by injured limb. If you are one of ACLR participants, you will perform on the non-injured limb followed by injured limb. If you are one of healthy controls, you will perform on the dominant limb followed by non-dominant limb. Each trial will be instructed with verbal cues for the start.

After you have completed the surveys and the hop testing, investigator(s) will record your brain activity while measuring knee joint motion (looseness) in both legs. You will wear a tight-fitting cap on your head that detects brain activity gel will be squirted into certain spots in the cap to help measure brain activity (electricity) (Figure 1). Similarly, six sensors will be attached to your face to detect movement of your eye and jaw muscles.
Following cap fitting, you will then be asked to lay on your back, on a padded table with your knee slightly bent and completely relaxed. Knee motion is measured by sliding the "shin" bone forward and backward (looseness) using a knee arthrometer device. The investigator will strap the device on your leg, then push and pull on your knee both forward (30lbs) and backward (20lbs) testing.

The investigator will first record brain activity for 1-min with your eyes open and eyes closed. You will next have a total of 5 testing blocks and the investigator(s) will record baseline measures again between each block. Each testing block will have10 pull-push cycles for measuring knee motion and 10 seconds of rest between motions. During knee motion tests, you will be asked to keep your eyes open, but blinking comfortably, and look to the ceiling during testing.

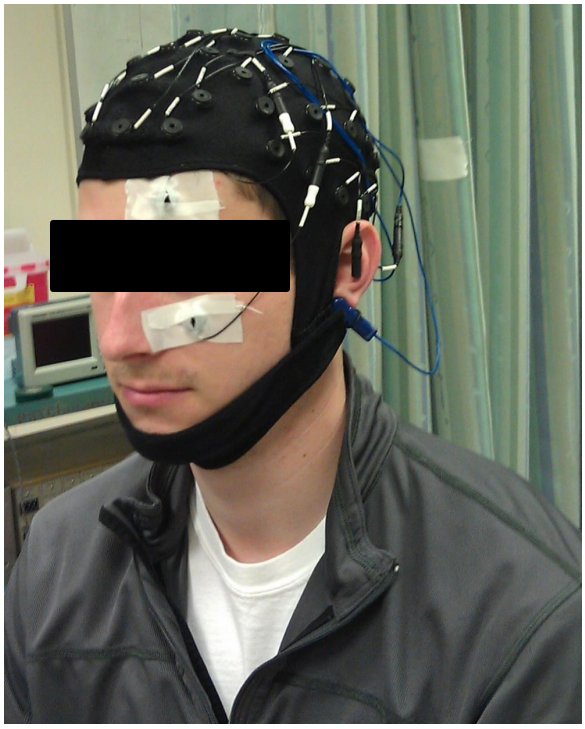


Figure 1. Fitting of cap with electrodes above and below the eye.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

All experimental techniques are not invasive, but there are few mild possible risks of participating in this research including soreness of muscles or joints after performing the hop tasks, similar to the soreness felt following a workout. There is minimal chance of experiencing injury to the muscles or joint (sprains, strains, fractures). There is also a risk of joints giving way during the hop testing. **You have the right to withdraw from this study at any time during testing.**

Single legged hop for distance testing
The performance of the single legged hop for distance testing is optional. Additionally, rest periods are allowed and designed as part of testing to allow leg muscles to relax between trials and minimize risk of injury.

Knee Arthrometer (KT-2000)

There may be minor discomfort during preparation and testing of passive knee joint motion using KT-2000 due to tightness of the pads and straps on the testing knee or if too much force is put on your knee. Proper knee joint loading will be applied to ensure a consistent force is used that does not exceed 30 lbs forward and 20 lbs backward.

Brain activity (EEG) testing
Although there is a possibility of headaches, scalp discomfort, or lightheadedness associated with EEG testing, these effects are usually mild and short lasting. There may be also some minor irritation of the skin/scalp around the site of the electrodes following the experiments.

WHAT ARE THE POTENTIAL BENEFITS?

There are no direct benefits to participating in this study.

HOW WILL CONFIDENTIALITY BE MAINTAINED?

We will make every effort to keep all research records that identify you confidential to the extent permitted by law. The primary researcher will keep all paper data including your consent form in locked file cabinets. Names and contact information will only be used to contact you for the purpose of data collection. When you begin participation, you will be assigned a code number that will not use your name or contact information. Only one computer file will contain information that could link your name with your code number, and this file will be encrypted and stored on a secure password protected-server as well as all other computer data. Three years following the completion of this study, all identifying information will be destroyed. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Completely de-identified data will be stored indefinitely for future research. The University of Delaware Institutional Review Board may view your research records, but the confidentiality of your records will be protected to the extent permitted by law.

WILL THERE BE ANY COSTS RELATED TO THE RESEARCH?

There are no costs associated with participating in this study.

WILL THERE BE ANY COMPENSATION FOR PARTICIPATION?

You will not receive compensation for participation in this study.

WHAT IF YOU ARE INJURED BECAUSE OF THE STUDY?

The investigator(s), some of who are certified Athletic Trainers, will provide initial care or first aid at no cost during all testing sessions if you are injured during research procedures. If you need additional medical treatment, the cost of this treatment will be your responsibility

or that of your third-party payer (for example, your health insurance). By signing this document you are not waving any rights that you may have if injury was the result of negligence of the university or its investigators.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is entirely voluntary. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are otherwise entitled. Your refusal will not influence current or future relationships with the University of Delaware. As a student, if you decide not to take part in this research, your choice will have no effect on your academic status or your grade in the class.

WHO SHOULD YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?

If you have any questions about this study, please contact the Principal Investigator, Yong Woo An at (302) 332-7083 or anyong@udel.edu or Buz Swanik at (302) 831-2306 (cswanik@udel.edu).
If you have any questions or concerns about your rights as a research participant, you may contact the University of Delaware Institutional Review Board at 302-831-2137.

Your signature below indicates that you are agreeing to take part in this research study. You have been informed about the study's purpose, procedures, possible risks and benefits. You have been given the opportunity to ask questions about the research and those questions have been answered. You will be given a copy of this consent form to keep.
By signing this consent form, you indicate that you voluntarily agree to participate in this study.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

OPTIONAL CONSENT TO BE CONTACTED FOR FUTURE STUDIES:

Do we have your permission to contact you regarding participation in future studies?
Please write your initials next to your preferred choice.

_____ YES _____ NO

Appendix F

AIM2 & 3: INFORMED CONSENT FORM

Title of Project: Role of Fear in Neuromuscular Control following Knee Injury

Principal Investigator(s): Yong Woo An, MS, ATC

You are being invited to participate in a research study. This consent form tells you about the study including its purpose, what you will be asked to do if you decide to take part, and the risks and benefits of being in the study. Please read the information below and ask us any questions you may have before you decide whether or not you want to participate.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to learn more about why some people complain that their knees continue "giving way" following a knee ligament injury, while others do not complain of their knees "giving-way". We will examine knee function, fear of re-injury or movement, along with brain activation and joint stiffness. We measure these while showing you different kinds of pictures chosen to cause emotion (neutral, fear-related, and knee injury-related pictures). Additionally, we will provide two mental programs to see if they help knee function and fear of re-injury.

You will be one of approximately 40 participants in this study.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You are being asked to participate if you are (have)…

- Between the age 18 and 45 years AND
- Physically active at least three days per week with no history of knee injury OR
- A surgical repair (reconstruction) after ACL (anterior cruciate ligament) injury to one knee

You will not be able to participate in this study if you are (have)…

- History of an injury or surgery on lower extremity within the past 6 months
- History of ACL rupture or reconstruction to both knees

- Has an implanted cardiac pacemaker
- Has metal implants in the head or face
- Has skull abnormalities or factures
- Have temporomandibular joint dysfunction
- History of neurologic disease or surgery
- History of recurring or severe headaches/migraine
- History of a concussion within the last 6 months
- History of heart or brain surgery
- History of seizures or epilepsy
- History of or currently experiencing hearing impairments
- Pregnant
- Currently undergoing medical treatment for any psychiatric disorders
- Currently taking any medication of neurologic disease or psychiatric disorders

WHAT WILL YOU BE ASKED TO DO?

As part of this study you will be asked to report to the Neuromechanics Laboratory at the Fred Rust Ice Arena located on the south campus at the University of Delaware for two testing sessions: up to a 3 hour evaluation session and a single 45-minute follow up visits 4 weeks later. During the entirety of testing, you will randomly start 4 weeks mental training programs provided from the brainHQ for at least 10-hours of time on your own at random between two testing sessions. We will provide you an anonymous user ID number and password to log into an encrypted website from your home computer or mobile device. Your personal information will not be saved and shared with the brainHQ. Investigator(s) will monitor your logged in hours and your performances. You will have a written instruction of how to do each mental training program as well as a live flash demonstration will be provided when you log in the website.

Your participation will be terminated by investigator(s) if you …

- Complete less than 10 hours of the mental training program.
- Have a new injury listed in the exclusion criteria between visits.
- Do not present for the follow up visit without a notification.

Day 1 (3-hour evaluation session)

Following completion of this consent, you will be asked to complete 2 questionnaires and 4 surveys assessing your history of knee injury and function. You will then be asked to perform a single legged hop on both limbs for maximum distance. You will have two practice trials followed by three real trials. If you are one of ACLR participants, you will perform on the non-injured limb followed by injured limb. If you are one of healthy

controls, you will perform on the dominant limb followed by non-dominant limb. Each trial will be instructed with verbal cues for the start. You will then be asked to complete a measure of online executive function assessment test, which measures your cognition.

After you have completed the online test, investigator(s) will record your brain activity and heart rate while you watch three sets of pictures. You will wear a tight-fitting cap on your head that detects brain activity and gel will be squirted into certain spots in the cap to help measure brain activity (electricity) (Figure 1). Similarly, four sensors will be attached to your face to detect movement of your eye and jaw muscles, and three sensors will be attached to your both shoulders with hip to record your heart rate changes.

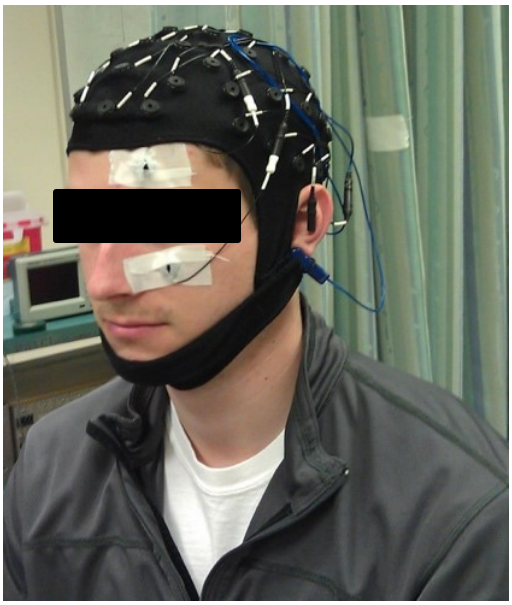


Figure 1. Fitting of cap with electrodes above and below the eye

Following cap fitting and heart rate setting, you will then be asked to sit and watch comfortably a screen that shows a 2-sec black screen before a picture onset, and a 6-sec picture presentation, and then a 12-sec emotional rating interval in which the picture will not be displayed. During the 12-sec emotional rating interval, you will be asked to rate the picture (1-9) (Figure 2) based on how pleasant or unpleasant, excited or calm, and not fearful or fearful. Some images may cause strong emotions and you can stop the testing at any point during a picture presentation.

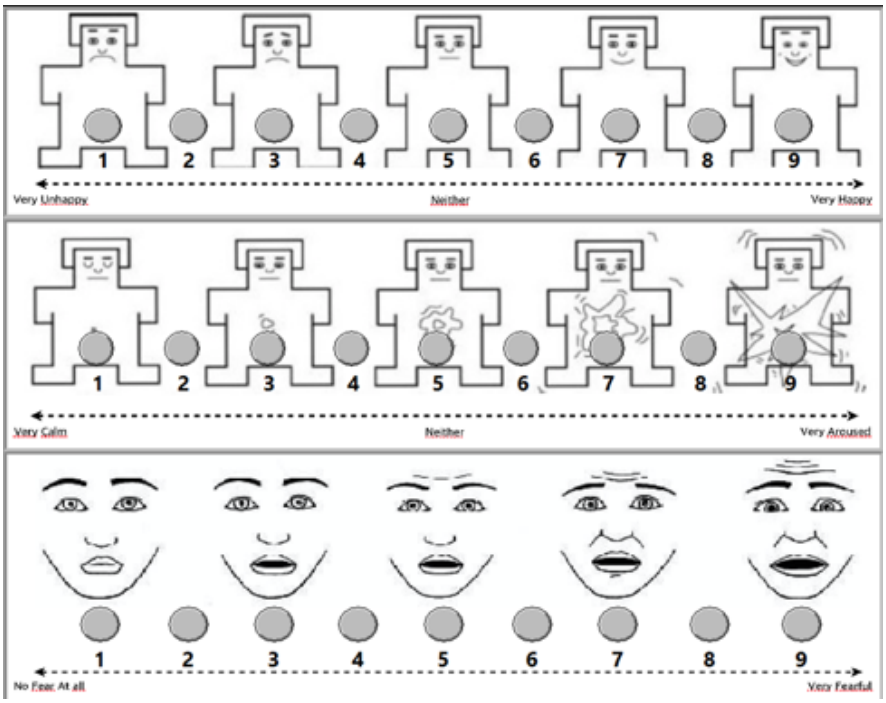


Figure 2. Emotion Rating Scales (***Top***; Valence, ***Middle***; Arousal, ***Bottom***; Level of Fear)

You will have three testing blocks and each testing block will have 30 picture presentations, which consist of three domains; 10 neutral, 10 fear-related, and 10 knee injury-related pictures (figure 3). You will be familiarized with two pictures prior to the first testing block. The investigator(s) will record brain activity for 1-min with your eyes open and eyes closed between each block. During the tests, you will be asked to keep your eyes open, but blinking comfortably.

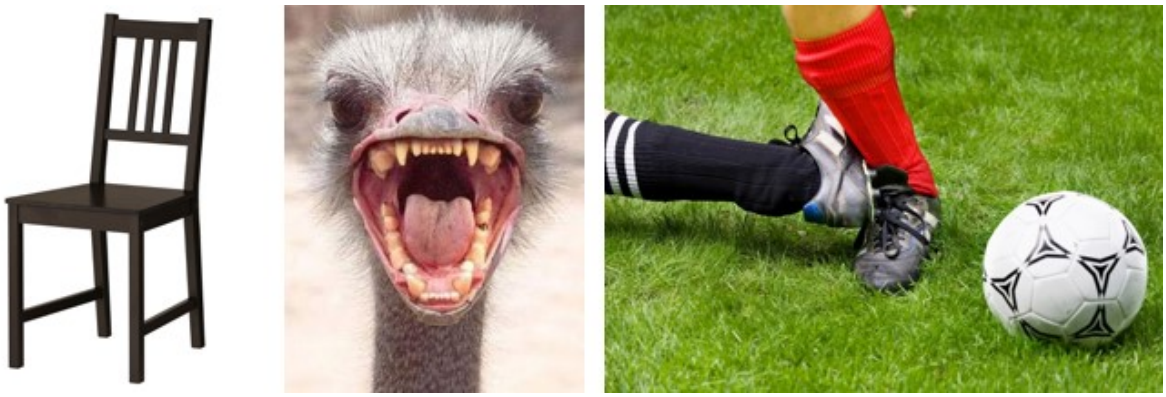


Figure 3. Example of emotional evocative pictures:
(***Left***; Neutral, ***Middle;*** Fear-related, ***Right***; Sport Injury-related)

For joint stiffness and muscle activity testing, the cap and HR sensors will be disconnected from you and four EMG sensors will be attached to the front and back of your thigh of the dominant or injured leg. Prior to application, your thigh may be shaven, abraded, cleaned with alcohol pads, and wrapped with non-adhesive tape in order to secure sensors. You will then be asked to sit on a chair that will measure the stiffness in your knee, called the Stiffness and Proprioception Assessment Device (SPAD; Figure 4). The investigator(s) will secure your trunk and thigh by using a pad and a belt to remove unwanted motion at the hip and trunk. Your lower leg will be placed upon an extension of the chair and into a splint to stabilize from unwanted movement at your ankle. You will be given an emergency stop switch to hold throughout the experiment, which will turn off the device at any time you wish.

After being secured, the leg will be moved into a bent position, where you will be asked three times to push or pull as hard as you can to test your maximum strength for a period of 10 seconds. For stiffness trials, you will be asked to remain completely relaxed and watch a picture presentation, until you feel the device moves your leg into a more bent position. As soon as you feel the movement, you will be asked to "kick up as hard as you can" with maximum effort, until you are asked to relax. You will have randomly assigned nine pictures (3 neutral, 3 fear-related, and 3 knee injury-related pictures). During the entirety of testing, you will be required to wear one sensor above your left eyes. You will be given a set of headphones, which will give a high-pitched tone (100dB). Throughout the testing session this perturbation and acoustic tone will occur at random with any given picture category (neutral, fear-related, and knee injury-related). This part of testing will see how you and your muscles react to an unexpected situation given by the sound.

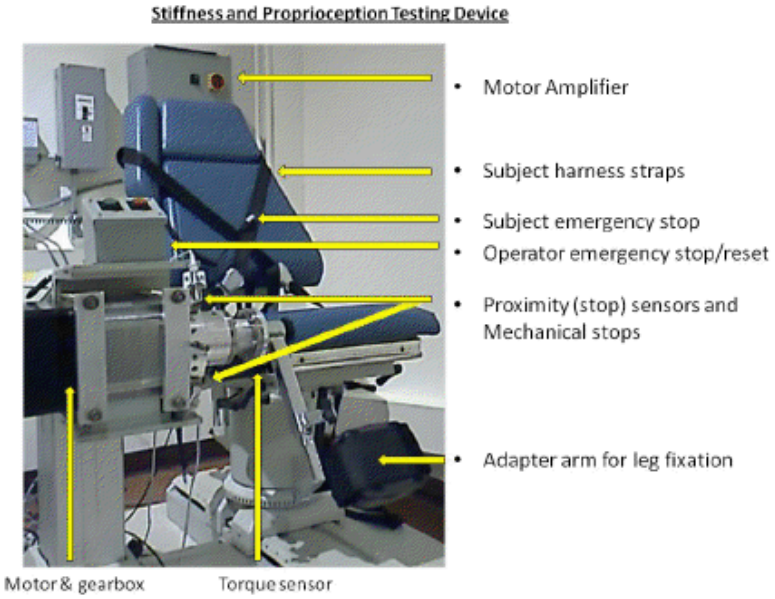


Figure 4. Stiffness and Proprioception Assessment Device (SPAD)

After completion of the joint stiffness and muscle activity testing, you will be asked to complete a mental training program at least 10 hours or greater for 4 weeks until the follow up visit (i.e.; 30 minutes a day, 5 days a week or 25 minutes a day, 6 days a week). You will not be limited for normal daily activities.

Day 2 (45-minute follow up session)

Four weeks after the first day of testing, you will be asked to report to the facility for the follow up testing. You will be first asked to complete 4 surveys assessing knee function and measure of the single legged hop for distance followed by measure of the online executive function assessment test. Two heart rate sensors will then be attached to the both shoulders and you will be asked to sit and watch comfortably the screen with one picture presentation set, which has not yet been displayed. You will watch 30 pictures and rate scores of valence, arousal, and level of fear of the pictures, but brain activity will not be performed at this time. You will be then asked to sit on a chair to measure joint stiffness and muscle activity testing with another picture presentation set, which has not yet been displayed.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

All experimental techniques are not invasive, but there are few mild possible risks of participating in this research including soreness of muscles or joints after performing the hop tasks or stiffness testing, similar to the soreness felt following a workout. There is minimal chance of experiencing injury to the muscles or joint (sprains, strains, fractures). There is also a risk of joints giving way during the hop testing as well as you may feel uncomfortable or anxiety with the fear-related or knee injury-related pictures. **You have the right to withdraw from this study at any time during testing.**

Single legged hop for distance testing.
Rest periods are allowed and designed as part of testing to allow leg muscles to relax between trials and minimize risk of injury.

Stiffness testing
Rest periods are allowed and designed as part of testing to allow leg muscles to relax between trials and minimize risk of injury. Emergency stop switches will be available when involved in stiffness testing on the SPAD, which you may use if feeling uncomfortable or wishes to stop.

EEG testing
Although there is a possibility of scalp discomfort, headaches, or lightheadedness associated with EEG testing, these effects are usually mild and short lasting. There may be also some

minor irritation of the skin/scalp around the site of the electrodes following the experiments. The electrodes only detect brain activity and do not emit electrical energy.

Images
Some images used in this study may cause strong emotional responses and you may feel uncomfortable or anxiety viewing them. Resting period between trials will minimize the unpleasant feeling.

WHAT IF YOU ARE INJURED DURING YOUR PARTICIPATION IN THE STUDY?

Close supervision will be provided throughout the entirety of the testing period by a certified athletic trainer. If you are injured during research procedures, you will be offered first aid at no cost to you. If you need additional medical treatment, the cost of this treatment will be your responsibility or that of your third-party payer (for example, your health insurance). By signing this document, you are not waiving any rights that you may have if injury was the result of negligence of the university or its investigators.

WHAT ARE THE POTENTIAL BENEFITS?

There are no direct benefits to participating in this study. However, the knowledge gained from this study may contribute to your understanding of joint instability following knee injuries and help improve future patient oriented rehabilitation strategies.

NEW INFORMATION THAT COULD AFFECT YOUR PARTICIPATION:

During the course of this study, we may learn new information that could be important to you. This may include information that could cause you to change your mind about participating in the study. We will notify you as soon as possible if any new information becomes available.

HOW WILL CONFIDENTIALITY BE MAINTAINED? WHO MAY KNOW THAT YOU PARTICIPATED IN THIS RESEARCH?

We will make every effort to keep all research records that identify you confidential to the extent permitted by law. The primary researcher will keep all paper data including your consent form in locked file cabinets as well as we will keep all electronic data on a secure password protected server. Names and contact information will only be used to contact you for the purpose of data collection. Your personal information will not be saved and shared with the brainHQ. When you begin participation, you will be assigned a code number that will not use your name or contact information. Only one computer file will contain information that could link your name with your code number, and this file will be

encrypted and stored on a secure password protected-server as well as all other computer data. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Completely de-identified data will be stored indefinitely for future research. Your research records may be viewed by the University of Delaware Institutional Review Board, which is a committee formally designated to approve, monitor, and review biomedical and behavioral research involving humans. Records relating to this research will be kept for at least three years after the research study has been completed.

WILL THERE BE ANY COSTS TO YOU FOR PARTICIPATING IN THIS RESEARCH?

There are no costs associated with participating in this study.

WILL YOU RECEIVE ANY COMPENSATION FOR PARTICIPATION?

There is no compensation associated with participating in this study.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is entirely voluntary. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are otherwise entitled. Your decision to stop participation, or not to participate, will not influence current or future relationships with the University of Delaware. As a student, if you decide not to take part in this research, your choice will have no effect on your academic status or your grade in the class.

WHO SHOULD YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?

If you have any questions about this study, please contact the Principal Investigator, Yong Woo An at (302) 831-8222 or anyong@udel.edu or Buz Swanik at (302) 831-2306 (cswanik@udel.edu)

If you have any questions or concerns about your rights as a research participant, you may contact the University of Delaware Institutional Review Board at hsrb-research@udel.edu or (302) 831-2137.

Your signature on this form means that: 1) you are at least 18 years old; 2) you have read and understand the information given in this form; 3) you have asked any questions you have about the research and those questions have been answered to

your satisfaction; 4) you accept the terms in the form and volunteer to participate in the study. You will be given a copy of this form to keep.

_____	_____
Printed Name of Participant Date	Signature of Participant
_____	_____
Person Obtaining Consent Date	Person Obtaining Consent
(PRINTED NAME)	(SIGNATURE)

<u>OPTIONAL</u> CONSENT TO BE CONTACTED FOR FUTURE STUDIES:

Do we have your permission to contact you regarding participation in future studies? Please write your initials next to your preferred choice.

_____ YES _____ NO

Appendix G

PERMISSION FOR THE IAPS PICTURES

We provide email respond for permission of the IAPS pictures from the Center for the Study of Emotion and Attention at the University of Florida as following:

IAPS:

Dear Colleague: This email regards your request to receive the affective ratings in the International Affective Picture System (IAPS), data that have been collected, analyzed and distributed by researchers at the NIMH Center for the Study of Emotion and Attention at the University of Florida.

Please read the following important points regarding download and use of the IAPS pictures:

1. The IAPS was conceived as a catalog of pictures that represents the entire range of emotional reactions potentially obtainable in this medium. Therefore, users are advised that it contains some images of violence, as well as some images that are judged to be erotic, fear evoking, disgusting, and/or repellent by some viewers. The IAPS is intended exclusively for the research use of applicant investigators. In downloading the IAPS, the investigator is assuming personal responsibility for the download and use of these materials and their subsequent exposure to participant populations.

2. In publications, if possible, we encourage authors to include in a footnote the catalog numbers of the IAPS pictures used in the experiment, as this assists in replication and extension.

3. IAPS pictures should not be published in any print format -- including JOURNALS, newspapers, magazines, etc. -- or in any other media format (TV, films, etc.) and can not be posted on the Internet in any form. IAPS pictures are not in the public domain, and permission can not be given to use IAPS pictures in any published venue. Prior to distributing the IAPS, we ask researchers to sign a statement indicating the pictures will not be published or posted in any format, but we are increasingly receiving more and more requests for permission to publish IAPS pictures in various venues; on the other hand, they often just appear in journals etc., without permission. Therefore, we would like to remind you that IAPS pictures should not be published in any venue. If you would like to include examples of the type of pictures used in your experiments in journal publications (or in videos shot in your laboratories for TV/film/internet purposes), we recommend that you download pictures with similar content (e.g., babies, food, violence, etc.) that are in the public domain on the Internet and use these pictures as examples in media outlets. There is nothing unique about the specific PICTURES in the IAPS set. Rather, it is the inclusion of the normative ratings that we have collected, obtained from hundreds of participants, which allows researchers to select pictures with known hedonic valence and arousal properties, as well as the availability of a stimulus set that different researchers can use in their experiments. Because of this, using pictures in the public domain to demonstrate the type of pictures used in an experiment is quite reasonable. There are many other reasons for why the IAPS pictures themselves should not

be published or shown on TV, not the least of which is to retain their integrity for use in experimental studies.

We appreciate your attention to these important issues regarding the use of IAPS pictures.

Below, you will find a link and a time-limited (1 week) username and password that enables you to download the IAPS. You will be asked to fill out a brief form priormto the actual download. Please do not share your password with other people.

Thank you,
Margaret Bradley & Peter Lang
CSEA Media Core

Google apps @UDel.edu

Charles Swanik <cswanik@udel.edu>

CSEA IAPS Request Confirmation

1 message

CSEA <media@cseamedia.org> Wed, Aug 6, 2014 at 4:49 PM
Reply-To: media@cseamedia.org
To: cswanik@udel.edu

Hello, Charles Buz Swanik.

Your request has been received. Please read, print out, sign, scan, and email this agreement to media@cseamedia.org if you have not already done so.

IAPS Statement of Use

In accepting the IAPS materials, I agree to not to make the IAPS available to the media (television, magazines, etc.) or to place them on any internet or computer-accessible websites. I also agree not to publish the IAPS in any print format-- including JOURNALS, newspapers, etc. I also agree that I will not provide the IAPS materials to profit making companies or organizations and I agree not to distribute my username and password to unauthorized parties.

Name: Charles Buz Swanik
Email: cswanik@udel.edu

Date 8/6/14
Signature _____

*Important- Access to the downloads is only possible after we have received a signed and scanned copy of the IAPS Statement of Use.

Within 30 days of receiving your signed copy of the IAPS Statement of Use, you will receive a username and password, and the link to download the IAPS. This link should not be shared, distributed, or linked to from another website.

If you have any questions or concerns, please contact us at media@cseamedia.org. Please do not call the CSEA or email other members of our center with matters pertaining to the request and download of the IAPS. Thank you.

--
Phorm v3.5.2 by Holotech Enterprises http://www.holotech.net/

Appendix H

PERMISSION FOR THE NIH TOOLBOX

We provide email respond for permission of the NIH Toolbox assessments from the NIH Toolbox team as following:

Thank you for your interest in the NIH Toolbox. To ensure the security and responsible use of NIH Toolbox measures, we require the following steps to be completed before access can be granted.

1. The person responsible for the research and/or clinical use of the Toolbox (e.g., lead researcher, PI, or independent clinician) must send an email to info@nihtoolbox.org, indicating agreement with the NIH Toolbox Terms and Conditions (attached). The email should read (can be cut and pasted, if desired):

I have read and agree to the "NIH Toolbox Terms and Conditions, Effective 11/12/2012." I acknowledge that I am the person responsible for overseeing the research or clinical application in which the NIH Toolbox will be used.

(Type your full name here as signature)

2. The individual requesting access must send documentation that he/she has the experience and training necessary to use the measures requested, or is working under the supervision of someone qualified to use those measures. Acceptable forms of documentation include:

For access please send:

CV of the person responsible for the research or clinical application, indicating a PhD, Master's or equivalent degree in a field related to the request. If the person requesting access does not have C-Level qualifications, please be sure to have the assigned PI or person responsible for overseeing the research send their current CV and the Terms and Conditions. Please have PI or person responsible cc' the requestor on the email as well. Please don't forget to set up an account with assessment center.

3. Create an account with Assessment Center. You must create your own study, to obtain the instruments and or batteries from the original Toolbox studies. Once this is complete your requested instruments will become visible in your study.

Send all required documentation as follows:

By Email: Send PDF(s) to info@nihtoolbox.org

By Fax: Fax required documents to 312-503-4800, Attention: NIH Toolbox

By Mail/Fedex: NIH Toolbox
625 North Michigan, Suite 2700
Chicago, IL 60611

While we are reviewing you documents please take the time to review NIH Toolbox documentation here:
http://www.nihtoolbox.org/Resources/NIH%20ToolboxManualsandGuides/Pages/default.aspx

Also recommended to review the platform where the NIH Toolbox runs off which is the Assessment Center. The manual and tutorials can be found here: http://www.assessmentcenter.net.

Thank you for your cooperation. You will be notified that you have been granted access after we have received all required documentation.

Thank you,

The NIH Toolbox Team

info@nihtoolbox.org

NIH Toolbox Terms and Conditions
Effective 11/12/2012

The NIH Toolbox Terms and Conditions contained in this document (hereinafter referred to as "NTAC") serve as an agreement between Northwestern University (NU) and the National Institutes of Health (NIH), hereinafter referred to as "NU/NIH," and users of any and all aspects or components of the NIH Toolbox, hereinafter referred to as "You" or "User."

Use of the NIH Toolbox measures/instruments, related materials, and services require acceptance of all terms and conditions stated herein. You agree to abide by all of NTAC as a condition of reviewing or using the NIH Toolbox. No modifications or additions to these terms and conditions are binding upon NU/NIH unless previously agreed to in writing by an authorized representative of NU or the NIH. NU/ NIH reserves the right to update the NTAC at any time. Changes in the NTAC shall apply to new users, new measures and to new projects created by existing users after such changes are posted.

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Any publication or presentation of results obtained from studies conducted using NIH Toolbox measures should include a statement that NIH Toolbox version 1.0 measures/instruments were used, and reference the NIH Toolbox website (www.NIHToolbox.org) for further information.

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disclosure of trade secrets in a manner inconsistent with the provisions of this Agreement may cause NU/NIH irreparable damage, for which remedies other than injunctive relief may be inadequate. Accordingly, User agrees that in any request by NU/NIH to a court of competent jurisdiction for injunctive or other equitable relief seeking to restrain such use or disclosure, User will not maintain that such remedy is not appropriate under the circumstances.

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Maintenance of Test Security and Test Use

Each person or institution using the NIH Toolbox must agree to comply with these basic principles of test security:

Test takers must not receive test answers before beginning the test.

Test questions are not to be reproduced or paraphrased in any way.

Access to test materials must be limited to qualified persons with a responsible, professional interest who agree to safeguard their use.

Test materials and scores may be released only to persons qualified to interpret and use them properly.

If a test taker or the parent of a child who has taken a test wishes to examine test responses or results, the parent or test taker may be permitted to review the test and the test answers in the presence of a representative of the school, college, or institution that administered the test. Such review should not be permitted in those jurisdictions where applicable laws require the institution to provide a photocopy of the test subsequent to review. If You are not certain of the effect of the laws in Your jurisdiction, please contact Your jurisdiction's professional organization.

No reproduction of test materials is allowed in any form or by any means, electronic or mechanical without advance, written permission of NU/NIH. Requests to copy any test materials must be submitted through the NU/NIH Contact Us page on the website, at www.nihtoolbox.org. (Please enter request details in the message box.)

User Qualifications

Test users must have the appropriate knowledge, skills, training and experience to responsibly use NIH Toolbox measures. "Test users" are those persons responsible for the selection, administration, scoring and interpretation of tests and the communication of results. Therefore, NU/NIH reserves the right to ask individuals requesting access to NIH Toolbox measures to provide documentation that they have the experience and training necessary to use those measures, or are working under the supervision of someone qualified to use those measures. In particular, User may be asked to provide documentation of qualifications for measures classified as "C-Level." C-Level tests require a high degree of expertise in test interpretation, and thus can only be requested by a User with state licensure or certification to practice in a field related to the request, or a doctorate degree in psychology, education, or a closely related field, with formal training in the ethical administration, scoring, and interpretation of clinical assessments related to the intended use of the assessment. Any users of C-Level assessments must be supervised by one or more users with C-Level qualifications, which must have been provided in advance to NU/NIH per this process.

Rules Governing Use of the NIH Toolbox by Various Categories of Users

Universities, schools, organizations, businesses, clinics, and hospitals are subject to the guidelines set forth above and must have appropriately qualified individuals on staff in

order to use the NIH Toolbox tests. These individuals must complete a Registration Form and provide information as to their qualifications.

Protective Orders. User agrees to seek a protective order safeguarding the confidentiality of test materials classified by NU/NIH as "C-level" assessments if User is required to produce such materials in court or administrative proceedings.

No Warranty. NU/NIH make no warranties, expressed or implied, including warranties of merchantability or fitness for a particular purpose. NU/NIH will not, under any circumstances, be liable for User's expense for delays, for costs of substitute materials, or for possible lost income, grants, profits, or any other special or consequential damages that may result from using the NIH Toolbox.

Limitation of Liability. In no event will NU/NIH be liable for damages arising under this agreement, or otherwise arising from the order(s) contemplated under this agreement.

Notices. Any required notices shall be given in writing to User at the most recent contact information provided by User to NU/NIH. NU/NIH may send You notice by electronic mail as an alternative to conventional mail.

C. Buz Swanik, PhD, ATC, FNATA
Assoc. Professor, KAAP, BIOMS
151 Human Performance Laboratory
c/o Fred Rust Arena, 547 South College
Newark, Delaware 19716
Office: (302) 831-2306
Email: cswanik@udel.edu

Department of Kinesiology and Applied Physiology

Monday, July 29, 2013

This letter is to request permission to use the NIH Toolbox for data collection and NIH grant submissions. While I am not a psychologist, I have been conducting human subjects research in neurophysiology, neuropsychology and biomechanics for approximately 19 years, many of which included a variety of instruments related to neuropsychological function, quality of life, pain, functional status, and the perception of somatosensations like proprioception, kinesthesis and joint stiffness. I have also conducted research using questionnaires / instruments evaluating personality constructs such as anxiety, stress, fear, locus of control and risk-taking. I am also a licensed Athletic Trainer with many years of clinical experience treating patients from triage through surgery/rehabilitation and return to physical activity.

Our previous work on injury proneness and coping shows that after major joint sprains like the anterior cruciate ligament (ACL) rupture, some patients may be able to return to pre-level of activity (copers), but many others fail to gain normal function due to continuous episodes of joint giving way (noncopers). Many researchers have investigated biomechanical characteristics to identify causation, but limited data is available regarding cognitive functions and/or emotions. The purpose for use the NIH-TB is to examine the role of individual cognition and emotional stability that may exist in injured patients. We will use elected tasks in the cognition and emotion subdomains of the NIH-TB. Investigators in this study have the appropriate knowledge, skills, training and experiences to responsibly use the NIH-TB measures in conjunction with the online and video tutorials. These investigators, including Yong Woo An, are working under my supervision and I will monitor all procedures associated with NIH-TB measures.

Sincerely,

Charles Buz Swanik