

THE EFFECTS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION ON
PROPRIOCEPTION FOLLOWING EXERCISE-INDUCED MUSCLE DAMAGE

A Thesis
BY
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Abstract

The Effects of Transcutaneous Electrical Nerve Stimulation on Proprioception Following Exercise-Induced Muscle Damage

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Musculoskeletal injuries cause pain and inflammation that if left unresolved can lead to further sequelae that reduce quality of life. This pain is theorized to contribute to maladaptive changes in the nervous system, termed neuroplasticity, which causes sensorimotor deficits that may increase risk for reinjury. Eccentric muscle damage protocols are designed to induce myofibril tearing, causing pain and similar reductions to proprioception occurring after musculoskeletal injuries. Joint position sense (JPS) is a common measure of proprioception that assesses the ability for one to locate a part of their body segment in space. JPS is decreased after eccentric exercise and in multiple models of injury, which may arise from alteration of muscle spindle afferent information in the brain due to pain. Transcutaneous electrical nerve stimulation (TENS) is a common clinical tool used to modulate pain by gating transmission at the spinal cord or descending inhibition. The evidence of TENS reducing delayed pain after eccentric exercise warrants the exploration for it to improve proprioception in this fashion. Therefore, we investigated the role of motor and sensory TENS on JPS after eccentric exercise in 24 subjects, hypothesizing the use of TENS to modulate pain following eccentric damage improves proprioception during a JPS assessment. Subjects

underwent eccentric exercise at the knee joint followed by TENS; outcome measures included: thigh circumference, pain during sit to stand (PDSS) and maximal volitional isometric contraction (MVIC) and JPS before and after the exercise and 48 hours later before and after TENS. Pain increased significantly after the protocol (Day 1 Pre: 0.59 ± 0.73 ; Day 1 Post: 2.49 ± 1.79 , $P = 0.001$), but no changes occurred in MVIC and thigh circumference. Furthermore there were no significant reductions to PDSS after TENS in any of the groups. JPS constant error significantly decreased ($p=0.02$), indicating eccentric exercise caused subjects to underestimate JPS angles but was not recovered after the use of TENS. The results indicate that muscle spindle sensitivity is changed due to pain after EIMD, thus causing worse proprioception. The proprioceptive reductions after eccentric exercise needs to be highlighted by clinicians as injury risk may be greater. Further studies need to be conducted to assess the role of motor and sensory TENS on proprioception after eccentric exercise.

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Chapter 1: Specific Aims

Musculoskeletal injuries cause pain and inflammation that if left unresolved can lead to further sequelae that reduce quality of life.¹ Pain reduces a person's daily function and activity, creating a barrier to physical activity after an injury as it engenders fear avoidance behaviors when physical activity is resumed, and thus reduces adherence to therapy programs.^{2,3} Pain is theorized to contribute to maladaptive changes in the nervous system, termed injury-induced neuroplasticity.⁴ This theory implies that pain interferes with somatosensory function, the ability for the body to match actions with sensory information. This phenomenon has been investigated using proprioceptive tests, such as testing a person's ability to recreate a target joint angle, termed joint position sense (JPS) assessment.⁵ JPS errors are reported to be higher in individuals with previous injuries compared to healthy individuals in ACL and ankle sprain models.^{5,6} Furthermore, the sensorimotor decrements potentially increase injury recurrence due to altered movement patterns.⁷ Due to the difficulty in testing individuals in the acute stages of injury, little is known about the acute effects of pain on sensorimotor and neurological function, leaving the role of pain management in preventing injury-induced neuroplasticity ambiguous.

During eccentric exercise, myofibrils are torn leading to exercise-induced muscle damage (EIMD).⁸ contributing to pain and muscle soreness lasting 12-72 hours after exercise.^{8,9} Typically decreased neuromuscular activation and force production occur within the first 12 hours, while pain onsets at 12-24 hours post-exercise.¹⁰ The process of strategically tearing myofibrillar structures reduces force generation and generates significant release of inflammatory proteins that selectively

activate nociceptors and relay pain.^{8, 11, 12} Among the array of nociceptive metabolites, histamine, bradykinin and lactate and have been reported to be responsible for the delayed progression of pain after EIMD.^{11, 13} This myriad of inflammatory products relaying the effects of pain become active in a similar manner observed in models of joint injury.¹⁴ Furthermore, similar inflammatory products are present after other acute injuries, especially at the knee joint.¹⁵ Since similar products of musculoskeletal injuries are present after EIMD, these protocols could be used to better understand the role of pain in acute injuries.

A common measure of sensorimotor function, JPS, tests a subject's ability to identify where their joint is in space.⁵ Increased JPS error is indicative of worse sensorimotor performance and has been observed in multiple injury models including, ACL injury⁵, EIMD¹⁶ and chronic ankle instability.¹⁷ This is suspected to occur from the stream of nociceptive information or peripheral deafferentation that would both alter receptor function or central processing.^{16, 18, 19} Therefore, such decrements to sensorimotor functioning occurring after EIMD protocols are potentially similar to sensorimotor functioning decrements after joint injuries.¹⁰ In order to understand the role of the central nervous system following injury, electroencephalography (EEG) has characterized cortical adaptations in both muscle damage and ligament damage models.^{4, 10, 17, 18, 20} As JPS is reduced across multiple models of injury, this may occur due to the nature of pain disrupting the brain's ability to discriminate afferent muscle spindle activity with nociceptive activity. This phenomenon has been described in one study comparing JPS between healthy subjects and those with previously injured joints, where subjects with previous joint injuries display increased dependence on working memory, compensating for poor sensorimotor functioning.¹⁷ This is inferred from altered brain activity indicating decreased somatosensory activation in those with a reconstructed ACL. More

recently, this phenomenon has also been reported in those who have sustained EIMD 12-48hrs afterwards during a biceps brachii movement task.²¹ As sensorimotor function decreases after EIMD similar to true injuries, EIMD protocols can perhaps extrapolate pain mechanisms on sensorimotor functioning.

Transcutaneous electrical nerve stimulation (TENS) is a common clinical tool used to modulate pain by either activating descending efferent inhibitory pain pathways or inhibiting ascending afferents of pain.²² TENS activates different neuronal fibers by adjusting the electrical amplitude, frequency and phase duration.²³ This procedure utilizes high frequency stimulation to disproportionately stimulate large sensory fibers, inhibiting pain signaling to the spinal cord. Under proper frequency and phase duration, TENS turned up to the motor level (mTENS) may initiate endogenous opioid release after transient muscle stimulation, similarly producing analgesia; however, this is far less understood.^{23,24} This procedure stimulates the muscle at 1-10Hz to the point of contraction thus causing the release of endogenous opioids. Moreover, the evidence of TENS significantly reducing the pain from delayed onset muscle soreness (DOMS)²⁵ justifies the use to potentially reverse negative effects of pain from EIMD on sensorimotor functioning.

Injuries impose pain and inflammation which lead to long-term neural changes that may increase injury recurrence. To identify the role of pain on proprioception, EIMD protocols can homogeneously simulate effects from injuries while tracking sensorimotor functioning. Utilizing TENS, pain can be modulated to measure if optimal sensorimotor function is maintained while monitoring cortical rhythms. Therefore, the objective of this study is to investigate the role of mTENS and sTENS in maintaining sensorimotor performance following pain induced by EIMD. We hypothesize the use of TENS to modulate pain following EIMD improves proprioceptive

performance and decreases somatosensory activation during a JPS assessment. Our rationale is since previous studies have reported decreased sensorimotor performance subsequent to pain associated with EIMD and joint injury models, pain being attenuated via TENS should maintain sensorimotor performance and reverse cortical rhythms during proprioceptive tests. Our specific aims will test the following hypotheses:

Specific aim 1

To determine the effects of EIMD on joint position sense at the knee during a proprioceptive test.

Hypothesis 1.1: JPS will decrease after EIMD in the sham TENS group, as evident by increased constant, absolute and variable errors on day 1 and 2.

Specific aim 2: To determine the effects of motor and sensory-level TENS on proprioception after a bout of EIMD.

Hypothesis 2.1: JPS will increase following motor and sensory-level TENS, as evident by decreased constant, absolute and variable errors on days 1 and 2.

Upon conclusion we will understand the role of TENS affecting sensorimotor function, which may serve as an aid in understanding neuroplastic effects after injury. This contribution is significant because further evidence is required for therapeutic techniques to combat neuroplasticity and injury recurrence. The proposed research is novel because it utilizes EIMD protocols to simulate injury and TENS to mitigate sensorimotor function decrements and restore cortical rhythms. Insight into amending nociceptive pathways via TENS establishes a link in how somatosensory pathways play in injury recurrence, propelling the field of neuroplasticity in injury research by adding to the arsenal of tools used during acute care following injury.

Chapter 2: Literature Review

Thesis aim

The proposed study's purpose is to determine the effects of exercise-induced muscle damage and motor and sensory-level TENS on proprioception in an able bodied population. This study design will allow us more insight on the role of pain and pain-relief interventions on the potentially maladaptive neuroplasticity following injury. Therefore, this literature review aims to describe the role of pain after injury on neuroplasticity, and then discuss how this may negatively affect somatosensory function.

Pain

Among many neurologically derived sensations, pain is considered one of the most fear-inducing perceptions.²⁶ Pain has been shown to cause negative emotions from its engrossing and often crippling nature.²⁶ Reductions in quality of life are concomitant with chronic pain as many who experience pain succumb to these symptoms and develop various psychological issues.²⁷ Thus, lying an important link in the interplay between physical and psychologically experienced phenomena. Pain is a highly limiting and multimodal sensation consisting of often severely distressing sensations in different body regions. Among types of pain, chronic pain is one of the most common and studied pain modalities. Pain is often experienced chronically, although it can be an acute sensation accompanied by potential or actual tissue damage. However, in most cases people experiencing neurological pain report it in the absence of tissue damage.²⁶ Pain plays a major role in decreasing quality of life in our population. Currently various nuances of chronic regional pain affect

up to 25% of our population, it can reduce daily efficiency at work and impose factors that contribute to further injury in populations during otherwise routine tasks.² Pain contributes to a multitude of sequela that further reduce outcomes in populations with different conditions of pain, such as osteoarthritis, fibromyalgia, spinal cord pain, etc.²⁸⁻³⁰

The mechanisms that cause pain are disparate for different modalities of pain. Neuropathic pain is commonly caused from disorders in the somatosensory pathway of the brain tracts, specifically at nociceptive fibers (A β , A δ and C fibres), although not everyone who experiences damage at various spinal pathways also experiences neuropathic pain.²⁷ Fibromyalgia is a form of neuropathic pain that encompasses widespread muscle pain and tenderness, causing headaches and consistent fatigue. A central sensitization at the afferents entering the spinal dorsal horn is the main form that gives rise to pain from fibromyalgia.³¹ These changes are from spinal and supraspinal levels, arousing greater afferent insults of nociceptive compounds (NMDA receptor activation, release of nociceptive transmitters, namely substance P, nitric oxide, nerve growth factor, and glutamate). Furthermore reduced activity in supraspinal regions regulating pain pathways allows for impaired production of dopamine, serotonin, norepinephrine, epinephrine, and endogenous opioids, consequently allowing excessive nociceptive stimuli to reach the dorsal horn and contribute to this widespread pain.³¹

Nociceptors

Noxious stimuli arriving at tissues with specialized sensory receptors called nociceptors activate these receptors.²⁶ Although, nociception does not always arise the sensation of pain. Perception of pain underlies how the brain transduces individual nociceptive stimuli.³¹ Therefore, in clinical conditions pain may be a present factor causing an individual to seek treatment. However, in

other conditions one may not be perceptive to their pain until they are in an instable environmente.g., athletics. It is also important to note that pain is a sensory feature that allows us to react to harmful situations. Acute pain from a thorn stick can make an individual wary of that threat and therefore avoid it. However, chronic pain typically incurs debilitating conditions to individuals, rendering them miserable depending on the severity of the pain.³¹

Stimuli that target the skin or muscles and joints activate various nociceptors. The soma of these sensory neurons lies within the dorsal root ganglion and the trigeminal ganglia.³² Among the types of nociceptors that transduce pain, there are three basic classes: thermal, mechanical and polymodal. Thermal nociceptors transduce pain relating to abnormal temperatures, i.e., above 45 °C or below 5 °C (32). This information travels along thin myelinated A- δ fibers at 5-30m/s. Mechanical nociceptors transduce information during intense pressure to the sensory area. This pain information also travels along thin myelinated A- δ fibers at a velocity of 5-30m/s.³² Polymodal nociceptors transduce various nociceptive information such as intense mechanical, chemical or thermal stimuli. This information travels along small-diameter nonmyelinated C fibers at slower velocities of less than 1m/s.³²

Another type of nociceptor called a silent nociceptor has its firing threshold reduced in the presence of inflammation and various nociceptive chemicals; therefore, although the receptors don't respond directly to nociceptive components, they play a role in hyperplasia and central sensitization.^{1,33} Most nociceptors function as free nerve endings, which transmit information from nociceptive stimuli via action potentials that depolarize the membrane.³² This is seen in capsaicin where a thermal nociceptor contains capsaicin receptors that convert the thermal energy into an action potential which is relayed to the brain. These nociceptors all function to carry nociceptive

information from the dorsal spinal column to the spinothalamic tract via structures: lumbar spinal cord (pain from lower body), cervical spinal cord (pain from upper body), caudal medulla, middle medulla, mid pons, midbrain, ventral posterior lateral nucleus of the thalamus, cerebrum, primary somatic sensory cortex (S1), all arriving at the brain.³²

Injury leads to pain and dysfunction

After musculoskeletal injuries, various severities of acute pain follow. These are experienced after ligament sprains and ruptures, joint dislocations and bone fractures.³³ Often after surgical mediation, lasting pain remains an issue as it sensitizes the nervous system leading to greater and more persistent pain, which contributes to chronic pain conditions that are hypothesized to increase injury risk.³⁰ Orthopedic procedures reportedly cause more intense pain than other forms of surgery, as the periosteum bone layer has a very low pain tolerance compared to other soft tissue.³⁴ The primary issue of these surgical procedures is they engender profound inflammatory products: bradykinin, histamine and substance P at the joint. This inflammation, if improperly treated, contributes to chronic pain states that prolong rehabilitation and potentially reduced daily life functioning.³⁴ Therefore, acute pain poses a major contributor to the development of pain conditions, but in its nascent may be modulated to reduce long term changes.

Among the array of musculoskeletal injuries, it is estimated 900,000 knee injuries occur yearly in the United States, 12% of which account for rates of osteoarthritis.³⁵ Post-traumatic osteoarthritis is a condition engendered from damage of varying degree to capsuloligamentous structures. Such damage to ligaments at the knee joint imposes morphological changes such as biomechanical misalignment, narrowing of the joint space and cartilage erosion.³⁵ All of these are reported to contribute to physiological changes that cause cartilage lesions from degenerative

enzymes: aggrecanases and metalloproteinases, which amplify catabolic processes in the joint. ³⁶

This array of osteoarthritic constituents severely augments effects on pain generation via central sensitization, where pain pathways generate greater response to nociceptive insults. ³² Furthermore, this cycle operates via positive feedback where the catabolic enzymes continuously degrade the joint, causing those to experience greater pain that further impairs joint mobility in more than 50% of those with ligament damage at the knee. ³⁵ Similar to osteoarthritis, other chronic pain conditions, fibromyalgia and musculoskeletal disorders operate under nociceptive hypersensitivity.

Neuroplasticity following injury

Pain and inflammation diminish afferent signaling to the brain, which may contribute to further injuries by forcing neural alterations after surgery. ^{37, 38} Several reports describe how changes in neurological functioning following joint injuries affect proprioception and sensorimotor function. ^{4, 19, 39} Such changes in sensorimotor function further place the affected area at a risk of reinjury, due to the lack of kinesthesia and proprioception. ⁴ Pain cascades contribute to this decrease in sensorimotor functioning as reports have described decreased JPS, postural control, muscle strength, muscle reaction time and force matching. ^{4, 17, 40-42} Such changes in sensorimotor functioning are in deficits typically arising from loss of ligamentous tissue leading to functional ailments. ^{1, 17}

Therefore, reduced function to capsuloligamentous and musculotendinous sensory organs contribute to arthrogenic muscle inhibition (AMI), a phenomenon where pain and inflammation cascades inhibit musculature around an injured joint by reflexive deactivation. ⁴³ Quadriceps activation has been reported to be reduced simultaneously with experimental pain and joint effusion protocols. ⁴³ AMI presents complications to therapy as decreased neuromuscular activation as a function of

increased nociceptive afferents constrain strength development, thus reducing the effectiveness of therapy programs on osteopathic pathologies.⁴⁴

Injuries have revealed changes in the brain at the somatosensory cortex, a vastly malleable region responsible for integrating sensory information with motor responses.¹⁹

Electroencephalography (EEG) is an electrophysiological tool used to record brain activity in several fashions.⁴⁵ Brain activity is captured in the form of frequencies: delta (0-4Hz), theta (4-7Hz), alpha (8-13Hz), beta (13-30Hz) and gamma (30-80Hz), which are expressed under different activation/deactivation demands.⁴ Modification of brain activity has been reported in several different models (ankle, knee, experimental).^{18, 20, 40, 46} Studies investigating somatosensory disparities between patients with reconstructed ACL's compared to healthy individuals have revealed interesting findings. One study conferred results using somatosensory evoked potentials (SEP) showing modification of afferent transmission at the spinal cord in subjects with reconstructed ACLs. This was determined from N14 potentials that indicate afferents arriving at the spinal cord being unaltered, despite P27 potentials being absent.⁴⁷ Furthermore, these alterations and deficits in JPS persisted after surgery.¹⁷ Functionally, these appear to provide an advantage since copers, who have suffered an ACL rupture without subsequent functional ailments, lack these changes unlike those with instability,⁴⁸ thus indicating no differences in neuronal signaling after ACL rupture. As greater cortical activity occurs during different tasks, functionally this is relevant to the discrimination of afferent activity at the brain. Increased alpha, theta, delta and beta activity were reported to be higher at frontal and parietal brain regions in injured ACL patients compared to healthy ones during walking, jogging and landing tasks, and it was inferred that this is due to the differences in signal processing after injury.⁴⁵ Additionally, a study reported increased theta activity in the motor cortex and increased alpha activity in the somatosensory areas between subjects with healthy knee joints

and those with previously injured ACLs during a JPS task.⁵ Increased frontal-theta power has been linked to concentrating, indicative of subjects focusing on cognitively demanding tasks.⁵ Increased alpha activity is linked to deactivation and therefore indicative of the suppression of a process.⁴ Thus, our prediction of greater alpha activity in the parietal area is justified as pain may diminish the ability to distinguish afferent information at the somatosensory area. Our rationale is that pain will play a similar role as injuries in causing signal disruption, the increased frontal-theta power indicates focus during the JPS task, which is facilitated by the higher parietal-alpha activity, enabling deactivation of some cortical processing to concentrate.

EIMD as an Injury Model

Experimental models of exercise induced muscle damage (EIMD) protocols have become a ubiquitous tool allowing researchers to gauge the effects of various substances affecting muscle recovery and the nervous system.^{4,49} These studies have conferred a bevy of results demonstrating altered aspects of muscle pain (myalgia) after the protocol.⁵⁰ Commonly, eccentric contractions causing acute damage in the muscle are used in these protocols. Often this damage incurs myalgia lasting for several days, a condition called delayed onset muscle soreness (DOMS). Creatine kinase levels, visual analog scales (VAS), force generating capacity, localized swelling and functional magnetic resonance imaging (fMRI) are tools often used to depict EIMD.⁵⁰ However, when characterizing features of myalgia there appears to be some conjecture in the literature. Exercise order rather than dominant leg has been reported to cause greater DOMS and muscle damage to the knee extensors in one study.⁵¹ Inconsistent sex differences have been reported in DOMS, speculated from strength and hormonal dissimilarities.⁵² However one experiment using maximal eccentric knee extensions found similar decrements to torque and increased muscle soreness in males and

females.⁵² Other experiments controlling for sex have utilized protocols resisting isokinetic eccentric activation of the knee extensors found profound decreases to force and transient increase in pain over the time-course for EIMD protocols.⁵² These findings warrant the use of other objective electrophysiological tools to also assess effects of EIMD protocols to provide greater reliability.

The pain ensued from DOMS after EIMD causes a cascade of afferent neural signaling from nociceptive substances relaying pain inducing information caused by excessive muscle damage, although concentrations of these substances do not correlate to subjective pain intensity.⁵⁴ Thus, lies the utility for an objective, minimally invasive and sustainable measure for muscle pain after intense eccentric exercise such as EEG perhaps.²² Constraints on muscle function are imposed via damage to the myofibrillar structures, thus compromising muscle function. This ensues a horde of nociceptive insults (bradykinin, prostaglandins, histamine, and nerve growth factor), contributing to afferents from type 3 (A δ) and 4 (C) nociceptors.^{11, 17} These inflammatory constituents further cycle around the recovery period of satellite cell recruitment after EIMD.⁵⁵ As this sensory traffic continues to relay to the nervous system, specific sensorimotor tasks are reduced such as joint position sense and force matching, therefore presenting EIMD protocols as a potential model of injury, since these effects are also present after musculoskeletal injury.^{16, 22}

EIMD to myofibrillar intracellular muscle structures negatively affect excitation-contraction processes, thus causing metabolic impairments that impose constraints on optimal muscle function.^{9,}⁵⁶ This generates a marked release of inflammatory proteins that signal myoblasts which elicit robust satellite cells to attenuate the muscular micro-trauma depending on the magnitude of the insult, thus facilitating hypertrophy over a period of regeneration from the trauma.⁵⁵ It is important to indicate consequences arising from DOMS resulting in prolonged (1-14 days) strength reduction of up to 10-

70%.⁴² This is postulated to arise from micro-traumatic damage inducing a cellular milieu, activating proteolytic pathways that exacerbate EIMD, sarcomeric Z-line streaming, disorganization of contractile (actin-myosin) and structural (Desmin and dystrophin) proteins, and ionic impairment from damage to junctophilins that connect to the sarcoplasmic reticulum and enable calcium kinetics (57-59).

Furthermore, a bevy of the inflammatory agents (bradykinin, prostaglandins, histamine, and nerve growth factor) originating from EIMD relay afferents to type 3 (A δ) and 4 (C) nociceptors.^{11, 17} Utilizing EIMD to reveal mechanisms surrounding muscle atrophy and pain (myalgia) can perhaps be extrapolated to augment recovery in clinical populations. Myalgia causes considerable neuroplasticity in disparate populations, which further contribute to injury, such as atrogenic muscle inhibition, a reflexive inactivation of the muscle.^{1,17, 39, 43} Not only does muscle pain deactivate muscles, but considerable joint swelling has caused decreased quadriceps activation in conjunction with pain during joint effusion studies.⁴³ EIMD can therefore be used as a model to simulate post-injury neural changes due to the marked reductions in strength production, neurological deficits in joint proprioception, and force perception associated with EIMD.⁶⁰

Independent of any pathologies, proprioception can be negatively affected for up to 2-4 days, therefore impacting daily life tasks.^{61, 62} Under experimental conditions eccentric exercise induced damage models have been reported to alter muscle proprioception through a series of mechanisms of pain and inflammation.^{20, 22} Such alterations arising from reversible micro-muscular trauma include myalgia, neuromuscular impairment, reduced awareness of position and movement. These are postulated to occur via modulation of both segmental and supraspinal pathways.⁶² Typically, the transient reduction in proprioceptive deficit follows the time course of intramuscular inflammation

and concomitant myalgia incurred from the exercise-induced muscle damage. One sensory receptor susceptible to EIMD is the muscle spindle, responsible for the stretch reflex.⁶³ Incurred pain from EIMD causes dysfunction in the stretch reflex likely by impairing function in the gamma motoneuron, thus impeding alpha-gamma coactivation. Not only has actual EIMD identified modifications in sensitivity of muscle spindle afferent function, moreover intra-muscular injections of inflammatory and pain inducing substances has conferred similar effects in animal models.⁶⁴ However, EIMD protocols have pinpointed mechanisms that cause greater change to muscle afferents, such as increased intramuscular temperature and pressure, which are absent during intramuscular injections.⁶⁵

Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) functions as a non-pharmacological method to reduce pain in a multitude of populations. Such effective means of inhibiting pain experienced from an array of painful conditions provides substantial value clinically.²¹ TENS is used clinically and experimentally in two common modalities to evoke analgesia: motor TENS (mTENS) and sensory TENS (sTENS). sTENS acts by frequency stimulation of an area at 50-150Hz to stop nociceptive stimuli entering the dorsal horn of the spinal cord.⁶⁶ Motor level TENS causes endogenous opioid release after continuous muscle stimulation at 1-10Hz.^{22,23} The procedural use of TENS focuses on gate control, a model of analgesia to stimulate large sensory fibers nociception at the spinal cord, therefore “closing the gate.” The mechanism of action had been described in rat model and occurs by blocking nociception at neuronal structures: the periaqueductal gray and rostral ventromedial medulla.⁶⁷ Another primary mechanism TENS reduces hyperalgesia through is by inhibiting muscarinic receptors (M1 and M3) and GABA_A receptors in the spinal cord.²¹

Endogenous opioid theory and evidence.

The release of endogenous opioids is described to occur during exercise and other points of stimuli. TENS has been a solution to precipitate the release of such opioid components and allow the adherence to certain clinical practices.⁶⁸ High frequency or sensory (sTENS) TENS allows for the release of β -endorphins into circulation that decrease the perception of pain.⁶⁹ Utilizing motor TENS (mTENS), Endogenous opioid release has been reported to increase pain threshold during phasic heat stimulation.⁷⁰ In other clinical settings, the application of TENS at various areas has shown to reduce the need of pharmacologic opioid use.²¹ Furthermore, reduced effects on pain control have arose from continuous stimulation of endogenous opioid systems due to consistent use of TENS, thus requiring modulation during treatment.²¹

Under experimental conditions various forms of TENS protocols have elicited analgesia.^{22,}
²³ An important factor that needs to be considered in TENS use is accommodation, the gradual adjustment to TENS stimulation, which decreases the overall treatment effectiveness. Studies have controlled for this occurrence via increasing the TENS intensity gradually throughout the procedure
²⁴ While varying parameters of TENS stimulation: pulse duration, frequency, stimulation time and amplitude, have been studied and different experiments have identified ideal parameters to generate analgesia and other positive effects^{71, 72} sTENS protocols using 100Hz frequency, 100 μ s pulse duration, 20 minutes stimulation time and an amplitude considered “strong but comfortable,” engendered analgesia and increased proprioceptive ability during a JPS task in patients with osteoarthritis.⁷¹ mTENS protocols have used similar protocols to sTENS; however, pulse frequency and duration are most effective in reducing pain at 4Hz and 200 μ s respectively.^{72, 73} The use of these

tools to preserve JPS may serve as a novel tool in reducing injury recurrence after intense exercise bouts.

It remains unknown if the pain attenuated from eccentric exercise induced muscle damage leads to restored sensorimotor performance and reversed cortical rhythms at alpha, beta and theta frequencies in frontal-parietal regions. These sensorimotor and cortical alterations are present in those who have sustained ligamentous injuries, who are at greater risk of experiencing other injuries due to these changes. Since these changes are also present after EIMD protocols, then if TENS does amend these decrements, this contribution this would bring would potentially combat maladaptive neuroplasticity with a non-pharmacological agent to reduce pain after intense exercise.

Chapter 3: Methods

Experimental Design

This is a randomized controlled study utilizing a repeated-measures design. The independent variables are Group (mTENS, sTENS, and control) and time (pre-EIMD, post-EIMD and 48 hours later pre-TENS and post-TENS). The dependent variables are constant, variable and absolute errors during JPS tasks, thigh circumference and PDSS. The order of testing is presented in figure 1, measurements will occur before TENS, 30 minutes after TENS and 48 hours later in the same fashion.

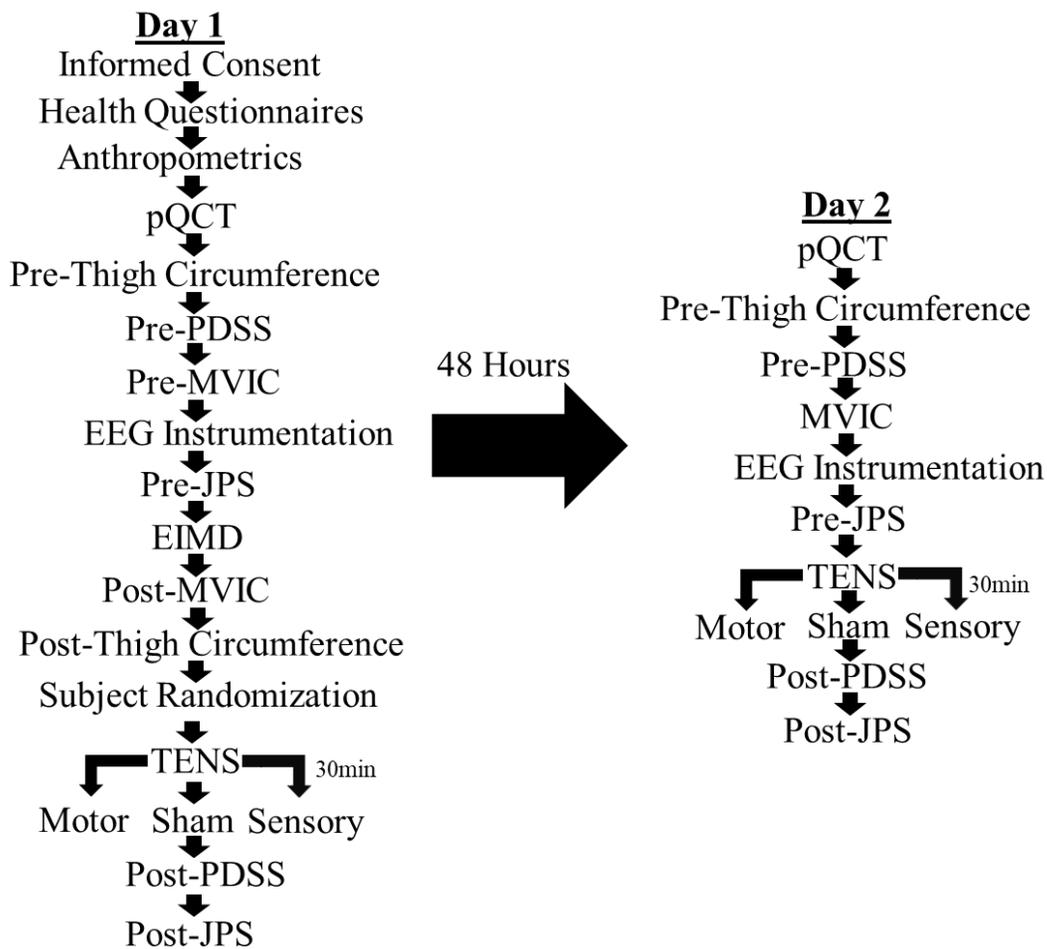


Figure 1. Methods flow chart

Participants

We recruited 24 subjects to participate in 2 measurement sessions, primarily from Appalachian State University and the Boone, NC community. All subjects that completed the full study were between the ages of 18-35, healthy and untrained. Healthy is defined as healthy enough to engage in physical resistance exercise activity and no history of chronic pain diseases or recent

musculoskeletal trauma that would complicate physical exercise. Untrained is defined as a subject who has not participated in consistent organized programs focused on consistently maximizing strength gains within the past year. Subjects being untrained ensured damage to the quadriceps, as damage to a trained individual is subject to their level of training. Subjects were excluded if they performed regular resistance training exercise, had a history of surgery or fracture to the legs, have a history of injury that prevented the participant from performing physical activity within the last 3 months, or have a recent history of concussion (<6 months). No exclusions occurred based on race, gender, religion or any other creeds. Subjects were asked to refrain from caffeine and alcohol 8 hours before the testing procedure. Upon arrival subjects were required to provide Appalachian State University-approved informed consent (18-009) and complete a physical activity readiness questionnaire (PAR-Q) to rule out contraindications of exercise. Subjects were randomly assigned to either an experimental or control group using block randomization, allowing for 12 subjects per group.

Procedures

Peripheral quantitative computational tomography

Subjects had localized swelling of the quadriceps assessed with peripheral quantitative computational tomography (pQCT) when they first arrived and 48hrs after the EIMD protocol. pQCT is a tool used to assess density of different tissues via stress strain index (SSI) in mm³, a unit of measurement unique to pQCT. We utilized this technology to assess the change in swelling before and 48hrs after EIMD and compared SSI values across treatment groups. Prior to measurements, we performed a calibration technique, code phantom scan, to ensure adequate pQCT readings. Participants came to a room, where we used a STRATEC XCT 3000 pQCT model (Pforzheim,

Germany) that uses a scanning, specially developed X-ray tube with a 50 μ m spot size (high voltage 50 kV, anode current <0.3 mA, mean X-ray energy 37 keV, energy distribution after filtration 18 keV full width (FWHM)). The orientation of the subject on the pQCT machine is presented in figure 2, where the exercised leg was placed in a carbon shell attached to a sliding stabilizer to reduce motion of the leg. There was a clamp attached just above the patella, allowing the scanner to measure across the mid-thigh (distance between the lateral condyle and greater trochanter). An initial X-ray was taken to determine where the 3D measurement will occur. Once identified the pQCT machine took multiple cross-sectional scans of the limb for a 3-minute process. Standard protocol procedures were conducted with the following settings: X-ray tube current = 95mA, X-ray tube potential = 60 kVp, voxel size = 82m, and a 1536 \times 1536 matrix. This occurred before the EIMD protocol and once more before the TENS protocol 48 hours later. Values were compiled in μ m to calculate mean changes between groups for the measurement after the EIMD protocol. Post-measurement analyses were conducted to gather mean SSI for group comparisons.



Figure 2. Subject and pQCT position

Pain during a sit to stand (PDSS)

We used an active movement to assess subjective pain levels, where subjects completed a sitting and standing movement procedure. Subjects were initially seated in a chair and told to slowly (~ 1.5 seconds) stand and hold that position for 2 seconds and sit (~ 1.5 seconds). To standardize this procedure, subjects had the movement demonstrated to them and were allotted several practice trials to control for the rate of standing. Subjects were visually presented a visual analogue (VAS) from a 1-10cm line where they rated their pain over the course of the movement. This occurred before and after the EIMD protocol and once more after the TENS protocol, then before and after the TENS protocol 48 hours later.

Thigh circumference

As an indicator of swelling from the EIMD protocol, we used measuring tape to also assess the change in swelling at the center of the mid-thigh. Subjects were standing as we measured 5, 10, 15 and 20cm from the top of patellar cap and the center of the distance from the greater trochanter to the lateral condyle to determine the mid-thigh. Each distance was marked in which to measure around. Data in cm was compiled to calculate a difference in swelling between groups after EIMD. This occurred before the EIMD protocol and once more before the TENS protocol 48 hours later.



Figure 3. Thigh circumference measurement.

MVIC assessment

Subjects were seated with the hip flexed at 85° and the lower leg secured in padding at 45° of knee flexion, as pictured in Figure 4. Each subject was assessed for their individual MVIC by maximally extending their knee joint against an immovable load for 5 seconds during 3 trials with one-minute rests in between each trial. The highest torque value was used to determine the load for each subject during the EIMD protocol.

Cortical activity

Subjects were instrumented with electroencephalography (EEG) to capture electrocortical brain activation during the JPS procedure. Subjects were instrumented with a tight-fitting elastic cap with 64-embedded Ag/AgCl electrodes aligned in the international 10:20 system. Electrode contact with the scalp was achieved using QuickCell sponges filled with an electrolyte solution and used to lightly abrade the scalp to allow for direct electrode contact. Impedance of the electrodes was monitored online during subject preparation and throughout testing to ensure appropriate impedance ($<5\Omega$) across all electrodes. Prior to the start of the JPS, to control for artifacts, subjects were prepped on reducing swallowing and blinking, all which affect EEG activity in the 0-30Hz range. Additional electrodes were placed on the mastoid processes to serve as linked grounds $[(A1+A2)/2]$, and surrounding the eye (VEOU, VEOL, HEOR, HEOL) to allow for ocular movement artifact removal. The cap was connected to two cascading Grael EEG amplifiers (Compumedics Neuroscan, Charlotte, NC) and transmitted to Curry 8 software at 24 Hz. An external trigger was synchronized with EEG data to allow for synchronization with joint position sense from testing. EEG activity data was divided into several frequencies and analyzed at a later date.

JPS

The JPS procedure examined the subject's ability to identify a reference angle by pressing a button when the subject perceives the joint has reached the angle where the joint was previously placed. JPS was tested using A HUMAC Norm isokinetic dynamometer (CSMI inc. Stoughton, MA). Subjects were seated on a dynamometer as described in the MVIC protocol. Subjects were equipped with glasses disabling them from seeing below and have earphones to control for visual and auditory influences. The dynamometer slowly ($3^\circ/s$) flexed the subject's knee from 20° to 90° to

establish the range of motion of the movement. Next, the dynamometer slowly ($3^\circ/\text{s}$) flexed the subject's knee to a random reference joint angle and held that position for 5 seconds. Prior to the test, the subject was told to concentrate and remember the position of the reference angle. After the subject undergoes movement to the initial reference angle, they underwent movement throughout the full range of motion. Next the dynamometer moved the leg through the full range of motion (20° to 90°) for a total of 10 times per random angle, then the subjects were tasked to press the button when they believe they are at the location of the previous angle. This process was repeated in 5 blocks with 10 repetitions in each, for a total of 50 times. In between each block, there was a silent period of 60 seconds of no movement activity in order to stabilize EEG activity.

The JPS starting angle had the knee flexed at 20° , where the knee flexed towards the initial reference angle. Reference angles for the extension to flexion movements were a random angle between 60° - 80° . For statistical analyses, constant error (CE) was calculated from this formula: $CE = \Sigma(I-T)/N$, where I is the identified angle, T is the target angle and N is the number of trials; absolute error (AE) was calculated from this formula: $AE = \Sigma|I-T|/N$, where I is the identified angle, T is the target angle and N is the number of trials; variable error (VE) was calculated from the standard deviation each subject had within a trial of one reference angle. Mean errors were used for analysis from each of the starting angles positions.⁷⁴ During the button press in the JPS procedure, EEG data was synchronized to another computer and post-measure analyses were conducted to identify changes in alpha and theta spectral power during the button press for the identified angle.



Figure 4. Dynamometer seating position.

Exercise induced muscle damage Protocol

Subjects were seated on a dynamometer as described in the JPS procedure. Prior to the start of the EIMD protocol, subjects performed a warmup consisting of 3 maximal eccentric contractions. Using the quadriceps muscles of the right leg, subjects were instructed to extend their knee as the dynamometer forced them thru 70° of flexion at 120°/s. The exercise began with the knee angle at 20° and ended at 90°. After each contraction the dynamometer raised the subject's leg at 60°/s back to 20° as this minimizes fatigue and maximizes eccentric damage. Subjects repeated this for 6 sets of 12 with 1 minute in between sets to rest. The torque threshold was 90% of the subject's concentric MVIC from the start of the experiment. As fatigue onset, indicated by subjects needing help to generate the torque threshold, the force for each subject was reduced by 10% of the previous set in order to ensure subjects complete each set and maximize muscle damage volume. Subject's received

loud verbal motivation and had a visual cue of their output force on the dynamometer to ensure consistent effort.

Transcutaneous electrical nerve stimulation (TENS)

Subjects were randomly allocated into one of three groups to receive either motor-level, sensory-level or sham electrical stimulation, called TENS, immediately and 48 hours after the EIMD protocol. A commercially available electrotherapy system (Vectra, Chattanooga Vista, CA, USA) was used for both TENS procedures. Each subject first had their quadriceps muscles vastus lateralis and medialis cleansed with isopropyl alcohol and abraded to ensure proper contact with the TENS unit. Next square 5cm² self-adhesive electrodes were attached at the cleansed site of distomedially and proximolaterally of each quadriceps muscle. The mTENS procedure encompassed 30 minutes of electrical stimulation at 4Hz frequency and 200µs pulse duration. The sTENS procedure encompassed 30 minutes of electrical stimulation at 80Hz frequency and 100µs pulse duration. Prior to the stimulation for mTENS and sTENS, subjects were told they will feel a pricking sensation, leading to muscle contraction. The stimulation was turned on using channel 1 and the amplitude increased until the patient confirmed the sensation is “strong but comfortable” in order to receive proper analgesia. Subjects in the mTENS group were also monitored for muscle contractions. Subjects in the sTENS group also had their stimulation turned to as high as tolerably possible but turned back down to 10% lower than that which induced muscle contractions. To control for TENS accommodation, the amplitude was gradually increased every 5 minutes over the course of the procedure. This ensures subjects maintain the perception of their verbal confirmation "strong but comfortable." The sham TENS (control) procedure had subjects prepped and situated just as the mTENS and sTENS group, however they received no true electrical stimulation for a 30-minute

period, as the TENS electrodes was plugged into channel 2, supplying no actual electrical stimulation. Subjects still had pads placed on them to measure the effect on their soreness levels.

48hrs Retesting

After the TENS procedure, the subjects completed a final JPS to track acute sensorimotor changes. Subjects then returned after 48 hours to complete pQCT, thigh circumference MVIC and VAS measurements as indicators of the changes in pain and swelling after the initial intervention. Next subjects completed an initial JPS assessment, then TENS treatment and lastly a final JPS assessment. The JPS assessments at 48 hours were to measure the effects of progressive pain from delayed onset muscle soreness on sensorimotor function.

Statistical analyses

PDSS and sensorimotor function were analyzed with an analysis of variance with repeated measures using time (Pre-day 1, Post-day 1, Pre-day 2 and Post-day 2) and effect (mTENS, sTENS and sham) factors across each time. An a priori level of significance was set at 0.05. Partial eta squared was computed to measure the effect sizes, which ranged from small (0.01 – 0.05) to medium (0.06 – 0.13) to large (≥ 0.14).

Chapter 4: Results

RESULTS

Anthropometrics

There was no significant main effect of group for mass ($F_{[2, 21]} = 0.74$; $p = 0.49$; $\eta_p^2 = 0.07$).

There was no significant main effect of group for height ($F_{[2, 21]} = 1.81$; $p = 0.19$; $\eta_p^2 = 0.15$). There was no significant main effect of group for age ($F_{[2, 21]} = 0.23$; $p = 0.80$; $\eta_p^2 = 0.02$).

Table 1: Mean \pm standard deviation of group mass, height and age.

Group	Mass (kg)	Height (cm)	Age (yrs)
mTENS	71.01 \pm 13.59	173.35 \pm 6.85	21.3 \pm 1.9
sTENS	63.29 \pm 9.67	166.41 \pm 7.17	20.8 \pm 0.9
Sham	66.14 \pm 14.52	171.38 \pm 7.99	21.1 \pm 1.2

PDSS

There was no significant time-by-group interaction effect for PDSS ($F_{[6, 63]} = 1.343$; $p = 0.252$; $\eta_p^2 = 0.113$). There was a significant main effect of time ($F_{[3, 63]} = 10.339$; $p < 0.001$; $\eta_p^2 = 0.330$). There was no significant main effect of group ($F_{[2, 21]} = 2.087$; $p = 0.149$; $\eta_p^2 = 0.166$). Fisher's LSD comparisons revealed significant differences between pre-day 1 and post-day 2 ($p < 0.001$).

Significant increases were also observed between pre-day 1, post-day 1 and pre-day 2 ($p < 0.001$,

Table 2).

Table 2: Mean \pm standard deviation of group pain during sit to stand (cm) at pre-day 1, post-day 1, pre-day 2, and post-day 2. Significance from baseline is indicated by *.

Group	Pre Day 1 (cm)	Post Day1 (cm)*	Pre Day 2 (cm)*	Post Day 2 (cm)*
mTENS	0.6 \pm 0.4	2.9 \pm 2.3	2.3 \pm 1.5	3.1 \pm 1.4
sTENS	0.6 \pm 0.7	2.4 \pm 1.8	3.3 \pm 2.2	1.8 \pm 0.7
Sham	0.5 \pm 0.9	2.1 \pm 1.1	1.6 \pm 1.5	1.4 \pm 1.0

Thigh circumference

There was no significant time-by-group interaction effect for thigh circumference ($F_{[4, 42]} = 0.22$; $p=0.93$; $\eta_p^2=0.02$). There was no significant main effect of time ($F_{[2, 42]} = 1.6$; $p=0.2$; $\eta_p^2=0.1$). There was no significant main effect of group ($F_{[2, 21]} = 0.29$; $p=0.75$; $\eta_p^2=0.03$).

Table 3: Mean \pm standard deviation of group thigh circumference (cm) at pre-day 1, post-day 1 and day 2.

Group	Timepoint	5cm	10cm	15cm	20cm
mTENS	Pre Day 1	44.83 \pm 5.32	49.79 \pm 4.97	53.78 \pm 4.96	57.47 \pm 5.48
	Post Day 1	44.82 \pm 5.11	50.48 \pm 5.26	53.96 \pm 5.32	58.44 \pm 5.76
	Day 2	44.56 \pm 3.56	49.21 \pm 4.51	54.50 \pm 5.76	58.32 \pm 6.91
sTENS	Pre Day 1	44.66 \pm 4.53	48.94 \pm 5.31	52.89 \pm 5.43	56.07 \pm 5.60
	Post Day 1	44.94 \pm 3.61	49.57 \pm 5.41	53.21 \pm 5.35	56.23 \pm 5.41
	Day 2	44.08 \pm 4.24	48.14 \pm 4.11	52.96 \pm 5.25	57.77 \pm 6.72
Sham	Pre Day 1	43.15 \pm 5.99	47.75 \pm 7.6	51.78 \pm 6.74	54.99 \pm 7.24
	Post Day 1	43.90 \pm 5.76	48.40 \pm 7.39	52.50 \pm 7.22	55.69 \pm 6.84
	Day 2	42.81 \pm 5.66	47.66 \pm 7.5	51.82 \pm 8.04	54.76 \pm 7.41

MVIC assessment

There was no significant time-by-group interaction effect for MVIC ($F_{[4, 42]}=0.76$; $p=0.55$; $\eta_p^2=0.06$). There was no significant main effect of time ($F_{[2, 42]}=0.91$; $p=0.41$; $\eta_p^2=0.04$). There was no significant main effect of group ($F_{[2, 21]}=0.51$; $p=0.61$; $\eta_p^2=0.04$).

Table 4: Mean \pm standard deviation of maximal volitional isometric contraction torque (N \cdot m/ kg) at pre-day 1, post-day 1, pre-day 2, and post-day 2.

Group	Pre Day 1	Post Day 1	Day 2
mTENS	1.75 \pm 0.52	1.92 \pm 0.44	2.15 \pm 0.67
sTENS	1.65 \pm 0.38	1.84 \pm 0.54	1.79 \pm 0.65
Sham	1.86 \pm 0.62	1.98 \pm 0.52	1.68 \pm 0.55

JPS

Constant Error

There was no significant time-by-group interaction effect for constant error ($F_{[6, 63]}=0.52$; $p=0.59$; $\eta_p^2=0.05$). There was a significant main effect of time ($F_{[3, 6]}=3.51$; $p=0.02$; $\eta_p^2=0.14$). There was no significant main effect of group ($F_{[1, 21]}=12.72$; $p=0.81$; $\eta_p^2=0.37$). Fisher's LSD comparisons revealed significant differences between pre-day 1 and post-day2 ($p=0.03$, Table 5). Significant differences were also observed between post-day 1 and post-day2 ($p=0.03$, Table 5).

Absolute Error

There was no significant interaction effect of time by group for absolute error ($F_{[6, 63]}=0.56$; $p=0.76$; $\eta_p^2=0.04$). There was no significant main effect of time ($F_{[3, 6]}=3.51$; $p=0.02$; $\eta_p^2=0.14$). There was no significant main effect of group ($F_{[1, 21]}=12.72$; $p=0.81$; $\eta_p^2=0.37$).

Variable Error

There was no significant time-by-group interaction effect for variable error ($F_{[6, 63]}=0.56$; $p=0.76$; $\eta_p^2=0.05$). There was no significant main effect of time ($F_{[3, 6]}=2.61$; $p=0.06$; $\eta_p^2=0.11$). There was no significant main effect of group ($F_{[2, 21]}=0.15$; $p=0.86$; $\eta_p^2=0.01$).

Table 5: Mean \pm standard deviation of group JPS constant error (CE), absolute error (AE) and variable error (VE) at pre-day 1, post-day 1, pre-day 2, and post-day 2. Significance from Pre-day 1 is indicated by *.

Group	Time	CE	AE	VE
mTENS	Pre Day 1	-3.42 \pm 5.98	8.73 \pm 6.12	6.15 \pm 1.58
	Post Day 1	-3.92 \pm 8.03*	8.89 \pm 4.58	5.95 \pm 2.03
	Pre Day 2	-4.97 \pm 8.29*	9.47 \pm 5.45	7.08 \pm 2.05
	Post Day 2	-8.03 \pm 8.98*	11.05 \pm 6.51	6.86 \pm 2.74
sTENS	Pre Day 1	-2.18 \pm 4.75	8.10 \pm 2.68	5.99 \pm 1.42
	Post Day 1	-1.03 \pm 3.45*	7.47 \pm 2.10	4.21 \pm 4.83
	Pre Day 2	-6.04 \pm 6.38*	8.70 \pm 5.07	6.60 \pm 2.03
	Post Day 2	-5.53 \pm 7.78*	11.98 \pm 10.08	7.31 \pm 4.33
Sham	Pre Day 1	-2.75 \pm 6.15	8.09 \pm 3.43	6.48 \pm 2.34
	Post Day 1	-2.69 \pm 5.20*	7.18 \pm 2.54	6.00 \pm 1.32
	Pre Day 2	-3.79 \pm 5.39*	7.70 \pm 4.64	6.33 \pm 2.59
	Post Day 2	-4.56 \pm 7.07*	9.43 \pm 4.96	6.94 \pm 2.69

Chapter 5: Discussion

Eccentric muscle damage has previously been established to cause pain, muscle stiffness and neuromuscular dysfunction.^{8,9,10} This study investigated whether the effects of EIMD could be attenuated via electrical stimulation and performance could be improved during a proprioceptive test. Pain increased significantly causing subjects to consistently undershoot JPS angles with time. Although pain increased significantly after the eccentric exercise, there were no reductions in pain after electrical stimulation. There were also no improvements in JPS error after the electrical stimulation, as evident by the lack of changes in variable and absolute error. Because pain increased, it is interesting that there were only decrements in constant error, which could be due to a subject bias towards shorter knee angles. Our results potentially lend support that neither motor-level nor sensory-level TENS have an effect on improving proprioception or pain following EIMD.

Exercise Induced Muscle Damage

Pain increased from baseline after the EIMD protocol, but no changes occurred to muscle circumference nor muscle force during the MVIC. The pain our subjects expressed after the EIMD led us to expect marked swelling and reduced strength, which has been demonstrated in other EIMD protocols.^{8,9,10,13,16} Given the results of our study it appears that the presence of pain lends support to the hypothesis that true EIMD may be able to occur while absent of these other symptoms (i.e. swelling, strength deficits). It is probable that the EIMD caused myofibril tearing, consistent with this type of exercise.⁸ The generation of pain after EIMD occurs from a sequela of events originating from structural damage to myofibrils that impair excitation-contraction coupling and causes a local to potentially systemic inflammatory response.⁸ The inflammatory products circulate around the area of damage, activating nociceptors and contributing to the DOMS experienced after

this insult. Thus, we suspect the increased pain is a strong support of EIMD. There were notable effect sizes indicating the EIMD was close to causing significant changes in the indirect measures, such as a medium effect size of time on thigh circumference increasing among the groups from Pre-Day 1 and Pre-Day 2. There was also a large effect size of time in PDSS, as each group's soreness increased significantly from Pre-Day 1 and Post-Day 2.

We posit that the lack of swelling and force deficits in this investigation do not rule out the probability of myofibril tearing. Increased thigh swelling would be indicative of inflammatory products circulating in the muscle area due to the eccentric damage, while strength loss after eccentric exercise has been attributed to the disruption of contractile proteins within the sarcomere, limiting the ability for the muscle to generate force during excitation-contraction coupling,⁸ or neuromuscular deficits attenuating motor unit recruitment. Although thigh circumference did not increase significantly, we can't rule out the presence of this inflammation as our measurement tool may not have been sensitive enough to detect this. Other measures such as fMRI and pQCT have accurately captured changes to muscle volume and cross sectional area following different interventions.^{50, 74, 75} The use of the dominant leg possibly reduced the ability for each subject to sustain a greater amount of muscle damage, as studies using the non-dominant leg to test MVIC reported significant increases in pain.^{13, 16} The lack of reductions to muscle force could also be explained by neural mechanisms where greater motor unit recruitment was facilitated by the eccentric exercise so higher agonist muscle activation occurred. Furthermore, subjects could have potentially become more accustomed to the dynamometer and more efficiently generated force during the MVIC. Thus, the generation of pain alone after EIMD can hint at sufficient muscle damage after eccentric exercise.

The timing of our other measurements in relation to the EIMD protocol may have been a variable of interest. Several studies report the greatest decrements between 12-36 after EIMD.^{13, 20, 49} Since pain was significantly higher after the EIMD, we can be sure immediately to 48hrs after the protocol is an adequate time to measure pain. It is worth exploring whether we tested MVIC at the most optimal angle, as decreases in quadriceps muscle activity as the knee angle increases have been reported.⁷⁶ Furthermore, it is likely that differences in each subjects' contraction strategies affected MVIC and EIMD,⁷⁷ as many expressed soreness at different areas of their leg. Thigh circumference measurements have been reported to have low reliability to lower leg measurements with spring tape,⁷⁸ it is worthwhile exploring other approaches to measure girth after EIMD. We often helped subjects start each EIMD repetition since their leg was too far extended and could not generate enough force to make the dynamometer move. While we deemed this necessary to only get each subject moving, ideally, no assistance was given during the mid-range of motion, however, there is still potential that during the first half second of a rep each subject's susceptible damage could have been reduced.

Joint Position Sense

Each subject's JPS was tested before and after TENS and again in this pattern 48 hours later. There was a significant decrease in CE over time, in which the negative CE became more negative, which indicates pain is causing subjects to consistently undershoot target angles. Thus, proprioception during this test was reduced, which is consistent with a bevy of other literature in EIMD models^{16, 20} and injury models.^{17, 18} However, no changes were observed for AE or VE, suggesting that the absolute magnitude of proprioceptive deficits or proprioception was not recovered after the administration of mTENS and sTENS, as there were no changes in either JPS errors.

The results of our study are consistent with other literature where pain experienced after EIMD decreased sensorimotor performance by causing subjects to underestimate joint angles.^{13, 16, 60} This is implicated to occur via dysfunction to peripheral mechanoreceptor and muscle spindle sensitivity during JPS.⁷⁹ The mechanism as to how this occurs likely lies within the differences between mechanoreceptors, muscle spindles and nociceptors and how their inputs modulate central processing of proprioception. Large diameter proprioceptive neurons have been reported to alter cutaneous input after eccentric exercise potentially via increased feedback.^{80, 81} Thus, the undershooting we report in our subjects is likely caused via increased sensitivity from muscle spindles from the pain and leads to neuromuscular dysfunction. The reduced performance for CE during the JPS may indicate how the function of muscle spindles and mechanoreceptors in the joint may be altered after eccentric exercise. The consistent undershooting that occurred in our subjects may have resulted from each subject's own intrinsic feedback being changed perhaps due to pain during the JPS. Each subject consistently pressing the button when their leg was under-extended could highlight the dysfunction to muscle spindles, as it appears they perceive their leg may be less extended. Since muscle spindles provide the primary amount of information during muscle lengthening, our study suggests the pain is causing discrimination of sensory processing during the JPS and causing subjects to perceive their leg at a shorter angle. Therefore, the reductions to JPS may be secondary to the changes at the input from the muscle spindle.

AE is indicative of the magnitude of error between the target angle and identified angle, whereas constant error is similar to AE but it indicates directional error, thus highlighting higher and lower scores. VE indicates the deviation and thus variability of multiple identified angles compared to the reference. No changes occurring in JPS VE indicates the consistency that subjects had when

sensing their leg during each of the JPS trials did not change. Likewise the lack of changes to AE indicates the precision subjects maintained during the JPS trials. AE would have needed to be more often further from the reference angle in order to cause significance in this measure. So while CE did decrease subjects may not have been less accurate, but consistently missing in the same direction. Our findings may indicate the pain from the eccentric exercise, while causing subjects to underestimate joint angles, was not effective in changing their proprioception compared to all of JPS trials as the magnitude nor variability of mismatch between the identified angle and reference angle were not significantly high enough to change AE and between JPS trials. This may be due to the magnitude of muscle damage as muscle spindle activity has been reported to be sensitized due to inflammatory products in the joint after injections ⁶⁴ and fatiguing exercise. ⁸¹ Therefore this might explain the one-sided changes to JPS as the muscle spindle activity was altered enough to causing undershooting, but not high enough to cause significantly higher error between or within the trials.

The lack of variable and absolute differences occurring during the JPS could have resulted from subjects employing greater focus to their legs during the test. This phenomenon has been observed in studies measuring the effects of ACL reconstruction on proprioception. By using EIMD as a potential model of acute effects of injuries, ¹⁵ we aimed to measure changes in proprioception by using the EIMD protocol to reduce proprioception during the JPS. Utilizing neuroimaging techniques, Baumeister et al ⁵ described the differences in JPS between subjects who underwent ACL reconstruction surgery compared to controls. They reported reconstruction subjects performed worse during the JPS task while employing greater theta-power, which is indicative of higher focus during complex tasks. They also report lower alpha-power that indicates subjects are resourcing neural focus from somatosensory regions to perform the task better. Since our JPS task required high

focus, as we encouraged subjects to attempt to focus on the angle their leg was moved to when pushing the button, it is likely our subjects were performing under similar conditions, which may be why no differences occurred in variable error.

We attempted to minimize the occurrence of a learning effect, by randomizing speeds and angles of each movement, while effective, this could have increased task complexity. It is also interesting the pain subjects experienced did not deter their variable error, as numerous studies have reported how pain after eccentric exercise has a profound impact on proprioception.^{10, 82, 83, 84} It is plausible JPS variable error was unchanged due to the timing of our measurement. There is potential that pain from EIMD could have had a greater effect earlier on, perhaps 12-36 hours after EIMD. This is the implication other studies have drawn, as pain was reported to peak during this time.^{10, 16} Furthermore, it is likely that muscle metabolites are still concentrated, potentially altering proprioception of mechanoreceptors in the joint. Furthermore, there could be a necessary delay from these inflammatory products to develop and reduce sensorimotor function by activating nociceptors.^{11, 13} Thus, it is worth exploring testing the effects of pain on JPS and reducing pain earlier. Our study could have benefitted from an active measure of JPS where subjects can freely move their leg within the sagittal plane to an angle of target and experience slight pain by actively contracting muscles within the range of motion. Paschalis et al had procedures like this, where subjects moved their leg to an angle and held it for a few seconds before and after eccentric exercise, which yielded significant decreases to proprioception.

Transcutaneous Electrical Nerve Stimulation

Pain is relayed to the dorsal horn of the spinal cord via A- δ fibers and C-fibers along the spinothalamic tract,³¹ while sensory information travels along the dorsal medial lemniscal pathway

and then converges at the spinal cord.⁸⁵ Although the pathways between nociception and proprioception are different, they meet at the dorsal horn of the spinal cord.^{85,86} sTENS capitalizes on this interaction by stimulating large diameter fibers to activate the inhibitory interneurons and gate the transmission of pain. Thus, decreasing the probability for pain to be received from small diameter fibers carried from nociceptors, as the inhibitory interneurons hyperpolarize neurons downstream of the pathway. The gate control theory states that stimulating larger diameter neuronal fibers will disallow nociceptive information to come through the gate and thus reduce the perception of pain by closing the gate before pain can be relayed to the spinal cord and thalamus.^{1,31} Typically neurons in the spinal cord fire at their own rate, but when combined with pain, activity of inhibitory interneurons is reduced to allow nociceptive input toward the brain.¹ mTENS acts peripherally by stimulating small diameter A- δ fibers, initiating extra-segmental descending pathways of pain inhibition originating from the midbrain periaqueductal grey and rostral ventromedial medulla.^{1,67} This mechanism is disparate to that of sTENS as high frequency TENS activates large diameter A- β fibers to inhibit second order neuron firing at the spinal cord and cease nociceptive transmission.^{1,68}

We hypothesized that following the eccentric exercise, TENS would improve proprioception by decreasing constant, absolute and variable errors secondary to decreases in pain. However, there was no effect on pain from mTENS or sTENS after the eccentric muscle damage, nor 48 hours later. Furthermore JPS error was not reduced by mTENS nor sTENS, (table 6). This was interesting as we expected our intervention to improve JPS by reducing pain relayed to the nervous system and allow for sensorimotor function to be maintained after EIMD.²²⁻²⁴ Our results may indicate how different types of pain are reduced after eccentric exercise. For instance sTENS would work to reduce mechanical pain, occurring from free nerve endings at the site of muscle damage, while mTENS works to reduce chemical pain from nociceptive constituents such as bradykinin, prostaglandin and

histamines, but also taps into reducing mechanical pain as well since it causes muscle contractions that can stimulate A- β fibers.^{1, 68} Therefore the lack of reduction from either type of TENS could indicate the difference in pain each subject experienced. Furthermore the use of mTENS after EIMD could have caused more pain, as this elicits further contraction of the already exercised muscle. Additionally the lack of reductions to pain could be explained by other factors in our study. Denegar et al., used an exercise protocol consisting of eccentric and concentric contractions to induce muscle damage to the biceps brachii in all female subjects.²⁴ While our study caused significant pain similar to theirs, it is likely the quadriceps muscle group was less likely to be damaged and thus have lowered effects of pain from TENS afterwards. Lastly our study used a 10cm scale, which subjects reported their pain on, whereas Denegar et al., used a 24cm scale, thus presenting a ceiling from which our subjects could have reported reductions to pain after TENS.

Our results indicate the need to tease out the effects of TENS on different types of pain. EIMD is a model to induce pain, however this can be mechanical, occurring with movement, or chemical, occurring at rest.^{11, 12} Our EIMD induced significant pain that was measured with an active movement, thus would indicate mechanical pain. However, sTENS would reduce mechanical pain ensued from the sensory response to movement, while mTENS may have the ability to reduce mechanical and chemical pain as it reduces the perception to pain from muscle contraction and limits chemical nociception.^{67, 68} Therefore, measuring the effects of both types of TENS on pain in both states, e.g., resting and moving or damaged vs. non-damaged leg would identify the type of pain that is occurring and what may be more effective.

Chapter 6: Conclusion

Pain is present after many musculoskeletal injuries and EIMD protocols. Although our EIMD protocol did not cause swelling and force reductions, due to the increase in pain, reduction to constant error during the JPS and other notable effect sizes, we can confirm our protocol was effective in causing muscle damage and sensorimotor dysfunction similar to other protocols. Due to TENS having no effect on pain nor proprioception, our study may lend support to TENS lacking evidence in reducing pain to improve JPS after eccentric exercise.

Clinician's should recognize the proprioceptive reduction after eccentric exercise as this could raise the chance for injury. Moreover, exploring alternative analgesics to relieve pain while improving proprioception is warranted. While TENS is a feasible device to use, currently there is ambiguity in its overall effectiveness. Our study highlights the need for future studies to be conducted to delineate the role of TENS between different pain states post-eccentric exercise. Utilizing resting vs. acting measures of pain after eccentric exercise might indicate the effectiveness of TENS on that type of pain.

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Vita

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