Neurophysiological Mechanisms Underlying Functional Knee Instability Following an Anterior Cruciate Ligament Injury

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PURPOSE: Functional knee instability, which is defined as repetitive episodes of the knee “giving way” during physical activity, has received great attention to identify mechanisms due to serious pathological complications. Growing evidence suggests that insufficient neural adaptation in the central nervous system (CNS) may result in permanent functional deficits in patients with anterior cruciate ligament (ACL) injuries. The purpose of this review was to address neurophysiological mechanisms underlying functional joint instability following an anterior cruciate ligament rupture.

METHODS: Previous studies conducted from PubMed with particular emphasis on mechanisms underlying joint instability and neuromuscular control deficits after an anterior cruciate ligament were reviewed.

RESULTS: Inappropriate neuromuscular control, inconsistent correlations between joint laxity and functional outcomes, and altered neural activation in the brain during proprioceptive tasks may underscore the idea that persistent functional joint instability is an indication not only of the peripheral deafferentation input, but also neuromechanical decoupling between the injured ACL and CNS due to neuroplasticity.

CONCLUSIONS: Persistent functional instability can develop following knee joint injury due to altered neural processing in the CNS. Therefore, it must be considered for improving patient outcomes, minimizing functional disability, and returning to one's chosen physical activity in ACL patients.

Key words: Anterior cruciate ligament injury, Functional joint instability, Neuroplasticity, Neuromechanical decoupling, Joint laxity

INTRODUCTION

It is well defined that functional joint stability protects a joint through simultaneous dynamic control of muscles surrounding the joint [1], while structural (mechanical) stability is provided by anatomical limits of the joint properties, such as ligaments in the knee [2,3]. 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 a ligamentous injury [3-5]. For these reasons, functional joint instability, which is defined as repetitive episodes of a joint “giving way” or “buckling” during physical activity, has received great attention in anterior cruciate ligament (ACL) ruptures and other peripheral joint pathologies,

such as ankle sprains and shoulder subluxations [6-10]. This increased interest 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 [11]. Moreover, approximately 50% of ACL patients develop early knee osteoarthritis and experience a diminished health-related quality of life [9]. Therefore, many researchers have attempted to examine the 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 excessive joint laxity (mechanical instability) [12], and its consequential proprioception deficits [2,4,13] and inappropriate muscle stiffness strategies [2,4,13], may put individuals at risk of having un-

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pleasant knee-giving-way episodes and subsequent disability or recurrent peripheral knee injury [4,14]. On the other hand, recent studies have also advocated that an inefficiently reorganized central nervous system (CNS) following a ligamentous tear may be the primary factor leading to the long-term declines in knee function [15-20]. It is possible that such altered neural processing in the CNS may disrupt the normal responses of the nervous system to prepare and react to excessive joint loads during high velocity maneuvers. Hence, this reduced ability of the neuromuscular control system may increase the risk of these persistent pathological complications in patients with ligamentous injury [15-20].

The appropriate paring between ligamentous and neurological constituents of a joint to external stimuli is known as neuromechanical coupling [21]. In fact, it has been demonstrated that this successful neuromechanical coupling and motor planning capabilities for muscle coordination can optimize modulation of the muscle stiffness necessary for maintaining functional joint stability during physical activity [2,4,13,17]. This may indicate that the CNS plays an important role in the regulation of neuromuscular control [1]. Thus, the nervous system must appropriately remodel existing neural networks in the brain to regulate muscle coordination after musculoskeletal injury because the neuromechanical links between joint tissue and the CNS may be uncoupled [1,22-24]. Therefore, it is crucial to explore the neurophysiological mechanisms underlying functional joint instability through the review of literature on the role of the nervous system in the maintenance of joint stability. Understanding the cascade of neural processing in the CNS following a ligamentous injury will help to develop advanced rehabilitation programs and maximize patient outcomes. Thus, this paper will discuss 1) the role of the neuromuscular control system in joint stability, 2) the interrelationship between the damaged ACL and CNS, and 3) the neurophysiological theory behind reorganization of the CNS that may lead to persistent functional joint instability.

1. Role of the sensorimotor system in joint stability

In order to understand neurophysiological mechanisms underlying functional joint instability following ligament injury, it is imperative to understand how the nervous system regulates neuromuscular control and protects the body's joints. The sensorimotor system maintains joint integrity during physical activity through complex neurophysiological events involving series and parallel networks [1]. 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 [1,22,23]. Neurological responses underlying the maintenance of functional joint stability generally begin in the PNS, by detecting joint proprioceptive information [22]. Several ligamentous mechanoreceptors in the joint then convey associated neural signals to the higher cortical levels via the spinal cord (SC) [22]. 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 [22,25,26].

It is well recognized that the knee joint is secured mechanically and functionally by static and dynamic restraint systems, respectively [2,3]. 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, 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 [1-3]. 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 [2,27]. 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 [3]. 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 encountered during intense activities [28].

The neuromuscular control system regulates dynamic restraint by two neural mechanisms. The reflexive feedback mechanism is continuously modulating reactive muscular contractions based on the proprioceptive feedback from a joint to the CNS [2,26]. 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 stiff-

ness needed for each motor task [26]. Direct measures of sensory neural conveyance obtained through microneurography recordings of peripheral nerve traffic have demonstrated positive correlations between ankle joint force, ligamentous laxity, and afferent sensory traffic transmitted from muscle spindles to the CNS [29]. This suggests that the dynamic feedback mechanism underlying neuromuscular control, which also modulates the stiffness of the knee muscles responding to joint loading, is dependent upon neuromechanical coupling [26]. The involvement of muscle spindles in this feedback process is important because their sensitivity can be modulated by the brain and affect muscle tone, even though 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, there is often a latency period in the reactive muscular contraction in response to a sudden perturbation [30,31]. The delayed reactive muscle contractions can be compensated for by anticipating future loads through the dynamic feed-forward neuromuscular control mechanism [32].

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 unrelated to current movements [2,9]. As a result, this preparatory neural processing initiates early muscle activation prior to anticipated joint perturbations [2,26]. These preactivated muscle patterns are regulated directly by cognitive processing through preprogrammed recruitment strategies [2,4,33]. As a result, muscles surrounding the knee joint can produce rapid and accurate excitation and inhibition as needed to project the joint [2,4,33]. This suggests that the preparatory feed-forward mechanism plays a critical role in regulating appropriate, task dependent levels 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 [1,4,9]. 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. However, between 44% and 56% of these patients still suffer persistent knee dysfunctions even with surgical reconstruction and extensive rehabilitation [34,35].

2. Structural and functional knee stability: copers vs. noncopers

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 [12,36,37]. 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 [37,38]. These mechanoreceptors in the ACL such as Ruffini endings and Pacini corpuscles transmit signals coding joint position and kinematic movement, respectively [39]. 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 [7,26,40,41]. Therefore, the increased displacement of the injured ACL 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 [26,39]. As a result, it is possible that the knee dynamic restraint system for both the preparatory and reactive muscle contraction mechanisms can be compromised. This means that the altered level of muscle stiffness is no longer capable of protecting joint structures [2,4,30,42-44].

For this reason, animal and in vivo human studies have suggested that anterior cruciate ligament reconstruction (ACLR) may not only recover mechanical stability, but also regenerates mechanoreceptors in the graft, which allows for restoration of proprioception and an improvement of knee function [37,38,45-47]. However, recent studies have shown 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 [48-50]. Indeed, both surgical and conservative treatments have shown successfully enhanced muscle contraction patterns and improved knee function outcomes, without having additional episodes of their knee "giving way" [51,52]. Nonetheless, some in the ACL population still suffer persistent functional joint instability, regardless of surgical procedure or type of post-ligamentous injury treatment [5,35,53]. Patients who restore normal knee function and return to previous levels of physical activity without limitations following ACL tears are defined as "copers," whereas other ACL patients who fail to return to function at a high-level of activity with complaints of instability are defined as "noncopers" [54]. 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 [34,49,51,55,56]. While a surgical procedure restores

mechanical stability to the knee joint, the high occurrence of ACLR noncopers and ACLD copers may suggest that joint laxity alone does not dictate the quality of neural integrity between the ACL and CNS, but some other factors are influencing neuromechanical coupling [50,54].

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 functioning of the knee [49,57]. Similarly, ACLR noncopers, who have had surgically restored mechanical stability and may sprout new mechanoreceptors after a reconstruction [37,47], reveal attenuated knee muscle strength and worse functional outcomes, such as lower scores on hopping tasks [58-61]. Some research has shown that excessive laxity is a risk factor leading to functional joint instability [12,50], but many have also demonstrated that it is not a reliable predictor of dynamic stability [54,57]. Eastlack [54] reported that ACL noncopers demonstrate diminished knee function outcomes, quadriceps strength, and more experiences of knee giving-way episodes, despite having less side-to-side laxity differences, when compared to other ACL copers. This neuromechanical decoupling then may result in incongruous neural integration and processing in the brain needed to prepare for and react to external load to the knee joint. Cluvenor et al. [62] demonstrated that ACLR patients revealed bilateral dynamic balance deficits during a single-leg squat task, when compared to healthy controls. With consideration to the contradictory clinical outcomes in ACL patients, bilaterally diminished proprioceptive function after an ACL injury may indicate insufficient neural adaptation in the brain, which has failed to simultaneously and properly reconcile and bind sensory inputs from both knees.

3. Theory: functional joint instability resulting from neuroplasticity following ACL rupture

Recent studies have suggested that continuous neuromuscular deficits following an ACL injury are the result of insufficient neural adaptation by the CNS [16,17,63]. 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 [14, 16,17]. 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 informa-

tion to provide fine and gross motor behavioral responses [3,64]. 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 [63]. 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 [65-67].

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 [9,22]. 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 [22,64]. Generally, the frontal lobe is responsible for planning of movement, while 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 [22,68]. It has been suggested that the somatosensory cortex projects perceived sensory outputs to other cortical areas responsible for recognition and planning of desired movements [69-71]. 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 [72,73]. Several neuroimaging studies have shown altered cortical activation in ACL patients. Electrocortical activation in ACLR patients using electroencephalograph (EEG) revealed greater errors and higher neural processing in the frontal and parietal cortices during proprioceptive tasks, when compared to healthy controls [18,74]. These results support neuroplasticity in several regions of the brain responsible for muscle coordination after an ACL injury. Increased cortical activation in the frontal and parietal cortices in conjunction with the greater error during proprioceptive tasks may underline neural maladaptation as an indicative of neuromuscular

control deficits.

The subcortical structures, such as thalamus and basal ganglia, have also been linked to muscle coordination and control [63,75,76]. 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 hearing [22,64,77]. 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 [64]. 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 [64]. 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 [64]. Consciously integrated information in the prefrontal cortex responsible for cognitive management processes can influence the filtering of information at the thalamus [78]. Moreover, the thalamus receives significant motor feedback output, 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. This allows for a conscious execution of appropriate motor responses to targeted muscles [63,64,75]. 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. A functional magnetic resonance imaging (fMRI) study showed that ACLR patients had altered cortical activation in the cerebellum during active knee flexion-extension task, presumably due to subcortical reorganization [79]. 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. This leads to decoupling of 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 [16]. Clinical outcome differences between copers and noncopers in returning to pre-injury level of physical activity and altered cortical activation during physical function tasks may suggest that these networks undergo plastic changes after ACL injury.

CONCLUSION

Following an ACL injury, regardless of the treatment option followed, some ACL 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 may underscore the idea that persistent functional joint instability is an indication not only of the peripheral deafferentation input, but also of its neuromechanical decoupling with the CNS as a result of neuroplasticity, rather than being due to mechanical laxity [16,17,80]. Neurophysiological mechanisms underlying functional joint instability following ligamentous injury have not been fully understood yet due to a lack of knowledge and limitations of the nature of research settings, which have involved invasive procedures in the past [81,82]. However, the evolution of versatile functional neuroimaging techniques, such as fMRI, transcranial magnetic stimulation (TMS), and EEG, has allowed for the non-invasive exploration of cortical activation after injury [83]. In addition, many researchers using new neuroimaging techniques have demonstrated direct and indirect neuroplasticity following peripheral injuries at the ankle and knee joints [18-20,24]. The results of these studies have not yet successfully determined whether the altered brain's function reflects optimal a neural adaptation to protect the joint or evidence of a predisposing factor that requires modification and corrections to prevent diminished joint function. Nonetheless, it is implied that the neuroplastic changes after an ACL injury must be considered and targeted in interventions [15,84]. There is no consensus on neuroplastic rehabilitation programs yet. However, facilitating neural integrity among several regions of the brain in conjunction with traditional neuromuscular control exercise programs will improve neuromechanical coupling. For example, using visual or biofeedback techniques during proprioceptive tasks may advance simultaneous signal processing between brain's regions as well as with both joints [15]. Therefore, further study that emphasizes on the emerging area of neural activity and its connectivity within the brain is needed to not only provide evidence of CNS adaptation underlying functional joint instability, but also help improve patient outcomes, minimize functional disability, and aid return to one's chosen physical activity in ACL patients.

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