Corticomotor excitability and proprioceptive acuity in chronic lateral epicondylalgia

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by

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List of abbreviations

AA: affected arm
ACL: anterior cruciate ligament
CNS: central nervous system
DASH: Disabilities of arm shoulder and hand
ECR: extensor carpi radialis
EMG: electromyography
FCR: flexor carpi radialis
GPT: grooved pegboard test
LE: Lateral epicondylagia
MANOVA: multivariate analysis of variance
MEG: magnetoencephalogram
MEP: motor-evoked potential
MVC: maximal voluntary contraction
NSAP: non specific arm pain
rMT: resting motor threshold
S/R: stimulus-response
S_c: comparison weight
SI: primary somatosensory cortex
SP: silent period
S_w: standard weight
TMS: transcranial magnetic stimulation
UA: unaffected arm
Abstract

Chronic lateral epicondylalgia (LE) is a common musculoskeletal condition which has been associated with the presence of distinct local sensorimotor abnormalities. Despite this, little is known about central motor system function and forearm/wrist kinesthetic acuity in cases of chronic LE. The purpose of this pilot study was to determine whether there are adaptive neurophysiological changes occurring at the corticomotor level in individuals presenting with chronic unilateral lateral epicondylalgia, and whether the same individuals present deficits in proprioceptive acuity for weight discrimination and manual dexterity. METHODS: For this descriptive, case-controlled study, 14 individuals with chronic LE and 16 age- and gender-matched controls were recruited. LE-related disability was measured with the quickDASH questionnaire and proprioceptive acuity was estimated by way of a weight discrimination task. The Grooved Pegboard Test was used to derive an index of manual dexterity and transcranial magnetic stimulation was used to assess four indices of corticomotor excitability in wrist extensor muscles. RESULTS: Proprioceptive acuity was decreased in the affected arms of LE participants (p=0.001). There were no differences in manual dexterity or indices of corticomotor excitability between arms (p > 0.05) for both groups, but manual dexterity of each the affected and unaffected arms was correlated with resting corticomotor thresholds (p=0.0001 and p=0.04, respectively) a relationship which was not found in the control group. DISCUSSION: Proprioceptive acuity was deteriorated in our sample of chronic LE. Though the clinical significance in this population is unknown, it is hypothesized that such deficits may hamper force perception during functional activities. The relationships existing bilaterally between manual dexterity and motor thresholds suggest that “crossed” modulation of corticomotor excitability may be further influenced by the presence of musculoskeletal dysfunction and/or chronic musculoskeletal pain. While mechanisms responsible for such changes are unclear, these findings merit confirmation in larger patient samples.
Introduction

An undeniable consequence of the industrialization of modern society has been the toll placed on the health of its labour force. Compounded by the prevalence of prolonged exposure to computer keyboard-based work, the incidence of work-related injury has led to the creation of a family of disorders known as "repetitive strain injuries". In the U.S. in 2001, 65% of newly reported occupational illnesses were attributed to exposure to repetitive movement (Bureau of Labor Statistics News, United States Department of Labor). Along with carpal tunnel syndrome and DeQuervain's tenosynovitis, forearm muscle strain is among the most reported work-related musculoskeletal lesions of the upper extremity (Barr & Barbe, 2002). More importantly, conditions of the wrist and hand cause of the greatest loss of work productivity and wages (Barr, Barbe, & Clark, 2004). Therefore, optimising care for forearm muscle strain is of clear significance in the matter of occupational health and productivity.

Lateral epicondylalgia (LE), or its lay-term tennis elbow, is a soft tissue musculoskeletal disorder affecting primarily the tendinous origin of the wrist and finger extensors at the elbow. The condition's association to tennis has its origins in its first description as observed in players of English lawn tennis (Morris, 1882). The layperson therefore might be deceived as to the cause of "tennis elbow" where in fact, only a minority of persons affected with lateral elbow pain actually plays tennis. As mentioned above, its significance in society is largely related to occupational disease.

Yet, despite decades of research on this injury, effective management of this condition remains elusive. Though chronic LE presents a reasonably uncomplicated clinical picture, this is overshadowed by a lack of understanding of its etiology and a dearth in clinical research as to
how to best treat it (L. Bisset, Paungmali, Vicenzino, & Beller, 2005; Ljung, Forsgren, & Friden, 1999; Vicenzino, 2003). The importance of an inflammatory component in the pathogenesis has been rejected by numerous histological studies of extensor tendons of people with chronic LE. Rather, generally accepted is an “overuse” model where mechanical overloading of the tendon causes damage beyond regenerative capacities of the tissue. Furthermore, evidence now suggests that this tissue degeneration in chronic LE is associated with a “sensitized state”, where alterations in central pain pathways lead to amplification of nociceptive inputs. While pain is certainly of primary importance in the management of patients with LE, very few studies have actually looked at how persistent pain and dysfunction could alter sensorimotor processes in persons presenting with chronic LE. No research to date has examined the state of the central motor system in cases of LE, and thus, little is known about how changes in corticomotor excitability could affect the clinical presentation of this condition.
Chapter 1. Review of the literature
1.1. Lateral epicondylalgia: Definition and clinical manifestations

In a larger context, the economic and emotional impact of chronic musculoskeletal pain disorders may be measured in terms of lost productivity and human suffering (Capra, 2004). As demonstrated above, the impact of upper extremity injury on occupational health is clear, and LE is a frequent musculoskeletal condition for which treatment is sought. In the U.S., seven of every 1000 general practitioner visits are for LE. This condition typically affects the common origin of the wrist extensors and particularly the extensor carpi radialis brevis muscle (Alfredson, 2000). This muscle is considered the most active wrist extensor during grasping activities (Neumann, 2002). Specific risk factors thought to be associated with the development of LE are: repeated movements of resisted pronation and supination of the forearm, repetitive or forceful grasping, frequent use of pinch grip, and lifting with the palm facing downward (Coonrad & Hooper, 1973). Clinically, LE is diagnosed on the basis of pain symptoms arising from palpation of the lateral epicondyle of the elbow or pain elicited during gripping activities or during resisted wrist or finger extension (Vicenzino, 2003). The impact of LE in terms of disability can be quite dramatic with the condition leading to limitations in daily activities, domestic tasks, and occupational productivity (Bisset et al., 2005).

The prevalence of LE in the U.S. is estimated between 1-3% (Bisset et al., 2006), with the prevalence increasing up to 15% in at risk populations, such as industry workers engaged in repetitive manual tasks (i.e. time pressured, assembly-line type workers) or regular tennis players (Vicenzino, 2003). In fact, 50% of all tennis players experience some type of elbow pain, and 75-80% of these elbow complaints are attributed to LE (Bisset et al., 2005). This condition typically affects those between 35 to 54 years of age and is most often a self-limiting
condition, with an average duration of six months to two years, though most patients (89%) usually recover within one year (Smidt et al., 2002). It should be noted, however, that persistent and recurrent symptoms associated with LE may occur in up to 56% of cases with the interruption of medical care possibly leading to an underestimation of the prevalence of chronic LE (Clarke & Woodland, 1975). There appears to be no difference in incidence between genders, but LE is likely more common in Caucasians (Coonrad & Hooper, 1973).

Conservative physiotherapy management for LE often includes education, thermotherapy, electro-modalities, stretching and strengthening exercises, and manual therapy. Yet, available evidence for the effectiveness of conservative interventions is limited, with the results showing little benefit compared to a “wait and see” approach (Bisset et al., 2005; Smidt et al., 2002). This may, at least in part, be attributed to the strategies that drive conservative management of chronic LE where interventions are aimed at reducing presumed local tissue inflammation to relieve pain. Accordingly, non-steroidal and corticosteroidal anti-inflammatory agents are popular treatment strategies for LE (Khan & Cook, 2000). Yet, there is little evidence from biopsies of affected muscle tissues to support the presence of an on-going chronic inflammation, as an etiological mechanism for LE (Alfredson, 2000; Khan & Cook, 2000; Ljung et al., 1999). Rather, it appears that the pain in chronic cases of LE is the result of local connective tissue degeneration and not the consequence of a persistent inflammatory process. In fact, there is reason to believe that even if an inflammatory phase does exist in the acute period of the condition, it is very brief (Khan & Cook, 2000). Thus, evidence suggests a rather different pathophysiology than previously thought.

This has led to debate in regards to the choice of nomenclature in identifying the chronic form of this condition; “tennis elbow” is anatomically vague and implies the practice of tennis in
its etiology which is certainly not representative of many encountered cases (Stasinopoulos & Johnson, 2006). Furthermore all terms including the suffix “itis” such as “tendonitis” or “epicondylitis” imply an inflammatory process and should be avoided unless obtained histological evidence legitimizes their use. Consensus on the new terminology to be employed seem to converge on either “lateral elbow tendinopathy” which emphasizes the degenerative process and over-use nature of the condition, or “lateral epicondylalgia” which emphasizes the nociceptive process involved but has been criticized as it does not discriminate between manifestations similar in presentation such as radial nerve or cervical nerve root entrapment, for example (Stasinopoulos & Johnson, 2006). However, proponents of the use of “lateral epicondylalgia” argue that the multiple etiological factors involved in this condition justify a more comprehensive consideration in the diagnostic process (Vicenzino & Wright, 1996). This latter term has been embraced by several rehabilitation journals and, as such, shall encompass the described condition and all synonyms in the present work.

1.2. Peripheral & central sensitization in chronic pain

Pain associated with tissue injury and inflammation leads to sensitization of the nociceptive system, resulting in both primary and secondary sensitization (Sluka & Rees, 1997; Woolf & Decosterd, 1999). Primary, or peripheral sensitization, arises when high threshold nociceptive fibers are excited by chemicals (i.e. bradykinine, serotonin, and prostaglandin E2) released by injured tissues. These algesic substances rapidly interact with receptors located in free nerve endings, leading to reduced threshold for activation and increased response to stimulation (Ljung et al., 1999). Clinically, sensitized peripheral nociceptors are responsible for
producing the exaggerated local pain response to noxious stimuli – a phenomenon known as “primary hyperalgesia” (Sluka & Rees, 1997). By comparison, secondary hyperalgesia results from central sensitization following tissue injury as a result of excitability changes within the spinal cord (Woolf & Decosterd, 1999). Central sensitization refers to changes affecting second order neurons activated by primary nociceptors within the dorsal horn (Sluka & Rees, 1997). The process of central sensitization leads not only to secondary hyperalgesia but also to mechanical allodynia¹ (Sluka & Rees, 1997).

Since sensitization mechanisms are believed to be important in the development of chronic pain conditions (Capra, 2004; Wilder-Smith, Tassonyi, & Arendt-Nielsen, 2002), their involvement in chronic LE is not surprising. As discussed above, muscle hyperalgesia and allodynia are reported as manifestations of nociceptive sensitization (Capra, 2004) and there is evidence to suggest their implication in chronic LE. Slater et al. (2005) have reported that, in comparison with healthy controls², patients with unilateral chronic LE demonstrate hyperalgesia to pressure over the common extensor origin, and quicker pain onset, larger referred pain areas and longer duration of pain induced by hypertonic saline injected in the affected common extensor origin. Leffler and colleagues (2000) have also shown lowered thresholds at rest to noxious heat in the area of pain referral (distal forearm) in cases of sub-acute/chronic LE. In sum, an alternative etiology of chronic LE is emerging where the pain mechanism involves primary and secondary hyperalgesia resulting from peripheral and central sensitization of nociceptive signals (Alfredson, 2000; Slater, Arendt-Nielsen, Wright, & Graven-Nielsen, 2005; Sluka & Rees, 1997; Wright, Thurnwald, O'Callaghan, Smith, & Vicenzino, 1994).

¹ The sensation of pain in response to non-noxious stimuli.
² Controls had exercise-induced delayed onset muscle pain.
1.3. Nociception and central somatosensory plasticity

There is now considerable evidence that motor and somatic maps in the CNS are continuously modulated in response to sensory inflow, including when tissues are injured (Chen, 2002). Cortical activation in response to pain occurs primarily in the primary and secondary somatosensory areas, as well as the anterior cingulate and insular cortices (Sluka & Rees, 1997). The effect of pain on the somatosensory cortex has been reported under experimental conditions, as early reports (Melzack & Casey, 1968) of changes in excitability of the sensory cortex during nociceptive discharges first suggested. For instance, experimentally induced pain in the thumb in healthy humans has been shown to cause a rapid spatial shift (but not extension) of the cortical somatosensory representations of the neighboring fingers and lower lip on magnetoencephalography (MEG) (Soros et al., 2001). This suggests that the presence of pain could be a critical factor in the disinhibition of overlapping synapses in the primary somatosensory (S1) cortex; similar disinhibition of latent neuron assemblies has been associated with reorganizational plasticity in the S1 cortex in monkeys (Soros et al., 2001).

The idea that nociceptive inflow associated with peripheral tissue injuries may modify somatic sensory maps is not new (Wilder-Smith et al., 2002). Yet, little is known about the effects of chronic musculoskeletal pain on cortical sensory maps. Evidence from positron emission tomography indicates that rheumatoid arthritis patients have reduced frontal and cingulate cortical response to noxious heat stimulation of the hand (Jones & Derbyshire, 1997). Research on persons affected with focal unilateral hand dystonia, a specific repetitive strain disorder, demonstrates a difference in the location of the hand representation in S1 cortex and lower amplitudes of somatosensory evoked fields on MEG than healthy controls. Furthermore,
findings of deficits in the orderly representation of the digits in the S1 cortex were found bilaterally, indicating a degradation of the sensory map of the hand (Byl, Nagarajan, Merzenich, Roberts, & McKenzie, 2002). Similar results have been reported in patients affected with unilateral carpal tunnel syndrome in whom changes in cortical hand somatotopy in S1 cortex was related to self-referred assessment of symptoms and hand disability in daily activities (Tecchio, Padua, Aprile, & Rossini, 2002). The latter results confirm earlier findings in primates which demonstrated the neural consequences of movement repetition. Byl and colleagues (1996) trained owl monkeys in the execution of highly repetitive hand movements. After little more than a month of training, the subjects demonstrated a significant deterioration of hand motor control which was associated with a degradation of somatotopic representation of the hand (Byl, Merzenich, & Jenkins, 1996). Though the authors did not consider the animals’ pain as a variable, motor behaviour consistent with limb protection mechanisms were observed in the subjects. Surprisingly, no histological evidence of acute inflammation in the distal upper limb was found.

Other research has argued in favour of central sensitization occurring with musculoskeletal conditions on the basis of bilateral alterations in sensory function in otherwise unilateral lesions. For example, Greening (Greening, Lynn, & Leary, 2003) compared sensory and autonomic nervous system function in hands3 of office workers diagnosed with non-specific arm pain (NSAP)4, asymptomatic office workers and healthy controls. Their results demonstrated measurable bilateral dysfunction in the local vibration detection thresholds and autonomic functions examined in the NSAP group. The presence of a deficit in vibration

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3 Assumedly unilateral symptoms, as it is not specified in the article.
4 NSAP is a symptom-based diagnosis and, as the term implies, is used in the presence of diffuse regional arm symptoms and in the absence of objective physical signs. It is therefore an exclusion-based diagnosis and infers no precise tissue-based etiology.
detection suggests a concurrent loss in proprioceptive function. In a study of unilateral chronic LE previously discussed (see above), Slater et al. (2005) reported significant bilateral hyperalgesia in the common extensor origin in patients with unilateral chronic LE in comparison with healthy controls.

In summary, there is now clear evidence that the nociceptive system exhibits considerable plasticity in response to peripheral tissue injuries. Where it is has been suggested that central mechanisms underlie occupational muscle pain and injury (Edwards, 1988), neuroplastic changes are now increasingly recognized as critical factors behind the development of chronic musculoskeletal pain conditions.

1.4. Neurophysiological impact of musculoskeletal injuries and pain on motor excitability

The refinement of methods of measuring neurophysiological properties in humans has enabled the study of changes in motor system function following joint and muscle injuries. The development and use of transcranial magnetic stimulation (TMS) over the last twenty years has provided a large contribution in the study of central nervous system function and representational cortical plasticity. The procedure, in which excitable cortical neurons are depolarized non-invasively via electro-magnetic induction by a coil over the scalp, enables the study of regional cortical reorganization rather than synaptic plasticity at a neuronal level (Siebner & Rothwell, 2003). A single pulse of TMS over the motor cortex results in a succession of direct and indirect descending volleys through the corticospinal tract (Abbruzzese, 2002). The summation of these volleys can be measured by electromyography (EMG) over the contralateral muscles as responses known as motor evoked potentials (MEPs). The neurophysiological responsiveness to
TMS can thus be measured under various conditions and motor excitability inferred from peripheral MEP characteristics (Abbruzzese, 2002).

The applications of these methods have enabled investigation of changes in corticomotor excitability in cases of musculoskeletal injury. For example, the significant deficit in quadriceps muscle contraction following anterior cruciate ligament (ACL) injury in the knee is readily acknowledged by anyone familiar with the rehabilitation process of these individuals. Many studies have reported persistent quadriceps weakness following ACL lesions, with suggested mechanisms classically involving reflexive inhibition due to disrupted joint afference and/or joint effusion (Konishi, Fukubayashi, & Takeshita, 2002). However, evidence suggests that additional mechanisms beyond reflex-mediated inhibition must be considered (Héraux & Tremblay, 2006). For instance, Urbach (Urbach, Nebelung, Weiler, & Awiszus, 1999) examined the extent of quadriceps activation during maximal voluntary contraction (MVC) in patients with confirmed ACL rupture using the interpolated twitch technique. Compared to controls, patients with sub-acute and chronic ACL rupture exhibited mild, but significant, deficits in voluntary contraction in both the injured and non-injured knees to the same degree. To explain this bilateral deficit associated with a unilateral lesion, the authors suggested inhibition of spinal motoneurons by descending pathways receiving altered afferent inflow, pointing to the importance of central mechanisms in the modulation of descending motor commands in the presence of chronic musculoskeletal pathology. Recent experimental evidence supports this assertion, at least in conditions of experimentally-induced tonic pain. Farina et al. (2005) have demonstrated the action of a central inhibitory motor control mechanism associated with tonic muscle pain using hypertonic saline injections in the tibialis anterior muscle. They demonstrated a decrease in voluntary EMG activation to the muscle following bolus injection, yet the M-wave to the same
muscle was unaffected (Farina, Arendt-Nielsen, & Graven-Nielsen, 2005). This work confirms an earlier report by the same authors in which motor unit firing rate was shown to decrease following bolus injection, yet no change in motor unit conduction velocity appeared (Farina, Arendt-Nielsen, Merletti, & Graven-Nielsen, 2004). Le Pera et al. (2001) have reported that acute experimental pain in the first dorsal intersossei and abductor digiti minimi muscles of the hand resulted in a rapid decrease of MEPs measured in the latter muscle, and this shortly followed by a reduction in the spinal H-reflex. The authors contend that the initial absence of changes in excitability at the spinal level suggests cortical (or at least supraspinal) origins of these MEP changes and that spinal mechanisms likely emerge shortly after as shown by H-reflex depression. These effects were not present following subcutaneous injection in the same area, which again suggests a specific role for the muscular nociceptors, this time to incur changes in central motor excitability (Le Pera et al., 2001). The mechanisms of such alterations in central motor drive are not clear, but it is suggested that reflex inhibition via activity of small diameter muscle afferents may be involved (Farina et al., 2004).

In regards to corticomotor effects of chronic pain, TMS studies in intact nervous systems have shown that individuals diagnosed with unilateral complex regional pain syndrome type 1 of the hand demonstrate a significant reduction of intracortical inhibition in both sensorimotor cortices, and that the presence of allodynia significantly decreased motor thresholds over the cortex contralateral to the affected hand (Schwenkreis et al., 2003). Similar results on cortical excitability have been reported in fibromyalgia and rheumatoid arthritis, suggesting that common changes in the central motor system are likely caused by chronic pain processing, and are not condition-specific (Salerno et al., 2000). Research on individuals with chronic unilateral patellofemoral pain has demonstrated an increase in MEP size to the quadriceps of the affected knee.
compared to the unaffected limb, despite a significant reduction in M-wave and stretch reflex to the same muscle (On, Uludag, Taskiran, & Ertekin, 2004). This result, indicating MEP facilitation in muscles proximal to injury, is similar to research demonstrating increased MEP recruitment in the hand immediately following upper limb immobilization (Zanette, Manganotti, Fiaschi, & Tamburin, 2004) with both studies demonstrating no corresponding increase in measures of spinal excitability. Along the same lines, Héroux & Tremblay (2006) reported a significant decrease in resting motor thresholds of the affected quadriceps in individuals with chronic ACL-deficient knees. Therefore, it appears that sensorimotor restriction, either due to immobilization or the presence of musculoskeletal dysfunction tends to increase corticomotor excitability. This contrasts with studies on acute experimental pain discussed above showing a decrease in cortical and spinal motor excitability in painful muscles (Farina et al., 2004; Farina et al., 2005; Le Pera et al., 2001). Recently, however, Del Santo et al. (2007) have shown that experimental muscle pain may also lead to an increase in motor excitability during contraction. In a TMS study, they demonstrated that if subjects are instructed to maintain constant-force with a painful (saline-induced) muscle, MEP and EMG activity in the painful muscle increased in comparison to no-pain condition. The authors suggested that this increase in central motor drive was to compensate for the pain-induced reduction in the efficiency of descending activation (Del Santo, Gelli, Spidalieri, & Rossi, 2007). Thus, the net effect of muscle pain on cortical and spinal excitability may vary depending on the testing conditions (e.g., resting vs. active states) and also on the type of pain (experimentally acute vs. chronic clinical pain).

In summary, pain and sensorimotor restriction associated with musculoskeletal injuries appear to have profound modulating influences on motor excitability both at the cortical and spinal levels. At the present time, however, it remains to be determined whether corticomotor
excitability may be changed in patients affected by chronic LE.

1.5. Impacts of muscle injuries and chronic muscle pain on motor function and proprioception

Proprioceptive abilities generally encompass the usual kinesthetic senses, i.e. the sense of static joint position and movement detection, along with the lesser known sense of effort and weight perception (Gandevia, 1996). The first two kinesthetic senses are usually examined under passive or active conditions involving single joint mobilizations (Proske, Wise, & Gregory, 2000), while the sense of force and weight perception requires active lifting actions on the part of the subject (Gandevia, Smith, Crawford, Proske, & Taylor, 2006; Jones, 1986). Three kinds of sensory receptors are thought to be important for kinesthesia: muscle receptors, skin receptors and joint receptors (Proske et al., 2000). The sense of effort and weight perception is thought to involve integration of peripheral afferent information about muscle tension (Ib afferents) with central descending commands to generate a percept of force or heaviness associated with a muscular effort (Gandevia et al., 2006; Jones, 1986). The impact of musculoskeletal injury on proprioceptive abilities has been reported in various studies. For instance, following cervical whiplash injuries, Sterling et al. (Sterling, Jull, Vicenzino, Kenardy, & Darnell, 2003) found evidence of altered kinesthetic awareness measured by cervical joint position error in both acute and chronic cases in close association with pain persistence duration and indices of neck disability. Deficits in joint position sense following injury have also been reported at the ankle and knee (Issa & Sharma, 2006; Lee, Lin, & Huang, 2006; Lephart, Pincivero, & Rozzi, 1998), the shoulder (Warner, Lephart, & Fu, 1996; Wilk, Meister, & Andrews, 2002) and following anterior cruciate ligament (ACL) injury (Barret, 1991). A deficit in the ability to discriminate
weights in individuals with an ACL-deficient knee was also found, confirming the distinct proprioceptive deficits associated with this condition (Héroux & Tremblay, 2005). In interpreting their findings, Heroux & Tremblay suggested a neural basis for this deficit on the basis of a defective integration of peripherally driven “sense of muscle tension” and an internally generated “sense of effort”. One hypothesis given for the observed reduction in weight-discrimination accuracy is impaired appreciation of force signals related to partial failure of the calibration process of the descending motor commands (Héroux & Tremblay, 2005).

In regards to kinesthesia at the elbow, Proske and colleagues (Proske et al., 2003) have demonstrated the negative effects of delayed onset muscle soreness following eccentric biceps exercise on a force matching task in healthy subjects: subjects consistently overestimated the reference force. The authors attributed this error to the post exercise soreness in the indicator arm. This result is in line with those of Weerakkody et al. (2003) who used hypertonic saline injections in the biceps muscle to induce pain. In comparison to superficial pain induced by noxious heat, experimentally-induced muscle pain produced systematic force-matching errors between limbs. The authors concluded that muscle nociceptive afferents had specific detrimental effects on the ability of subjects to match forces at the elbow (Weerakkody, Percival, Canny, Morgan, & Proske, 2003). Other research has also demonstrated the effect of muscle nociception on proprioception. Using experimentally induced tonic pain in hand muscles, Rossi (Rossi et al., 2003) reported deficits in joint finger position sense. They suggested that pain could interfere with the processing of non-painful proprioceptive stimuli. However, recent data from LE patients remains less conclusive in regards to the existence of potential changes in elbow position sense. Juul-Kristensen and colleagues compared joint position sense at the elbows in a sample of LE patients and healthy control subjects. Though affected elbows demonstrated greater movement
detection thresholds as compared to the left\(^5\) elbows of control subjects, differences between affected and unaffected elbows were not significant (Juul-Kristensen, Lund, Hansen, Christensen & Danneskiold-Samsoe, 2008). In addition, no differences were noted in absolute joint position sense across any of the elbows tested. All conclusions considered, the absence of differences between joint position sense in affected and unaffected elbows of LE patients renders questionable the authors' assertions of an existing deficit in proprioception as indicated by the difference in movement detection thresholds alone. Further, no data was collected on the duration of the LE symptoms, precluding analysis of the effects of LE chronicity. Also in patients affected with LE, Bisset et al. (2006) has provided evidence of sensorimotor dysfunction in the form of changes in the kinematics of wrist motion during a gripping task. They observed a tendency in patients to adopt inefficient flexed wrist postures bilaterally during gripping. In addition, patients also exhibited slower reaction times and slower speed of movement during reaching tasks than healthy controls. The changes in the movement kinematics were consistent with previous observations by Pienimaki and colleagues (Pienimaki, Kauranen, & Vanharanta, 1997). Such changes in movement kinematics in patients with LE are also in line with changes reported in subjects with experimentally-induced muscle pain on a pointing task in terms of attenuated acceleration profiles, reduced movement amplitude and velocity, and prolonged reaction times (Ervilha, Arendt-Nielsen, Duarte, & Graven-Nielsen, 2004a). Recently, Skinner (Skinner & Curwin, 2007) has demonstrated highly significant deficits in fine motor performance on both the Purdue Peg Board and the Complete Manual Dexterity Test in individuals with unilateral chronic LE\(^6\). Further to this, an electromyographic study of forearm muscles during a simulated tennis backhand volley showed that patients with LE had decreased

\(^{5}\) No differences existed between affected LE elbows and right control elbows.

\(^{6}\) Bilateral effects were not investigated as only the affected upper limb was tested.
wrist extensor muscle activation just prior to ball impact followed by greater activation of the extensors at ball impact in comparison to controls (Kelly, Lombardo, Pink, Perry, & Giangarra, 1994). In the same study, high-speed cinematography demonstrated more internal rotation of the shoulder in the LE group, which was associated with an increase in wrist extension at ball impact - somewhat explaining the temporal wrist extensor activation patterns observed.

To summarize, there is evidence of deficits in proprioception and motor function in patients presenting with acute and chronic pain associated with musculoskeletal conditions including LE. Specifically, experimentally-induced muscle pain and pain associated with musculoskeletal injuries has been associated with deficits in joint position sense and other kinesthetic abilities (e.g., perception of force). Recent research involving LE patients has sought to demonstrate alterations in elbow joint position sense, though the conclusions drawn remain inconclusive regarding the actual breadth of changes across the continuum of proprioceptive function. As such, we still have little information as to how proprioception is affected in individuals presenting with LE.

1.6. Research Hypothesis

There is an emerging body of evidence linking neurophysiological dysfunction to musculoskeletal disorders given the inadequacy of the traditional structural/anatomically-based model of pain chronicity development. In the case of LE, chronic pain is now thought to reflect a “sensitized state”, where alterations in peripheral and central nociceptive transmission pathways lead to amplification of pain responses. In spite of this, factors involved in the etiology of chronic LE remain obscure, and there is a dearth of neurophysiological data regarding this
condition. Yet a body of evidence is emerging supporting the development of a model of lateral epicondylalgia that identifies impairment of the sensorimotor system as secondary or possibly pathogenic. It is hypothesized that when compared to healthy controls, measurable changes exist in central excitability and kinesthetic acuity in the forearms of persons affected with chronic LE.

1.7. Objectives of the present work

The primary objective of the present work is to determine whether there are adaptive neurophysiological changes occurring at the corticomotor level in individuals presenting with chronic unilateral lateral epicondylalgia. A secondary objective is to examine whether the same individuals present with deficits in proprioceptive acuity for weight discrimination, and manual dexterity in comparison with matched control subjects. Finally, we wish to determine whether there are any associations between changes in central excitability and clinical indices of arm function in people with chronic LE.

The results of this master's research are described in the following chapters in the form of two scientific articles. A general discussion of the main findings and significance is found in the final chapter.
Chapter 2. Association between corticomotor excitability indices and measures of impairment and disability in cases of chronic unilateral epicondylalgia

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Running Title: Corticomotor excitability and manual dexterity in chronic lateral epicondylalgia

Key words: lateral epicondylalgia, elbow, corticomotor excitability, motor threshold, transcranial magnetic stimulation, manual dexterity

This work served for the partial completion of Liam Dessureault’s Master of Science degree from the University of Ottawa in Human Kinetics.

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Abstract

Chronic lateral epicondylalgia (LE) is a common musculoskeletal condition of the upper extremity leading to unilateral pain and symptoms in the affected arm. In the present study, we used transcranial magnetic stimulation to examine whether there are adaptive changes occurring at the corticomotor level in chronic cases of unilateral LE. We were also interested in determining whether such changes could be related to impairment and disability measures of arm function. Participants (chronic LE, n=14; age-matched healthy controls, n=16) underwent TMS over the primary motor cortex to assess corticomotor excitability with the extensor carpi radialis (ECR) as the target muscle. Four indices of excitability were derived on each arm: resting motor threshold (rMT), stimulus-responses (S/R) curve, silent period and MEP facilitation. Disability and Impairment were measured with the quickDASH questionnaire and the Grooved Pegboard Test (GPT) for dexterity, respectively. A multivariate analysis of variance was performed to determine the impact of ARM (affected/unaffected; right/left), Gender, Disability and Dexterity on the corticomotor indices. The results showed no main effect of any of the factors on corticomotor indices with the exception of GPT scores, for which a significant trend was found (F=2.28, p=0.09). Further analysis revealed that GPT scores had a significant impact on rMT values in the LE group (F=12.2, p=0.002). In fact, GPT scores on the affected side were highly correlated with rMT (r²=0.76, p<0.01). A similar, though weaker relationship, was found on the unaffected side (r²=0.29, p=0.04). No such associations were found in healthy controls. These findings suggest that subtle changes affecting the core excitability of the wrist extensors motor representation in cases on chronic unilateral LE might be linked to clinically important change in arm function as reflected in dexterity tests. The mechanisms driving such changes between motor excitability and function in case of LE remain unclear and merit more attention in future work.
2.1. INTRODUCTION

Lateral epicondylalgia (LE) is a common condition of the upper extremity accounting for about seven out of 1000 general practitioner visits in the U.S. (Bisset et al., 2005). Considered a repetitive strain injury of the tendinous origin at the elbow of the wrist and/or finger extensors, the condition manifests itself as pain arising from palpation of the lateral epicondyle of the elbow or pain elicited during gripping actions or resisted wrist or finger extension (Vicenzino, 2003). Although the majority of LE cases present with a favorable evolution within a year after onset (De Smedt, De Jong, Van Leemput, Lieven, & Van Glabbeek, 2007; Smidt et al., 2002), recurrent, treatment-resistant bouts of LE symptoms are common (Bisset et al., 2005; Stasinopoulos & Johnson, 2006; Vicenzino & Wright, 1996) and approximately 50% of cases are left with persisting or recurring symptoms leading to chronicity (Clarke & Woodland, 1975). Thus, the actual prevalence of chronic LE is likely underestimated.

In addition, the etiology of LE remains poorly defined as the role of chronic inflammation has been questioned in recent years (Bisset et al., 2005; Slater et al., 2005; Vicenzino, 2003). Although local tissue degeneration is generally linked to the development of chronic tendinopathy (Ashe, McCauley, & Khan, 2004; Khan, Cook, Bonar, Harcourt, & Astrom, 1999; Kraushaar & Nirschl, 1999), recent evidence points to nociceptive sensitization as an etiological factor in the development of chronic LE (Alfredson, 2000; Sluka & Rees, 1997; Wright et al., 1994). The process of sensitization involves the initial release of algesic substances related to tissue injury (i.e. bradykinine, serotonin, and prostaglandin E2) thus altering the transmission of peripheral and central nociceptive inputs and leading to hyperalgesia and allodynia in the affected area (Ljung et al., 1999; Wright et al., 1994). Sensitization is suggested
in cases of LE by the presence of extensor muscle pressure hyperalgesia (Slater et al., 2005) and lowered cutaneous thresholds to noxious heat in the forearm (Leffler et al., 2000). Thus, an alternative etiology of chronic LE is emerging where the pain mechanism involves peripheral and central sensitization of nociceptive information (Alfredson, 2000; Slater et al., 2005; Sluka & Rees, 1997; Wright et al., 1994). The potential changes in central or peripheral neural activity could lead, not only to pain (Harris, 1999), but to other impairments in arm function.

Current evidence suggests that persistent pain secondary to musculoskeletal injuries can lead to central adaptations. For instance, persistent quadriceps weakness has been reported following ACL injuries (Lewek, 2002; McHugh, Malachy P Tyler, Timothy F Browne, Michael G Gleim, Gilbert W Nicholas, Stephen J., 2002; Urbach et al., 1999) consistent with the idea that disrupted joint afferents and/or chronic joint effusion might lead to reflex muscular inhibition (Konishi et al., 2002). Additional mechanisms beyond reflex-mediated inhibition have also been considered (Héraux & Tremblay, 2006). Urbach et al. (1999), for example, showed that patients with confirmed unilateral ACL rupture exhibited bilateral deficits in quadriceps activation. This bilateral deficit, according to the authors, suggested impaired descending commands reflecting altered afferent inputs, pointing to the importance of central adaptations secondary to musculoskeletal injuries. Recent experimental evidence supports this assertion in cases of experimentally-induced tonic pain. Farina et al. (Farina et al., 2005) demonstrated the action of a central inhibitory motor control mechanism associated with tonic muscle pain using hypertonic saline injections in the tibialis anterior muscle. They reported a decrease in the voluntary drive to the target muscle following bolus injection without change in the M-wave. This work confirmed an earlier report by the same authors in which motor unit firing rate was shown to decrease following bolus injection without change in muscle conduction velocity (Farina et al., 2004). In
the same vein, Le Pera et al. (2001) reported that acute experimental pain induced in the first dorsal intersossei and abductor digiti minimi muscles of the hand resulted in an early decrease in motor evoked potentials (MEP) elicited by TMS, followed by a reduction in the H-reflex. The authors contended that the early changes likely reflected alterations at the cortical level and that later changes were attributable to spinal mechanisms as shown by H-reflex depression. These effects were not present following subcutaneous injection, suggesting a specific role for muscular nociceptors in altering central motor excitability (Le Pera et al., 2001). The mechanisms of such alterations in central motor drive are not clear, but it is suggested that reflex inhibition via activity of small diameter muscle afferents may be involved (Farina et al., 2004).

In chronic musculoskeletal conditions, TMS studies have revealed several types of alterations in corticomotor excitability parameters. For instance, in individuals diagnosed with type 1 unilateral complex regional pain syndrome, a significant reduction in intracortical inhibition in both sensorimotor cortices was found along with a decrease in motor thresholds on the hemisphere contralateral to the affected hand in association with tactile alldynia (Schwenkreis et al., 2003). Similar results have been reported in cases of fibromyalgia and rheumatoid arthritis (Salerno et al., 2000), suggesting that common alterations in corticomotor excitability might occur in chronic pain states. Research on individuals with chronic unilateral patello-femoral pain has demonstrated an increase in MEP size to the quadriceps of the affected knee compared to the unaffected limb, despite a significant reduction in M-wave and stretch reflex to the same muscle (On et al., 2004). This result, suggesting increased facilitation in muscles proximal to the injury, is similar to other reports of increased excitability in hand muscles following a period of immobilization (Zanette et al., 2004). Along the same lines, Héroux & Tremblay (Héroux & Tremblay, 2006) recently reported a significant decrease in
resting motor thresholds in the quadriceps of individuals with chronic unilateral ACL-deficient knees. Therefore, it appears that sensorimotor restriction, either due to imposed immobilisation or associated with musculoskeletal dysfunction, seems to increase corticomotor excitability in muscles proximal to the affected joint. This contrasts with studies on experimentally-induced pain discussed above showing a decrease in cortical and spinal motor excitability in the presence of acute muscle pain (Farina et al., 2004; Farina et al., 2005; Le Pera et al., 2001). Recently, however, Del Santo et al. (Del Santo et al., 2007) have shown that experimental muscle pain may also lead to an increase in excitability during active contraction. They demonstrated that if subjects are instructed to maintain constant-force during experimentally-induced muscle pain, both MEPs and EMG activity is increased in comparison to the no-pain condition. The authors suggested that an increase in central motor drive likely compensated for the pain-induced reduction in the efficiency of descending activation (Del Santo, 2007). Thus, central adaptations in response to muscle pain and dysfunction may vary depending on the testing conditions (e.g., resting vs. active states) and also on the type of pain (experimentally acute vs. chronic clinical pain).

In summary, pain and decreased activity associated with musculoskeletal injuries appear to have modulating influences on excitability at the cortical and spinal levels. Neuroplastic changes are now increasingly recognized as critical factors associated with the development of chronic musculoskeletal pain conditions (Capra, 2004; Edwards, 1988; Wilder-Smith et al., 2002). At the present time, however, it remains to be determined whether corticomotor excitability is changed in patients affected by chronic LE. In the present study, we sought to determine with TMS whether persisting pain and symptoms associated with unilateral chronic LE might lead to measurable alterations in the corticomotor excitability of wrist muscles and, if
so, whether those alterations could be linked to impairment and disability, as judged from clinical tests of arm function.

2.2. MATERIALS AND METHODS

2.2.1. Participants

Participants recruited for this study consisted of two groups. The first group (n=14) was formed of patients presenting with a diagnosis of unilateral LE, clinically defined as localised pain or tenderness over the lateral epicondyle elicited by palpation, gripping and/or resisted finger or wrist extension movements (Bisset et al., 2006). The condition was determined to be chronic if the LE symptoms had persisted for at least 3 months duration (Slater et al., 2005). The second group consisted of healthy controls (n=16) recruited from the general population and matched to the LE group for age, gender and hand dominance. Participants were recruited via advertisements and posters located at various athletic clubs, or referred from local physiotherapy clinics. Participants were excluded if they presented concomitant symptoms in the neck or upper extremities, neurological impairment, elbow surgery in the last 12 months, loss of elbow ROM resulting from prior wrist or elbow fractures, or history of rheumatoid disease. Participants were instructed to abstain from using analgesic or anti-inflammatory medications in the 12 hours preceding participation in the study. Participants were carefully screened with a specific health questionnaire to eliminate those with potential risks for TMS (e.g., epilepsy, pregnancy). Hand dominance was determined using the Edinburgh Handedness Inventory (Oldfield, 1971).
The characteristics of participants by group are listed in Table 1. All subjects provided informed written consent before participation and the study’s procedures were approved by the Institutional Research Ethics Board.

2.2.2. Assessment of disability, pain, and manual dexterity

A disability index was obtained for each LE participant using the original quickDASH version (Beaton et al., 2005) of the DASH (Disability of Arm-Shoulder-Hand) self-report questionnaire which has previously been used to measure disability in LE (Rompe, Overend, & MacDermid, 2007). The QuickDASH score ranges from 0-100 with higher scores indicating greater levels of symptom-related disability. Maximum pain intensity over the last 24 hours was measured using the visual analog scale and recorded in centimeters, where 0 indicated no pain.

The Grooved Pegboard Test (GPT) (Lafayette Instrument CO, IN 47904, USA) is a standardized manipulative dexterity test consisting of a pegboard and 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be inserted with performance measured as the time needed to successfully insert all 25 pegs. Following one practice trial, participants performed two trials with each hand, with the order of testing balanced according to hand dominance (control group) or side affected (LE group). The mean time (in seconds) of each two trials was calculated.

2.2.3. Electromyography

Small auto-adhesive disposable surface electrodes (1 cm², AgCl) were used to record MEPs using a bipolar configuration (2 cm inter-electrode distance, cathode proximal) over the extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles at standardized locations.
referenced to anatomical landmarks (Hermens et al., 1999) and following skin cleansing with alcohol. The ground electrode was placed proximal to the elbow joint on the arm being measured. The EMG signals were amplified and filtered (bandwidth, 10 Hz to 1000 Hz) using a polygraph amplifier (RMP-6004, Nihon-Kohden Corp.). EMG signals were digitized at a 2 kHz sampling rate and analyzed offline using custom software on a PC running Microsoft® Windows® XP and equipped with a digital/analog acquisition card (BNC-2090, National Instrument Corp.). All MEP recordings were saved on this computer for offline analysis.

2.2.4. Transcranial Magnetic Stimulation

Motor evoked potentials were studied using TMS produced by a Magstim 200 (Magstim Co. Dyfed, UK) connected to a figure-of-eight coil (70-mm loop). The optimal hot spot for right ECR and FCR stimulation (see next section) was identified and marked with small adhesive markers on a skull cap worn by the participant to serve as a visual reference against which the coil was positioned and maintained by the experimenter.

2.2.5. Assessment of corticomotor excitability

Resting motor threshold

Participants were seated in a recording chair with their elbows, forearms, and wrists supported by adjustable foam armrests (see figure 1). EMG activity of the ECR and FCR was continuously monitored on an oscilloscope to ensure appropriate EMG silence prior to stimulation. The stimulating coil was positioned over the participant's left or right motor cortex (sequence balanced across participants) and then moved in 1-cm steps in the anterior–posterior and medial–lateral directions to determine the optimal scalp position for eliciting MEPs.
simultaneously from both the ECR and FCR muscles of the contralateral arm. The coil was positioned tangentially to the scalp with the handle pointing backwards at an angle of 45° to the midline; the direction of the induced current being from posterior to anterior to optimally activate the corticospinal system transynaptically (Abbruzzese, 2002). At least five seconds elapsed between each TMS pulse. The hot spot was defined as the lowest threshold site giving a 25 μV minimum response specifically in ECR at rest. Next, the resting motor threshold (rMT) was determined according to a previously described method (Mills & Nithi, 1997) where stimulation intensity is increased by steps of 1% from the highest intensity that elicits no MEPs of 10 trials to the lowest intensity that elicits 10 MEPs out of 10 trials. These limits define the lower and upper thresholds respectively, with the motor threshold (expressed as a percentage of maximal stimulator output) being the mean of these two intensities (Mills, 1997). Ten MEPs at 110 % of the participants’ rMT were then recorded simultaneously in the ECR and FCR muscles at rest.

**Stimulus-response curves**

Stimulus-response (S/R) curves at rest, measuring the rise in MEP amplitude with increasing stimulus intensities were then obtained for the target muscles. MEP of five trials were recorded for each 10% increment of baseline motor threshold intensity (i.e., 90, 100, 110, 120, 130% rMT) until no further increase in MEP amplitude was observed (Ray, McNamara, & Boniface, 2002). S/R curves were obtained by plotting variations in MEP amplitude (mean, peak-to-peak) against corresponding increases in TMS intensity. As suggested by Ray et al. (2002), we used simple linear regression analysis to compute the slope parameter of each S/R curve. The slope, summarizing the strength of the S/R curve, provided a single parameter for statistical comparisons.
MEP facilitation and silent period (SP) duration during active contraction

Finally, the duration of the SP was measured by asking participants to perform a voluntary submaximal grip contraction (approximately 20% MVC) for the duration of a 5000 ms auditory tone while holding a small exercise ball in the same position as above (Figure 1). TMS at 110% rMT was delivered at a fixed delay of 2000 ms during the course of the contraction. Five trials were performed with ten second rest periods between each. Facilitated MEP amplitude (peak-to-peak) and durations of the SP were measured and averaged offline for each arm. The SP duration was defined as the interval between MEP onset and the return of EMG activity (i.e. 30% of peak-to-peak activity prior to stimulation, see figure 3A, B). All TMS measurements were then be repeated on the participant’s opposite arm.

2.2.6. Data analysis

For TMS parameters, only data collected from the ECR muscle was considered for statistical analysis because recordings from the FCR provided inconsistent results across participants. To determine the overall impact of the LE condition on measures of excitability selected indices from individual subjects (ie, rMT, MEP amplitude at rest, S/R slope, facilitated MEP amplitude and SP duration) were entered into a multivariate analysis of variance (MANOVA) with Arm (Right/Left/Affected/Unaffected) and Gender (M/F) as the independent variables and performance in the GPT as a co-variate. A subsequent separate MANOVA was performed in the LE group, to determine the respective influence of chronicity (pain duration), arm function (DASH scores) and dexterity (GPT) on the selected indices of corticomotor excitability. All the statistical tests were performed with SPSS v. 12.0 for Windows. The graphs were prepared with GraphPad Prism v. 5.0 for Windows (GraphPad Software, San Diego, CA,
USA). The level of statistical significance was set at $p<0.05$; $p$ values from 0.06-1.0 are mentioned as statistical trends.

2.3. RESULTS

2.3.1. General observation on bilateral variations in corticomotor excitability

In general, no major bilateral differences were observed between the two arms on the selected indices of excitability and this, both in the LE and control groups. This can be seen on inspection of Figure 2 showing the group means of ECR rMT, MEP, and S/R slope of the two arms. In the case of rMT, values derived from the ECR of either the affected or unaffected arm (39.4 ± 8.8%; 40.9 ± 9.7%, respectively) were comparable, much like those obtained from the left and right arm of healthy controls (39.6 ± 5.9%; 40.5 ± 7.6%, respectively). Similarly, MEP’s recorded at rest and slope values derived from the S/R curves were also highly comparable between the two arms in each group. Figures 3A and B illustrate typical examples of SP and facilitated MEP’s measured during active contraction of wrist muscles from subject in each group. Again, no major difference was noticed between the two arms in each group or across groups (Figure 3C and D).

The fact that indices of corticomotor excitability derived from each individual were not affected by the “Arm” factor was confirmed by the MANOVA ($F=0.78$, $p=0.71$). No gender effect was detected either ($F=0.86$, $p=0.56$). The overall impact of GPT scores on corticomotor indices was also found to be not significant ($F=1.16$, $p=0.34$).
2.3.3. Impact of impairment and disability measurements on motor excitability

In the LE group, the distribution of GPT scores (mean unaffected 66.6 ± 10.6s; affected 62.8 ± 11.4s) measured from each arm was comparable, as was the case in the control group (right 64.6 ± 9.8s; left 68.5 ± 10.7s). Still, the MANOVA revealed a significant trend for the overall impact of GPT scores (F=2.28, p=0.09) on excitability indices, whereas the other variables (i.e., DASH scores, pain duration in months) had no effect. Further analysis showed that this effect of GPT scores was linked with rMT values (F=12.2, p=0.002). In fact, as shown in Figure 4A, the effect reflected a close and strong relationship between performance in the GPT and rMT values determined in the affected arm. A similar relationship, though weaker, was also found on the unaffected side (Figure 4B). No such associations were found in healthy controls.

2.4. DISCUSSION

In this study, bilateral comparisons of corticomotor indices of excitability in individuals with chronic LE revealed no significant inter-hemispheric asymmetries in ECR motor projections. These results differ from similar studies investigating corticomotor excitability in persons with chronic conditions affecting the musculoskeletal system. For instance, resting motor thresholds, which represent membrane excitability of core neuronal projections to the target muscle (Abbruzzese, 2002), have been reported to be decreased for quadriceps muscles following ACL injury (Héroux & Tremblay, 2006); this is in contrast to reports of motor threshold increases for erector spinae muscles in those with chronic low back pain (Strutton, Theodorou, Catley, McGregor, & Davey, 2005) or calf muscles in those with unilateral chronic
sciatica (Strutton, Catley, McGregor, & Davey, 2003). Since our data demonstrated no alterations in ECR motor thresholds, this suggests that neurological mechanisms responsible for such changes appear condition-specific with no systematic trend found in the limited literature available. It must be noted, however, that methodological differences for motor threshold estimation exist between the latter two reports and Héroux & Tremblay (2006) who employed an estimation procedure identical to ours. These differences, existing partly because there is no agreed protocol for measuring corticomotor threshold (Mills & Nithi, 1997), limit the comparability of the results as presented. Stimulus-response curve slope parameters, indicating the spatial extent of central motor representations (Siebner & Rothwell, 2003), were similar between groups due to notable variability among arms. For similar reasons, there were no differences found in cortical silent period durations (representing intracortical inhibition) or in MEP facilitation during active muscle contraction. This finding is similar to that reported in the sample of ACL injured individuals examined by Heroux & Tremblay (2006). It remains that the literature reporting these TMS variables in musculoskeletal populations is very limited. Furthermore, it is recognized that the reports cited here emerge from small patient samples and this pilot data requires replication from larger patient samples.

Concerning manual dexterity, our findings indicate that LE did not affect performance on the GPT when controlling for dominance and gender. Though our LE sample had only one left handed participant, and thus yielded low statistical power regarding the effect of hand dominance, it has been previously demonstrated that hand dominance is insignificant regarding performance on the GPT (Ruff & Parker, 1993). The distribution of LE participants reporting symptoms in the dominant arm in our sample (71%) appears to coincide with epidemiological
data in the general LE population in which 76% are affected in the dominant arm (Rotini, Fontana, Catamo, Noia, & Magnani, 2000).

Though a recent report on exercise-induced forearm muscle damage demonstrated that muscle discomfort did not alter performance on several hand dexterity tasks (Tiidus, Brown, Brant, Enns, & Bryden, 2008), our finding of an insignificant impact of LE on measures of manual dexterity is different from that reported in a study of 28 unilateral LE patients using the Purdue Pegboard Test. Employing the single-handed pin placement portion of the test (similar to the GPT), Skinner & Curwin (2007) have reported a significant decrement in performance associated with LE in comparison to a control group. Included in their LE sample were both acute and chronic (duration at least 3 months) cases, and within-group analysis demonstrated no differences in performance due to the duration of LE symptoms. One possible explanation for the differences in our findings may be the properties of the Purdue & Grooved Pegboard Tests themselves. Though both tests involve rapidly placing pegs in the pegboard, the GPT requires a greater degree of peg manipulation whereas the Purdue test involves more hand transport distance and less peg manipulation. Kinematic data from LE patients during upper limb pointing tasks—similar to the movements in these pegboard tests—demonstrate increased movement times in chronic LE (Bisset et al., 2006; Pienimaki et al., 1997).

Though no differences on the GPT for manual dexterity were found between arms in the LE group or between groups, a strong association was found between dexterity scores and ECR motor threshold in both arms of the LE group. No such relationship existed in the control group. The positive correlation in the LE group indicated that lower motor thresholds were associated with better performance on the GPT. It has recently been demonstrated that motor learning in normal subjects following training in a novel motor task is associated with a concurrent lowering
in corticomotor thresholds in laboratory conditions (Boudreau et al., 2007). These findings coincide with results from neurologically injured patients, in which lower corticomotor thresholds in hand muscles were associated with better hand performance during finger tapping and peg-placing tasks post-stroke (Brouwer & Schryburt-Brown, 2006); and decreases in hand motor thresholds over time correlate with functional gains in chronic hemiparetic limb rehabilitation (Koski, Mernar, & Dobkin, 2004). Lending further support to our findings, correlations between corticomotor measurements and performance on peg placing tasks have been reported as insignificant in healthy controls (Brouwer, Sale, & Nordstrom, 2001), although an earlier report suggests that a significant association may exist (Triggs, Calvanio, & Levine, 1997). Further evidence of an association between corticomotor thresholds and motor performance has been reported in chronic fatigue syndrome for upper limb reaction time tasks (Davey et al., 2003). Though this remains a pilot study, it is unanticipated to find correlations as strong as reported here occurring between neurophysiological excitability measures and behavioural measures, co-existing with a lack of significant differences within- or between-groups in the neurophysiological variables themselves. Mechanisms driving such relationships in this LE sample remain unclear and merit more attention in future work.

Concerning the significant correlations occurring bilaterally in an otherwise unilaterally affected LE sample, this data contributes to evidence in the normal population of interhemispheric transfer of information between homologous cortical areas during unilateral motor tasks (Bonato et al., 1996; Stinear, Walker, & Byblow, 2001). This evidence suggests that “crossed” modulation of corticomotor excitability may be further influenced by the presence of musculoskeletal dysfunction and/or chronic musculoskeletal pain.
Further insight may be found in the work of Lund & Donga (Lund, Donga, Widmer, & Stohler, 1991) who have proposed a “pain-adaptation” model where chronic musculoskeletal pain causes protective adaptation whereby movement parameters in the painful region such as range, velocity and force production are reduced. It may be that corticomotor thresholds of forearm extensors in cases of LE are reactive neurophysiological manifestations to such an occurrence, where decreases in thresholds over time associated with nociceptive sensitization infer improved sensorimotor function, in this case manipulative dexterity, thus counteracting protective adaptation.

2.5 CONCLUSION

The present pilot study demonstrates no significant changes in measures of corticomotor excitability in cases of unilateral chronic LE. However, of interest is the significant association between motor thresholds and distal manual dexterity uniquely found in the LE group. To our knowledge, this is the first such finding in an orthopedic sample and merits replication using larger samples and further investigation in other forms of chronic muscle pain conditions.
Table 1. Group characteristics

<table>
<thead>
<tr>
<th></th>
<th>LE Group (n=14)</th>
<th>Control group (n=16)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)\textsuperscript{a}</td>
<td>44.4 ± 9.0</td>
<td>48.9 ± 9.4</td>
</tr>
<tr>
<td>Gender</td>
<td>9 M / 5 F</td>
<td>10 M / 6 F</td>
</tr>
<tr>
<td>Hand dominance</td>
<td>13 R / 1 L</td>
<td>13 R / 3 L</td>
</tr>
<tr>
<td>Dominant arms affected</td>
<td>10/14</td>
<td></td>
</tr>
<tr>
<td>Symptom duration (months)</td>
<td>14.6 ± 16.0</td>
<td></td>
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<tr>
<td>quickDASH score</td>
<td>25.0 ± 12.8</td>
<td></td>
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<tr>
<td>Pain VAS\textsuperscript{b} (cm)</td>
<td>5.3 ± 2.8</td>
<td></td>
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F: female; M: male. R: right arm; L: left arm
\textsuperscript{a}: No difference between means of group ages (t=1.62, p=0.12)
\textsuperscript{b}: Greatest perceived pain over last 24 hours, visual analog scale (10 = extreme pain)

Figures

Figure 1. Experimental setup for transcranial magnetic stimulation.

Figure 2. Group means across arms of ECR (A) resting motor thresholds; (B) MEP amplitudes at 110% rMT; and (C) stimulus-response curve slopes.

Figure 3. Examples of individual MEP in ECR muscles from the LE group (A) and the control group (B); group means across arms of silent period duration (C) and facilitated MEP amplitude (D) of ECR muscles during sustained gripping action.

Figure 4. Correlations in LE group between GPT time and ECR rMT of same arm in (A) affected arm and (B) unaffected arm.
Figure 1
Figure 2
Figure 3
Figure 4

A

GPT place (s)

r^2=0.76
p=0.0001

rMT affected arm
(% stimulator output)

B

GPT place (s)

r^2=0.29
p=0.04

rMT unaffected arm
(% stimulator output)
Chapter 3. Proprioceptive acuity for weight perception in cases of chronic unilateral epicondylalgia

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Running Title: Weight discrimination in chronic lateral epicondylalgia

Key words: lateral epicondylalgia, elbow, proprioception, weight discrimination, rehabilitation

This work served for the partial completion of Liam Dessureault's Master of Science degree from the University of Ottawa in Human Kinetics.

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Abstract

Chronic lateral epicondylalgia (LE) is a common musculoskeletal condition of the upper extremity leading to unilateral pain and symptoms in the affected elbow. In the present study, we sought to determine whether the presence of unilateral chronic LE affected proprioceptive acuity for weight discrimination and whether such changes could be related to disability measures of arm function. A convenience sample of 14 patients with LE of at least 3 months duration (median 7 months) and 16 age- & gender-matched health controls participated in this descriptive study. Upper-limb disability was measured in LE participants using the quickDASH questionnaire. Psychophysical testing was performed using a custom set of weighted canisters (100-130g, 2 g steps) which participants lifted using a controlled wrist extension/radial deviation movement. Weber fractions, expressed as a percentage difference from the standard weight (100g) that could be reliably detected (criterion 75% correct) were derived for each wrist to provide an index of proprioceptive acuity. An analysis of variance (ANOVA) was used to determine the impact of "arm" (affected/unaffected; right/left), "gender", and "hand dominance" on Weber fraction values. In healthy controls, acuity for weight discrimination was comparable in the two arms (right, 5.3 ± 2.7 %; left, 5.4 ± 2.1 %). In the LE group, acuity was decreased on the affected (as compared to the unaffected) side, as reflected in the increase in Weber's fraction (8.2 ± 3.0% and 4.9 ± 3.2%, respectively). The main effect of "arm" (F=3.7, p=0.02) on proprioceptive acuity was confirmed by the ANOVA. Post-hoc comparisons also confirmed that this effect as due to the poorer acuity measured in the affected arm in the LE group (affected vs. unaffected, p=0.001). There was no main effect of hand dominance or gender (p>0.05). There was no significant relationship between quickDASH scores and Weber fractions (p>0.05). Yet a significant trend (p=0.05) was seen for the correlation between poor acuity in the affected arm and longer symptom duration. Altogether, these findings indicate the presence in patients with chronic LE of a proprioceptive deficit in the ability to judge small differences in weight and in monitoring force signals generated during active lifting. It is possible that the presence of chronic muscle pain interferes with the processing of proprioceptive signals from the affected muscle. Our pilot data suggest that symptom chronicity may be associated with these deficits.
3.1. INTRODUCTION

Lateral epicondylalgia (LE) is a common condition of the upper extremity accounting for about seven out of 1000 general practitioner visits in the U.S. (Bisset, PAungmali, & Vicenzino, 2005). Considered a repetitive strain injury of the tendinous origin at the elbow of the wrist and/or finger extensors, the condition manifests itself as pain arising from palpation of the lateral epicondyle of the elbow or pain elicited during gripping actions or resisted wrist or finger extension (Vicenzino, 2003). Although the majority of LE cases present with a favorable evolution within a year after onset (De Smedt et al., 2007; Smidt et al., 2002), recurrent, treatment-resistant bouts of LE symptoms are common (Bisset et al., 2005; Stasinopoulos & Johnson, 2006; Vicenzino & Wright, 1996) and approximately 50% of cases are left with persisting or recurring symptoms leading to chronicity (Clarke & Woodland, 1975). Thus, the actual prevalence of chronic LE is likely underestimated.

In addition, the etiology of LE remains poorly defined as the role of chronic inflammation has been questioned in recent years (Bisset et al., 2005; Slater et al., 2005; Vicenzino, 2003). Although local tissue degeneration is generally linked to the development of chronic tendinopathy (Ashe et al., 2004; Khan et al., 1999; Kraushaar & Nirschl, 1999), recent evidence points to nociceptive sensitization as an etiological factor in the development of chronic LE (Alfredson, 2000; Sluka & Rees, 1997; Wright et al., 1994). The process of sensitization involves the initial release of algesic substances related to tissue injury (i.e. bradykinine, serotonin, and prostaglandin E2) thus altering the transmission of peripheral and central nociceptive inputs and leading to hyperalgesia and allodynia in the affected area (Ljung et al., 1999; Wright et al., 1994). Sensitization is suggested in cases of LE by the presence of extensor muscle pressure hyperalgesia (Slater, 2005) and lowered cutaneous thresholds to noxious heat in
the forearm (Leffler et al., 2000). Mechanisms of sensitization are believed to be important factors in the development of chronic musculoskeletal pain conditions (Capra, 2004; Wilder-Smith et al., 2002). The potential changes in central or peripheral neural activity could lead, not only to pain (Harris, 1999), but to other impairments involving the integration of sensory information, such as proprioception.

Proprioceptive abilities generally encompass the usual kinesthetic senses, i.e. the sense of static joint position and movement detection, along with the less known sense of effort and weight perception (Gandevia, 1996). The first two kinesthetic senses are usually examined under passive or active conditions involving single joint mobilizations (Proske et al., 2000), while the sense of force and weight perception requires active lifting actions on the part of the subject (Gandevia et al., 2006; Jones, 1986). Three kinds of sensory receptors are thought to be important for kinesthesia: muscle receptors, skin receptors and joint receptors (Proske et al., 2000). The sense of effort and weight perception is thought to involve integration of peripheral afferent information about muscle tension with central descending commands to generate a percept of force or heaviness associated with a muscular effort (Gandevia et al., 2006; Jones, 1986).

The impact of musculoskeletal injury and pain on proprioceptive function has been reported for a variety of conditions. For instance, following cervical whiplash injuries, evidence of altered kinesthetic awareness measured by joint position error in both acute and chronic cases has been shown to be in close association with pain persistence duration and indices of neck disability (Sterling et al., 2003). Deficits in joint position sense following injury have also been reported at the ankle and knee (Issa & Sharma, 2006; Lee et al., 2006; Lephart et al., 1998; Warner et al., 1996; Wilk et al., 2002), the shoulder (Warner et al., 1996; Wilk et al., 2002), and
in individuals with anterior cruciate ligament (ACL) injury (Barret, 1991). A deficit in the ability
to discriminate weights in individuals with an ACL-deficient knee has been found, confirming
the distinct proprioceptive deficits associated with this condition (Héroux & Tremblay, 2005).
Also at the knee, losses in quadriceps' force-matching abilities in cases of knee osteoarthritis
have been reported (Hortobagyi, Garry, Holbert, & Devita, 2004). In regards to kinesthesia at the
elbow, Proske and colleagues have demonstrated the negative effects of delayed onset muscle
soreness following eccentric biceps exercise on a force matching task in healthy subjects:
subjects consistently overestimated the reference force (Proske et al., 2003). The authors
attributed this error to the post exercise soreness in the indicator arm. This result is in line with
that of Weerakkody et al. (2003), who injected hypertonic saline in the biceps muscle. In
comparison to superficial pain induced by noxious heat, experimental muscle pain produced
systematic force-matching errors between limbs (Weerakkody et al., 2003). Using a similar
paradigm, Rossi et al. (Rossi et al., 2003) reported deficits in joint finger position sense leading
them to suggest that pain could interfere with the processing of non-painful proprioceptive
stimuli. However, recent data from LE patients remains less conclusive in regards to the
existence of potential changes in elbow position sense in this population. Juul-Kristensen and
colleagues (2008) compared joint position sense at the elbows in a sample of LE patients and
healthy control subjects. Though affected elbows demonstrated greater movement detection
thresholds as compared to the left elbows of control subjects, differences between affected and
unaffected elbows (or right elbows of controls for that matter) were not significant (Juul-
Kristensen, Lund, Hansen, Christensen & Danneskiold-Samsoe, 2008). In addition, no
differences were noted in absolute joint position sense across any of the elbows tested. All

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7 No differences existed between affected LE elbows and right control elbows.
conclusions considered, the absence of differences between joint position sense in affected and
unaffected elbows of LE patients renders questionable the authors’ assertions of an existing
deficit in proprioception as indicated by the difference in movement detection thresholds alone.

In patients affected with LE, Bisset et al. (2006) have provided evidence of sensorimotor
dysfunction in the form of changes in the kinematics of wrist motion during a gripping task.
They observed a tendency in patients to adopt inefficient flexed wrist postures bilaterally during
opening. In addition, patients also exhibited slower reaction times and slower speed of
movement than healthy controls. The changes in the movement kinematics were consistent with
previous observations by Pienimaki, Kauranen, & Vanharanta (Pienimaki et al., 1997). Such
changes in movement kinematics in patients with LE are also in line with changes reported in
subjects with experimentally-induced muscle pain on a pointing task in terms of attenuated
acceleration profiles, reduced movement amplitude and velocity, and prolonged reaction times
(Ervilha, Arendt-Nielsen, Duarte, & Graven-Nielsen, 2004b).

Thus, both experimental and clinical evidence points to deficits in proprioceptive abilities
(joint position sense, perception of force) in individuals affected with either acute or chronic
musculoskeletal pain. However, at present, we still have very little information as to how
proprioception is affected in individuals presenting with chronic LE. In the present study, we
sought to determine whether persisting pain and symptoms associated with chronic LE might
interfere with the ability to perceive differences in weight in the context of active lifting actions
involving forearm muscles. We also looked at possible relationships between changes in
proprioceptive acuity and associated upper extremity function, and pain chronicity.
3.2. MATERIALS AND METHOD

3.2.1. Participants

Participants recruited for this study consisted of two groups. The first group (LE, n=14) consisted of patients presenting with a diagnosis of unilateral LE, clinically defined as localised pain or tenderness over the lateral epicondyle elicited by palpation, gripping and/or resisted finger or wrist extension movements (Bisset, Russell, Bradley, Ha, & Vicenzino, 2006). All patients presented with symptoms for at least 3 months (range 4-60 months, see Table 1) and were thus considered to be in the chronic stage (Slater et al., 2005). Patients were excluded if they presented concomitant symptoms in the neck or upper extremities, neurological impairment, elbow surgery in the last 12 months, loss of elbow ROM resulting from prior wrist or elbow fractures, or history of rheumatoid disease. Participants were instructed to refrain from using analgesic or anti-inflammatory medications in the 12 hours period before testing. The second group consisted of healthy controls (n=16) recruited from the general population and matched to the LE group for age, gender and hand dominance. Participants were recruited via advertisements and posters located at various athletic clubs, or referred from local physiotherapy clinics. The characteristics of each group are listed in Table 1. All subjects provided written informed consent before participation and the study’s procedures were approved by the Institutional Research Ethics Board.

3.2.2. Materials

To test proprioceptive acuity for weight discrimination, a set of 16 custom-made light discrimination weights (ranging between 100 to 130 grams, in 2-g increments) was used as stimuli. Each weight consisted of an identical small plastic canister filled with metal pellets and...
sand to add weight (measured on a precision force-plate, resolution of ± 0.01 g). Each canister was identical in color, size and texture (Fig. 1).

3.2.3. Functional assessment

A disability index was obtained for each LE participant using the original quickDASH version (Beaton et al., 2005) of the Disability of Arm-Shoulder-Hand (DASH) self-report questionnaire which has previously been used to measure disability in LE (Rompe et al., 2007). The QuickDASH score ranges from 0-100 with higher scores indicating greater levels of symptom-related disability. Maximum pain intensity over the last 24 hours was measured using the visual analog scale and recorded in centimeters where 0 indicated no pain. Finally, hand dominance was determined using the Edinburgh Handedness Inventory (Oldfield, 1971).

3.2.4. Weight discrimination protocol

Participants were tested in a quiet, isolated room. For testing, participants were seated at a table with their forearm and hand hidden from view by a cardboard screen, their forearm in a semi-pronated position supported by light padding (see Fig 1). Both arms were tested for each participant. The order of testing for both arms was randomized across subjects according to hand dominance (control group) or side affected (LE group). A two-alternative forced-choice paradigm was used for testing. On each trial, participants were presented with two weights to discriminate: a standard weight ($Sw=100g$) and a comparison weight ($Sc > 100g$). Participants were instructed to lift each weight using a thumb-index grip and a controlled extension/radial deviation at the wrist only (see figure 1) and report which weight felt heavier (ie, Right or Left) by pointing to it. No restriction was imposed as to the number of lifts or on the duration of
comparisons. The testing sequence involved 14 presentations for each pair of weights starting with the largest comparison weight (120g) and proceeding with increasingly lighter weights. Within each block of 14 trials, the position of the standard and comparison weights (right or left relative to the participant) was alternated according to a pseudo-random sequence with the two possibilities being equally probable. Practice trials with verbal feedback from the examiner were performed prior to beginning each block of weight pairs. Care was taken to ensure that no LE pain was provoked during trials and frequent rest periods were offered to avoid fatigue.

Discrimination acuity thresholds were determined by interpolating the minimal weight difference that yielded a 75% correct discrimination (mid-way between perfect and chance discrimination) from performance values just above and below this criterion level (see figure 2). These weight differences at threshold were then expressed relative to the standard weight (100g) for each arm, a value known as the *Weber fraction* according to this formula

$$\text{Weber fraction} = \frac{\Delta s_{\text{at threshold}}}{s_w} \times 100$$

Thus, a relatively lower Weber fraction is indicative of greater proprioceptive acuity and vice versa.

3.2.5. Data Analysis

Weber fractions from each arm were entered into a three-way ANOVA model with the arm (right/left/affected/unaffected), gender, and hand dominance as grouping factors. Tukey's post hoc tests were used to make pairwise comparisons for between- and within-group analyses. Associations between proprioceptive acuity and (a) quickDASH (disability) scores or (b)
symptom duration in the LE group were also examined using the Pearson-product moment correlation coefficient. The level of significance for main effects was set at \( p < 0.05 \). The statistical analysis was performed using SPSS (v. 15.0) for Windows. GraphPad Prism version 5.01 for Windows was also used for some tests and for graph production (GraphPad Software, San Diego California USA, www.graphpad.com).

3.3. RESULTS

3.3.1. Performance for Weight discrimination

In general, healthy participants demonstrated a fine acuity in discriminating between weights using the two arms, whereas patients in the LE group demonstrated various degrees of deficits on the affected side. Representative examples of individual performances from each group are shown in figure 2.

Figure 3 shows the distribution of individual Weber fractions derived from the discrimination performance of the two arms in each group. In healthy controls, acuity for weight discrimination was comparable in the right and the left arm (5.31 ± 2.67 % and 5.43 ± 2.09 %, respectively). In the LE group, there was a clear tendency for acuity to be decreased on the affected, as compared to, the unaffected side (mean 8.2 ± 3.0% and 4.9 ± 3.2%, respectively). The impact of the factor “ARM” on acuity for weight discrimination, as reflected in Weber fractions, was confirmed by the ANOVA (\( F = 3.7 \), \( p = 0.02 \)). Post-hoc analysis confirmed that the main effect of “ARM” was attributable to the difference seen between the AA vs. UA in the LE group (\( p = 0.001 \)). Differences between left and right arms of controls and unaffected arms were
not significant (p>0.5). No main effects were demonstrated for either gender or hand dominance (P>0.1), nor was there a significant interaction between the three independent variables (P>0.5).

3.3.2. Relationship between proprioceptive acuity, function and symptom duration

There was no relationship between Weber fractions of the affected arms and either the quickDASH disability scores or the symptom duration in the LE group.

3.4. DISCUSSION

The ability to accurately perceive the weight of lifted objects is an important task for upper extremity function. The first purpose of this study was to determine if individuals with unilateral chronic lateral epicondylalgia exhibit changes in proprioception as reflected in the ability to discriminate weight actively. Previous reports on active weight discrimination at the elbow showed that human observers can discriminate comparative weight differences in the order of 5-10% (Brodie & Ross, 1984). In the present study, Weber fractions were in the lower limit of the reported range for the elbow (ie, ~5-6% on average) suggesting that acuity for weight discrimination is greater at the wrist for a comparable lifting task. In the LE group, weight discrimination in the affected arm was decreased as compared to the unaffected arm and the arms of healthy controls. To our knowledge, this is the first report to demonstrate such a proprioceptive deficit in cases of LE. Our observations in patients with LE are in line with recent reports showing alterations in force perception in experimentally-induced muscle pain (Proske et al., 2003; Weerakkody et al., 2003). In those reports, the presence of acute pain in the target muscle was considered as a potential source of interference in the ability to integrate force signals during the force-matching tasks. In the present study, participants in the LE group, when
questioned, did not report pain during the lifting task and thus interferences from pain signals cannot be considered as a major source affecting the performance. The present observation of a unilateral deficit in weight discrimination in cases of LE echoes the previous finding of Heroux & Tremblay (2005) who observed a similar deficit in the quadriceps of patients having sustained a unilateral ACL injury. Although this type of condition is dissimilar to LE in that it most frequently is a result of direct trauma, likely includes significant joint effusion, and involves non-contractile ligamentous tissue, it seems that deficits in the ability to appreciate difference in weights are a common feature in chronic musculoskeletal conditions leading to predominantly unilateral dysfunction, such as LE or ACL-deficient knee.

In the recent work by Juul-Kristensen et al. (2008), it is suggested that thresholds for detecting passive movement is higher in affected elbows of individuals with LE. In their discussion, the authors state that this threshold depends on afferents which code rates of dynamic muscle length and force changes. This is opposed to joint position sense (shown by their data to be mostly spared in LE), which is elicited by a static response to muscle length changes (Juul-Kristensen et al., 2008). It appears that our findings, indicative of deficits in detecting differences in muscle force signals, taken with data from Juul-Kristensen et al. (2008) together constitute evidence for the existence of changes occurring in muscle force signal sensitivity in the elbows affected with LE. The etiology of these changes remains unclear and further research could identify the role played by pain or degeneration of the musculotendinous tissues at the lateral epicondyle in this process.

The present findings are also in line with earlier reports showing that alterations in sensorimotor integration exist in cases of chronic LE. Pain-related reductions in tactile thresholds for pressure and noxious heat at the elbow have been described in chronic LE, with the pattern of
these sensory changes suggesting—as with force-perception errors at the knee—mechanisms possibly originating at the central level (Leffler et al., 2000). Furthermore, alterations in kinematics such as ineffective wrist postures during gripping (Bisset et al., 2006), deficits in hand reaction & movement time (Bisset et al., 2006; Pienimaki et al., 1997) and alterations in wrist extensor muscle temporal activation patterns during tennis backhand shots (Kelly et al., 1994) suggest widespread sensorimotor abnormalities in chronic LE. In the light of these findings, one can propose that the deficit reported here in the ability to detect small differences in weight in LE cases might reflect an impaired sensorimotor processing of proprioceptive feedback information arising from the affected wrist extensors leading to impaired ability to appreciate force and effort associated with active lifting. Despite the statistical significance of the reported deficit, the clinical impact of such a kinesthetic loss is unknown.

In the present report, no relationship was found between weight discrimination acuity and LE-related disability as measured by quickDASH scores. This lack of association may reflect the inherent limitations of the quickDASH as an index of LE-related disability. In spite of its widespread use and its accepted validity regarding elbow conditions (Turchin, Beaton, & Richards, 1998), the quickDASH items may be too general to measure specific LE-related disability level. The use of self-report questionnaire specifically designed for LE such as the Tennis Elbow Function Scale (Audrey-Lowe, 1999) or the Patient Rated Tennis Elbow Questionnaire (Rompe et al., 2007) may address this limitation in future studies. Our findings also demonstrate no association between LE symptom duration and proprioceptive acuity in the LE group. This suggests that the observed decline in proprioceptive acuity appears unrelated to chronicity, though a wider range in symptom duration (i.e., from acute to longstanding LE...
dysfunction) may provide a more representative distribution from which to draw such conclusions.

An obvious limitation of this study is the sample size, which limited analysis of within group factors such as hand dominance and gender, and restricted our ability to generalize these results to the larger population of chronic LE cases. Second, it was chosen to allow the participants to actively lift the weights with a fingertip grasp which allowed for slight variability in individual lifting strategies. This method was preferred over passive weight sampling found in previous work (Brodie & Ross, 1984) as it was judged to represent a more functional movement pattern typical of daily upper extremity tasks. Though frequent rest periods were provided as needed, undeclared or subclinical fatigue may have occurred to a greater extent in the arms with LE and this may have affected proprioceptive performance.

3.5. CONCLUSION

The exact impact of proprioceptive deficits in LE is difficult to ascertain given the overlapping contribution of multiple factors, defined and undefined, to patient function and injury recovery. However it is reasoned that a deficit in neuromuscular control is a predisposing factor in the maintenance and recurrence of musculoskeletal symptoms (Lephart, Pincivero, Giraldo, & Fu, 1997; Yamashita, Minaki, Takebayashi, Sakamoto, & Ishii, 1999) and is associated with poorer patient outcomes. Moreover, it has been suggested that disturbances in proprioception and altered force perception during arm movement with muscle injury can account for disruptions in movement control and interfere with optimal completion of work-related and practical functional tasks (Tiidus et al., 2008). As such, the present report contributes
to an evolving model of sensorimotor impairment encountered in chronic LE, specifically concerning alterations in the perception of muscle force signals elicited from the elbow. Further research is needed to identify the specific level of sensorimotor processing at which adaptive modifications resulting in proprioceptive deficits occur. Furthermore it is not known whether these changes predispose one to developing chronic LE or occur as a result of the condition secondary to musculoskeletal impairment as suggested, for example, by the pain-adaption model (Lund et al., 1991) in which protective adaptations in sensorimotor function result in observable, but not causative, performance deficits.
Table 1. Group characteristics

<table>
<thead>
<tr>
<th></th>
<th>LE Group (n=14)</th>
<th>Control group (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)(^a)</td>
<td>44.4 ± 9.0</td>
<td>48.9 ± 9.4</td>
</tr>
<tr>
<td>Gender</td>
<td>9 M / 5 F</td>
<td>10 M / 6 F</td>
</tr>
<tr>
<td>Hand dominance</td>
<td>13 R / 1 L</td>
<td>13 R / 3 L</td>
</tr>
<tr>
<td>Dominant arms affected</td>
<td>10/14</td>
<td></td>
</tr>
<tr>
<td>Symptom duration (months)</td>
<td>14.6 ± 16.0</td>
<td></td>
</tr>
<tr>
<td>quickDASH score</td>
<td>25.0 ± 12.8</td>
<td></td>
</tr>
<tr>
<td>Pain VAS(^b) (cm)</td>
<td>5.3 ± 2.8</td>
<td></td>
</tr>
</tbody>
</table>

F: female; M: male; R: right arm; L: left arm
\(^a\): No difference between means of group ages (t=1.62, p=0.12)
\(^b\): Greatest perceived pain over last 24 hours, 10 cm visual analog scale

Figures

Figure 1. Weight discrimination task: Participants were instructed to lift each weight using a finger-tip grip and a controlled extension/radial deviation at the wrist only and then to report which weight (standard or comparative, i.e. left or right) felt heaviest.

Figure 2. Discriminative functions derived from performance of each arm during the weight discrimination task from a representative participant from the control group (A) and LE group (B). Each value represents the percent of correct answers for each corresponding weight difference (comparative minus standard weight) across trials. The dotted horizontal line indicates the 75% correct discrimination level, which corresponds by convention to the differential threshold (see Methods).

Figure 3. Proprioceptive acuity for weight discrimination for each arm in the 2 groups of participants. An upward trend in the Weber fractions in the affected arm of the LE
participants indicates a reduced ability to detect differences in weight. Group means of Weber fractions for weight discrimination acuity across arms tested. * Significant difference ($p=0.001$) between affected arm and unaffected arm.

Figure 1
Figure 2
Figure 3
The overall purpose of this thesis was to examine for potential changes at the neurophysiological and behavioral levels in patients presenting with chronic LE. In study I, we used TMS over the motor cortex to assess for changes in the corticomotor excitability of the wrist motor representation. Different indices of excitability (rMT, S/R curves, MEP facilitation, SP) were derived on each side to detect possible asymmetries. Our working hypothesis was that some asymmetries should be present in the LE patient's group, owing to the presence of unilateral arm pain and dysfunction. However, our results revealed no major bilateral differences in excitability in both patients and healthy controls. A similar study performed in patients with chronic unilateral knee dysfunction (Heroux & Tremblay, 2005) also found no major differences in excitability between the two limbs, with the exception of rMT, which were reduced on the affected side. On the other hand, our results did show a strong relationship between rMT and dexterity scores derived from the GPT in the LE group and not the control group. Such a strong relationship between measures of corticomotor excitability and behavioral function has rarely been seen in the TMS literature. This relationship suggests a link between decreased excitability of the wrist motor representation and arm function as reflected in manual dexterity.

In study II, the same participants underwent psychophysical testing to assess their proprioceptive acuity for weight discrimination in the two arms to investigate for changes in sensorimotor integration related to force perception. We also looked at whether those
changes could be related to pain duration and impaired arm function (dexterity) and
disability (quickDASH). The results revealed that patients with LE had reduced acuity for
discriminating weight in the affected when compared to the unaffected arm and with the
arms of healthy controls. As said earlier, this is, to our knowledge, the first study to
document a proprioceptive deficit of this nature in the case of patients with chronic elbow
pain. Our findings are in total agreement with a previous study performed in this lab in
patients having sustained knee ligament injuries. Thus, the presence of alterations in force
perception in the context of weight lifting actions seems a common pattern in patients
presenting with unilateral musculoskeletal dysfunction. The reason as to why force
perception is altered remains unclear but, as we have emphasized, the presence of
persisting pain and secondary changes linked with disuse, may be factors that interfere
with central integration when judging force produced by active lifting actions. Whatever
the reasons, it remains that the present results provide clinically important evidence
demonstrating that chronic elbow pain may lead to detectable changes in weight
perception, which may translate into difficulties in daily tasks involving lifting action at
the wrist. Project II also provides important insights for future studies to investigate
changes in proprioception in cases of chronic LE.

Altogether, the results presented in this thesis provide a significant contribution to
a growing body of evidence linking chronic musculoskeletal pain with alterations in
sensorimotor integration at the peripheral and central level. The results open the door for
further investigations to link changes in function with alterations in motor excitability in
patients with chronic LE.
References


Appendix
Appendix A. Modified DASH questionnaire

QuickDASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

<table>
<thead>
<tr>
<th>Activity</th>
<th>NO DIFFICULTY</th>
<th>MILD DIFFICULTY</th>
<th>MODERATE DIFFICULTY</th>
<th>SEVERE DIFFICULTY</th>
<th>UNABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Open a tight or new jar.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Do heavy household chores (e.g., wash walls, floors)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Carry a shopping bag or briefcase.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Wash your back</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Use a knife to cut food.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Recreational activities in which you have some force in your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During the past week, to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT AT ALL</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT LIMITED AT ALL</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Please rate the severity of the following symptoms in the last week. (circle number)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>NONE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
<th>EXTREME</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Arm, shoulder or hand pain.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Tingling (pins and needles) in your arm, shoulder or hand.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO DIFFICULTY</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

QuickDASH DISABILITY/SYMPTOM SCORE = \( \frac{\text{Sum of n responses}}{n} - 1 \) \times 25, where n is equal to the number of completed responses. A QuickDASH score may not be calculated if there is greater than 1 missing item.

Source: Institute of Work and Health, Toronto, Canada (retrieved April 24th at http://www.dash.iwh.on.ca)
Appendix B. Institutional Ethics Certificate

Université d’Ottawa University of Ottawa

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD

CERTIFICATE OF ETHICAL APPROVAL

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board has examined the application for ethical approval of the research project entitled Corticostriatal Excitability and Proprioceptive Acuity in Chronic Tennis Elbow (File H 06-07-04) submitted by Liam Deshaireault, Master’s student in Human Kinetics and supervised by François Tremblay from the School of Human Kinetics of the University of Ottawa. The Board found that this research project met appropriate ethical standards as outlined in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards, and accordingly gave it a Category 1a (approval). This certification is valid one year from the date indicated below.

Catherine Paquet
Protocol Officer for Ethics in Research
For Daniel Lagace, Chair of the
Health Sciences and Science REB

July 17, 2007
Date