Evidence of Neuroplasticity and Neuroimaging Techniques following Anterior Cruciate Ligament Injury

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PURPOSE: Recent evidence has linked neural changes in the brain, known as neuroplasticity, to anterior cruciate injury, possibly explaining why some patients suffer repetitive functional instability. Therefore, the purpose of this article was to review the manifestation of central nervous system reorganization following anterior cruciate ligament injury and establish further the application of neuroimaging assessment tools in the evaluation of neuroplasticity after ligamentous injury.

METHODS: Previous research articles emphasizing neuromuscular deficits, functional joint instability, and anterior cruciate ligament injury and neuroimaging techniques searched from PubMed databases were reviewed. Additionally, more relevant research articles through a cited reference search from the original research articles were reviewed.

RESULTS: Diminished neuromuscular control such as proprioception, muscle activation, and joint stiffness regulation appears to be indirect evidence of neural adaptations that may lead to persistent functional joint instability and future pathological complications. Results of direct measurement of the brain's function using a variety of neuroimaging tools supports altered cortical activation in the brain corresponding to diminished knee function.

CONCLUSIONS: Knee functional deficits after an anterior cruciate ligament injury may be associated with neural adaptations in the brain. Neuroimaging techniques that allow for examination of neural activity in the central nervous system help to better understand the neurophysiological mechanisms underlying the link between the brain's function and functional joint instability, to develop more effective rehabilitation programs, and to improve patient outcomes.

Key words: Anterior cruciate ligament injury, Functional joint instability, Neuroplasticity, Neuroimaging technique

INTRODUCTION

After a tear of the anterior cruciate ligament (ACL), persistent knee functional deficits such as experiences of repetitive joint "giving way," known as functional joint instability, have received great attention by many investigators because of the healthcare burden, low success rates of return to pre-injury levels of physical activity, and higher incidence rates of recurrent rupture [1-7]. Moreover, these diminished knee functions and loss of dynamic stability are observed not only in the injured knee, but also in the contralateral knee in which the ACL is still intact, regardless of a contact or non-contact mechanism [5,8-11]. Damage to the ACL can lead to deafferentation of mechanoreceptors in the knee [12,13] and it may alter sensitivity of the neural connectivity within the central nervous system (CNS) [14-16]. This diminished sensory integration between the injured ACL and CNS may interfere with the normal neural processing associated with the uninjured knee function [17]. Therefore, identifying neurophysiological alterations that may be associated with functional joint instability after an ACL injury is critical to prevent recurrent ligamentous tears and to develop rehabilitation programs to optimize patient outcomes without persistent clinical impairments.

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 previous physical performance [18,19]. This may be an indication of continuous

cortical adaptation of existing neural networks at different levels of the CNS [20,21]. Recent evidence has linked reorganization of the CNS, which is known as neuroplasticity, to decreased knee function after ACL injury. This may possibly explain why some patients that suffer repetitive functional instability have recurrent knee sprains and/or contralateral injuries, and fail to return to pre-injury levels of physical activity, despite restoration of mechanical laxity [17,22,23]. In addition, prolonged disruption of the CNS in conjunction with the bilateral joint deficits may also imply that the ACL injury also induces neural adaptations in the CNS associated with function of the contralateral knee [17]. A variety of neuroimaging techniques evaluating neurophysiological events in the brain suggest that a tear of the ACL may alter the normal cascade of neural processing responsible for both sensory perception and motor output in the CNS [24-28]. Therefore, the purpose of this review article is to provide a comprehensive and succinct review of the evidence for neuroplastic changes in the CNS after ACL injury and an overview of neuroimaging techniques that can be utilized in examining neurophysiological responses in the brain in ACL patients.

NEUROPHYIOLOGICAL DEFICTS AFTER ACL INJURY

Following an ACL injury, dissimilar neuromuscular control responses such as altered proprioception and muscle stiffness regulation strategies have been observed among ACL patients [29-31]. Diminished proprioception and muscle coordination failure during physical activity may be an indication of indirect evidence of neuroplastic changes in the CNS after an ACL injury. Beard et al. [32] reported the timing of reflex hamstring contraction latency (RHCL) as an indirect measure of knee proprioception in ACL deficient (ACLD) patients who had conservative rehabilitation program without a surgical procedure. It was found that ACLD individuals showed 46.1 ms slower RHCL in the injured limb than the uninjured limb, when compared to the interlimb difference in healthy controls (4.2 ms). These patients also reported a higher frequency of "giving-way" episodes, regardless of joint laxity. Such 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 the muscle inhibitory or excitatory strategies implicated in the neuromuscular control [33,34].

Furthermore, a number of studies have also reported conflicting results on joint position sense awareness in ACL reconstruction (ACLR)

patients who had a surgical repair and were 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. [35] and Mir et al. [36] demonstrated that ACLR patients had a restored 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 were also observed in the ACLR patients when comparing performance to healthy controls [37]. These proprioceptive deficits are also observed in the opposite intact limb in ACL patients, regardless of surgical procedure [8]. Some ACL noncopers, who failed to return to pre-injury levels of physical function with experiences of functional joint instability, have developed bilateral knee dysfunction and suffered a secondary rupture of their ACL, not only in the ipsilateral knee but also the contralateral side [5,8-11]. Arockiaraj et al. [8] 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 the dynamic restraint system [17,38].

Following an ACL injury, ACLD patients have demonstrated quadriceps inhibition following knee perturbations [39,40]. Swanik et al. [41] showed that an ACLD group displayed attenuated quadriceps, and exhibited greater hamstrings reactive activation in response to joint loading during high velocity movement tasks (landing and running), when compared to healthy controls. Results also showed that this neuromuscular control deficit occurred in both the deficient and healthy knees. As the hamstrings and quadriceps muscles reciprocally inhibit each other [42], this information 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 processes [41].

Swanik et al. [19] also reported that ACLD patients had enhanced preparatory activity of the hamstring muscles, which acts as a restraint to anterior displacement of the ACL during landing tasks. Although each patient had varied amounts of 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 [43]. Conversely, other studies have reported that ACL patients with long-term disability show 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 [44,45]. These findings imply that ACL copers, who successfully return to normal physical functions after an ACL injury, compensate for neuromechanical decoupling between the knee and CNS, regardless of joint laxity. Therefore, ACL copers can protect knee joints bilaterally by optimizing muscle contraction strategies to maintain functional joint stability during a complex physical activity known to stress the ACL, whereas ACL noncopers do not [2,18,19,46].

Moreover, several subsequent ACL injury studies have reported that once ACL 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 [47], to 12% within 5 years [48], and almost 30% within 10 years [49]. 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 [11,48,50]. Evidence of the development of proprioceptive and neuromuscular control deficits leading to secondary ACL sprains to the contralateral side may be indicative of persistent neural maladaptation in the cerebral cortex, which can diminish neuromuscular control system over time [26,37,51,52]. However, most of these findings are speculative, based on either indirect measures of the CNS's responses during proprioceptive tasks or clinical outcomes from prospective cohort studies. Therefore, direct observation of cortical activity in the brain should offer better insight into the manifestation of neuroplasticity in ACL patients after an ACL injury in order to precisely explore the neural origin of these neuromuscular control deficits.

EVALUATION OF NEUROPLASTICITY IN ACL PATIENTS

During the past several decades, the evolution of versatile functional neuroimaging techniques has allowed for the non-invasive exploration of cortical activation after injury [53]. 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 technique 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 [53-56]. When specific areas in the brain are activated in response to sensory inputs, neurons in those areas require greater supplies of glucose and oxygen to be delivered 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 [53]. 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 adaptations following an ACL injury.

Kapreli et al. [24] found changes in cortical activation patterns in the CNS during a simple knee flexion/extension task observed by using fMRI technique 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 output. 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 [57,58]. The author suggested that the increased neural demand of visual perception could compensate for diminished proprioception in ACLD patients by enhancing recognition of significant visual cues for early planning of movement [24]. Grooms et al. [59] also demonstrated altered cortical activation in ACLR patients with fMRI during active knee flexion/extension motor task. The results supported that neural activation patterns in the brain may be altered as a result of ACL injury [24], but showed more cortical activation in the sensorimotor cortices and cerebellum when compared to healthy controls. This increased somatosensory cortex activation may be an alternative protective compensatory mechanism for increased neural demands as a result of decreased proprioception after ACL injury [28]. This fMRI technique provides better spatial resolution, which is the accuracy in the location and dimension of brain activity [53,60]. As chronic functional deficits after an ACL injury may manifest permanent neural maladaptation in the

brain [61], fMRI techniques may help to identify the origin of the neuroplasticity. However, it has limitations to adequately offer observation of the critical neural mechanisms underlying neuromuscular control during unanticipated events in physical activity that lead to functional instability episodes [53,62]. 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 [53,62]. ACL injuries can occur in less than 70 ms and the neuromuscular control system can regulate muscle stiffness strategies in less than 50 ms [63,64]. Therefore, the fMRI's temporal resolution is too slow for accurately measuring cortical events within the injury timeline of interest [53].

The second group of measurement techniques for brain activity is growing in popularity, including transcranial magnetic stimulation (TMS), electroencephalography (EEG) and magnetoencephalography (MEG) techniques [53,65]. 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" [53,62]. 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 implies 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 [66]. Kuenze et al. [52] used the TMS technique to examine motor-evoked potentials (MEPs) of the primary motor cortex during isometric knee extension contraction at 5% of maximum voluntary isometric contractions (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 a greater MEP indicates less cortical excitability and facilitation of muscle contractions [67]. 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 [68,69]. Contralateral cortical excitability patterns were also observed by Heroux and Tremblay [66] and Pietrosimone et al. [69]. These studies found that ACLR patients had increased 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 contralater-

al limbs' dynamic restraint needed for the maintenance of functional joint stability following ACL injury [21]. Therefore, this TMS technique is an excellent neuroimaging tool to identify the relationship between detection of proprioceptive inputs at the somatosensory cortex and an efferent neuronal excitability at the corticomotor level, reflecting reactive muscle activity through the proprioceptive feedback mechanism [66]. However, 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, which are necessary to maintain functional joint stability.

Substantial advantages of EEG and MEG over other noninvasive functional neuroimaging of the brain, such as fMRI and PET, are the level of temporal resolution in the order of milliseconds, as well as direct recording of the cascade of neuronal electrical currents of the entire cerebral cortex [53,62]. 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 [53]. 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 [53,70].

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 [71-73]. 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 area is associated with task-related cognitive processing, as well as emotional regulation [74-76]. Baumeister et al. [25,26] demonstrated in EEG studies that ACLR patients had dissimilar cortical activation in the frontal and parietal cortices 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 [77], thus supporting the findings reported by Kapreli et al. [24]. 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 in order to better perceive, process and integrate decreased

proprioceptive inputs after ACL injury [28]. 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 [78]. Enhanced neural activity occurring simultaneously in these cortices reflects heightened neurocognitive processing [26,79]. 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 [19,80]. However, the CNS reorganization, as a result of an ACL rupture, may not provide enough neural resources in response to sudden knee perturbation, as brain regions for task-related cognitive processing could be compromised after the ACL rupture, leading to interrupted neuromuscular control. For this reason, an individual's executive function capabilities may be linked to ACL injury proneness, and may have a substantial role in restoration and maintenance of functional joint stability following an ACL injury [81,82].

CONCLUSION

Regardless of injury mechanisms (contact or non-contact) or treatment of option (surgical or conservative), an ACL injury could lead to failure in muscle coordination and development of pathological complications such as a recurrent rupture to either ipsilateral or contralateral and early onset of knee osteoarthritis. Changes of neural activity in the brain have been thought to be the primary reason for functional limitations after the ACL injury. Diminished proprioception, such as greater errors in joint position and force reproduction, not only in the injured limb but also in the healthy knee and the altered muscle contraction strategies; i.e. decreased joint stiffness to a sudden perturbation or excessive or less muscle activation, may be indirect evidence of insufficient neural adaption in the CNS. Moreover, recent knee studies that utilize versatile functional neuroimaging techniques allow direct examination of cortical activation in the brain in ACL patients corresponding to knee function tasks, and the results of these studies have demonstrated that altered brain function in ACL patients is highly associated with diminished knee proprioception and motor control. To date, the results of the neuroimaging studies are not yet conclusive in terms of identification of the interrelationship between knee function and neural adaption in the CNS underlying functional joint instability. Moreover, due to the limitation of the nature of neuroimaging study setting, it is important that investigators understand the advantage and disadvantage of each neuroimaging techniques and choose an appropriate technique according to the purpose of the study. Future study combining advantage of each neuroimaging technique may provide further insight into the structural and functional neural adaptation in the brain after an ACL injury and it will advance our knowledge on the role of the brain associated with functional joint instability and help to develop rehabilitation programs and improve patient outcomes [83].

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