Original Article

# Quadriceps Weakness is Associated with Neuroplastic Changes Within Specific Corticospinal Pathways and Brain Areas After Anterior Cruciate Ligament Reconstruction: Theoretical Utility of Motor Imagery-Based Brain-Computer Interface Technology for Rehabilitation

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**Abstract:** Persistent quadriceps weakness is a problematic sequela of anterior cruciate ligament reconstruction (ACLR). The purposes of this review are to summarize neuroplastic changes after ACL reconstruction; provide an overview of a promising interventions, motor imagery (MI), and its utility in muscle activation; and propose a framework using a brain-computer interface (BCI) to augment quadriceps activation. A literature review of neuroplastic changes, MI training, and BCI-MI technology in postoperative neuromuscular rehabilitation was conducted in PubMed, Embase, and Scopus. Combinations of the following search terms were used to identify articles: "quadriceps muscle," "neurofeedback," "biofeedback," "muscle activation," "motor learning," "anterior cruciate ligament," and "cortical plasticity." We found that ACLR disrupts sensory input from the quadriceps, which results in reduced sensitivity to electrochemical neuronal signals, an increase in central inhibition of neurons regulating quadriceps control and dampening of reflexive motor activity. MI training consists of visualizing an action, without physically engaging in muscle activity. Imagined motor output during MI training increases the sensitivity and conductivity of corticospinal tracts emerging from the primary motor cortex, which helps "exercise" the connections between the brain and target muscle tissues. Motor rehabilitation studies using BCI-MI technology have demonstrated increased excitability of the motor cortex, corticospinal tract, spinal motor neurons, and disinhibition of inhibitory interneurons. This technology has been validated and successfully applied in the recovery of atrophied neuromuscular pathways in stroke patients but has yet to be investigated in peripheral neuromuscular insults, such as ACL injury and reconstruction. Well-designed clinical studies may assess the impact of BCI on clinical outcomes and recovery time. Quadriceps weakness is associated with neuroplastic changes within specific corticospinal pathways and brain areas. BCI-MI shows strong potential for facilitating recovery of atrophied neuromuscular pathways after ACLR and may offer an innovative, multidisciplinary approach to orthopaedic care. **Level of Evidence:** V, expert opinion.

Anterior cruciate ligament (ACL) rupture is one of the most common knee injuries, with 100,000 to 200,000 ruptures per year in the United States.[1] Arthroscopic ACL reconstruction (ACLR) confers excellent surgical outcomes; however, traumatic disruption of the native joint continues to adversely

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*The authors report the following potential conflicts of interest or sources of funding: K.S. is CEO of iBrainTech. B.F. is on the Scientific Advisory Board of i-BrainTech. Full ICMJE author disclosure forms are available for this article online, as supplementary material.*

*Received March 27, 2022; accepted November 9, 2022.*

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*2666-061X/22416*

*https://doi.org/10.1016/j.asmr.2022.11.015*

affect postoperative rehabilitation.[2] Specifically, persistent quadriceps weakness is a frequently reported barrier impeding recovery, with strength deficits and atrophy persisting for years after surgery.[3-5] The ACL is not only a mechanical stabilizer but also provides critical afferent input. Animal studies have suggested that loading the ACL produces feedback from mechanoreceptors in the joint to gamma motor neurons, which then recruit the appropriate pool of motor units needed for muscle contraction.[6] An ACL injury, which by nature disrupts this intrinsic mechanoreceptor feedback, results in decreased motor unit recruitment of the quadriceps and a subsequent decline in strength.[7,8] Additionally, patients with ACL injury also demonstrate poorer proprioception, a critical factor in attaining satisfactory functional outcomes and subjective feeling of stability in the reconstructed knee.[9]

Collectively, the neural inhibition leading to diminished voluntary quadriceps activation is termed arthrogenic muscle inhibition (AMI). Mechanisms underlying this inhibition include alteration in resting motor thresholds, diminished articular afferent outflow, altered spinal-reflexive pathway excitability, and abnormal cortical activity.[10-12] It serves as the body's protective and reflexive response to "shut down" the surrounding musculature with the goal of preventing further knee joint damage. Because AMI involves central nervous system feedback, quadriceps activation failure after ACLR is not an isolated phenomenon, with evidence in the literature describing its presence in both the reconstructed and contralateral limbs.[13,14] The resulting muscle weakness causes a wide range of consequences including extension deficit, gait abnormalities, quadriceps atrophy, dynamic instability, persistent knee pain, and early osteoarthritis.[15-21]

Given the extensive consequences of persistent quadriceps weakness after ACL injury and reconstruction, it is imperative to understand existing therapies, as well as develop and implement modalities to treat the source of muscle weakness. Traditional rehabilitation has focused on regaining motion, strengthening, and balance/proprioception through physical training exercise.

Despite the importance of muscular conditioning, there is a growing amount of evidence in the literature suggesting substantial benefits from incorporating interventions targeting the neurophysiological changes that underlie quadriceps activation failure after knee injury.[22-27] In lieu of our constantly evolving understanding regarding the topic, the purposes of this review are to summarize neuroplastic changes after ACL reconstruction; provide an overview of a promising intervention, motor imagery (MI), and its utility in muscle activation; and propose a framework using a brain-computer interface (BCI) to augment quadriceps activation. We hypothesize that ACL injury will lead to diminished activity in motor cortical pathways and that brain-computer technology rooted in MI techniques can be used to recover these neural connections.

## Methods

The authors searched PubMed, Embase, and Scopus using a combination of the following key words: "quadriceps muscle," "quadricep," "muscle strength," "muscle inhibition," "muscle activation," "biofeedback," "neurofeedback," "neurological rehabilitation," "neuromuscular," "neurobiofeedback," "motor learning," "neural learning," "cortical plasticity," "motor imagery," "visuomotor," "neuromodulation," "motor preparation," "anterior cruciate ligament," "anterior cruciate ligament reconstruction," and "ACL." All searches were performed in September 2021. Based on our literature review, we present a discussion of the neuromuscular changes occurring after ACL injury, effect of motor imagery training on muscular activation, and the theoretical utility of a brain-computer interface technology in recovering atrophied neural pathways.

## Discussion

### Neuroplastic Changes After ACL Injury and Reconstruction

#### Corticospinal Pathway Changes

Neuroplastic adaptations contributing to persistent quadriceps strength and activation deficits involve the corticospinal (motor signals from brain to muscles), intracortical (brain-to-brain signals that refine motor responses), and spinal-reflex (reflex movements relayed through the spinal cord) pathways. Transcranial magnetic stimulation (TMS) studies, which use a magnet to induce an electric current at a specific area of the brain, can assess changes in excitability of the corticospinal tract (CST) in response to a motor cortex stimulus after both ACL injury and reconstruction.[28-33] Most of these studies measure a certain muscle group's active motor thresholds (AMT), or level of electrochemical activity that initiates an action potential to signal muscle contraction. A higher AMT correlates with diminished neural excitability, while a lower AMT suggests a muscle more primed for contraction.

In the only longitudinal study exploring TMS-stimulated corticospinal excitability during multiple time-points, Lepley and colleagues[30] demonstrated higher AMT of the vastus medialis at 6 months after ACL reconstruction relative to uninjured controls. Additionally, case-control studies have shown that, after ACL reconstruction, patients demonstrate both asymmetric and higher AMTs up to 48 months after surgery compared to controls.[28,31] Furthermore, a recent systematic review and meta-analysis by Rodriguez et al.[34] showed that the AMT is significantly higher in both reconstructed and nonreconstructed

limbs after an ACL injury and that these changes were associated with subsequent bilateral reductions in quadriceps strength and voluntary activation compared to healthy controls. The implication of this relationship is broad, with research using AMT as a prognostic marker to help determine which patients are likely to return to satisfactory knee function after ACLR.[35]

### Intracortical Pathway Changes

Human motor physiology studies have implicated intracortical pathways, consisting of interneurons that relay signals between motor and sensory-type neurons, in modulating the AMT as well.[36] Paired-pulse TMS uses a conditioning and test stimulus of differing intensities administered at specific predetermined intervals to evaluate the $GABA_A$ and glutaminergic systems in the motor cortex. By using paired-pulse TMS as used by Chen,[36] researchers have studied intracortical inhibitory and facilitatory activity. Prior studies investigating ACL injury, knee osteoarthritis, and experimental models of knee injury have found no changes in intracortical inhibition between injured patients and noninjured controls.[32,37-39] None of these studies examined intracortical inhibition beyond the acute setting (<2 weeks); therefore it is likely that alterations in another pathway (i.e., spinal reflexive) may be influencing quadriceps voluntary activation during this time period. Since then, Luc-Harkey and colleagues[40] probed the relationship between short interstimulus intracortical inhibition (SICI), intracortical facilitation (ICF), and quadriceps voluntary activation after at least 6 months following ACLR. They discovered that ACLR patients had greater SICI activity acting on neurons of the primary motor cortex that signal activation of the lower quadriceps. Luc-Harkey et al.[40] proposed that the increase in SICI in ACLR patients can be explained by the loss of sensory connections to the spinal cord and cerebrum after removal of the torn ligament and ligation of small sensory nerves of the joint capsule during surgical reconstruction. Although surgery may restore mechanical stability, it does not restore sensorimotor function, as evidenced by proprioceptive deficits persisting for months after operation.[40,41] These chronic sensorimotor alterations may result in reorganization of various cortical areas, including those involved in initiating and inhibiting voluntary contraction.

### Spinal-Reflexive Pathway Changes

After an acute insult, spinal-reflexive pathways are activated and represent an unconscious mechanism of preventing further harm. After this insult, however, it appears that spinal-reflexive pathway activity is reduced. Biomechanical knee joint effusion models in humans, which simulate acute injury, have illustrated diminished spinal-reflexive excitability.[42-45] In a 6-month longitudinal study of patients with ACLR, Lepley et al.[30] expanded on these findings by demonstrating similar early deficits in the spinal-reflexive pathway in the first 2 weeks after surgery. After 2 weeks, reductions in spinal-reflexive excitability also appeared in the contralateral nonreconstructed limb; however, by 6 months these neural changes normalized, and no differences were found when compared to healthy, matched controls.[30] In other words, spinal-reflexive excitability is diminished in the acute setting, with neural adaptations eventually normalizing. Prior literature has shown that a combination of pain and effusion may alter afferent signaling from the joint and is associated with decreased quadriceps spinal-reflexive excitability, strength, and voluntary activation.[42-44,46-48] Considering that patients in the study by Lepley et al.[30] suffered an acute injury and subsequently experienced the physiological joint trauma inherent to reconstructive surgery, it is likely that a systemic and bilateral neuromuscular response occurred (i.e., reduced spinal-reflexive excitability) acutely to prevent further joint damage, which then normalizes as inflammatory changes resolve.[5,49,50]

### Central Control: Functional MRI

The neuromuscular adaptations that occur following ACLR has spurred investigations utilizing functional magnetic resonance imaging (fMRI) technology to probe specific brain activation pattern differences between ACLR patients and healthy controls. By using a knee flexion-extension task, Grooms et al.[51] showed increased contralateral primary motor cortex activity in ACLR patients compared to matched controls, corroborating previous research indicating reduced CST excitability in this cohort.[30,31] Because of disrupted sensory input and the development of compensatory motor behaviors after ACL injury and reconstruction, the motor cortex must produce stronger and more complex demands for even simple motor output.[51-54] Additionally, the ipsilateral secondary somatosensory cortex is activated to a greater degree in ACLR participants.[51,54] The secondary somatosensory cortex performs sensorimotor integration from both halves of the body. Because a reconstructed ACL does not have the capability to send the same sensory signals to the primary sensory cortex as the native ligament, sensory processing for movement reconfigures in a way that requires the activation of higher-order integrative areas.[51,55] The lingual gyrus, a brain region located near vision centers in the occipital lobe, exhibits increased ipsilateral activity after ACLR.[51] This is congruent with recent fMRI data suggesting the existence of neuronal feedback mechanisms between the higher-order visual cortex and the sensorimotor cortex, thus allowing visual cues to affect motor output.[56,57] Therefore it is likely that the increased lingual gyrus activation in

ACLR patients represents a sensory feedback adaptation after the loss of joint mechanoreceptors, in which patients compensate for reduced proprioception and sensory signals from the injured knee by relying more often on visual cues.[55,57-60]

Overall, studies demonstrate that an ACLR restores mechanical stability of the joint but disrupts sensory pathways that help control knee movement. This lack of sensory information leads to a reduction in quadriceps' sensitivity to electrochemical neuronal signals, increase in central inhibition of neurons regulating regions of the motor cortex responsible for quadriceps activation, and dampening of reflexive motor activity in the knee. Traditional rehabilitation may assist with recovery of neuromuscular signals over time but relies on actual activation of atrophied muscle groups. Considering the pain and fatigue involved in knee movement in the early postoperative period, this approach may harbor delays in recovery of neuromuscular signals. Therefore there is a need for technologies that preserve neuronal activation of the knee movement pathways lost during acute injury without requiring actual movement of the injured joint.

## Motor Imagery

MI is the mental reproduction of an action in the absence of overt motor output. Simplistically, MI practice helps make conscious actions habitual by "training your brain" to automatize certain neuronal connections. A more detailed explanation involves neuroplastic changes in both the central and peripheral nervous system, as summarized in Fig 1. During the first weeks of learning, the cortical map representing the trained muscles and corticospinal pathway excitability increase as learning takes place; this short-term change then eventually reverses as the motor behavior becomes automatized and excitability overall decreases.[61] The cortico-cerebellum and cortico-striatal networks are activated during learning, with the former "fine-tuning" movement during the training period and the latter assisting in motor pattern recollection during automization.[61-63] At both the cortical and spinal levels, neuromodulatory changes occur, such as upregulation of certain neurotransmitters or receptors, to potentiate long-term changes in neuronal pathway connections and amplitude.[64-66]

The "imagined" motor output generated during MI increases the sensitivity and conductivity of the corticospinal tracts emerging from the primary motor cortex,[67] which helps "exercise" the connections between the brain and target muscle tissues. At the spinal level, MI training is thought to decrease presynaptic inhibition on alpha-motor neurons by increasing the activity of the descending CST.[61] Modulation of the CST results in enhanced excitatory input to alpha-motor neurons while simultaneously decreasing the activity of inhibitory interneurons in the local spinal circuitry.[68,69] These neural adaptations optimize cortical and spinal motor pathways, allowing for greater voluntary muscle contraction.

**Figure 1.** Illustration of a professional athlete in a BCI-MI session targeted at improving fundamental soccer skills.

In the first study examining the use of MI in ACL rehabilitation, Cupal and Brewer[70] conducted a randomized controlled trial of 30 participants examining the utility of relaxation and guided motor imagery sessions on knee strength, reinjury anxiety, and pain. They demonstrated greater knee strength with reduced reinjury anxiety and pain. A major limitation of their study was that measurements were taken at 24 weeks after operation, providing little evidence supporting the use of MI training during the early rehabilitation period. In a randomized controlled trial of 12 patients with ACLR, Lebon and colleagues[71] showed that motor imagery training elicited greater muscle activation with no significant changes in pain levels during the early postoperative period. Notably, Lebon et al.[71] attempted to mitigate the effect of pain on muscle activation by providing a strong analgesic treatment administered during the first week after surgery, which may have confounded this endpoint. Nonetheless, participants in the MI group demonstrated a trend toward a larger increase in electromyography (EMG) activity compared to the control group.[71]

The association between increased EMG activity and strength gains after MI training is likely dependent on motor neuron, interneuron, and reflex pathways changes.[61,72,73] Prior fMRI and positron emission tomography studies have demonstrated that MI training activates motor cortex areas[74,75] and facilitates the excitability of neural pathways,[76] which likely drives the muscles to higher activation and therefore higher EMG output. Four additional randomized controlled trials[77-80] investigating motor imagery in the ACLR population have reported improvements in International Knee Documentation Committee scores,[77,80] pain,[79] knee laxity,[78] and lower levels of urine

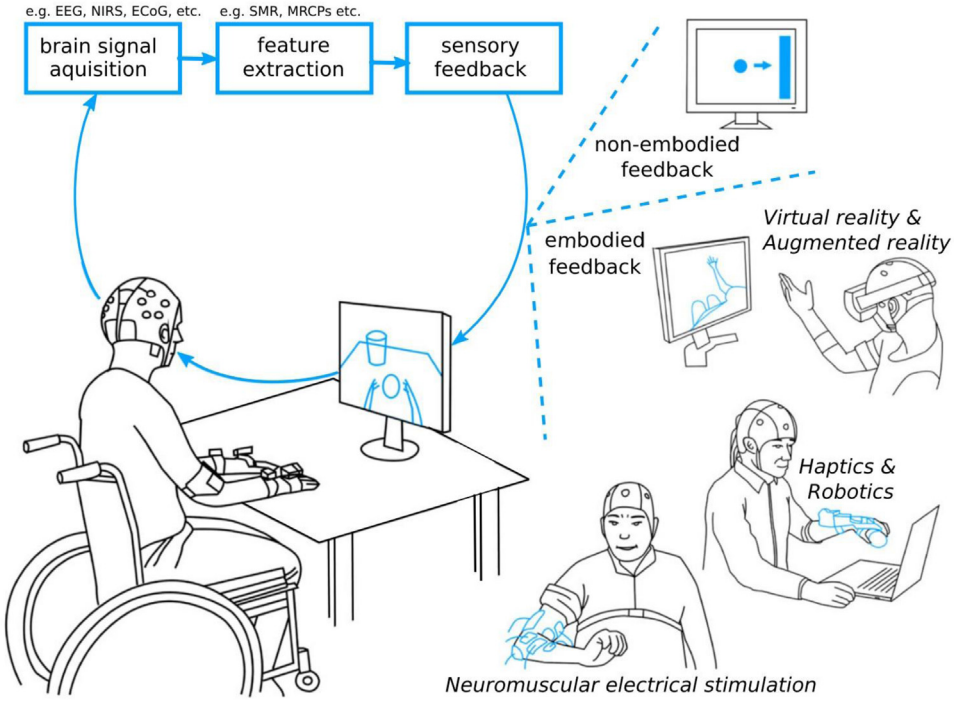


**Figure 2.** Illustration of a typical brain-computer interface (BCI) system used in post-stroke motor rehabilitation highlighting various compatible sensory feedback modalities. EEG, electroencephalography; NIRS, near-infrared spectroscopy; ECoG, electrocorticography; SMR, sensorimotor rhythm; MRCP, motor-related cortical potential. Image adapted from Cervera et al.[83]

noradrenaline and dopamine.[78] However, these trials are limited by inconsistent methodologies, short-term follow-up, and small sample sizes; in a recent systematic review, Pastora-Bernal et al.[81] recommended a need for greater homogeneity between studies to draw evidence-based conclusions regarding the impact of MI in ACLR. Only 2 RCTs included in the review [77,80] were adequately powered (N = 101 and N = 58, respectively), with the remaining drawing conclusions from samples of 13, 10, 7, and 5 patients.[81] Furthermore, 3 of the 4 randomized controlled trials did not have a follow-up period past 2 months, with only 1 study[78] reporting data up to 6 months after operation.[81] Given these limitations, there is a need for more adequately powered long-term investigations to confidently delineate an evidence-based protocol using MI training in the ACLR population.

## BCI

A BCI is a technology that translates electric, magnetic, or metabolic brain activity into control signals capable of operating external devices or a computer.[82] Rehabilitative technologies involving BCI—referred to as neurofeedback BCI—use electroencephalography electrodes placed on the scalp (Fig 1). The subsequent electrical activity is decoded in real-time to drive a simulated or actual motor response (Fig 2). A prototypical trial involves the user engaging in motor imagery, which triggers electrical activity in the motor cortex that is picked up by the electrodes. Subsequently, this intention to move can then be delivered in an embodied form (e.g., visual representations of the user's body part over a virtual avatar on a computer screen or activation of a neuromuscular electrical stimulation device) to enhance motor learning.[83-85] Investigations of BCI have demonstrated associations with increased excitability of the motor cortex,[86,87] corticospinal tract,[88] spinal motor neurons,[89] and disinhibition of GABAergic inhibitory interneurons.[90] Importantly, these neuroplastic changes complement the motor imagery neural adaptation model proposed by Ruffino et al.[61] (Fig 3), suggesting that a BCI may work via MI-facilitated neuroplastic changes.

BCI technology incorporating MI has shown promise for motor rehabilitation. Most studies in the literature examining the implementation of BCI technology focus on motor and brain function recovery in post-stroke patients.[91-95] A recent systematic review and meta-analysis by Kruse et al.[96] showed a significant benefit of BCI on both motor and brain function recovery after stroke. The pooled analysis, involving 11 studies, displayed a statistically significant improvement on physical performance of the affected upper extremity that correlated with improved motor symmetry with the unaffected side; there was an increased laterality index (i.e., hemispheric dominance) and diminished brain symmetry index (i.e., assessment of ischemic brain tissue damage).[96]

Fewer studies have assessed motor function recovery of the lower extremity after BCI and MI training.[97-99] The investigations by Chung et al.[97,99] combined BCI and MI with functional electrical stimulation, a method

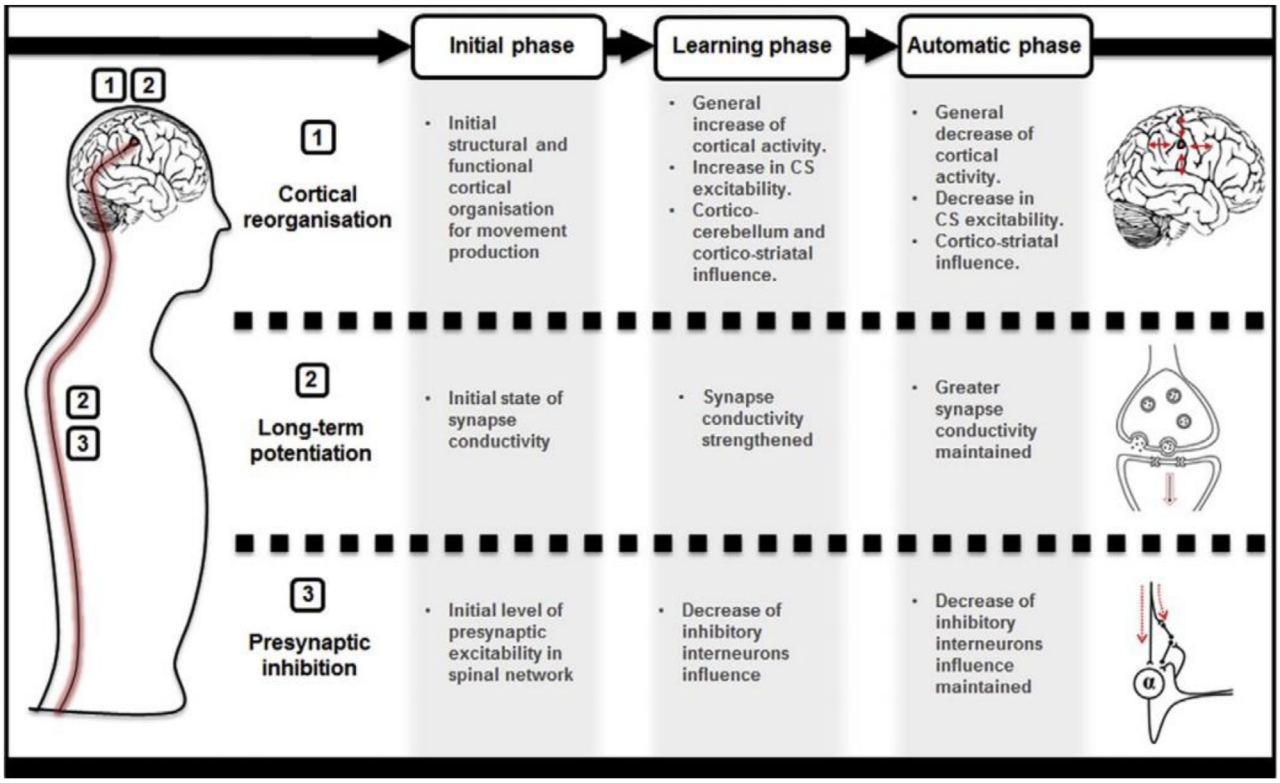


**Figure 3.** Neural adaptation model of motor imagery. There are three phases related to learning: the initial, learning, and automatic phases. These phases occur in relation to three neurophysiological processes (cortical reorganization, long-term potentiation, and presynaptic inhibition). The first picture shows increases and decreases in cortical map modulation within the primary motor cortex. The second picture depicts greater synapse sensitivity through the conduction of neurotransmitters. The third picture demonstrates diminished presynaptic inhibition at the alpha-motor neuron level. The dotted red line illustrates the subliminal motor output generated during motor imagery and its impact on presynaptic interneurons. Adapted from Ruffino et al.[61]

of inducing muscle contraction in non-innervated muscles, and showed significant improvements in both balance and gait. The second study examining the ability of BCI to improve functionality of the lower limb used a different methodology involving Hebbian principles of associativity.[98] Hebbian theory states that synaptic strength increases when repeated firing of presynaptic neurons leads to persistent stimulation of the postsynaptic neuron.[100] Within Stefan et al.'s[101] experiment, a patient would engage in intentional, physiologically generated brain activation (i.e., presynaptic activation), which was timed so it simultaneously occurred with an artificially-induced peripheral sensory stimulus (i.e., postsynaptic activation).[100] Stefan and his contemporaries[101] showed that these paired stimuli (brain activation from the patient, sensory stimulus from a machine) induce a significant change in the excitability of cortical projections to target muscle tissue. Mrachacz-Kersting et al.[98] applied these principles to the lower extremity and demonstrated increases in the motor-evoked potentials, or frequency of muscle activation, of the tibialis anterior muscle after only 3 sessions of BCI use. Mrachacz-Kersting et al.[98] did not measure interim timepoints, so it is difficult to assess if sessions impact motor-evoked potentials in a dose-dependent manner. However, based on the findings of similar studies in the upper extremity,[102] it is likely that greater improvements may have been observed if the intervention had been applied over a longer duration. Despite these promising findings, certain limitations must be kept in mind: both studies had low sample sizes, used different methodologies, and had large confidence intervals.[96] Nonetheless, the implications of such results are broad and warrant further investigation of postoperative orthopaedic care after ACLR.

At present, numerous BCI-MI technologies exist that encompass sports performance through neurorehabilitation. In the realm of sports performance, i-BrainTech uses motor imagery and electroencephalography to translate motor cortical activity to fuel a virtual avatar into performing specific soccer and basketball drills with accuracy and precision. A small pilot study on 8 professional soccer players has

demonstrated a 33% to 35% increase in passing accuracy and ball speed (unpublished data, internal validation study). Nonetheless, numerous larger-scaled investigations are needed before establishing a causal relationship. With regard to rehabilitation, g.tec has developed a system incorporating motor imagery, virtual reality, and functional electrical stimulation to train the upper and lower extremities of patients who suffer from motor impairments after a stroke. An analysis of g.tec's BCI-MI technology in 51 stroke patients, found improvements in the Fugyl-Meyer Assessment of Upper Extremities, a validated motor assessment tool, that surpass the pre-established clinically important difference.[103] In other words, BCI-MI treatment was effective in facilitating functional recovery in stroke patients with mild to severe impairment. Evidently, in addition to sports performance and motor rehabilitation, other potential areas of future application include sensory restoration, injury prevention, and psychological readiness in return to play/work after surgery.

### Overview: A Case for BCI-MI in ACLR

After ACL injury and reconstruction, AMI impedes voluntary quadriceps activation leading to a host of detrimental consequences ranging from gait instability and muscle weakness to early osteoarthritis.[15-21] Robust evidence in the literature suggests that quadriceps muscle weakness is associated with neuroplastic changes within specific corticospinal pathways and brain areas. By affecting cortical organization and activation pathways, interventions such as MI training have the ability to positively impact muscle activation in ACLR patients.[61] The advent of noninvasive BCI technology has revolutionized motor rehabilitation. BCI-MIs have been validated and successfully applied in the recovery of atrophied neuromuscular pathways in stroke patients. However, they have not been applied in patients recovering from motor deficits caused by sports-related musculoskeletal injuries. By applying these technologies to stimulate quadriceps activation in the patient who has undergone ACLR, well-designed clinical studies may elucidate whether BCI-MI has an impact on clinical outcomes and recovery time. We propose that future research be direct toward expanding its utility in rehabilitation after ACLR. Successful implementation of BCI-MI would allow for an innovative clinical approach blending neuroscience, rehabilitative science, and orthopaedic care to optimize patient outcomes after ACLR.

## Conclusions

Quadriceps weakness is associated with neuroplastic changes within specific corticospinal pathways and brain areas. BCI-MI shows strong potential for facilitating recovery of atrophied neuromuscular pathways following ACLR and may offer an innovative, multidisciplinary approach to orthopaedic care.

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