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REVIEW ARTICLE

Central Nervous System Adaptation After Ligamentous Injury: a Summary of Theories, Evidence, and Clinical Interpretation

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Abstract The array of dysfunction occurring after ligamentous injury is tied to long-term clinical impairments in functional performance, joint stability, and health-related quality of life. To appropriately treat individuals, and in an attempt to avoid sequelae such as post-traumatic osteoarthritis, investigators have sought to better establish the etiology of the persistent dysfunction present in patients who have sustained joint ligament injuries to the lower extremities. Recent evidence has suggested that changes within the brain and central nervous system may underlie these functional deficits, with support arising from direct neurophysiologic measures of somatosensory dysfunction, motor system excitability, and plasticity of neural networks. As research begins to utilize these findings to develop targeted interventions to enhance patient outcomes, it is crucial for sports medicine professionals to understand the current body of evidence related to neuroplasticity after ligamentous injury. Therefore, this review provides (1) a comprehensive and succinct overview of the neurophysiologic techniques utilized in assessing central nervous system function after ligamentous injury, (2) a summary of the findings of previous investigations utilizing these techniques, and (3) direction for further application of these techniques in the prevention and rehabilitation of joint injury.

Key Points

Ligament injury, such as that to the anterior cruciate and lateral ankle ligaments, has notable effects on the somatosensory and motor areas of the cortex.

Neurological adaptations appear to be associated with clinical deficits that may contribute to poor long-term outcomes among these populations.

Research must continue to identify therapeutic techniques targeted towards recognizing and correcting potential cortical maladaptation after injury.

1 Introduction

Ligamentous injury, such as a tear of the anterior cruciate ligament (ACL) or a lateral ankle sprain, has become a healthcare burden over the past several decades [1–3]. These injuries, associated with both contact and non-contact mechanisms, have consistently been observed to lead to functional deficits beyond the increased laxity associated with the loss of static joint stabilizers. Most notably, the loss of dynamic stability or sensation of the joint giving way associated with ligamentous injury leads to persistent functional deficits that may persist even following surgical restoration of static stability [4, 5]. Furthermore, both the

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initial joint injury and the subsequent instability are tied to reports of early-onset osteoarthritis for the injured and contralateral joints [6, 7]. The disrupted sensory function of the injured ligaments, bilateral nature of joint dysfunction (despite unilateral injury), prolonged altered motor control, and recent neurophysiological evidence indicate that musculoskeletal trauma may induce neuromechanical effects [8–10]. Therefore, it is crucial to understand the neuromechanical alterations following injury in order to aid the secondary prevention of their long-term sequelae and make advances in therapeutic treatments.

Although previous hypotheses have used reflexive mechanisms to explain deficits in clinical function, termed arthrogenic muscle inhibition (AMI) [11], a rapidly growing amount of evidence has begun to identify changes in the brain following injury to the ligaments of the ankle and knee joints [12–15]. The link between a ligament rupture and neuroplasticity has the potential to explain the array of clinical symptoms and dysfunction experienced in these populations and provide a novel therapeutic target. In fact, considering the constraints presented by musculoskeletal injury, it is only reasonable that the highly adaptive central nervous system will adjust to maintain function, and clinicians need to accommodate this system in rehabilitation [16]. These changes are associated with both sensory and motor components of the nervous system. For instance, ligament injury has been tied both to short-term increases in afferent activity secondary to pain and swelling [11] and to long-term deficits in somatosensation due to peripheral deafferentation [17] (Fig. 1). Meanwhile, reflexive adaptations lead to a decreased ability to activate the muscle, creating a greater demand on the central nervous system to generate sufficient muscular force to stress-shield the joint [11]. The net result of these constraints is a functional reorganization of the cortex, forcing secondary sensorimotor areas to increase their contributions to normal movement patterns [15]; altering proprioception, postural control, strength, and neuromuscular control; and potentially reducing the ability of the nervous system to prepare for and react to unanticipated events and joint loads [18–20]. More importantly, these deficits seem to exist across multiple models of ligament injury despite clear differences between an ACL rupture (total disruption) and lateral ankle sprain (varying grade of injury).

Research into central nervous system adaptations among these injured individuals has grown significantly over the past decade, with study of cortical activation patterns and nervous system excitability at the reflexive and cortical levels. However, this wealth of recent evidence requires synthesis to allow the clinician to understand the role of neuroplasticity following musculoskeletal injury. Therefore, the purpose of this review is to describe the theories, evidence, and interpretation behind neuroplasticity in the brain following ligamentous injury. The interpretation of these results will allow sports medicine practitioners to consider neuroplasticity in their intervention strategy to optimize patient function.

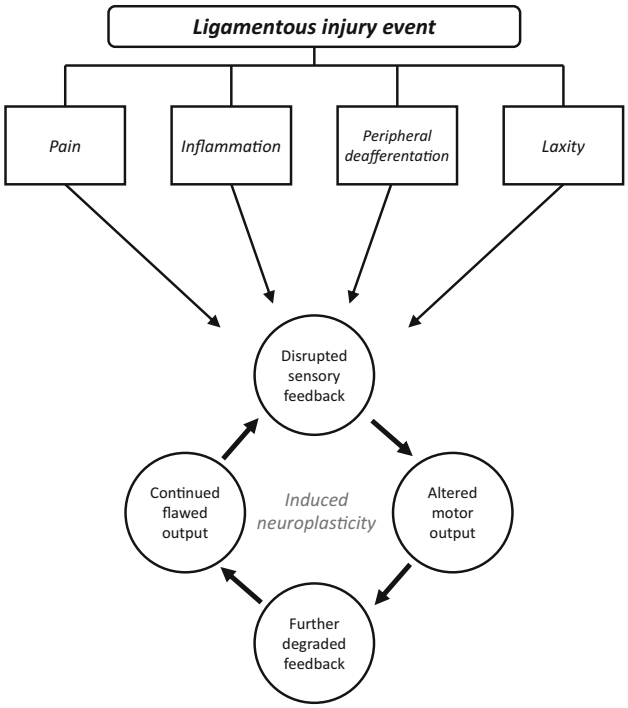

Fig. 1 Theorized paradigm of the role of ligamentous injury for inducing neuroplasticity, and its effects on sensorimotor function

2 Somatosensory Dysfunction

To understand neuroplasticity after ligament injury, it is vital to understand early theories of joint instability. These largely revolved around the concept of peripheral deafferentation—damage to the sensory receptors in the ligament and its subsequent effect on joint proprioception and the ability to reactively stabilize the joint [4]. While inconsistent evidence of proprioceptive sensory deficits exist among individuals with a history of ligamentous damage [21, 22], it has become clear that—even with the most precise proprioceptive acuity—an individual would not be able to generate a rapid enough reactive muscular response to prevent injury [23]. This suggests that preparatory (or feed-forward) muscle activation, rather than reactive (or feedback) control that would depend on precise sensory feedback, is necessary for preventing injury [23]. However, with evidence of proprioceptive deficits still emerging, perhaps changes to sensory receptors and the somatosensory cortex could affect risk of injury (and re-injury) by contributing to an altered *perception* of proprioception. This suggests that modifications in

somatosensation serve to alter an individual's perceived joint position and movement, placing the joints at angles in which they are vulnerable to injury (i.e. landing from a jump in more ankle inversion than originally intended) [24, 25].

2.1 Outcome Measures of Somatosensory Cortical Activation

The earliest evidence of cortical plasticity among individuals with joint injury focused on changes to the somatosensory cortex using electroencephalography (EEG) [26]. EEG offers excellent temporal but limited spatial resolution compared with other neuroimaging techniques. The primary applications of EEG after ligamentous injury are in understanding the timing and type of processing occurring during sensorimotor stimuli and functional tasks. This neurophysiologic technique uses surface electrodes to detect electrophysiological signals from the depolarization of excitatory and inhibitory action potentials in various areas of the cortex (Fig. 2) [27]. These continuous signals may then be evaluated relative to an 'event', such as the application of a stimulus, or analyzed continuously over a period of time, such as throughout an entire task (Table 1). To address the former, event-related potentials (ERPs) explore the magnitude and timing of cortical activity across all electrodes relative to a stimulus or movement initiation. In the case of somatosensory-evoked potentials (SEPs) a peripheral stimulus, such as electrical stimulation, is often implemented [28]. The measured cortical response via EEG represents a wave, with indicators of when the sensory potential reaches the spinal cord (N14 and N24 for peroneal and tibial nerves, respectively) as well as its arrival in the somatosensory cortex (P27 and P37 for peroneal and tibial nerves, respectively) [28, 29]. In the case of motor tasks, movement-related cortical potentials (MRPs) demonstrate not only the response to a movement but also the cortical events preceding that action [30–32]. Although this technique has been used in lower-extremity tasks that have a relation to ligamentous injury, such as postural control [30], these properties have only been documented among healthy individuals.

To investigate the role of the somatosensory cortex throughout a task, spectral power throughout EEG frequency bands has been investigated. While EEG recordings often appear to contain spontaneous and random oscillatory activity, the frequencies at which these oscillations emanate are indicative of various types of cortical processing [33, 34]. Commonly studied with regard to sensorimotor function are delta waves (0.5–4 Hz), associated with conscious awareness and cortical integration (combining multiple modalities of sensory information to determine motor response) [35]; theta waves (4–7 Hz), associated with memory tasks, including working memory (short-term memory required for determining action based on perceptions) [36]; and lower (8–10 Hz) and upper alpha (11–13 Hz) waves, associated with cortical deactivation and inhibition, as these often pertain to sensorimotor function [27, 37, 38]. As individuals initiate a task, excitation and suppression of processes in the cortex alter the strength of each frequency band across locations in the cortex. Therefore, rather than correlating separate measures of cortical activation and performance on joint proprioception tasks, the cortical activation throughout the proprioceptive task can be quantified [39]. However, recent studies have also aimed to establish how these cortical rhythms change throughout the execution of a task. Event-related desynchronization (ERD) and synchronization

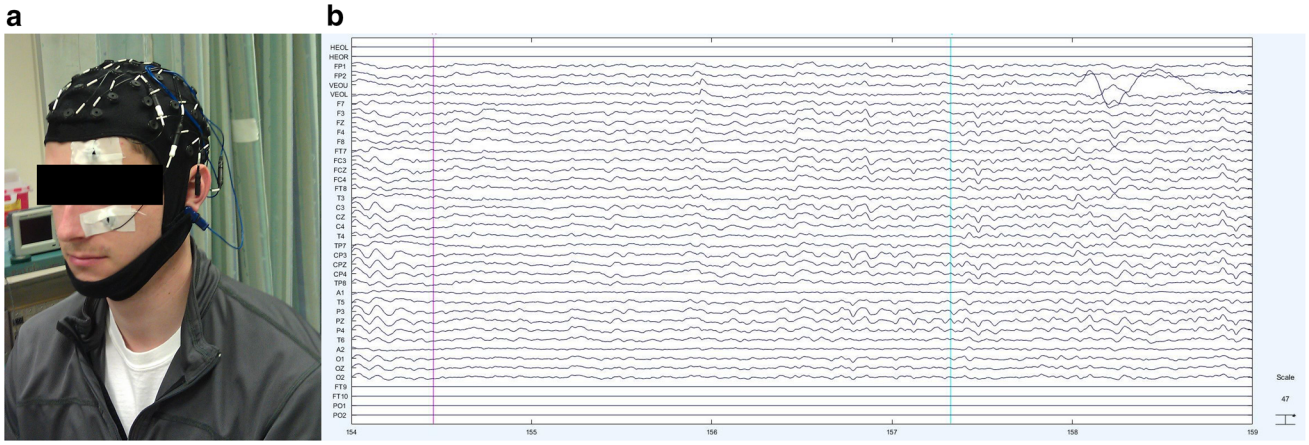

Fig. 2 Set-up and sample data using electroencephalography (EEG). **a** Placement of the EEG cap and electrodes on the head. Electrodes surrounding the eye are used to track blinking motions. **b** Sample of continuous EEG data. Each channel emanates a signal of varying frequencies and timing that is analyzed to determine changes related to events or tasks

Table 1 Interpretation of electroencephalography-derived measures investigated in joint stability research

EEG technique	Measurement	Neurophysiologic mechanism	Findings and interpretation
SEPs [14, 17–19]	Ensemble activation from a series of EEG electrodes are recorded in response to a stimulus (i.e., electrical pulse at knee or arthroscopically to ACL)	Stimulus ascends through spinal tracts to the somatosensory cortex, generating notable peaks/valleys of activity	P27 waves indicating arrival of sensory information to the somatosensory cortex were absent among ACL-deficient individuals, although whether these are restored after reconstruction is debated
Spectral analyses [23, 24]	EEG is measured continuously through a task (i.e., joint position reproduction, force matching). Fast-Fourier transforms are used to determine spectral power of specific frequencies at each electrode	Delta (0–4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–80 Hz) oscillations are associated with varying degrees of cortical activation and deactivation. For instance, alpha frequencies represent inhibitory thalamocortical activity, whereas delta frequencies indicate excitatory cortical activation	ACL-reconstructed individuals demonstrate increased alpha activity over the somatosensory cortex and altered theta activity in the frontal cortex during proprioceptive tasks. These indicate a greater working-memory demand during these functional tasks
ERD/ERS [28]	Continuous EEG recordings are measured relative to an event (i.e., applied joint load, initiation of movement, etc.). Time- and phase-locked changes allow investigators to determine frequency-specific changes relative to a stimulus	Combining the above techniques, specific frequency bands are assessed relative to a specific event. An increase (ERS) or decrease (ERD) in that band's power relative to a baseline period prior to the event determine event-related excitatory or inhibitory changes	Alpha activity desynchronizes during ankle loading, indicating increased somatosensory cortex activity; however, CAI patients only increased in the initial phase of loading, indicating potential deficits in discriminating differing amounts of load

ACL anterior cruciate ligament, *CAI* chronic ankle instability, *EEG* electroencephalography, *ERD* event-related desynchronization, *ERS* event-related synchronization, *SEPs* somatosensory evoked potentials

(ERS) combine the features of ERP and spectral analysis to understand changes in cortical frequency as they relate to an exogenous or endogenous stimulus. These techniques indicate how frequency-band activity changes from a period of baseline, whereby ERD indicates a decrease in that frequency and ERS represents an increase [40].

2.2 Evidence of Somatosensory Cortex Neuroplasticity

Valeriani et al. [26] first described an absence of P27 potentials among ACL-deficient subjects without N14 abnormalities, indicating a cortical change in somatosensation that correlated with clinical measures of errors in joint position sense. Following surgery, the same authors described that neither deficits in SEPs nor joint position sense were corrected [41]. These findings have since been refuted, although these authors utilized direct stimulation of a reconstructed ACL arthroscopically rather than stimulation of the nerve [42]. More recently, investigators have found that altered SEPs are specific to copers—those with a history of ACL tear but without functional deficits—but not those with instability, suggesting the absence of SEPs to be a potentially beneficial adaptation [43]. These studies provide strong evidence of cortical abnormalities following injury to the ACL, which suggests transmission of sensory information from the injured knee may fail to reach the somatosensory cortex, although the SEP technique is not without limitations. The most notable of these limitations is quantification of somatosensation through a discrete electrical stimulus rather than a functional sensory task or capsuloligamentous load, allowing for understanding of only the magnitude of the stimulus in the cortex.

Among individuals with reconstructed ACLs, a pair of studies identified alterations in spectral power during both joint position sense and force matching tasks [39, 44]. These studies reported two key findings: altered theta power in the frontal cortex and upper alpha power in the parietal cortex. These results are believed to imply changes in the anterior cingulate cortex that affect working memory, combined with an increased dependence on information from the somatosensory cortex to achieve the task following injury [44]. The authors suggest that, when combined, these changes represent alterations in the fronto-parietal cortex in the context of working memory processes, which are believed to be necessary to consistently compare perception with action. Interestingly, while both studies found alterations in the theta frequency, ACL-reconstructed knees were found to have decreased theta power during a joint position matching task but increased theta during a force matching task, indicating these deficits may be specific to the individual sensory modalities that make up proprioception [39, 44]. In other words, greater cortical resources may be required by individuals as they

attempt to gauge joint positions but not joint loads. However, limitations in this technique exist as analyses of cortical frequencies represent an overall measure of cortical activation during the task, but are not specific to a particular event, such as task initiation or termination.

A single study evaluated cortical activation in the unstable ankle using EEG. Needle et al. [8] evaluated the ERD of the upper alpha frequency in the electrodes overlying the area of the somatosensory cortex when subject's ankles were loaded using an instrumented arthrometer. In this scenario, ERD during ankle joint loading may have indicated the suppression of baseline thalamocortical pacemaker cells emanating at rest as the transmission of sensation from capsuloligamentous structures arrived in the area of the somatosensory cortex [45]. Between subsets of healthy and functionally unstable ankles, as well as individuals with a history of one sprain and no recurrent injury and instability (copers), it was found that whereas upper alpha ERD increased in all individuals as the joint was loaded, the unstable ankles only increased in the initial phase of loading, suggesting the cortex could not discriminate between higher levels of load on the ankle ligaments [8].

2.3 Summary and Implications

Investigations using EEG to assess cortical plasticity have yielded mostly consistent evidence indicating changes to somatosensation and proprioception associated with ligamentous injury of the knee and ankle. These deficits may persist beyond rehabilitation and reconstruction efforts. It has been hypothesized that alterations to the ascending pathways from that ligament secondary to pain or peripheral deafferentation may induce maladaptive neuroplasticity that contributes to a decreased perception of joint position, movement, and force. While it is unlikely that sensations of instability following ligament injury are secondary to feedback control, this decreased proprioception likely contributes to errors in coordination by placing the joint in a susceptible position for injury.

While additional analysis techniques using EEG exist, the techniques listed above represent those most commonly seen throughout sensorimotor tasks and with applications to musculoskeletal injury. Furthermore, therapeutic techniques incorporating brain–computer interfaces (BCIs) have demonstrated effectiveness in understanding and treating motor deficits following neural injury but have not yet been incorporated to enhance neuromuscular control in patients with musculoskeletal injuries [37]. As research advances, these techniques may have implications for the restoration of neuromuscular control following ligamentous injury.

To date, research in musculoskeletal pathology has primarily utilized EEG with sensory stimuli and proprioceptive tasks, demonstrating differences between individuals with ligamentous injury and control individuals. However, these changes are observed not only in the area of the somatosensory cortex but also involve motor and frontal regions of the brain. The involvement of motor cortical regions after injury may partially explain the inconsistencies in the relationship between injury and proprioceptive acuity. The disrupted sensory processing may not impair proprioception to a clinically significant degree, but may lead to alterations in preparatory and reactive motor abilities in these patients.

3 Motor System Excitability

Alterations in somatosensory function following musculoskeletal injury cannot explain the entirety of persistent deficits in motor function commonly experienced by these patients. Specifically, strong evidence exists regarding the presence of motor impairments following joint injury—clinically manifesting in the form of muscle weakness, activation deficits, and abnormal movement patterns—as these have been discovered in a variety of patient populations, including patients with ACL injury and reconstruction [46–49], those with ankle sprains and instability [50–52], those with long-term sequelae such as osteoarthritis [46, 53, 54], and in patients after joint arthroplasty [55–57]. Original theories suggested this motor dysfunction results from reflexive inhibition of the musculature surrounding an injured joint, termed AMI [11]. AMI is thought to occur from changes in afferent signaling from an injured joint secondary to mechanoreceptor damage, swelling, and pain that serve to inhibit descending motor neurons and influence motor dysfunction, regardless of whether or not these altered signals are sent to the brain for processing [11, 58, 59]. Although alterations in reflexive excitability have been observed following experimental effusion models of injury [58, 60–65] and immediately following acute joint injury [66, 67], recent work has found that alterations in excitability of descending cortical pathways, originating from the primary motor cortex, contribute to motor deficits and ultimately influence the persistent nature of this dysfunction [9, 68, 69]. As these data imply, neuroplasticity of the human motor cortex occurs potentially in response to somatosensory and mechanical deficits. Given these new revelations, our understanding of AMI appears to be shifting, guiding new research to understand the role of the motor cortex in persistent neuromuscular dysfunction.

3.1 Outcome Measures of Motor Cortex Excitability

To understand how the motor cortex adapts in response to musculoskeletal injury, transcranial magnetic stimulation (TMS) has been used as a tool to investigate the alterations of the primary motor cortex and the functional integrity and excitability of descending motor pathways to control muscle following joint injury. In particular, excitability of descending motor pathways refers to the ability of the motor cortex to activate and transmit descending motor impulses to the muscle of interest [70]. TMS serves as a technique in which an investigator can exogenously deliver a non-invasive, pain-free, and isolated magnetic stimulus to the motor cortex tissue, which in turn elicits a response in the corresponding muscle that receives descending input from the stimulated area [71]. Because the magnetic stimulation of motor cortex tissue elicits a descending action potential to the muscle, investigators can then evaluate these magnetically evoked motor potentials (MEPs) through the use of electromyographic (EMG) surface electrodes on the muscle of interest (Fig. 3) [70]. A variety of clinically significant outcomes regarding excitability of the descending motor system can then be assessed, including motor thresholds (MT), characteristics of MEPs, and measures of intracortical excitability (Table 2). Measures of intracortical excitability allow investigators to examine the underlying mechanisms of neuroplastic changes in cortical excitability through intracortical neurotransmitter receptors, specifically gamma-aminobutyric acid (GABA) and N-methyl-$_D$-aspartate (NMDA) [72, 73]. While evidence obtained from these methods is useful, it is important to note that it is indirect as it is derived from peripheral recordings via EMG placed on the muscle of interest [74].

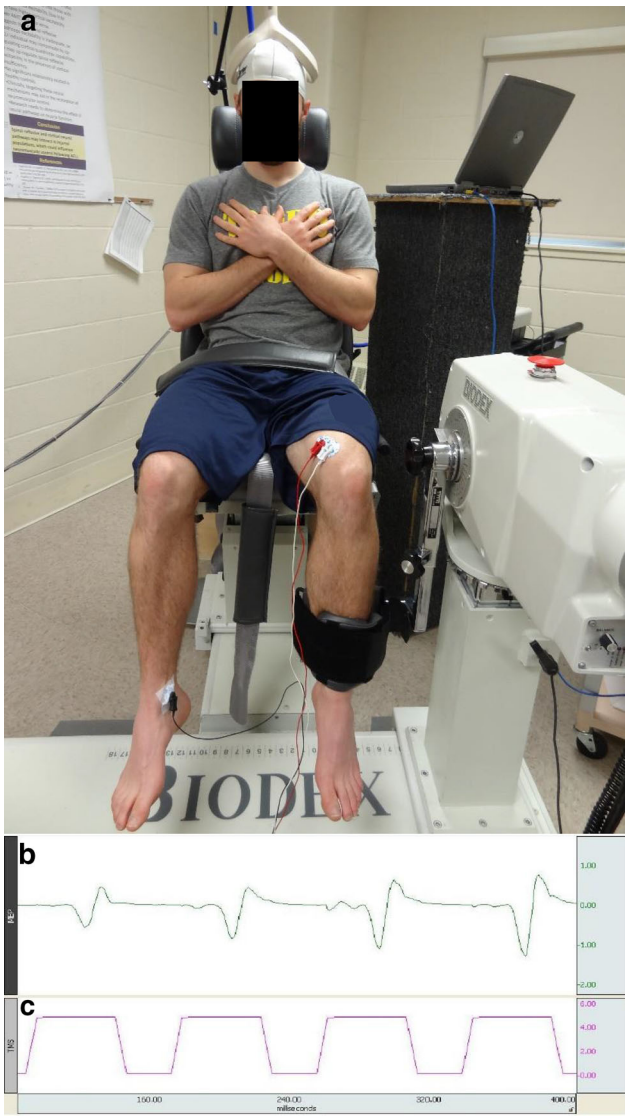

Fig. 3 Set-up and sample data from transcranial magnetic stimulation testing. **a** Positioning of electromagnetic coil over the area of the motor cortex responsible for muscle being tested. Electromyography (EMG) recording electrodes are placed on the muscle belly of interest (pictured on left vastus medialis). **b** Sample of motor-evoked potentials collected via EMG and **c** concurrent timing of magnetic stimuli

3.2 Evidence of Motor Cortex Neuroplasticity

Early work using TMS to evaluate motor cortex neuroplasticity in subsets of patients with musculoskeletal injury has shed new light on the origins of persistent motor dysfunction in such patients. For instance, the use of TMS has helped to clarify our understanding of AMI and the previous hypothesis that suggested alterations in reflexive excitability were responsible for motor deficits following joint injury. Although reflexive alterations have been observed following experimental effusion models and acute injury, reflexive deficits have not been observed in chronic states of injury. Patients who were 2 years removed from ACL injury and remained deficient [75], those who were 6 months [76] or 4 years [76] removed from ACL surgical reconstruction, and patients with chronic ankle instability (CAI) [77–79] all demonstrated minimal reflexive excitability alternations but significantly altered cortical excitability (Fig. 4). Studies utilizing TMS have also demonstrated that cortical changes are not present following experimental effusion models or acute joint injury [80–82]. Therefore, as a result of recent work utilizing TMS, it now thought that reflexive excitability is likely affected in the early stages of injury, whereas motor cortex excitability is altered (and contributes to persistent dysfunction) in chronic states of injury.

Evidence demonstrates that MT values are generally increased in patients with ACL reconstruction [67, 76, 83] and CAI [77, 78], indicating that a larger stimulus is needed to excite descending cortical neurons. Although these

Table 2 Outcome measures obtained through transcranial magnetic stimulation with clinical interpretation

TMS outcome	Neurophysiological mechanism measured	How it is measured	Clinical interpretation
Motor threshold	Cell membrane threshold of descending pyramidal neurons needed to transmit an action potential	Can be measured in active or resting state. Test MEPs are elicited at varying stimulator intensities until a consistent measurable MEP is obtained	Higher motor threshold is interpreted as lower motor cortex excitability, i.e., inability to adequately excite descending neurons. This would result in an inability to generate appropriate motor responses
MEP amplitude	Magnitude/amount of stimulus able to be transmitted through descending motor pathways	MEPs are investigated using EMG recordings. The peak-to-peak amplitude or area of the response at the muscle is evaluated	Lower MEP amplitude indicates less information is transmitted through motor pathways. Motor output would be decreased at the muscle
Central motor conduction time	Conduction time (delay) for the motor pathways to transmit motor information	Using MEP latency and a measure of peripheral latency (peripheral nerve stimulation), one can estimate the amount of time (ms) it takes motor pathways to transmit a motor signal	Longer central motor conduction time indicates a delay in motor system to transmit signal. This would result in motor dysfunction
Cortical mapping	Cortex area directly responsible for controlling muscle of interest	Multiple MEPs are elicited at various places on the brain and—using a grid drawn on a swim cap—one can determine the area of most direct fast-conducting cortical motor neuronal fibers to the target muscle	A change in cortical mapping from session to session (or pre- to post-test), indicates plasticity of the motor cortex area
Cortical silent period	Long-lasting intracortical inhibition mediated by $GABA_B$ receptors	Only measured in active state. A brief period of inhibition is induced by TMS, the time elapsing from the onset of MEP to resumption of EMG activity of the muscle is measured	Longer silent period indicates greater levels of inhibition mediated by $GABA_B$. This would result in inhibition of the muscle
Intracortical inhibition (SICI, LICI)	Intracortical inhibition mediated by $GABA_A$ or $GABA_B$ receptors	Requires paired-pulse TMS. A conditioning pulse is used to reduce the amplitude of synaptically evoked intracortical volleys. A subsequent test stimulus is given <5 ms later, creating an environment for inhibition, or a decrease in test MEP amplitude	Larger SICI and LICI measurements indicate greater levels of inhibition mediated by $GABA_A$ or $GABA_B$, respectively. This would result in inhibition of the muscle
Intracortical facilitation	Intracortical facilitation mediated by NMDA receptors	A conditioning pulse is used in the same manner as inhibition measures; however, time between stimulus is >5 ms. This creates an environment for facilitation, or increase in test MEP amplitude	Lower intracortical facilitation measurements indicate lower levels of intracortical facilitation mediated by NMDA. This would result in less facilitation of the muscle

EMG electromyography, *GABA* gamma-aminobutyric acid, *LICI* long interval intracortical inhibition, *MEP* motor evoked potential, *NMDA* N-methyl-$_D$-aspartate, *SICI* short interval intracortical inhibition, *TMS* transcranial magnetic stimulation

responses were generated via external stimulation, we can infer that a greater internal stimulus would also be needed, and the ability of the corticomotor system to excite the neurons would be diminished [9, 68, 70]. Clinically, this would result in an inability to generate appropriate motor responses to the needed muscle of a given task, and would manifest as muscle weakness, activation failure, and abnormal movement patterns in these patients [9, 68]. In addition to MT deficits, patients with ACL injury and CAI have also demonstrated smaller MEP amplitudes in the musculature surrounding the injured joint, particularly the vastus medialis and fibularis muscles, respectively [67, 77]. It appears that, following musculoskeletal injury, patients experience deficiencies in their ability to excite descending motor neurons from the motor cortex, and when an action potential is produced, less of that information is received at the muscle [9, 68, 69]. An important note is that these motor cortex alterations are observed in both injured and non-injured limbs following injury [67, 75, 77, 78]. These bilateral changes in motor cortex excitability suggest a *functional reorganization of motor networks* and a systemic effect on the motor system above and beyond somatosensory and mechanical deficiencies following unilateral joint injury.

Although data are limited, investigations have not observed differences in intracortical excitability, either inhibition or facilitation, in populations with musculoskeletal knee or ankle injuries. Specifically, Kittelson et al. [84] found no differences in short-interval intracortical inhibition (SICI) or intracortical facilitation (ICF) of the quadriceps muscles between older patients with knee osteoarthritis and healthy controls. Likewise, Heroux and

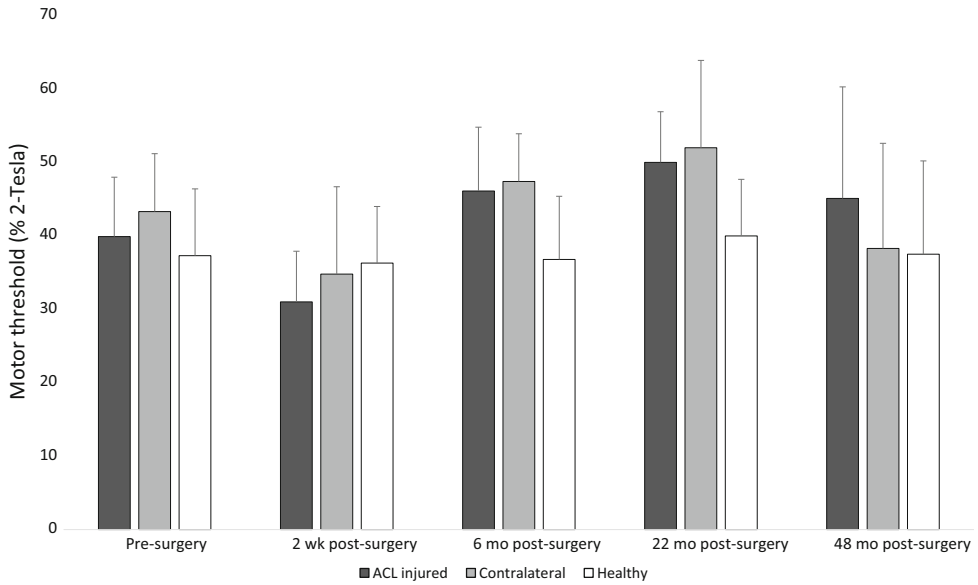

Fig. 4 Motor cortex excitability (quantified via motor threshold, mean ± standard deviation) of quadriceps muscles over time following anterior cruciate ligament (ACL) injury. No differences in motor threshold are observed in early stages of injury (pre-surgery and 2 wk post-surgery); however, increased motor thresholds are observed bilaterally at 6 month post-surgery and 22 mo post-surgery in those who remain ACL deficient, and increased in the injured limb in those 48 month post-surgery. The increased motor threshold indicates an inability to adequately excite descending neurons, resulting in an inability to generate appropriate motor responses and manifesting clinically as muscle weakness [64, 72, 73]

Tremblay [75] observed similar cortical silent period (CSP) values between participants with ACL injury and healthy matched controls, indicating there were no differences in intracortical excitability. SICI and ICF values in the quadriceps muscle also remained unchanged following experimental knee joint effusions [81] and simulated pain [85]. At the ankle, no differences in fibularis muscle CSPs were observed between patients with a history of ankle sprains (who also remained unstable), and those with no previous injury [86]; however, this investigation reported a significant negative correlation between anterior ankle joint displacement and fibularis longus CSP, indicating that higher intracortical inhibition is associated with greater ankle joint laxity. Clearly, more research is needed to understand the role of intracortical excitability on muscle dysfunction in patients with injured ligaments and the underlying influence of intracortical pathways on other measures of cortical excitability. Despite a lack of musculoskeletal research, methodological advancements in the measurement of intracortical excitability, such as the combination of TMS and EEG assessments, are allowing investigators to directly investigate mechanisms of intracortical excitability at the cortical level. This growing area of research will help to add new insights into plasticity of intracortical excitability pathways and its influence on motor function.

It should be noted that the current published data do include a few discrepancies regarding corticomotor changes following joint injury. Chronic ACL-deficient patients have demonstrated unilateral decreases, as opposed to bilateral, in MT of the injured limb quadriceps muscles compared with the uninjured limb [75]; however, these authors did not include a comparison with a healthy control group. Further, in patients 4 years removed from ACL reconstruction, a higher MT was only observed in the ACL-reconstructed limb, as the MT of the uninjured limb was equal to that in healthy controls. [76]. Importantly, alterations in motor cortex excitability relative to healthy controls are related to muscle strength and voluntary activation [76, 83]; with a greater degree of clinical relevance, post-injury differences in motor cortex excitability are occurring concomitantly with, and have been shown to influence clinical deficits in, muscle strength and activation [67, 75, 76, 83, 86, 87], movement patterns [47], and self-reported disability [87]. This information indicates that clinicians have the potential to optimize muscle function following musculoskeletal injury by using targeted interventions to influence excitability of descending motor pathways.

3.3 Summary and Implications

These emerging data indicate that neuroplasticity of the motor cortex develops as a chronic adaptation to joint injury, which has the potential to influence clinical outcomes in patients with musculoskeletal injury, such as

persistent muscle weakness and aberrant biomechanical adaptations. Similar to alterations in somatosensory function, if these neural contributions to motor impairments are not resolved, optimal recovery remains unlikely. These data have contributed to a shift in theory regarding the treatment of strength and activation deficits towards addressing the cortex rather than the muscle, although specific intervention techniques for modifying motor cortex excitability in these populations are unclear.

Some limitations exist in the application of how researchers assess neural impairments to motor function, notably the interpretation of TMS data and the tasks under which TMS is performed. Most research in these populations has performed TMS seated with or without some degree of controlled muscular preactivation; however, the excitability of the nervous system may change relative to the task [88, 89]. TMS methods make it difficult to assess motor excitability during more dynamic tasks such as walking or athletic maneuvers. Additionally, changes in TMS position isolate the portion of the brain being stimulated, typically the primary motor cortex, making it difficult to understand changes in intracortical and subcortical networks.

4 Neuroimaging and Plasticity of Neural Networks

Optimal sensorimotor control goes beyond activation of the sensory cortex and excitability of the motor cortex, as proper function of accessory areas and intracortical connections must also function appropriately. While EEG and TMS both have advantages that allow investigators to explore task-specific alterations in sensorimotor function with excellent temporal resolution, neither technique offers spatial resolution that allows for the differentiation of cortical and sub-cortical structure and function. Neuroimaging techniques such as diffusion imaging and functional magnetic resonance imaging (fMRI) offer superior spatial resolution capable of capturing the entire brain rather than targeting a small area [90, 91]. However, this comes with the disadvantage of performing less functional tasks, as these techniques require head movement to be minimized [90].

4.1 Functional Magnetic Resonance Imaging (fMRI)

Recent years have seen increased use of imaging technology in neuroscience, psychology, and—most recently—kinesiology through the use of non-invasive fMRI (Fig. 5). This technique is used to visualize hemodynamic changes occurring across the entire brain by quantifying the hemodynamic response function (HRF) from blood oxygen level-dependent (BOLD) reactions. The HRF is captured by the change in magnetization between oxygen-rich and oxygen-poor blood detected by the magnetic field freezing and aligning molecular protons in the brain [92]. This technique has been refined to pinpoint activation clusters within the brain to a spatial resolution of 1 mm and temporal resolution of approximately 1 s. Although this is slower than direct neuron recording, it allows patterns of brain activation to be assessed with relative safety and ease.

The ‘brain activation’ recorded through fMRI is based upon statistical parametric mapping and relative subtraction. In its simplest form, a level of resting state or baseline brain activity is recorded, followed by execution of a task [93]. The baseline activity is subtracted from the task activation so that only the brain regions active during the task remain [94]. Studies employing fMRI are routinely conducted, with positive results mapping the full brain response during motor control with high reliability (Table 3) [95, 96].

4.2 fMRI and Ligamentous Injury

The use of neuroimaging to evaluate the neurophysiological sequelae associated with musculoskeletal trauma has become a recent initiative. In a seminal work, Kapreli et al. [15] used fMRI during a knee extension task to assay the brain activation pattern for knee movement in those with ACL-deficiency versus healthy controls. The ACL-deficient cohort had increased activation of motor planning, visual processing, and sensory regions to generate knee extension compared with the control cohort [15]. These motor control changes are not rectified with reconstruction, as follow-up investigations have demonstrated that despite surgical reconstruction, rehabilitation, and return to activity, visual-motor, motor control, and sensory processing differences remain in ACL-reconstructed (ACLR) individuals [97–99], a finding consistent with those observed through EEG [41]. These specific brain activation differences in patients with ligamentous injury and instability observed using neuroimaging seem to indicate a fundamental change in how the brain generates motor drive, potentially due to disruptions in somatosensory input and cortical integration. This disruption in sensory feedback increases the visual–spatial contribution to program motion and maintain sufficient input into the motor cortex [100, 101]. If musculoskeletal trauma forces increased utilization of visual feedback to maintain motor control, this has clear implications for rehabilitation settings.

At the time of this review, no peer-reviewed publications have described alterations in CAI using fMRI. However, in unpublished thesis data during an ankle movement tracking task, functionally unstable ankles had

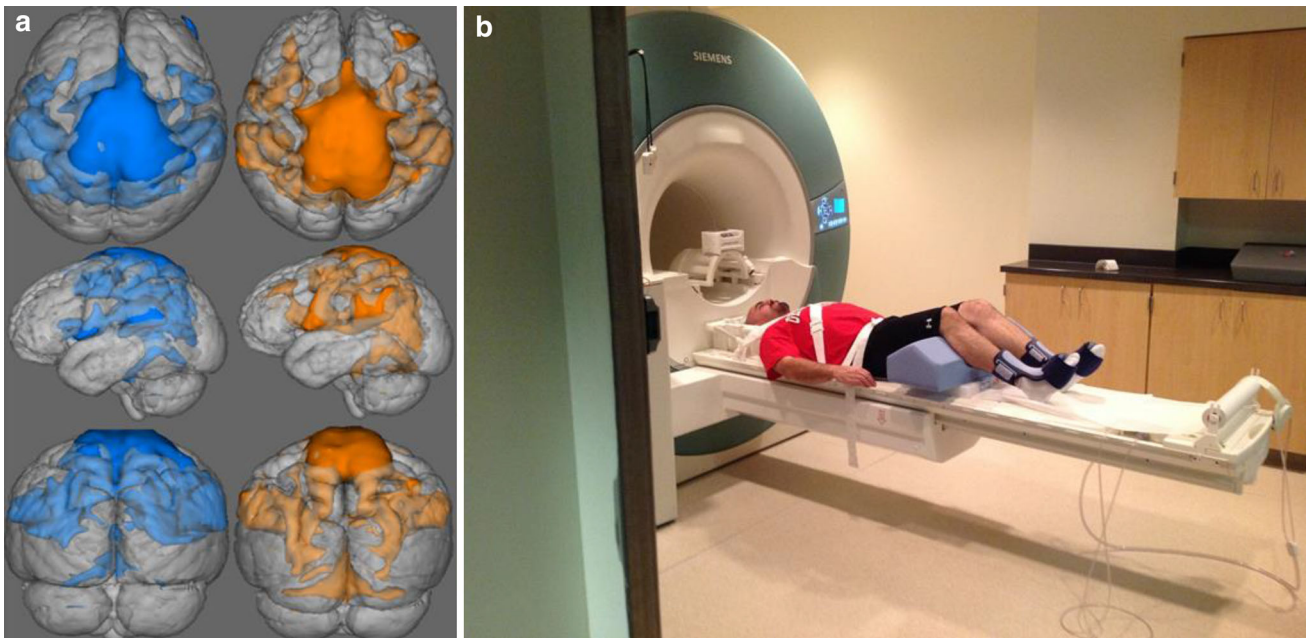

Fig. 5 Set-up and sample data from functional magnetic resonance imaging (fMRI) testing. **a** Brain activation pattern during knee movement in a single anterior cruciate ligament reconstructed individual (*orange*) and a matched control (*blue*). These images are not thresholded to show relative level of activity; only regions of the brain that demonstrated significantly greater activity during knee movement than baseline are presented. **b** Positioning of subject within fMRI machine, with stabilization provided to the torso as lower extremity movement is allowed

Table 3 Neuroimaging techniques with physiologic mechanisms measured and clinical interpretations

Imaging technique	Neurophysiological mechanism measured	How it is measured	Clinical interpretation
Positron emission tomography	Biological active molecules	Radioactive tracers	Depends on tracer molecule (may indicate metabolism, neurotransmitter, or pharmacological uptake)
Single-photon emission computed tomography	Biological active molecules	Gamma-emitting radioisotope	Depends on tracer radioisotope (may indicate metabolism, neurotransmitter or pharmacological uptake)
Resting state fMRI	Blood oxygen level dependent signal as a *correlate of* neural activation	Rapid changes in magnetic field, the signal is created by blood flow hemodynamics	Evaluation of resting state networks, including motor, visual, auditory, cognitive, and default
Task fMRI	Blood oxygen level dependent signal as a *correlate of* neural activation	Rapid changes in magnetic field, the signal is created by blood flow hemodynamics	Brain regions with increased activation are utilized more during the task; this may indicate reduced efficiency, increases in processing speed or volume, or altered connectivity
Diffusion tensor imaging	Water diffusion	Quantifies volume and direction of water diffusion along axon fiber tracts	Change in brain structural connectivity or white matter integrity
Structural imaging	Structural identification; gray and white matter volume	Segmentation and identification based on image tissue intensity distributions	Brain structural changes in volume of cell bodies (gray matter) or axons (white matter)

fMRI functional magnetic resonance imaging

greater lateralization in somatosensory cortices as well as increased activation in the contralateral somatosensory cortex, premotor cortex, and anterior cingulate gyrus compared with healthy controls [102]. These differences were observed without concurrent changes in ankle function during step-down tasks. Although this represents

limited evidence in the ankle sprain model, brain activation has served as a predictor of lower extremity function, motor control, and balance ability [103, 104].

Examining lower extremity function using fMRI has traditionally been a challenge because of artefacts from head motion that make large gross movement difficult. As motion correction algorithms improve with MRI technology to limit head motion, we anticipate the volume of this evidence will increase [105]. One technique that has been investigated that is able to circumvent these movement restrictions is motor imagery [106]. Between 10 and 60% of neurons that are activated to perform physical movement are also active during preparation to move, imagining movement, and viewing movement (hence the common label, mirror neurons) [107, 108]. This technique has been used to quantify neural mechanisms behind tasks such as walking [109], drop landing [98], and even sport skill [110]. A recent series of investigations in patients with shoulder instability used video observation of shoulder movements that tend to induce pain or apprehension [111, 112]. They found increased connectivity and activation in sensory-motor, cognitive, pain, and emotional processing regions relative to baseline and controls, indicating a more complex and distributed network related to shoulder control in those patients. However, the relevance and generalization of mirror neurons are debated [113], with validation occurring primarily with small hand movements and limited validity to multi-joint movements and environmental stimuli [114]. Nonetheless, brain motor-related regions activate when seeing or visualizing motion, with rehabilitation implications extending from the role of imagery to improving the manner in which feedback is provided to patients [115, 116].

4.3 Summary and Implications

Although fMRI is the least studied of the techniques described in this paper, its use has drastically increased our knowledge of neuroplasticity following ligamentous injury by highlighting discrete areas in the cortex that have undergone changes in injured subsets. Most importantly, these studies have highlighted changes in sensorimotor networks responsible for movement of the knee and ankle joints. Given models of joint instability previously described, these data support not only changes in somatosensation or muscle activation, but a modification to the number of cortical resources required to perform a motor task. As increased resources from accessory and premotor areas contribute to a task, the flexibility of the nervous system to handle unanticipated movement or loads could theoretically decrease, leading to subsequent injury or sensations of giving way.

Data using imaging technique are relatively new compared with EEG and TMS studies because of recording constraints and costs associated with testing. Consequently, there are many future directions for these techniques in the assessment and treatment of these injuries. One such technique would be structural imaging. As opposed to fMRI, which quantifies and identifies the location of activation, structural imaging quantifies anatomical changes in the gray and white matter as well as brain region connectivity [117]. This technique has been utilized through motor task training and is associated with increased synaptic size, neuron cell density, and other histological changes underlying training-dependent brain adaptations [91]. Variations of this technique, such as diffusion imaging and tractography, can additionally provide measures of interconnectivity in the cortex by detecting changes in water diffusion across the brain [118, 119]. These techniques have been applied to motor control, demonstrating increased directional diffusion (direction of connectivity) and mean diffusivity (level of connectivity) between the hypothalamus and hippocampus after only 2 h of spatial–motor training [120]. More long-term training-induced increased connectivity has been observed using these techniques in professional musicians with increased connectivity in the corticospinal tract relative to controls. [121]. It is highly probable that the sensory disruptions and subsequent motor compensations of musculoskeletal injury similarly create unique neuroplastic connectivity changes within hours of injury. Along similar lines, the altered motor patterns demonstrated even years after ACL injury and reconstruction may further induce brain structural connectivity changes that underlie the bilateral nature of motor dysfunction and subsequent joint loading that leads to early osteoarthritis progression.

5 Implications for Treatment of Injury

Evidence of cortical alterations following ligamentous injury is still very novel and rapidly growing. Only now are consistent patterns of deficits beginning to emerge; few studies have investigated how therapeutic treatments may alter cortical function throughout sensorimotor tasks. Notably absent from the literature are the effects of typical rehabilitation techniques (i.e., strength, balance, and perturbation training, etc.) on neurological function after ligamentous injury. However, some investigations into novel modalities that alter CNS function and quantification of the neural response in healthy participants may lend insight into theoretical effects in those with injury.

Efforts to improve sensorimotor function after ligamentous injury have utilized combinations of mechanical and electromagnetic modalities as well as rehabilitative exercise. Interventions such as joint mobilizations [122], massage [123], and stochastic resonance [124] have all

been proposed as modalities to improve sensory function via stimulation of capsuloligamentous, cutaneous, and musculotendinous receptors, respectively. These therapeutic techniques could likely alter cortical function, as both capsuloligamentous loading and massage have been observed to generate effects in the cortex [8, 125], although whether they can generate long-term plasticity in subsets of injured patients is unclear. Theoretically, these changes in somatosensation would serve to correct the perception of joint position, movement, and load, subsequently allowing an individual to appropriately position his/her joint to avoid injury. However, to date, no evidence has emerged to provide support for this theory.

Electromagnetic therapy techniques have frequently been employed among injured populations to achieve various goals that include decreasing pain and subsequent AMI through the gate control mechanism as well as stimulation of endogenous opioids. Strong evidence exists regarding the role of transcutaneous electrical nerve stimulation (TENS) to alter EEG cortical rhythms secondary to sensory-level and noxious stimulation [126–128]. Using TMS as an assessment tool, TENS has also been observed to disinhibit volitional quadriceps activation, which is of specific interest to ACL-deficient patients [129, 130]. Electrical stimulation can also induce contraction of impaired musculature in addition to modifying sensory function to improve neuromuscular function. Evidence has emerged regarding the use of neuromuscular electrical stimulation (NMES) in improving corticospinal excitability [131]. TMS itself has been used as a modality to this effect, where repeatedly stimulating neural tissue of the motor cortex has been shown to increase quadriceps muscle activation in patients with meniscectomy [132]. Although these interventions may serve to enhance sensorimotor function following injury by stimulating both afferent and efferent neurons in the periphery, simpler interventions such as EMG biofeedback may achieve similar results [133].

While the aforementioned modalities have demonstrated some abilities to modify discrete aspects of sensory and motor function at reflexive and cortical levels, the role of therapeutic exercise on neuroplasticity is clearly of interest to the practicing clinician. Although there is a dearth of investigations into the effects of rehabilitative exercise on nervous system plasticity and function, a robust body of literature supports neuroplasticity following simple exercise, balance and resistive training, and motor task training. These techniques have been documented to enhance neurogenesis, improve cognitive function, and modify nervous system excitability, thereby enhancing the behavioral capacity that forms the foundation of physical rehabilitation [134–137]. Although reviewing all documented effects of exercise on nervous system plasticity is beyond the scope of this review, a notable observation has been a decrease in cortical and reflexive excitability to the lower leg following balance training. While this may seem an undesired effect leading to diminished motor capacity, it has been proposed that decreased excitability in this context represents an increased role of subcortical structures in maintaining balance [135, 138]. The positive role of this adaptation is evident in the associated improvements in sensorimotor performance present with these neurological changes [135].

Although the use of neuroimaging is novel among patients with musculoskeletal trauma, findings to date have the potential to allow clinicians to target components of muscle inhibition, atrophy, movement dysfunction, and injury risk from a new perspective. The increased primary and planning motor regions and decreased subcortical and cerebellar activation after ACL injury support the use of new motor learning strategies to target specific neural correlates [139]. For instance, reliance on internal focus of attention and constant visual or auditory feedback may increase cortical activation and mitigate the ability to retain motor patterns [140], but utilizing an external focus of attention and reducing feedback to allow patient error correction may help transfer motor abilities and increase activation of more autonomic subcortical brain regions [141–143]. Additionally, addressing neurocognition is a vital component of addressing sensorimotor function, as the vast amount of neural computation involved in sensorimotor planning and integration has been minimally involved in instability research [144, 145].

6 Future Directions

Given the novel nature of research in this area, evidence continues to rapidly grow to identify deficits between subsets of injured and uninjured joints and techniques that may serve to modify neuroplasticity. An important missing component of investigations has been towards the understanding of acute ligamentous injury and its transition to chronic dysfunction. This review has described acute changes in the form of pain and swelling causing AMI, but how these short-term adaptations transition to chronic dysfunction, and what interventions may curb this transition remains unclear. Wikstrom and Brown [146] recently proposed that, at the ankle joint, a neurological cascade approximately 2–4 weeks from the time of injury may be responsible for positive or negative adaptation after injury. It may be in this window that AMI extends beyond the segmental level and causes cortical changes; however, no evidence has described this transition at the cortical levels. At the knee, pain and swelling appear to drive reflexive neural alterations in the early stages of

injury, specifically in the weeks following injury and up to 2 weeks following surgical intervention [67]. Cortical neural alterations begin to develop around 3–6 months following reconstruction, with reflexive neural alterations subsiding [67, 129, 147]. Future research should focus on this proposed timeline to help identify the neural mechanism underlying the transition of short-term adaptations to chronic dysfunction.

Emerging technologies may have further implications for the identification of central nervous system changes in a clinical setting as well as for potentially treating dysfunction. Functional near-infrared spectroscopy (fNIRS) is a method to assess local blood oxygenation (estimated activation level) of the superficial cortical structures via capturing light in the near-infrared electromagnetic spectrum. This is possible because oxygenated and deoxygenated hemoglobin have different optical properties in this range. fNIRS offers relatively high spatial resolution compared with EEG, but it is only useful for quantifying superficial aspects of the cortex. The greatest strength of fNIRS is that, aside from being highly affordable, it can be utilized during dynamic tasks (including gait and postural control) with minimal motion artefact [148–150]. Relative to other neuroscience tools, it is in its infancy as current investigations have focused on validation rather than identifying group differences [149, 151]. Preliminary results show great promise for measuring motor control, with potential utility to clinically assess both neural substrates and biomechanical outcomes of injury or movement assessment.

One additional technique that may have impact in the treatment of these alterations is transcranial direct current stimulation (TDCS). This technique is similar to TMS but does not use a magnetic field to stimulate cortical neurons, instead delivering a low-level constant electrical current to the brain through the skull and scalp. This serves to directly increase cortical excitability by raising the resting membrane potential, thus requiring less excitatory post-synaptic stimuli to achieve an action potential [152]. Although TDCS is still in the early stages of clinical research, with exact dosage and efficacy still under investigation, it has been found to be safe [153]. Clinical findings have included restorative effects on muscle strength and activation across short-term treatment paradigms and a variety of patient impairment levels and training techniques [153]. While this has not been investigated in subsets of patients with ligamentous injury, the ability to directly influence cortical excitability and subsequent motor neuron pool excitability and motor control is a promising avenue for restoring function in musculoskeletal conditions.

6.1 Integration of Imaging Modalities

The ability to quantify the immense volume of neural computations that allow the human nervous system to regulate sensorimotor control, and the implications of injury on this processing stream, will present a challenge to researchers for years to come. The use of EEG, TMS, fMRI, and other tools simply provide researchers a small glance into discrete processes related to the complex performances achieved by the central nervous system. The unique attributes of each tool make integration and synthesis of the varied literature difficult, as they each measure a different aspect of nervous system function with ambiguous relationships across techniques. However, by examining this body of literature as a whole, it allows us to identify patterns of change occurring after injury.

Unfortunately, literature using a comprehensive neurophysiological assessment of patients following musculoskeletal injury does not exist. However, a few investigations have compared cortical excitability and cortical activation during similar tasks in neurologically impaired populations (i.e., stroke, spinal cord injury) and have identified a relationship between increased activation in the area of the motor cortex and greater cortical excitability [154, 155]. Separate investigations have identified that patients with ACLR demonstrate decreased quadriceps motor cortex excitability [67, 76] and increased motor cortex activation for quadriceps contractions [99], which is in agreement with this relationship. If this relationship applies in populations with musculoskeletal injury, it is possible that patients with higher cortical activation are simply compensating for depressed cortical excitability [67] and have successfully adapted cerebral processing to improve neuromuscular function. Similar complementary findings are present for ACLR in regards to individual EEG and fMRI paradigms. EEG studies following ACLR have exclusively utilized position or force matching tasks, whereas the published works with fMRI utilized simple knee movement; however, both paradigms found adapted sensory region processing [39, 44, 99]. A direct comparison between fMRI, EEG, and TMS work is difficult, as they measure different aspects of the nervous system across fundamentally different tasks (i.e., active knee extension during fMRI, isometric knee extension during TMS, proprioception during EEG). More comprehensive assessments are needed to better understand the relationships between cortical excitability and activation utilizing fMRI and TMS along with behavioral assessment of neuromuscular control in the same subjects.

7 Conclusions

With consistent technological advances in neuroimaging, and its increased availability in clinical and research settings, our understanding of neuroplasticity following musculoskeletal and specifically ligamentous injury has vastly expanded. We now understand that damage to the ACL, lateral ankle ligaments, and even glenohumeral ligaments go beyond the mechanical alterations and peripheral sensory deficits and have dramatic effects on the somatosensory and motor cortices that may contribute to persistent aberrant biomechanical patterns predisposing these individuals to further bouts of instability and re-injury.

As consistent patterns of neuroplasticity after ligament injury emerge, research must begin to shift in two directions. First, because devices such as EEG, TMS, and fMRI— or the personnel necessary to operate them and interpret findings—are not available in the majority of sports medicine clinics, clinical measurements must be identified that may be representative of these measures and may allow clinicians to identify somatosensory and motor excitability changes in their patients. Second, with deficits identified, further research is required to identify what modalities and therapeutic techniques would be most effective in correcting this neuroplasticity and restoring normal movement patterns and optimal clinical function.

Compliance with Ethical Standards

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