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Cortico-Motor Adaptations and Proprioceptive Acuity in Patients with Unilateral Anterior Cruciate Ligament Deficiency

by

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ABSTRACT

The purpose of this project was to study proprioceptive deficits and corticomotor adaptations in following ACL injuries. METHODS: Ten participants with chronic ACL injuries and eight controls participated. Subjective function (KOS-ADLS) and quadriceps strength (MVC) were measured. Proprioceptive acuity was assessed with a weight discrimination task. Transcranial magnetic stimulation was used to assess four indices of cortico-motor excitability and the quadriceps H-reflex was measured. RESULTS: On the injured side in the ACL group, KOS-ADLS, MVC (p<0.018) and proprioceptive acuity (p<0.01) were reduced. RMT were lower on the injured side (p=0.019). H-reflex amplitude was smaller on the injured side (n=5). The extent of quadriceps motor representation (input-output curve) was correlated (r²=0.523) with MVC values on the injured side. DISCUSSION: Reduced proprioception may reflect an impaired capacity to process force signals centrally, whilst increased corticomotor excitability may reflect a greater voluntary control to ensure joint stability.
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LIST OF ABBREVIATIONS

ACL: Anterior cruciate ligament

cm: centimetre

EMG: Electromyography

g: Gram

I-O: Input-output

kg: Kilogram

KHz: Kilohertz

KOS-ADLS: Knee Outcome Survey--Activities of Daily Living Scale

MEP: Motor evoked potentials

MVC: Maximum voluntary contraction

mm: millimetre

ms: milliseconds

n: sample size

RMT: Resting motor threshold

s: second(s)

SP: Silent period

TMS: Transcranial magnetic stimulation
SUMMARY

Persistent weakness and reduced proprioception are the most common impairments seen in individuals having sustained an anterior cruciate ligament (ACL) injury (Friden et al., 1999; Snyder-Mackler et al., 1995). In the context of this thesis project, we have attempted to get further insights as to the nature of the proprioceptive deficits affecting individuals with ACL injuries and possible adaptations at the cortico-motor level resulting from unilateral knee dysfunction. Ten participants with chronic ACL injuries (age: 27.1±8.2) and eight healthy controls (age: 22.6±2.8) were recruited for the study. The Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS) was used to assess subjective knee function and quadriceps strength was measured on a KIN-COM dynamometer during isometric maximum voluntary contractions (MVC; 3 trials, 2-3 s each). In the first experiment, proprioceptive acuity for force signals was assessed by asking participants to discriminate small differences in weight according to a two-alternative forced choice procedure. The mass of the standard weight (3 kg) was increased by adding metal weights in successive blocks of trials (n=14) in a sequence of increasing difficulty (i.e., 0.50 kg, 0.28 kg, 0.20 kg and 0.09 kg increment). In a second experiment, transcranial magnetic stimulation (TMS) was used to estimate the cortico-motor excitability of the quadriceps motor representation. Magnetic stimulation was administered over the primary motor cortex and motor evoked potentials (MEPs) were recorded with EMG electrodes. Four indices of cortico-motor excitability were derived: resting motor thresholds (RMT), input-out (I-O) curves, MEP facilitation and silent period (SP) duration during voluntary contraction. The H-reflex was also measured to estimate spinal excitability. Comparison of discrimination thresholds determined in the
first experiment revealed a significant difference ($t=3.51, p<0.001$) between the two legs in the ACL group; the injured leg being significantly poorer at discriminating weights (mean threshold, 199.9±68.3 g) than the uninjured leg (mean 144.1±33.9 g). No such difference was noted in the control group (right leg, 161.2±42.6 g; left leg, 171.6±40.2; $t=0.74, p=0.48$). On the injured side in the ACL group, no correlation was found between proprioceptive acuity and subjective scores of knee functions ($r^2=0.10$), although a tendency was observed for proprioceptive acuity to be better for those with lower quadriceps muscle strength as opposed to those with greater quadriceps strength ($r^2=0.18$). In the second experiment, comparison between the two hemispheres indicated that RMT to magnetic stimulation were significantly lower in the contra-hemisphere controlling the injured leg (mean 54.5 ± 12.1 %, vs mean, 58.5 ± 14.5%, $t=2.87$, $p=0.019$). In contrast, RMT measured in the control group were comparable between hemispheres. Besides this difference in RMT, no other significant difference was detected for the other cortico-motor indices (i.e., I-O curve slope values, facilitated MEP amplitude and SP duration). As expected, quadriceps H-reflex amplitude was found to be smaller on the injured side for those individuals with elicitable quadriceps H-reflex ($n=5$). Interestingly, the extent of the quadriceps motor representation, as reflected in the steepness of the I-O curve, correlated strongly ($r^2=0.71$) with the amount of torque produced during quadriceps MVC. No other correlations could be established between the remaining indices of excitability and measures of knee dysfunction (i.e., subjective function ratings, quadriceps muscle strength) Altogether, these results provide important new insights as to the nature of proprioceptive deficits in ACL injury and how the neuromuscular system adapts to unilateral chronic knee dysfunction. The reduced ability
to discriminate weight on the injured leg likely reflects an impaired capacity to process
force signals at the central level, whilst the increase in cortico-motor excitability detected
on the hemisphere contra-lateral to the injured leg might be interpreted as a adaptation to
poor mechanical stability of the injured knee by substituting greater voluntary control
over more automatic reflex-driven muscle activity. Further research with large sample
sizes is needed to further examine these issues.
CHAPTER 1: General introduction
1.1 Introduction

Among the many orthopaedic injuries involving the knee joint, those involving the anterior cruciate ligament (ACL) are the most common (Arnold et al., 1979). Injury to this ligament leads to instability of the knee as well as persistent quadriceps weakness and decreased proprioception (Harter et al., 1988; Iwasa et al., 2000; Wojtys & Huston, 1994). Quadriceps weakness and proprioceptive deficits are both associated with, and contribute to, the functional decline following ACL injuries (Friden et al., 1999; Snyder-Mackler et al., 1995).

With regard to proprioception, the nature of the deficits has been described almost exclusively in terms of impaired static joint position and increased angular thresholds for movement detection (Friden et al., 1999; Iwasa et al., 2000), neglecting other important sensory attributes of the proprioceptive system like the ability to sense muscle force and to appreciate effort (Jones, 1986). In addition, deficits in joint position and movement detection are generally small when present (e.g., difference < 1-2° between legs) and therefore, of questionable functional significance (Matthews, 1982; Proske et al., 2000). Compared to joint position and movement detection, which rely primarily on signals coming from the periphery (i.e., muscle spindles), the sense of force and effort is thought to arise from a comparison of signals generated by the contracting muscles (i.e., tension receptors: golgi tendon organs) with those generated centrally through the voluntary drive (i.e., corollary discharges) (Gandevia & Burke, 1992; Matthews, 1982). Thus, the sense of force and effort provides an opportunity to assess how the processing of complex proprioceptive inputs can be affected as a result of unilateral knee dysfunction.
As stressed earlier, another important consequence of ACL injuries is the presence of persistent residual weakness in the quadriceps muscle, affecting individuals months and even years after the initial injury (Andersson et al., 1991; Wojtys & Huston, 1994). While this muscle weakness has traditionally been ascribed to reflex inhibitive influences of peripheral origin (Huber et al., 1998; Suter et al., 2001; Young & Stokes, 1986), recent investigations have demonstrated that alterations in the central drive also play a major role (Lorentzon et al., 1989; Urbach et al., 1991). The fact that central adaptations contribute to persistent extensors weakness after ACL injuries is evident when one considers that the strength deficit is still detectable even when signs of effusion or pain have long disappeared. It remains that few studies have examined how the corticospinal system may be changed as a result of chronic unilateral knee dysfunction.

In the context of the present work, we recruited a sample of participants with a history of chronic unilateral knee dysfunction secondary to ACL injuries. First we studied their ability to discriminate weights to assess their acuity to detect changes in force signals. Comparisons were performed between legs and also with a group of age-matched healthy participants that served as controls. In a second experiment, we magnetically stimulated the leg motor representation to derive several indices of cortico-motor excitability for the quadriceps muscle in each hemisphere. Overall, the goal of these descriptive studies was to provide further insights as to how the neuromuscular system is affected, and subsequently adapts, to a primary mechanical unilateral knee dysfunction.
CHAPTER 2: Review of the Literature
The knee joint is situated at the end of two long lever arms, the femur and the tibia. Because it is a shallow bi-condylar articulation, the knee relies on muscles and ligaments for stability. This anatomical configuration and the enormous reaction forces generated at the knee joint during high-speed weight-bearing movements render this articulation susceptible to injuries (Arnold et al., 1979). The incidence of ACL injuries is greatest in athletes aged 15-25 years participating in "pivoting" sports such as football and basketball; non-contact mechanisms being the primary cause (Arendt & Dick, 1995; Griffin et al., 2000). Due to smaller diameter ACLs, women suffer three to five times more ACL injuries than men (Arendt et al., 1999; Gwinn et al., 2000; Hewett, 2000). Re-injury rates are six times higher in individuals having previously suffered ACL injuries and treated conservatively, and three times higher following an ACL reconstruction (Oates et al., 1999).

The biomechanical role of the ACL is to prevent both anterior displacement of the tibia on the femur and hyperextension of the knee. Thus, injury to this ligament commonly leads to instability (Harter et al., 1988; Snyder-Mackler et al., 1997) and functional decline (Arendt & Dick, 1995; Snyder-Mackler et al., 1995). Subjective function, which is closely related to episodes of "giving way", is extremely important in individuals with ACL injuries since it reflects their ability to cope in the context of activities of daily living. Also, healthcare professionals use subjective function as a criterion to determine whether surgery is warranted (Fitzgerald et al., 2000). Research indicates that both proprioception and quadriceps strength are related to the level of function following ACL injuries (Chmielewski et al., 2001; Fischer-Rasmussen & Jensen, 2000; Friden et al., 1999; Rudolph et al., 2001).
As emphasized in the introduction, studies looking at proprioceptive deficits in individuals with ACL injuries have focused almost exclusively on static joint position sense and movement detection, ignoring other important proprioceptive capacities like the ability to discriminate weights and sense effort. Clearly, there is a need for further research regarding the exact nature of proprioceptive deficits in ACL injuries.

The following sections will examine the neural basis of proprioceptive abilities and persistent muscle weakness following ACL injuries in order to present key concepts and highlight the need for further studies.

2.1 Neural Basis of Proprioceptive Abilities Following ACL Injuries

Proprioception encompasses several sub-modalities including our ability to perceive static joint position and detect movement of the extremities as well as our capacity to sense force and assess effort (Brodie & Ross, 1984; Jones, 1986, 1994; Matthews, 1982, 1988). In 1900, Sherrington referred to proprioception as a “muscular sense” (Matthews, 1982), which originated from specific sensor organs in muscles, tendons, and joints; with those located in muscles being of primary importance. Sherrington’s view was almost entirely rejected in the 1960’s by physiologists who firmly believed joint afferents were solely responsible for proprioceptive abilities. Interestingly, Sherrington’s theory was reinstated in the 1970’s after several studies demonstrated the important contribution of muscle afferents to sense static joint position and limb displacements (Burgess & Clark, 1969; Goodwin et al., 1972).
2.1.1 Sense of Position

The sense of position refers to our ability to perceive static joint positions. Joint, cutaneous and muscle receptors are all stimulated by changes in joint position. The relative contribution of each group of receptors seems to vary depending upon the joint (e.g., large proximal joints vs. small distal joints) and a certain amount of redundancy is believed to exist (Matthews, 1982). At the knee joint, there is a large consensus that position sense results primarily from the integration of afferent signals generated by muscle spindles (Clark et al., 1986; Jones, 1994; Matthews, 1988; Proske et al., 2000). This consensus relies on multiple observations, from preservation of joint position sense after blockade of joint receptors to illusion of joint displacement induced by vibrating (thereby stimulating spindles) in knee muscles.

Although a variety of protocols have been developed to assess position sense at the knee, most studies have adopted passive-active or active-active matching procedures. In passive-active protocols, the knee is passively moved from a starting position to a predetermined index angle and returned to the starting position. Participants are then asked to actively reproduce the index angle with the ipsilateral knee (Fischer-Rasmussen & Jensen, 2000; Good et al., 1999; Iwasa et al., 2000). The active-active protocol follows essentially the same procedure, except that participants actively mobilize their joint to the index angle (Birmingham et al., 2001; Good et al., 1999). Clinician commonly use a variation of the active-active and passive-active matching procedures, where participants are asked to reproduce an index angle, which is being maintained by the contralateral limb (Schmitz, 2001).
Studies investigating position sense in individuals with ACL injuries have produced somewhat conflicting results. While Good et al. (1999) found no significant difference in position sense between uninjured and acute injured knees (average of 6 weeks post-injury), others have found small but significant deficits in both ACL injured and ACL surgically reconstructed knees (Fischer-Rasmussen & Jensen, 2000). Recently, Iwasa et al. (2000) reported a decrease in position sense pre-operatively in the knee of ACL injured patients, which gradually improved within 24 months after surgical reconstruction.

2.1.2 Sense of Movement

The sense of movement refers to one's ability to detect both the start and direction of limb movement. Although joint, cutaneous and muscle receptors are all stimulated by joint movement (Edin, 2001; Matthews, 1988; Proske et al., 1988; Proske et al., 2000), muscle spindles afferent signals are critical in signalling knee joint displacements (Matthews, 1982, 1988; Proske et al., 2000).

Various sitting and lying apparatus' have been developed to assess the sense of movement of the knee. The equipment is generally comprised of a support mechanism for the leg and a motorized system to mobilize the tibia in relation to the femur at a predetermined speed. With participants comfortably positioned, the knee is slowly moved (0.1°/s to 2°/s) into flexion or extension from various start positions (20° to 45° of knee flexion). Participants are instructed to indicate, either verbally or by pressing a button, when they have a clear sensation of movement. Studies typically measure threshold values, given by the minimum amount of angular displacement needed to detect the start
of a movement (Fischer-Rasmussen & Jensen, 2000; Friden et al., 1998; Friden et al., 1999). The most recent development in movement detection testing, which has yet to be used in ACL proprioceptive studies, is the integration of a signal detection theory (Weiler & Awiszus, 2001). Testing is very similar to the studies previously mentioned. The novelty of this approach consists of adding “shame” movement to the testing protocol, allowing researchers to determine the contribution of subjective bias (e.g., shift in decision criteria) in the central processing of movement detection.

Similar to joint position sense testing, studies on movement detection in individuals with ACL injuries have produced rather inconsistent results. Fisher-Rasmussen & Jensen (2000) found small but significant differences in movement detection thresholds (< 1°) when comparing injured and non-injured legs in individuals with ACL injuries. No such difference was observed when the comparison was made between individuals with ACL injuries and a control group. In a longitudinal study, Friden et al. (1999) reported important deficits in individuals with chronic ACL injuries where threshold values as high as 15° were reported in some individuals. These findings contradict previous results by the same authors where no proprioceptive deficits were found (Friden et al., 1998). Pap et al. (1999) also found no difference in movement detection thresholds between legs (injured versus uninjured) and between groups (ACL injured versus control). These authors did, however, report significant deficits in the ability to detect the start of a movement at various slow angular velocities (i.e., <1 °/s) on the injured side. Therefore, the extreme threshold values (i.e. 15°) reported by Friden et al (1999) most probably reflect a failure to detect the start of the movement and not, as suggested by the authors, large deficits in movement detection. Overall, although deficits in the ability to sense
knee position and detect limb movement have been reported, these deficits appear to be rather small and inconsistent across individuals. Such a conclusion is not surprising given that signals from muscle receptors are still available after ligament injuries; a fact seldom acknowledged in most reviewed studies. Possible methodological reasons for the lack of consistent results regarding the nature of proprioceptive deficits in ACL injuries will be examined in the next section.

2.1.3 Criticisms on Methodological Aspects of Studies Looking at Position Sense and Movement Detection in ACL Injuries

One important limitation of proprioceptive studies involving individuals with ACL injuries pertains to the influence of muscle conditioning (i.e., contraction history of muscles surrounding the joint prior to testing) on proprioceptive acuity [see Prosko et al. (2000) for a review]. As shown by Wise et al. (1996), failure to account for muscle conditioning (i.e., taking up the slack caused by a previous contraction) may translate into a shift of 0.3°-0.7° in threshold values for detecting limb movement, which is highly significant considering that reported deficits ranged between 0.2-2.0°. The selection of angular velocities to test movement detection is another major limiting factors in published studies. Muscle primary endings are highly dynamic receptors sensitive to the speed of joint displacements, as demonstrated by a steep decrease in detection threshold with movement speeds > 1°/s. For instance, Hall & McCloskey (1983) calculated that, in the large proximal joints of the extremities, a 10-fold increase in the angular displacement would be required in order to detect a movement performed at 0.15°/s compared to 1.25°/s. The problem is that in the vast majority of studies performed in individuals with
ACL injuries, movement detection was tested under conditions of angular velocities \( \leq 1^\circ/s \). Such an observation may explain many of the inconsistencies reported regarding movement detection abilities in individuals with ACL injuries.

### 2.1.4 Sense of Force and Effort

In 1834, Weber was the first to fully appreciate the importance of weight perception in relation to what was then termed the "muscular sense" (Jones, 1986). Evidence that signals from contracting muscle participated in weight perception came from Weber's seminal observation that weight discrimination was far more accurate when objects were actively lifted compared to when it was passively applied on the skin. More recent studies have helped better understand this proprioceptive ability and it is well accepted that both central and peripheral sensory signals contribute to the perception of force and effort (Ross & Brodie, 1987). The perception of weight and force signals is thought to arise from the comparison of sensory signals coming from the contracting muscles via tension receptors with those generated centrally in the form of corollary discharge associated with the voluntary drive required to activate the agonist muscles (review in Jones, 1986). Similar to movement sense, the human proprioceptive system is highly sensitive to changes in force, as differences in weight in the order of 5-10% are reliably discriminated during active lifting movements (Brodie & Ross, 1984; Ross & Brodie, 1987). Thus, the study of force perception provides a means to assess the processing of complex sensory signals arising from peripheral and central sources. In addition, the study of force perception relates more closely to actual functional performance of the proprioceptive system, since we rely on weight discrimination every day when grasping and transporting...
objects of different mass. Yet, to date, possible alterations in the sense of force and effort have not been studied in individuals with ACL injuries.

2.2 Persistent Muscle Weakness Following ACL Injuries

Muscles surrounding the knee joint play an important role in increasing joint stiffness and dissipating forces, both of which help protect the soft tissue structures of the knee (Farley & Gonzalez, 1996; Goldfuss et al., 1973; Markolf et al., 1978; Wang & Liu, 1995; Winter, 1983).

In the acute phase following an ACL injury, pain, effusion and immobilization lead to muscle wasting and weakness (Booth, 1977; Young et al., 1987). Surprisingly, weakness persists for months and years following the initial injury (Messner & Maletius, 1999; St Clair Gibson et al., 2000; Wojtys & Huston, 1994), long after a course of conventional rehabilitation has been completed and acute symptoms have subsided (Hurley & Newham, 1993; Wojtys & Huston, 2000). Whilst it is generally agreed upon that muscle atrophy and reflex inhibition contribute to persistent weakness (Booth, 1977, 1987; Suter et al., 2001; Young & Stokes, 1986), numerous authors have indicated that changes in cortico-motor excitability may also play an important role in quadriceps weakness following ACL injuries (Elmqvist, 1988; Lorentzon et al., 1989; Johansson et al., 1988; Gauffin et al., 1990; Wojtys & Huston, 1994; Young, 1993).

The next two sections will examine the pattern of muscle weakness in individuals with ACL injuries and the various techniques used by researchers to investigate the source of this persistent weakness. This will be followed by an overview of various factors that may contribute to persistent quadriceps weakness following ACL injuries.
2.2.1 Patterns of Muscle Weakness Following ACL Injuries

The quadriceps is most affected by an ACL injury with a 15-40% decrease in isometric maximal voluntary contraction and isokinetic peak torque (Hurley et al., 1992; Rudolph et al., 2001; Wojtys & Huston, 1994, 2000). This weakness is velocity dependant, with greater weakness at lower movement velocity (Newham et al., 1989), and is twice as important during eccentric contractions compared to concentric contractions (St Clair Gibson et al., 2000). Quadriceps endurance, although not often evaluated, is also decreased following ACL injuries (Wojtys & Huston, 2000).

Knee flexor weakness following ACL injuries has received considerably less attention. Some studies have reported deficits of 9-15% in isometric maximal voluntary contraction (concentric and eccentric) and isokinetic peak torque (St Clair Gibson et al., 2000; Wojtys & Huston, 1994), whereas others found no knee flexor weakness (Hurley et al., 1992; Wojtys & Huston, 2000).

Traditionally, strength testing has relied on the controlateral limb for control values. When evaluating individuals with ACL injuries, however, this practice can lead to an underestimation of muscle weakness. Using a control group matched for age and activity level, Urbach et al. (2000) demonstrated that isometric knee extensor torque is decreased on the injured (31%) and uninjured side (14%) following an ACL injury. Such results raises many questions regarding the source of bilateral weakness in individuals with unilateral knee dysfunction as well as the validity of traditional strength testing in individuals with orthopaedic injuries.
Researchers have identified a group of individuals that present no strength deficits following an ACL injury (Wojtys & Huston, 1994). These individuals are akin to what Rudolph et al. (2001) described as "copers": a rare subgroup of individuals who do not suffer from knee joint instability following ACL injuries. In their study, Rudolph et al. reported that copers have normal quadriceps strength, whereas non-copers had a 25% decrease in strength. Although very little is known as to why some individuals are able to maintain a stable knee and relatively normal quadriceps strength following ACL injuries, it is important to be aware that such cases exist since the presence of copers in studies with small sample sizes may skew research results. Also, these individuals provide researchers with the opportunity to study various adaptations and strategies that lead to strength and stability to be maintained following ACL injuries.

2.2.2 Methods to Assess the Source Muscle Dysfunction: Various

Electrophysiological and Biomechanical Techniques

Arthrogenic muscle inhibition, a vague term referring to the inability to fully activate a muscle due to the presence of joint pathology, has guided much of the persistent muscle weakness research (Hopkins & Ingersoll, 2000; Hurley et al., 1994; Hurley et al., 1992; Hurley & Newham, 1993; Stokes & Young, 1984a).¹ Integrated EMG, voluntary force output, interpolated-twitch techniques as well as the H-reflex have all been used to measure reflex inhibition. A brief review of each technique follows.

A significant difference in the amount of EMG activity of a muscle compared to the contralateral side during a maximal voluntary contraction has been proposed to be a

¹ In order to avoid confusion as well as use a more precise and appropriate term, reflex inhibition will replace the term arthrogenic muscle inhibition from this point forward.
measure of reflex inhibition (Stokes & Young, 1984b). For integrated EMG to be valid, participants must be willing to produce a maximal voluntary contraction, which may not be possible in the presence of a pathological condition affecting the knee joint (Doxey & Eisenman, 1987; Hopkins & Ingersoll, 2000). The validity of maximal voluntary torque output measured by motorized dynamometer is limited since it too requires a maximal contraction of muscles acting across a possibly painful or unstable joint. Also, the bilateral quadriceps weakness noted in individuals with ACL (Hurley et al., 1994; Urbach et al., 1991) renders side-to-side comparisons of torque values a poor estimate of reflex inhibition. Interpolated-twitch technique uses a brief electrical stimulation of the femoral nerve during a maximal isometric knee extension performed on a motorized dynanometer [see Suter et al. (2001) for a detailed description of this technique]. The electrical twitch produces an increase in torque when the quadriceps is not fully activated. Although many authors have reported reduced voluntary activation in the quadriceps on the side of the injury in individuals with ACL injuries (Hopkins & Ingersoll, 2000; Stokes & Young, 1984a; Suter et al., 2001; Young, 1993), the validity of this technique has been questioned recently. Antidromic and reflex effects induced by the electrical stimulation reduce the amplitude of the interpolated twitch (Herbert & Gandevia, 1999). Also, a non-linear relationship between the interpolated twitch and motoneuron pool excitation has been reported (Behm et al., 1996; Dowling et al., 1994; Lloyd et al., 1991) indicating that an increase in stimulus intensity produces relatively small changes in interpolated twitch amplitude when testing at maximal or near-maximal contraction intensities (Herbert & Gandevia, 1999). Similar to other evaluation techniques, the inability of some individuals to generate maximal contractions due to pain, swelling or apprehension may influence
interpolated-twitch technique results (Behm et al., 1996). The final technique is the H-reflex, which measures the excitability of a portion of the motoneuron pool of the muscle being tested. Electrical stimulation of a mixed nerve in the periphery stimulates primary (Ia) afferent fibres, which reach the anterior horn of the spinal cord and synapse with α-motoneurons. Reflex muscle activity induced by the depolarization of α-motoneurons is captured with EMG electrodes on the surface of the skin overlying the muscle. The H-reflex may be influenced by various external (e.g., room temperature, limb and neck position) and internal (e.g., mental arousal) factors (Kameyama et al., 1989), thus care must be taken to standardize the evaluation procedure. Also, the H-reflex varies a great deal from one muscle to the next. For example, the soleus H-reflex is easily elicited in most individuals by stimulating the posterior tibial nerve in the popliteus fossa, whereas the quadriceps H-reflex is notoriously difficult to elicit (Garland et al., 1994; Schieppati, 1987). This difficulty is largely due to anatomical factors relating to the location of the femoral nerve (Hopkins et al., 2000), which also renders quadriceps H-reflex latency unreliable due to the extreme proximity of M and H waves (Kameyama et al., 1989). As opposed to the previously mentioned techniques, the H-reflex can be elicited at rest, eliminating the need for a maximum voluntary contraction.
2.2.3 Factors Contributing to Persistent Muscle Weakness

a) Immobilization, Disuse and Atrophy

In the acute phase following ACL injuries, the knee may be immobilized to prevent further injury and facilitate healing. Unfortunately, immobilization leads to rapid-onset muscular atrophy, with a 14-17% loss of muscle fibre size in the first 72 hours (Booth, 1977). Also, half of the total muscle mass that will be lost during long-term immobilization occurs within the first nine days (Lindboe & Platou, 1984). Recently, Hortobagyi et al. (2000) found a 10% decrease in muscle fibre area (type I 13%, IIa 10% and IIx 10%) in the vastus lateralis muscle following a three-week period of immobilization of the knee in healthy individuals. This reduction in muscle fibre areas coincided with a 47% reduction in eccentric, concentric and isometric quadriceps strength, reflecting the close relationship that exists between muscle cross-sectional area and force generating capabilities (Maughan et al., 1983a, 1983b; Schantz et al., 1983).

Although not all individuals with acute ACL injuries undergo periods of immobilization, most are instructed in crutch walking for a period ranging from a few days to a few weeks. This type of unloading leads to a shift in muscle fibre type in lower extremity muscles (i.e., from slow twitch to fast twitch) and a 20% decrease in quadriceps strength (Berg et al., 1991; Pette et al., 1999; Scott et al., 2001). Alteration of the walking pattern is another form of unloading. Gait adaptations are common following ACL injuries (Roberts et al., 1998; Rudolph et al., 2001; Wexler et al., 1998) and the quadriceps avoidance pattern adopted is thought to reduce anterior tibial shear (Berchuck et al., 1990; DeVita et al., 1998). There is, however, much debate surrounding this issue.
and recent findings indicate that gait adaptations are actually compensatory mechanisms
used by individuals with ACL injuries to increase knee stability during walking (Roberts
& al., 1999; Zang et al., 2003). Whatever the reason for these adaptations, knee extensor
torque is decreased during walking following ACL injuries, which may contribute to
persistent muscle weakness.

Muscular atrophy is common following a joint injury and is primarily in the
quadriiceps when the knee is involved (Ingemann-Hansen & Halkjaer-Kristensen, 1980;
LoPresti et al., 1984; Sargeant et al., 1977; Young et al., 1980). Although both
immobilization and joint injury cause muscle weakness and atrophy, the mechanisms
involved may not be the same (MacDougall et al., 1980; MacDougall et al., 1977).
Following a three-week period of immobilization, quadriiceps strength and vastus lateralis
atrophy are greatly improved after only two weeks of spontaneous recovery, with a return
to baseline values within 12 weeks (Hortobagyi et al., 2000). This is in direct opposition
to the persistent muscle weakness observed following ACL injuries. As previously stated,
the force generating capacity of a muscle is direcontroly related to its cross-sectional
area, however, Lorentzon et al. (1989) found no correlation between quadriiceps atrophy
and quadriiceps weakness following ACL injuries. Since muscle atrophy could not, by
itself, account for the muscle weakness, the authors’ suggested that a decrease in
voluntary activation was responsible for the excessive weakness. Lorentzon and his
colleagues pushed forth the idea, as have numerous other authors (Elmqvist, 1988;
Johansson et al., 1988; Gauffin et al., 1990; Wojtyts & Huston, 1994; Young, 1993), that
changes in cortico-motor excitability are involved in persistent quadriiceps weakness
following ACL injuries. Unfortunately, current research has yet to investigate such changes.

b) Reflex Inhibition

Numerous authors have reported reflex inhibition in individuals with ACL injuries and believe it play a key role in persistent quadriceps weakness (Hopkins & Ingersoll, 2000; Stokes & Young, 1984a; Suter et al., 2001; Young, 1993). In the sub-acute and chronic phases, free-nerve endings, acting as nociceptors, and mechanoreceptors located in the ligaments, menisci and joint capsule of the knee are thought to reflexively inhibit quadriceps α-motoneurons in response to clinical or sub-clinical joint effusion and unnatural joint translation (Cole et al., 1996; Ferrell, 1980; Young & Stokes, 1986; Zimny, 1988).

Recently, tonic and phasic reflexes were shown to contribute 30-50% of the total extensor torque during low to moderate intensity contraction (0-60% MVC) and 5-30% during high intensity contraction in healthy individuals (Mrachacz-Kersting & Sinkjaer, 2003). Thus, reflex inhibition in individuals with ACL injuries may reduce the normal reflex contribution to knee extensor torque (especially during low to moderate intensity contractions) and lead to quadriceps weakness. To date, however, no study has confirmed that reflex inhibition influences the normal reflex contribution. Also, the contribution of reflexes reaches a minimum (>10% of the total extensor torque) during maximal contractions, which is the intensity used in studies reporting reflex inhibition in individuals with ACL injuries.

In summary, it seems probable that reflex inhibition contributes to persistent muscle weakness in individuals with ACL injuries. There is, however, a definite need to
determine if reflex inhibition is present at low to moderate intensity contractions in this patient population whether this type of inhibition influences the normal reflex contribution to total extensor torque.

c) Cortical Adaptations

Although only indirect evidence exists, several authors have stressed the possible contribution of changes in supraspinal excitability to persistent quadriceps weakness following ACL injuries (Elmqvist, 1988; Johansson et al., 1988; Gauffin et al., 1990; Lorentzon et al., 1989; Wojtys & Huston, 1994; Young, 1993). Consistent with this possibility, Urback et al. (1991) demonstrated that quadriceps weakness affected both sides in individuals with unilateral ACL injuries. Reflex inhibition induced by afferent signals (knee joint receptors) may decrease α-motoneurons excitability on the ipsilateral side, contralateral effects of this nature are believed to results from transcallosal pathways causing inhibition of cortical output (Kossev et al., 2001). Whilst current research supports the view that disuse atrophy and reflex inhibition contribute to persistent weakness following ACL injuries, there is mounting evidence indicating that cortical adaptation likely contribute to this muscular dysfunction.

With the introduction of new non-invasive techniques such as functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS), it has now become possible to assess the effect of various conditions, such as strokes and spinal cord injuries, on cortical representations. Changes in the size of cortical representations and in cortico-motor excitability have been described after lesions at the spinal and cortical levels (Cohen et al., 1991; Levy et al., 1990; Nudo et al., 1996). Peripheral nerve lesions
(Donoghue et al., 1990) and limb amputations (Cohen et al., 1991; Ridding & Rothwell, 1995) also induce reorganization of the cortico-motor system, which occurs within hours of the initial injury (Donoghue et al., 1990; Huntley, 1997). Although these types of central nervous system injuries are extreme examples, cortical adaptations have also been reported following joint immobilization (Liepert et al., 1995; Zanette et al., 1997). Interestingly, such changes in cortical excitability return to baseline following a month of spontaneous recovery, which coincides with the normal time-course of strength recovery following a period of immobilization (Hortobagyi et al., 2000). These observations point to a possible link between muscular deficits and changes in cortico-motor excitability in orthopaedic injuries.

2.3 Conclusions

Trauma to the ACL is the most common orthopaedic injury involving the knee and leads to functional limitations. Two impairments associated with this functional decline are knee joint proprioception deficits and persistent quadriceps weakness. A review of proprioceptive deficits following ACL injury reveals a major focus on joint position sense and movement detection along with a dearth of information regarding other important sensory aspects of proprioception, like force and effort perception. In addition, many inconsistencies and methodological limitations have hampered any definitive conclusion as to the exact nature of these deficits in this population. Clearly, there is a need for more studies to examine issues pertaining to proprioceptive deficits in individuals with ACL injuries. Similarly, studies that have looked at persistent muscle weakness following ACL injuries has focused almost entirely on reflex inhibition, in spite
of a growing body of evidence suggesting that alterations at the supraspinal level do occur and may play an important role.

2.4 Objectives of the Present Work

In the context of this thesis project, we have attempted to gain further insights as to the nature of the proprioceptive deficits affecting individuals with ACL injuries and the possible adaptations at the cortico-motor level resulting from unilateral knee dysfunction. More specifically, our goal was to:

1) Better characterize the nature of proprioceptive deficits following ACL injuries with regard to the perception of force, as reflected in the ability to discriminate small differences in weight.

2) Examine how the corticospinal system may be changed as a result of chronic unilateral knee dysfunction by looking at several indices of cortico-motor excitability derived from TMS of the quadriceps motor representation.

2.5 Experimental Design

We adopted a case-control descriptive design (Hopkins, 1998) to study the effect of unilateral chronic knee instability on knee joint proprioception and quadriceps cortico-motor excitability. Clinical and neurophysiological measurements were performed on each leg to allow bilateral comparisons between the injured and uninjured side. A group of age-matched healthy participants, with no previous history of knee injuries, was also recruited to serve as controls. All testing procedures were done bilaterally and the order
of testing (i.e., uninjured/injured or right/left leg tested first or second) was randomly chosen for all participants.

The results of the two experiments (proprioception and TMS) are described in the following chapters in the form of two scientific articles. A general discussion addressing the overall impact and significance of the results from the two experiments follows.
CHAPTER 3:

Proprioceptive acuity for weight discrimination

after unilateral ACL injury
3.1 Introduction

Injury of the ACL is the most common knee pathology in sports and occupational activities (Arnold et al., 1979). The mechanism usually involves production of large reaction forces during high-speed pivoting movements, leading to excessive stress on knee ligaments (Wojtyś & Huston, 1994). In the long-term, ACL injuries often leave individuals with a chronic instability, which has been traditionally linked to persistent weakness of the quadriceps and deficient proprioception (Arnold et al., 1979). With regard to proprioceptive deficits, most studies have focused on joint position sense and movement detection to examine differences in proprioceptive acuity between uninjured and injured knees. While many authors have found significant deficits in the ability to sense joint position and to detect movement in the injured knee of affected individuals (Friden et al., 1999; Iwasa et al., 2000), the differences reported were often small (usually <1-2° between limbs) and often of questionable functional significance given the range of passive joint velocities (< 2 °/s) tested to reveal the deficits. It is not surprising, therefore, to find other reports in which authors failed to find deficits in joint position sense and movement detection after ACL injuries (Friden et al., 1998; Good et al., 1999; Pap et al., 1999). One likely reason for such inconsistencies is that muscle receptors (i.e., spindles), and not joint receptors, are known to be the major source of information for joint position sense and movement detection in the large joints of the lower extremity [see Matthews (1982) and Proske et al. (2000) for a review], a fact often overlooked in many studies on proprioceptive deficits associated with ACL injuries. Thus, even with an impaired ligament function, knee position and movement can still be inferred on the basis of
sensory input encoded in the discharge of spindle afferents supplying the quadriceps and hamstrings.

It needs to be emphasized that joint position and movement detection (i.e., kinaesthesia) are not the only sensory attributes of the proprioceptive system. Indeed, the ability to perceive force and effort is another major attribute of proprioception, one of which we are relying to in everyday tasks (e.g., comparing the weight of apples at the groceries). In fact, the ability to perceive weights and appreciate muscle force is quite acute in humans considering that differences in weight in the order of 5% to 10% can be reliably discriminated with active lifting movements (Brodie & Ross, 1984; Ross & Brodie, 1987). The sense of force and effort differs from the peripherally-driven kinesthetic senses (joint and movement) in that they originate both from signals arising peripherally, golgi tendon organs being the most likely source (Gandevia & Burke, 1992), and also from signals arising centrally in the form of descending motor commands (i.e., corollary discharges). Both sources, peripheral and central, appear to contribute to our ability to compare and match weights of different mass (Jones, 1986; Matthews, 1982).

In the present study, we sought to determine whether the ability to perceive small differences in weight remained accurate in individuals presenting chronic unilateral knee instability secondary to ACL injuries. We also looked at whether deficits in proprioceptive acuity for weight discrimination could be commensurate with subjective reports of knee dysfunction and observed deficits in knee extensor strength.
3.2 Methods

3.2.1 Participants

Eighteen participants were recruited for this study. Of these, ten presented chronic ACL injuries. The ACL injury occurred between four months and nine years prior to participation, with no knee joint swelling or pain in the month prior to testing. The clinical and demographic characteristics of participants with ACL injuries are described in Table 1. The remaining eight participants consisted of healthy controls (mean age, 22.6 ± 2.8 years; 4 female). Participants with chronic ACL injuries were recruited in outpatient orthopaedic physiotherapy in the Ottawa-Gatineau region (Ontario, Canada). Healthy controls were recruited from the population of undergraduates in the Faculty of Health Sciences. The University of Ottawa Human Research Ethics Board approved the study’s procedures, and written informed consent was obtained prior to participation.

3.2.2 Subjective Assessment of Knee Function

To assess subjective knee function, we used the Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS). The KOS-ADLS is a valid and reliable (test-retest reliability coefficient of 0.97) tool to assess subjective knee function (Irrgang et al., 1998). The scale consists of 17 questions assessing the relationship between subjective symptoms related to knee pathology (e.g., pain and swelling) and functional limitations in various activities of daily living (e.g., walking and stair climbing) on an ordinal scale. A maximum of score 80 represents no functional limitations or symptoms.
3.2.3 Knee Extensors Strength

Muscle strength was measured on a KIN-COM® 500H dynamometer (Chattecx Corporation, Chattanooga Group, TN) during maximal static voluntary contractions (MVC) of the quadriceps. For this assessment participants were seated with the lateral epicondyle of the femur aligned with the axis of rotation of the dynamometer. Participants were secured to the testing chair with a seatbelt and an additional Velcro strap (6-inch wide) across their upper torso. Following a brief warm-up of five submaximal contractions, participants were asked to build up force over a two second period and hold the MVC for an additional two to three seconds. Three MVC were performed for each leg with a one-minute rest period between each trial. The order of testing (i.e., uninjured/injured or right/left leg tested first or second) alternated for all participants. The peak torque values produced in the three trials were averaged for each leg to provide an index of knee extensors strength.

3.2.4 Weight Discrimination Protocol

The weight-discrimination protocol was similar to that used in a previous study in our lab (Tremblay et al. 2001) with only slight modifications to the mass of the reference weight and the addition of new comparison weights. The standard weight (3.00 kg) corresponded to the weight of the unloaded lever system (2.50 kg) with an additional 0.50 kg increment. The comparison weights consisted of four metric metal weights (0.09, 0.20, 0.28, 0.50 kg; Elgin Co, Elgin, IL), which were added to the standard weight to increase its mass. Besides these changes, the overall testing procedure and sequence of weight presentations was identical to that described previously (see Tremblay et al. for a detail
description). Briefly, for testing, participants were comfortably seated on a conventional leg exercise table (Model 2400, Midland Co, Columbia, SC). The exercise tables' leg pad was adjusted 10 cm proximally from the lateral malleolus of the ankle (see figure 1). Subjects were blindfolded and provided with a series of practice trials consisting of five easy discriminations (0.50 kg increment) and five more difficult discriminations (0.09 kg increment). Each trial consisted of two weight representations: standard weight and comparison weight. Following a tap on the knee, participants lifted each weight successively and report which of the two weights (first or second) was heavier according to a two-alternative forced choice procedure. Participants were free to choose the movement range (90°-180°) and speed of contraction they deemed most appropriate to estimate the presented weight. The lever arm was pulled away from the subjects' leg when loading and unloading the lever to avoid pressure cues. During practice trials, participants were given verbal feedback on their discriminative performance. The testing session began once the participants felt comfortable with the task.

During testing, participants remained blindfolded and were given earplugs to eliminate auditory cues. Blocks of 14 trials of weight comparisons were performed on each leg in all participants. In each block, the two alternatives (first or second) were equally probable with the order of presentation of the first and second weight being pseudorandom from trial-to-trial. Comparison weights were presented in four successive blocks of increasing difficulty (i.e., from 0.50 kg increment down to 0.09 kg increment). No feedback was provided to participants concerning their discriminative performance during or after testing. The order of testing between legs (i.e., uninjured/injured or right/left leg) alternated between participants.
The performance of each participant (ACL and control) in the weight-discrimination task (i.e., the number of correct discriminations for each comparison weight) was calculated and a discriminative function was constructed by plotting performance values in percentages against increments in weight. From performance values, discrimination thresholds were derived for each leg. In a two-alternative forced choice procedure the discrimination threshold corresponds by convention to the difference from the standard that yields a 75% correct discrimination. Unless observed performances matched that level exacotroly, discrimination thresholds were obtained from linear extrapolation of performance values just above and below the criterion-level to estimate the minimal increment in weight yielding a 75% correct level. In one control participant and one participant with an ACL injury, performance was greater than 75% at the lightest increment (i.e., 0.09 kg), in which case the threshold was set at 0.09 kg for statistical purposes.

3.2.5 Data Analysis

In each group, KOS-ADL scores, knee extensors strength (peak torque in Nm) and weight-discrimination thresholds (in g) obtained in each leg were compared using paired t-tests (ACL group, uninjured versus injured; control group, left versus right). Pearson’s coefficients of correlation were also used to assess the strength of the relationship between proprioceptive acuity thresholds and corresponding KOS-ADLS scores and peak torque values. All statistical tests were performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com"). The level of significance was set at $p < 0.05$ for all tests.
3.3 Results

3.3.1 Subjective Knee Function and Knee Extensors Strength

As expected, participants in the ACL group reported significantly lower functional scores ($t=3.34; p=0.012$) on the injured (mean, 66.2 ± 10.2) compared to the uninjured side (Figure 2 A). In fact, all participants reached the maximum functional score of 80 on the uninjured side (Figure 2 A). In the control group, apart from one participant scoring 79 on the right side, all scored the maximum (i.e., 80), indicating no perceived limitations in knee function. Individual peak torque values for knee extensors strength are shown in Figure 2 B. Although there was a large inter-individual variability in terms of absolute strength, 8/10 participants in the ACL group produced lower torque on the injured side, a difference that was statistically significant ($t=2.92; p=0.017$). A closer inspection of the data revealed that this difference was largely attributable to participants with grade III injuries (mean reduction in torque, 16%, n=7). As evident in Figure 2 B, peak torque values for the two legs were very similar in the control group ($t=1.551; p=0.164$).

3.3.2 Proprioceptive Acuity for Weight Discrimination

Figure 3 illustrates the discriminative function derived in each group from performance in the weight discrimination task. It can be seen that discrimination performance decreased with smaller weight increments, as comparisons with the standard weight became more and more difficult. As evident in the figure, the shape of the discriminative function varied between the two legs in the ACL group (Figure 3 A),

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whereas the two functions were very similar in control participants (Figure 3 B). On the
uninjured side, participants in the ACL group exhibited performance levels similar to the
control group, although they tended to make more errors in judging the second largest
increment in weight (i.e., 0.28 Kg). On the injured side, the same participants tended to
make more errors in judging the heavier weight even with presentation of the largest
increment, and the overall level of performance was degraded compared to the uninjured
side. The degraded performance of participants with ACL injuries in judging weights on
the injured side was reflected in the discrimination thresholds computed for that leg
(Figure 3 C), which were found to be significantly higher than those determined on the
uninjured side (injured, 199.9±68.3 g; uninjured, 144.1±33.9 g; \( t=3.51, p<0.01 \)). In
contrast, bilateral threshold estimates obtained in control participants were not
significantly different (right, 161.7±42.6 g; left, 171.6±40.2 g; \( t=0.74, p=0.48 \)).

3.3.3 Relationship between Proprioceptive Acuity Thresholds and Indices of Knee
Function

In Figure 4 A, individual functional scores derived from the KOS-ADLS
questionnaire on the injured side of participants in the ACL group have been plotted
against corresponding weight discrimination threshold values. Although subjective
ratings of knee function tended to be lower in participants with decreased discriminative
ability (i.e., higher threshold), the low \( r^2 \)-value indicates the two variables were poorly
correlated. A similar representation for the association between knee extensors strength
and weight discrimination threshold values is shown in Figure 4 B. Knee extensors
strength was poorly correlated with proprioceptive abilities on the injured and injured
side. Elimination of one outlier revealed a slight trend between the ability to produce
greater extensor torque and greater weight discrimination thresholds for both the injured
($r^2=0.18$, $p=0.270$) and uninjured legs ($r^2=0.18$, $p=0.252$). A similar trend was noted on
the right side in the control group ($r^2=0.28$, $p=0.177$).
3.4 Discussion

In this study, proprioceptive acuity, as reflected by the ability to perceive small differences in weight, was significantly reduced on the injured side in participants with unilateral ACL injuries. In the ACL group, participants were able to discriminate an increase of 144 g from the standard weight (i.e., 3 kg) on the uninjured side, compared to an increase of 200 g from the standard weight on the injured side. Participants from the control group presented no significant side-to-side differences. In the following discussion, we will analyse our results in the context of current proprioceptive research and address the possible causes for the proprioceptive deficits noted in the ACL group.

3.4.1 Deficits in Weight Discrimination Following an ACL Injury

Participants with ACL injuries were able to discriminate ~5% increase from the standard weight with their uninjured leg compared to ~7% increase with their injured leg, a significant difference of 2% between sides. The same comparison with the control group reveals a 0.3% difference between sides (right, 5.4% increase; left 5.7% increase). Although proprioceptive acuity was significantly decreased on the injured side in participants with ACL injuries, threshold values from both ACL and control groups were within the normal perceptual range reported for detecting differences in weight [5-10%, (Brodie & Ross, 1984)]. This finding indicates that, although acuity was different between the two legs, the ability to discriminate weights is still relatively preserved in individuals with chronic ACL injuries. The fact that proprioceptive acuity for force discrimination was relatively preserved in the injured leg may explain why no correlations could be established between proprioceptive thresholds and subjective
ratings of knee function. However, a larger sample of participants may be required in order to resolve this issue given the large inter-individual variability observed in the present study.

3.4.2 Sources Contributing to Deficits Observed in Weight Discrimination

The ability to precisely estimate force and effort is the result of an integration of sensory signals from peripheral receptors (i.e., GTO) and descending motor commands (i.e., corollaries). There is still much debate as to the relative importance of these two factors (Jones, 1986) and it has been suggested that one source of sensory information may be favoured over another depending of the individual and whether or not a pathological process is present (Carson et al., 2002; Tremblay et al., 2001). Therefore, changes in both peripheral and central factors associated with an ACL injury may have contributed to the deficits observed in weight discrimination.

Golgi tendon organs are believed to be the prime contributors to the sense of force and effort due to their sensitivity to changes in muscle tension (Crago et al., 1982). In principles, ligament injuries should not affect GTO, which are located in the myotendinous area, although such a possibility cannot be excluded entirely. Another more likely possibility, however, is that signals from group II, III and IV joint afferents located in the surrounding capsular tissues, might have been altered as a result of the lesion. These joint afferents, whilst poorly responsive to passive mobilizations, are known to be highly active during active muscle contractions; making them a possible additional source to monitor force signals during contraction (Gandevia & Burke, 1992). Accordingly, altered or diminished inputs from group II-IV joint afferents may have impaired the
ability to appreciate changes in muscle force in the discrimination task. On the other hand, in the presence of significant muscle weakness, it has been shown that individuals tend to rely more on centrally generated signals than on peripheral signals (Carson et al., 2002). Therefore, it is possible that our participants used different sensory strategies to discriminate weights, those with relatively well preserved force relying more on peripheral signals (albeit altered) and those with weaker quadriceps relying more on corollary discharges from central commands. Such a possibility may explain why stronger individuals in the ACL group tended to exhibit poorer acuity thresholds, whereas the reverse trend was observed in those with weaker quadriceps. Again, a larger sample of participants with ACL injuries is needed to further examine this issue. It remains that, for some individuals in our ACL group, an alteration in the peripheral input signalling muscle tension along with an inability to calibrate this signal centrally might underlie the reduced capacity for weight discrimination on the injured side.

3.4.3 The Functional Importance of Unilateral Weight Discrimination Deficits

Whilst the difference observed between the two legs in terms of discriminative capacity seems quite small (2% on average), functionally speaking it could translate into major differences in everyday life. To appreciate this, one has to consider that in daily life the quadriceps functions at very low level of activation most of the times (i.e., >20% of the MVC, Kern et al 2001), so the functional range of muscle forces that has to be monitored centrally could be quite low. It follows that an inability to properly assess even small differences in force could lead to difficulties in activities such as walking on uneven ground or ascending stairs. It is important to emphasize that our task paradigm
with weight discrimination bears more resemblance to what people actually do in everyday activities in terms of sensori-motor operations (i.e., sensing the effort and force destined to muscles) instead of looking at abilities to reproduce static joint angles and detect very slow movements. It remains that more studies are needed in order to further characterize the nature of deficits affecting the perception of force and effort. It would be interesting, in particular, to pursue this line of investigation with studies using weight matching protocols to assess perceived effort in individuals with ACL injuries to determine if similar deficits would be present and if they would be better correlated to the level of function compared to deficits in weight discrimination.

3.4.4 Conclusion

Our study was the first to investigate weight discrimination capacity in individuals with chronic ACL injuries. We found small, but significant, deficits in the ability to discriminate weights on the injured side. Although certain factors possibly contributing to these deficits have been identified, the exact source of the proprioceptive deficits remains unclear. There is a need to study larger, more homogenous groups to determine if similar deficits characterize this patient population.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Dominance</th>
<th>Injury</th>
<th>KOS-ADLS*</th>
<th>Post-injury</th>
<th>Severity of injury**</th>
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<td>Left</td>
<td>52</td>
<td>&lt; 1 year</td>
<td>Grade III ACL tear</td>
</tr>
<tr>
<td>ACL02</td>
<td>20</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>75</td>
<td>1-2 years</td>
<td>Grade II ACL tear</td>
</tr>
<tr>
<td>ACL03</td>
<td>23</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>56</td>
<td>&gt; 2 years</td>
<td>ACL repair with laxity</td>
</tr>
<tr>
<td>ACL04</td>
<td>35</td>
<td>Female</td>
<td>Right</td>
<td>Right</td>
<td>79</td>
<td>&gt; 2 years</td>
<td>Grade III ACL tear</td>
</tr>
<tr>
<td>ACL05</td>
<td>24</td>
<td>Male</td>
<td>Right</td>
<td>Left</td>
<td>60</td>
<td>&gt; 2 years</td>
<td>Grade II ACL tear</td>
</tr>
<tr>
<td>ACL06</td>
<td>21</td>
<td>Male</td>
<td>Left</td>
<td>Left</td>
<td>74</td>
<td>1-2 years</td>
<td>Grade III ACL tear</td>
</tr>
<tr>
<td>ACL07</td>
<td>23</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>72</td>
<td>&lt; 1 year</td>
<td>Grade III tear (contralateral ACL repair 4 years ago)</td>
</tr>
<tr>
<td>ACL08</td>
<td>21</td>
<td>Male</td>
<td>Right</td>
<td>Right</td>
<td>56</td>
<td>&lt; 1 year</td>
<td>Grade III ACL tear (with grade II MCL tear)</td>
</tr>
<tr>
<td>ACL09</td>
<td>44</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>61</td>
<td>&lt; 1 year</td>
<td>Grade III ACL tear</td>
</tr>
<tr>
<td>ACL10</td>
<td>36</td>
<td>Female</td>
<td>Right</td>
<td>Right</td>
<td>77</td>
<td>1-2 years</td>
<td>Grade III ACL tear (with grade II MCL &amp; PCL tear)</td>
</tr>
</tbody>
</table>

*KOS-ADLS: Knee Outcome Survey Activities of Daily Living Scale (maximum score of 80)

**ACL: anterior cruciate ligament
PCL: posterior cruciate ligament
MCL: medial collateral ligament
Grade II: partial tear
Grade III: complete tear
FIGURE LEGEND

Figure 1. Experimental set-up. The participants' position on the exercise table is shown with the 0.28 kg increment weight on the lever. Note that the standard weight (3 kg) corresponded to the weight of the unloaded lever system (2.50 kg) with an additional 0.50 kg weight increment.

Figure 2. Subjective knee function and maximum voluntary contraction.
A) Individual scores from the Knee Outcome Survey–Activities of Daily Living Scale (KOS-ADLS) for the injured and uninjured leg of participants from the ACL group. B) Maximum isometric knee extensor torque values for participants in the ACL and control groups. Each marker represents an average of three trails. (* $P<0.05$)

Figure 3. Performance in the weight-discrimination task and weight-discrimination thresholds. Performance of A) control participants and B) participants with ACL injuries in the weight discrimination task. Each value represents the mean performance of all participants who attempted each increment in weight (when performance fell below 50%, the next increment in weight was not tested) with the associate standard error mean in one direction. The dotted line indicates the 75% correct discrimination level, which corresponds by convention to the differential threshold. Note the symmetry between the performance of the right and left knee in control participants compared the asymmetrical poor performance of B) participants with ACL injuries, with the injured lower extremity falling under the 75% correct discrimination level at the 0.20 kg comparison weight. C)
Weight-discrimination values for participants from the ACL and control groups. (*
\[ P < 0.05 \])

**Figure 4. Weight-discrimination correlation analysis.** A) KOS-ADLS scores plotted against weight-discrimination thresholds for the injured leg of participants in the ACL group. B) Maximum knee extensor torque values plotted against weight-discrimination thresholds for the injured leg of participants in the ACL group. Note the outlier with a peak torque value of 201 Nm. Statistical analysis with the outlier removed revealed a slight trend between peak torque values and weight-discrimination thresholds \( r^2 = 0.18 \).
FIGURE 2

A

ACL

KOS-ADLS score

*  

uninjured  |  injured

Side

B

Peak Torque (Nm)

*  

uninjured  |  injured  |  right  |  left

ACL  |  CTL

52
FIGURE 3

A

ACL

Correct discrimination

\[
\begin{array}{ccc}
\text{Increment in weight (kg)} & 0.09 & 0.2 & 0.28 & 0.5 \\
\hline
\text{uninjured} & \text{---} & \text{---} & \text{---} & \text{---} \\
\text{injured} & \text{---} & \text{---} & \text{---} & \text{---} \\
\end{array}
\]

B

CTL

Correct discrimination

\[
\begin{array}{ccc}
\text{Increment in weight (kg)} & 0.09 & 0.2 & 0.28 & 0.5 \\
\hline
\text{right} & \text{---} & \text{---} & \text{---} & \text{---} \\
\text{left} & \text{---} & \text{---} & \text{---} & \text{---} \\
\end{array}
\]

C

Discrimination Threshold (g)

\[
\begin{array}{ccc}
\text{Discrimination Threshold (g)} & 50 & 100 & 150 & 200 & 250 & 300 \\
\hline
\text{uninjured} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} \\
\text{injured} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} \\
\text{right} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} \\
\text{left} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} & \text{---} \\
\end{array}
\]

ACL

CTL
FIGURE 4

A

Knee Function

\( r^2 = .10 \)

KOS-ADLS score

\[ \text{Discrimination Threshold (g)} \]

B

Strength

\( r^2 = .03 \)

Peak Torque (Nm)

\[ \text{Discrimination Threshold (g)} \]
CHAPTER 4:

Cortico-motor adaptations in patients with chronic unilateral knee instability secondary to ACL injury
4.1 Introduction

Injury of the ACL is the most common knee pathology in sports and occupational activities (Arnold et al., 1979). In the long-term, ACL injuries often leave individuals with a chronic knee instability and persistent quadriceps weakness (Arnold et al., 1979). This weakness, which represents a 15-40% decrease in knee extensor torque, persists for months and even years following the initial injury and is associated with a decrease in function (Chmielewski et al., 2001; Hurley et al., 1992; Rudolph et al., 2001; Snyder-Mackler et al., 1995; Wojtys & Huston, 2000). In the acute phase, quadriceps weakness is the result of muscle atrophy caused by disuse and immobilization as well reflex inhibition caused by joint effusion and pain (Booth, 1977; Young et al., 1987). It remains unclear, however, why weakness persists long after a course of conventional rehabilitation has been followed and acute symptoms have subsided (Hurley & Newham, 1993; Wojtys & Huston, 2000). Current research has focused on the role of reflex inhibition in persistent weakness following ACL injuries. Many authors have reported reduced voluntary activation in the quadriceps on the side of the injury using paired-pulse stimulation (Hopkins & Ingersoll, 2000; Stokes & Young, 1984a; Suter et al., 2001; Young, 1993). However, the validity of this technique has been questioned recently (Gandevia et al., 1999; Herbert & Gandevia, 1999). Recent evidence also indicates that the contribution of phasic and tonic reflexes to knee extensor torque decreases at high intensities, reaching a minimum (<12% total extensor torque) during maximal contractions (Mrachacz-Kersting & Sinkjaer, 2003). Reflex inhibition may contribute to muscle weakness during low to
moderate intensity contractions since reflexes contribute 30-50% of the total extensor torque at these intensities (Mrachacz-Kersting & Sinkjaer, 2003).

Another factor contributing to persistent muscle weakness is muscle atrophy (Booth, 1977, 1987). However, Lorentzon et al (1989) discovered that individuals with chronic unilateral ACL injuries have quadriceps weakness proportionally greater than the amount of muscle atrophy. In the absence of the usual correlation between muscle cross-sectional area and strength (Maughan et al., 1983a; Schantz et al., 1983), Lorentzon et al suggested changes in supraspinal centres were responsible for the excessive weakness. Although only indirect evidence exists, several authors have stressed the possible contribution of changes in supraspinal excitability to persistent quadriceps weakness following ACL injuries (Elmqvist, 1988; Johansson et al., 1988; Gauffin et al., 1990; Wojtys & Huston, 1994; Young, 1993). Consistent with this possibility, Urback et al. (1991) demonstrated that quadriceps weakness affected both sides in individuals with unilateral ACL injuries.

To date, there is little information as to whether the corticospinal system, and cortico-motor excitability in general, are altered as a result of long-term unilateral knee ligament injuries. Thus, there is a need to determine if changes in cortico-motor excitability are present following ACL injuries and whether they contribute to persistent quadriceps weakness. The advent of TMS in the mid 1980’s has allowed researchers to investigate the effect of various pathological (e.g., strokes, Parkinson’s disease) and experimental conditions (e.g., peripheral electrical stimulation, pain, local anesthesia) on cortico-motor excitability in a safe and non-invasive way (Chen et al., 1999; Kukowski & Haug, 1992; Le Pera et al., 2001; Ridding et al., 2000; Valeriani et al., 1999). Although
individuals with ACL injuries have yet to be studied, joint immobilization has been
shown to induce significant changes in cortico-motor excitability, which return to
baseline following a month of spontaneous recovery (Liepert et al., 1995; Zanette et al.,
1997). The return to baseline values coincides with the return of normal muscle strength
(Hortobagyi et al., 2000), indicating the possible presence of a relationship between
changes in cortico-motor excitability and muscle strength following orthopaedic injuries.

In the present study, we sought to determine whether changes in quadriceps
cortico-motor excitability were present in individuals with chronic unilateral knee
instability secondary to ACL injuries. We also looked at whether changes in cortico-
motor excitability were correlated with subjective reports of knee dysfunction and
observed deficits in knee extensor strength.
4.2 Methods

4.2.1 Participants

The clinical and demographic characteristics of participants have been described in the previous chapter (see Table 1, chap. 3). Briefly, participants consisted of neurologically normal young adults who had sustained unilateral ACL injuries months or years (chronic) before the experiment. A second group of age-matched healthy adults was also recruited to serve as controls (control; mean age, 22.6 ± 2.8 years; 4 female). The University of Ottawa Human Research Ethics Board approved the study’s procedures, and participants gave written informed consent before participation.

4.2.2 Clinical Evaluation

Clinical evaluation consisted of assessing subjective knee function and knee extensor strength. The methods for the clinical evaluation have been described in the previous chapter. Briefly, participants had to complete the Knee Outcome Survey Activities of Daily Living Scale (KOS-ADLS), which is a valid and reliable scale used to assess subjective knee function (Irrgang et al., 1998). Next, knee extensor strength was determined using a KIN KOM dynamometer during three maximal static voluntary contracts (MVC, 3 s contraction with a one-minute rest period between each trial).

4.2.3 Assessment of Cortico-Motor Excitability

We used TMS to assess cortico-motor excitability of both lower limb motor representations with the quadriceps as the target muscle. For TMS assessments, participants were seated in a recording chair with 70° of hip flexion and 60° of knee
flexion. Magnetic stimulation was produced using a MagStim 200 (MagStim Co., Dyfed, UK). The first few participants (n=4) were assessed using a 90 mm circular coil, but later in the course of the project, a more efficient double-cone coil became available and thus we used the later for the remaining assessments (n=14). The fact that two different coils were used for assessments was taken into account in the analysis (see below). All procedures were done on one side, starting with the injured leg for the ACL group and the right leg for the control group, and then repeated on the contralateral side.

a) Recordings of Motor Evoked Potentials (MEPs)

For recording in the target muscle (i.e., quadriceps), we followed the procedure of Garland et al. (1994) with the proximal electrode placed at the border between rectus femoris and vastus lateralis and the distal electrode approximately 10 cm above the centre of the patella. The electromyographic signal (EMG) was amplified by 1000 with a time constant of 3 ms and a low-pass filtering of 2 kHz. Data acquisition was controlled using custom software in a PC running under Windows 98® equipped with and acquisition card (BNC-2090, National Instrument Corp.). All signals were digitized at 2 kHz sampling rate and saved for later analysis.

b) Determination of the Optimal Site

To determine the optimal site on the contralateral hemi-scalp to evoke MEPs in the quadriceps, the coil was moved in 1-cm step from the vertex while stimulating at high intensity. For most participants, the optimal site was on the vertex or slightly anterior (2 cm) and lateral (1 cm) to the vertex. Once the optimal position was determined on the
scalp, the site was marked with small adhesive markers to ensure consistency of stimulation.

c) Resting Motor Threshold (RMT)

To determine the RMT, we used the procedure described by Mills and Nithi (1997). The procedure consists of eliciting a series of consecutive responses to determine an upper (10/10 stimuli) and a lower threshold (0/10 stimuli) and taking the mean between the two as the threshold intensity. Because we investigated the lower limb in the present study, we used seven instead of 10 consecutive responses to avoid too many stimuli and prevent coil heating. To speed up the process, the initial intensity used to locate the optimal stimulation spot on the skull was first decreased in steps of 5% stimulator maximum output until no MEPs could be evoked. The intensity was then gradually increased until a MEP reappeared. From this point, the intensity was decreased in 1% steps to find the maximal intensity that produced no response out of seven consecutive magnetic stimuli (i.e., lower threshold). The intensity was then gradually increased in 1% steps to find the minimal intensity that produced seven MEPs out of seven stimuli (i.e., upper threshold). The threshold intensity was taken as the mean between the lower and upper threshold limits. For both upper and lower threshold determinations, an interval of at least 5 s was used between each stimulus. EMG activity was continuously monitored on an oscilloscope at high gain to ensure there was no voluntary muscular activity.
d) Input-Output (I-O) Curves

To measure the I-O curves (Ridding & Rothwell, 1997), the coil was placed on the optimal site over the contralateral scalp and stimulator intensity was set to the previously determined lower threshold value, rounded down to the closest multiple of five (e.g., lower threshold = 58%, stimulator intensity set to 55%). Five MEPs were recorded at this intensity. Next, stimulator intensity was increased in steps of 5% and at least five MEPs were recorded at each increasing intensity. Testing ended when MEP amplitude no longer increased after two successive increments in stimulation intensity (i.e. point of saturation). Similar to threshold determination, EMG activity was continuously monitored on an oscilloscope at high gain to ensure there was no voluntary muscular activity during recording of MEPs.

e) Facilitation of MEPs and Silent Period (SP) during Active Contraction

To study the facilitation of MEPs with contraction and record the SP participants were asked to actively extend their knee (180°) in response to a tone signal lasting 1000 ms. Participants were trained to time their movement to the duration of the tone. TMS was delivered 500 ms after the tone, with the stimulator output set at threshold +10%. Eight trials were recorded with a 15 s rest period between each contraction.

f) H-reflex

To derive an index of excitability at the spinal motoneuronal level, the H-reflex was measured in some participants. To measure the H-reflex in the Quadriceps, we followed the procedure advocated by Guiheneuc et al. (1974). Briefly, participants were
seated with 50° of hip flexion and 60° of knee flexion in a specially adapted chair fitted with a headrest, armrests and footrests. Participants rested their head in forward orientation on the headrest and were instructed to relax during the testing (Kameyama et al., 1989). Electromyography signals were recorded with conventional disposable surface EMG electrodes (2 cm in diameter). After appropriate skin preparation, a pair of electrodes was positioned over the inferior aspect of the vastus lateralis, an area suitable for recording maximal H-reflex in the quadriceps (Garland et al., 1994). The indifferent electrode was positioned over the ipsilateral gluteus medius area.

The femoral nerve was stimulated (1 ms square pulse; S88 Stimulator Grass, Co.) where it passes through the superior aspect of the femoral triangle, 1-2 cm lateral to the femoral artery. Ten trials (75 ms epoch) were recorded with a delay of 20 s between each.

4.2.4 Data Analysis

Individual RMT, derived from the mean between upper and lower threshold limits, were determined for each hemisphere of each participant. Input-output curves were analysed first by computing individual mean MEP amplitude (peak-to-peak) at each intensity tested. Then, using the procedure advocated by Ray et al (2002), linear regression analysis was used to determine the slope of each individual I-O curve, allowing a single parameter to be used for statistical comparison between legs. Finally, to determine the amplitude of facilitated MEPs and SP duration, individual trials were overlaid to derive a mean MEP amplitude (peak-to-peak) and a mean SP for each leg. The SP was defined as the interval between MEP onset and the return of EMG activity.
(i.e., 30% of EMG prior to artefact). For the H-reflex, mean amplitude (peak-to-peak) was calculated for each leg.

4.2.5 Statistical Analysis

Individual RMT, slopes, MEP amplitude and SP duration derived in each leg were compared using paired t-test (ACL group, uninjured versus injured; control group, left versus right). Pearson's coefficients of correlation were computed to examine the relationship between selected indices of cortico-motor excitability (i.e., RMT and slopes of I-O curves) and clinical evaluation results in participants with ACL injuries and control participants. For RMT correlation analysis, ratios where used for the ACL group (uninjured/injured) and the control group (right/left). All statistical tests were performed using GraphPad Prism version 4.00 for Windows, (GraphPad Software, San Diego California USA, www.graphpad.com) with the level of significance being set at 0.05 for all tests.
4.3 Results

4.3.1 Resting Motor Thresholds

The distribution of individual RMT values in the two groups is shown in Figure 2. It can be seen that participants in the ACL group exhibited lower RMT in the hemisphere contralateral to the affected leg as compared to the unaffected leg, a difference that was highly significant ($r=2.87, p=0.019$). In contrast, in the control group, RMT threshold values tended to be comparable and no significant difference was found between legs ($t=0.60, p=0.567$).

4.3.2 Input-Output Curves

No systematic difference or pattern emerged when I-O curves derived from each leg were compared in the ACL group. However, a closer look at individual I-O curves revealed the presence of three different patterns. First, 3/10 participants showed increased responsiveness, and therefore a steeper slope, on the uninjured side. Figure 3A and 3B are examples of such a pattern. While no difference is seen at the lower stimulator intensity (Figure 3A), MEPs recorded at higher stimulator intensity are clearly larger on the uninjured side (Figure 3B). The increase in responsiveness to TMS on the uninjured side is also evident in Figure 3C, showing the greater steepness of the slope on the uninjured side compared to the uninjured side. Four participants in the ACL group showed the reverse pattern, with increased responsiveness (and steeper slopes) on the side of the injury. Finally, the three remaining participants in the ACL group presented a pattern closely resembling the one found in control participants, i.e. equal responsiveness to
increasing TMS intensities on both sides. An example of this pattern typical of control participant is shown in Figure 3 (D and E). Thus, in the absence of any systematic pattern, no difference was found in the ACL group in terms of responsiveness to increasing magnetic stimulator intensity, as reflected in the slope of the I-O curve.

4.3.3 Facilitation of MEPs and Silent Period During Active Contraction

An example of MEPs recorded during active contraction and the subsequent silent period is shown in Figure 4A. Note the presence of EMG activity prior to and immediately after the stimulus artefact in the fist part of the recording generated by the voluntary contraction of the quadriceps muscle. Next are the large facilitated MEPs (peak-to-peak: uninjured, 922 μV, injured, 945 μV) followed by a period of EMG silence. The interval between the onset of the MEP and the return of EMG activity (i.e., the silent period) was 80.4 ms for the injured side and 94.5 ms for the uninjured side. As shown in the distributions illustrated in Figure 4 (A and B), both the amplitude of facilitated MEPs and the duration of SP measured in the two legs were very similar in the two groups. Accordingly, no difference was found in either group.

4.3.4 H-reflex

Only a minority of participants had measurable H-reflex in the quadriceps (ACL group, n=5) due to inherent physiological difference between individuals. For those individuals with elicitable H-reflex, there was a strong tendency for H-reflex to be smaller on the injured, as compared to, the uninjured side. An example of H-reflex
attenuation on the injured side is shown in Figure 5A. The tendency of H-reflex amplitude to be smaller on the side of the injury is evident in Figure 5B.

4.3.5 Relationship between Indices of Cortico-Motor Excitability and Knee Function

The relationship between slope values derived from I-O curves and muscle strength for both ACL and control groups is shown in Figure 6 (A and B). It can be seen that, in individuals in ACL group, increased responsiveness to TMS on the hemisphere contralateral to the injured leg (i.e., steeper slopes) was associated with increased torque produced during maximal voluntary contraction of the quadriceps. No such a relationship could be established on the uninjured side of the same participants (Figure 6A), nor in participants of the control group (Figure 6B). With regards to RMT, there was no correlation with muscle strength for both the ACL group ($r^2=0.03$) and the control group ($r^2=0.01$). No relationship could be established between any of the indices of cortico-motor excitability and subjective knee function derived from the KOS-ADLS questionnaire in both groups ($r^2$ range=0.018 to 0.12).
4.4 Discussion

In the present study we investigated cortico-motor excitability changes in individuals with chronic unilateral knee instability due to ACL injuries. We found small but significant differences in RMT values in the ACL group. No consistent pattern was seen among other indices of cortico-motor excitability. In addition, the extent of the Quadriceps representation, reflected in the steepness of the I-O curve, was found to strongly associated with knee extensor torque developed in the injured leg during MVC. In the following section we will discuss the functional significance of our results as well as various factors that may have contributed to the changes in cortico-motor excitability noted in the present study.

4.4.1 Resting Motor Threshold

Measuring RMT provides information on membrane excitability of neurons located in the central core region of a muscles representation in the primary motor cortex (Chen, 2000). Resting motor thresholds were significantly lower on the hemisphere contralateral to the side of the injury in the ACL group, suggestive of an increase in cortical and/or spinal excitability. An increase at the cortical level is more likely given the evidence of inhibitive influences at the spinal level indicated by reductions in quadriceps H-reflex amplitude. The significance of this lowering of RMT in the ACL group is further evident given that thresholds to TMS are usually symmetrical in healthy individuals (Civardi et al., 2000; Mills & Nithi, 1997; Tremblay et al., 2001; Van der Kamp et al., 1996), which was the case in our control group.
The presence of a unilateral increase in motor cortical excitability in ACL participants remains difficult to reconcile with the traditional view that spinal inhibition is prevalent in these individuals (Elmqvist, 1988; Suter et al., 2001; Young & Stokes, 1986). In this respect, the lowering of RMT may reflect some form of cortical compensatory mechanism owing to the presence of spinal inhibition. Reflex inhibition following an ACL injury may decrease the normal reflex contribution to total knee extensor torque [estimated at 30-50% of the MVC (Mrachacz-Kersting & Sinkjaer, 2003)], especially during low to moderate intensity contractions. The increase in motor cortex excitability (i.e., decrease in RMT) may be a compensatory mechanism used to normalize the inflow of excitation during activation of the quadriceps in the presence of reflex inhibition. Alternatively, the increase in cortical excitability may reflect an adaptation of the corticospinal system in response to long standing unilateral knee dysfunction. Indeed, while regular locomotion does not depend heavily on descending projections from the corticospinal tract (Capaday et al., 1999; Marder & Calabrese, 1996; Shik et al., 1966), specialized locomotor activities, for instance those requiring precise placement of the foot, do rely heavily on corticospinal projections (Drew, 1988).

Subjective reports of individuals with ACL injury often contain allusions to the fact that they are now more "aware" of their knee, avoiding large forces and positions that are too extreme. This suggests that they have switched to a more voluntary driven mode of control over their lower limb. In studies of the kinematics and kinetics of gait patterns in individuals with ACL injuries, many subtle changes, like hamstring and gastronomius activity to produce tibial external rotation and valgus have been reported, likely reflecting voluntary interventions to prevent further injury (Houk & Yack, 2003; Zang et al., 2003).
Thus, an increased reliance of cortical control over the affected limb could be one possibility to explain why the excitability of the motor representation of the quadriceps was enhanced in our group of ACL participants.

Another possibility resides in anatomical and functional differences between the different heads of the quadriceps. The quadriceps consists of four muscular heads (i.e., rectus femoris, vastus lateralis and vastus medius). The vasti generate significantly larger EMG signals during voluntary contraction in healthy individuals, which reflects their greater contribution to total knee extensor torque (Pincivero et al., 2003). Muscle atrophy is significantly greater in the vasti following a period of immobilization since the rectus femoris, a bi-articular muscle, still contributes to hip flexion when the knee is immobilized (Lieber et al., 1989a; Lieber et al., 1989; Mckee-Woodbum et al., 1989). In the present study, since we targeted the rectus femoris, it is possible that the enhanced cortical excitability reflected the greater use of this muscle to compensate for the weakened and atrophied vasti muscles. Note that this possibility is not incompatible with the previous explanation regarding the greater reliance on cortical voluntary control.

4.4.2 Input-Output Curves

Input-output curves and corresponding slope values provide information on the spatial extent of excitable elements in the motor representation, steeper slopes indicating larger cortical representation (Chen, 2000; Siebner & Rothwell, 2003). In the present study, no consistent pattern could be discerned in examination of individual I-O curves in ACL participants. Nevertheless, as noted in the Results section, certain trends emerged in the ACL group, making it possible to group participants together based on varying levels
of responsiveness on the injured and uninjured side. These groupings were not associated with any other factors (i.e., severity of injury, time since injury, level of function, etc.), reflecting the inherent variability of ACL injuries. A strong correlation did emerge, however, between I-O curve slope values and quadriceps strength on the injured side in the ACL group. This finding indicates that the extent of the quadriceps motor representation, as reflected in the steepness of the slope, co-varied with the amount of residual weakness measured in the contralateral, affected knee extensors. Thus, it seems that relative sparing of the anterior thigh motor representation could be related to preserved quadriceps strength after long-standing ACL injury. It is difficult at present to further speculate on this relationship but it certainly requires further investigations with larger samples of participants to reduce variability.

4.4.3 Facilitation of MEPs and Silent Period During Active Contraction

MEP facilitation during active contraction reflects enhanced excitability at the cortical and spinal level through the increase in the size and number of descending volleys (Hess et al., 1986; Hess et al., 1987). Voluntary activity is known to normalize any changes in excitability that may have been present prior to the contraction (Ridding & Rothwell, 1997). It follows that if observed changes in corticospinal excitability are apparent both at rest and during active contraction, it is likely that these changes are due to long-term modifications in synaptic efficacy (Ridding & Rothwell, 1997). The fact that MEP amplitude measured during contraction was not changed in our experiment indicates that long-term changes in synaptic efficacy are unlikely following ACL injuries.
As for the SP, its duration provides information about the excitability of intra-cortical inhibitory circuits in the motor cortex (Chen, 2000). The initial phase of the silent period (0-50 ms) corresponds to the spinal refractory period, while the later phase (<50 ms) reflects the suppression of cortical excitability and is believed to reflect long lasting GABAergic inhibitory post-synaptic potentials (Chen et al., 1999). The SP is prolonged following strokes and in response to certain drugs like L-Dopa (Kukowski & Haug, 1992; Proiori et al., 1994) while it is shortened in Alzheimer’s and Parkinson’s disease (Nakashima et al., 1995; Perreti et al., 1996). In this experiment, no difference was noted in terms of SP duration between the two legs in the two groups. Our observations in this regard indicate that intra-cortical inhibitory mechanisms do not appear to be altered following ACL injuries.

4.4.4 Conclusion and Consideration for future Research

The present study has shed new light as to the possible cortical adaptations that may be induced as a result of chronic unilateral ACL injuries. Besides a consistent lowering of RMT on the contra-lateral hemisphere of the injured leg, the results revealed an important heterogeneity in response to increasing intensities of TMS and no evidence of alterations in intra-cortical inhibitory mechanisms. Further studies are needed with larger sample of participants to explore the possible links between changes at the motor cortical level and changes at the functional level. Also, there is a definite need to determine whether similar cortico-motor adaptations could be detected in the other muscular heads of the quadriceps and other muscles of the lower limb.
FIGURE LEGEND

Figure 1. Experimental set-up. Participants position during TMS testing. Note the double-cone coil held over the scalp and a pair of EMG electrodes located on the quadriceps muscle of the leg being tested. The same chair was used for H-reflex testing.

Figure 2. Resting motor threshold. Resting motor thresholds for participants in the ACL and control groups expressed as a percentage of the stimulator maximum output (* $P<0.05$)

Figure 3. Input-output curve. Motor evoked potentials measured at A) 40% and B) 65% of stimulator maximum output (SMO) for a participant in the ACL group (ACL01). Note the large response on the uninjured side and 65% SMO compared to the injured side. The increased responsiveness in the uninjured leg is responsible for the C) steeper slope of uninjured I-O curve (slope=0.28) compared to the injured I-O curve (slope=0.056). Next, motor evoked potentials measured at D) 40% and E) 65% of SMO for a participant in the control group. Note the symmetry between the right and left leg at 65% SMO, which explains the similar I-O curves (F) for the right (slope=0.077) and left (slope=0.068) leg.

Figure 4. Facilitation of MEPs and Silent Period During Active Contraction. A) An example of a facilitated MEP immediately followed by a silent period (overlay of five trials). Note the EMG activity prior to onset of the MEP, which
returns to indicate the end of the silent period. B) Amplitude of facilitated MEPs and C) silent periods for participants in the ACL and control groups.

**Figure 5. Quadriceps H-reflex.** A) A pair of H-reflexes from a participant in the ACL group (ACL09). Although slightly different in shape, H-reflex amplitude is visibly smaller on the injured side (overlay of five trials). B) H-reflex amplitude was smaller on the injured side in all participants from the ACL group who had a measurable H-reflex in the quadriceps.

**Figure 6. Correlations between input-output curve slope values and muscle strength.** Knee extensor torque values plotted against I-O curve slope values for participants in the A) ACL and B) control groups. Note the strong correlation between knee extensor torque and slope values on the injured side in the ACL group. The Uninjured leg closely resembles the right and left leg of participants in the control group. Note that data from subject control08 right leg (slope value, 0.65) does not appear here only for illustrative purposes.
FIGURE 3

A

ACL10

uninjured
injured

100 μV
10 ms

D

CTL04

right
left

100 μV
10 ms

B

ACL10

uninjured
injured

100 μV
10 ms

E

CTL04

right
left

100 μV
10 ms

C

ACL10

uninjured
injured

MEP amplitude (mV)

30 40 50 60 70

% stimulator output

F

CTL04

right
left

MEP amplitude (mV)

0 8

40 50 60 70

% stimulator output
FIGURE 4

A

silent period

uninjured

injured

100 μV

25 ms

B

C

uninjured
injured
right
left
ACL
CTL

uninjured
injured
right
left
ACL
CTL

MEP amplitude (mV)

silent period (ms)

0.0
0.5
1.0
1.5
2.0
2.5
0
100
200
300
FIGURE 6

A

• injured $r^2 = .713$
• uninjured $r^2 = .001$

knee extensor torque (Nm)

I-O curve slope value (mV/% stimulator output)

B

• left $r^2 = .135$
• right $r^2 = .226$

knee extensor torque (Nm)

I-O curve slope value (mV/% stimulator output)
CHAPTER 5:

Conclusion
Considering the important role proprioceptive abilities and muscle strength play in function and functional deficits, the purpose of this thesis project was to gain further insight as to the nature of the proprioceptive deficits affecting individuals with ACL injuries and the possible adaptations at the cortico-motor level resulting from unilateral knee dysfunction.

Proprioceptive testing revealed that the ability to discriminate small differences in weight was significantly decreased on the injured side in individuals with chronic knee instability secondary to an ACL injury. It was interesting to discover that thresholds values from individuals in both the control group and the ACL group were within the normal perceptual range, indicating that the ability to sense differences in force is relatively preserved following this type of injury. This finding does no imply, however that these proprioceptive deficits do not have the potential to significantly impact the functional status of individuals with ACL injuries. Given the low range of muscle forces that are monitored by the somatosensory system during the course of a day, the inability to properly assess even small differences in force could lead to difficulties in activities such as walking on uneven group or ascending stairs.

Injury to the ACL appears to cause an increase in cortico-motor excitability of the knee extensor muscles. Resting motor thresholds were significantly lower on the side of the injury in the ACL group, which suggests of an increase in cortical level excitability in the presence of reflex inhibition. Also, I-O testing revealed that the extent of the quadriceps motor representation varied in relation to the amount of residual weakness on the injured side in individuals
with ACL injuries. On the whole, the increase in cortico-motor excitability detected on the hemisphere contralateral to the injured leg might be interpreted as an adaptation to poor mechanical stability of the injured knee by substituting greater voluntary control over muscle activity that is usually more automatic and reflex-driven.

In conclusion, this thesis project was the first to report deficits in the proprioceptive ability of sensing varying levels of force and to provide preliminary observations of cortical adaptations induced as a result of chronic unilateral ACL injuries. Given the inherent variability of this patient population, studies with larger sample sizes are needed to further examine these issues. Hopefully our results will serve as a stepping stone for further research to explore the possible links between changes at the cortical and functional levels as well as the impact of deficits in the ability to sense force, and possibility also effort, have on functional outcome.
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ANNEXES
ANNEXE 1

Health Questionnaire for Transcranial Magnetic Stimulation*

Please Answer YES or NO to the following questions:

Have you ever been diagnosed by your doctor with any of the following conditions:

☐ Epilepsy

☐ Stroke or TIA (transient Ischemic Attack)

☐ Heart conditions

☐ Sciatica or disc problems

☐ Arthritis (rheumatoid arthritis or osteoarthritis)

☐ Diabetes

☐ Any other chronic condition involving your lower extremity like patellofemoral knee pain, intra-articular loose body, recurrent dislocation of the knee cap, hip or knee bursitis, patellar tendonitis.

Are you presently (in the last month) taking any prescribed medication?

☐ YES, please specify: ____________________________

☐ NO

Are you presently suffering from any other medical condition?

☐ YES, please specify: ____________________________

☐ NO

Have you recently suffered a traumatic injury?

☐ YES, please specify: ____________________________

☐ NO

Are you presently receiving any form of medical treatment?

☐ YES, please specify: ____________________________

☐ NO

Are you pregnant?

☐ YES

☐ NO
Do you have any metal implants in your body?
☐ YES, please specify where:
☐ NO

Do you consider yourself in good health?
☐ YES
☐ NO, please specify:

Do you have any other health condition of which we should be made aware?
☐ YES, please specify:
☐ NO

I acknowledge that my answers are truthful and in accordance with my medical records at this time.

_________________________  ________________________
Signature of Participant     Date

ANNEXE 2

Knee Outcome Survey
Activities of Daily living Scale*

Instructions: The following questionnaire is designed to determine the symptoms and limitations that you experience because of your knee while you perform your usual daily activities. Please answer each question by checking the statement that best describes you over the last 1 to 2 days. For a given question, more than one of the statements may describe you, but please mark ONLY the statement that best describes you during your usual daily activities.

Symptoms

1. To what degree does your pain in your knee affect your daily activity level?

   5  I never have pain in my knee.
   4  I have pain in my knee, but it does not affect my daily activities.
   3  Pain affects my activity slightly.
   2  Pain affects my activity moderately.
   1  Pain affects my activity severely.
   0  Pain in my knee prevents me from performing all daily activities.

2. To what degree does grinding or grating of your knee affect your daily activity level?

   5  I never have grinding or grating in my knee.
   4  I have grinding or grating in my knee, but it does not affect my daily activities.
   3  Grinding or grating affects my activity slightly.
   2  Grinding or grating affects my activity moderately.
   1  Grinding or grating affects my activity severely.
   0  Grinding or grating in my knee prevents me from performing all daily activities.

3. To what degree does stiffness in your knee affect your daily activity level?

   5  I never have stiffness in my knee.
   4  I have stiffness in my knee, but it does not affect my daily activities.
   3  Stiffness affects my activity slightly.
   2  Stiffness affects my activity moderately.
   1  Stiffness affects my activity severely.
   0  Stiffness in my knee prevents me from performing all daily activities.
4. To what degree does swelling of your knee affect your daily activity level?
   
   _5_ I never have swelling in my knee.
   _4_ I have swelling in my knee, but it does not affect my daily activities.
   _3_ Swelling affects my activity slightly.
   _2_ Swelling affects my activity moderately.
   _1_ Swelling affects my activity severely.
   _0_ Swelling in my knee prevents me from performing all daily activities.

5. To what degree does slipping of your knee affect your daily activity level?
   
   _5_ I never have slipping of my knee.
   _4_ I have slipping of my knee, but it does not affect my daily activities.
   _3_ Slipping affects my activity slightly.
   _2_ Slipping affects my activity moderately.
   _1_ Slipping affects my activity severely.
   _0_ Slipping in my knee prevents me from performing all daily activities.

6. To what degree does buckling of your knee affect your daily activity level?
   
   _5_ I never have buckling of my knee.
   _4_ I have buckling of my knee, but it does not affect my daily activities.
   _3_ Buckling affects my activity slightly.
   _2_ Buckling affects my activity moderately.
   _1_ Buckling affects my activity severely.
   _0_ Buckling of my knee prevents me from performing all daily activities.

7. To what degree does weakness or lack of strength of your leg affect your daily activity level?
   
   _5_ My leg never feels weak.
   _4_ My leg feels weak, but it does not affect my daily activity.
   _3_ Weakness affects my activity slightly.
   _2_ Weakness affects my activity moderately.
   _1_ Weakness affects my activity severely.
   _0_ Weakness of my leg prevents me from performing all daily activities.
Functional Disability with Activities of Daily Living

8. How does your knee affect your ability to walk?
   _5_ My knee does not affect my ability to walk.
   _4_ I have pain in my knee when walking, but it does not affect my ability to walk.
   _3_ My knee prevents me from walking more than 1 mile.
   _2_ My knee prevents me from walking more than ½ mile.
   _1_ My knee prevents me from walking more than 1 block.
   _0_ My knee prevents me from walking.

9. Because of your knee, do you walk with crutches or a cane?
   _3_ I can walk without crutches or a cane.
   _2_ My knee causes me to walk with 1 crutch or a cane.
   _1_ My knee causes me to walk with 2 crutches.
   _0_ Because of my knee, I cannot walk even with crutches.

10. Does your knee cause you to limp when you walk?
    _2_ I can walk without a limp.
    _1_ Sometimes my knee causes me to walk with a limp.
    _0_ Because of my knee, I cannot walk without a limp.

11. How does your knee affect your ability to go up stairs?
    _5_ My knee does not affect my ability to go up stairs.
    _4_ I have pain in my knee when going up stairs, but it does not affect my ability to go up stairs.
    _3_ I am able to go up stairs normally, but I need to rely on use of a railing.
    _2_ I am able to go up stairs one step at a time with use of a railing.
    _1_ I have to use crutches or a cane to go up stairs.
    _0_ I cannot go up stairs.

12. How does your knee affect your ability to go down stairs?
    _5_ My knee does not affect my ability to go down stairs.
    _4_ I have pain in my knee when going down stairs, but it does not affect my ability to go down stairs.
    _3_ I am able to go down stairs normally, but I need to rely on use of a railing.
    _2_ I am able to go down stairs one step at a time with use of a railing.
    _1_ I have to use crutches or a cane to go down stairs.
    _0_ I cannot go down stairs.
13. How does your knee affect your ability to stand?

  5  My knee does not affect my ability to stand. I can stand for unlimited amounts of time.
  4  I have pain in my knee when standing, but it does not limit my ability to stand.
  3  Because of my knee I cannot stand for more than 1 hour.
  2  Because of my knee I cannot stand for more than ½ hour.
  1  Because of my knee I cannot stand for more than 10 minutes.
  0  I cannot stand because of my knee.

14. How does your knee affect your ability to kneel on the front of your knee?

  5  My knee does not affect my ability to kneel on the front of my knee. I can kneel for unlimited amounts of time.
  4  I have pain when kneeling in the front of my knee, but it does not limit my ability to kneel.
  3  I cannot kneel on the front of my knee for more than 1 hour.
  2  I cannot kneel on the front of my knee for more than ½ hour.
  1  I cannot kneel on the front of my knee for more than 10 minutes.
  0  I cannot kneel on the front of my knee.

15. How does your knee affect your ability to squat?

  5  My knee does not affect my ability to squat. I can squat all the way down.
  4  I have pain when squatting, but I can still squat all the way down.
  3  I cannot squat more than ¾ of the way down.
  2  I cannot squat more than ½ of the way down.
  1  I cannot squat more than ¼ of the way down.
  0  I cannot squat at all.

16. How does your knee affect your ability to sit with your knees bent?

  5  My knee does not affect my ability to sit with my knee bent. I can sit for unlimited amounts of time.
  4  I have pain when sitting with my knee bent, but it does not limit my ability to sit.
  3  I cannot sit with my knee bent for more than 1 hour.
  2  I cannot sit with my knee bent for more than ½ hour.
  1  I cannot sit with my knee bent for more than 10 minutes.
  0  I cannot sit with my knee bent.
17. How does your knee affect your ability rise from a chair?

____ 5 ____ My knee does not affect my ability to rise from a chair.

____ 4 ____ I have pain when rising from a seated position, but it does not limit my ability rise from a chair.

____ 2 ____ Because of my knee I can only rise from a chair if I use my hands and arms to assist.

____ 0 ____ Because of my knee I cannot rise from a chair.

ANNEXE 3

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD
CERTIFICAT 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 for the research project **Cortico-motor Adaptations to Chronic Knee Instability in Patients with Unilateral Anterior Cruciate Ligament Deficiency** submitted by Martin Héroux and supervised by Louis Tremblay and François Tremblay (File H05-02-01). The members of the REB 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 Board, and accordingly gave it a Category 1 a (approval). This certification is valid for one year from the date indicated below.

Catherine Lesage  
Protocol Officer for Ethics in Research,  
For the Chairperson of the Health Sciences and Science REB  
Daniel Lagarec

August 12, 2002  
Date