Effects of cutaneous input and resistance training on motor output

by

Trevor Scott Barss
BSc. Kinesiology (Honours and Great Distinction), University of Saskatchewan, 2008
MSc. Kinesiology (Exercise Physiology), University of Saskatchewan, 2011

A Dissertation Submitted in Partial Fulfillment
of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

In the School of Exercise Science, Physical and Health Education

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University of Victoria

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Supervisory Committee

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Abstract

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An entire field of research was born when a paper entitled ‘On the education of muscular control and power’ first discussed a “psychical rather than a physical” bilateral adaptation to a unilateral training program. Although the true relevance of this paper would not be recognized for over a century, its novel findings, describing adaptations resulting from physical and skilled training, continue to influence scientific literature to this day. Most notably, Scripture coined the term ‘cross-education’ to describe the improvement in strength or functional performance of not only the trained limb but also in the untrained contralateral limb. Recently, unilateral training or ‘cross-education’ has been highlighted as a possible rehabilitation strategy during recovery from unilateral injuries. However, a number of limitations must be addressed within the scientific literature in order to properly apply unilateral resistance training as an effective rehabilitation strategy. Therefore, the primary goal of this dissertation was to address a number of fundamental issues related to optimizing unilateral resistance training.

One such issue is knowledge on the time course of strength increase during unilateral resistance training. The primary purpose of Chapter 2 was to characterize the time-course of strength changes in both the trained and untrained limbs during unilateral handgrip training. Experiment 1 assessed the time-course with a ‘traditional’ training protocol (3x/week for 6 weeks: 18 total sessions) while Experiment 2 assessed a “compressed” protocol in which the number of sessions and contractions were matched but participants trained for eighteen consecutive days. An anticipated outcome was the determination of the minimum number of sessions required to induce contralateral strength gains in the upper limb. A secondary purpose of this study was to examine whether spinally-mediated adaptations in muscle afferent reflex pathways occur after unilateral handgrip training.
Experiment 1 indicated six weeks of handgrip training significantly increased force output in both trained and untrained limbs. This strength increase was accompanied by changes in the maximal muscle activation in the trained limb only. Time course data indicated the trained limb was significantly stronger than baseline after the 3rd week of training (session 9) while the untrained limb was stronger after 5 weeks (15 sessions) of unilateral handgrip training. Interestingly, the rate at which strength increased in the untrained limb was similar to the trained side. These strength increases were also accompanied by significant changes in the current needed to produce H@50 in the trained, and $H_{\text{max}}$ in both the trained and untrained limb indicating alterations in spinal cord excitability. Experiment 2 showed a similar number of sessions was needed to induce significant strength gains in the untrained limb. This indicates training without rest days may be the most efficient protocol within a clinical population when the trained limb is not the focus of recovery.

It remains necessary to determine if specific strategies can be employed to optimize unilateral resistance training interventions to increase strength gains. To date, no study has directly assessed the relative contribution of afferent pathways to cross-education. Cutaneous feedback from the skin provides perceptual information about joint position and movement. Unilateral training involves forceful contractions that activate cutaneous receptors in the skin, producing widespread and powerful effects between limbs. Providing “enhanced” cutaneous stimulation during unilateral contractions may alter excitability of interlimb reflex pathways, modifying the contralateral increase in strength. Therefore, the purpose of Chapter 3 was to determine the relative contribution of cutaneous afferent pathways as a mechanism of cross-education by directly assessing if unilateral cutaneous stimulation alters ipsilateral and contralateral strength gains.

Participants were randomly assigned to either a voluntary contraction (TRAIN), cutaneous stimulation (STIM), or cutaneous stimulation during voluntary contraction (TRAIN+STIM) group. Each participant completed 6 sets of 8 reps 3x/week for 5 weeks. TRAIN included unilateral maximal voluntary isometric contractions (MVCs) of the wrist extensors. STIM training included cutaneous stimulation (2xRT for 3sec @ 50Hz) of the superficial radial (SR) nerve at the wrist only. TRAIN+STIM included MVCs of the wrist extensors with SR stimulation provided for the duration of the contraction. Two pre-training and 1 post-training session assessed the relative increase in force output during MVCs for wrist
flexion, wrist extension and handgrip strength. Results indicated unilateral wrist extension training alone (TRAIN) increased force output in both trained and untrained wrist extensors. Providing ‘enhanced’ sensory feedback via electrical stimulation during training (TRAIN+STIM) led to similar increases in strength in the trained limb compared to TRAIN. However, the major finding revealed that ‘enhanced’ feedback in the TRAIN+STIM group completely blocked interlimb strength transfer to the untrained wrist extensors. It appears the large mismatched sensory volley which was provided may have interfered with the integration of the appropriate sensory cues to the untrained cortex and impaired the ability to induce “cross-education”.

It may be possible to enhance effects of training by altering excitability via apparel such as compression garments. Currently, it is unknown whether tactile input to the skin induced via compression apparel may alter transmission of muscle afferent feedback within a limb. Thus, the purpose of Chapter 4 was to examine if sustained input to the skin via compression garment modulates sensory feedback transmission in the upper limb using the Hoffmann (H-) reflex as a probe. The purpose of these experiments was to: 1) explore the effects of compression gear on sensory feedback transmission in the upper limb during a static task, and 2) if the task (locomotor vs. reaching) or phase of a movement differentially modulated this transmission of sensory information. Furthermore, differences in performance of the discrete reaching task were assessed to provide data on whether a compression garment leads to alteration in motor task performance. Combined results from both parts of the study suggest that tactile input provided to the skin via compression garments modulates the excitability of afferent connections independent of descending input. The alteration in excitability occurs across multiple sensory pathways and across multiple movement tasks. Interestingly, there was a significant reduction in the number of errors made during the reaching task, which provides preliminary evidence of an improved performance while wearing a compression garment. Therefore, the compression sleeve appears to increase precision and sensitivity at the joint where it is applied.

Overall, these results address many fundamental questions which have previously limited effective translation for rehabilitative interventions. These results provide preliminary guidelines for subsequent strength training interventions to prescribe the optimal ‘dose’ of unilateral strength training to maximize benefits while minimizing intervention burden. These studies also help refine a unifying model of unilateral strength training to include contributions from central
motor output as well as afferent feedback. These studies highlight the importance of appropriate sensory feedback during maximal force production and the impact that sensory information from the skin can have on motor output in the nervous system.
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Acknowledgments

The past five years has been a time of growth from both an academic and personal perspective. I feel very fortunate to have had the opportunity to undertake my doctoral studies in the Rehabilitation Neuroscience Lab. There is no way I could have imagined the diverse array of experiences I would undergo and the many doors these experiences would open. Moving to Victoria to do my PhD was one of the best decisions I’ve made and it is a time I will look back on with great fondness.

I would like to thank my Supervisor, Dr. E. Paul Zehr for the wonderful and immeasurable expertise, feedback, teaching and mentorship that he has provided me throughout the process of completing my graduate training. I am honoured to have had the opportunity to work with such an innovative and positive force within the research community. I could not have asked for a better experience during my time in Victoria.

I am fortunate to have a supportive and unconditionally loving family who have consistently demonstrated a strong work ethic, compassion, and enjoyment for their careers. It is because of their affirmation and positive demonstration I felt empowered to follow my own path with its many winding twists and turns.

Thank you to the Supervisory Committee for their valuable feedback throughout the process allowing for each stage of my doctoral training to run as smoothly as possible.

As well, a huge thank you to the Heart and Stroke Foundation of BC, Canadian Stroke Network, National Sciences and Engineering Research Council of Canada (NSERC), and University of Victoria who funded a large part of this research.
Dedication

This dissertation is dedicated to my mother and father, Karen and Barry Barss, who have supported me wholeheartedly in not only this endeavour but provided me every opportunity to explore my interests and passions. To my wife, Dalyce Barss, whose love and support during this journey has been unwavering. I will be forever grateful for the many sacrifices you have made throughout this process.
1. General Introduction

“Thus, training of one portion of the body trains at the same time the symmetrical part and also neighboring parts...The training seems to be of a psychical rather than of a physical order and to lie principally in steadiness of attention.”

Edward Wheeler Scripture, 1894.

An entire field of research was born when a paper entitled ‘On the education of muscular control and power’ first discussed a “psychical rather than a physical” bilateral adaptation to a unilateral training program (Scripture et al., 1894). Although the true merits of this paper would not be recognized for over a century, its novel findings, describing adaptations resulting from physical and skilled training, continue to influence scientific literature to this day. The captured opening quote highlights Scripture’s hypothesis that the contralateral training effect was of a ‘psychical’—located within the nervous system—rather than a ‘physical’ one—meaning at the level of the muscle—in order to describe early evidence for training-induced neuroplasticity. Most notably, Scripture coined the term ‘cross-education’ describing the improvement in strength or functional performance of not only the trained limb but also in the untrained contralateral limb. More recently, it has been referred to as ‘intermanual transfer’, ‘inter-limb transfer’, or the ‘cross-transfer’ effect. While these terms continue to be used interchangeably, ‘cross-education’ continues to be the prevailing term within the scientific literature for reasons of historical context and literature continuity. Scripture’s findings provided one of the first references to a remote input influencing motor output in a meaningful way.

While ‘cross-education’ provided an early example of neuroplasticity, it has been well established that adaptations with the nervous system contribute to the early improvements in strength or task performance in the trained limb as well. ‘Resistance’ or ‘strength’ training is not only for those trying to maximize performance but is an important component of a healthy lifestyle (Murton & Greenhaff, 2010). The ability to increase force output through resistance training has received significant attention due to implications for rehabilitation and disease management (Folland & Williams, 2007). Its effectiveness in increasing force output, promoting functional improvement, and improving quality of life have been clearly established (Pak & Patten, 2008; Harris & Eng, 2010). The populations in which strength training is now being recommended as a primary intervention strategy are growing quickly and currently include...
stroke, spinal cord injury, aging, multiple sclerosis, post-surgery, immobilization, and osteoporosis. Within these populations, there may be instances in which one limb is unable to actively participate in training because of physiological or mechanical constraints. Only recently has implementing unilateral training or ‘cross-education’ received noteworthy consideration as a possible rehabilitation strategy during recovery from unilateral injuries (Hendy et al., 2012; Farthing & Zehr, 2014; Barss et al., 2016).

In order to properly integrate resistance training as an effective rehabilitation strategy, a number of fundamental issues require attention. One such issue is improving our understanding of underlying mechanisms and sites of adaptation which contribute to increased strength in the trained and untrained limbs. As well, establishing the time-course during which these adaptations occur so we can effectively prescribe a minimum time for the dose of resistance training to achieve minimally significant outcomes. Finally, it remains necessary to determine if there are specific strategies which can be incorporated to optimize resistance training interventions by enhancing strength increases. One such way is by influencing or altering the availability of specific sensory information. It is well established the widespread effects that cutaneous afferent feedback can have on multiple levels of the nervous system throughout ongoing movement (Zehr, 2006). By providing enhanced sensory feedback during strength training via electrical stimulation or mechanically altering sensory feedback via compression apparel, it may be possible to alter motor output in a beneficial way for neuro-rehabilitation.

Improving our understanding of remote influences on motor output and coordination patterns may be valuable in an applied motor re-training setting. The following literature review highlights cross-education from its inception in a historical context to our current understanding of the phenomenon. The neurological mechanisms responsible for increased force output in both the trained and untrained limbs will then be reviewed with a brief discussion on the proposed rehabilitation implications of this intervention strategy. The focus will then shift to the contributions that feedback from cutaneous afferents can have on motor output. This will include an outline of cutaneous afferent feedback transmission and our current understanding of how this information can be incorporated into ongoing motor output. A brief review of the methodologies being employed throughout this thesis will then provide the necessary background information to discuss three distinct projects which aim to determine how to optimally implement the use of remote inputs in order to improve functional recovery during rehabilitation (Chapter 2-4).
Chapter 2 will explore the time course of unilateral handgrip training in both the trained and untrained limb while determining the role of spinally mediated adaptations in the human wrist flexors. Chapter 3 will explore whether providing ‘enhanced’ sensory input via electrical stimulation during resistance training can alter the improvements in strength in the human forearm. Chapter 4 will explore whether a compression garment has measureable influence on motor output and whether this corresponds to changes in movement and performance. The primary goal of this dissertation is to better understand inter-limb connections with resistance training in the upper limb and how alterations in cutaneous afferent transmission can alter ongoing motor output.

1.1 Cross-education in historical context

In the literature, Scripture’s findings are commonly discussed yet the work on which his approach was based is often overlooked. Examining the early influences on Scripture provides important insight into broader picture of training-induced plasticity in the nervous system. Gustav Fechner (1801-1887) was a philosopher, physicist, and experimental psychologist whose formative work in 1857 documented how intensive task training could increase performance. Fechner was the lead author and sole participant in a protocol involving lifting 2 dumbbells (~9 lbs in each hand) over his head as many times as he could, every day, for 60 consecutive days (Fechner, 1857). Fechner’s performance improved from an initial 104 to a staggering 692 repetitions on day 55 (See Figure 1.1). While the scope of his research and the results may seem underwhelming based on our current understanding of training adaptation, the detailed time-course that was documented has rarely been explored or detailed even to this day.
While Fechner’s work clearly illustrated that motor performance improvements to strength training existed in the trained limbs, further work by Alfred Wilhelm Volkmann (1801-1877), a physiologist, anatomist, and philosopher who specialized in the nervous system, revealed that training of a single limb can also affect an untrained limb. The focus of his work attempted to uncover whether perceptual tactile sensitivity could be improved by training. A paper in 1858 showed that training the ability to detect touch of only the left fingertip for several weeks resulted in an improved ability to perceive tactile sensation not only of the trained finger but also of the untrained right, contralateral fingertip despite not using it at any point in the training protocol (Volkmann, 1858). Further experiments also found that practice on the third phalanx increased touch sensitivity on the first phalanx. This work was not only the first to identify the phenomenon of what would later be coined ‘cross-education’, but highlights the effect of using cutaneous afferent sensitivity training and the specificity of adaptations.
Because of the work by Fechner and Volkmann, Scripture recognized a relation between training and cross-limb tactile effects and decided to explore the effects of strength or skill training using only one limb. In a similar fashion to the Fechner paper, Scripture had two co-authors of his work perform training with a single arm (Scripture et al., 1894). The first participant, identified as Miss Brown, completed a strength training (“muscular power”) task by squeezing a rubber bulb (similar to those used on a blood pressure cuff). The second participant was identified as Miss Smith and completed a skill training (“muscular control”) protocol involving passing a needle through an electrified drill board with holes of decreasing diameter. If the needle touched the metal on the board, the trial ended. The task appears to be similar to the popular modern board game “Operation” (Hasbro, Inc.).

Miss Smith improved her percentage of successful trials by ~40% while Miss Brown increased her strength by almost 70% in the trained right limb which are referred to as effects of ‘practice’. Interestingly, results in the untrained limbs showed that Miss Smith increased accuracy by 50% and, Miss Brown got ~43% stronger, which Scripture suggested were due to ‘indirect practice’. This work directly relates to this thesis as many of the same pathways which were responsible for this initial study exploring inter-limb transfer of strength and skill may be influenced by remote sensory input from the skin (Zehr, 2006; Ruddy & Carson, 2013).

1.2 Neural mechanisms of resistance training

Generally, strength gains which occur within the first four weeks of a resistance training program have been attributed to adaptations in the nervous system with further increases being mainly due to morphological changes in contractile proteins and muscle fibre hypertrophy. When prescribing exercise programs to the general public with the goal of improving overall strength and health, this level of understanding is sufficient. However, implementing resistance training programs within clinical populations requires targeted strategies which focus on overcoming the specific deficits due to the injury or lesion efficiently and in an expeditious fashion. Therefore, it is of vital importance to understand the mechanism and site of adaptation in terms of nervous system adaptation to resistance training. The regulation of motor coordination and output, from simple to complex patterns, is highly organized. In broad terms, this organization consists of interaction within a tripartite system of supraspinal input, spinal circuits, and sensory feedback (Zehr & Duysens, 2004).
1.2.1 Preliminary evidence for adaptation in the nervous system

Cross-education has been generally attributed to neurological factors affecting motor output because minimal changes in cross-sectional area have been shown with MRI imaging (Ploutz et al., 1994) and biopsy studies have shown no change in enzyme activity or fibre type in the contralateral limb after unilateral training (Houston et al., 1983; Hortobágyi et al., 2005). These early studies directed researchers to the nervous system as a likely contributor to the initial increase in strength in both the trained and untrained limb. However, they provided very little information about possible sites or time course of adaptation.

Electromyography (EMG) has been the backbone of neurophysiological studies for the past thirty years allowing researchers to assess gross changes in activity of the muscle. Common adaptations seen with surface EMG (Mean absolute value or root mean square) are increases in signal amplitude in the agonist muscle, as well as reductions in activation of antagonist muscle groups which lead to a reduction in co-contraction (Gabriel et al., 2006; Folland & Williams, 2007).

More detailed information can be gathered with intramuscular recordings of single motor unit activity. One mechanism which could account for the initial increases in strength would be an increase in maximal motor unit firing rate with training. Maximal motor unit discharge rates have been assessed in both young and old adults after six weeks of resistance training of the knee extensor quadriceps femoris (Kamen & Knight, 2004). Training included three sets of ten dynamic knee extension contractions at 85% 1RM three days per week. Increases in maximal voluntary force in both the young and old groups were accompanied by increases in maximal motor unit discharge rates of 15% and 49% respectively. No changes in discharge rates were observed for either group at 10% or 50% maximal voluntary contraction (MVC) after exercise training. Interestingly, these increases in maximal discharge rates were observed during the second of two baseline tests and did not increase further with six weeks of resistance training. This suggests an adaptation in maximal motor unit firing contributes to the early rise in force output with resistance training. However, changes in motor unit firing rate, like most neural adaptations, appears to be specific to the training task and may not be revealed at sub-maximal intensities of contraction.
The presence of doublet firing, defined as an interspike interval (ISI) that is <20 ms, has also been assessed by single motor unit recording to determine if firing frequency can be altered. A doublet firing pattern is most commonly seen at the initiation of a contraction with a high rate of force development or contraction speed. This was assessed when participants completed ten sets of ten fast dorsiflexion contractions five days per week for twelve weeks (Van Cutsem et al., 1998). After twelve weeks of training, a 30.2% increase in dynamic dorsiflexor strength and an increased speed of voluntary ballistic contraction was accompanied with an increase in doublet discharges from 5.2% to 32.7%. Motor units were also shown to have a greater maximal firing frequency. Taken together, these studies indicate increases in doublet firing and maximal motor unit firing rates likely contribute to the initial increases in strength and speed of contraction.

Differences in motor unit synchronization between strength trained participants have been compared in a cross-sectional study comparing musicians and untrained controls (Semmler & Nordstrom, 1998). This result led to the idea that an increase in motor unit synchronization could occur with resistance training. If more motor units are firing synchronously, there will be a greater force output during a single maximal contraction. This idea was explored in participants that performed six sets of ten maximal isometric finger abductions three times per week for four weeks (Kidgell et al., 2006). They found a 54% increase in force output of the first dorsal interosseous (FDI) muscle. However, this was not accompanied by any alterations in motor unit synchronization. An important consideration is that motor unit synchronization may be more important for coordinating activity of multiple muscles during the learning and performance of gross motor tasks compared to the simple motor task with few motor units.

Although techniques of electromyography provide important information about the characteristics of neuromuscular change, little information is obtained about specific sites of adaptation within the nervous system. Until recently, all of the evidence for possible sites of adaptation in humans has been indirect and speculative. However, improved techniques and technology are now providing a body of literature which researchers can use to develop a more holistic model of adaptation.

1.3 Spinally mediated adaptations in the ipsilateral trained limb

It is commonly established that spinal reflex pathways affect the excitability of the alpha motor neuron-- what Sir Charles Sherrington referred to as the ‘final common pathway’ during a
given task (Sherrington, 1903). However, a limited number of studies have been published which assess these pathways after resistance training. Preliminary evidence indicates that adaptations in reflex pathways may contribute to early increases in strength. One of the first studies to assess changes in spinal reflex pathways before and after a resistance training intervention explored H-reflex amplitudes on the ascending limb of the recruitment curve after unilateral, isometric plantar-flexion resistance training in which participants completed five sets of eight contractions three times per week for five weeks (Lagerquist et al., 2006). MVC of the plantar flexors increased 15% on the trained ipsilateral limb which was accompanied by an increase in H-reflex amplitude after training.

More recently, the effects of unilateral dorsiflexion resistance training on H-reflex excitability were assessed after participants completed five sets of five contractions, three days per week for five weeks (Dragert & Zehr, 2011). A more detailed analysis of the full recruitment curves was performed allowing for the assessment of more subtle changes in thresholds and relative reflex sizes. This study indicated that an increase in dorsiflexion MVC of 15% in the trained ipsilateral limb was accompanied with an increase in H_{thresh} in the trained tibialis anterior and soleus. As well, there was a decrease in H_{max} in the antagonist soleus muscle. This result highlights the importance of assessing reciprocal antagonists during peak muscle contractions and provides further validation of previous observations using EMG amplitude to show reduced co-activation after resistance training.

The interaction between agonist and antagonist muscle groups after resistance training reveals adaptation in segmental spinal reflex pathways. Disynaptic reciprocal inhibition between the tibialis anterior and soleus has been explored after explosive ankle dorsiflexor training during which the participants completed three sets of sixteen contractions, three days per week, for four weeks (Geertsen et al., 2008). Reciprocal inhibition was measured as the depression of the soleus H-reflex following conditioning stimulation to the peroneal nerve. After the intervention, MVC strength increased between 24 – 33% as they measured force over a period of 30 – 200 ms after initiation of the contraction. Reciprocal inhibition at the onset of dorsiflexion increased from 6% to 22% and the authors speculated that this may function to ensure efficient suppression of antagonist muscles to allow expression of the increased strength in dorsiflexor muscles.

The literature indicates that multiple afferent pathways likely contribute to the changes in alpha motor neuron excitability that occurs with training (Lagerquist et al., 2006b; Geertsen et
al., 2008; Dragert & Zehr, 2011). These changes in excitability could lead to a reduction in antagonist activity with greater agonist activation which could lead to changes in maximal motor unit firing frequency and doublet firing (Van Cutsem et al., 1998; Kamen & Knight, 2004). The cause of increased excitability could be due to adaptations in reciprocal inhibition where the antagonist muscle is suppressed to a greater extent to facilitate the agonist contraction (Geertsen et al., 2008). As well, it is very likely that changes in presynaptic inhibition could alter the excitability of Ia afferent fibres which in turn could alter the excitability of the alpha motor neuron during muscle contraction (Harrison & Zytnicki, 1984; Burke et al., 1992). Adaptations in any number of these pathways could account for many of the changes that are seen with both surface and intramuscular EMG. The data indicates that more sensitive techniques are needed in order to assess the more subtle changes in thresholds and relative reflex sizes that occur with training. These studies also highlight the importance of assessing neurophysiological measures in both agonist and antagonist muscles which may both contribute to the changes in the force output of a muscle.

1.4 Supra-spinal adaptations in the ipsilateral trained limb

More recent tools for assessing neuromuscular adaptations have generally focused on adaptations at the cortical level as well as the main efferent transmission pathways to the alpha motor neurons, including the primary motor cortex (M1) and the corticospinal tract. Techniques involving targeted activation of the brain or measurement of brain activity have provided information about specific sites of adaptation that account for the initial increases in force output observed with training.

1.4.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is widely used for assessing supraspinal contributions to resistance training due to its low level of discomfort and ability to test excitability within a given pathway and state before and after a training intervention. Many inputs can affect the amplitude of motor evoked potentials (MEPs) which emphasises the importance of standardized protocols. MEPs are collected by measuring the force production or amplitude of response measured by surface EMG in a given muscle when the corresponding site on M1 is stimulated by induction with a magnetic impulse. A similar technique can also be used at the cervicomedullary junction near the pyramidal decussation to produce an evoked potential.
A CMEP is primarily the result of motoneuron activation by a single descending volley elicited by excitation of corticospinal axons although other descending and ascending pathways will inherently be activated as well (McNeil et al., 2013).

In a recent study, participants performed three sessions of radial deviation resistance training per week for four weeks (Carroll et al., 2009). Four sets of 8 radial deviation movements ranging from 70% - 85% 1RM were performed during each training session. Radial deviation force output increased 11% with wrist extension increasing by 9%. This was accompanied by increased amplitudes of MEPs and cervicomedullary evoked twitches during a 10% contraction in the resistance training group with no change in the control group. Structural changes are unlikely to account for this finding because training did not affect the amplitude of twitches elicited by supra-maximal nerve stimulation. This suggests that resistance training increased corticospinal transmission to motoneurons in the trained muscles at the wrist.

During a voluntary maximal contraction, all of the motor units innervating a muscle are not recruited at a given time. If supramaximal TMS or peripheral nerve stimulation is applied during a maximal contraction the remaining motor units which were not voluntarily recruited will be activated and recorded as an increase in force upon stimulation. This technique is commonly referred to as the ‘interpolated twitch’ technique. With this approach, the percentage of force that is able to be produced voluntarily provides information on whether the number of motor units being voluntarily recruited changes after training. Strength as well as cortical voluntary activation via interpolated twitch has been assessed after four weeks of wrist abduction training three times per week (Lee et al., 2009). Four sets of eight dynamic wrist abduction contractions were performed at training loads between 70-85% 1RM. MVC force was increased by 11% after the intervention and the average size of the superimposed twitches produced by cortical stimulation was significantly larger after resistance training. Interestingly, the direction of the twitches produced by cortical stimulation during wrist abduction and maximal wrist extension shifted towards the training task. However, there were no significant changes in the number of motor units being recruited during MVCs with supramaximal nerve or M1 stimulation. This provides evidence that there is an increase in excitability of this pathway which contains directionally specific adaptations, which may indicate a more coordinated cortical recruitment.
Repetitive TMS (rTMS) when delivered to the motor cortex stimulates inhibitory interneurons which project bilaterally to the contralateral M1 (Carroll et al., 2011). Recently, rTMS was used to assess whether altering M1 excitability via interhemispheric inhibition can alter the increase in strength after resistance training (Hortobágyi et al., 2011). Participants were split into five different groups. The first group (VOL) completed isometric first dorsal interosseus (FDI) abduction contractions at 70-80% MVC. Five sets of 10 contractions were performed during each of the ten training sessions over a period of 4 weeks. The second group (VOL + rTMS) completed the resistance training program and also received 1Hz rTMS to the FDI motor area at 120% of the resting motor threshold during one minute rest intervals between sets throughout the training program. The third group (VOL + SHAM) completed the training and were provided with a sham rTMS protocol. The fourth group (rTMS only) only received the rTMS for the four weeks and did not complete the training protocol. The fifth group was a control group who did not receive any intervention over the four weeks. The VOL and VOL + SHAM groups showed relatively equivalent increases in MVC strength of 37.5% and 33.3% respectively, both of which were significantly greater than the VOL + rTMS group who only increased in strength by 18.9%. Both the rTMS only and control groups did not change in strength from baseline. This indicates that the 1Hz rTMS interfered with the participant’s ability to increase their force output. Single pulse TMS revealed that MEP size and recruitment curve slopes were reduced in the VOL + rTMS and rTMS only groups after ten sessions. There were no changes in MEP amplitudes after the resistance training intervention. This study provides evidence that M1 mediates neural adaptations to resistance training.

1.4.2 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) has been used to assess possible changes in cortical activation patterns after strength training. Previously, participants performed up to six sets of eight maximal isometric ulnar deviation contractions, four times per week, for six weeks (Farthing et al., 2007). The resistance training program increased strength in the trained limb by 45.3%. This was accompanied by activation in the contralateral primary motor (M1) and sensory (S1) cortices that was unique to the post-test fMRI scan. An interesting finding was new activation in the cerebellum after training which highlights the importance for future studies to explore the possible strengthening of connections between M1 and the cerebellum. This study
provides evidence that the integration of multiple brain areas may contribute to improved coordination of a motor plan which facilitates the early increase in the strength after resistance training.

A follow-up study again explored the changes in cortical activation patterns that occurred with maximal isometric handgrip contractions (Farthing et al., 2011). Six sets of eight handgrip contractions were performed five days per week for three weeks. Handgrip force increased by 10.7% after the resistance training intervention. This strength increase was associated with an increase in the volume of activation in the trained motor cortex. As well, there was evidence of increased activation bilaterally in the dorsal stream (visual and parietal cortex) for the trained limb. This may be an indication that pathways involved in visual control of action may be related to the observed effects (Creem-Regehr, 2009). The results from these studies indicate that resistance training is associated with bilateral adaptation at the cortical level and is not restricted to the motor cortex alone.

1.4.3 Electroencephalography

Electroencephalography (EEG) measures electrical activity in the brain. Surface negative potentials detected at the scalp around the time of movement are referred to as movement related cortical potentials (MRCPs). EEG has been measured before and after explosive leg extension contractions which were performed three times per week for three weeks (Falvo et al., 2010). Participants were instructed to maximally accelerate the leg extension load which progressively increased from 4-6 sets and 70-85% of 1RM. There was a 21.6% increase in leg extensor MVC after the explosive resistance training program. This was accompanied by a 31.6% increase in rate of force development and a 47.2% increase in muscle activation as measured by average EMG. The authors speculated that plasticity exhibited at multiple supraspinal centers following training may alter the MRCPs. During submaximal contractions, MRCP amplitudes were attenuated at several scalp sites overlying motor-related cortical areas which included Cz, C1, and C2. The authors suggested that by increasing strength, comparable motor tasks can be performed with a lower neural effort.

The literature appears to indicate that many small changes occur at multiple levels of the nervous system. These adaptations appear to overlap in both time course and effect. Cortical, subcortical and spinal networks likely all contribute to early adaptations after resistance training.
in the trained ipsilateral limb. Interestingly, it also appears that a portion of these adaptations are being transferred to the contralateral motor system as unilateral resistance training produces bilateral increases in strength.

1.5 Adaptations in the contralateral untrained limb (cross-education)
Cross-education has been highlighted in recent literature for its possible use as a tool for rehabilitation from unilateral injury (Hendy et al., 2012; Farthing & Zehr, 2014). The term cross-education, which has typically been used to describe inter-limb strength transfer in the literature, occurs in the homologous muscle of the untrained contralateral limb after unilateral resistance training (Munn et al., 2004). More recently, it has been referred to as ‘intermanual transfer’, ‘interlimb transfer’, or the ‘cross-transfer’ effect. While these terms continue to be used interchangeably, ‘cross-education’ continues to be the prevailing term within the scientific literature for reasons of historical context and literature continuity.

1.5.1 Characteristics of Cross-education
Meta-analyses have determined the strength increases in the untrained contralateral limb are approximately 35% of the strength that is gained in the trained limb (Munn et al., 2004; Lee & Carroll, 2007). On average, this represents a 7.8% increase in strength from baseline in the untrained contralateral limb. Cross-education has been shown to occur with training by maximal voluntary contractions (Farthing & Chilibeck, 2003), electrical stimulation (Hortobagyi et al., 1999) or mental practice of unilateral contractions (Yue & Cole, 1992).

Cross-education has been generally attributed to neurological factors since minimal changes in cross-sectional area has been shown with MRI imaging (Ploutz et al., 1994) and biopsy studies have shown no change in enzyme activity or fibre type in the contralateral limb after unilateral training (Houston et al., 1983; Hortobagyi, 2005). As well, studies have shown contralateral strength gains with little muscle activity in the untrained muscle during unilateral exercise (Devine et al., 1981; Hortobagyi et al., 1997; Munn et al., 2004; Magnus et al., 2010).

Cross-education occurs in all homologous muscle groups that have been investigated in both the upper and lower body (Hortobágyi, 2006; Lee & Carroll, 2007). The contralateral strength gains are largest when assessed during the same type of contraction and parameters involved in the training (Hortobagyi et al., 1997). For example, after training using eccentric
(lengthening) contractions, the magnitude of cross-education was greatest when maximal voluntary contractions (MVC’s) were measured with eccentric compared to concentric or isometric contractions (Hortobagyi et al., 1997; Farthing & Chilibeck, 2003). Electrically stimulated contractions have also been shown to produce a fivefold greater increase in electrically evoked force after training than during eccentric contractions (Hortobagyi et al., 1999). Interestingly, the group that trained with eccentric contractions saw significantly greater increases in eccentric force compared with electrically evoked force in the untrained limb after training. This specificity of cross-education is another strong indication neural mechanisms are responsible for the increase in contralateral strength after unilateral training.

A possible asymmetry of strength transfer in the upper body has been shown in the dominant to the non-dominant hand in right handed individuals (Farthing et al., 2005). Therefore, the dominant arm may not increase in force output after unilateral training of their non-dominant arm. Non-dominant arm training may not induce changes in the motor plan, neural drive, or afferent feedback provided to the dominant right arm due to the strength and coordination advantages already present. No studies have assessed asymmetry of strength transfer in left handed individuals. As well, no studies have assessed asymmetry of strength transfer in the lower limbs, leaving a gap in the literature that will be important to address if unilateral training is to be used in a rehabilitation setting.

To maximize the possible role of cross-education in a rehabilitation setting, an understanding of the neural mechanisms and sites of adaptation responsible for the effect is essential. A number of reviews have been published on the possible mechanisms of cross-education (Zhou, 2000; Hortobágyi, 2006; Lee & Carroll, 2007; Farthing, 2009; Ruddy & Carson, 2013). Within this section a number of proposed mechanisms will be discussed at two main sites of adaptation. The presented mechanisms are not mutually exclusive as many sites many contribute to the overall cross-education effect.

### 1.5.2 Spinal adaptations in the untrained limb

The literature suggests spinal adaptations that occur with unilateral training may also mediate cross-education. The initial evidence stems from the finding of a greater increase in contralateral strength with electrically stimulated training compared to voluntary training (Hortobagyi et al., 1999; Maffiuletti et al., 2006). This finding indicates that mechanisms other
than an increase in cortical drive to the motor neuron contribute to the untrained limbs increase in strength. In theory, there should be less activity in cortical motor areas and descending inputs to the untrained muscle during electrically evoked contractions (Hortobágyi & Maffiuletti, 2011). Unilateral training may increase the excitability of spinal motoneurons through adaptations in afferent pathways affecting interneurons in the contralateral limb. Few studies have observed bilateral spinal reflex pathways in relation to a unilateral training paradigm limiting our current understanding.

Possible pathways which could account for crossed effects in the spinal cord have previously been identified. There are no direct connections between spinal motoneurons in the contralateral limb at a given segmental level of the spinal cord. However, reflex pathways are able to modulate interlimb coordination (Sherrington, 1910) and are most likely mediated through commissural interneurons (Jankowska et al., 2005) and propriospinal relays (Burke et al., 1992; Jankowska, 2001). Activation of group Ia afferents inhibits contralateral homologous motoneurons (McCrea, 2001) via the Ia inhibitory interneurons (Delwaide & Pepin, 1991). This has been functionally demonstrated when contraction of an ipsilateral muscle depresses H-reflex amplitude in the homologous contralateral muscle (Hortobágyi et al., 2003; Carson et al., 2004). H-reflex amplitudes are suppressed in human wrist flexors during strong unilateral flexion and extension of the contralateral wrist which can persist up to 30 seconds after the contraction terminates (Hortobágyi et al., 2003). Contraction of the ipsilateral limb could modulate, via presynaptic inhibition of Ia afferents, segmental inputs to spinal motoneurons. Further research is needed to determine the mechanisms by which other afferent modalities may modulate excitability of the contralateral motoneurons. However, preliminary studies indicate modulation of the Ia afferent pathway may contribute to the cross-education effect.

Studies which have observed the effects of unilateral training on fixed H-reflex amplitudes in neurologically intact participants have found no change in the agonist muscle in the untrained contralateral side despite an increase in strength (Lagerquist et al., 2006b; Del Balso & Cafarelli, 2007; Fimland et al., 2009). However, H_{max} amplitude has been shown to be reduced in the antagonist muscle after unilateral plantar flexion training in a neurologically intact group, (Dragert & Zehr, 2011) while spinal reflex excitability and reciprocal inhibition within the untrained more affected tibialis anterior were altered in a post-stroke population (Dragert & Zehr, 2013). Future well-controlled basic and applied cross-education studies are needed in order
to determine the contralateral connections of afferent pathways and how they are modulated in the contralateral limb after unilateral training.

### 1.5.3 Supra-spinal adaptations in the untrained limb – ‘Cross-activation’ hypothesis

In recent years, evidence of a cortical contribution to cross-education has been established. Two main theories have been proposed which include the ‘cross-activation’ and ‘bilateral access’ hypotheses (Lee & Carroll, 2007; Anguera et al., 2007; Ruddy & Carson, 2013). The ‘cross-activation’ hypothesis is predicated on unilateral training causing bilateral cortical activity leading to adaptations in both hemispheres. The use of TMS to produce MEPs has led to a body of evidence indicating that bilateral activation of primary, premotor, and supplementary motor cortices occurs during unilateral muscle contractions (Kristeva et al., 1991; Boroojerdi et al., 2001; Hortobágyi et al., 2003; Reis et al., 2008). During a key-tapping task it was shown by positron emission tomography (PET) that as the level of force is increased during a unilateral contraction, the activity of the ipsilateral cortex is increased (Dettmers et al., 1995). As well, the size of the ipsilateral MEP elicited by TMS is graded with the intensity of the voluntary muscle contraction with a steep rise in the slope of the recruitment curve at about 50% MVC (Muellbacher et al., 2000; Stinear et al., 2001; Hortobágyi et al., 2003). Also, at least some of the bilateral activity occurs independently in each motor cortex since both primary motor cortices are active during unilateral motor activity in individuals where the corpus callosum connections have been disrupted via antiepileptic drugs which reduce intracortical excitability (Ziemann et al., 1999). Since high force unilateral contractions produce bilateral activation, it is possible that corticospinal connections are strengthened with unilateral training. This may lead to a stronger descending signal to the contralateral muscle leading to an increased force output.

A pair of studies have used the twitch interpolation method in which supramaximal pulses are evoked via TMS during maximal contractions to explore the motor units which are being recruited during voluntary muscle activation. These studies aimed to show evidence of adaptation in cortical activation and corticospinal connections after unilateral strength training. Significant increases in voluntary activation in the untrained plantar flexors (Shima et al., 2002) and increased cortical voluntary activation of the untrained wrist extensors (Lee et al., 2009) have been shown to accompany the increase in strength in the untrained contralateral limb. Unilateral practice of a ballistic finger abduction task was shown to improve performance by 82% in the
untrained left hand (Carroll et al., 2008). This was accompanied by bilateral increases in the amplitude of responses to TMS. A follow-up paper again found bilateral increases in performance and corticospinal excitability after training of a unilateral ballistic motor task (Lee et al., 2010). Corticospinal excitability was assessed by MEP amplitude after TMS. Repetitive TMS was applied to the trained and untrained motor cortex to induce a ‘virtual lesion’. The authors found that rTMS of either the right or left cortex reduced performance gains in the contralateral hand. They concluded early retention of ballistic performance improvements in the untrained limb are due to adaptations in the untrained motor cortex. Farthing et al. (2011) found with fMRI that increased output of the untrained motor cortex contributed to the maintenance of strength in the untrained limb after limb immobilization. Thus, intense unilateral muscle contractions produce bilateral cortical activation and corticospinal plasticity. These studies taken together indicate that increases in corticospinal excitability from a single session may improve voluntary activation in the contralateral limb with unilateral training causing an increase in strength associated with cross-education.

1.5.4 Supra-spinal adaptations in the untrained limb - ‘Bilateral access’ hypothesis

Another proposed cortical explanation for cross-education is the ‘bilateral access’ hypothesis, in which motor plans developed in the trained hemisphere can be accessed by the opposite untrained hemisphere to facilitate task performance (Anguera et al., 2007; Lee et al., 2010; Ruddy & Carson, 2013). Practicing a given motor task with one arm can improve performance of the same task in the opposite homologous limb (Teixeira & Caminha, 2003; Weeks et al., 2003). Resistance training may be considered a form of motor learning. Several studies indicate that cross-education of strength and skills (finger tapping or mirror-drawing) show similar patterns of asymmetrical transfer and may be controlled by related mechanisms that originate in the cerebral cortex (Carroll et al., 2001; Farthing, 2009; Ruddy & Carson, 2013). For example, increases in ipsilateral motor cortex activation and changes in interhemispheric inhibition may be common adaptations to both strength and skill transfer (Farthing et al., 2007, 2011; Hortobagyi et al., 2011). During a voluntary contraction of the untrained limb, the untrained hemisphere may access changes in premotor, supplementary, and motor cortices in the trained hemisphere through interhemispheric connections to enhance the descending cortical drive causing greater force output.
There are strong connections between cerebral hemispheres which may allow for the sharing of an improved motor plan. The corpus callosum provides an anatomical connection between the two hemispheres providing a direct route by which information regarding motor learning from the trained hemisphere can be utilised by the opposite hemisphere during unilateral motor tasks (Karni et al., 1995). Adaptations in connections between primary motor cortices (M1) through transcallosal routes have shown significant plasticity with training (Perez et al., 2007; Hortobagyi et al., 2011). These transcallosal connections convey diffuse inhibitory influences from M1 on one side of the brain to the contralateral M1 (Chen, 2004). Previously, it was shown that interhemispheric inhibition suppresses MEPs evoked by TMS but not transcranial electrical stimulation (Ferbert et al., 1992). Electrical and magnetic stimuli are thought to activate the same descending pathways, but in different ways (Edgley et al., 1990). Magnetic stimuli may excite the initial segment of pyramidal tract neurons, or the synaptic input onto these neurons while electrical stimuli most likely activate the pyramidal axons directly within the white matter (Ferbert et al., 1992). Therefore, it is thought interneurons may play a significant role in transferring information from one M1 to the other. The majority of the interhemispheric connections are inhibitory as repetitive TMS reduced the MEP amplitude in the contralateral M1 (Wassermann et al., 1998). However, paired pulse TMS has produced intracortical facilitation between homologous muscles when triggered by self-paced movements of the other hand (Sohn et al., 2003). This may indicate a neuroanatomical basis for cross-education (Chen, 2004; Hortobagyi, 2005).

TMS studies indicate that the intensity of stimulation may play a role in both interhemispheric plasticity and cross-education. Wassermann et al. (1998) found that when one M1 was subjected to low-intensity repetitive TMS, the MEPs decreased in the opposite M1. However, when 30 minutes of 1Hz TMS was applied to M1 it induced lasting modulation of excitability thought to reflect changes in interhemispheric interactions. Therefore, a relationship seems to exist between the intensity of M1 activation and the level of inhibition in the contralateral M1. When the excitability of M1 in one hemisphere is functionally compromised by increasing cortical excitability with rTMS, the contralateral M1 compensates in order to maintain force output during a unilateral repetitive finger-tapping task. Simultaneous bilateral M1 stimulation designed to prevent this compensation increased the tapping force during the finger-tapping task due to the increased cortical excitability (Strens et al., 2003). However, it is
important to note that just because the intensity of TMS stimulation impacts interhemispheric inhibition in training studies doesn’t necessarily mean the intensity of unilateral contractions will have a similar role.

It is possible that the alterations in interhemispheric inhibition that occur within a single session could lead to long term changes in excitability with repeated training. Perez et al., (2007) found bilateral improvements in performance of a key tapping task after unilateral training. This was accompanied by decreased interhemispheric inhibition between ipsilateral and contralateral M1 as assessed by MEP amplitudes (TMS). Recently, the first evidence for plasticity of interhemispheric connections mediating cross-education of a simple motor task was produced (Hortobágyi et al., 2011). After 1000 submaximal voluntary contractions of the right first dorsal interosseous (FDI) the untrained FDI’s force output increased 28.1% with interhemispheric inhibition being reduced by 30.9%. TMS evoked MEP amplitudes also showed an up-regulation of motor cortical excitability in the non-trained primary motor cortex. These studies taken together indicate not only that plasticity in interhemispheric inhibition is possible but may play a role in transfer of strength to the untrained contralateral limb after unilateral training.

Recent evidence indicates a motor learning mechanism may be contributing to cross-education. Studies using fMRI have noted inter-hemispheric communication due to contralateral cortical adaptation in premotor, supplementary, and primary motor cortices after unilateral training (Farthing et al., 2007, 2011). Farthing et al. (2007) provided evidence, via functional magnetic resonance imaging (fMRI), that cross-education is associated with changes in brain activation with training. The participants performed up to six sets of eight maximal isometric ulnar deviation contractions, four times per week, for six weeks. They found enlarged areas of activation in M1 in the contralateral hemisphere associated with the 47.1% increase in strength in the untrained contralateral limb. Due to fMRI limitations it was not possible to determine if this increase in activation led to a greater neural drive to the muscle. They also found ipsilateral temporal lobe activation uniquely associated with the untrained limb which may suggest a possible role of memory retrieval acquired by the trained arm. This may offer the untrained limb with a reference for preparation and execution of future movement. Farthing et al. (2011) detected with fMRI an increase in the untrained motor cortex after unilateral handgrip training. Participants completed six sets of eight maximal handgrip contractions five days per week for three weeks. After training, there were also increases in activation in the untrained ipsilateral
premotor, sensory, and visual cortex areas. This could suggest that information in the trained hemisphere is accessed during execution of the task with the untrained limb. The current literature provides evidence of a cortical contribution to cross-education. It is suggested that modulation of interhemispheric inhibition may increase motor cortical activation in the untrained hemisphere, leading to increased corticospinal excitability to the untrained limb after training.

Understanding the neural mechanisms responsible for the effect of resistance training are vitally important for appropriately implementing any rehabilitation program within a clinical population. However, it is of equal importance to ensure we are maximizing the benefit of unilateral resistance training. Establishing strategies which ultimately enhance strength or performance gains is the obvious next step. The original work by Gustav Fechner highlighted the bilateral effects of cutaneous afferent sensitivity training with a single hand. This work provided the initial evidence that similar sites of adaptation may be accessed or contribute to the improvement seen in the untrained limb in both the motor and sensory systems. Since then it has been well established that cutaneous sensory information can have widespread effects on motor output (Duysens, 1977; Zehr & Stein, 1999; Collins et al., 2000; Panek et al., 2014). It is therefore plausible that enhancing this sensory feedback in functionally specific ways may improve strength performance gains. In order to understand how this might be possible, it is first vital to understand how tactile information is detected, relayed, and incorporated into ongoing movement.

1.6 Cutaneous receptors in humans

“The experimentalist has in general to be content to tacitly treat these skin reflexes as of a single kind. But the variety of species of sensation elicitable from the skin suggests that possibly different reflex motor reactions attach to the different species of end-organs undoubtedly coexisting in one and the same skin field”

Sir Charles S. Sherrington (1903)

The majority of our understanding of motor control neuroscience began with the seminal work of Sir Charles Sherrington who is rightly considered to be the “father of neurophysiology”. Although he identified the skin as conveying a diverse array of information to the central nervous system, his own experiments did not appear to support a strong role for cutaneous feedback in controlling posture or locomotion in the cat (Sherrington 1903). Interpretation of this
view undoubtedly skewed experimental approaches on the topic for almost 100 years. Only recently has the true functional importance of cutaneous sensory information to movement, proprioception, and kinesthesia been identified.

The skin is the most extensive and versatile of the body’s organs and in a fully grown adult covers a surface area of approximately 2 m² (McGlone & Reilly, 2010). As early as Sherrington (1903) the skin was identified as conveying a diverse array of information to the central nervous system. In regards to motor control, information from the skin has most commonly been thought of as important in determining the size, shape, and texture of objects. Less attention has been paid to its impact on more complex functional tasks including proprioception. The importance of sensory information from the skin during such tasks has led researchers to explore the numerous functional connections the skin possesses. Rehabilitation strategies may be able to tap into these connections in order to provide specific cutaneous sensory feedback at functionally relevant movements to alter motor output in an advantageous way. In order to address possible rehabilitation applications of sensory information from the skin, it is of vital importance to understand how the nervous system detects, transports, and integrates cutaneous afferent feedback.

1.6.1 Classes of cutaneous mechanoreceptors

The mechanoreceptive types discussed in this section are large myelinated fibers with conduction velocities in the Aβ range (35-70m/sec) (Winkelmann, 1988). Touch and pressure receptors found in the skin are used to transduce mechanical stimuli into electrical signals (Gillespie & Walker, 2001; Lewin & Moshourab, 2004). Initial investigations explored single afferent fibre activity by the method of percutaneous microelectrode recording (Vallbo & Hagbarth, 1968). This pioneering work identified four main classes of receptors based on adaptation properties and receptive field size. Together these receptors provide the ability to discriminate to a very precise degree about the size, pressure, and surface of the external environment (Knibestol, 1973; Knibestol, 1975; Knibestöl & Vallbo, 1970). These studies also confirmed that human skin contains similar types of receptors which are found supplying the glabrous skin of the cat and monkey (Werner & Mountcastle, 1965; Lindblom, 1965).

In terms of adaptation properties, cutaneous receptors are divided into two classes based on their response rate to a stimulus. Slowly adapting (SA) receptors (Merkel discs and Ruffini
endings) signal the pressure and shape of objects by their average firing rate. They continuously and faithfully respond while a stimulus is present where the number of action potentials is proportional to the indentation force applied to the receptor (Knibestol, 1975). Rapidly adapting (RA) receptors (Meissner’s corpuscles and Pacinian corpuscles) sense motion of objects on the skin and respond during the period when the position of the stimulus changes. Their firing rates are proportional to the speed of motion, and the duration of activity signals the duration of motion (Knibestol, 1973). A further classification relates to the receptive field properties. The surface area of skin to which each receptor is sensitive is determined by the anatomical location within the skin. Type I receptors (Merkel discs and Meissner’s corpuscles) are near the surface and possess small receptive fields. Type II receptors (Ruffini endings and Pacinian corpuscles) lie deeper within the dermis have larger receptive fields (Hsiao et al., 2010).

**Table 1.1 Summary of receptor characteristics in the glabrous skin of the human hand** (Bolanowski et al., 1988)

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>SAI (Merkel disk)</th>
<th>SAII (Ruffini ending)</th>
<th>RAI (Meissner corpuscle)</th>
<th>RAII (Pacinian corpuscle)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency Response</strong></td>
<td>&lt;0.3 - &gt;100 Hz</td>
<td>15 - 400 Hz</td>
<td>40 - 80 Hz</td>
<td>3 - 100 Hz</td>
</tr>
<tr>
<td><strong>Threshold (re 1 µm)</strong></td>
<td>28 dB @ 3Hz</td>
<td>10 dB @ 300 Hz</td>
<td>&lt;20 dB @ 300 Hz</td>
<td>28 dB @ 3 Hz</td>
</tr>
<tr>
<td><strong>Sensation</strong></td>
<td>Pressure</td>
<td>Unknown</td>
<td>Vibration</td>
<td>Flutter</td>
</tr>
<tr>
<td><strong>Temporal summation</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Spatial summation</strong></td>
<td>No</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Initially, a discussion of cutaneous receptor classes will be addressed based on the four main classes (SAI, SAII, RAI, RAII) which were initially identified in the glabrous skin of the human hand. Although different naming conventions have been used in the literature, the majority of work exploring the functional role of cutaneous receptors has been done using this classification system. It should be acknowledged that differences in receptor type, distribution, and density occurs between skin surfaces throughout the body. The results of these studies will be presented and followed by a discussion of the functional implications. The evidence from the literature indicates that each of the four receptor classes underlie distinctly different aspects of tactile perception (Johnson, Yoshioka, & Vega-Bermudez, 2000). While there is a large body of literature on the lower limbs, the majority of the discussion will revolve around cutaneous sensory information in the upper limbs.
**Merkel Discs (SAI)**

Merkel discs are concave, flattened, disc-like formation of cells within the stratum granulosum of the epidermis. They are classified as slowly adapting type 1 (SAI) units which have small receptive fields ranging from 2-10 mm² (Johansson & Vallbo, 1983). Merkel disks are primarily responsible for form and roughness perception and densely innervates the skin at the fingertip with about 100 receptors per cm² (Johnson, Yoshioka, & Vega-Bermudez, 2000). Merkel discs emerge from the subdermal plexus and loses its myelin sheath at the dermal-epidermal junction, branching many times to each Merkel disc over an area of about 5mm² (Vega-Bermudez & Johnson, 1999). This leads to several points of maximal sensitivity within the field which correspond to individual branches of the afferent axon (Phillips & Johnson, 1981).

SAI units produce very little discharge at rest but have a maintained discharge to constant pressure (Connor et al., 1990). They respond only to localized vertical pressure on the surface of the ‘touch dome’ and do not respond to lateral stretch of the skin. Merkel discs are sensitive to mechanical stimuli (especially at the edges of objects) which cause indentation of the skin. SAI impulse rates are ten times greater when an individual’s finger scans across a Braille dot compared to placing the finger on the dot without horizontal movement (Johnson & Lamb, 1981). Placing ones finger on the edge of a surface evokes SAI impulses twenty times greater than placing it on a smooth surface (Phillips & Johnson, 1981). When single afferent fibres innervating the human hand are activated, the sensation from the Merkel discs is local pressure or indentation (Johnson et al., 2000).

**Ruffini endings (SAII)**

The Ruffini endings are found within the dermal layer, and consist of nerve terminals from a single axon intimately associated with collagen fibrils which merge with dermal collagen. The whole structure is surrounded by a fluid-filled space which is enclosed by a thinly lamellated capsule (Rothwell, 1994). Ruffini endings are classified as slow adapting type 2 (SAII) units which respond to stimuli applied over an area of innervation which is approximately five times larger than SAI afferents (Johansson & Vallbo, 1980). The SAII mechanoreceptors are the only receptor to provide background discharge rates with approximately one-third of the fibres being active at rest (Vallbo, Hagbarth, Torebjork, & Wallin, 1979).
It appears there are two major roles for SAII receptors. The first is perception of the direction of object motion or force when it produces skin stretch (Olausson et al., 2000). These receptors are responsive to stretch of the skin over a wide area (up to 25 cm$^2$), and have a slowly adapting response to continuous stimulation (Johnson, 2001). However, within this field there is only a single point of maximal sensitivity, suggesting a single terminal end organ. Stretch of the skin along the long axis of the structure stimulates a discharge while stretch at right angles produces inhibition. This provides the receptors with directional sensitivity, which may also contribute to proprioception via their response to skin stretch (Edin, 1992).

The second role is the perception of hand shape and finger position through the pattern of skin stretch produced by each hand and finger conformation. Previous work has shown that stretching the skin to activate SAII receptors produces the illusion of finger flexion (Collins & Prochazka, 1996; Edin & Johansson, 1995). The SAII afferents appear shielded from the confounding effects of the indentation produced by an object, leaving it free to signal the object’s direction of motion and hand conformation. This is mainly due to its deep location and lack of sensitivity to indentation (Johnson, 2001).

Meissner corpuscles (RAI)

Meissner corpuscles are classified as rapidly adapting type 1 (RAI) units which have small receptive fields between 3-5 mm in diameter with relative uniformity and therefore resolve spatial detail poorly. In general, the RA system has greater sensitivity but poorer spatial resolution and limited dynamic range. Meissner corpuscles are ovoid and are found with their long axis perpendicular to the surface of the skin within a dermal papillum (Rothwell, 1994). The number of corpuscles in the finger pad is estimated to be 150/cm$^2$ (Johnson et al., 2000). There are several points of maximal sensitivity within the field, suggesting that the axon terminates with a number of end organs spread within a small area of skin. Anywhere from two to six separate axons innervate each Meissner corpuscle and form a complex network within the structure. The receptive field of a single axon is small, and the discharge to maintained pressure adapts extremely rapidly lasting only a few seconds (Johnson, 2001).

One of the main functional roles of these receptors appears to be the detection of the slip of an object which requires reflexive changes in grip force. RAI units are four times more sensitive to skin motion than SAI afferents (Johnson et al., 2000). RAI units fire impulses in
response to rapidly changing or moving stimuli and can follow sinusoidal displacements up to about 100 Hz. RAI receptors appear to be responsible for detecting slip between the skin and an object held in the hand (Srinivasan et al., 1990). Only RAI afferents respond consistently and with sufficiently short latency to account for reflexive changes that accompany sudden changes in load force (Macefield, Häger-Ross, & Johansson, 1996).

Pacinian Corpuscles

Pacinian corpuscles are classified as rapidly adapting type 2 (RAII) units which respond to stimuli applied over a much wider area, which in some cases can be almost as large as the whole palm. Pacinian corpuscles are found within the subdermal fasciae and are the largest receptors in the skin, and may be 1-4 mm in size. RAII afferents terminate in single corpuscles that are distributed throughout the palm and fingers (Johnson, 2001). The bare nerve terminal is sensitive to the mechanical deformation which it receives through the ‘onion skin’ capsule (Johnson et al., 2000). The layered lamella of the PC corpuscle function as a selective cascade high-pass filter. This filters any slow frequency components of the signal, leaving the Pacinian corpuscle sensitive only to very rapidly changing stimuli (Loewenstein & Skalak, 1966).

Rapidly changing pressure stimuli travel in a wave of vibration through the tissues of the skin and the bones, and are thus picked up by the Pacinian corpuscle from over a wide area (Brisben et al., 1999). Within this field there is only a single point of maximal sensitivity, suggesting a single terminal end organ. The Pacinian corpuscle is exquisitely sensitive to rapidly changing stimuli having a threshold of skin indentation of approximately 10 µm (Brisben et al., 1999). A given unit may be driven to respond by a single tap with a pencil applied anywhere on the skin of the hand and fingers. When single afferent fibres innervating the human hand are discharged the sensation from the Pacinian corpuscles is diffuse vibration. Interestingly, when incorporating a tool into our body schema, the events are perceived at the working surface of the tool as though our fingers were present. The PC afferents are responsible for the perceptual capacity to perceive events at a distant surface such as incorporating a tool. (Johnson, 2001)

1.6.2 Distribution differences of receptor density

The spatial resolution of touch and pressure information varies throughout the body, based on the number of dorsal roots innervating mechanoreceptors in that area. Areas of high
spatial resolution include the fingertip, palmer surfaces of the hand, foot sole, and lips. Pioneering work estimated the densities of each type of cutaneous receptor in the glabrous skin of the hand via microneurography (Johansson & Vallbo, 1979). As demonstrated in table 1.2, there is a concentration of type I units in the fingertip which is reduced in the finger and further reduced in the palm of the hand. The type II units appeared to be more evenly distributed throughout the entire glabrous skin area.

**Table 1.2 Summary of receptor density in the glabrous skin of the human hand**
(Johansson & Vallbo, 1979)

<table>
<thead>
<tr>
<th>Location</th>
<th>SAI (Merkel disk)</th>
<th>SAII (Ruffini ending)</th>
<th>RAI (Meissner corpuscle)</th>
<th>RAII (Pacinian corpuscle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingertip</td>
<td>70/cm(^2)</td>
<td>9/cm(^2)</td>
<td>141/cm(^2)</td>
<td>21/cm(^2)</td>
</tr>
<tr>
<td>Palm</td>
<td>8/cm(^2)</td>
<td>16/cm(^2)</td>
<td>25/cm(^2)</td>
<td>9/cm(^2)</td>
</tr>
</tbody>
</table>

There are approximately 300 mechanoreceptor nerve fibers per square cm in the finger tips whereas half that many were found in the proximal phalanges and palm (Johansson & Vallbo, 1979). Variations in receptor density explain differences in two-point thresholds which measure the minimum distance at which two stimuli are resolved as distinct. Two-point thresholds vary greatly between body regions. There is approximately a 2 mm two-point threshold on the fingertip but this increases to 10 mm on the palmer surface and increases to 40 mm on the arm (Blumenfeld, 2002).

### 1.6.3 Distribution differences between skin surfaces
In mammals, two distinct skin surfaces provide functionally distinct information to the nervous system due to anatomical and physiological differences in receptors beneath the skin. Glabrous skin is characterized by a regular array of ridges formed by folds of the epidermis and contains a dense matrix of mechanoreceptors. It has tight connections to subcutaneous tissues that are absent in the hairy skin. Hairy skin is characterized by a greater degree of stretch in response to joint movement. Hairy skin may be more suited to convey information about joint orientation, while afferents in the glabrous skin of the hand or foot may be more important for signalling contact with an object or the ground. The majority of knowledge on the distribution of mechanoreceptors in human is due to the application of single-fiber preparations and microelectrode recording (Hensel & Boman, 1960; Vallbo & Hagbarth, 1968).
Table 1.3. Summary table on the distribution of cutaneous mechanoreceptors in humans

<table>
<thead>
<tr>
<th>Authors</th>
<th>Nerve</th>
<th>Site</th>
<th>SAI (%)</th>
<th>SAII (%)</th>
<th>SAIII (%)</th>
<th>RAI (%)</th>
<th>RAII (%)</th>
<th>Hair (%)</th>
<th>Field (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson, 1976</td>
<td>Median</td>
<td>Glabrous Hand</td>
<td>29</td>
<td>29</td>
<td>-</td>
<td>29</td>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Westling, 1986</td>
<td>Median</td>
<td>Glabrous Hand</td>
<td>25</td>
<td>19</td>
<td>-</td>
<td>43</td>
<td>13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Johansson et al., 1980</td>
<td>Median</td>
<td>Glabrous Hand</td>
<td>26</td>
<td>15</td>
<td>-</td>
<td>46</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Edin and Abbs, 1991</td>
<td>Superficial Radial</td>
<td>Hairy Hand</td>
<td>32</td>
<td>32</td>
<td>-</td>
<td>28</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vallbo et al., 1995</td>
<td>Lateral Antebrachial Cutaneous</td>
<td>Forearm</td>
<td>38</td>
<td>27</td>
<td>-</td>
<td>4</td>
<td>22</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Kennedy and Inglis, 2002</td>
<td>Tibial</td>
<td>Foot Sole</td>
<td>14</td>
<td>15</td>
<td>-</td>
<td>57</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trulsson, 2001</td>
<td>Sural</td>
<td>Lateral Foot Dorsum (Glabrous)</td>
<td>26</td>
<td>14</td>
<td>-</td>
<td>50</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trulsson, 2001</td>
<td>Sural</td>
<td>Lateral Foot Dorsum (Hairy)</td>
<td>35</td>
<td>9</td>
<td>-</td>
<td>48</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Edin, 2001</td>
<td>Lateral Cutaneous Femoral</td>
<td>Thigh</td>
<td>9</td>
<td>4</td>
<td>30</td>
<td>11</td>
<td>44</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Values are displayed as a percentage of total number of mechanoreceptors identified.

The literature indicates functional differences in the coding of tactile information between the glabrous and hairy skin surfaces of the hand. Initial investigations identified both SA and RA types of receptors and provided an approximate estimate of the sensitivity of mechanoreceptors to vibratory stimuli in human glabrous skin (Knibestöl & Vallbo, 1970). Similar studies exploring the distribution of mechanoreceptors in the hairy skin of the human hand found the same types of SA and RA fibres as in the human glabrous skin (Jarvilehto et al., 1976). However, these initial studies were unable to provide detailed analysis of the subtypes of receptors in order to address questions of distribution. The first investigation to directly assess differences between skin surfaces provided single mechanical pulses to the hairy or glabrous skin of the hand by means of a fixed electrometrical vibrator (Hämäläinen & Järvelähti, 1981). It was determined that sensation (touch) thresholds were significantly higher on the hairy skin compared to the glabrous skin.

This finding was followed by a second paper published in the same journal issue which provided a detailed exploration of human mechanoreceptors in the hairy skin via microelectrode measurements from the superficial branch of the radial nerve (Jarvilehto et al., 1981). It was determined that the relative number of SA units was larger (especially that of SAII units) in the hairy skin than in the glabrous skin. In the glabrous skin the relative number of RA units is more
than 50% of the total number of units (Johansson & Vallbo, 1979) whereas in the hairy skin it is approximately 34%. The smaller proportion of RA units is similar to what has been found via microdissection by Hensel and Boman (1960). It also appears that RA1 (Meissner’s Corpuscles) receptors are infrequent in the hairy skin of the human hand (Jarvilehto et al., 1981). This is similar to the hairy skin of the cat and rabbit which do not exhibit any RA1 afferents (Brown & Iggo, 1967; Brown et al., 1999; Burgess, Petit, & Warren, 1968). This work has since been confirmed with the majority of the hairy skin mechanoreceptive units being SA (Edin & Abbs, 1991).

There may be differences between dorsum of the hand and other hairy skin surfaces in regards to hair density. This was explored by Vallbo, Olausson, Wessberg, and Kakuda (1995) via microneurographic recordings from the lateral antebrachial cutaneous nerve which innervates the forearm. As presented in table 1.3, the hairy skin of the human forearm contains five different types of mechanoreceptors including SAI (Merkel discs), SAII (Ruffini endings), as well as three types of fast adapting units (hair, field, Pacinian corpuscles). These are the same five types of receptors which have been previously identified in other mammals (Iggo, 1974). Interestingly, in both human and animal studies no RAI units were present. The two main rapidly adapting units of the forearm (field and hair units), have a significantly larger receptive field than RAI units of the glabrous skin (Johansson & Vallbo, 1980). However, the receptive field size for the SAI fields was very similar between the forearm and glabrous skin on the hand (Johansson & Vallbo, 1979). Distribution differences between hand and forearm skin surfaces may play an important functional role in the characteristics and intensity of any cutaneous input being used in a rehabilitative setting.

For a given skin surface the thresholds, densities, and distributions of mechanoreceptors in the skin are different throughout the body and appear to be related to the functional implications of a particular skin surface. Information from cutaneous mechanoreceptors is not only important for determining the size, shape, and texture of objects but also provides accurate perceptual information about joint position and movement. Furthering our understanding of these functional networks may allow future researchers to alter motor output during movement to enhance performance in an athletic or rehabilitation setting.
1.7 Using reflexes to probe for spinally mediated excitability changes

When exploring motor output in humans, it is typically the ‘final common pathway’ of neural processing which is measured via integration at the level of the spinal motoneuron (Sherrington, 1906). No matter what level of the nervous system is being explored, the impact on motor output is assessed when activation produces changes in motoneuronal excitability and muscle activation patterns (Pierrot-Desilligny & Burke, 2005). In order to assess spinally mediated changes in excitability with either resistance training or a compression garment, changes in muscle activation must be reliably assessed and quantified via valid and reproducible methods. Within the following sections, both cutaneous and Hoffmann reflexes will be used to evoke specific afferent pathways to probe how sensory feedback is being integrated at multiple levels of the nervous system (Zehr & Stein, 1999; Zehr, 2002, 2006). In humans, studying responses to stimulation allows observations to be made during voluntary movement in order to evaluate how it modulates ongoing motor function (Hagbarth, 1960).

Reflexes are generally evoked by activating peripheral receptors or the afferents which innervate them by either electrical or mechanical perturbation. In humans, sampling motoneurons directly is extremely difficult which means assessing changes in motoneuron excitability from electrical stimulation must be indirectly interpreted by recording on the descending limb of the reflex arc from a muscle of interest (Brooke et al., 1997). The use of these methods will provide the foundation in order to assess if spinally mediated adaptations are contributing to excitability changes due to resistance training or ‘enhanced’ cutaneous input.

1.7.1 Evoking and measuring cutaneous reflexes

Once cutaneous mechanoreceptors are activated, sensory information diverges through an unknown number of polysynaptic connections which include both inhibitory and excitatory interneurons. This volley of sensory information is then integrated at multiple levels of the nervous system which modulates ongoing muscle activity at multiple latencies to produce functionally relevant movement modifications (Zehr & Stein, 1999; Zehr, 2006). Electrical stimulation of cutaneous nerves is the most common experimental approach to artificially mimic mechanical activation of cutaneous receptors and evoke activity in the cutaneous reflex pathway. In general, electrodes are affixed to the skin surface and deliver electrical pulses in order to activate proximal receptive fields (Jenner & Stephens, 1982; Yang & Stein, 1990; Duysens et al., 1992; Brooke et al., 1997). Previous literature indicates responses to natural stimulation closely
mirror those observed following electrical stimulation of the same nerves (Forssberg, 1979; Buford & Smith, 1993; Sinkjaer et al., 1994; Van Wezel et al., 1997; McCrea et al., 1998). Therefore, reflex pathways of cutaneous receptors can be studied with electrical stimulation used as a limited proxy to natural cutaneous activation.

For electrical cutaneous nerve stimulation, electrodes are placed over a nerve comprised of mostly cutaneous afferents fiber types (type III, IV sensory fibers). Generally, these nerves are located at their most superficial location before mixing cutaneous afferents with other muscle afferent nerve fibers. Stimulation parameters are specifically chosen to activate afferents from cutaneous receptors which evoke sensations of buzzing, fluttering, or tickling in the innervated area of interest. While a single stimuli does produce a measurable cutaneous response in afferent pathways, it has little measurable effect on motor output which leads to trains of stimuli generally being used (Jenner & Stephens, 1982).

1.7.2 Recruitment of cutaneous mechanoreceptors

Altering the intensity of stimulation recruits different afferent nerve fiber classes (Gasser, 1941). At the lowest stimulation intensities myelinated Group I muscle afferent axons are initially activated. These large diameter axons have the lowest impedance and are therefore recruited at a lower stimulation intensity. Myelinated Group II than Group III cutaneous afferents from tactile receptors in the skin become activated as stimulation intensity increases (Duysens, 1977; Duysens et al., 1998). At the highest levels of stimulation intensities, Group IV unmyelinated fibers are recruited, which are associated with a painful and nociceptive sensation. For studies of cutaneous reflexes, intensities of electrical stimulation are set to activate large myelinated fibers with conduction velocities in the Aβ range (35-70m/sec) (Winkelmann, 1988). In mixed nerves, the intensity of electrical stimulation most commonly used to evaluate cutaneous reflexes will likely recruit both motor and other sensory axons in the nerve bundle including Group Ia and Ib fibers.

As with other neurophysiological techniques, stimulation intensity needs to be referenced in order to make appropriate comparisons between participants or time points. A particular challenge in this regard when evoking cutaneous reflexes is that many cutaneous nerves don’t have motor innervation to be used to normalize. In this case there are two main ways that the relative stimulation intensity remains constant. The first is a multiple of perceptual threshold,
defined as the intensity that elicits a minimal but perceptible tactile sensation (Brooke et al., 1997). It is most commonly used when electrical stimulation is applied to a skin surface where mechanoreceptors are being directly activated instead of a nerve. When stimulating a nerve trunk the technique which is most commonly used is a multiple of the radiating threshold, determined as the minimum intensity that evokes a clear radiating sensation in the entire perceptive field (Delwaide et al., 1981; Duysens et al., 1990; De Serres et al., 1995; Brooke et al., 1997). Generally, 2 or 3 times radiating threshold, is low enough to producing a buzzing or fluttering sensation in the innervation area indicative of cutaneous mechanoreceptor activation which producing measurable changes in motor output (Zehr & Stein, 1999; Zehr, 2006).

Powerful responses can be obtained from stimulating cutaneous nerves that innervate the palmer and dorsal surfaces of the hands, making these locations among the most widely studied. These nerves are not only easily accessed but provide unique functional information on the role of specific cutaneous surfaces during movement. In the hand, the superficial radial nerve (SR) is often studied along with the cutaneous innervations of the median nerve. The median nerve can be accessed with electrodes placed on the ventral surface of the forearm proximal to the radial head, while the SR nerve can be accessed on the dorsal surface of the forearm just proximal to the radial head and crease of wrist joint (Zehr & Chua, 2000; Zehr & Duysens, 2004).

1.7.3 Measuring cutaneous responses via surface electromyography

Given the difficulty in measuring directly from spinal motoneurons in humans, responses to cutaneous stimulation are most commonly recorded on the descending limb of the reflex arc (Brooke et al., 1997). The net effect of cutaneous input on motoneuron excitability is inferred from surface EMG recorded in the muscle of interest. Modulation of ongoing activity can be seen by averaging data that are time-locked to the known stimulus. To obtain a pure reflex response, the averaged data after a provided input is subtracted from data when no input was present leaving mainly reflex activity to be assessed (Brooke et al., 1997; Zehr & Stein, 1999). This technique allows for measurement of both facilitatory and inhibitory responses (Baken et al., 2005). Due to the variability and complex patterns from stimulation of cutaneous nerves, many individual sweeps of data are averaged and extensive smoothing of the signal are required (Brooke et al., 1997). Monitoring the effect cutaneous stimulation has on muscle activity
provides reasonable temporal resolution to accurately document the amplitude and latency of the responses (Brooke et al., 1997).

Most commonly, some amount of activity in a muscle is required for cutaneous stimulation to modulate motoneuron excitability (Duysens, 1977; Abraham & Loeb, 1985; Zehr et al., 2007a). Due to the divergence of cutaneous input at multiple levels of the nervous system, a baseline level of muscle activity is required in order to assess a cutaneous reflex. This is done in order to identify not only excitatory inputs, which might bring a motoneuron closer to threshold, but also identify inhibitory influences which may reduce spinal excitability leading to a reduction in ongoing motor output (Mazzocchio et al., 1994; Zehr, 2006). The level of background activity significantly modulates cutaneous responses such that as activity increases, the reflex response also increases in a fairly linear fashion (Yang & Stein, 1990; Burke et al., 1991; Aniss et al., 1992; Van Wezel et al., 1997; Komiyama et al., 2000).

1.7.4 Quantification of cutaneous reflexes

The presence of more than one reflex response is a distinguishing characteristic of cutaneous reflexes measured in ongoing EMG. This can be seen as periods of excitation and inhibition in the rectified EMG response. (Hagbarth, 1960; Dimitrijevic & Nathan, 1969; Jenner & Stephens, 1982; Duysens et al., 1996; Zehr & Stein, 1999). Although multiple methods for evaluation exist, one common convention is to assess cutaneous reflexes as triphasic responses at varying delay latencies which can be excitatory or inhibitory depending on the nerve being stimulated, muscle being measured, and the context of the experiment (Jenner & Stephens, 1982; Yang & Stein, 1990; Duysens et al., 1992; Gibbs et al., 1995; De Serres et al., 1995; Van Wezel et al., 1997). The early latency component can be recorded before 75 ms, the middle component between 70-120 ms and the late component measured after 120 ms (Duysens et al., 1992; Brooke et al., 1997).

A time window can be used around a peak response and data within the window are quantified the same way regardless if the response is categorized as early or middle latency (Yang & Stein, 1990; Duysens et al., 1992; De Serres et al., 1995; Van Wezel et al., 1997). The chosen time windows can either be established visually or set using the responses in which the maximum EMG exceeds one or two standard deviations of the corresponding background activity (Zehr & Chua, 2000). Within a given time window, all the data are averaged together,
and the maximum value, or a band (10-20ms) around the maximum response is used, to obtain a single value. These data can be left raw, normalized with respect to the maximum background activity of each muscle, or normalized by some other means. Time windows should be the same for each muscle nerve combination within a subject.

A second method which is most commonly used in terms of functional quantification of cutaneous reflexes is to evaluate the average cumulative reflex over the entire response time. Usually the response is integrated over 100 or 150ms post stimulation (Komiyama et al., 2000). This value is obtained by subtracting pre-stimulus EMG from the EMG modulation curve to obtain the pure reflex response. These data are then cumulatively summed from 0 to 150ms and divided by the duration of integration. A positive value indicates overall facilitation while a negative value indicates overall inhibition (Komiyama et al., 2000). This method provides an overall view of the net reflex and simplifies interpretation by averaging all activity. The major limitation with this method is the inability to observe latency specific changes in excitation, which means losing some of the temporal and spatial characteristics of the response (Brooke et al., 1997; Komiyama et al., 2000).

The multi-component EMG response to cutaneous nerve stimulation is thought to arise due to differences in the number of interneurons in a particular pathway within the spinal cord (Zehr & Stein, 1999; Zehr, 2006). Based on the latency of the earliest responses it is assumed that the earliest components of cutaneous reflexes can be mediated by pathways in the spinal cord (Dimitrijevic & Nathan, 1969; Zehr & Stein, 1999; Baken et al., 2005). Responses at longer latencies are likely the result of transmission through longer pathways which may contain multiple interneurons at multiple levels of the nervous system (Eccles & Lundberg, 1959; Jenner & Stephens, 1982). Generally, it is accepted that responses occurring prior to 70 ms after stimulation are likely modulated mainly by spinal centres (Deuschl & Lücking, 1990; Nielsen et al., 1997). Therefore, middle and long latency cutaneous reflex components may be influenced by supraspinal pathways including the cortex (Nielsen et al., 1997).

1.7.5 Influence of cutaneous mechanoreceptive feedback on movement

The integration of cutaneous afferent information into the nervous system not only produces the sensation of touch but plays a vital role in both proprioception, and movement related control of force. Electromyographic (EMG) responses in the muscles represent the net
neural result of stimulation (Zehr & Stein, 1999). Stimulation of cutaneous fields in the skin produces a complex but highly organized response. The functional nature of cutaneous reflexes is dictated by the anatomical innervation of the stimulated site. Evidence from single tactile afferents recorded from the median nerve indicates that 33% of the afferents show a short-latency response in ongoing EMG activity (McNulty et al., 1999). This supports the notion that input from a single cutaneous afferent in the glabrous skin of the hand is strong enough to drive, via interneurons, motoneurons supplying muscles acting on the digits. This work was expanded to address the specific receptor types which were able to modulate ongoing EMG activity. Microelectrodes inserted into the median and ulnar nerves found 52% SAI, 37% RAI, and 20% RAI evoked a reflex response in muscles of the human hand (McNulty & Macefield, 2001). Interestingly, muscle spindles, joint afferents, and SAI units were unable to modify ongoing voluntary EMG.

Initial work indicated stretch of the skin plays a role in the conscious perception of joint position (Edin & Johansson, 1995; Edin, 2004; Hulliger, Nordh, Thelin, & Vallbo, 1979). In the glabrous skin of the human hand 66% of SAI, 94% of SAI, 57% of RAI, and 100% of RAI afferents were active during hand movements (Hulliger et al., 1979). Similar work in the hairy skin of the hand indicated 92% of the afferents in the radial nerve responded to hand or finger movements (Edin & Abbs, 1991). Skin stretch applied to the back of the hand which was meant to mimic the stretch during finger joints indicated SAI and SAI afferents showed dynamic and static sensitivity to skin stretch which could influence proprioception (Edin, 1992). Induced skin strain near an anesthetized joint also produces perceived joint movement. However, when the skin strain is eliminated, movement in the anesthetized joint is not perceived indicating its possible importance to joint position (Edin & Johansson, 1995).

In order to more specifically address this issue, a line of research explored whether ensemble activity in human cutaneous sensory afferents evoked by the stretching of the skin over and around the finger joints contributed to the conscious perception of movement. Cutaneous afferents were activated by mechanical stretching of the skin over and around the finger joints. Perceived movements were then mimicked by voluntary movements of the fingers of the contralateral hand. They found a mismatch between actual joint position and perceived joint position which indicated input from the skin stretched during finger movement contributes to the conscious perception of movement (Collins & Prochazka, 1996). A follow up study aimed to
explore if cutaneous feedback is providing specific kinaesthetic information as to which joint is moving (Collins et al., 2000). Movement illusions were again measured by matching the perceived finger joint position with the contralateral finger. Combining skin stretch and mechanical vibration produced larger movement illusions than either condition alone. Interestingly, when the appropriate regions of skin were stimulated, movement illusions were focused to the joint under the stimulated skin.

In order to expand the applicability of these previous findings illusory movements were evoked in the index finger, elbow, and knee via cutaneous and muscle spindle receptors separately and together. Results showed that at all three joints combined feedback from cutaneous and muscle spindle receptors resulted in greater movement illusions than vibration alone. Together, these studies illustrate that cutaneous feedback provides accurate perceptual information about joint position and movement and this is integrated with feedback from muscle spindles to provide judgements of position and movement for joints throughout the body.

1.7.6 Evoking and measuring the Hoffmann reflex

The Hoffmann reflex is probably the most widely studied spinal reflex pathway due to its known primarily monosynaptic connection. When properly controlled, the Hoffmann reflex provides a measure of spinal interneuronal excitability and has the ability to detect measurable differences in both pre and post synaptic effects. Detailed reviews of the Hoffmann reflex methodology have been published previously (Zehr, 2002; Aagaard et al., 2002; Misiaszek, 2003; Knikou, 2008).

The Hoffmann reflex is elicited by providing electrical stimulation to a mixed peripheral nerve containing both sensory (Ia afferent) and motor (alpha-motoneuron) axons which innervate a muscle of interest (Zehr, 2002). The neural circuitry is characterized by a predominantly monosynaptic projection of group Ia afferents, which innervate muscle spindles, onto homonymous alpha-motoneurons within the spinal cord (See Figure 1.2)(Misiaszek, 2003). The efferent axons then activate the muscle across the neuromuscular junction which is recorded by bipolar surface EMG electrodes. The reflex bypasses the muscle spindle and is thus characterized as the electrical analogue to the stretch reflex. The major experimental advantage of the H-reflex compared to the stretch reflex is the ability to precisely control stimulus intensity between conditions and not account for changes in the muscle spindle (gamma-motoneuron excitability).
Figure 1.2 Simplified schematic diagram illustrating the Group Ia neural pathway between a target muscle and the spinal cord.

When electrical stimulation depolarizes the Ia afferents an H-reflex is then generated (Knikou, 2008). The resulting action potentials travel along the afferent axon from the points of stimulation to a monosynaptic connection with alpha-motoneurons. If a motoneuron receives adequate neurotransmitter release to reach firing threshold from this and other inputs, an action potential will be generated to depolarize the innervated muscle fibres. This generates a compound motor unit action potential, which appears in an unrectified EMG trace as a short-latency triphasic waveform (Tucker et al., 2005). At low stimulation intensities the Ia afferents are depolarized prior to motor axons due to their larger diameter which means only an H-reflex will appear in the surface EMG initially (Zehr, 2002).

As stimulation intensity is increased, the smaller diameter motor axons will begin to be recruited, and will appear as a similar triphasic waveform in the EMG trace at an earlier latency to the H-reflex due to the short distance from the site of motor stimulation to the recording site. The Ia afferents will continue to be recruited as stimulation intensity is increased until the maximum number have been recruited. The largest amplitude H-reflex that is able to be generated is known as H-max. Theoretically, after H-max is reached it should plateau in a similar fashion to the maximally evoked motor response (M-max). Confounding this issue is that electrical stimulation of a nerve produces activation in both an ortho and anti-dromic direction. This means when the motor axon is activated, action potentials also travel from the site of stimulation back to the soma of the alpha-motoneuron. These antidromic signals collide with
orthodromic Ia afferent activation of the alpha-motoneuron. Therefore, as stimulation intensity increases and more motor axons are activated, the antidromic signal will gradually allow less and less afferent activation to reach the muscle and therefore H-reflex amplitude appears to be reduced (Zehr, 2002). This creates an H-reflex recruitment curve that has an ascending and descending limb while the M-wave recruitment curve has only an ascending limb and then reaches plateau (Misiaszek, 2003; Tucker et al., 2005).

1.7.7 Methods of assessing the H-reflex

There are two main methods for assessing H-reflexes during studies or motor control. The first involves recording H-reflexes while maintaining a stable size of M-wave response. This method ensures the same relative input is being provided to the nervous system to be compared between conditions (Zehr, 2002). Any differences in H-reflex amplitude can then be deduced to be due to changes in pre-synaptic inhibition of the Ia afferent or post-synaptic alterations in motoneuron excitability. An important consideration for this method is to use a relatively small m-wave amplitude to match between conditions in order to keep the antidromic activity influencing H-reflex amplitude to a minimum (Misiaszek, 2003). Using a small m-wave to match conditions also ensures the ability for both inhibition and facilitation of the H-reflex between experimental conditions (Klimstra & Zehr, 2008). The main advantage to using this method is being able to directly compare amplitude and waveforms between conditions. The major limitation to this technique is only a given population of Ia afferents are being recruited. The low or high threshold afferents will not be recruited which means potential differences in recruitment thresholds, slope, or maximal response will be overlooked. When a more detailed full spectrum of Ia recruitment may be advantageous, a second method is employed.

A more detailed method to study the H-reflex occurs when it is evoked at multiple stimulus intensities throughout a trial ranging from sub-threshold intensities to supra-maximal intensities. H- and M-wave peak-to-peak amplitudes are measured offline and plotted against the amount of known current need in order to produce that size response (Zehr et al., 2007a; Klimstra & Zehr, 2008; Mezzarane et al., 2011). Plotting these data points will produce a quantified recruitment curve which has been shown to be reliable at the foot and plateau of the ascending limb of the curve (Klimstra & Zehr, 2008). As previously described, experimental protocols may differentially affect excitability of distinct populations of motor units; thus it is
pertinent to acquire multiple measures that reflect H-reflex waves from various sized afferents (Klimstra & Zehr, 2008). Many H-reflex measures can be extrapolated from the ascending limb of a recruitment curve, including threshold of the response, H-reflex maximum and slope (Zehr, 2002). Further, the corresponding stimulation current for these measures can be used to compare to the same measure in a test condition. For example, the current at Hmax from a control condition is applied to the recruitment curve generated during a compression apparel condition, and corresponding H-reflex amplitude size at the current is documented. This allows for assessment of change in H-reflex excitability at similar stimulus levels across conditions, with such comparisons referred to as ‘fitted curve’ variables (Zehr et al., 2007a; Klimstra & Zehr, 2008; Dragert & Zehr, 2011; Mezzarane et al., 2011).

When used as a neural probe, modulation of H-reflex amplitude can assess effects of conditioning volleys in peripheral afferents or descending tracts on interneuronal excitability. Indeed, H-reflex amplitudes are a complex mix of alpha-motoneuron excitability, as well as presynaptic inhibition (PSI) of Ia afferent to alpha-motoneuronal synapses, i.e. inhibition of neurotransmitter release presynaptic to the motoneuron (Zehr, 2002; Rudomin, 2009). Neural signaling that elicits PSI may reduce the H-reflex amplitudes recorded from that muscle, but EMG level will remain constant. Thus, PSI alters afferent transmissions without affecting the postsynaptic membrane potential (Capaday & Stein, 1987; Zehr, 2002). This is especially of interest when investigating modulatory effects of muscle activation, as communication occurs via these and similar spinal pathways during both local and remote activation conditions. For example, resistance training has been found to alter alpha-motoneuron pool excitability as well as Ia PSI from descending projections, leading to modulated H-reflex amplitude in the trained muscle (Aagaard et al., 2002; Lagerquist et al., 2006a; Dragert & Zehr, 2011). In assessing resistance training-induced plasticity, the Hoffmann reflex has been used as a neural probe (Aagaard et al., 2002; Lagerquist et al., 2006b; Fimland et al., 2009).
1.7.8 Conditioning of H-reflexes with cutaneous inputs

While the Hoffmann reflex is able to provide information on excitability changes in the spinal cord in humans, the technique is limited in its ability to detect whether effects are due to alterations in pre-synaptic input onto Ia afferent transmission or whether it is a post-synaptic effect influencing motoneuron excitability. However, it is possible to explore presynaptic inhibition of Ia afferent transmission to alpha motoneurons in the pathway for the H-reflex arc by using a conditioning input (Berardelli et al., 1987; Nakashima et al., 1990; Nakajima et al., 2013). For example, by providing a known input to a cutaneous nerve at the wrist, a sensory volley is initiated, which through a series of interneurons, has a strong input on the Ia inhibitory interneuron of the forearm flexors (See Figure 1.3). This activation of the Ia inhibitory interneuron will alter transmission of sensory information along the Ia afferents, ultimately being measured as H-reflex amplitude. It is well established that providing cutaneous nerve (superficial radial nerve, SR) stimulation facilitates FCR H-reflex amplitude by reducing Ia PSI within the human forearm (Nakashima et al., 1990; Nakajima et al., 2013). While it is less clear the effects that conditioning with the mixed distal median nerve will have, these conditioning paradigms...
may provide an indication as to particular pathway involvement in altered sensory feedback transmission within the upper limb.

1.8 Thesis objectives

Only recently has implementing unilateral training or ‘cross-education’ received noteworthy consideration as a possible rehabilitation strategy during recovery from unilateral injuries (Hendy et al., 2012; Farthing & Zehr, 2014; Barss et al., 2016). In order for unilateral resistance training to be properly integrated a number of fundamental issues must be addressed within the scientific literature. One such issue is knowledge on the minimum time course for emergence of the crossed effects. Currently, little is known about the time-course of strength increase in each limb during resistance training. Therefore, the primary purpose of Chapter 2 was to characterize the time-course of strength changes in both the trained and untrained limbs during unilateral handgrip training. The time-course was assessed during both a ‘traditional’ training protocol (3x/week for 6 weeks: 18 total sessions) and a ‘compressed’ protocol in which the number of sessions and contractions were matched but participants trained for eighteen consecutive days. An anticipated outcome was the determination of a minimum number of sessions required to induce cross-education in the upper limb. It was hypothesized that training 18 consecutive days would show a similar time-course of cross-education in the untrained limb and thus be an improved method for rapid improvement after unilateral injury. A secondary purpose of this study was to examine whether spinally-mediated adaptations in muscle afferent reflex pathways occur after unilateral handgrip training. Establishing the time-course in which these adaptations occur will allow future researchers and clinicians to effectively prescribe a ‘dose’ of resistance training.

It also remains necessary to determine if there are specific strategies which can be incorporated to optimize resistance training interventions by enhancing strength increases. To date, no study has directly assessed the relative contribution of afferent pathways to cross-education. Cutaneous feedback from the skin provides perceptual information about joint position and movement. Unilateral training involves forceful contractions that activate cutaneous receptors in the skin, producing widespread and powerful effects between limbs. Providing “enhanced” cutaneous stimulation during unilateral contractions may alter excitability of interlimb reflex pathways, modifying the contralateral increase in strength. Therefore, the purpose of Chapter 3 was to determine the relative contribution of cutaneous afferent pathways as a mechanism of cross-
education by directly assessing if unilateral cutaneous stimulation alters ipsilateral and contralateral strength gains. It was hypothesized that providing ‘enhanced’ sensory feedback via electrical stimulation during resistance training would improve strength gains compared to training alone. If providing unilateral cutaneous stimulation alters the strength gains in either the trained or untrained limb it will provide the first evidence of a cutaneous afferent contribution to the cross-education effect. This study will help refine a unifying model of unilateral strength training to include contributions from central motor output as well as afferent feedback.

It may also be possible to enhance effects of training by altering excitability via wearable apparel such as a compression garment. Currently, it is unknown whether constant tactile input to the skin via compression apparel may alter transmission of muscle afferent feedback within a limb. Thus, the purpose of Chapter 4 was to examine if sustained input to the skin (compression garment) modulates sensory feedback transmission in the upper limb. Using the Hoffmann (H-) reflex as a probe, the purpose of these experiments was to: 1) explore the effects of compression gear on sensory feedback transmission in the upper limb during a static task, and 2) if the task (locomotor vs. reaching) or phase of a movement differentially modulated this transmission of sensory information. Furthermore, differences in performance of the discrete reaching task were assessed to provide preliminary data on whether a compression garment can alter motor task performance.
1.9 References


Sherrington CS (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping


2. Time course “dose” of inter-limb strength transfer after handgrip training

2.1 Abstract

‘Cross-education’ is the increase in strength or functional performance of an untrained contralateral limb after unilateral training. Recently, its rehabilitation application during recovery from unilateral injury has been highlighted. However, a major limitation for clinical translation includes knowledge on the minimum time requirement for the emergence of crossed effects. Therefore, the primary purpose was to characterize the time-course of bilateral strength changes during both ‘traditional’ and ‘compressed’ unilateral handgrip training. A secondary purpose examined whether unilateral handgrip training produced bilateral spinal-mediated adaptations in muscle afferent reflex pathways. ‘Traditional’ training consisted of 11 participants who completed 6 weeks of unilateral handgrip training 3 times/week whereas ‘Compressed’ training consisted of 8 participants who completed the same total number of sessions but over 18 consecutive days. Each session consisted of 5 sets of 5 maximal voluntary handgrip contractions using the dominant right hand. Three baseline and one post-test measure evaluated strength, muscle activation, and reflex excitability in both trained and untrained limbs. The time-course of strength changes in the trained limb was assessed by recording handgrip force from all training contractions while, for the untrained limb, handgrip force was measured once a week from a single contraction. After 6 weeks of ‘traditional’ training, handgrip force increased 14.6% and 12.5% in the trained and untrained limbs, respectively. This was accompanied by changes in peak muscle activation in the trained limb only. Time-course data indicated the trained limb was significantly stronger than baseline after the 3rd week of training (session 9) while the untrained limb was stronger after 5 weeks (15 sessions). Interestingly, the rate at which strength increased in the untrained limb was similar to the trained side. These strength increases were also accompanied by significant changes in the stimulation current needed to produce 50% $H_{\text{max}}$ in the trained and $H_{\text{max}}$ in both the trained and untrained limb, indicating alterations in spinal cord excitability. ‘Compressed’ training revealed a similar number of sessions were required to induce significant strength gains in the untrained limb. Therefore, training without rest days may be the most efficient protocol when the trained limb is not the focus of recovery. These results emphasize the importance of establishing a “dose” for the time-course of functional and neurological adaptations in strength training for effective translation to rehabilitative interventions.
2.2 Introduction

‘Cross-education’, ‘inter-limb strength transfer’, or the ‘cross-transfer’ effect, as it has more recently been described, is a neural adaptation defined as the increase in strength or functional performance of the untrained contralateral limb after unilateral training. (Scripture et al., 1894; Farthing & Chilibeck, 2003; Lee & Carroll, 2007). Only recently has implementing unilateral training or ‘cross-education’ received noteworthy consideration as a possible rehabilitation strategy during recovery from unilateral injuries (Hendy et al., 2012; Farthing & Zehr, 2014; Barss et al., 2016). In order for unilateral resistance training to be properly integrated within a clinical setting, a number of fundamental issues must be addressed within the scientific literature.

In a clinical setting, time truly is of the essence. As such, an issue impeding translation is the minimum time required for emergence of crossed effects to unilateral training. Currently, little is known about the time-course of strength increase during the initial period of resistance training (4-6 weeks) which has generally been attributed to adaptations in the nervous system (Gabriel et al., 2006; Folland & Williams, 2007). Although, protein synthesis rates are elevated after just a single bout of resistance exercise (Gibala et al., 1995; Macdougall et al., 1995), increases in MVC in the first 2-3 weeks of training are not associated with an increase in either muscle cross sectional area (CSA) (Akima et al., 1999) or myofibrillar density (Claassen et al., 1989). Unfortunately, there is a limited consensus on the time-course of strength gain in the trained limb. Furthermore, little empirical evidence is available on the time-course of adaptation in the untrained contralateral limb, which limits the ability for researchers and clinicians to make appropriate and efficient recommendations for training. The ability to develop a prescribed temporal “dose” of resistance training in the trained and untrained limb is a fundamental issue that requires clarification.

A limited body of evidence has tracked strength increase over time with different training durations, intensities, tasks, and measurement frequencies. Historically, Gustav Fechner (1801-1887) established himself as a pioneer of resistance training when he meticulously documented lifting 2 dumbbells (~9 lbs in each hand) over his head as many times as he could, every day, for 60 consecutive days (Fechner, 1857). Fechner performed 104 and 692 repetitions on days 1 and 55, respectively, while reporting the values for every training session throughout his study.
Despite more than 150 years of ongoing research in strength adaptations, this type of detailed time-course has rarely been replicated in the literature.

Bi-weekly measurements of strength have been assessed for the squat, leg press, and leg extension exercises (Staron et al., 1994). Participants completed 3 sets of 6-12 repetitions, 2 days per week, for 8 weeks. Significant increases in strength were seen for all three strength exercises after the 4th week of training. Similarly, biweekly measures of chest press and knee extension exercises were assessed during a training program consisting of 1 or 3 sets of 8-12 repetitions, 3 days per week, for 12 weeks (Abe et al., 2000). Strength was significantly increased after the 4th week of training for the females, while the males increased knee extension and chest press strength at weeks 2 and 6, respectively. Overall, the mean increase in knee extension and chest press 1 RM were 19% and 19% for men and 19% and 27%, respectively. Weekly measurements of leg extension strength were assessed during a training protocol consisting of 3 sets of 8-12 repetitions, 3 days per week, for 12 weeks (DeFreitas et al., 2011). The researchers found a significant 14.6% increase in MVC strength after the 4th week of training. One of the only studies to assess strength during each training session consisted of 6 sets of 10 plantar flexor contractions, 3 days per week, for 4 weeks (Del Balso & Cafarelli, 2007). They found MVC torque increased 20% over the duration of the study and was significantly different than baseline after the third training day and persisted for the remainder of the 4 week study. Results indicate the time-course and proportions of the increase in strength are similar for both men and women (Staron et al., 1994; Abe et al., 2000).

A training program similar to Fechner’s original work included maximal isometric contractions of wrist flexion (10 s/bout) 3 times a day, every day (except Sunday) for 100 days (Ikai & Fukunaga, 1970). Time-course in the trained limb was assessed on the 20th, 40th, and 100th day with significant increases in strength from baseline of 18.4, 47.5, and 91.7 %, respectively. Interestingly, this study also assessed the untrained contralateral limb over the same measurement days and found increases in strength of 7.1, 12.5, and 32.1 % respectively, although strength was not significantly increased until the 40th session. To our knowledge, this is the only time-course data on the untrained contralateral limb in the literature. Improving the resolution of time course data in the untrained limb during the early phase of resistance training (4-6 weeks), when neural contributions have the largest magnitude of effect, would improve implementation of unilateral training during neuro-rehabilitation.
A related issue in clinical translation of unilateral resistance training to a rehabilitation setting is improving understanding of the sites of adaptation and neural mechanisms responsible for the effect. When prescribing exercise programs within clinical populations a targeted strategy is required which focuses on overcoming the specific deficits that are presented with each unique condition. A number of excellent reviews have been published on some possible mechanisms of cross-education (Zhou, 2000; Hortobágyi, 2006; Lee & Carroll, 2007; Farthing, 2009; Ruddy & Carson, 2013). A clear outcome of this synthesis is that, as with many adaptations in the nervous system, ‘cross-education’ arises from a truly multi-level and multi-factorial set of adaptations. However, the understanding of alterations in sensory feedback transmission and spinal cord excitability with resistance training remains limited.

Studying the modulation of reflexes can be used to probe inter-limb neural activity (Burke et al., 1991; Zehr et al., 2004). On the trained side, previous studies have shown increased H-reflex amplitude (Lagerquist et al., 2006b), increased H@thresh (Dragert & Zehr, 2011), and increased reciprocal inhibition (Geertsen et al., 2008). Studies which have observed the effects of unilateral training on H-reflex amplitudes in neurologically intact participants have found no change in the agonist muscle in the untrained contralateral side despite an increase in strength (Lagerquist et al., 2006b; Del Balso & Cafarelli, 2007; Fimland et al., 2009). However, Dragert et al. (2011) found $H_{\text{max}}$ amplitude was reduced in the antagonist muscle in the untrained limb. This is the first study to show a change in crossed spinal reflex pathways that may contribute to the cross-education effect. Unilateral strength training in chronic stroke was recently shown to produce changes in maximal dorsiflexion, altered spinal reflex excitability and reciprocal inhibition within the untrained more affected tibialis anterior muscle (Dragert & Zehr, 2013). It was postulated that resistance training could lead to increased contralateral sensitivity of the Ia inhibitory interneurons and larger suppression of alpha-motoneuron excitability. However, little to no information exists on alterations in spinal reflex excitability to resistance training in the upper limb.

Typically, when an individual performs resistance training, the focus is on improving strength and function within the particular muscle group that is trained. In this case a number of excellent evidence based resources on resistance training prescription and progressions can be found (Peterson, 2005; Ratamess et al., 2009; Fisher et al., 2011). However, when a significant impairment is present unilaterally, the primary goal of physical rehabilitation is to improve the more affected side as this will most drastically improve quality of life. Therefore, when applying
unilateral resistance training in a translational context, the goal should be to increase strength in the more affected and untrained limb to the greatest extent in the shortest possible timeframe.

With this in mind, fundamental ideas such as rest days to allow recovery of the trained limb may no longer be as important since the adaptation in the untrained contralateral limb is strictly neural. The optimal training program may not be based on the number of training sessions but rather on the number of total inputs (i.e. repetitions) used to “train” the nervous system. It is important to determine whether the time over which the training occurs is the most important factor, or if there may be a threshold number of inputs that are needed to produce long-term excitability changes at multiple levels of the nervous system.

Therefore, the primary purpose of this study was to characterize the time-course of strength changes in both the trained and untrained limbs during unilateral handgrip training. Experiment 1 assessed the time-course with a ‘traditional’ training protocol (3x/week for 6 weeks: 18 total sessions) while Experiment 2 assessed a ‘compressed’ protocol in which the number of sessions and contractions were matched but participants trained for eighteen consecutive days. An anticipated outcome was the determination of a minimum number of sessions required to induce contralateral strength gains in the upper limb. It was hypothesized that training for 18 consecutive days would show a similar time-course of cross-education in the untrained limb and thus be an improved method for rapid improvement after unilateral injury. A secondary purpose of this study was to examine whether spinal-mediated adaptations in muscle afferent reflex pathways occur after unilateral handgrip training. Establishing the time-course in which these adaptations occur will allow future researchers and clinicians to effectively delineate the temporal ‘dose’ of unilateral resistance training.

2.3 Methods

2.3.1 Participants

Eleven (6 female; 5 male, 24.0 ± 3.0 years, 169.5 ± 10.5 cm, 70.6 ± 14.5 kg) neurologically intact right-handed participants completed Experiment 1 of this study while eight (2 female; 6 male, 22.5 ± 3.5 years, 175.6 ± 9.4 cm, 76.8 ± 14.3 kg) right-handed participants completed Experiment 2. Participants provided informed written consent to a protocol approved by the University of Victoria Human Research Ethics Committee and performed according to the Declarations of Helsinki.
2.3.2 Experimental Procedures

Experiment 1 – Assessing bilateral effects of ‘traditional’ unilateral handgrip training

The study used a within subjects repeated-measures design, with all participants completing 3 baseline measures, and 1 post-test measure. Multiple baseline sessions were used to allow for participants to serve as their own controls. Participants completed 6 weeks of unilateral handgrip training 3 times/week. Most participants completed training on Monday, Wednesday and Friday with each session including 5 sets of 5 maximal voluntary isometric contractions (MVCs) using a handgrip dynamometer in their dominant right hand. Dependant variables included bilateral measures of strength, muscle activation, and reflex excitability which were measured at all three pre-test time points as well as the post-test. MVCs assessed strength during handgrip, wrist extension, and wrist flexion. Muscle activation was concurrently measured via electromyography (EMG) in the flexor carpi radialis (FCR) and extensor carpi radialis longus (ECR). Reflex excitability was assessed via Hoffmann reflex (H-reflex) recruitment curves during two distinct tasks: 10% CONT (10% contraction of the flexor carpi radialis), 10% + SR (Contraction + superficial radial nerve conditioning).

2.3.3 Multiple Baseline and Post-test Measures

A multiple baseline within-subject control design was used for this study (Bütefisch et al., 1995; Klarner et al., 2014). This design allowed for the creation of a reliable and consistent pre-test measure and provided baseline data against which changes could be evaluated. Multiple baseline measurements were obtained from participants in three baseline experiments, with at least three days between sessions. During these sessions, the same measures were assessed in the same order and environmental conditions (i.e. temperature, noise, lighting, participant position) and session time of day was kept as consistent as possible (Zehr, 2002; Lagerquist et al., 2006a; Dragert & Zehr, 2013). Similar measures have been previously shown to have high reliability across multiple baseline points (Klarner et al., 2014).
2.3.4 Strength - Maximal Voluntary Contractions

The primary outcome measure was maximal voluntary force during handgrip. Isometric handgrip was chosen due to its convenience of measurement in both a laboratory and at-home setting, as well as its clinical relevance as a predictor of old-age disability (Rantanen et al., 1999). Maximal wrist extension and flexion torque were also collected bilaterally. Participants completed 3 MVCs, which were each held for 3 seconds and separated by a minute of rest. The experimenter provided verbal encouragement in a similar fashion for all measures and time-points. For each task, the contraction with the highest peak force was used for comparison at each pre- or post-test time point. Participants were familiarized with the isometric strength tasks prior to MVCs and completed a standardized warm-up prior to each session. All MVCs were recorded in a seated position with the non-tested arm placed in the participant’s lap. Wrist extension and flexion were assessed in a custom-built forearm support attached to a Gamma Sensor force transducer (ATI Industrial Automation, Model FT06598, Apex, USA). The forearm was secured and all joint angles were maintained across testing time-points. Handgrip MVC was recorded via dynamometer.
in a seated position that was the same for both testing and training with all settings maintained through the data collection process.

2.3.5 Activation - Electromyography

Electromyographic (EMG) data from the FCR and ECR were collected bilaterally over the mid-muscle bellies of interest. Once the skin was cleaned with alcohol wipes, surface electrodes were placed in a bipolar configuration on the skin, oriented longitudinally along the fibre direction, in accordance with SENIAM procedures (Freriks & Hermens 2000). A reference electrode was placed on the medial epicondyle to serve as a common ground for the EMG signal. Electrodes were placed in the same position at each testing session. Land marking measurements were taken at the initial pre-test to ensure correct placement at each subsequent time point. During MVCs a 0.5 second window of time around peak muscle activity was used to calculate the peak mean absolute value (MAV). The peak MAV associated with the corresponding peak MVC from each baseline and post-test measure was used for assessment. Since peak handgrip force depends on balance between flexor and extensor activity, a co-contraction ratio was assessed to see whether the balance of activation was altered with training. The co-contraction ratio was calculated by dividing the peak FCR muscle activity by the peak ECR muscle activity.

During MVCs, EMG was pre-amplified 5000x (GRASS P511, AstroMed) and band pass filtered 100-300 Hz. The output was sent to the A/D interface (National Instruments Corp. TX, USA) where it was converted to a digital signal and sampled at 1000 Hz using custom built continuous acquisition software (LabVIEW, National Instruments, TX, USA). During H-reflex recruitment curves, EMG was pre-amplified 1000x (GRASS P511, AstroMed) and band pass filtered 30-1000 Hz. The output was sent to the A/D interface (National Instruments Corp. TX, USA) where it was converted to a digital signal and sampled at 2000 Hz using custom built acquisition software (LabVIEW, National Instruments, TX, USA).
Figure 2.2 Schematic diagram outlining possible neural pathways for integration of inputs on Ia afferents arising from somatosensory conditioning stimulation to the superficial radial (SR) nerve.

2.3.6 Reflex Excitability - Hoffmann Reflex (H-reflex)

To establish whether training produced measurable changes in sensory feedback transmission, reflex measures were assessed in a static position. The right forearm, wrist, and hand were fixed in a customized brace in order to restrict movement and maintain joint angles throughout the experiment (Figure 2.2). Participants were asked to maintain a consistent low-level contraction [~10% of maximal voluntary contraction (MVC)] of their right flexor carpi radialis (FCR) using visual feedback of the rectified and filtered EMG signal, which was displayed in real time on a computer screen. H-reflexes were elicited and recorded following procedures previously described (Zehr, 2002; Loadman & Zehr, 2007; Dragert & Zehr, 2011; Nakajima et al., 2013). M-H recruitment curves were collected by applying 40 stimuli over a range of intensities delivered pseudo-randomly with an inter-stimulus interval of 2–4 seconds. Stimulation was delivered during two separate conditions (10% CONT, 10% + SR). Stimulation current was concurrently measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL). Peak-to-peak amplitudes of M- and H-waves were calculated offline from the single unrectified sweeps of EMG with custom-written software (Matlab, Nantick, MA).
Curve fit analysis assessed differences in thresholds or amplitudes when different pools of afferents are activated at different stimulation intensities. For these comparisons, the 40 data points from each of the pre-tests were merged into a single averaged 120 data point PRE recruitment curve in order to be compared to POST. The ascending limb of each recruitment curve was fit using a general least squares model of a custom three-parameter sigmoid function, as described elsewhere (Zehr et al., 2007b; Klimstra & Zehr, 2008). Briefly, the current intensities that coincide with the H-reflex variables taken from the average PRE recruitment curves were then used as inputs to the equations describing the post-intervention recruitment curves. This procedure allows for the comparison of reflex amplitudes at the same relative current intensities between PRE and POST conditions. Average H$_{\text{max}}$ and M$_{\text{max}}$ were calculated from the three largest H-reflexes and M-waves, respectively for each of the pre-tests as well as the post-test. Reflexes for each subject were normalized to maximally evoked motor responses (M$_{\text{max}}$) to allow for comparisons across multiple time points.

### 2.3.7 Somatosensory conditioning of Ia afferent transmission

The integration of cutaneous sensory information on Ia afferent transmission was evaluated through a conditioning paradigm used previously (Nakajima et al., 2013). Electrical stimulation was provided to the SR nerve at the wrist 37 ms prior to proximal median nerve stimulation during a 10% FCR contraction (Figure 2.2). A train of five 1ms pulses @ 300 Hz was delivered at 2 times the radiating threshold (RT). Perceptual and radiating thresholds were determined as the point at which nerve stimulation produces a perceivable stimulation and the point at which a stimulation produced radiating paresthesia in the cutaneous receptive field of that nerve, respectively. Non-noxious intensities were found for each participant and stimulation intensities were set to 2 x RT for the SR nerve.

*Experiment 1 – Time course of ‘traditional’ unilateral handgrip training*

In order to track the time course of force changes in the trained limb, handgrip MVC force was recorded for every contraction throughout the training program which consisted of 5 sets of 5 maximal handgrip contractions performed 3 times/week for 6 weeks (18 sessions total). The training program was completed using a handgrip dynamometer in the same fashion as MVC measurements. For the untrained limb, handgrip force was measured once a week during a single
contraction. While performing a single contraction in the untrained limb could itself be considered training, it was viewed as the minimum interference to get a window into the time course of adaptation in the untrained limb.

Experiment 2 – Time course of ‘compressed’ unilateral handgrip training

In order to assess if strength gains in the untrained contralateral limb are related to the total time of the training regime or may be related to the number of inputs to the nervous system, and ‘compressed’ training program was assessed. Participants completed 5 sets of 5 maximal handgrip contractions every day for 18 consecutive days. The only dependant measure was handgrip MVC force, which was assessed during every contraction of the trained right limb throughout the intervention. In the untrained left limb, handgrip MVC force was assessed during a single contraction every three sessions of training in order to match intensity, volume, and number of inputs between training interventions.

Control Experiment 1 – Muscle activity of untrained limb during training

In order to address a common concern associated with the cross-education phenomenon, a sub-sample of four participants had their average muscle activity recorded during a single training session to determine the level of muscle activity in the untrained forearm during training. When noticeable muscle activity was present, a window of MAV across the contraction was chosen based on visual inspection. When little or no muscle activity was present the average window was chosen based on the known time of each contraction in the trained limb. A percentage of peak muscle activity was then calculated from each individual’s baseline maximal muscle activation on the untrained side.

Control Experiment 2 – Effect of a single contraction over 6 weeks

Since an integral part of this study is the time course component in the untrained limb it was necessary to test this limb at a regular interval throughout the training protocol. It was determined that a single contraction each week would be the least invasive way to track peak strength of the untrained limb over time. Even within this minimal approach it may be possible that a single maximal contraction one time a week would provide enough stimulus to increase strength over a six-week period. Therefore, a second control experiment was completed in order
to ensure our once a week test was not providing a significant training stimulus. Therefore, a sub-sample of 6 participants completed a single maximal handgrip contraction in their non-dominant left hand 1 time per week for 6 weeks. This was the same minimal intervention used to assess strength in the untrained contralateral limb during both training protocols.

2.3.8 Statistics

Experiment 1 – Assessing bilateral effects of ‘traditional’ unilateral handgrip training

Initially, in order to assess if the intervention produced significant changes in the measured variables a pre/post comparison was performed. Using commercially available software (SPSS 20.0, Chicago, IL), the three baseline measures were compared using a 1 x 3 (Pre-1, Pre2, Pre3) repeated-measures ANOVA to examine differences across the three pre-test sessions. If no differences were found, data were pooled to create an average pre-test (PRE\text{Avg}) value, which was then compared to post-test (POST) values with a one-way ANOVA. For reflex measures, a 2 (Time; PRE\text{Avg}, POST) x 2 (CONDITION; unconditioned, conditioned) ANOVA was used in order to determine if the conditioning paradigm differentially altered Ia afferent excitability. Assumptions for ANOVA and paired-samples t-tests were evaluated for parametric tests for a within-subject design. In the presence of significant sphericity violations, Greenhouse-Geisser adjustments were made to adjust degrees of freedom accordingly.

In order to provide an idea of the effectiveness of the training protocol on each dependant measure, a separate analysis was conducted within individual participants utilizing their own variability established during the 3 baseline measures. For each participant, a 95% confidence interval was established based on their individual baseline assessments. If an individual’s post-test value fell outside of this established 95% confidence interval, their individual post-test value was considered significant. This analysis was only performed for measures in which a significant group result was present. Data is displayed as the number of participants out of 11 whose values were significantly outside of the established 95% confidence interval.

Time course of ‘traditional’ and ‘compressed’ unilateral handgrip training

In order to comprehensively determine the time point at which strength was significantly different from the established baseline in both the trained and untrained hands, two separate analyses were performed. For peak strength in the trained limb a total of 20 data points were
included in each analysis (Average pre, 18 training sessions, post-test). For peak strength in the untrained limb a total of 8 data points (Average pre, 6 assessments, post-test) were included in each analysis. The first analysis was performed on the averaged group data for both handgrip strength and muscle activation. Initially a repeated measures ANOVA determined overall differences. If the ANOVA was significant, LSD pairwise comparisons for each data point against baseline were performed in order to determine at which point the group data was significantly different than baseline. The time point of statistical significance was set at $p \leq 0.05$.

A second analysis was utilized to provide an idea of individual time-course, utilizing each participant’s own variability of the 3 baseline measures. Based on each participant’s multiple baseline assessments, a 95% confidence interval was established. When an individuals’ training values fell and remained outside of the 95% confidence interval, this session number was used as the point at which they were significantly stronger. The session number at which each individual participant was significantly stronger was then averaged across the group. This averaged value could then be used and compared with the value determine in ANOVA and pairwise comparisons.

Control Experiment 2 – Effect of a single contraction over 6 weeks

A repeated measures ANOVA comparing a within subjects factor of time (6 weeks) was used with LSD pairwise comparisons used to determine where significant differences occurred.

2.4 Results
Experiment 1 – Assessing bilateral effects of ‘traditional’ unilateral handgrip training
2.4.1 Strength – Maximal Voluntary Contractions

**Figure 2.3.** Effects of 6 weeks (18 sessions) of unilateral handgrip training on peak forearm strength in both the trained (Right) and untrained (left) limb. A) Group average of peak handgrip force. B) Group average of peak wrist extension torque. C) Group average of peak wrist flexion torque. * Indicates a significant increase in strength after 6 weeks of unilateral handgrip training. Values are mean ± SE ($p < 0.05$).

Results indicate 6 weeks of handgrip training increases strength of multiple tasks. One-way ANOVA indicates handgrip strength POST was significantly higher than PREavg in both the trained (41.5±13.7 kg vs. 37.6±12.8 kg; $F(1,10)=13.438$, $p=0.004$; 10 out of 11) and untrained (38.9±14.0 kg vs. 34.8±12.6 kg; $F(1,10)=18.074$, $p=0.002$; 10 out of 11) limb (Figure 2.3). Wrist extension torque POST was significantly higher than PREavg in both the trained (98.6±36.5 Nm vs. 83.0±30.5 Nm; $F(1,10)=10.378$, $p=0.009$; 10 out of 11) and untrained (98.5±34.1 Nm vs. 77.2±33.8 Nm; $F(1,10)=51.735$, $p<0.000$; 11 out of 11) limb. Wrist flexion torque POST was significantly higher than PREavg in both the trained (112.8±47.8 Nm vs. 96.1±42.9 Nm; $F(1,$
10)=20.763, \( p = 0.001 \); 10 out of 11) and untrained \( (110.6\pm43.9 \text{ Nm vs. } 95.1\pm44.0 \text{ Nm}; F(1,10)=12.558, \ p = 0.005; 11 \text{ out of } 11) \) limb.

**Table 2.1.** Baseline assessment of strength for handgrip, wrist extension, and wrist flexion

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pre 1</th>
<th>Pre 2</th>
<th>Pre 3</th>
<th>ANOVA</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trained Grip Strength (kg)</td>
<td>37.7 ± 13.6</td>
<td>37.1 ± 12.2</td>
<td>37.8 ± 12.9</td>
<td>( F_{(2, 20)}=0.337, p=0.718 )</td>
<td>NS.</td>
</tr>
<tr>
<td>Untrained Grip Strength (kg)</td>
<td>34.6 ± 12.6</td>
<td>34.9 ± 12.9</td>
<td>34.6 ± 12.7</td>
<td>( F_{(2, 20)}=0.047, p=0.954 )</td>
<td>NS.</td>
</tr>
<tr>
<td>Trained Wrist Extension (Nm)</td>
<td>72.4 ± 26.6*</td>
<td>86.2 ± 36.3</td>
<td>90.4 ± 32.8</td>
<td>( F_{(2, 20)}=6.367, p=0.007 )</td>
<td>*</td>
</tr>
<tr>
<td>Untrained Wrist Extension (Nm)</td>
<td>76.6 ± 33.9</td>
<td>75.9 ± 35.3</td>
<td>79.2 ± 33.6</td>
<td>( F_{(2, 20)}=0.665, p=0.525 )</td>
<td>NS.</td>
</tr>
<tr>
<td>Trained Wrist Flexion (Nm)</td>
<td>91.0 ± 41.8</td>
<td>98.5 ± 44.0</td>
<td>98.5 ± 44.3</td>
<td>( F_{(2, 20)}=3.200, p=0.062 )</td>
<td>NS.</td>
</tr>
<tr>
<td>Untrained Wrist Flexion (Nm)</td>
<td>92.0 ± 43.1</td>
<td>97.8 ± 45.7</td>
<td>95.5 ± 44.6</td>
<td>( F_{(2, 20)}=1.565, p=0.234 )</td>
<td>NS.</td>
</tr>
</tbody>
</table>

Values are displayed mean ± standard deviation.

* Indicates significantly lower peak strength than Pre 2 or Pre 3.

Repeated measures ANOVA indicated that for all strength tasks except trained wrist extension, there were no significant differences between baseline measures \( (p > 0.05) \). Trained wrist extension pairwise comparisons indicate that pre-test 1 was significantly lower than both pre-test 2 \( (72.4 \pm 26.6 \text{ Nm vs. } 86.2 \pm 36.3 \text{ Nm}; p=0.032) \) and pre-test 3 \( (72.4 \pm 26.6 \text{ Nm vs. } 90.4 \pm 32.8 \text{ Nm}; p=0.020) \). However, there was no difference between pre-test 2 and 3 \( (86.2 \pm 36.3 \text{ Nm vs. } 90.4 \pm 32.8 \text{ Nm}; p=0.217) \) indicating there may have been more of a learning effect of the wrist extension task compared to the others. However, since pre-test 2 and 3 were not different any learning effects would be accounted for within these initial pre-test sessions.

**2.4.2 Muscle Activation – Electromyography**

After 6 weeks of handgrip training, peak muscle activation during handgrip MVC in the trained right limb was significantly higher at POST compared to \( \text{PRE}_{\text{avg}} \) in the FCR \( (4.1\pm2.4 \text{ vs. } 2.8\pm1.6; F(1,10)=9.620, p = 0.011; 8 \text{ out of } 11)(\text{Figure 2.4}). There was also a significant increase in the co-contraction ratio at POST compared to \( \text{PRE}_{\text{avg}} \) \( (0.86\pm0.49 \text{ vs. } 0.67\pm0.29; F(1,10)=4.955, p = 0.05; 7 \text{ out of } 11) \). There were no differences between \( \text{PRE} \) and POST in peak muscle activation during handgrip in the ECR \( (p > 0.05) \).
Figure 2.4. Effects of 6 weeks (18 sessions) of unilateral handgrip training on peak muscle activation during handgrip maximal voluntary contraction. A) Group average of peak muscle activation in the flexor carpi radialis (FCR) during maximal handgrip. Values are displayed as peak activation normalized to maximally evoked motor responses ($M_{\text{max}}$). B) Group average of peak muscle activation in the extensor carpi radialis (ECR) during maximal handgrip. Values are displayed in raw units. C) Group average of the co-contraction ratio comparing the balance of activation between FCR and ECR during maximal handgrip. * Indicates a significant increase in peak muscle activation after 6 weeks of unilateral handgrip training. Values are mean ± SE (p < 0.05).
### Table 2.2 Baseline assessment of peak muscle activation in the FCR and ECR

<table>
<thead>
<tr>
<th>Measure</th>
<th>Muscle</th>
<th>Pre 1</th>
<th>Pre 2</th>
<th>Pre 3</th>
<th>ANOVA</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trained Grip Strength</strong></td>
<td>FCR</td>
<td>3.4 ± 2.5</td>
<td>2.1 ± 0.9</td>
<td>2.8 ± 1.9</td>
<td>$F_{(1.2, 12)}=3.552, p=0.079$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>85.1±31.3</td>
<td>101.3±37.5</td>
<td>96.6±30.1</td>
<td>$F_{(1.1, 11.2)}=2.087, p=0.150$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Co-contraction ratio</strong></td>
<td>FCR</td>
<td>0.75 ± 0.36</td>
<td>0.58 ± 0.25</td>
<td>0.67 ± 0.5</td>
<td>$F_{(2, 20)}=2.081, p=0.151$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>85.1±31.3</td>
<td>101.3±37.5</td>
<td>96.6±30.1</td>
<td>$F_{(2, 20)}=2.081, p=0.151$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Untrained Grip Strength</strong></td>
<td>FCR</td>
<td>0.69 ± 0.32</td>
<td>0.59 ± 0.33</td>
<td>0.65 ± 0.27</td>
<td>$F_{(2, 20)}=0.595, p=0.561$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>102.4±65.5</td>
<td>95.2±44.6</td>
<td>85.4±44.5</td>
<td>$F_{(2, 20)}=0.840, p=0.446$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Co-contraction ratio</strong></td>
<td>FCR</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>0.8 ± 0.6</td>
<td>$F_{(2, 20)}=2.490, p=0.108$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>103.8±37.9</td>
<td>103.9±42.0</td>
<td>112.3±43.9</td>
<td>$F_{(2, 20)}=0.427, p=0.659$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Untrained Wrist Extension</strong></td>
<td>FCR</td>
<td>0.7 ± 0.4</td>
<td>0.7 ± 0.6</td>
<td>0.6 ± 0.3</td>
<td>$F_{(2, 20)}=0.165, p=0.849$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>101.9±37.9</td>
<td>81.0±44.2*</td>
<td>112.3±43.9</td>
<td>$F_{(2, 20)}=5.194, p=0.015$</td>
<td>*</td>
</tr>
<tr>
<td><strong>Trained Wrist Flexion</strong></td>
<td>FCR</td>
<td>7.2 ± 3.5</td>
<td>7.4 ± 5.8</td>
<td>7.1 ± 3.0</td>
<td>$F_{(1.2, 11.7)}=0.010, p=0.990$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>30.8±15.1</td>
<td>31.0±11.4</td>
<td>30.0±13.1</td>
<td>$F_{(2, 20)}=0.720, p=0.499$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Untrained Wrist Flexion</strong></td>
<td>FCR</td>
<td>6.4 ± 3.2</td>
<td>5.3 ± 1.7</td>
<td>6.6 ± 3.6</td>
<td>$F_{(2, 20)}=1.636, p=0.220$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>ECR</td>
<td>30.8±15.1</td>
<td>24.9±13.3*</td>
<td>38.3±21.7</td>
<td>$F_{(2, 20)}=3.767, p=0.041$</td>
<td>*</td>
</tr>
</tbody>
</table>

FCR values are peak MAV normalized to M-max (µV/µV*100). ECR values are peak MAV (µV).
Values are displayed mean ± standard deviation.
* Indicates significantly lower peak strength than Pre 1 and Pre3.

Repeated measures ANOVA indicated that for peak muscle activation across tasks there were no significant differences between baseline measures across muscle except for the ECR during both wrist extension and flexion in the untrained limb ($p > 0.05$). Untrained wrist extension and flexion peak muscle activity in the untrained limb indicated pre-test 2 was significantly lower than both pre-test 1 and pre-test 3.
2.4.3 Spinal Reflex Excitability – Hoffmann Reflex

Figure 2.5. Effects of conditioning paradigm. A) Individual subject traces which show the effect of conditioning on H-reflex amplitude while M-wave is maintained constant. B) Group average of maximally evoked M-wave ($M_{\text{max}}$) amplitude across arm and conditioning paradigm. C) Group average of maximally evoked H-reflex ($H_{\text{max}}$) amplitude pooled across time (Pre/Post). * Indicates a significant increase in $H_{\text{max}}$ amplitude when conditioning stimulation is applied. Values are mean ± SE ($p < 0.05$).

| Table 2.3. Baseline assessment of both unconditioned and conditioned M-Max and H-Max values |
|-----------------------------------------------|--------------|--------------|--------------|-----------------|--------------|
| Measure                              | Pre 1        | Pre 2        | Pre 3        | ANOVA          | Result        |
| Trained M-Max                        | 2.56 ± 1.33  | 2.55 ± 1.34  | 2.64 ± 1.52  | $F_{(2, 20)}=0.227$, $p=0.799$ | NS.          |
| Trained M-Max (Cond)                 | 2.67 ± 1.44  | 2.52 ± 1.30  | 2.70 ± 1.51  | $F_{(2, 20)}=0.936$, $p=0.409$ | NS.          |
| Untrained M-Max                      | 2.35 ± 1.45  | 2.55 ± 1.45  | 2.60 ± 1.43  | $F_{(2, 18)}=1.943$, $p=0.172$ | NS.          |
| Untrained M-Max (Cond)               | 2.38 ± 1.41  | 2.54 ± 1.42  | 2.62 ± 1.44  | $F_{(2, 18)}=1.714$, $p=0.208$ | NS.          |
| Trained H-Max                        | 53.6 ± 21.6  | 57.8 ± 30.3  | 54.0 ± 25.4  | $F_{(2, 20)}=0.410$, $p=0.669$ | NS.          |
| Trained H-Max (Cond)                 | 64.1 ± 23.6  | 64.2 ± 27.9  | 65.4 ± 25.6  | $F_{(2, 20)}=0.036$, $p=0.964$ | NS.          |
| Untrained H-Max                      | 56.5 ± 24.8  | 46.9 ± 18.4  | 51.4 ± 24.0  | $F_{(2, 18)}=1.866$, $p=0.180$ | NS.          |
| Untrained H-Max (Cond)               | 58.8 ± 22.9  | 54.1 ± 25.7  | 58.7 ± 22.3  | $F_{(2, 18)}=0.402$, $p=0.675$ | NS.          |

$M_{\text{max}}$ is displayed in mV. $H_{\text{max}}$ amplitude is normalized to $M_{\text{max}}$ (mV/mV*100). Values are displayed mean ± standard deviation.
Six weeks of handgrip training did not change $H_{\text{max}}$ or $M_{\text{max}}$ from PREavg to POST ($p>0.05$) (Figure 2.5). There was a main effect of CONDITION for $H_{\text{max}}$ indicating there was a significant increase in $H_{\text{max}}$ amplitude when the conditioning stimulus was provided in both the trained (56.6±6.4% vs. 65.9±6.5%; $p=0.002$) and untrained limb (53.1±7.2% vs. 59.4±6.8%; $p=0.024$). There were no differential effects between unconditioned and conditioned H-reflex parameters ($p>0.05$), therefore only main effects of TIME pooled across CONDITION will be discussed further. In the trained limb, there was a significant reduction in the current needed to produce an H-reflex at 50% of peak between PRE and POST (79.6±12.3mA vs. 71.1±12.6mA; $F_{(1,10)}=4.722$, $p=0.050$) (Figure 2.6). There was also a significant reduction in the current needed to produce $H_{\text{max}}$ between PRE and POST (104.6±22.1mA vs. 89.3±15.6mA; $F_{(1,10)}=4.989$, $p=0.050$). In the untrained limb there was a significant reduction in the current needed to produce $H_{\text{max}}$ between PRE and POST (105.6±16.7mA vs 89.6±23.5mA; $F_{(1,10)}=4.989$, $p=0.043$). There were no other differences in H-reflex recruitment parameters between PRE and POST in the trained or untrained limb after training ($p>0.05$). Repeated measures ANOVA indicated that there were no significant differences between baseline measures across tasks ($p>0.05$) for $M_{\text{max}}$ and $H_{\text{max}}$. 
Figure 2.6. Effects of 6 weeks of unilateral handgrip training on H-reflex excitability in the trained and untrained limb. A) Group average of $H_{\text{max}}$ normalized to $M_{\text{max}}$ across both conditioning paradigm and limb. B) Group average of the current needed in order to produce an H-reflex at 50% of $H_{\text{max}}$. C) Group average of the current needed to produce $H_{\text{max}}$. * Indicates a significant reduction in the current needed to produce the indicated H-reflex amplitude after 6 weeks of unilateral handgrip training. Values are mean ± SE (p < 0.05).

Time course of ‘traditional’ unilateral handgrip training

In the trained right limb a 1x20 ANOVA indicated a significant effect of TIME on peak handgrip strength throughout the training protocol ($F_{(19, 190)}=5.559$, $p<0.000$). Pairwise comparisons indicate that peak handgrip strength was first significantly different than PRE$_{\text{avg}}$ at session 9 (37.6±12.8kg vs. 39.4±12.8kg; $p=0.045$) and remained different beginning at session 13 (37.6±12.8kg vs. 40.6±13.0; $p=0.007$). Time course was also assessed within individual participants in order to determine the session at which they were significantly stronger than PRE$_{\text{avg}}$, based on establishing a 95% confidence interval around their three baseline sessions. The average
training session number in which participants were significantly stronger than baseline and remained stronger was 11.8±6.0 sessions (Figure 2.9).

**Figure 2.7.** Peak handgrip force for every contraction during both 6 weeks and 18 consecutive days of unilateral handgrip training. A) Group average of peak handgrip force during 6 weeks (18 training sessions) of handgrip strength training. B) Group average of peak handgrip force during 18 days consecutive of handgrip strength training. For each figure, peak handgrip force during each of the 25 maximal handgrip contractions performed during the initial training session is bolded with triangle markers and a dashed line. Peak handgrip force during each of the 25 maximal handgrip contractions performed during the final (18th) training session is bolded with square markers and a solid line. The other 16 training sessions are provided via grey lines. Values are displayed as the group mean.

In the untrained left limb a 1x8 ANOVA indicated a significant effect of TIME on peak handgrip strength over the training protocol ($F(7, 70)=7.352, p<0.000$). Pairwise comparisons indicate that peak handgrip strength was first significantly different, and continued to be different than PREavg after the 4th week of handgrip training (34.8±12.6kg vs. 36.9±13.9kg; $p=0.042$). Individual participant’s data indicates participants were significantly stronger than PREavg after 3.9±2.0 weeks of training (Figure 2.10).
Effects of ‘compressed’ unilateral handgrip training

Figure 2.8. Effects of 18 consecutive days of unilateral handgrip training on peak handgrip strength. Group average of peak handgrip force in both the trained (Right) and untrained (left) limb. Indicates a significant increase in strength after 18 consecutive days of unilateral handgrip training. Values are mean ± SE (p < 0.05).

Table 2.4. Baseline assessment of handgrip strength in the trained and untrained limb

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pre 1</th>
<th>Pre 2</th>
<th>Pre 3</th>
<th>ANOVA</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trained Grip Strength</td>
<td>48.4 ± 13.8</td>
<td>47.5 ± 13.6</td>
<td>48.3 ± 14.5</td>
<td>$F_{(2, 14)}=1.468, p=0.264$</td>
<td>NS.</td>
</tr>
<tr>
<td>Untrained Grip Strength</td>
<td>45.9 ± 12.9</td>
<td>45.4 ± 12.3</td>
<td>45.4 ± 12.3</td>
<td>$F_{(2, 14)}=0.210, p=0.813$</td>
<td>NS.</td>
</tr>
</tbody>
</table>

Values are displayed mean ± standard deviation.

Performing handgrip training for eighteen consecutive days increases peak force output bilaterally. One-way ANOVA indicates handgrip strength POST (52.8±15.7kg) was significantly higher than PRE_avg (48.0±13.9kg) in the trained right limb ($F_{(1, 7)}=9.286, p=0.019$; 6 out of 8)(Figure 2.7). One-way ANOVA also indicates handgrip strength POST (49.3±14.0 kg) was significantly higher than PRE_avg (45.6±12.4) in the untrained left limb ($F_{(1, 7)}=9.140, p=0.019$; 7 out of 8).
Figure 2.9. Time course of peak handgrip strength in the trained right limb. A) Group average of peak handgrip force at each session of handgrip training over 6 weeks. B) Group average of peak handgrip force at each day of handgrip training for 18 consecutive days. C) Group average of the percentage change from PRE for both 6 weeks (White) and 18 days (Black) of training. * Indicates a training session is significantly stronger than PRE according to pairwise comparisons. The arrow indicates the group average of the training session when individual participants peak handgrip force was maintained outside of their established 95% confidence interval calculated from their 3 baseline sessions. Values are displayed as the group mean.

In the trained right limb a 1x20 ANOVA indicated a significant effect of TIME on peak handgrip strength over the training protocol ($F_{(19, 133)}=5.559$, $p=0.001$). Pairwise comparisons indicate that peak handgrip strength was only significantly different than PRE$_{avg}$ at the POST measure (48.0±13.9kg vs. 52.8±12.8kg; $p=0.019$). Interestingly, peak handgrip strength was also significantly higher at POST compared to training session 18 (49.6±14.8kg vs. 52.8±15.7kg; $p=0.001$). The average training session number in which participants were significantly stronger than baseline and remained stronger was 14.6±5.6 sessions (Figure 2.9).
In the untrained left limb a 1x8 ANOVA indicated a significant effect of TIME on peak handgrip strength over the training protocol \( (F(7, 49)=3.044, p=0.010) \). Pairwise comparisons indicate that peak handgrip strength was first significantly different, and continued to be different than \( \text{PRE}_{\text{avg}} \) after the 15\textsuperscript{th} day of handgrip training (45.6±12.4kg vs. 47.5±13.6kg; \( p=0.050 \)). Individual participant’s data indicates they were significantly stronger than \( \text{PRE}_{\text{avg}} \) after 4.0±2.4 weeks of training. Percentage change of peak force was calculated for both the ‘traditional’ and ‘compressed’ handgrip training time points. Results of the 2 (Group) x 7 (Time) ANOVA indicated
no interaction or condition main effects occurred (p>0.05). To assess if there was a significant difference in the % strength increase in one type of training a 1-way ANOVA was performed on % change in peak strength at POST between ‘traditional’ and ‘compressed’ training. Results indicate no difference in % change of handgrip strength between types of training (Figure 2.10).

2.4.4 Control Experiment 1 – Muscle activity of untrained limb during training

In order to address a common concern associated with the cross-education phenomenon, a sub-sample of four participants had their average muscle activity recorded during a single training session to determine the level of muscle activity in the untrained forearm during training. Results indicate that the average muscle activity in the untrained forearm was 5.2 % ± 5.4 and 9.2 % ± 8.9 of peak muscle activation in the FCR and in the ECR, respectively. These values are similar to studies which have assessed muscle activity in the untrained limb during unilateral training and indicated little effect on the contralateral increase in strength (Devine et al., 1981; Hortobágyi et al., 1997; Munn et al., 2004; Magnus et al., 2010).

2.4.5 Control Experiment 2 – Effect of a single contraction over six weeks

The ANOVA indicated an overall significant effect of time, $F(5, 25) = 5.237, p=0.002$, indicating an overall reduction in strength over the course of 6 weeks. Pairwise comparisons indicate a significant reduction in strength in weeks 4 ($p=0.017$) and 5 ($p=0.028$) compared to week 3.

<table>
<thead>
<tr>
<th>Week</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Strength (kg)</td>
<td>35.0 ± 12.6</td>
<td>35.5 ± 13.4</td>
<td>35.7 ± 12.9</td>
<td>34.2 ± 12.5*</td>
<td>33.8 ± 12.9*</td>
<td>33.5 ± 12.5</td>
</tr>
</tbody>
</table>

Values are displayed mean ± standard deviation.
* Indicates significantly lower peak strength than week 3.

2.5 Discussion

Six weeks of ‘traditional’ unilateral handgrip training significantly increased peak force output of multiple tasks in both the trained and untrained limbs. In the trained limb, handgrip increased strength was accompanied by increased peak muscle activation. Bilateral plasticity of spinal reflex pathways was evidenced by alterations in excitability of Ia afferent transmission, regardless of conditioning input. Time-course data indicates the trained limb was significantly
stronger than baseline at the end of the 3rd week of training (session 9) and continued to increase in strength during the remainder of the study. The untrained limb was significantly stronger than baseline after the 4th week of training without further increases in force after the 5th week of training. 18 days of ‘compressed’ unilateral handgrip training also significantly increased peak force output in both the trained and untrained limbs. Time-course data indicated that there was an absence of strength increases in trained right limb throughout the training program, but there was an increase at the post-test assessment. In the untrained left limb, handgrip strength was increased around the 15th day of handgrip training.

2.5.1 Effects of ‘traditional’ handgrip training (6 weeks)

*Improvements in strength*

Six weeks of handgrip training three times per week increased strength across multiple tasks in both the trained and untrained limb (Figure 2.4A). Three baseline measures of peak force/torque were assessed prior to the training program in order to establish each individual’s baseline variability for each of the measures tested. This was also done in order account for any effects of task learning, which could inaccurately contribute to increases in peak force. Overall, minimal differences existed in baseline strength for handgrip, wrist flexion, or untrained wrist extension providing an excellent measure of baseline stability prior to each intervention (Table 1). There was a significant increase in strength from Pre 1 (72.4 ± 26.6) to Pre 2 (86.2 ± 36.3) for trained wrist extension, but no difference between Pre 2 and Pre 3 (90.4 ± 32.8). The wrist extension and flexion tasks were unfamiliar and untrained for all participants, which required explicit instructions from the tester. When looking at table 1 it becomes evident there was potentially a greater learning component to these tasks compared to the handgrip, which highlights the importance of the multiple baselines.

Six weeks of handgrip training three times per week increased strength across multiple tasks in both the trained and untrained limb (Figure 2.4 B and C). Peak handgrip force increased 14.6% in the trained right, and 12.5% in the untrained left limb. Interestingly, the strength transfer was very similar to the increase in strength on the trained right side. Generally, the transfer of strength is a percentage of what occurs in the trained side. Meta-analyses have determined the strength increases in the untrained contralateral limb are approximately 35% of the strength that is gained in the trained limb (Munn *et al.*, 2004; Lee & Carroll, 2007). On
average, this represents a 7.8% increase in strength from baseline in the untrained contralateral limb. However, this meta-analysis included studies that primarily assessed knee extension and elbow flexion. A task such as handgrip, which is a commonly performed motor pattern regardless of training status, may have less ability to increase strength compared to a task and muscle group that is rarely performed.

The effectiveness of the intervention can be shown based on the individual 95% confidence interval calculated from the three baseline sessions. Ten out of Eleven participants POST handgrip strength was outside of the established interval in both the trained and untrained limb. This result provides important information on the effectiveness of the intervention across participants. These results are similar to previous studies, which have explored strength increases with unilateral handgrip training. A study by Farthing et al., (2011) explored the changes that occurred with 3 weeks of maximal isometric handgrip contractions performed 5 days/week. Handgrip force increased by 10.7% after the resistance training intervention without a corresponding increase in muscle thickness.

Peak wrist extension and flexion torque increased by 19% and 19.5% in the trained limb while increasing 32.6% and 19.2% in the untrained limb, respectively. Ten out of eleven participants showed an increased peak torque for extension and flexion in the trained limb while all eleven participants increased peak torque in the untrained limb. This result is confirmation of previous work which reported that electrical stimulation training of the dominant wrist flexors increased strength of not only the contralateral wrist flexors but extensors as well (Sariyildiz et al., 2011).

The percentage increase in strength was larger for both the flexion and extension tasks compared to the increase in handgrip strength. This is not surprising as previous work has indicated strength increase is related to the training task familiarity. Training a novel task that is likely untrained will not only show greater improvements in the limb that is trained but the transfer of strength will also be greater (Farthing, 2009). The structures and pathways which contribute to maximal force output have yet to be optimized during a novel, untrained task. This is shown in simple unfamiliar tasks such as isometric ulnar deviation (Farthing et al., 2007) in which the transfer effects were quite large (47.1%) compared to more complex dynamic movements with multiple agonist and antagonist muscles such as concentric (23.5%) or eccentric
elbow flexion (22.8%) at a fast velocity (Farthing & Chilibeck, 2003). This can be compared to a task such as handgrip, which is utilized on a daily basis, and is incorporated in most resistance training activities regardless of intended muscle group. The motor system would have a finely controlled motor plan for handgrip which may be optimized with training but the amplitude of change will be smaller compared to more novel tasks.

**Muscle Activation**

Peak muscle activation during handgrip was significantly increased in the trained right limb after 6 weeks of training (Figure 2.5A). During maximal handgrip, peak muscle activity in the wrist flexors increased 54% from baseline with eight out of 11 participants showing significant effects. During handgrip, there were no differences in muscle activity in the wrist extensors. Similar results were found in the trained limb after 3 weeks of unilateral handgrip training 5 times/week with an increase in flexor carpi ulnaris activation and no change in extensor carpi radialis activation (Farthing et al., 2011).

In order to provide an idea of the balance of muscle activation between flexor and extensors a co-contraction ratio was calculated (Figure 2.5C). Since peak handgrip force is produced through synergistic actions of the flexors and extensors, a measure which assesses the relative balance of muscle activation between the wrist flexors and extensors could provide valuable information. There was a 30.7% increase in co-contraction ratio after training, indicating a much stronger contribution from the wrist flexors in producing overall force. No differences in peak activation were present between the three baseline measures for handgrip. Overall, this provides strong evidence of a neural contribution to the increase in strength on the trained right side. Since all FCR muscle activity was normalized to maximally evoked motor responses (M_max), differences in electrode placement, altered contractile properties, or muscle hypertrophy are not able to explain the result. Increased peak muscle activation measured via surface EMG has been a hallmark adaptation to resistance training in the literature. This result is confirmation of a large body of literature showing neural adaptations to resistance training (Gabriel et al., 2006; Folland & Williams, 2007).

Within this study, changes seen in peak muscle activation were limited to the task which was trained. Peak muscle activation during handgrip within the untrained limb was not different after 6 weeks of training. As well, there were no changes in muscle activity to accompany in the increases in strength for wrist extension or flexion in either limb. While this result may seem
auspicious, it remains a result that has been inconsistent within the literature for a number of reasons (Hortobagyi, 2005). In a general sense, all adaptations in the motor system with training should be incorporated into ongoing muscle activity during a maximal contraction. While this is true in a general sense, many sites of adaptation have been shown to be making contributions to the cross-transfer effect including spinal, subcortical, and cortical mechanisms (Lee & Carroll, 2007; Ruddy & Carson, 2013). Although cross-education is identified as an overall increase in strength, many small contributions at multiple levels of the nervous system most likely contribute. In the trained right limb, many of the same adaptations are occurring but the effect size is likely larger having been repeatedly activated throughout training. Although there is likely an improved or optimized recruitment strategy in the untrained limb, the smaller neuromuscular changes may not be detectable via surface EMG. There are many forearm flexor and extensor muscles, all of which contribute force to a maximal handgrip task. Small differences in many muscles may be undetectable via surface EMG. There were also no differences in muscle activation during the flexion and extension tasks to accompany the increases in strength. It would appear that any detectable changes using surface EMG were specific to the trained task.

2.5.2 Spinal Reflex Excitability – Trained Limb

While a limited number of studies have assessed spinal reflex pathways after resistance training, evidence indicates alterations in excitability of these pathways may contribute to early increases in strength. One of the first studies to assess changes in spinal reflex pathways after resistance training explored H-reflex amplitudes on the ascending limb of the recruitment curve after five weeks of unilateral, isometric plantar-flexion resistance training (Lagerquist et al., 2006b). MVC of the plantar flexors increased 15% on the trained ipsilateral limb, which was accompanied by an increase in H-reflex amplitude after training.

More recently, the effects of five weeks of unilateral dorsiflexion resistance training on H-reflex excitability was assessed (Dragert & Zehr, 2011). A more detailed analysis of the full recruitment curves was performed allowing for the assessment of subtle changes in thresholds and relative reflex sizes. This study indicated that an increase in dorsiflexion MVC of 15% in the trained ipsilateral limb was accompanied by an increase in $H_{\text{thresh}}$ in the trained TA and soleus. As well, there was a decrease in $H_{\text{max}}$ in the antagonist soleus muscle. The interaction between agonist and antagonist muscle groups after resistance training shows adaptation in segmental
spinal reflex pathways. Previously, reciprocal inhibition of the soleus H-reflex after tibialis anterior contraction was explored before and after four weeks of explosive ankle dorsiflexion training (Geertsen et al., 2008). After the intervention, the rate of torque development increased 24 – 33% which was assessed at 30, 50, 100, and 200 ms after initiating isometric dorsiflexion. The authors found that reciprocal inhibition at the onset of dorsiflexion increased from 6% to 22% and speculated that this may function to ensure efficient suppression of antagonist muscles with increased strength in dorsiflexors.

In order to provide a measure of spinal reflex excitability within the current study, unconditioned and conditioned H-reflex recruitment curves were assessed during a 10% contraction. Table 3 indicates there was no differences at baseline between any of the reflex measures and no differences in $M_{max}$ existed between conditioning paradigm or time points across arm (Figure 2.5B). This indicates that a similar number of the highest threshold motor units were recruited regardless of the paradigm or time they were measured. This allows for confidence that a similar population of motor and sensory axons were recruited between sessions and is an ideal value to normalize our EMG and reflex measure. The conditioning paradigm was employed as it has been well established that stimulating the cutaneous SR nerve at the wrist reduces Group Ia pre-synaptic inhibition of the wrist flexors as evidenced by the significant increase in $H_{max}$ amplitude when the conditioning was applied (Nakajima et al., 2013) (Figure 2.5C). With the same relative sensory volley, the motor unit pool was recruited to a greater extent with conditioning (Figure 2.6 A and C).

While conditioning was effective in removing pre-synaptic inhibition in the current study, there were no differential responses between unconditioned and conditioned recruitment curve variables so all data was pooled in order to assess differences between $PRE_{avg}$ and $POST$ time points. Similar to previous findings in the tibialis anterior and soleus, six weeks of resistance training had minimal effect on $H_{max}$ amplitude (Dragert & Zehr, 2011, 2013). Although this has previously been explored in the lower limb, this is the first study to assess effects of resistance training on spinal reflex pathways in the upper limb. This result indicates that the number of highest threshold sensory axons recruited is similar before and after handgrip training. While similar results have previously been shown, only exploring the highest threshold afferents has previously led to researchers to make claims that spinal cord excitability is not altered with resistance training.
Similar to previous results, it is not until subtle differences are explored that significant alterations are noticed (Dragert & Zehr, 2011, 2013). While the $H_{\text{max}}$ amplitude remains unchanged with training, alterations in the level of current needed in order to evoke this response provides evidence of altered Ia excitability. Results indicate that across conditioning paradigm, there was a significant reduction in the amount of current needed to reach $H_{@ 50\%_{\text{max}}}$ and $H_{\text{max}}$ in the trained wrist flexors. This indicates that unilateral handgrip training of the wrist flexors reduces pre- or post-synaptic inhibition and allows for a similar level of recruitment in the Ia afferent reflex arc with less input.

### 2.5.3 Spinal adaptations in the untrained limb

While there are no direct connections between motoneurons on the contralateral side, afferent projections mediated by crossed commissural interneurons (Jankowska et al., 2005) and propriospinal pathways do modulate interlimb coordination which could alter excitability bilaterally with unilateral training (Sherrington, 1910; Burke et al., 1992; Jankowska, 2001). Activation of group Ia afferents inhibit contralateral homologous motoneurons (McCrea, 2001) via the Ia inhibitory interneurons (Delwaide & Pepin, 1991). Functionally, contraction of an ipsilateral limb has been shown to depress H-reflex amplitude in the homologous contralateral muscle (Hortobágyi et al., 2003; Carson et al., 2004). H-reflex amplitudes are suppressed in human wrist flexors during strong unilateral flexion and extension of the contralateral wrist and can persist up to 30 seconds after the contraction (Hortobágyi et al., 2003). Contraction of the ipsilateral limb could modulate, via presynaptic inhibition of Ia afferents, segmental inputs to spinal motoneurons.

Studies which have observed the effects of unilateral training on H-reflex amplitudes in neurologically intact participants have found little change in the agonist muscle in the untrained contralateral side despite an increase in strength (Lagerquist et al., 2006b; Del Balso & Cafarelli, 2007; Fimland et al., 2009). However, Dragert et al. (2011) found $H_{\text{max}}$ amplitude was reduced in the antagonist muscle in the untrained limb. This is the first study to show a change in spinal reflex pathways that may contribute to the cross-education effect. Recently, unilateral strength training in the form of maximal dorsiflexion, altered spinal reflex excitability and reciprocal inhibition within the untrained more affected tibialis anterior in a post-stroke population (Dragert & Zehr, 2013). It was postulated that resistance training could lead to increased contralateral
sensitivity of the Ia inhibitory interneurons and larger suppression of alpha-motoneuron excitability. Overall, a limited body of evidence indicates that multiple afferent pathways likely contribute to the changes in alpha motor neuron excitability that occurs with training (Lagerquist et al., 2006; Geertsen et al., 2008; Dragert & Zehr, 2011).

In the current study, $H_{\text{max}}$ amplitude remained unchanged with training in the untrained limb. However, alterations in the level of current needed in order to evoke this response provides evidence of altered Ia excitability. Results indicate that across conditioning paradigm, there was a significant reduction in the amount of current needed to reach $H_{\text{max}}$ in the untrained wrist flexors. This indicates that unilateral handgrip training of the wrist flexors reduces pre- or post-synaptic inhibition and allows for a similar level of recruitment in the Ia afferent reflex arc with less neural input. This is the first evidence of an alteration in spinal reflex excitability in the untrained limb after unilateral training in the upper limb. Overall, alterations in Ia afferent transmission with training provides convincing evidence of segmental level contributions to the transfer of strength with unilateral training.

2.5.4 Time course of ‘Traditional’ vs ‘Compressed’ in the trained limb

Clinical application warrants the high priority to establish the minimum level of training needed in order to see the majority of the benefits to cross-education. While the majority of unilateral resistance training protocols have arbitrarily chosen a training program due its success previously, this is unsatisfactory justification when implementing unilateral training in a clinical population attempting to recover function in one side of their body. In order to address this, the minimum threshold for inducing significant increases in strength in the untrained contralateral limb was determined.

Figure 2.8A provides the group average for every handgrip contraction performed during the 6 weeks of unilateral handgrip training. It is common scientific practice to report change before and after an intervention with pre-post measures and proper statistical analysis as described previously. However, figure 2.8A provides all of the required information on the effectiveness and magnitude of the intervention. Peak strength during session 18 is higher than the first training session. This figure provides valuable information on the relationship of peak force during the training session such as the similarity in fatigue within a training session across the entire 6 weeks of training. While this type of data is not possible for all intervention
strategies, with technology becoming increasingly portable, affordable, and easy to integrate, recording an entire training intervention provides the researcher with more detailed information about the effectiveness and compliance to the research protocol.

The current results confirm those of related previous studies, which have shown similar time-courses of strength increase during different tasks and training protocols. 8 weeks of resistance training in the lower limbs produced a significant increases in squat, leg press, and leg extension strength after the 4th week of training (Staron et al., 1994). Similarly, 12 weeks of full body resistance training 3 times per week significantly increased chest press and knee extensor strength after the 4th week of training for the females, while the males increased knee extension and chest press strength at weeks 2 and 6 respectively (Abe et al., 2000). 8 weeks of leg extension training showed a significant increase in MVC strength at the 4th week of training (DeFreitas et al., 2011).

Figure 2.9A highlights the effectiveness of 6 weeks of unilateral handgrip training within the trained limb. Although strength is continually increasing, the first time that strength is significantly increased is at session 9 or after 3 weeks of training. Strength becomes continuously different than baseline at session 13 or just after the 4th week of training. This corresponds very closely to the information gathered by assessing the time point at which each participant was outside of their 95% confidence interval determined by their own baseline scores, which is highlighted as session 12.

The linear profile to peak force during 6 weeks of training is a stark contrast to the profile to peak force over 18 days of training in a row. There is no longer a clear linear increase in strength over time as the strength increase per day during the training intervention is 0.67 % during 6 weeks of training while it is 0.17 % per day when training 18 consecutive days. In fact, at multiple time points throughout the training protocol, peak strength is either the same or lower than at baseline. This is similar to previous work in which maximal eccentric contractions were performed every second day for 20 days in order to induce rapid hypertrophy. Peak strength was assessed at each session and after 8 days was significantly reduced which remained for the duration of the study. It is clear in both cases that the recovery interval was inadequate to allow adaptation to occur. Interestingly, within the current study there was no significant increase in strength over time until the post-test session during which a large almost 3 kg increase in peak force output is seen which was measured between 48-72 hours after the final training session.
Figure 2.9C provides a clear example of how training each day may in fact be detrimental over time if the goal is to improve strength within that limb. However, when the goal is to maximize improvement in an inaccessible limb it may be less relevant what is occurring in the trained limb if it optimizes the benefit in the untrained limb.

2.5.5 Time course of ‘Traditional’ vs ‘Compressed’ in the untrained limb

Initially, the goal was to map the time-course of strength gain to unilateral handgrip training performed 3x/week. This was assessed in the most non-invasive way possible, which was to perform a single contraction of maximal handgrip one time per week throughout the training protocol in order to assess at what point participants were significantly stronger than baseline. When 6 weeks of unilateral handgrip training was performed, participants were stronger during the 4th week of training. Interestingly, strength peaked after 5 weeks of training and was maintained for the duration of the training protocol. It was clear from this initial data that 5 weeks of unilateral training would be optimal for receiving the majority of benefit not wasting time once a plateau has been reached.

However, once this data was collected, a larger question remained unanswered which could significantly impact the application of unilateral training within clinical populations. Is the increase in untrained strength primarily related to the total time of intervention or is it primarily related to the number of inputs to the nervous system? During ‘compressed’ training, untrained handgrip force was significantly stronger than baseline on the 15th day of training compared to the 12 session of training during 6 weeks of training. However, session 12 occurred on approximately day 28 of training, almost twice as long as the ‘compressed’ protocol. After the intervention, approximately 21 days in the ‘compressed’ and 45 days in the ‘traditional’ paradigm, the increase in strength was 7.8% compared to 12.5%, respectively.

Only a single study has mapped any type of time-course in the untrained limb with unilateral training. Maximal isometric contractions of wrist flexion 3 times (10second/bout) a day, every day (except Sunday) for 100 days were completed (Ikai & Fukunaga, 1970). Time-course in the untrained limb was assessed on the 20th, 40th, and 100th day with increases in strength from baseline of 7.1, 12.5, and 32.1% respectively, although not significantly increased until the 40th session. To our knowledge, this is the only time-course data on the untrained contralateral limb. There is a similar level of strength gain after the 20th training session being
7.1% compared with the current study incorporating ‘compressed’ training, which showed after 18 consecutive days of handgrip training increased strength by 7.8%.

Based on the number of training sessions, strength increased faster and to a greater extent when participants trained 3x/week for 6 weeks. The percentage increase per 3 sessions of training when training 3x/week was 1.87% while participants only increased 0.98% per 3 sessions when training 18 consecutive days. However, there was not a significant difference between post-test % change values indicating a similar level of overall strength increase in the untrained limb occurred between training protocols. The main difference being the ‘compressed’ protocol was done in less than half the time of the ‘traditional’ protocol. When the goal of rehabilitation is not a final destination but a stepping-stone to the next type of intervention, the goal should not be to look for peak performance, but the largest representation possible of that effect within the shortest timeframe. When participants trained for 18 consecutive days there was no plateau in peak force production, which was seen after the 5th week of training in the ‘traditional’ protocol. This indicates that perhaps during a ‘compressed’ protocol, more than 18 sessions are required in order to optimize the contralateral increases in strength. Since unilateral strength training (cross-education) is a stepping stone therapy, the least time we can spend incorporating it while maximizing its benefit the better for researcher, clinician, and participant.

2.5.6 Are we that different from Fechner’s research in 1867?

Many fundamental ideas like the time-course of adaptation to overload are often overlooked and assumed to be known when actually, they are entirely based on previous research, which showed the desired effect. When the question arises as to why the particular parameters were chosen within a given training study, more often than not, the response is because that is what another study chose which was effective for them.

In terms of establishing the time-course of adaptation to resistance training, the innovator was Gustav Fechner who tracked his ability to lift a weight above his head every day as many times as possible. Assessing the shape of his data during the first 18 days of overhead training compared to the 18 days of maximal handgrip training employed within the current study provides an interesting comparison. The first 18 days of data from his original 1867 paper has been graphed against the 18 days of strength training in the current paper (Figure 11). Although obvious differences between tasks are present, what remains similar is the maximal nature of
each task on that particular day of training. What is exceedingly interesting is the similar shape of response throughout the 18 days of maximal training. Ultimately, the relative difference between where training started on day 1 and ended on day 18 appears very similar.

Fig 2.11. Comparison of 18 consecutive days of maximal training. A) Replotted original tabulated data from Fechner, G. (1857). Data points represent 55 days consecutive of lifting a dumbbell in each hand, overhead, for the maximal amount of repetitions. B) Comparison between 18 consecutive days of unilateral handgrip training and unilateral overhead press training. Peak handgrip force is was assessed during experiment 2 while the maximal number of overhead repetitions are from Fechner’s original work (1857).

2.6 Practical Applications:

For the first time, this study provides a practical timeline of strength increases in both the trained and untrained limb. This preliminary data provides a guideline as to the minimum number of sessions needed in order to see a significant increase in strength in the untrained contralateral limb. When comparing a ‘traditional’ type of resistance training program, which includes three sessions per week, it appears the minimum amount of time to induce a significant increase in strength in the untrained limb is 4 weeks. Interestingly, after the 5th week of handgrip training a plateau in strength was reached. This data indicates when incorporating a ‘traditional’ resistance training protocol, the optimal amount of time to implement unilateral handgrip training would be 5 weeks. This would allow individuals to receive the majority of the effect, while not continuing
to train without subsequent increases in strength once the plateau has been reached. When implementing a ‘compressed’ training protocol the minimum number of days needed to significantly increase strength in the untrained limb was approximately 15 days. Strength continued to increase until the end of the study indicating that potentially 18 consecutive days was not enough to reach the plateau noted with 6 weeks of training. An important consideration is the similar increase in force with ‘traditional’ (12.5%) and ‘compressed’ (7.8%) training protocols, which was acquired in 45 days compared with 21 days of training.

The focus for implementing these findings shouldn’t be to use unilateral training until the maximum increase in strength and function is seen on the untrained side. The goal should be to implement unilateral training at a point in rehabilitation where one side is weak, unable to train, or requires supplementation. The goal should be to have the untrained arm receive \( \approx 95\% \) of the possible benefits from training the other side in order to ‘boost’ the nervous system. Once this has been accomplished there needs to be a progression by incorporating the previously untrained limb in order to keep improving over time. Applying cross-education should not be implemented in isolation. It is a tool in the toolbox, which may be used as a specific adjunct therapy when one side is unable to perform the required rehabilitation. This has obvious implications after stroke when one side of the body is significantly affected due to cortical damage.

2.7 Limitations:

While this is the first study to assess the time course of strength training in both the trained and untrained limbs, caution should be taken when directly applying the time-course data from the described interventions. While the general trend of the results, and shape of the figures should be similar between different tasks and muscle groups, the magnitude of change and effect sizes may be drastically different depending on numerous factors. The task chosen for training, the intensity of contraction, type of contraction (concentric, eccentric, isometric, electrically evoked), volume of training (sets, reps, times/week), and muscle group chosen will all interact in order to determine the overall effect of training. This study is not meant to provide a one size fits all ‘dose’ for unilateral strength training but to provide a tightly controlled, clear data set with which to base future research studies, and rehabilitation interventions on in order to find the optimal strategy for individual participants in recovery.
While every effort was made to maintain tight control on data collection, due to logistical issues throughout the study, compromises were made. The first of which was the ability for all training sessions to be done in lab under supervision from a research assistant. During the 6 weeks of handgrip training, all training sessions were performed in the lab during the normal work-week, and most commonly on Monday, Wednesday, and Friday. However, when participants were training for 18 days consecutive, it was necessary to provide participants with a device to perform their training outside of the lab without supervision. Thus it cannot be guaranteed that maximal effort was achieved for every contraction during training in the same fashion as it was when performed in the lab. However, an indication that the training was performed in a similar manner during both protocols is provided in figure 2.8. This figure contains the group average of every contraction performed throughout the training study. It is clear that the general trend both within a session, and the adaptation over time are both similar and repeatable over time. This figure provides an excellent assessment of compliance, and effectiveness of intervention.

2.8 Conclusions:

This study provides important considerations concerning implementation of unilateral training into rehabilitation practice. With recovery of an inaccessible limb, the primary goal becomes how to optimize strength and function of the more affected limb in a minimal amount of time. After 6 weeks of ‘traditional’ training, handgrip force increased significantly in both trained and untrained limbs. These strength increases were also accompanied by significant changes in the current needed to produce 50% \( H_{\text{max}} \) in the trained and \( H_{\text{max}} \) in the trained and untrained limb indicating alterations in spinal reflex excitability. Strength increases in the trained limb were also accompanied by changes in the maximal muscle activation. Time course data indicated the trained limb was significantly stronger than baseline after the 3rd week of training (session 9) while the untrained limb was stronger after 4 weeks (12 sessions). ‘Compressed’ training indicates approximately 15 sessions were needed to induce significant strength gains in the untrained limb. Therefore, training without rest days may be a more efficient approach within a clinical population when the trained limb is not the focus of recovery. Overall, establishing a ‘dose’ of unilateral training will provide researchers and clinicians with a bar with which to begin distributing it as an adjunct rehabilitation technique.
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3. Effects of enhanced cutaneous sensory feedback on inter-limb strength transfer between the wrist extensors

3.1 Abstract

An increase in strength of the untrained limb after unilateral training of the opposite homologous limb is commonly referred to as ‘cross-education’. To date, no study has directly assessed the relative contribution of somatosensory feedback to an inter-limb strength transfer. Unilateral training involves forceful contractions that activate cutaneous receptors in the skin, producing widespread and powerful effects between limbs. Providing “enhanced” cutaneous stimulation during unilateral contractions may alter excitability of interlimb reflex pathways, modifying the contralateral increase in strength. Therefore, the purpose was to determine the relative contribution of cutaneous afferent pathways as a mechanism of cross-education by directly assessing if unilateral cutaneous stimulation alters ipsilateral and contralateral strength gains. Twenty seven right handed participants were randomly assigned to either a voluntary contraction (TRAIN), cutaneous stimulation (STIM), or cutaneous stimulation during voluntary contraction (TRAIN+STIM) training group. Each participant completed 6 sets of 8 reps 3x/week for 5 weeks. TRAIN included unilateral maximal voluntary contractions (MVCs) of the wrist extensors. STIM training included cutaneous stimulation (2xRT for 3sec @ 50Hz) of the superficial radial (SR) nerve at the wrist only. TRAIN+STIM included MVCs of the wrist extensors with SR stimulation provided during the contractions. Two pre-training and 1 post-training session assessed the relative increase in force output during MVCs for wrist extension, wrist flexion, and handgrip strength. Simultaneous maximal voluntary muscle activation (EMG\text{max}) recordings were measured over the flexor and extensor carpi radialis. Changes in cutaneous reflex pathways were evaluated through stimulation of the SR nerve (3xRT for 5x1ms @ 300Hz) during graded ipsilateral contractions of 5, 10, 25, and 50 % of EMG\text{max}. Muscle activation and reflex measures were normalized to maximally evoked M-waves. Results indicate unilateral wrist extension training alone (TRAIN) increased force output in both trained and untrained wrist extensors. Providing ‘enhanced’ sensory feedback via electrical stimulation during training (TRAIN+STIM) led to similar increases in strength in the trained limb compared to VOL. However, the ‘enhanced’ feedback in the TRAIN+STIM group blocked any inter-limb strength transfer to the untrained wrist extensors. It appears the large mismatched sensory volley which was provided may have interfered with the integration of the appropriate sensory cues to the untrained cortex. This study provides information
about the importance of appropriate cutaneous sensory feedback during maximal force production and the strength that sensory information from the skin can have on motor output in the nervous system.

3.2 Introduction

Unilateral training or ‘cross-education’ has recently been highlighted for its possible use as a rehabilitation strategy during recovery from unilateral injuries (Hendy et al., 2012; Farthing & Zehr, 2014; Barss et al., 2016). ‘Cross-education’, ‘inter-limb strength transfer’, or the ‘cross-transfer’ effect, as it has more recently been described, is a neural adaptation defined as the increase in strength or functional performance of the untrained contralateral limb after unilateral training. (Scripture et al., 1894; Farthing & Chilibeck, 2003; Lee & Carroll, 2007; Ruddy & Carson, 2013). While its use as an adjunct therapy during rehabilitation from unilateral injury continues to be explored, a major focus of research has shifted into optimizing how unilateral training will be incorporated in order to maximize strength or performance gains. The idea of “enhanced” sensory integration during unilateral training has recently been explored through the use of mirror box therapy (Howatson et al., 2013). It is unknown if incorporating other sensory modalities (e.g. tactile somatosensory feedback) during resistance training may provide a similar enhancement effect.

While the original work on cross-education by Scripture et al., (1894) was published over a century ago, its origins stem from Alfred Wilhelm Volkmann (1801-1877) who found performing unilateral sensory acuity training using a two point discrimination task improved performance bilaterally (Volkmann, 1858). This work was not only the first to identify part of a phenomenon that would later be coined ‘cross-education’, but highlights the effect using cutaneous afferent sensitivity training. This work provided the initial evidence that similar sites of adaptation may be accessed or contribute to bilateral improvements in the motor and sensory systems whether the goal is to train strength, skill, or sensory acuity.

Since then it has been well established that cutaneous sensory information can have widespread effects on sculpting motor output (Duysens, 1977; Zehr & Stein, 1999; Panek et al., 2014). Cutaneous sensory feedback provides accurate perceptual information about joint position and movement proprioception and kinesthesia (Collins & Prochazka, 1996; Collins et al., 2000, 2005; Proske & Gandevia, 2012). The regulation of motor coordination and output, from simple
to complex patterns, is highly organized. In broad terms, this organization consists of interaction within a tripartite system of supraspinal input, spinal circuits, and sensory feedback (Zehr & Duysens, 2004). Given that sensory feedback during motor practice can increase motor output, one possibility is that providing ‘enhanced’ feedback may interact with mechanisms and pathways responsible for cross-education and alter the transfer of strength to the untrained limb.

Previously, adaptations in spinal reflex pathways have been shown to occur with unilateral training which may mediate cross-education. On the trained side, previous studies have shown increased H-reflex amplitude (Lagerquist et al., 2006b), increased $H_{@\text{thresh}}$ (Dragert & Zehr, 2011), and increased reciprocal inhibition (Geertsen et al., 2008). Studies which have observed the effects of unilateral training on H-reflex amplitudes in neurologically intact participants have found no change in the agonist muscle in the untrained contralateral side despite an increase in strength (Lagerquist et al., 2006b; Del Balso & Cafarelli, 2007; Finland et al., 2009). However, $H_{\text{max}}$ amplitude has been shown to be reduced in the antagonist muscle after unilateral plantar flexion training in a neurologically intact group, (Dragert & Zehr, 2011) while spinal reflex excitability and reciprocal inhibition within the untrained more affected tibialis anterior were altered in a post-stroke population (Dragert & Zehr, 2013). Unfortunately, little to no work has explored the role of cutaneous sensory feedback at any level of the nervous system during resistance training. Understanding if cutaneous sensory information can impact strength gains in the trained or untrained limb will provide information towards a unifying model of cross-education.

In recent years, evidence of a cortical contribution to cross-education has been established. Two main theories (which are not mutually exclusive) have been proposed which include the ‘cross-activation’ and ‘bilateral access’ hypotheses (Lee & Carroll, 2007; Anguera et al., 2007; Ruddy & Carson, 2013). The ‘cross-activation’ hypothesis is predicated on unilateral training causing bilateral cortical activity leading to adaptations in both hemispheres while the ‘bilateral access’ hypothesis postulates that motor plans developed in the trained hemisphere can be accessed by the opposite untrained hemisphere to facilitate task performance (Anguera et al., 2007; Lee et al., 2010; Ruddy & Carson, 2013). Both models, suggest that the ‘untrained’ motor cortex, ipsilateral to the trained limb, plays a critical role in mediating the cross-transfer effect (Ruddy & Carson, 2013). As well, recent chronic voluntary strength studies using TMS and fMRI have confirmed that reduced interhemispheric inhibition and increased activation of
specific areas in the non-exercised hemisphere are key moderators of cross education in healthy adults (Hortobagyi et al., 2011; Farthing et al., 2011).

It has recently been suggested that heightened afferent input associated with electrical muscular stimulation plays a key role in neural adaptations to electrically stimulated strength training. A barrage of cutaneous sensory information reaches the sensorimotor cortex and provides input to motor areas in the brain, giving rise to volleys that descend in corticospinal and motor neurons (Hortobágyi & Maffiuletti, 2011). Providing electrical stimulation to the wrist extensor muscles has been shown to increases activation of the primary sensorimotor cortex contralateral to the side of stimulation and produce bilateral activation of the supplementary motor areas (Han et al., 2003). A more detailed study exploring electrical stimulation in the wrist extensor and flexor muscles, found via fMRI significant activation of the contralateral primary motor cortex, primary somatosensory cortex, premotor cortex, ipsilateral cerebellum, bilaterally secondary somatosensory cortex, supplementary motor area, and anterior cingulate cortex (Blickenstorfer et al., 2009). Providing a large sensory volley during unilateral resistance training may interact with many of these same cortical areas which contribute to cross-education.

Altering bilateral excitability of both sensory and motor areas of the cortex has been explored using other paradigms. Repetitive transcranial magnetic stimulation (rTMS) has been used to create a ‘lesion’ in the ipsilateral M1 and found that when the untrained ipsilateral M1 was disrupted, performance gains in the untrained limb were nearly abolished (Lee et al., 2010). As well, after completing a single unilateral exercise session of pinch grip, participants improved their error of force in the untrained contralateral hand by almost a third. However, when rTMS was applied to the contralateral cortex during the exercise session, no transfer of improved error of force occurred (Goodall et al., 2013). Recently, it was shown that local tonic cutaneous pain induced by capsaicin cream interferes with the retention of a newly learned locomotor adaptation task despite the fact that baseline gait and motor acquisition were unimpaired by pain (Bouffard et al., 2014).

Recently, the effects of a single session of unilateral strength training combined with a a-tDCS applied to the ipsilateral (untrained) M1 on strength was assessed (Hendy & Kidgell, 2014). They found strength of the untrained, left extensor carpi radialis (ECR) increased following training of the right ECR with a-tDCS of the right M1, but not following training of the right ECR with sham-tDCS or a-tDCS alone. This was accompanied by neural modulation in
the ipsilateral M1, including an increase in corticospinal excitability, a decrease in SICI, and an increase in cross-activation during maximal contractions in the right ECR. This provides specific evidence for experimentally induced plasticity (a-tDCS) and dependant use plasticity (strength training) working together to provide an enhanced effect above resistance training alone.

While studying the modulation of reflexes can be used to probe inter-limb neural activity (Burke et al., 1991; Zehr et al., 2004), no study has directly assessed the relative contribution of afferent pathways to an inter-limb strength transfer protocol. Unilateral training involves forceful contractions that activate cutaneous receptors in the skin, producing widespread and powerful effects between limbs. Providing “enhanced” cutaneous stimulation during unilateral contractions may alter excitability of inter-limb reflex pathways, modifying the contralateral increase in strength. Therefore, the purpose of this study was to determine the relative contribution of cutaneous afferent pathways as a mechanism of cross-education by directly assessing if unilateral cutaneous stimulation alters ipsilateral and contralateral strength gains. It was hypothesized that providing ‘enhanced’ sensory feedback via electrical stimulation during resistance training would improve strength gains compared to training alone. If providing unilateral cutaneous stimulation alters the strength gains in either the trained or untrained limb it will provide the first evidence of a cutaneous afferent contribution to the cross-education effect.

3.3 Methods
3.3.1 Participants
A total of 27 neurologically intact right handed participants were recruited and randomly assigned to 1 of 3 groups which included maximal voluntary training (TRAIN) (7 female; 2 male, 22.1±4.2 years, 168.2±9.7cm, 69.6±11.0 kg, 14.8±4.4 WHQ), cutaneous nerve stimulation only (STIM) (6 female; 3 male, 23.2±2.8 years, 170.8±12cm, 64.5±13.2 kg, 18.4±2.8 WHQ), or cutaneous nerve stimulation during maximal voluntary contraction (TRAIN + STIM) (5 female; 4 male, 22.4±2.8 years, 175.1±10.8cm, 70.3±16.1 kg, 15.9±4.0 WHQ). Handedness was determined using a 10-item version of the Waterloo Handedness Questionnaire which ranged from -20 to +20, where a negative score indicates left handedness and a positive score indicates right handedness. Protocols used in the experiments were approved by the University of Victoria
Human Research Ethics Committee and performed according to the Declaration of Helsinki (1964).

3.3.2 Experimental Procedures

**Figure 3.1.** Illustration of the testing and training protocol. A) Experimental position for measurement of peak handgrip MVCs. B) Experimental position for measurement of cutaneous reflexes. B) Experimental position for measurement of peak wrist extension and flexion MVCs. EMG electrodes placed over the FCR and ECR with stimulation electrodes placed over the SR nerve at the wrist.
Each participant completed two pre-training (PRE 1, PRE 2) and one post-training (POST) session during which dependent measures of strength, muscle activation, and cutaneous reflex excitability were assessed. Multiple baseline sessions were used in order to account for learning effects. During these sessions, tests were performed in the same order and under the same environmental conditions (i.e. temperature, noise, lighting, participant position) and session time of day were kept as consistent as possible (Zehr, 2002; Lagerquist et al., 2006a; Dragert & Zehr, 2013). Participants completed training in the right arm only within their specified group 3x/week for 5 weeks, most commonly on Monday, Wednesday, and Friday. The training program was progressive in nature, beginning with four sets of eight repetitions and increasing in volume by one additional set each training day, up to a maximum training volume of six sets of eight repetitions. The training program included a taper down to four sets of eight contractions over the final two training sessions in order to ensure recovery from training prior to post-test session. Each training session consisted of 6 sets of 8 repetitions of the specified training. All training sessions were performed in a supervised laboratory setting while sitting with the right arm placed in a secured custom-built forearm brace. For all training sessions the forearm was secured in place with joint angles being maintained throughout training. The TRAIN group protocol consisted of unilateral maximal voluntary contractions (MVCs) of the right wrist extensors (Figure 3.1A). The STIM group received only cutaneous stimulation (2 times radiating threshold for 3sec @ 50Hz) of the superficial radial (SR) nerve at the right wrist. The TRAIN + STIM group protocol included MVCs of the right wrist extensors while the SR nerve was stimulated.

3.3.3 Strength – Maximal Voluntary Contractions

Maximal voluntary contractions of wrist extension, wrist flexion, and handgrip were assessed bilaterally at PRE 1, PRE2, and POST. Three MVCs were recorded for each task bilaterally and held for 3 seconds each with 1 minute of rest between contractions. Verbal encouragement was provided by the tester in a similar fashion for all measures and time-points. Although wrist extension was the primary strength measure, forearm strength assessments were performed in a manipulandum to assess for transfer of strength to the untrained limb across multiple tasks using the same musculature. For each task, the contraction with the highest peak force was used for comparison at each time-point. Participants were familiarized with the isometric
strength tasks prior to MVCs and completed a standardized warm-up prior to each session. All MVCs were recorded in a seated position with the non-tested arm placed in the participants lap. Wrist extension and flexion were assessed in a custom built forearm support attached to a Gamma Sensor force transducer (ATI Industrial Automation, Model FT06598, Apex, USA). The forearm was secured and all joint angles were maintained across testing time-points. Handgrip MVC was recorded via dynamometer in the same seated position at an approximate 45° angle away from the body. All settings were maintained through the data collection process.

3.3.4 Muscle Activation – Electromyography

Electromyography was recorded bilaterally from the muscle bellies of the FCR and ECR in the forearm. Once the skin was cleaned with alcohol wipes, surface electrodes (Thought technologies Ltd.) were placed in a bipolar configuration on the skin using a 2cm inter-electrode distance, oriented along the fibre direction, in accordance with SENIAM procedures (Freriks & Hermens, 2000). A reference electrode was placed on the medial epicondyle to serve as a common ground for the EMG signal. Electrodes were placed in the same position at each testing session. Land marking measurements were taken at the initial pre-test to ensure correct placement at each subsequent time point. During MVCs a 0.5 second window of time around peak muscle activity was used to calculate the peak mean absolute value (MAV). The peak MAV associated with the corresponding peak MVC from each baseline and post-test measure was used for assessment.

EMG was pre-amplified 5000x (GRASS P511, AstroMed, Inc) and band pass filtered 100-300 Hz. The output was sent to the A/D interface (National Instruments Corp. TX, USA) where it was converted to a digital signal and sampled at 1000 Hz using custom built continuous acquisition software (LabVIEW, National Instruments, TX, USA) and stored to a computer for off-line analysis.

3.3.5 Cutaneous Nerve Stimulation

Cutaneous reflexes were evoked via stimulation of the superficial radial nerve (SR) innervating the dorsum of the hand. Electrodes for SR nerve stimulation were placed just proximal to the radial head (Zehr & Chua, 2000; Zehr & Duysens, 2004). Appropriate stimulation location was checked by ensuring that radiating paresthesia was evoked into the appropriate cutaneous innervation area of the SR. In order to assess cutaneous reflexes, trains of 5 x 1.0ms pulses at 300
Hz were delivered at an intensity of 3 x radiating threshold via isolated constant current stimulator (Grass S88 stimulator with SIU5 stimulus isolation and a CCU1 constant current unit AstroMed-Grass Inc., Canada). In order to provide the same relative intensity of stimulation between participants a multiple of the radiating threshold (RT) was used, determined as the minimum intensity that evokes a clear radiating sensation in the entire perceptive field (Delwaide et al., 1981; Duysens et al., 1990; De Serres et al., 1995; Brooke et al., 1997). Cutaneous reflexes were assessed during graded ipsilateral contractions of the wrist extensors of 5, 10, 25, and 50 % of EMG$_{\text{max}}$. The level of background activity significantly modulates cutaneous responses such that as activity increases, the reflex response also increases in a linear fashion (Yang & Stein, 1990; Burke et al., 1991; Aniss et al., 1992; Van Wezel et al., 1997; Komiyama et al., 2000).

For the groups that received cutaneous stimulation during their training, trains of 1.0ms pulses at 50 Hz were delivered at an intensity of 2 x RT for 3 seconds (same duration as the training MVCs). 50Hz frequency was chosen as it most closely resembled the sensation of pressure on the back on the hand which would be the pressure surface during wrist extension. Cutaneous stimulation intensity was set low enough to producing a buzzing or fluttering sensation in the innervation area while producing measurable changes in motor output (Zehr & Stein, 1999; Zehr, 2006). Non-noxious stimulation intensities were found for each participant to ensure non-nociceptive pathways were stimulated. All reflex measures were normalized to the corresponding maximally evoked motor response (M$_{\text{max}}$).

### 3.3.6 Data Analysis

EMG data were analyzed for background amplitudes and reflexes using custom-written software programs (MATLAB, The Mathworks, INC., Natick, MA). The net effect of cutaneous input on motoneuron excitability is inferred from surface EMG recorded in the muscle of interest. Modulation of ongoing activity can be seen by averaging data that are time-locked to the known stimulus. The reflex response was determined by taking the averaged data after SR stimulation and subtracting the data when no input was present leaving reflex activity to be assessed (Brooke et al., 1997; Zehr & Stein, 1999). This technique allows for measurement of both facilitatory and inhibitory responses (Baken et al., 2005). Monitoring the effect cutaneous stimulation has on muscle activity provides reasonable temporal resolution to accurately document the amplitude and latency of the responses (Brooke et al., 1997). The stimulus artifact was removed from the
subtracted reflex trace and data were then low-pass filtered at 30 Hz using a dual-pass, fourth order Butterworth filter.

Initially, reflexes were quantified as the average cumulative reflex over 150 ms following stimulation. This value is determined as the integral obtained at 150 ms divided by the time interval of integration to yield the overall reflex effect. If the value is positive, overall facilitation has occurred, if the value is negative, overall inhibition has occurred. This quantification method allows for interpretation of modulation of reflex pathways from spinal, brainstem and supraspinal centers (Komiyama et al., 2000). Triphasic responses at varying delay latencies, which can be excitatory or inhibitory were recorded bilaterally in the ECR and FCR during graded ipsilateral wrist extension contractions. (Jenner & Stephens, 1982; Yang & Stein, 1990; Duysens et al., 1992; Gibbs et al., 1995; De Serres et al., 1995; Van Wezel et al., 1997). An early latency component was identified as occurring before 75 ms, the middle component between 70-120 ms and the late component measured after 120 ms (Duysens et al., 1992; Brooke et al., 1997). The time window for each latency was visually chosen around the peak response which was said to be a significant reflex if the peak was two standard deviations outside of the background muscle activity (Zehr & Chua, 2000). Within each time window, all data was averaged together, and a 10 ms band around the maximum response was used to obtain a single value.

3.3.7 Statistics

Using commercially available software (SPSS 20.0, Chicago, IL) strength data were analyzed using a one-way ANCOVA with the between subjects factor of group, using pretest scores as the covariate and post-test scores as the dependent variable. This was performed due to baseline differences in strength between groups in both the right and left arms. Peak muscle activity, PT, and RT data were analyzed using a between-within 3 (Group; TRAIN, STIM, TRAIN+STIM) x 2 (Time; PREavg, POST) ANOVA with each muscle tested separately. Background muscle activity and cutaneous reflex data were analyzed using a between-within 3 (Group) x 2 (Time) x 3 (Contraction intensity; 5, 10, 25, 50% EMGmax) ANOVA. For cutaneous reflex data, a-priori comparisons within each training group were also assessed by a 2 (Time) x 3 (Contraction intensity) repeated measures ANOVA. Mmax was analyzed using a between-within (Group) x 3 (Time) ANOVA with each muscle tested separately. Each arm was tested separately in analysis. Mmax was used to normalize peak muscle activity and reflex measures at each time
point. If significant main effects or interactions were detected, simple main effects analysis followed using one-way ANOVA and LSD post-hoc or pairwise comparisons where appropriate. Assumptions for ANOVA and paired-samples t-tests were evaluated for parametric tests for a within-subject design. Statistical significance was set at \( p \leq 0.05 \).

3.4 Results

3.4.1 Strength – Maximal Voluntary Contractions

Results indicate 5 weeks of voluntary wrist extension training increases strength in the trained wrist extensors regardless of cutaneous stimulation. One-way ANCOVA indicated a significant effect of GROUP (\( F_{(2,23)}=4.809, \ p=0.018 \)). Adjusted wrist extension torque at POST was significantly higher than STIM in both the TRAIN (85.0±6.2 Nm vs 59.8±6.1 Nm; \( p = 0.004 \)) and TRAIN + STIM Groups (79.3±6.3 Nm vs 59.8±6.1 Nm; \( p=0.037 \)) with no difference between TRAIN and TRAIN+STIM (\( p=0.538 \)) (Figure 3.3).

![Graph showing effects of 5 weeks (15 sessions) of unilateral wrist extension training on peak wrist extension strength in the A) trained (right); B) untrained (left) limb. * Indicates a significant increase in strength from the adjusted pre measure after 5 weeks of unilateral wrist extension training. Values are mean ± SE (\( p < 0.05 \)).](image-url)
In the untrained contralateral limb, results indicate the TRAIN group increased peak wrist extension torque after the intervention. One-way ANCOVA indicated a significant effect of GROUP ($F_{(2,23)}=5.101$, $p=0.015$). After the intervention, adjusted wrist extension torque was significantly higher in the TRAIN group compared to STIM (73.9±3.5 Nm vs 58.8 Nm; $p=0.005$) and TRAIN+STIM (73.9±3.5 Nm vs 63.0±3.7 Nm; $p=0.049$).

**Table 3.1** Adjusted strength measures

<table>
<thead>
<tr>
<th></th>
<th><strong>PRE_ADJUSTED</strong></th>
<th><strong>POST_TRAIN</strong></th>
<th><strong>POST_STIM</strong></th>
<th><strong>POST_TRAIN_STIM</strong></th>
<th><strong>Sig.</strong></th>
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<tbody>
<tr>
<td><strong>Right Handgrip</strong></td>
<td>36.1 kg</td>
<td>36.8 ± 2.0 kg</td>
<td>35.2 ± 1.9 kg</td>
<td>35.5 ± 2.0 kg</td>
<td>NS.</td>
</tr>
<tr>
<td><strong>Left Handgrip</strong></td>
<td>35.6 kg</td>
<td>34.2 ± 2.3 kg</td>
<td>34.5 ± 2.2 kg</td>
<td>34.7 ± 2.3 kg</td>
<td>NS.</td>
</tr>
<tr>
<td><strong>R Flexion</strong></td>
<td>85.0 Nm</td>
<td>82.3 ± 16.8 Nm</td>
<td>74.2 ± 16.4 Nm</td>
<td>89.2 ± 18.2 Nm</td>
<td>NS.</td>
</tr>
<tr>
<td><strong>L Flexion</strong></td>
<td>66.9 Nm</td>
<td>72.8 ± 17.8 Nm</td>
<td>64.9 ± 17.5 Nm</td>
<td>73.5 ± 18.1 Nm</td>
<td>NS.</td>
</tr>
</tbody>
</table>

NS. No significant differences between any groups ($p > 0.05$). Values are adjusted based on analysis or covariance. Please explain in the table (legend or title) what “adjusted” means.

There were no significant differences in peak strength after training for any group during peak handgrip and wrist flexion contractions ($p > 0.05$).

### 3.4.2 Peak Muscle Activation
After 5 weeks of voluntary wrist extension training there is a differential response in peak muscle activation of the trained ECR between TRAIN and TRAIN+STIM compared to STIM only (Figure 3.3). Repeated measures ANOVA indicated a significant GROUP x TIME interaction ($F_{(2,23)}=3.816$, $p=0.037$). Pairwise comparisons indicate significant reduction in peak muscle activation for STIM after the intervention ($9.2\pm4.0$ vs $7.7\pm3.4$; $p=0.032$). Pairwise comparisons indicate there was no significant difference in peak muscle activation after the training intervention for TRAIN or TRAIN+STIM ($p>0.05$). Results of ANOVA indicate no differences in peak muscle activation of the trained ECR for handgrip or wrist flexion with no differences for any group in
the untrained limb. Results of ANOVA indicate no differences in peak muscle activation of the FCR for wrist extension, flexion, or handgrip in either limb after the intervention ($p>0.05$).

### Table 3.2 Peak muscle activation normalized to maximally evoked motor responses ($M_{\text{max}}$)

<table>
<thead>
<tr>
<th>Group</th>
<th>PRE</th>
<th>POST</th>
<th>PRE</th>
<th>POST</th>
<th>PRE</th>
<th>POST</th>
<th>SIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Ext</td>
<td>1.4±1.1</td>
<td>1.5±0.8</td>
<td>0.9±0.6</td>
<td>1.2±1.1</td>
<td>0.8±0.3</td>
<td>1.0±0.6</td>
<td>NS.</td>
</tr>
<tr>
<td>Left Ext</td>
<td>2.1±1.9</td>
<td>1.5±1.0</td>
<td>2.0±1.8</td>
<td>1.5±2.2</td>
<td>1.2±1.0</td>
<td>1.6±2.0</td>
<td>NS.</td>
</tr>
<tr>
<td>Right Flx</td>
<td>7.6±3.9</td>
<td>6.2±3.2</td>
<td>5.9±2.4</td>
<td>5.9±2.4</td>
<td>8.7±3.8</td>
<td>6.8±3.7</td>
<td>NS.</td>
</tr>
<tr>
<td>ECR</td>
<td>2.5±1.2</td>
<td>1.9±1.0</td>
<td>2.0±0.9</td>
<td>1.8±1.0</td>
<td>2.6±1.2</td>
<td>1.7±0.8</td>
<td>NS.</td>
</tr>
<tr>
<td>Left Flx</td>
<td>6.5±3.2</td>
<td>5.4±2.0</td>
<td>7.7±6.1</td>
<td>5.3±3.1</td>
<td>6.4±2.7</td>
<td>5.8±3.5</td>
<td>NS.</td>
</tr>
<tr>
<td>Right Handgrip</td>
<td>2.2±0.9</td>
<td>1.6±0.7</td>
<td>2.5±0.9</td>
<td>3.0±2.5</td>
<td>2.0±1.0</td>
<td>2.6±3.0</td>
<td>NS.</td>
</tr>
<tr>
<td>ECR</td>
<td>3.9±2.5</td>
<td>3.5±1.2</td>
<td>3.4±2.1</td>
<td>3.3±1.5</td>
<td>4.3±3.8</td>
<td>4.0±2.1</td>
<td>NS.</td>
</tr>
<tr>
<td>Left Handgrip</td>
<td>5.9±2.6</td>
<td>6.7±3.0</td>
<td>8.4±1.7</td>
<td>7.4±3.3</td>
<td>6.9±2.7</td>
<td>6.4±5.0</td>
<td>NS.</td>
</tr>
<tr>
<td>ECR</td>
<td>4.7±1.8</td>
<td>4.2±2.0</td>
<td>5.1±2.9</td>
<td>4.5±2.4</td>
<td>4.1±1.7</td>
<td>3.3±1.9</td>
<td>NS.</td>
</tr>
<tr>
<td>ECR</td>
<td>7.0±4.0</td>
<td>5.4±1.5</td>
<td>10.5±5.1</td>
<td>11.6±5.1</td>
<td>7.1±1.7</td>
<td>6.0±3.9</td>
<td>NS.</td>
</tr>
</tbody>
</table>

NS. No significant differences between any groups ($p>0.05$). Values are normalized to maximally evoked motor responses (mV/mV*100).

#### 3.4.3 Maximally evoked motor responses ($M_{\text{max}}$)

Results indicate maximally evoked motor responses ($M_{\text{max}}$) were similar across time-points providing a valid normalization technique for EMG and reflex measures. A 3 x 3 repeated measures ANOVA indicated a significant effect of GROUP in the right FCR ($F_{(2,24)}=4.083$, $p=0.030$), left FCR ($F_{(2,24)}=5.367$, $p=0.012$) and left ECR ($F_{(2,24)}=3.398$, $p=0.050$). Group differences were expected since there was a significant differences in baseline strength between groups. There was a significant main effect of TIME in the left ECR only ($F_{(2,48)}=4.057$, $p=0.024$). Pairwise comparisons indicate that PRE2 was significantly lower than both PRE1 ($1293.6±67.9$ µV vs $1388.5±66.2$ µV; $p=0.022$) and POST ($1293.6±67.9$ µV vs $1395.4±67.9$ µV; $p=0.012$). There were no significant differences in $M_{\text{max}}$ over any time point in the right FCR, right ECR, and left ECR ($p>0.05$) (Figure 3.4).
Figure 3.4. Average of maximally evoked motor response (Mmax) amplitude pooled across group. Values are displayed in the FCR and ECR in both the trained (right) and untrained (left) limb for Pre1, Pre2, and Post. * Indicates a significant decrease in M-wave amplitude at Pre 2 compared to Pre 1 and Post. Values are mean ± SE (p < 0.05).

3.4.4 Background EMG during cutaneous reflexes

Results from the 3 x 2 x 3 ANOVA indicate there were no significant interactions or main effects of group or time for background muscle activity during cutaneous reflex measurement (p>0.05). There was a significant effect of contraction intensity in both the right ($F_{(3,72)}=96.724$, $p<0.001$) and left ECR ($F_{(3,72)}=76.194$, $p<0.001$). Pairwise comparisons indicate there was a significant increase in muscle activity between all levels of contraction in both the right and left ECR ($p<0.001$).
**Figure 3.5.** Background muscle activity during cutaneous reflex measurement pooled across group and time. Bar graphs are presented for both the trained (right) and untrained (left) arms at contraction intensities of 5, 10, 25, and 50% EMG\textsubscript{max}. * Indicates significant differences between all other contraction intensities.

### 3.4.4 Cutaneous Reflexes

Results from the 3 x 2 x 3 ANOVA assessing ACRE 150, early latency, and middle latency reflexes indicate there were no significant interactions or main effects for GROUP or TIME ($p>0.05$). For ACRE 150 there was a significant main effect of contraction intensity in both the trained right ($F_{(3,72)}=28.380$, $p<0.001$) and untrained left limb ($F_{(3,72)}=21.494$, $p<0.001$). For early latency reflexes there was a significant main effect of contraction intensity in both the trained right ($F_{(3,72)}=78.231$, $p<0.001$) and untrained left limb ($F_{(3,72)}=53.081$, $p<0.001$).
Figure 3.6. ACRE 150 subtracted reflex amplitude pooled across group in both the A) Trained and B) Untrained limb. EMG is recorded from the ECR during SR nerve stimulation. Values are displayed across contraction intensity (5, 10, 25, 50 %) and between pre and post measurements. Values are normalized to maximally evoked motor responses ($M_{\text{max}}$). Values are mean ± SE (p < 0.05).
Figure 3.7. Early latency subtracted reflex amplitude pooled across group in both the A) Trained and B) Untrained limb. EMG is recorded from the ECR during SR nerve stimulation. Values are displayed across contraction intensity (5, 10, 25, 50 %) and between pre and post measurements. Values are normalized to maximally evoked motor responses ($M_{\text{max}}$). Values are mean ± SE ($p < 0.05$).

For middle latency in the untrained left limb there was a main effect of time pooled across contraction intensity and group ($F_{(1,24)}=6.550, p=0.001$). Results from a-priori 2 x 3 ANOVAs for each group indicate no significant interactions or main effects of time for any group for either limb ($p>0.05$). There was a significant main effect of contraction intensity in both the trained right ($F_{(3,72)}=5.129, p=0.003$) and untrained left limb ($F_{(3,72)}=6.427, p=0.001$).
Figure 3.8. Middle latency subtracted reflex amplitude pooled across group in both the A) Trained and B) Untrained limb. EMG is recorded from the ECR during SR nerve stimulation. Values are displayed across contraction intensity (5, 10, 25, 50 %) and between pre and post measurements. Values are normalized to maximally evoked motor responses (M_{max}). * Significant main effect of time pooled across group and contraction intensity. No differences between groups were present existed. Values are mean ± SE (p < 0.05).

For long latency reflexes in the trained right limb there was a significant contraction x time interaction ($F_{(3,24)}=4.487, p=0.006$). Results from a-priori 2 x 3 ANOVAs for each group indicate no significant interactions of main effects of time for TRAIN or STIM ($p>0.05$). However, for the TRAIN+STIM group there was a significant contraction x time interaction ($F_{(3,24)}=8.574, p<0.001$) and time main effect ($F_{(1,8)}=14.201, p=0.005$). Paired samples t-tests
indicate a significant difference in reflex amplitude at 25% (p=0.010) and 50% (p=0.006) contraction intensities.

**Figure 3.9.** Long latency subtracted reflex amplitude in the trained limb for the A) TRAIN B) STIM and C) TRAIN+STIM Groups. EMG is recorded from the ECR during SR nerve stimulation. Values are displayed across contraction intensity (5, 10, 25, 50 %) and between pre and post measurements. Values are normalized to maximally evoked motor responses (M_max). * Significant difference in subtracted reflex amplitude between pre and post time points in the TRAIN+STIM group only. Values are mean ± SE (p < 0.05).
Figure 3.10. Long latency subtracted reflex amplitude in the untrained limb pooled across group. EMG is recorded from the ECR during SR nerve stimulation. Values are displayed across contraction intensity (5, 10, 25, 50 %) and between pre and post measurements. Values are normalized to maximally evoked motor responses (M\textsubscript{max}). Values are mean ± SE (p < 0.05).

3.4.6 Perceptual and Radiating Thresholds

Results of the 2 x 3 ANOVA indicate there was no change over time or across group for either perceptual or radiating threshold as no significant interactions or main effects were present (p>0.05).

Table 3.3 Perceptual and Radiating Thresholds

<table>
<thead>
<tr>
<th></th>
<th>PRE\textsubscript{avg} (mA)</th>
<th>POST (mA)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right PT</td>
<td>1.6±0.37</td>
<td>1.6±0.5</td>
<td>NS.</td>
</tr>
<tr>
<td>Right RT</td>
<td>4.5±0.6</td>
<td>4.9±1.3</td>
<td>NS.</td>
</tr>
<tr>
<td>Left PT</td>
<td>1.7±0.4</td>
<td>1.6±0.4</td>
<td>NS.</td>
</tr>
<tr>
<td>Left RT</td>
<td>4.3±0.7</td>
<td>4.5±1.3</td>
<td>NS.</td>
</tr>
</tbody>
</table>

3.5 Discussion

Unilateral wrist extension training alone (TRAIN) increased peak force output in the trained wrist extensors. Providing ‘enhanced’ sensory feedback via electrical stimulation during training (TRAIN+STIM) led to a similar increase in strength in the trained limb compared to TRAIN. However, the major finding of the current investigation is that providing ‘enhanced’ cutaneous feedback in the TRAIN+STIM group blocked inter-limb strength transfer to the untrained wrist extensors. This is the first study which has directly assessed the cutaneous sensory...
contribution to resistance training in the trained and untrained limb. While it was hypothesized that providing ‘enhanced’ cutaneous feedback would facilitate the strength gain in the untrained contralateral side, it appears the large mismatched sensory volley which was provided may have interfered with the integration of the appropriate sensory cues to the untrained cortex.

3.5.1 Absence of inter-limb strength transfer with ‘enhanced’ cutaneous input

The original intension of this project was to design an ‘enhanced’ training protocol in which cutaneous afferent input would facilitate the increase in strength in the untrained contralateral limb. While the increase in strength was similar between both the TRAIN and TRAIN+STIM group in the trained limb, the group that received the 50 Hz stimulation during the maximal wrist extension training protocol saw no transfer of strength to the untrained limb. While this result is contrary to our hypothesis, this study is further confirmation of the important role of cutaneous afferent feedback to ongoing movement. This result also provides evidence for the motor and sensory cortices being heavily involved in the transfer of strength from the trained hemisphere to the untrained hemisphere (Ruddy & Carson, 2013).

The most likely issue is that the timing of the enhanced sensory volley was not linked to the actual intention to contract. If we consider the human nervous system to exhibit properties of a “Hebbian” synapse with “neurons firing together and wiring together”, by providing a mismatched sensory volley, fundamental properties associated with acquisition of novel motor skills may have been altered (Carson, 2006; Hebb, 2005). Neurons that release action potentials at the same time have an increased probability that synaptic connections will be formed while uncorrelated activity diminishes functional connectivity (Russmann et al., 2009). In the TRAIN+STIM group, each maximal wrist extension contraction throughout the training protocol was initiated by the electrical stimulator which meant a volley of cutaneous sensory information was being provided prior to initiation of the contraction. This is opposed to initiating the movement which then produces the appropriate volley of sensory information based on timing, intensity, and task. Not only was the timing of the stimulation provided mismatched but the intensity of the stimulation remained constant throughout each contraction for the duration of the study. A more natural type of stimulation would have been to increase the stimulation frequency proportionally as muscle activation increased. As well, the intensity of the sensory volley may have been too high which bombarded sensorimotor cortical areas (Han et al., 2003;
Blickenstorfer et al., 2009). This may not have allowed for appropriate sensory cues from the wrist extension contractions to be incorporated and shared between hemispheres (Ruddy & Carson, 2013). It remains possible that an appropriately timed stimuli with intensity dependant frequency and amplitude may have shown differential results under the same experimental settings.

3.5.2 Possible cortical interactions with ‘enhanced’ cutaneous feedback

Providing a large and non-synchronous sensory volley during unilateral resistance training may interact with many of the same cortical areas which contribute to cross-education. Changes in multiple cortical areas in both hemispheres have been shown after unilateral training via fMRI (Farthing et al., 2007, 2011), positron emission tomography (PET) (Dettmers et al., 1995), and TMS (Kristeva et al., 1991; Boroojerdi et al., 2001; Hortobágyi et al., 2003; Perez et al., 2007). As well, adaptations in connections between primary motor cortices (M1) through transcallosal routes have shown significant plasticity with training (Perez et al., 2007; Hortobagyi et al., 2011). These transcallosal connections convey diffuse inhibitory influences from M1 on one side of the brain to the contralateral M1 (Chen, 2004). Plasticity of interhemispheric connections mediating cross-education of a simple motor task has previously been shown (Hortobágyi et al., 2011). After 1000 submaximal voluntary contractions of the right first dorsal interosseous (FDI) the untrained FDI’s force output increased 28.1% with interhemispheric inhibition being reduced by 30.9%. TMS induced MEP amplitudes also showed an up-regulation of motor cortical excitability in the non-trained primary motor cortex. These studies taken together indicate not only that plasticity in interhemispheric inhibition is possible but may play a role in transfer of strength to the untrained contralateral limb after unilateral training.

While this is the first study to ‘block’ inter-limb strength transfer due to ‘enhanced’ cutaneous input during unilateral strength training, previous investigators have shown an ability to alter transfer of skill or strength via other methods which may provide information on possible sites of interference within the current investigation. Previous studies have shown the importance of the motor cortex to the transfer of skill or strength using a diverse array of methods. Unilateral practice of a ballistic finger abduction task has been shown to improve performance by 82% in the untrained left hand and was accompanied by bilateral increases in corticospinal
excitability (Carroll et al., 2008). A follow-up paper found bilateral increases in performance and corticospinal excitability after unilateral training of a ballistic motor task (Lee et al., 2010). What was most interesting was that they also applied repetitive TMS to the trained and untrained motor cortex to induce a ‘virtual lesion’. This was induced by applying rTMS to either the right or left cortex, which reduced performance gains in the contralateral hand. They concluded early retention of ballistic performance improvements in the untrained limb are due to adaptations in the untrained motor cortex.

The ability to alter the acquisition of a novel motor task through interhemispheric excitability of both sensory and motor areas of the cortex has been shown using a diverse array of tasks. After completing a single unilateral exercise session of pinch grip, participants improved their error of force in the untrained contralateral hand by almost a third. However, when rTMS was applied to the contralateral cortex during the exercise session, no transfer of improved error of force occurred (Goodall et al., 2013). Local tonic cutaneous pain induced by capsaicin cream also interferes with the retention of a newly learned locomotor adaptation task despite the fact that baseline gait and motor acquisition were unimpaired by pain (Bouffard et al., 2014). Taken together these studies indicate cutaneous sensory information can have dramatic effects on the retention of a novel motor task, and interference of interhemispheric connections may be a contributing site of adaptation. Interestingly, providing a combination of anodal tDCS over M1 during a single session increased force production in the untrained limb while training with sham tDCS or anodal tDCS alone showed no increase in contralateral strength (Hendy & Kidgell, 2014). This was accompanied with changes in interhemispheric inhibition and corticospinal excitability in the untrained limb in the group that received anodal tDCS. What becomes apparent is that learning, regardless of the type or task can be transferred between hemispheres and directly impacted by altering excitability of the cortex facilitating this transmission.

Providing electrical stimulation to the wrist extensor muscles has been previously shown to increase activation of the primary sensorimotor cortex contralateral to the side of stimulation and produce bilateral activation of the supplementary motor areas (Han et al., 2003). A more detailed study exploring electrical stimulation in the wrist extensor and flexor muscles, found via fMRI significant activation of the contralateral primary motor cortex, primary somatosensory cortex, premotor cortex, ipsilateral cerebellum, bilaterally secondary somatosensory cortex,
supplementary motor area, and anterior cingulate cortex (Blickenstorfer et al., 2009). The main result from the current investigation of a ‘block’ of transfer between limbs due to a mismatched sensory volley interfering with learning in the untrained hemisphere may occur via similar pathways to the studies discussed above. The current evidence is in support of a barrage of cutaneous sensory information reaching the sensorimotor cortex and areas in the brain, being shared with multiple sensorimotor areas and ultimately interfering with the learning of a motor task in the untrained hemisphere via transcallosal routes (Hortobágyi & Maffiuletti, 2011).

3.5.2 Reflex Excitability

Here, cutaneous reflexes provided a measure of whether the integration of sensory information from the skin was differentially relayed after resistance training, electrical stimulation, or a combination of both. Within the current investigation there was a significant facilitation of long latency reflex amplitude in the trained limb after the intervention for the TRAIN+STIM group. Once cutaneous mechanoreceptors are activated, sensory information diverges through an unknown number of polysynaptic connections which is integrated at multiple levels of the nervous system which then modulates ongoing muscle activity (Zehr & Stein, 1999; Zehr, 2006). The current results indicate there was an interaction between the ascending afferent pathways and the sensorimotor connections, likely within the cortex, which ultimately is represented by a facilitation of ongoing muscle activity. The multi-component EMG response to cutaneous nerve stimulation is thought to arise due to differences in the number of interneurons in a particular pathway within the spinal cord (Zehr & Stein, 1999; Zehr, 2006). Based on the latency of the earliest responses it is assumed that the earliest components of cutaneous reflexes can be mediated by pathways in the spinal cord (Dimitrijevic & Nathan, 1969; Zehr & Stein, 1999; Baken et al., 2005). Responses at longer latencies are likely the result of transmission through longer pathways which may contain multiple interneurons at multiple levels of the nervous system including cortical contributions (Eccles & Lundberg, 1959; Jenner & Stephens, 1982; Nielsen et al., 1997). This is the first evidence of altered transmission of cutaneous afferent information with resistance training. Since the facilitation was only seen in the group that received cutaneous stimulation during voluntary training, there appears to be an interaction between the two conditions which led to a long term alteration in excitability. This change in excitability is likely related to the lack of strength transfer
to the untrained cortex within this group as there were no changes in early and middle latency reflex excitability within this or any group.

### 3.5.3 Spinal Reflex Excitability

A limited body of literature exists on alterations in spinal reflex pathways with unilateral training, and no study has assessed whether cutaneous reflex excitability can be altered with resistance training. While there are no direct connections between motoneurons on the contralateral side, afferents do modulate interlimb coordination (Sherrington, 1910) and are most likely mediated through commissural interneurons (Jankowska et al., 2005) and propriospinal paths (Burke et al., 1992; Jankowska, 2001). Activation of group Ia afferents inhibit contralateral homologous motoneurons (McCrea, 2001) via the Ia inhibitory interneurons (Delwaide & Pepin, 1991). This has been functionally demonstrated as contraction of an ipsilateral limb has been shown to depress H-reflex amplitude in the homologous contralateral muscle (Hortobágyi et al., 2003; Carson et al., 2004).

Within the current investigation, cutaneous reflexes were elicited in order to determine if transmission of segmental responses was altered with resistance training. Results show there was no change over time and between any of the groups for early latency subtracted reflex amplitude. This indicates that excitability of these pathways during a static task was not altered. Cutaneous reflexes were assessed over a range of contraction intensities in order to assess whether excitability changes with training depend on the intensity of contraction. There was an early inhibition of ECR muscle activity with SR nerve stimulation which scaled linearly with contraction intensity in a similar manner to previous investigations exploring cutaneous reflexes in the FCR (Zehr & Kido, 2001; Carroll et al., 2005). However, the current investigation indicates excitability of segmental reflex pathways are not altered with resistance training or repeated sensory volleys evoked with electrical stimulation. Other studies which have found alterations in spinal reflex excitability have done so using techniques such as the H-reflex (Lagerquist et al., 2006; Dragert & Zehr, 2011) or reciprocal inhibition (Geertsen et al., 2008; Dragert & Zehr, 2013). To our knowledge this is the first study to assess cutaneous reflex pathways after resistance training.
3.5.4. Possible measures of altered cutaneous transmission

Originally it was thought that receiving cutaneous stimulation at a reasonably strong intensity over a period of five weeks may induce some type of chronic adaptation in detection thresholds of cutaneous afferents (Volkmann, 1858). If so it could be detected by measuring either the perceptual or radiating threshold (PT and RT) of the SR nerve at the wrist before and after the intervention. However, after five weeks of electrical nerve stimulation applied to the superficial radial cutaneous nerve, there were no differences for any group or time point for PT or RT indicating little adaptation to the detection thresholds or excitability of transmission with repeated activation or resistance training.

As well, to provide a measure of the overall cutaneous reflex effect with training, the ACRE 150 method was employed. This method provides an overall view of the net reflex and simplifies interpretation by averaging all activity 150 ms after SR nerve stimulation. Within the current investigation, there were no changes after the intervention across contraction intensity or between groups indicating that the net reflex effect was not altered. This study is the first to employ cutaneous reflexes as an assessment of spinal reflex.

3.5.5 Controls within the current investigation

A type of SHAM condition was used as the control group to test whether repeated cutaneous stimulation alone would provide alterations in excitability or strength changes in the trained or untrained limb. Participants who were assigned to the STIM group received the same volume of training in the lab in the same position as the groups completing voluntary contractions. The only difference was the participants only received passive stimulation which did not produce any motor response. The participants who received STIM only did not increase in strength, muscle activation or reflex excitability indicting that cutaneous stimulation itself had little to no impact on motor output during voluntary contractions.

3.5.5 Limitations and Future Directions

A limitation of the current investigation is an inability to assess the effect cutaneous stimulation to the SR nerve during wrist extension contractions had on the peak force production within each training session. It is possible that the voluntary drive during each training session was altered due to the large sensory volley. While there is no way to be entirely sure, the similar
improvement is strength between the TRAIN+STIM and TRAIN in the trained limb indicates a similar level of effectiveness of the training intervention.

An interesting possibility is how ‘enhanced’ cutaneous sensory information would have impacted strength transfer if it was applied to the untrained arm during unilateral training. While this was initially part of the study design, due to constraints on the number of conditions and comparisons it was determined to be beyond the scope of the current investigation. Taking into consideration the results from the current investigation, this may be a valuable approach which could provide the ‘enhancement’ of strength in the untrained limb we initially hypothesized. The results of the current investigation provide a clear example of the specific nature of cutaneous sensory information and the necessity to provide functionally meaningful information to the nervous system.

3.5.6 Conclusions

Providing ‘enhanced’ sensory feedback via electrical stimulation during training (TRAIN+STIM) led to similar increases in strength in the trained limb compared to VOL. However, providing a mismatched sensory volley during training in the TRAIN+STIM group alleviated any inter-limb strength transfer to the untrained wrist extensors. It appears the large mismatched sensory volley which was provided may have interfered with the integration of the appropriate sensory cues to the untrained cortex. While it is clear that stimulation that is delivered without specific timing will not facilitate cross-education, it provides important insight as to the strong contribution that cutaneous sensory information has on motor output both within a session and learning over time.
3.6 References


4. Effects of a compression garment on sensory feedback transmission in the human upper limb

4.1 Abstract

Compression apparel is popular in both medical and sport performance settings. Perceived benefits are suggested to include changes in sensory feedback transmission caused by activation of mechanoreceptors. However, little is known about effects of compression apparel on sensorimotor control. Our purpose was to mechanistically examine if compression apparel modulates sensory feedback transmission and motor task performance in the upper limb. Two experiments were completed under CONTROL and COMPRESSION (sleeve applied across the elbow joint) conditions. H-reflexes were elicited in wrist flexor muscles by stimulating the median nerve and were recorded via surface electromyography (EMG). In Experiment 1, H-reflexes and M-H recruitment curves were assessed at rest, during wrist flexion (10% EMG<sub>max</sub>), and during a cutaneous conditioning of the superficial radial (SR) or distal median (MED) nerve during wrist flexion. Cutaneous reflexes were elicited during 10% wrist flexion via stimulation of SR or MED. In Experiment 2, unconditioned H-reflex measures were assessed at rest, during arm cycling, and during a discrete reaching task. Results indicate compression apparel modulates spinal cord excitability across multiple sensory pathways and movement tasks. Interestingly, there was a significant improvement in reaching accuracy while wearing the compression sleeve. Taken together, the compression sleeve appears to increase precision and sensitivity around the joint where the sleeve is applied. Compression apparel may function as a “filter” of irrelevant mechanoreceptor information allowing for optimal sensory information related to proprioception.
4.2 Introduction

Compression garments have traditionally been thought to provide mechanical pressure to the body surface to stabilize or support the underlying tissue. A number of attempts have been made to investigate the effects (if any) of wearing compression apparel with varying outcomes. Two recent review papers and a meta-analysis concluded compression apparel promotes numerous physiological processes capable of assisting athletic performance and subsequent recovery (MacRae et al., 2011; Born et al., 2013; Hill et al., 2014). The majority of clinical work has focused on increasing venous return or other cardiovascular parameters in cases such as lymphedema, pulmonary embolism, or deep vein thrombosis (Gandhi et al., 1984; Kraemer et al., 2000; MacRae et al., 2011, 2012). Unfortunately, little evidence of possible mechanisms or loci of adaptation has been identified for many of the perceived benefits.

While some improvements with compression are likely due to mechanical or cardiovascular effects, (Berry & McMurray, 1987; Perrey, 2009; MacRae et al., 2012) reported benefits such as improved power output, joint position sense (Birmingham et al., 1998; Kraemer et al., 1998) and one leg balance (Michael et al., 2014) may be related to adaptation in the nervous system. A major limitation of the current literature is the lack of information on how compression apparel interacts with the nervous system and may impact sensorimotor control. It remains entirely possible that many perceived benefits of compression apparel may be due to alterations in sensory feedback transmission caused by activation of mechanoreceptors beneath and around the site of compression.

A recent review discussed the idea that compression apparel could improve proprioception, allowing for improved information on the direction, acceleration, and speed of the limbs during movement (Born et al., 2013). The majority of previous research on proprioception has focused on the primary and secondary endings of the muscle spindle, which are heavily involved in kinesthetic feedback (Proske & Gandevia, 2009). However, two separate lines of research using microneurography to record afferent discharge (Edin, 1992, 2004) and skin stretch to isolate the afferent input to cutaneous mechanoreceptors (Collins & Prochazka, 1996; Collins et al., 2000; Collins et al., 2005) indicate that cutaneous feedback from the skin also provides accurate perceptual information about joint position and movement (Proske & Gandevia, 2012). This information from the skin is then integrated with feedback from muscle spindles to provide judgements of position and movement at joints throughout the body.
Previous research has established both cutaneous and muscle afferent feedback is ‘tuned’ by the nervous system depending on the phase of the locomotor cycle and the type of task performed (Zehr & Kido, 2001; Zehr et al., 2003) and is required for smooth coordinated limb movements (Zehr & Stein, 1999). Although these contributions go largely unnoticed due to their relatively fast acting effects on motor output, they are integrated at multiple levels of the nervous system including the spinal cord and brain (Iles, 1996; Birmingham et al., 1998; Aimonetti et al., 1999; Zehr & Stein, 1999).

An interesting proxy for compression apparel is the use of tape applied under tension across joints or muscles. Previously, the H-reflex was employed to assess changes in excitability with different taping techniques in the trapezius muscle (Alexander et al., 2003). Results showed a 22% reduction in H-reflex amplitude when rigid tape was applied compared to no change when the tape was removed or only under tape was applied. A follow-up study found a 19% reduction in H-reflex amplitude when rigid sports tape was applied in parallel to the medial gastrocnemius compared to no change when the tape was applied across the muscle fibres (Alexander et al., 2008). Compression apparel is likely to activate both cutaneous and muscle mechanoreceptors at rest and during movement, which could modulate sensory feedback transmission and ultimately proprioception (Simoneau et al., 1997; McNair & Heine, 1999). Effects of sensorimotor integration could account for a significant portion of the perceived benefit of this technology, especially if performance of a motor task can be improved.

Thus, the overall objective of this experiment was to examine if compression apparel produces measurable modulation of sensory feedback and motor task performance in the arm. Using both Hoffmann (H-) and cutaneous reflexes as probes, the purpose of experiment 1 (Exp 1) was to explore the effects of compression gear on sensory feedback transmission in a stationary limb. Based on the limited available literature, it was hypothesized that compression apparel would inhibit H-reflex amplitude in a similar fashion as tape applied under tension. The twofold purpose of experiment 2 (Exp 2) was to assess: a) if a compression sleeve differentially modulated the transmission of sensory information based on the task (static vs. locomotor vs. reaching) or phase of movement; and, b) any differences in performance of a discrete reaching task.
4.3 Methods

4.3.1 Participants

Two separate experiments were performed with a total of 25 healthy participants: 13 (5 male; 8 female, 22.9 ± 3.0 years, 170.8 ± 9.0 cm, 69.8 ± 13.1 kg) performed Exp 1 while 12 participants (5 male; 7 female, 25.2 ± 2.3 years, 171.6 ± 8.9 cm, 68.6 ± 11.2 kg) participated in Exp 2. Participants were informed of all experimental procedures and signed a written consent form. Protocols used in the experiments were approved by the University of Victoria Human Research Ethics Committee and performed according to the Declaration of Helsinki (1964).

Participants were fitted with a custom made compression sleeve containing silicone at the proximal and distal ends to improve friction between the compression garment and the skin surface in order to optimize effects of skin stretch. Arm circumference was measured in each participant and the closest fit according to the circumference of both the forearm and upper arm was then assigned. This fit was sized in order to maintain a similar amount of compression (between 10 and 20 mmHg) between participants. Table 1 provides details of the six sizes that were used (along with the numbers who used each), and the average forearm and upper arm circumference along with the calculated compression applied to each site in Exp 1 of the study. Overall, the compression applied was similar to previous investigations (Beliard et al., 2014). Interestingly, this review concluded the mechanical characteristics of a compression garment (value or spatial patterns of the pressure applied) have not shown to impact its effects.

Table 4.1 Compression sleeve sizing with corresponding compression

<table>
<thead>
<tr>
<th>Sizing (n=13)</th>
<th>Forearm Circumference (cm)</th>
<th>Forearm Compression (mmHG)</th>
<th>Upper Arm Circumference (cm)</th>
<th>Upper Arm Compression (mmHG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Large (n=1)</td>
<td>28</td>
<td>17</td>
<td>36.5</td>
<td>12</td>
</tr>
<tr>
<td>Medium (n=2)</td>
<td>27.8</td>
<td>14</td>
<td>32.8</td>
<td>13</td>
</tr>
<tr>
<td>Small (n=2)</td>
<td>26</td>
<td>16</td>
<td>31.5</td>
<td>13</td>
</tr>
<tr>
<td>Female Large (n=1)</td>
<td>25</td>
<td>16</td>
<td>32.5</td>
<td>17</td>
</tr>
<tr>
<td>Medium (n=4)</td>
<td>22.9</td>
<td>15</td>
<td>29.1</td>
<td>17</td>
</tr>
<tr>
<td>Small (n=3)</td>
<td>21.5</td>
<td>15</td>
<td>25.3</td>
<td>17</td>
</tr>
</tbody>
</table>

4.3.2 Experimental procedures

Experiment 1 – Effects of compression on afferent transmission during a static task

To establish whether wearing a compression sleeve produced measurable changes in sensory feedback transmission, reflex measures were initially assessed in a static position. The
right forearm, wrist, and hand were fixed in a customized brace in order to restrict movement and maintain joint angles throughout the experiment (Figure 4.1). All measures were assessed without (CONTROL) or with a customized compression sleeve (COMPRESSION). H-reflex recruitment curves were collected during REST (No contraction), CONT (10% contraction of the flexor carpi radialis), SR (Contraction + superficial radial nerve conditioning), MED (Contraction + distal median nerve conditioning). M-wave matched H-reflexes were collected during CONT, SR, and MED. Cutaneous reflexes were elicited via stimulation of the SR or MED nerve. For all conditions except REST, participants were asked to maintain a consistent low level contraction (~10% of maximal voluntary contraction (MVC)) of the right flexor carpi radialis (FCR) using visual feedback of the rectified and filtered EMG signal displayed on a computer screen.

![Figure 4.1](image_url)

**Figure 4.1.** A) Experimental setup of exp 1 without compression sleeve. B) Experimental setup of exp 1 with compression sleeve. Stimulation electrode (test) placement on the median nerve proximal to the elbow to elicit H-reflexes in the flexor carpi radialis is depicted in both set-ups.

**4.3.3 Electrical nerve stimulation:**

Electrical stimulation of the median nerve evoked M-wave and H-reflex responses in the FCR using bipolar surface electrodes placed just proximal to the medial epicondyle, as in previous
studies (Zehr & Hundza, 2005; Zehr et al., 2007b; Vasudevan & Zehr, 2011; Nakajima et al., 2013). Square wave pulses (1ms) were delivered with a constant current stimulator (Digitimer model SD7A, Medtel, NSW, Australia) pseudo-randomly every 2-5s. Cutaneous nerve stimulation was used to condition H-reflexes and for generating cutaneous reflexes in trains of 5 x 1.0ms pulses at 300Hz using a Grass S88 stimulator with SIU5 stimulus isolation and a CCU1 constant current unit (Grass Instruments, Austin, TX, USA) (Nakajima et al., 2013)(Figure 4.2). All reflex measures were normalized to the corresponding maximally evoked motor response ($M_{max}$).

4.3.4 Electromyography (EMG):

EMG was recorded unilaterally from the FCR, extensor carpi radialis (ECR), biceps and triceps brachii. Once the skin was cleaned with alcohol wipes, surface electrodes were placed in a bipolar configuration on the skin, oriented longitudinally along the predicted fibre direction in accordance with SENIAM procedures (Freriks & Hermens 2000). EMG was pre-amplified (GRASS P511, AstroMed) and band pass filtered 30-1000 Hz (FCR) or 30-300 Hz (ECR, BB, TB). The output was sent to the A/D interface (National Instruments Corp. TX, USA) where it was converted to a digital signal and sampled at 2000 Hz using custom built continuous acquisition software (LabVIEW, National Instruments, TX, USA).

4.3.5 Hoffmann Reflex (H-reflex)

H-reflex amplitude was evaluated while M-waves were kept constant across all conditions. Initial M-wave amplitude was determined by finding an intensity which produced an H-reflex amplitude of approximately 70% $H_{max}$ on the ascending limb of the recruitment curve while producing a small but measurable motor response to minimize antidromic effects. M-waves were monitored across all conditions, and stimulation intensity was adjusted as needed to maintain consistent amplitude. 20 stimuli were averaged in order to directly compare the amplitudes of the H-reflex during CONTROL and COMPRESSION. FCR H-reflex and M-wave amplitudes were averaged for each condition and analyzed off line using Matlab© (Mathworks, Nantick, MA).

M-H recruitment curves were collected by applying 40 stimuli over a range of intensities while stimulation current was concurrently measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL). Peak-to-peak amplitudes of M- and H-waves were calculated offline from the single unrectified sweeps of EMG with custom-written software (Matlab, Nantick, MA).
Average $H_{\text{max}}$ and $M_{\text{max}}$ were calculated from the three largest H-reflexes and M-waves, respectively.

**Figure 4.2:** Schematic of H-reflex and conditioning pathways. Schematic diagram outlining possible neural pathways for integration of inputs on Ia afferents arising from a compression sleeve placed around the elbow joint.

### 4.3.6 Cutaneous reflex stimulation:

Cutaneous reflexes were determined by analyzing averages of 20 sweeps of rectified EMG. The stimulus artefact was removed from the reflex trace and data were then low-pass filtered at 30 Hz using a dual-pass, fourth order Butterworth filter. The peak long latency response (110 – 140 ms post-stimulus) was evaluated to assess whether compression resulted in altered integration of sensory information at supraspinal levels. Perceptual threshold (PT) and radiating threshold (RT) were determined as the point at which nerve stimulation produces a perceivable stimulation and the point at which a stimulation produced radiating parasthæsia in the cutaneous receptive field of that nerve, respectively.

**Experiment 2 - Effects of compression on afferent transmission and performance during movement**

In order to assess whether wearing a compression sleeve differentially modulates the transmission of sensory information based on the task (STATIC vs. CYCLING vs. REACHING)
or phase of a movement, 12 participants completed Exp 2. Once again, each participant completed all experimental protocols during both CONTROL and COMPRESSION. M-wave matched H-reflexes and M-H recruitment curves were elicited in a similar manner to Exp 1 by stimulating the median nerve at two different phases of movement (3 and 6 O’CLOCK) during three different tasks (STATIC, CYCLING, and REACHING). The stimulation was delivered pseudo randomly once every 1-3 seconds, 1-3 cycles, or 1-2 reaches for the static, cycling and reaching tasks, respectively. All three tasks were performed on a custom made hydraulic arm cycle ergometer. The movement cycle was divided into 12 equal phases of movement (bins), which correspond to a clock face when viewing the right arm from a lateral view. Details of each task are listed below.

Figure 4.3. Movement tasks during Experiment 2. Arm cycling was performed at a cadence of 1Hz (60 rpm). The discrete reaching task was initiated at the 12 o’clock position and ended at 8 o’clock. Stimulation for both tasks was provided at the 3 and 6 o’clock positions during separate trials.

4.3.7 Static grip:

To provide a position matched control for the cycling and reaching tasks and a reference point to Exp 1, participants were asked to grip the ergometer handle and maintain a 10% voluntary
contraction in the FCR muscle of the right forearm. Participants held the ergometer handle at the 3 and 6 o’clock positions during separate trials while H-reflexes were evoked.

4.3.8 Upper limb cycling:
Unloaded rhythmic arm cycling was performed using both limbs on a custom made hydraulic arm ergometer at a constant frequency of 1hz (~60 rpm) (Zehr et al., 2003). H-reflexes were evoked during separate trials at two positions corresponding to 3 and 6 o’clock (Figure 4.3).

4.3.9 Reaching task:
A discrete reaching task was performed with the right arm while the left arm remained in the participant’s lap. While holding the ergometer handgrip, the participants initiated a movement from the 12 o’clock position to an endpoint at the 8 o’clock position (Figure 4.3). H-reflexes were evoked during separate trials at the same 3 and 6 o’clock positions as during cycling. Five minutes of practice was provided to all participants in order to account for learning effects of the task itself. Participants were instructed to stop exactly at the 8 o’clock position, which was detected by optically encoded position sensors in the ergometer and visually represented on a monitor in front of them. Ten trials were performed under each condition with deviation from the intended target being used as a measure of reaching accuracy with and without the compression apparel. Differences in performance of the discrete reaching task were assessed to provide preliminary data on whether a compression garment can alter motor task performance. The cadence of reaching matched their previous self-generated cycling frequency of 1 Hz (60 rpm). Trials were collected after a familiarization period in a randomized order. A similar protocol has been used previously (Hundza & Zehr, 2007).

4.4 Statistical Analysis
Exp 1: To assess effects on sensory transmission in the upper limb, dependant measures of $M_{max}$, $H_{max}$, M-wave at constant M-value, H-wave at constant M-value, and long latency cutaneous reflex amplitude were assessed using SPSS Statistics 20 (Chicago, IL). Factorial ANOVAs
contained within subjects factors of condition (CONTROL vs COMPRESSION) and task (REST, CONT, SR, MED).

**Exp 2:** To assess effects on sensory transmission during movement, dependant measures of $M_{\text{max}}$, $H_{\text{max}}$, M-wave at constant M-value, H-wave at constant M-value, and reaching accuracy were assessed. Within subjects factors of condition (CONTROL vs COMPRESSION) and task (STATIC, CYCLING, REACHING) were compared using ANOVA, while each position (3 O’CLOCK, 6 O’CLOCK) was treated separately.

All values are expressed as means ± standard deviation except in the figures where standard error was used for clarity of display. If significant main effects or interactions were detected in experiment 1 or 2, simple main effects analysis and pairwise comparisons were used. Significance was accepted at $p < 0.05$.

### 4.5 Results

**Exp 1 – Effects of compression on afferent transmission during a static task**

#### 4.5.1. Effect of somatosensory conditioning on M-H$_{\text{max}}$

Somatosensory conditioning significantly altered $H_{\text{max}}$ but not $M_{\text{max}}$ amplitudes. Figure 4.4A demonstrates the trend of the group means with single subject average H-reflex traces. Greater H-reflex amplitude is evident during the SR condition compared to both CONT and MED conditions. Maximal M-wave amplitudes evoked in Exp 1 (ranged from 6.6-7.2 mV) were not affected by somatosensory conditioning or compression ($p > 0.05$). Figure 4.4B shows the $M_{\text{max}}$ amplitudes for each task and condition. For $H_{\text{max}}$ amplitude, a 2 (condition) x 4 (task) factorial ANOVA revealed a significant main effect for task ($F(1.924,23.094) = 10.570, p = 0.001$). Pairwise comparisons showed that the REST (22.3 ± 13.12%) was significantly lower than CONT (26.4 ± 13.31%, $p = 0.026$), SR (33.3 ± 12.56%, $p = 0.001$) and MED (29.5 ± 11.68%, $p = 0.014$). Furthermore, the SR $H_{\text{max}}$ amplitude was significantly higher than both the CONT ($p = 0.001$) and MED ($p = 0.023$) $H_{\text{max}}$ amplitudes (Figure 4.4C).
Figure 4.4: Effects of conditioning paradigm. A) Individual subject traces which show the effect of conditioning on H-reflex amplitude while M-wave is maintained constant. B) Group average of maximally evoked M-wave ($M_{max}$) amplitude across the four conditions, with and without compression. C) Group average of maximally evoked H-reflex ($H_{max}$) amplitude pooled between control and compression across all participants. # indicates significantly lower $H_{max}$ than all other conditions. * indicates significantly higher $H_{max}$ than all other conditions. Values are mean ± SE ($p < 0.05$).

4.5.2 Effect of the compression sleeve on maximally evoked M-waves and H-reflexes

Wearing the compression sleeve did not alter $M_{max}$ or $H_{max}$ values. There were no significant differences in $M_{max}$ between CONTROL and COMPRESSION at REST (6.7±1.8 vs. 6.6±1.8 mV), CONT (7.1±1.7 vs. 7.0±1.8 mV), SR (7.0±1.6 vs. 7.1±1.8 mV), or MED (7.2±1.6 vs. 7.1±1.7 mV) ($p > 0.05$). This indicates the ability to maximally recruit motor axons was not measurably affected by a compression sleeve. There were no significant differences in $H_{max}$ between CONTROL and COMPRESSION at REST (23.7±15.6% vs. 20.8±15.0%), CONT
(26.6±12.8% vs. 26.1±16.1%), SR (35.3±13.3% vs. 31.3±13.7%), or MED (31.0±12.9% vs. 28.1±13.4%) (p > 0.05). This indicates the ability to maximally recruit primarily Ia afferent axons was not measurably affected by a compression sleeve.

### 4.5.3 Effect of the compression sleeve on H-reflex amplitude evoked with a constant M-wave

Wearing the compression sleeve caused a general suppression of the H-reflex amplitude elicited with constant M-wave amplitude, regardless of somatosensory conditioning. Figure 4.5A shows single subject average traces representing the group trends of a reduction in H-reflex amplitude. Evoked M-wave amplitudes were ~8-9% of M_<sub>max</sub> and were not significantly different in amplitude across conditions (p > 0.05), as seen in figure 4.5B. For H-reflex amplitude, the 2 (condition) x 3 (task) factorial ANOVA revealed a significant main effect for condition (F<sub>(1,12)</sub> = 5.142, p = 0.043)(Figure 4.5C).

![Figure 4.5](image-url)

**Figure 4.5.** Effects of compression sleeve during Exp 1. A) Single subject traces of the average H-reflex amplitude during 10% contraction, SR nerve conditioning, and MED nerve conditioning. Solid traces indicate control averages, whereas dotted traces indicate inhibited compression averages. B) Group average of M-wave amplitude across conditions indicating same input provided. C) Group average of H-reflex amplitude with and without compression. * Indicates significant reduction in H-reflex amplitude while wearing compression sleeve across all three conditions. Values are mean ± SE (p < 0.05).
4.5.4 Effect of the compression sleeve on long latency cutaneous reflex amplitudes

Wearing the compression sleeve resulted in a general increase in long latency cutaneous reflex amplitude, regardless of nerve stimulated (Figure 4.6). A 2 (condition) x 2 (stimulation site) factorial ANOVA revealed that there was a significant main effect for condition \( F_{(1,12)} = 5.390, p = 0.039 \). The peak long latency response occurred at an average latency of 135 ms after stimulation. An alteration in long latency excitability indicates that the compression sleeve altered sensory transmission within multiple pathways including supraspinal excitability.

![Figure 4.6](image)

**Figure 4.6:** Effects of compression on long latency cutaneous reflex amplitude. * Indicates significant increase in long latency cutaneous reflex amplitude while wearing the compression sleeve. Values are mean ± SE (\( p < 0.05 \)).

*Exp 2 - Effects of compression on afferent transmission and performance during movement*

4.5.5 Effects of compression sleeve on maximally evoked M-wave and H-reflexes during movement

Similar to Exp 1, wearing the compression sleeve did not alter \( M_{max} \) or \( H_{max} \) values during static, cycling, or reaching task recruitment curves (\( p > 0.05 \)). This is consistent with findings above that the ability to maximally recruit motor and primarily Ia afferent axons was not affected by a compression garment.

4.5.6 Effects of the compression sleeve on H-reflex amplitudes during movement

Wearing the compression sleeve caused a general suppression of m-wave matched H-reflexes evoked at the 3 o’clock, but not 6 o’clock position across all tasks (Figure 4.7 C and D).
Evoked M-wave amplitudes ranged from 7.3-11.4% of $M_{\text{max}}$ and were not statistically different between conditions or tasks ($p > 0.05$) (7 A and B). At the 6 O’clock position, H-reflex amplitudes were not significantly different between any conditions ($p > 0.05$) (Figure 4.7D). However, a 2 (condition) x 3 (task) factorial ANOVA revealed a significant main effect for condition ($F_{(1,11)} = 7.523, p = 0.019$) seen as a reduction in H-reflex amplitudes at the 3 O’clock position (Figure 4.7C).

Figure 4.7: Effects of compression sleeve across movement tasks and positions in Exp 2. A) Maintenance of M-wave across condition and movement tasks at the 3 o’clock position. B) Maintenance of M-wave across condition and movement tasks at the 6 o’clock position. C) Effect of compression on H-reflex amplitude across movement tasks at the 3 o’clock position. * Indicates significant reduction in H-reflex amplitude pooled across movement task. D) Effect of compression on H-reflex amplitude across movement tasks at the 6 o’clock position. No differences were present at this position. Values are mean ± SE ($p < 0.05$).

4.5.7 Effects of the compression sleeve on discrete reaching accuracy

Wearing the compression sleeve reduced the average magnitude of errors during the discrete reaching task (Figure 4.2). Regardless of the position at which the participants received
the stimulation during the reaching task, a similar improvement in reaching accuracy was seen while wearing COMPRESSION. A 2 (condition) x 2 (stimulation position) factorial ANOVA revealed that there was a significant main effect for condition ($F_{(1,12)} = 6.713, p = 0.024$). The reduced magnitude of error was similar across two distinct positions of stimulation indicating the compression sleeve may impact performance on a discrete reaching task.

![Figure 4.8: Reaching accuracy across stimulation positions. * Indicates a significant reduction in the deviation from the intended target while wearing the compression apparel. Values are mean ± SE ($p < 0.05$).](image)

4.6 Discussion

The major finding is that a customized compression sleeve around the elbow joint alters reflex excitability and performance accuracy. This alteration in excitability occurs across multiple sensory pathways and across multiple movement tasks. The reduction in the deviation from intended target during the reaching task, provides evidence of an improved task performance while wearing a compression garment.

4.6.1 Altered sensory transmission during a static task

The main result from Exp 1 is expressed in figure 4.5. To ensure stability of the afferent test volley between conditions, M-wave amplitudes elicited in the FCR were maintained while the corresponding H-reflex amplitudes were observed (figure 4.5B). There were no significant differences in m-wave between CONTROL and COMPRESSION or across condition, suggesting the same relative input was provided to sensory and motor axons (Zehr, 2002).
Interestingly, with the same relative input, a consistent decrease in H-reflex amplitude was identified while the compression sleeve was worn regardless of paradigm. This indicates wearing a compression sleeve alters spinal cord excitability by inhibiting Ia afferent transmission pre-synaptically or motoneuron excitability post-synaptically (Zehr, 2002; Misiaszek, 2003; Knikou, 2008). The effects of compression on H-reflex amplitude are clearly expressed in the individual subject traces shown in figure 4.5A.

A reduction in H-reflex excitability while wearing the compression sleeve may seem counterintuitive but may not be all together that surprising. An interesting proxy for compression apparel is the use of tape applied under tension across joints or muscles. Tape applied in the direction of the muscle fibres has been suggested to facilitate the underlying muscle activity (Morrissey, 2000). Potential contributions to this effect included cutaneous afferent input altering motor neuron excitability (Simoneau et al., 1997; McNair & Heine, 1999). This question was explored in a series of two experiments in which the H-reflex was employed to assess changes in excitability with different taping techniques in the trapezius muscle. The first study (Alexander et al., 2003) used an average of 50 reflex sweeps at a consistent level of stimulation and M-wave amplitude being matched to compare four conditions. The conditions included: control, under tape (no tension), rigid tape (Endura sports tape), and after removal (no tape). The results showed a 22% reduction in H-reflex amplitude only during the rigid sports tape condition. When the under tape was applied, or the tape was removed the H-reflex amplitude remained unchanged from the control condition. Our results using a compression sleeve worn across the elbow joint are similar in principle to these results at the shoulder.

A follow-up study was then completed in the gastrocnemius muscle via stimulation of the tibial nerve under four conditions: i) before taping ii) under tape aligned across or along the direction of the medial gastrocnemius fibres iii) rigid tape application iv) both tapes removed (Alexander et al., 2008). Once again, there was a 19% reduction in H-reflex amplitude when the rigid sports tape was applied in parallel to the fibres of the medial gastrocnemius. Interestingly, when the rigid tape was applied across the muscle fibres there was no change in H-reflex amplitude. The similarity of results may provide an indication that activating specific cutaneous mechanoreceptors with either tape or compression apparel can directly alter sensory feedback transmission and thus motor output. This may be related to sensory information only being
altered at a phase of movement when significant stretch would have occurred and been functionally relevant to proprioception.

4.6.2 Effectiveness of conditioning paradigm

A conditioning paradigm was employed in an attempt to uncover if differential effects occurred when testing multiple afferent pathways during CONTROL and COMPRESSION. Figure 4.4 illustrates the conditioning paradigm was effective at altering excitability of the 1a reflex pathway as assessed by the H-reflex. At rest, stimulation of the median nerve activates both motor and sensory nerve fibres which produces the M-wave and H-reflex, respectively. Figure 4.4 (B) indicates that the maximally evoked motor response (M_max) did not differ across conditioning paradigm or between CONTROL and COMPRESSION. This indicates that the relative number of motor units recruited across conditions was similar. Furthermore, figure 4.4A and C clearly show with the same relative input to the spinal cord, more motor units were depolarized during a contraction and during SR conditioning, demonstrated by a significant increase in H_max amplitude. The 10% FCR contraction increased the excitability of the motor pool above REST as motor units are brought closer to their subliminal fringe. SR conditioning is known to reduce presynaptic inhibition on the 1a afferent pathway within the forearm (Nakajima et al., 2013). This was confirmed in the current experiment as the same relative input significantly increased H_max amplitude (Figure 4.4 C). Single subject data provided in figure 4.4A shows a clear waveform example of the effects that the conditioning paradigm had on averaged H-reflex sweeps.

The conditioning paradigm was employed in order to potentially identify whether specific pre-synaptic contributions to the altered sensory transmission could be identified (Nakajima et al., 2013). However, there were no differential results between unconditioned and conditioned H-reflexes. While this result does not provide specific information on pre-synaptic contributions to the inhibition, the similarity in amplitude of effect across paradigms provides important information on the robust nature of the inhibition. A schematic representation of possible integration sites for the compression sleeve is provided in Figure 4.2 which has been modified from Nakajima et al., (2013). Overall, wearing a compression sleeve at the elbow during a static task corresponds with a robust reduction in excitability across conditioning paradigm.
4.6.3 Role of cutaneous mechanoreceptors in altered sensory transmission

Wearing a compression sleeve altered excitability of long latency cutaneous reflexes as shown in figure 4.6. Cutaneous reflexes provide information on the relative contribution of sensory information from the skin being incorporated into ongoing motor output (Zehr & Stein, 1999). The convergence of excitatory and inhibitory effects on FCR motoneurons depends on the nerve being stimulated and the latency at which the response is measured. In a similar fashion to previous studies, long latency responses to SR nerve stimulation in the FCR produce a large facilitation (Zehr et al., 2001). Interestingly, when the compression sleeve was applied, there was a significant facilitation of the long latency response. Contributions to the facilitation of ongoing muscle activity at this latency can occur at multiple levels of the nervous system including segmental reflex, brainstem reflex or cortical descending inputs which ultimately converge on the motor neuron of the FCR (Iles, 1996; Birmingham et al., 1998; Aimonetti et al., 1999; Zehr & Stein, 1999).

Previous work has highlighted the important role of skin stretch to proprioception in the upper limb. In the hairy skin of the hand 92% of the afferents in the radial nerve responded to hand or finger movements (Edin & Abbs, 1991). Skin stretch applied to the back of the hand which was meant to mimic the stretch made my movement of finger joints indicated SAI and SAIII afferents showed dynamic and static sensitivity to skin stretch which could influence proprioception (Edin, 1992). Induced skin strain near an anesthetized joint also produces perceived joint movement. However, when the skin strain is eliminated, movement in the anesthetized joint is not perceived indicating its possible importance to joint position (Edin & Johansson, 1995).

An important line of research explored whether ensemble activity in human cutaneous sensory afferents evoked by the stretching of the skin over and around the finger joints contributes to the conscious perception of movement. Cutaneous afferents were activated by mechanical stretching of the skin over and around the finger joints. Perceived movements were then mimicked by voluntary movements of the fingers of the contralateral hand. The authors found a mismatch between actual joint position and perceived joint position which indicated input from the skin stretched during finger movement contributed to the conscious perception of movement (Collins & Prochazka, 1996). A follow up study aimed to explore if cutaneous feedback is providing specific kinaesthetic information as to which joint is moving (Collins et
Combining skin stretch and mechanical vibration produced larger movement illusions than either condition alone. Interestingly, when the appropriate regions of skin were stimulated, movement illusions were focused to the joint under the stimulated skin. Similar results have also been identified in the index finger, elbow, and knee (Collins et al., 2005). Together, these studies illustrate that cutaneous feedback provides accurate perceptual information about joint position and movement and this is integrated with feedback from muscle spindles to provide judgements of position and movement for joints throughout the body.

Muscle contractions cause skin on one side of the joint to be stretched while skin on the other side becomes slackened or possibly folded. It is possible that wearing a compression sleeve around a joint tightens the skin at each end of the garment. Therefore, during a given muscle contraction, relatively more skin stretch occurs when wearing the compression sleeve. This increase in skin stretch could be identified in the nervous system as a greater discharge rate of the appropriate mechanoreceptors. The most likely candidate for this role are SAI\textsuperscript{II} receptors which have been shown to be directionally sensitive in a similar manner to muscle receptors in the underlying muscles making them a suitable candidate for generating kinesthetic sensations (Proske & Gandevia, 2012). A greater discharge rate of SAI\textsuperscript{II} cutaneous mechanoreceptors while wearing a compression sleeve could alter excitability at multiple levels of the nervous system (Gandevia et al., 2002). Inputs are combined, not just of individual afferent responses from one muscle but of pooled responses from combinations of muscles acting at a joint (Proske & Gandevia, 2012). The current investigation indicates there is an excitatory input acting on the forearm flexor motor pool which is seen as an increase in long latency reflex amplitude (Nielsen et al., 1997). The enhanced skin stretch from the compression garment may be unconsciously higher due to a greater discharge rates of these SAI\textsuperscript{II} receptors. A schematic representation of possible integration sites for the compression sleeve is provided in Figure 4.2.

Exp 2- Effects of compression on afferent transmission and performance during movement

Wearing a compression sleeve produced a similar effect as previously shown in Exp 1 across multiple types of movement tasks (Figure 4.7B). When the stimulation was provided at the 3 o’clock position, there was a significant reduction in H-reflex amplitude across all movement conditions (Figure 4.7C). Figure 4.7A and B provide evidence of a consistent level of input being provided to the motor and sensory axons. Similar to Exp 1 there was a robust
reduction in excitability regardless of the type of task that was being completed. The combined results of the experiment provide an indication that the robust reduction in H-reflex amplitude across conditioning and movement paradigms is most likely due to an increase in pre-synaptic inhibition of the Ia afferent (Rudomin, 2009). If a post-synaptic input was responsible for the robust inhibitory effect of compression apparel, it would likely inhibit the long latency cutaneous reflex along with Ia afferent transmission (Zehr & Stein, 1999; Zehr, 2002, 2006). Since the long latency cutaneous reflex was facilitated while wearing compression apparel it is likely that compression apparel is having differential effects at multiple levels of the nervous system. Further investigations will be needed in order to confirm the sites of adaptation and mechanism responsible for the effect.

4.6.4 Phase specific alterations in sensory transmission are similar across movement tasks

An interesting difference in Exp 2 is the presence of phase specific differences in the effect of a compression garment. Phase dependency are hallmarks of the human nervous system (Zehr & Kido, 2001; Zehr et al., 2003). There were no differences in reflex amplitude between CONTROL and COMPRESSION conditions across any of the movement tasks when the stimulation was provided at the 6 o’clock position. This is the first evidence of a position specific effect of compression apparel on sensory feedback transmission in the upper limb.

Phase specific differences may be accounted for due to the greater amount of stretch being applied to the skin on the medial aspects of the elbow and forearm by the compression garment while at full extension (3 o’clock). Cutaneous sensory information at the elbow has previously been shown to provide accurate perceptual information about joint position and movement and this is integrated with feedback from muscle spindles to provide judgements of position and movement around the joint (Collins et al., 2005). Phase specific differences in the relative contribution of SA II mechanoreceptors to proprioception could differentially alter the contribution of compression apparel across movement phase. Greater skin stretch due to the compression sleeve at an extended position would increase the discharge rate of SA II receptors and may provide a larger contribution to ongoing motor task. This is compared to the 6 o’clock position near maximal flexion when less skin stretch would be provided to the medial aspects of the elbow and forearm as the compression sleeve would be stretched over the olecranon. This
result highlights the importance of functionally specific sensory information that is constantly being incorporated into ongoing movement.

4.6.5 Are alterations in sensory transmission with compression related to functional improvements?

The most functionally relevant finding from the current investigation is that reaching accuracy was improved when participants wore the compression sleeve compared to the control condition (Figure 4.8). Participants had their deviation from the intended target measured during a discrete reaching task with stimulation provided at multiple positions. Across stimulation position there was a significant reduction in the magnitude of deviation from the intended target which is preliminary evidence of improved task performance. While this is the first study to highlight possible adaptations in sensorimotor control while wearing compression apparel, previous investigations have noted performance benefits during tasks or conditions which include a large proprioceptive component including improved power output, joint position sense (Birmingham et al., 1998; Kraemer et al., 1998) and one leg balance (Michael et al., 2014).

4.7 Summary

In summary, wearing a compression sleeve alters the excitability of multiple pathways within the central nervous system regardless of conditioning input or movement task. The overall effect appears to be a reduced gain of the sensory feedback transmission at functionally relevant phases of movement. The compression sleeve appears to increase precision and sensitivity at the joint where the sleeve is applied. Therefore, compression apparel may function as a filter of irrelevant mechanoreceptor information allowing the nervous system to obtain ‘enhanced’ sensory information related to proprioception. The most functionally relevant finding from the current investigation is that reaching accuracy was improved in the COMPRESSION condition compared to CONTROL. An important distinction is that the reduced magnitude of errors was similar regardless of the position at which the stimulation was delivered. Thus, providing compression around a joint may alter the availability of sensory information relevant to proprioception but further exploration is needed to refine our understanding. This is one of the first studies to show that compression apparel can alter fundamental properties of sensorimotor control within the nervous system.
4.8 References


12.


5. General Conclusions

Recently, unilateral training or ‘cross-education’ has been highlighted as a possible rehabilitation strategy during recovery from unilateral injuries (Hendy et al., 2012; Farthing & Zehr, 2014; Barss et al., 2016). However, a number of limitations within the scientific literature needed to be addressed in order to properly integrate unilateral resistance training as an effective rehabilitation strategy. Therefore, the primary goal of this dissertation was to address a number of fundamental issues related to optimizing unilateral resistance training in the upper limb.

One such issue was knowledge on the minimum time course for emergence of the crossed effects. Establishing a time-course of bilateral strength changes during both ‘traditional’ and ‘compressed’ unilateral handgrip training will allow future researchers and clinicians to effectively prescribe a ‘dose’ of resistance training. The primary purpose of Chapter 2 was to characterize the time-course of strength changes in both the trained and untrained limbs during unilateral handgrip training. The time-course was assessed during both a ‘traditional’ training protocol (3x/week for 6 weeks: 18 total sessions) and a ‘compressed’ protocol in which the number of sessions and contractions were matched but participants trained for eighteen consecutive days. Experiment 1 indicated six weeks of handgrip training significantly increased force output in both trained and untrained limbs. This strength increase was accompanied by changes in the maximal muscle activation in the trained limb only. Time course data indicated the trained limb was significantly stronger than baseline after the 3rd week of training (session 9) while the untrained limb was stronger after 5 weeks (15 sessions) of unilateral handgrip training. Interestingly, the rate at which strength increased in the untrained limb was similar to the trained side. These strength increases were also accompanied by significant changes in the current needed to produce $H_{@50}$ in the trained, and $H_{max}$ in both the trained and untrained limb indicating alterations in spinal cord excitability. Experiment 2 showed a similar number of sessions were needed to induce significant strength gains in the untrained limb, however, the strength gains were accomplished in much less time. Since cross-education can be thought of as a ‘stepping-stone’ therapy, reducing rest days with the goal of maximizing the number of nervous system inputs and minimizing rest days may be the most efficient training regimen within clinical populations in which the trained limb is not the focus of recovery.

It was also necessary to determine specific strategies that could be employed to optimize resistance training interventions by enhancing strength increases. To date, no study had directly
assessed the relative contribution of afferent pathways to cross-education. Providing “enhanced” cutaneous stimulation during unilateral contractions was thought to potentially increase contralateral strength gains with unilateral training. Therefore, the purpose of Chapter 3 was to determine the relative contribution of cutaneous afferent pathways as a mechanism of cross-education by directly assessing if unilateral cutaneous stimulation alters ipsilateral and contralateral strength gains. Results indicated unilateral wrist extension training alone (TRAIN) increased force output in both trained and untrained wrist extensors. Providing ‘enhanced’ sensory feedback via electrical stimulation during training (TRAIN+STIM) led to similar increases in strength in the trained limb compared to VOL. However, the major finding indicates ‘enhanced’ feedback in the TRAIN+STIM group alleviated any interlimb strength transfer to the untrained wrist extensors. It appears the large mismatched sensory volley which was provided may have interfered with the integration of the appropriate sensory cues to the untrained cortex. This study will help refine a unifying model of unilateral strength training to include contributions from central motor output as well as afferent feedback. As well, it will be of vital importance in the future to optimize an ‘enhanced’ sensory feedback to mimic natural proprioceptive cues including timing, frequency, and amplitude of input.

It was thought wearable apparel such as a compression garment may fundamentally alter excitability of spinal reflex pathways which could be contributing to many of the performance benefits which have been noted with the technology. While compression apparel has become widely popular in both medical and sport performance settings, little evidence of the mechanisms of action exist for many of the purported benefits. Previously, it was unknown whether constant tactile input to the skin via compression apparel altered transmission of muscle afferent feedback within a limb. Thus, the purpose of Chapter 4 was to examine if sustained input to the skin (compression garment) modulates sensory feedback transmission in the upper limb. Using the Hoffmann (H-) reflex as a probe, the purpose of these experiments was to: 1) explore the effects of compression gear on sensory feedback transmission in the upper limb during a static task, and 2) if the task (locomotor vs. reaching) or phase of a movement differentially modulated this transmission of sensory information. Furthermore, differences in performance of the discrete reaching task were assessed to provide preliminary data on whether a compression garment can alter motor task performance. Results indicate that wearing a customized compression sleeve alters the excitability in a robust fashion within the central nervous system across conditioning
paradigms and multiple movement tasks. Interestingly, sensory feedback transmission was accompanied by improved accuracy of reaching movements and determination of movement endpoint which provides preliminary evidence of an improved performance while wearing a compression garment. Therefore, the compression sleeve appears to increase precision and sensitivity at the joint where the sleeve is applied. Compression apparel may assist as a type of “filter function” of tonic and non-specific mechanoreceptor information leading to increased precision and movement sensitivity around the joint where compression is applied.

Overall, these results address many fundamental questions which have previously limited effective translation of unilateral resistance training for rehabilitative interventions. These results provide preliminary guidelines for subsequent strength training interventions to prescribe the optimal ‘dose’ of unilateral strength training to maximize benefits while minimizing intervention burden. These studies also help refine a unifying model of unilateral strength training to include contributions from central motor output as well as afferent feedback. Ultimately, these studies highlight the importance of appropriate sensory feedback during maximal force production and the impact that sensory information from the skin can have on motor output in the nervous system.

5.1. Future Directions

The results of this dissertation point to a number of research inquires that would be valuable to resolve in order to advance their field of rehabilitation neuroscience. The following questions are of specific interest, to build from the present work and further understand the fundamental role that sensorimotor integration plays in ongoing movement.

- Is the adaptation to unilateral training specific to the total number of inputs that are provided to the nervous system?
- What is the threshold for inducing long term adaptation within the nervous system during resistance training?
- Will providing ‘enhanced’ sensory input that is initiated by muscle activation, and is scaled with contraction intensity, allow for greater strength increases in the untrained limb?
- Would providing a tactile input on the contralateral limb during unilateral strength training improve strength increases above training only?
- Is the alteration in global excitability with a compression sleeve due to increased discharge 
  rates of cutaneous mechanoreceptors during skin stretch?
- Would a compression sleeve improve performance accuracy during a repeatable motor task 
  such as a free throw, or dart throw?
- Can specific compression garments be designed to alter excitability at specific phases of 
  movement in order to unconsciously improve performance through improved ‘feel’?
- Does limb dominance impact the ability for individuals after stroke, SCI, MS to increase 
  bilateral strength with unilateral training?
5.2 References

