

Effects of remote movement and strength training on motor output: basic studies and application after stroke

by

Katherine L. Dragert
BSc., University of Victoria, 2004

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

DOCTOR OF PHILOSOPHY

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Supervisory Committee

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Supervisor

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Outside Member

Abstract

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Similar to quadrupedal animals, there is evidence in humans of interlimb signalling during upper and lower limb muscular activation. A product of these interconnections is modulation of motor output via remote neural input. Such remote communication can take several forms; for example, movement modifies activity between upper and lower limbs (e.g. arms to legs) and between a limb pair (e.g. one leg to the other). A specific form of modulation between homologous muscles bilaterally (i.e. the corresponding motor unit pool across the spinal cord) is also seen with strength training. However, details of these motor connections are not well known. Improved understanding of remote influences on motor output and coordination patterns may be valuable in an applied motor re-training setting. Abnormal excitability within reflex pathways of lower limb musculature is common among various neurological disorders. Thus, it is of interest whether remote inputs could be exploited to help normalize dysfunctional motor output. The primary goal of this thesis was to better our understanding of neural interlimb connections; specifically, to examine modulatory responses within the ankle flexor and extensor muscles induced by remote muscular activation associated with both rhythmic arm movement and contralateral resistance training. Further, the final objective of this

work was to apply these earlier observations in the context of a post-stroke rehabilitation paradigm, aimed at normalizing muscle activation patterns within the more-affected limb.

Initially, this thesis examined spinal reflex excitability within functional antagonists of the lower leg, the ankle flexors and extensor muscles, and the impact of transient, rhythmic movement on these neural networks.

Hoffmann (H-) reflexes were first used as a measurement probe. Rhythmic arm cycling significantly suppressed reflex amplitude in extensors, but revealed a bidirectional (i.e. either suppression or facilitation) reflex modulation in flexor muscles. Thus, differential regulation of ankle flexor and extensor H-reflex amplitudes was evidenced during rhythmic arm movement. This may stem from differences in locomotor pattern generator output to these groups as well as increased involvement of cortical drive to the flexors relative to the extensors during rhythmic movement. These results support the presence of interlimb neural coupling, such that remote motor action (arm movement) influences lumbar spinal cord excitability. Additionally, these descending signals impact ankle flexors and extensors differentially, which illustrates a method of producing facilitative modulation of ankle flexor motor responses.

Second, reciprocal inhibition (RI) was used to examine regulation of excitability between these same lower limb functional antagonists during rhythmic arm movement. Arm cycling significantly increased RI in ankle extensors, but had no effect in the flexors. This extends observation of remote motor activity-induced modulation on spinal excitability to

the core circuitry that comprises the interaction between functional agonist/antagonist pairs. Moreover, the asymmetry of this effect highlights differences in descending supraspinal inputs to ankle flexors vs. extensors, and may be related to functional dorsiflexion requirements during locomotion.

Subsequently, this thesis explored long term plasticity of interlimb neural modulation resulting from remote motor activation in the form of resistance training. Specifically, the within limb pair ‘cross-education’ phenomenon was investigated via unilateral isometric strength training of the ankle flexors.

The first of these training interventions was implemented in a cohort of neurologically intact subjects who performed five weeks of one-sided maximal isometric dorsiflexion training. H-reflex recruitment curves were used to probe for training-induced spinal plasticity within the agonist (flexor) and antagonist (extensor) muscles bilaterally. Post-intervention, dorsiflexor torque significantly increased in the trained and untrained limbs. Further, significant changes in H-reflex excitability were detected in the trained flexor (agonist) muscle and in both extensor (antagonist) muscles. These findings reveal that muscular crossed effects can be obtained in the ankle dorsiflexor muscles, and provide novel information on agonist and antagonist spinal adaptations that accompany unilateral training. They also suggest potential for application of remote motor activation (resistance training) to induce interlimb neural plasticity within a clinical context, such as improving one-sided weakness and/or motor dysfunction following neurotrauma.

The final training intervention was implemented in a chronic (>6mo post-infarct) stroke clinical group who completed six weeks of maximal isometric dorsiflexion training in the less-affected leg. Voluntary isometric strength (dorsiflexion torque, muscle activation), reciprocal inhibition (RI), walking ability and clinical function were used to quantify training effects. Post-intervention, dorsiflexion torque and maximal flexor muscle activation significantly increased in both the more-affected (untrained) and less-affected (trained) legs. Further, the relation between size of RI and level of muscle activation in the more-affected flexor muscle was significantly altered by training, and the Timed Up and Go clinical test was significantly improved. Thus, significant gains in voluntary strength, muscle activation and spinal excitability on the untrained, more-affected side after stroke can be invoked through training the opposite limb. This translates into small but observable functional improvements.

Taken together, the data in this thesis provide a basis for novel motor re-training approaches. Improved understanding has been gained of the similarities and differences between remote motor influences received by ankle flexor and extensor muscles in the lower leg. These observations culminate in the implementation of a novel post-stroke training paradigm, which shows that remote muscle activation, i.e. the cross-education effect, can induce strength and functional gains in the more-affected limb.

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Dedication

To Alex, who has supported, encouraged and loved me throughout this graduate student adventure. You have my heart. Let's raise a science-loving kid together.

And

To my father, Dr. Herb Dragert, who inspired me and instilled in me a passion for science. It's not geophysics... but we'll never butt heads in our published theories, so it's probably better this way.

1. General Introduction

Interlimb signalling between the arms and legs affects muscle activation in humans in a manner similar to the coordination of fore- and hindlimbs in quadrupedal animals (Dietz 2002; Dietz and Michel 2009; Rossignol et al. 2006; Wannier et al. 2001; Zehr 2004). A product of these interconnections is the modulation of motor control via remote neural input. Such remote communication can take several forms: between upper and lower limbs (e.g. arms to legs) (Zehr 2004); between a limb pair (e.g. one leg to the other) (Zehr 2004; Balter and Zehr 2007; Mezzarane et al. 2011); and between homologous muscles bilaterally (i.e. the same motor unit pool across the spinal cord) (Lee and Carroll 2007). It has been suggested that such remote inputs could be used in rehabilitation following neurotrauma (Dietz 2002; Dietz and Michel 2009; Wolpaw 2012; Zehr et al. 2009). For example, abnormal excitability of reflex pathways of the lower limb is common after stroke (Kreisel 2006), and includes ankle flexor muscle (dorsiflexion) weakness combined with hyperactive ankle extensor activity (Patten et al. 2004; Thompson et al. 2009).

It is of interest whether remote neural signalling could be used to help normalize muscle activation patterns and improve functional locomotor movements post-stroke. Investigations on rhythmic arm movement (Barzi and Zehr 2008) and the transfer of training effects across limbs, i.e. “cross-education” (Delwaide et al. 1988; Farthing et al. 2009) lend credence to the use of this retraining approach to improve dorsiflexor motor output. However, details of remote motor connections are not well understood. Work is first required to enhance understanding of inter- and intralimb signalling before these connections can be effectively applied in a rehabilitation setting. For example, while

various remote inputs have been studied in the Soleus (SOL) muscle, an ankle extensor, much less work has applied these same inputs to that muscle group's functional antagonist, the ankle flexor Tibialis Anterior (TA) muscle. Establishing a clear understanding of the motor output within and between these antagonists is needed to build a backdrop for post-stroke strength and gait retraining protocols.

The following literature review highlights concepts related to the application of remote motor activation in post-stroke dorsiflexor retraining. First, a brief summary will be given on evidence of spinal control of muscular coordination in humans. Leading from this will be discussion of the use of reflexes as neural probes to investigate these effects, including methodological considerations. Then, specific evidence of and mechanisms underlying two forms of remote motor inputs on ankle flexor / extensor motor output will be presented: between upper and lower limbs, i.e. rhythmic arm movement; and between homologous muscle groups, i.e. the cross-education effect. Finally, post-stroke motor dysfunction will be reviewed, with a focus on the lower leg. References to neurotrauma and motor retraining are given throughout this review, in an attempt to provide context for application of these concepts in rehabilitation.

1.1 Evidence of spinal communication and motor control in humans

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 and Duysens 2004; Zehr 2005). Depending on the motor activity, different neural circuitry may be involved; for example, locomotion can be triggered via descending commands from the motor cortex and brain stem, which activate spinal central pattern

generating (CPG) networks that control motor output in the arms and legs (Zehr and Duysens 2004). Afferent feedback signals are then sent to these higher spinal and supraspinal levels to regulate ongoing movement. This example illustrates a key role of afferent and efferent spinal circuits in production and maintenance of desired motor output. Indeed, there is widespread evidence in humans, albeit indirect in nature, of the essential involvement of spinal communication in motor control. Specifically, an extensive body of literature points to involvement of spinal reflexes in the support of motor coordination, both in terms of transient effects, e.g. movement generation and regulation (Dietz 2002; Dietz and Michel 2009; Zehr and Duysens 2004) as well as lasting adaptations, e.g. training-induced motor activity change (Aagaard 2003; Zehr 2006).

Evidence of the contribution of spinal communication to motor output has emerged from investigations of the impact of afferent feedback on locomotion. For example, work in infants has illustrated an innate ability to generate rhythmic locomotor activity, as well as modify that locomotor pattern via afferent receptor signalling, in the absence of a fully myelinated corticospinal tract (Pang and Yang 2000). Furthermore, investigation of the effect of cutaneous afferent feedback from the arm and leg on motor output during walking has shown modulation of muscle activation across all limbs as well as kinematic changes in the ankles with both types of input (Haridas and Zehr 2003). These observations have been corroborated by other works during similar rhythmic movements (Balter and Zehr 2007; Zehr and Haridas 2003; Zehr and Loadman 2012), with findings expanded to include observation of task and phase-dependence of such modulation (Lamont and Zehr 2007; Zehr et al. 2003). In addition to active movement

paradigms, reflex modulation can be induced through passive remote movement between a limb pair (Delwaide et al. 1988; Brooke et al. 1997; McIlroy et al. 1992). Moreover, similar observations have been made with involuntary remote muscle activation (Delwaide and Pepin 1991). Within a limb, modulation of spinal communication in the lower leg has also been demonstrated between functional antagonist pairs during walking (Petersen et al. 1999). More recently, interesting effects of spinal activation on leg motor output were shown in a clinical case study of a complete spinal cord injured (SCI) patient (Harkema et al. 2011). This patient received locomotor retraining that included epidural stimulation within the lower spine (L1-S1 cord segments). Post-intervention, the patient regained the ability to free-stand, as well as to generate locomotor-like muscle activation patterns when stimulation parameters were optimised for stepping (Harkema et al. 2011). Thus, both static and movement-related activation patterns were changed by direct stimulation of the involved spinal circuitry.

Taken together, these findings illustrate the involvement of spinal signals in production and adaptation of interlimb coordination. They also highlight the heavy contribution of reflexes to motor output, and point to the potential usefulness of reflexes when evaluating remote signalling effects.

1.2 Using spinal reflexes to probe for intra- and interlimb signalling effects

Across investigations of motor output, researchers inevitably must consider the ‘final common path’ of neural signalling; that is, integration at the level of spinal motoneurons (Sherrington 1906). Indeed, no matter the pathway explored, impact on motor control is seen when activation produces changes in motoneuronal excitability and

resulting muscle activation patterns (Pierrot-Deseilligny and Burke 2005). Thus, to evaluate inter- and intralimb spinal effects on motor output, change in muscle activation must be reliably assessed and quantified via reproducible methods. A number of spinal reflexes can function in this role. Their suitability for use as a measure of interlimb signalling effects will depend on the specific experimental question(s) of interest. In the evaluation of lower limb motor output (often assessed in ankle muscles), extensive work has utilized the Hoffmann reflex as a neural probe to assess the impact of local and remote rhythmic movement (Hundza and Zehr 2009; Frigon 2004; Schneider et al. 2000; Zehr et al. 2007a; Zehr et al. 2007b), as well as resistance training-induced plasticity (Aagaard et al. 2002; Fimland et al. 2009; Lagerquist et al. 2006a; Vila-Cha et al. 2012) on spinal cord excitability. Reciprocal inhibition has also been assessed in past investigations of antagonist-muscle activation during locomotion (Petersen et al. 1999; Capaday et al. 1990; Kido et al. 2004; Crone et al. 1987; Morita et al. 2001; Thompson et al. 2006) and resistance training (Geertsens et al. 2008). These two measures of spinal interneuronal excitability involve related but distinct pathways, and as such offer different insight into the mechanisms underlying motor coordination patterns. Detailed reviews of their methodology and interpretation have been described previously (Pierrot-Deseilligny and Burke 2005; Misiaszek 2003; Pierrot-Deseilligny and Mazevet 2000; Stein and Thompson 2006; Tucker et al. 2005; Zehr 2002). A brief summary for each is provided below.

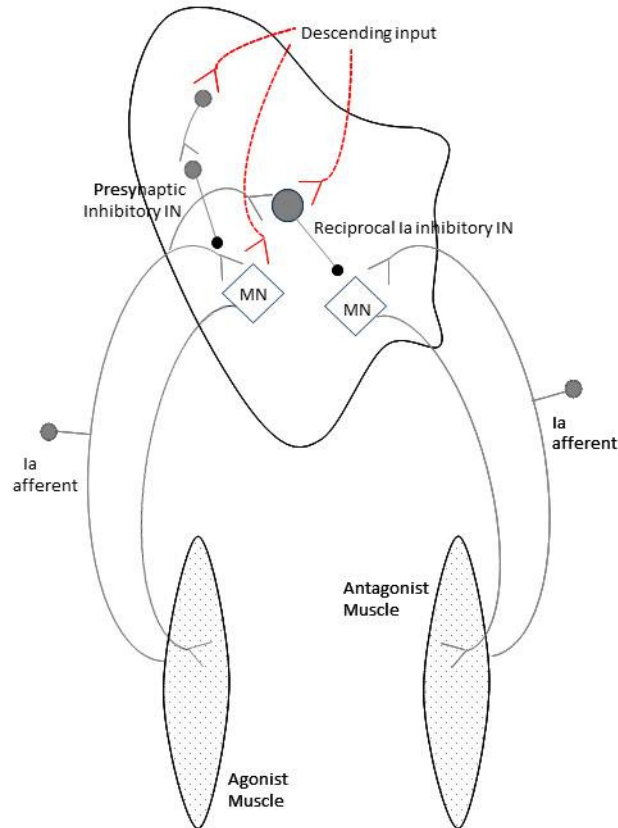


Figure 1.1: Simplified schematic illustrating the Ia afferent and Ia reciprocal inhibition neural pathways between a target muscle and the spinal cord. See text for description of each pathway's signalling. MN, motor neuron, or alpha-motoneuron.

1.2.1 Hoffmann reflex

The muscle afferent pathway that induces reflexive motor output in response to peripheral stimuli has been extensively studied, and helped form many early descriptions of 'simple' spinal reflexes (e.g. (Sherrington 1906)). This neural circuitry is characterized by a predominantly monosynaptic projection of group Ia afferents (innervating muscle spindle receptors) onto homonymous alpha-motoneurons within the spinal cord (Misiaszek 2003). These efferent axons then signal to the muscle via the neuromuscular junction. A simplified schematic of this spinal pathway is illustrated in Figure 1.1. The Hoffmann (H-) reflex is generated within this pathway via application of percutaneous

electrical stimulation to a mixed peripheral nerve containing both sensory (Ia afferent) and motor (alpha-motoneuron) axons (Misiaszek 2003; Zehr 2002; see Figure 1.1). The reflex bypasses the muscle spindle receptor, resulting in its characterization as the electrical analogue to the stretch reflex (Zehr 2002), and also providing the advantage of very precise quantification and application of particular stimulus intensities within an experimental paradigm.

The H-reflex itself is first generated at low stimulus intensities, whereby Ia afferents depolarize before the smaller diameter motor axons (Tucker et al. 2005; Zehr 2002). The resulting action potentials travel along the afferent axon from the point of stimulation to a monosynaptic connection with alpha-motoneurons. If the alpha-motoneuron pool receives adequate neurotransmitter release from this and other inputs to reach firing threshold, they will generate action potentials to depolarize the muscle fibres that they innervate (see Figure 1.1). This generates a population muscle action potential, i.e. an H-reflex, which appears in the EMG trace as a short-latency triphasic waveform (Zehr 2002), as illustrated in Figure 1.2. Increasing stimulus intensity increases H-reflex amplitude size, and builds what is referred to as a recruitment curve; it will also lead to depolarization of motor axons as well. Based on the short distance from site of stimulation to the neuromuscular junction, the motor axon's resulting muscular activation is visible as a second, shorter-latency waveform in the EMG trace, referred to as the motor (M-) wave (Tucker et al. 2005; Zehr 2002; see Figure 1.2). Both ortho- and antidromic signals are generated via electrical stimulation of a nerve (Tucker et al. 2005; Kudina and Pantseva 1988), and thus activation of the motor axon will also produce action potentials that 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, i.e. the H-wave, and obliterate activity within that axon. Thus, as stimulation intensity increases and more motor axons are directly activated, less Ia afferent activation is conducted to the muscle and H-reflex amplitude is reduced (Tucker et al. 2005). Overall, this generates an H-reflex recruitment curve that has an ascending and descending limb, whereas the M-wave recruitment curve has an ascending limb and then plateaus (Pierrot-Deseilligny and Burke 2005; Tucker et al. 2005; Zehr 2002).

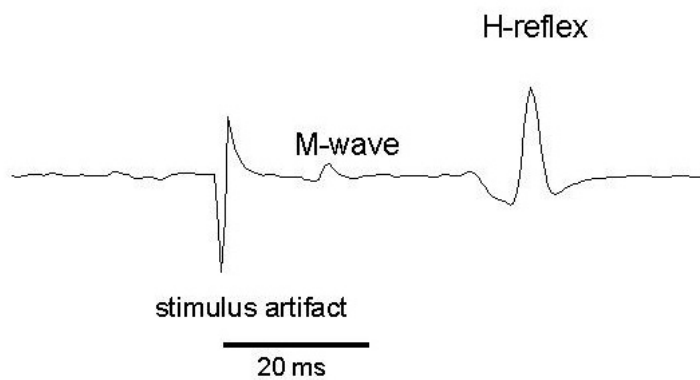


Figure 1.2: Example EMG trace containing H-reflex and M-wave responses triggered at one level of electrical stimulation intensity (used with permission from Zehr 2002).

There are several commonly used methods for the study of H-reflexes in motor control investigations. One involves recording H-reflex while maintaining a stable size of M-wave response, i.e. the stable M-wave method, which confirms that the same relative afferent input is compared between test conditions (Zehr 2002). Because of the orderly recruitment of motoneurons, H-reflex sensitivity to facilitation and inhibition depends on

the most recently activated motor axons by the test volley; that is, lower stimulation levels activate larger motor axons first, which have a high recruitment threshold into the H-reflex and thus do not interfere with H-reflex response (Pierrot-Deseilligny and Burke 2005; Pierrot-Deseilligny and Mazevet 2000). It is therefore important with the stable M-wave method that the chosen M-wave amplitude size is small, so that only large motor axons are activated and antidromic signalling has not begun to impact H-reflex size; i.e. H-reflex is on the ascending limb of its recruitment curve (Klimstra and Zehr 2008). This ensures that the reflex remains sensitive to the influences of conditioning. However, this requirement may also limit detection of conditioning effects in low or high threshold afferents, reflective of different motor unit populations and detected via measures such as H-reflex threshold and maximum. Indeed, these and other H-reflex measures taken from the ascending limb of the recruitment curve can be differentially modulated by the same remote motor input (Mezzarane et al. 2011; Zehr et al. 2007b; Klimstra and Zehr 2008). Thus, in the study of motor coordination it may be valuable to employ an H-reflex methodology with broader scope.

The second method used to study H-reflex is where the reflex is evoked at multiple stimulus intensities throughout a trial. H- and M-wave peak-to-peak amplitudes are then measured offline and plotted to produce a quantified recruitment curve. Plotting of H-reflex recruitment curves may be relative to the corresponding M-wave amplitude (i.e. H/M recruitment curve (Barzi and Zehr 2008)) or to stimulation current (Mezzarane et al. 2011; Zehr et al. 2007a; Zehr et al. 2007b; Klimstra and Zehr 2008), with the latter approach shown to be more reliable at the foot and plateau of the ascending limb of the curve (Klimstra and 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 and 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 (H_{\max}), 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 H_{\max} from a static condition is applied to the recruitment curve generated during a movement condition, and corresponding H-reflex amplitude size at that 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 (Mezzarane et al. 2011; Zehr et al. 2007a; Zehr et al. 2007b; Klimstra and Zehr 2008).

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). Neural signaling that elicits PSI may reduce the H-reflex recorded from that muscle, but EMG level will remain constant. Thus, PSI alters afferent transmissions without affecting the postsynaptic membrane potential (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 2003; Zehr 2006; Lagerquist et al. 2006b). Further, suppression of SOL H-reflex amplitude is induced via rhythmic arm movement and is also ascribed to descending effects on Ia afferent PSI (Mezzarane et al. 2011; Frigon 2004; de Ruyter et al. 2010; Loadman and Zehr 2007).

1.2.2 Reciprocal inhibition

Motor coordination across a joint requires organization of neural signalling between the involved musculature, originally described by Sherrington as reciprocal innervation (Sherrington 1913). Under this principle, a neural signal that has an excitatory or inhibitory influence on an alpha-motoneuronal pool also signals corresponding inhibition or excitation, respectively, to the antagonistic alpha-motoneuronal pool (Schade and Ford 1965). An example of this principle is reciprocal inhibition (RI), where motor afferent excitation in one muscle, such as a flexor, results in inhibition of the functional antagonist muscle, i.e. extensor (Stein and Thompson 2006). A simplified schematic of the RI spinal pathway is shown in Figure 1.1. The inhibitory signal is transferred via the Ia inhibitory interneuron, which receives inputs from various spinal sources and descending pathways (Kandel et al. 2000). Of these inputs, RI is strongly activated by group Ia afferent fibres that synapse directly onto the Ia inhibitory interneuron (Stein and Thompson 2006). As this RI can be mediated by only a single interneuron, its resulting inhibition has a short response latency and is considered disynaptic (Capaday et al. 1990; Kido et al. 2004; Stein and Thompson 2006).

There are two accepted methodological approaches for studying short-latency RI in motor control. One method involves pairing stimuli to two peripheral nerves in order to activate group I muscle afferents that innervate functional antagonists; these stimuli are timed so that one acts as a conditioning stimulus to suppress H-reflex amplitude in the opposing muscle group (Petersen et al. 1999; Crone et al. 1987; Stein and Thompson 2006). An example of this is stimulating the tibial and common peroneal (CP) nerves, which innervate the SOL and TA muscle antagonist pair, respectively. Tibial nerve stimulation intensity is set to evoke an H-reflex and M-wave in the SOL muscle. Activating the CP nerve slightly before (i.e. 2-4ms (Petersen et al. 1998)) the tibial nerve allows time for Ia afferent impulses to conduct to the spinal cord and excite the interneurons to inhibit SOL motor neurons. The result is reduced SOL H-reflex amplitude in the presence of the RI conditioning stimulus (Geertsen et al. 2008; Stein and Thompson 2006).

A second method to study short-latency RI involves measurement of the depression of ongoing voluntary muscle activity (Thompson et al. 2009; Capaday et al. 1990; Kido et al. 2004; Stein and Thompson 2006). With this method, a mixed nerve is stimulated and then EMG activation patterns in the functional antagonist muscle are monitored for depressed amplitude. For example, to observe RI in the SOL muscle the motor nerve innervating the TA muscle (i.e. CP nerve) is stimulated. Stimulation intensity is set at or around the M-wave or motor threshold (MT) for TA, while a steady contraction level is maintained in SOL. Given the disynaptic nature of the RI pathway, inhibition appears in the rectified SOL EMG trace following appearance of the monosynaptic TA H-reflex, at ~55ms post-stimulus (Kido et al. 2004). Duration of

suppression is similar to a brief synaptic current (~10ms) (Capaday et al. 1990; Kido et al. 2004; Stein and Thompson 2006; Turker and Powers 2005).

Though employed by many researchers, concerns have been raised over limitations related to the conditioned H-reflex RI method, specifically for its use in the study of inhibitory responses during voluntary activity. First, this method is traditionally measured at rest (e.g. (Crone et al. 1987)), as responses vary depending on level of contraction (Stein and Thompson 2006). Therefore, its use is generally limited to stationary tasks and in the few muscles where H-reflex can be evoked at rest (Pierrot-Deseilligny and Burke 2005; Stein and Thompson 2006; Zehr 2002). Further, while the voluntary contraction RI method varies directly with level of conditioning stimulation (Capaday et al. 1990; Kido et al. 2004; Stein and Thompson 2006), the conditioned H-reflex method does not, nor does it produce consistent suppression at higher stimulation levels ($>1.2 \times MT$) (Crone et al. 1987; Stein and Thompson 2006). Indeed, size of RI with this method varies depending on level of stimulation within two muscle groups, i.e. intensity of both conditioning stimulus and the stimulus used to evoke the target H-reflex. Further, response is dependent on the time interval between these two stimuli (Crone et al. 1987; Stein and Thompson 2006). Thus, these considerations must be attended to and controlled for when employing the conditioned H-reflex RI method to ensure reliable outcomes. The alternative voluntary contraction RI method may be a simpler and more appropriate protocol for use in voluntary muscle activity and movement studies. This may be especially true for investigations of neurological disorders, where additional challenges in maintaining the above described experimental controls are commonplace.

1.3 Effects of remote input on segmental motor output I. Between upper and lower limbs

In the context of remote motor effects, a specific area of interest lies in the spinal communication that occurs from arms to legs and vice versa. This is particularly true in the context of utilizing arm movement to enhance leg muscle activity, i.e. use of an arm or combined arm/leg cycle ergometer (see Figure 1.3), where the potential applications to locomotor retraining are recognized and supported by experimental evidence (Zehr et al. 2009; Ferris et al. 2006). However, for fruitful implementation of such a paradigm, further detail must be ascertained on certain aspects of this interlimb communication, including the intricacies of remote modulatory effects within different lower leg muscles. Still, the potential of such effects in a rehabilitation setting highlight the need for further investigations of this sort of remote motor input to be undertaken.



Figure 1.3: Example of an arm/leg cycle ergometer. This model allows for combined arms and leg cycling (in a coupled fashion), or independent limb pair movement, i.e. arm or leg cycling alone.

1.3.1 Descending effects of rhythmic arm movement on excitability of leg muscles

Effects of rhythmic arm movement on motor output in the lower limb have been demonstrated in various ways in the literature. For example, H-reflexes have been used to assess modulation of signalling received by the motoneuron pool. A number of studies have monitored SOL H-reflex, and observed reflex suppression in the presence of rhythmic arm cycling (Barzi and Zehr 2008; Zehr et al. 2007a; de Ruyter et al. 2010; Loadman and Zehr 2007; Frigon et al. 2007). Interestingly, short-term plasticity has been associated with this effect, such that reflex amplitude is reduced for up to 20 minutes following cessation of 30 minutes of rhythmic arm movement (Javan and Zehr 2008). Also of importance is the observation that arm cycling-related SOL H-reflex suppression persists in both legs following stroke, albeit to a lesser extent (Barzi and Zehr 2008). In this case the conditioning effects appeared to be biased towards the largest motor unit amplitudes as seen only in the largest H-reflexes. Investigations employing combinations of arm and leg movement have further confirmed the suppressive effect of rhythmic arm activity on SOL H-reflex and that these effects can be differentially specified based on motor unit size (Mezzarane et al. 2011). Yet a shortcoming of this body of evidence is the limitation of findings to the SOL muscle; that is, generalizability of the effects of rhythmic arm movement on H-reflex excitability within the lower leg musculature has not been confirmed. The TA muscle, an ankle flexor and the SOL muscle's functional antagonist, is of specific interest, given its role in locomotion. This is particularly true from a rehabilitation perspective, with ankle flexor activation patterns commonly altered following neurotrauma (Patten et al. 2004).

Some insight may be gained on responses in ankle flexor muscles from work that has studied effects of arm movement on lower leg cutaneous reflexes. One study

employed arm/leg cycling, and observed that cutaneous reflexes in many leg muscles, including TA, were significantly modulated by arm movement when combined with local leg movement (Balter and Zehr 2007). While their findings contradicted previous observations (Sakamoto et al. 2006), the authors suggested that the discrepancy was due to their own use of more detailed analytical procedures, as well as the presence of a mechanical linkage between the arm and leg ergometer used in their methods (Balter and Zehr 2007; see Figure 1.3) vs. previous work where arms and leg pairs cycled independently (Sakamoto et al. 2006). Indeed, similar modulatory effects of arm movement on cutaneous reflexes in the legs have since been observed during combined arm/leg recumbent stepping to reinforce these findings (Zehr et al. 2007). However, while providing further general evidence for influence of arm movement on the legs, one must bear in mind that cutaneous and H-reflexes may be modulated by different mechanisms during locomotor-like movements (Zehr et al. 2001). Specifically, modulation of H-reflex amplitude has been suggested to stem from a complex interaction between central drive and peripheral feedback, whereas cutaneous reflexes are likely governed by central influences of either the brain or spinal cord (Zehr et al. 2001).

Other evidence of modulatory arm movement effects has emerged from studies that have limited their observations to lower leg EMG recordings (Huang and Ferris 2004; Kao and Ferris 2005; Kawashima et al. 2008). As briefly touched on above (see Hoffmann Reflex), EMG is a measure of muscle activation produced by multiple spinal and supraspinal influences. Thus, EMG alone cannot definitively speak to the origin of an observed effect. Still, the support these studies provide for the presence of interlimb communication is of interest. For example, during combined arm/leg recumbent stepping,

active arm movement has been found to significantly increase activation in a number of leg muscles, including TA and SOL (Huang and Ferris 2004). Another study applied rhythmic arm swing during gait retraining in incomplete cervical SCI patients (Kawashima et al. 2008). Arm swing significantly altered SOL activation during rhythmic leg movement, to better emulate stereotypical patterns normally seen during different walking phases. Further, these effects were observed during both passive and active conditions, leading the authors to suggest that spinal input from upper limb movement played a significant role in shaping SOL motor output (Kawashima et al. 2008).

Another shortcoming in the remote arm movement literature is a lack of study on intralimb signalling in the legs. Of interest is RI communication between functional antagonist pairs such as the ankle flexor and extensor muscles, and whether rhythmic arm movement modulates these signals. Work has been done to investigate local limb movement effects, including walking and running, on ankle flexor/extensor disynaptic RI response (Petersen et al. 1999; Kido et al. 2004; Morita et al. 2001). However, to date the impact of remote rhythmic arm movement on lower leg RI is unknown. Further work in this area is warranted and may reveal novel information on ways that arm movement affects a core spinal circuitry of locomotion.

1.3.2 Mechanisms of remote arm movement effects

It is often challenging in a human model to definitively attribute observed effects to specific spinal mechanisms, due to an inability to collect direct measures of neural activity. However, the sum of many indirect observations, combined with some elegant

methodologies, have provided for the development of strong theories on the mechanisms that underlie remote arm movement-induced modulation.

First, on a broad scale, the reflexive muscle activation seen during both rhythmic arm and leg movement has been attributed to spinal CPG networks (Zehr and Duysens 2004). These networks are comprised of oscillating neural circuitry, i.e. half-centres: one half for flexor motor unit activation, one half for extensor activation, to form what is referred to as the half-centre model (Zehr and Duysens 2004; Brown 1911). These CPG networks allow for alternating flexor and extensor motor activation and inhibition as needed during rhythmic movement. Once activated, they are capable of sustained and independent output and as previously described have been observed to be modulated by afferent feedback (Pang and Yang 2000; Harkema et al. 2011). Indeed, each limb's CPG has afferent feedback loops that support changes between phases of movement, e.g. swing to stance while walking (Zehr and Duysens 2004). Transitions are further reinforced by linkages between and within limb pairs (Dietz 2002; Zehr 2005), such that activity of a flexor centre in one leg inhibits activity in the contralateral leg's flexor centre (Zehr and Duysens 2004). Thus, discussion of mechanisms underlying reflex modulation during arm movement should be superimposed over this basic feature of movement-related spinal signalling.

As previously described, the ascending limb of the H-reflex recruitment curve has been suggested to reflect spinal excitability within a motoneuron pool (Zehr 2002). Rhythmic arm cycling has been consistently observed to induce SOL H-reflex suppression, with many reports attributing the change to increased activation of the Ia presynaptic inhibitory interneuron (Zehr et al. 2007a; Zehr 2002). Such a mechanism has

been well evidenced in a sophisticated paradigm employed by Frigon et al. (2004). In this work SOL H-reflex was monitored during rhythmic arm cycling, both in the presence and absence of cutaneous conditioning stimuli in the same leg. SOL H-reflex was suppressed in the presence of arm cycling, while cutaneous reflex response itself remained unchanged. From this finding, it was concluded that movement-induced change in H-reflex amplitude was not due to changes in motoneuron excitability, such that modulation occurs at a pre-motoneuronal level. Thus, the authors suggested that arm movement increases PSI of the Ia afferent volley (Frigon 2004).

It is important to note that such signalling may differ depending on the muscle group tested. For example, a disparity in cortical influence on motor output during movement has been observed between ankle flexor and extensor muscles (Bawa et al. 2002; Capaday et al. 1999; Schubert et al. 1997). Specifically, cortico-motoneuronal connections to the TA motoneuron pool have been observed to be strong, while similar connections to the SOL are weaker (Bawa et al. 2002). This could translate into variation in descending influences on PSI received by TA Ia afferents. However, to date no work has evaluated the impact of rhythmic arm movement on TA H-reflex response. It is also of interest to consider whether similar descending effects of arm movement on PSI impact intralimb signalling, specifically disynaptic RI, between the ankle flexor and extensor muscles. The Ia inhibitory interneuron receives multiple descending inputs, including signals from the propriospinal tract (Lindstrom 1973), which has been suggested as a potential pathway for arm cycling-related PSI onto the SOL Ia afferent (Frigon 2004). No work has evaluated arm movement effects on leg RI response; however, the effect of unilateral arm movement on RI in the contralateral limb has been

studied (Delwaide et al. 1988). Both active and passive movement were found to increase the degree of contralateral RI, suggesting a direct effect of remote movement on Ia interneurons, likely from contralateral group I afferents (Delwaide et al. 1988).

1.3.3 Functional applications of remote rhythmic arm movement

The potential for utilization of remote movement in a functional context has not gone unnoticed, with many researchers suggesting that rhythmic arm movement may enhance lower limb muscle activation during neurological rehabilitation (Dietz 2002; Zehr et al. 2009; Ferris et al. 2006). This influence will likely be maximized when incorporated into combined arm and leg movement (Zehr et al. 2009; Ferris et al. 2006), though application of rhythmic arm movement alone in a clinical setting may also have value (Barzi and Zehr 2008).

Initial reports of arm movement paradigms in practice come from case studies that describe locomotor retraining after SCI (Behrman and Harkema 2000). This work evaluated the common use of arms for postural and weight-bearing activity in walking therapy, and compared that to reciprocating arm swing as seen with normal walking. The latter was reported to facilitate stepping, leading to the suggestion that arm swing is a significant component in improving motor output of the legs during walking (Behrman and Harkema 2000). More recent work has evaluated the impact of arm swing on gait EMG patterns in incomplete SCI (Kawashima et al. 2008). As described earlier, their findings show that neural signalling related to remote arm movement can improve motor output patterns in the legs (Kawashima et al. 2008).

Also described above, it is worth noting that lower leg reflex modulation induced by rhythmic arm cycling alone has been observed post-stroke, and persists despite the presence of exaggerated reflex amplitude in the more-affected leg (Barzi and Zehr 2008). Such hyperexcitability is typical post-stroke (Kreisel 2006; Thompson et al. 2009; Faist et al. 1994), and thus the suppressive effect of arm cycling here may have direct functional applications in post-stroke motor retraining (Barzi and Zehr 2008), even in the absence of combined leg movement.

1.4 Remote input effect on motor output II. Between homologous muscle groups

The signalling between homologous muscle groups within a limb pair is a long-recognized remote motor effect that in recent years has received considerable attention. The phenomenon, termed “cross-education”, occurs when targeted muscular activation and/or action in one limb results in motor output adaptation not only in the trained limb, but also in the same muscle of the untrained limb (Lee and Carroll 2007; Carroll et al. 2006; Scripture et al. 1894; Zhou 2000). The effect was first reported in the 19th century (Scripture et al. 1894), and more recently has been evaluated in earnest to uncover its breadth of action and underlying neural mechanisms. Great potential lies in the functional application of this type of interlimb communication to rehabilitation settings, such as in situations of unilateral limb immobilization (Farthing et al. 2009), as well as clinical conditions of one-sided weakness, such as foot drop during locomotion. However, further work is required before such clinical paradigms can be implemented. This includes dissemination of the effect in muscle groups relevant to the task of interest, such as ankle flexor and extensor muscles for walking.

Given this literature review's focus on spinal communication, the following discussion is limited in its address of supraspinal influences on the cross-education effect. Detailed reviews of potential supraspinal signalling mechanisms can be found elsewhere (Carroll et al. 2006; Farthing 2009; Hortobagyi 2005). Also, effects induced via resistance training are the main point of discussion here, though some key findings on transient movement-induced neural adaptations are also highlighted.

1.4.1 Evidence of cross-education

The presence of neural cross-transfer between homologous muscle groups has been assessed in different ways in the literature. The majority of research has explored lasting changes in motor output following targeted training of a muscle, i.e. strength gains, and thus "cross-education" has come to be defined under these terms. These resistance training studies have revealed common characteristics of the phenomenon. First, crossed strength gains produced via unilateral resistance training have been observed in multiple muscle groups of the upper and lower limbs (Carroll et al. 2006; Munn et al. 2004), with the elbow flexors and knee extensors most frequently tested. The relative increase in contralateral force output is less than that observed in the trained limb: a recent meta-analysis (Carroll et al. 2006) reported an average increase of 7.6% of initial strength in the untrained limb, which translates to an increase in contralateral strength that is ~52% of the ipsilateral training effect. This change has been interpreted as a small but robust increase in strength (Carroll et al. 2006). It is important to note that these are pooled estimates, and thus may underestimate the size of contralateral strength gains when different methods are employed. For example, while crossed effects are

induced irrespective of contraction type performed (Lee and Carroll 2007; Carroll et al. 2006; Zhou 2000), greater gains have been observed with eccentric contraction (Hortobagyi et al. 1997). Furthermore, recent work has shown an effect asymmetry based on limb dominance, such that greater contralateral strength gains are realized when the dominant arm is trained vs. the non-dominant arm (Farthing 2009; Farthing 2005). While such asymmetry has only been investigated in the upper limb, the findings highlight an additional consideration when interpreting experimental results.

Further characteristics of the cross-education effect are that strength increases occur in the untrained limb prior to significant muscle morphology change (Farthing 2005; Narici et al. 1989), and also in the absence of contralateral muscle activation during unilateral exercise (Farthing 2005). Moreover, maximal muscle activation detected via EMG recordings has been reported to increase within the untrained muscle in conjunction with increased force output (Fimland et al. 2009; Narici et al. 1989). Strength gains are also consistently reported to be confined to the homologous muscle of the untrained limb, with increases maximized during execution of the same movement/task that was performed in the trained limb (Lee and Carroll 2007). Such specificity of training, together with the other features of the effect just described, provide strong support for an underlying neural mechanism. Indeed, the involvement of neural signalling is highlighted by observations that even imagined unilateral training induces significant strength gains bilaterally (Yue and Cole 1992). Thus, the neural adaptations associated with cross-education are of interest. More recent studies have attempted to monitor cortical (Farthing et al. 2011; Hortobagyi et al. 2011; Lee et al. 2009), corticospinal (Carroll et al. 2008) and/or spinal changes associated with the cross-education effect (Fimland et al.

2009; Lagerquist et al. 2006b), and reveal further information on potential mechanisms that underlie it (see Mechanisms).

Finally, observations on the cross-education phenomenon have been recently expanded beyond standard strength gains to also include attenuation of strength loss associated with immobilization (Farthing et al. 2009; Farthing et al. 2011). In this work, the non-dominant arm was casted and the dominant arm was trained. While controls experienced significant decline in strength in their casted arm, those that completed uncasted arm training had no change in strength in the casted arm (Farthing et al. 2009). These are the first published reports to illustrate direct application of the cross-education effect in a clinical setting.

1.4.2 Mechanisms underlying the cross-education effect

A number of candidate mechanisms have been presented in the literature that may wholly or in-part underlie the cross-education effect. A major challenge in determining the nature and loci of adaptation has been a lack of quantitative neural measurement in much of the work in this field. Fortunately, many recent reports have begun to include such measures as part of their investigations, with some addressing spinal pathways that expand our understanding of motor input/output properties within the lower leg.

Currently, potential mechanisms can be grouped into two broad categories: adaptation of the neural signals that are related to motor drive; and adaptation of signalling related to motor planning and execution (Carroll et al. 2006). The latter, i.e. supraspinal changes within various motor planning areas of the brain, have been tied to work on motor learning and skill acquisition (Lee and Carroll 2007). As stated earlier, this review's

interest lies in spinal adaptation associated with remote motor activity. Thus, details of potential supraspinal mechanisms related to motor planning, i.e. signals upstream of the motor cortex, will not be presently expanded on, but can be found elsewhere (e.g. (Farthing 2009; Hortobagyi 2005)). When considering the first category of mechanism(s), the prevailing supposition is that there is re-organization within contralateral motor pathways that improves efficiency of neural drive to the untrained muscle group (Lee and Carroll 2007). This principle is supported by findings of both transient changes in spinal and cortical motor excitability during unilateral contraction (Delwaide et al. 1988; Hortobagyi 2003), as well as lasting adaptation in spinal and cortical signals following unilateral resistance training (Fimland et al. 2009; Lagerquist et al. 2006b; Farthing et al. 2011; Hortobagyi et al. 2011; Lee et al. 2009; Carroll et al. 2008).

Studies evaluating higher level motor drive as part of the resistance trained cross-education effect have employed measures of cortical and corticospinal excitability that include transcranial magnetic stimulation (TMS) (Carroll et al. 2008) and functional magnetic resonance imaging (fMRI) (Farthing et al. 2011). TMS methods reveal that unilateral ballistic movement training in the index finger increases motor cortex excitability bilaterally, as reflected via increased size of motor evoked potentials (MEPs) within EMG traces in the trained and untrained first dorsal interossei muscles (Carroll et al. 2008). fMRI techniques also demonstrate cortical involvement in crossed strength gains: this is evidenced by increased blood volume in the motor cortex associated with activation of the untrained hand following unilateral isometric handgrip training (Farthing et al. 2011). These results imply that a lasting increase in descending drive from the motor cortex can lead to increased force output within the untrained, homologous muscle

group. This proposed mechanism is also supported by modulatory effects seen during transient unilateral movement (Hortobagyi 2003). For example, it has been shown that one sided wrist flexion increases MEPs contralaterally, while cervicomedullary MEPs (CMEPs) remain unchanged. CMEPs are evoked via stimulation of the mastoid processes to activate axons in the corticospinal tract, and provide a measure of corticospinal (i.e. upper and lower motoneuron) excitability (Hortobagyi 2003; Petersen et al. 2002). Therefore, these findings support the presence of increased excitability that originates from cortical networks and not the corticospinal tract (Hortobagyi 2003).

Still, when considering cortical mechanisms as suggested by these works, it is important to note that evidence is limited to observations in small, distal muscles in the hand. Differences in cortical control and regulation of motor output have been noted previously between the distal and proximal muscle groups in the arms, and suggested to be related to differences in voluntary movement requirements, i.e. fine dexterity vs. gross movements (Petersen et al. 2003). Based on the functional movement requirements of the upper vs. lower limbs, e.g. fine dexterity and voluntary control for the hands and arms, vs. gross, generally involuntary movement needs within the ankles and legs, such differences in cortical excitation may be present between the limb pairs as well (Kandel et al. 2000). This rationale is bolstered by observed differences in the relative cortical area devoted to motor output to hands vs. feet and arms vs. legs (Penfield and Rasmussen 1950). Thus, it is unclear whether similar levels of cortical adaptation are present following unilateral training of a lower leg muscle, such as the ankle flexors or extensors, where spinal regulation may play a larger role in resulting motor output.

To assess involvement of spinal regulation, SOL H-reflex has been monitored during unilateral resistance training of the ankle flexors (Lagerquist et al. 2006b). While plantarflexor force output increased bilaterally following training, changes in spinal excitability were asymmetrical. Specifically, increased H-reflex amplitude was observed on the trained side, similar to other strength training reports (Aagaard et al. 2002; Holtermann et al. 2007), but no change was seen on the untrained side (Lagerquist et al. 2006b). Agonist H-reflex modulation is suggested to stem from increased alpha-motoneuron pool excitability as well as reduced PSI of the Ia afferent, due to modified signalling from descending projections to both of these sites within the pathway (Aagaard 2003; Zehr 2006; Aagaard et al. 2002; Lagerquist et al. 2006b). Given that no H-reflex amplitude change was observed on the untrained side, the authors concluded that contralateral strength gains associated with the cross-education effect differ in their origin from the trained side, and instead result from supraspinal change (Lagerquist et al. 2006b).

However, it is important to note limitations in the H-reflex methodology implemented for this work. First, though recruitment curves were collected, they were produced relative to M-wave (i.e. H/M recruitment curves). Further, only two H-reflex variables were reported from those curves, which were reflex amplitude at ~5% of M_{\max} (termed H_A) and H_{\max} . As previously discussed, H/M curves may lack reliability at the foot (i.e. threshold) and plateau (i.e. maximum amplitude) of the ascending limb of the curve (Klimstra and Zehr 2008). Indeed, only H_A (comprised of smaller motor units) was observed to increase on the trained side post-intervention, and not H_{\max} (Lagerquist et al. 2006b). This highlights a second limitation previously mentioned, which is that H-

reflexes evoked at fixed stimulus intensities only reflect excitability within a particular set of motor units (Klimstra and Zehr 2008). Thus, the question remains whether subtle contralateral spinal changes tied to the cross-education effect occur in populations of motor units not tested here, which might be revealed if additional points within the recruitment curve were assessed (Klimstra and Zehr 2008; Buchthal and Schmalbruch 1970). To date, these broader methods have not been implemented in a cross-education training paradigm. Furthermore, similar to almost all lower limb strength training studies to date (Carroll et al. 2011), investigations of cross-education that include H-reflex methods are limited to the SOL muscle (Fimland et al. 2009; Lagerquist et al. 2006b). It is therefore unknown whether contralateral H-reflex modulation would be detected in other muscle groups, such as the TA.

This leads the discussion of mechanisms to another area in the literature that is lacking, and that is the assessment of spinal excitability within muscle groups that oppose a strength trained movement. While agonist muscle H-reflex has been assessed, evaluation of spinal reflex modulation within the functional antagonist to a trained movement has been limited to one investigation (Geertsens et al. 2008). This study evaluated SOL RI following explosive dorsiflexor strength training, and observed increased RI (exhibited via suppressed SOL H-reflex). Similar changes in spinal signalling may contribute to the cross-education effect. For example, increased SOL muscle activation and plantarflexor force output on the untrained side may in part be a product of reduced RI to that muscle, and/or increased RI to the TA muscle, its functional antagonist (Lee and Carroll 2007). To date, disynaptic RI has not been used to probe for spinal modulation in a cross-education training paradigm. However, it has been evaluated

during both rhythmic unilateral arm movement (Delwaide et al. 1988) and unilateral muscle activation via electrical stimulation in the arms (Delwaide and Pepin 1991). Both of these studies observed RI modulation within the contralateral homologous muscle groups, and suggest that group I afferent signaling in the active limb crosses the midline of the spinal cord to change excitability within contralateral Ia inhibitory interneurons (Delwaide et al. 1988; Delwaide and Pepin 1991). Whether such spinal adaptations are present following unilateral resistance training remains to be seen.

1.4.3 Functional applications of cross-education

The present body of literature on the cross-education phenomenon points to a potential for its use in applied settings, specifically as part of rehabilitation for patients suffering conditions that prevent them from exercising one limb (Lee and Carroll 2007; Farthing 2009). For example, one-sided weakness, or hemiparesis, is common following neurotrauma such as stroke (Patten et al. 2004). Additionally, acute conditions may arise in a neurologically intact population that require limb immobilization for an extended period of time, such as casting of the extremities.

Still, the relatively small size of the induced contralateral effect has brought into question whether such adaptation will be clinically significant and/or functionally useful (Carroll et al. 2006). Further research in relevant clinical groups is therefore needed to determine efficacy of the effect in motor rehabilitation. To date, no such work has been completed in any clinical population suffering from hemiparesis. However, as described above, recent studies have explored effects in a casted upper limb (Farthing et al. 2009; Farthing et al. 2011). These works demonstrated attenuation of strength loss in the casted

arm following resistance training in the uncasted arm. Given the anticipated strength loss associated with limb disuse (Hortobagyi et al. 2000), as well as the time and effort involved with regaining that strength, this observed capacity to diminish losses pre- to post-immobilization shows great promise. However, findings are currently limited to the wrist only. Whether these same effects can be generalized to other muscles, such as more proximal groups within the arm or the ankle flexor/extensor muscles in the lower leg, is unknown and requires further study.

A final consideration in the discussion of functional applications of the cross-education effect returns to the description of mechanisms provided above; namely, that the true underlying mechanisms of these remote strength gains have not been clearly delineated. Thus, it is difficult to distinguish the effect's specific role(s) in exercise rehabilitation (Lee and Carroll 2007). For therapeutic benefits to be maximized, it is crucial that further research is employed, especially in the lower limbs, to improve understanding of the neural signalling involved in this adaptation (Lee and Carroll 2007; Farthing 2009).

1.5 Post-stroke motor dysfunction

Stroke is generally defined as neuronal damage secondary to the interruption of blood flow to some part of the brain, commonly due to a lesion, blood clot or rupture (Eng 2004; Zehr 2011). Following a stroke, neuronal damage leads to a loss of input to motoneurons on the side of the body opposite to the ischemic attack (Patten et al. 2004), as well as altered intra-cortical communication (Murase 2004). Depending on the location and size of the post-stroke infarct, severity of resulting motor deficits will vary (Kreisel

2006). In any case, the end result is impaired motor function that is typically further manifested on one side of the body, with the terms ‘more-’ and ‘less-affected’ side commonly used in the literature (Patten et al. 2004; Barzi and Zehr 2008; Zehr and Loadman 2012; Zehr 2011).

A primary aim of post-stroke rehabilitation is restoration of motor output needed to complete functional tasks of daily living. Control of muscular force production is crucial to performance of these tasks (Patten et al. 2004). Such control is compromised in stroke due to changes in descending regulation of interneuronal and motoneuronal excitability, producing symptoms such as unilateral weakness, hyperreflexia and spasticity (Patten et al. 2004). Thus, to achieve the goal of motor rehabilitation, it is first necessary to delineate the symptoms and underlying loci of post-stroke motor dysfunction. Level of dysfunction must then be accurately quantified, to assess the efficacy of a particular motor retraining strategy as well as to cater the program so that it addresses the deficits present (Duncan et al. 2005). To achieve full restoration of function, it is also essential that novel rehabilitation approaches be explored, as current methods are not effective for many. In the context of remote neural signalling, there are several approaches that await investigation in a post-stroke setting.

1.5.1 Evidence and underlying mechanisms of post-stroke motor dysfunction

The following section outlines dysfunctional motor characteristics that are common following stroke and have been evidenced in the literature.

First, paresis is defined as weakness of contraction and movement, which is due to difficulty or inability to voluntarily recruit motor units to generate torque (Patten et al.

2004; Gracies 2005a; Krakauer 2005). A general descriptor for these symptoms often used in the literature is 'post-stroke weakness' (Patten et al. 2004; Eng 2004; Zehr 2011); this terminology will be employed here so that 'weakness' and '(hemi-) paresis' are used interchangeably. Post-stroke weakness is more evident on one side, has been reported across a number of muscles, and is suggested to be more evident in distal vs. proximal groups (Patten et al. 2004; Eng 2004). Level of weakness can vary; for example, lower leg muscle strength in the more-affected side has been reported to range between 23 and 94% of the less-affected side (Adams et al. 1990). Recent work observed maximal voluntary torques in the plantar- and dorsiflexors on the more-affected side that were 55% and 38%, respectively, of the less-affected side (Barzi and Zehr 2008). Such lower leg weakness will impair many functional tasks of daily living, including walking and moving from sitting to standing (Zehr and Loadman 2012; Zehr 2011; Morris et al. 2004).

While muscular weakness could be attributed to muscle-level morphological changes in theory, no evidence of such change is apparent immediately following stroke (Patten et al. 2004; Gracies 2005a). Instead, neural components of muscular control at the motor unit level are suggested as underlying mechanisms. Specifically, neural alteration at multiple sites is the likely cause of inadequate motor unit recruitment and weak muscle contraction. Cortical neuronal damage affects supraspinal and corticospinal motor pathways (Murase 2004; Heiss 2006) and leads to segmental level transsynaptic degeneration (Patten et al. 2004; Chang 1998; McComas et al. 1973). This degeneration denotes a reduced number of synaptic connections with and therefore reduced excitation and output at the spinal segmental level, leading to motoneuron loss and disruption of

muscular activation (Patten et al. 2004). Thus, weakness may stem from several sources. Loss of motor units themselves has been suggested as a mechanism (McComas et al. 1973; McComas et al. 1971), as has increased motor unit innervation ratios due to post-stroke re-innervation of denervated muscle fibres (Patten et al. 2004; Heiss 2006). Activation impairment of motor units is another likely mechanism; that is, loss of descending input to the spinal motoneuron pool (Patten et al. 2004; Gracies 2005a). For example, electrically evoked contractile force in the TA muscle is similar in both legs post-stroke, which indicates impairment of central motor drive as the cause of reduced voluntary force output on the more-affected side (Landau and Sahrmann 2002). Further, post-stroke irregularities have been observed in motor unit recruitment thresholds and firing rates (Patten et al. 2004; Eng 2004; Gracies 2005a; Gemperline et al. 1995; Frontera et al. 1997). In the TA muscle, high-threshold motor units have been observed to either fire below their normal range or fail to be recruited in the more-affected limb (Frontera et al. 1997). Thus, the ability to increase voluntary dorsiflexion force output is compromised.

In the weeks and months following stroke, the neural alterations associated with hemiparesis can also contribute to development of abnormal responses to muscle stretch on the more-affected side (Gracies 2005b). These responses often manifest as an inability or difficulty in arresting motor unit activity within specific muscles; that is, the presence of increased motoneuronal output. This post-stroke symptom has been referred to as muscle overactivity, and may occur at rest or within one muscle during activation of another muscle (Gracies 2005b). Along with the observation of poor functional movement execution (Zehr and Loadman 2012), such overactivity has been evidenced by

the presence of hyperexcitable spinal reflexes, such as the muscle afferent pathways as assessed by SOL H-reflex (Thompson et al. 2009; Barzi and Zehr 2008). Spasticity is one well-known example of stretch-sensitive overactivity, where exaggerated stretch reflex response (Zehr 2011) leads to resistance to passive movement at a joint (Krakauer 2005; Gracies 2005b; Nielsen et al. 2005). A similar symptom of stretch-sensitive muscle overactivity can come in the form of spastic co-contraction (Gracies 2005b), where, instead of passive movement stretch as its trigger, excessive muscle activation results from voluntary contraction and stretch of that muscle's functional antagonist (Gracies 2005b). Such inappropriate co-activation has been evidenced from work that explored finger extensor movement on the more-affected side following anesthetic blockade of finger flexor activity (Kamper et al. 2003). Excessive flexor activity was noted during extension movement, and nerve blockade produced a more normalized active range of motion of finger extension. Thus, the authors suggested that excessive antagonist muscle co-activation contributes to impairment of voluntary agonist movement (Kamper et al. 2003).

Spasticity and spastic co-contraction are thought to stem from abnormal supraspinal signalling, such as loss of cortical inhibitory control (Krakauer 2005), and/or abnormal corticospinal descending drive (Gracies 2005b; Lamy et al. 2009). Additionally, such changes may be aggravated by peripheral adaptations, such as altered synaptic transmission in the spinal cord. Evidence of this comes from work that monitored post-activation depression (PAD, i.e. depression of neurotransmitter release from Ia afferents following previous activation) via SOL stretch (Grey et al. 2008) and H-reflexes (Lamy et al. 2009), and observed impaired PAD in the presence of post-stroke

spasticity. Reduction in PAD has also been correlated with spasticity severity (Lamy et al. 2009). From these findings, it has been suggested that adaptation in the efficacy of the Ia afferent – alpha-motoneuronal synapse follows the changes in activity of Ia fibres and motoneurons associated with impaired motor command (Lamy et al. 2009). Another avenue for modified peripheral signaling that may apply to spastic co-contraction is that of altered RI and PSI signalling. At the onset of dorsiflexion, both PSI and RI received by the antagonist SOL muscle Ia afferents are reduced in spastic multiple sclerosis patients compared to healthy controls (Morita et al. 2001). Thus, these authors suggest that such reflex changes may contribute to hyperactive stretch reflexes, which may apply to post-stroke spasticity as well.

1.5.2 Selected clinical approaches used to evaluate walking-related impairment and functional ability

Since no brain lesion is exactly the same, both severity and type of motor dysfunction can vary considerably between stroke patients. Therefore, the assignment of suitable motor rehabilitation strategies first requires quantitative evaluation of a patient's level of impairment and functional ability (Duncan et al. 2005). Such clinical evaluation is also needed to assess functional change in an experimental setting; for example, to investigate the effect of a training intervention. There are a number of standardized clinical measures that have been validated in the literature and which have been widely applied to post-stroke experimental cohorts. A typical feature shared among these measures is their ease of implementation, which is an important attribute for both clinicians and patients. However, such ease can also lead to a reduction in level of precision within the assessment, so that small differences and/or changes in function are

challenging to detect. The following is a brief summary of some commonly employed clinical test measures related to motor performance.

First, as it is a common post-stroke neurological symptom, it is of interest to quantify level of spasticity. The Modified Ashworth scale provides a ranking of therapist-led passive movements of between 1 (normal) and 5 (immovable) (Lee et al. 1989). This scale has the advantage of being simple to use and applicable over a wide range of arm and leg movements, and is reliable and reproducible between clinicians and over time (Lee et al. 1989). However, with these benefits comes a lack of precision, as it employs a fairly gross scale. Thus, it is important to note that subtle shifts in level of spasticity during a movement over time may not be detected by this measure. Quantitative reflex and/or EMG methodologies may be useful in detecting such changes, though due to their added complexity are generally difficult to employ in many clinical settings.

Beyond walking, clinicians often must determine how much assistance is required for a patient to carry out other basic activities of daily living, including ability to dress, eat, bathe and transfer from one position to another, as well as to comprehend and think critically. The Functional Independence Measure (FIM) is a comprehensive assessment tool for such activities (Keith et al. 1987). It was based on the International Classification of Impairment, Disabilities and Handicaps (Jochheim 1980), and assesses of level of disability as well as how much assistance a patient may require. The test itself ranks 18 separate items (13 motor and five cognitive tasks), each on a scale that ranges from 0 (cannot perform task) to 1 (requiring total assistance) to 7 (complete independence) (Keith et al. 1987), for a maximum score of 126. The test has been shown to have good validity (Pollak et al. 1996) and good intra- and inter-rater reliability (Kohler et al. 2009).

However, the test is lengthy to complete (30-45min) and may provide unnecessary information to a therapist interested specifically in locomotor rehabilitation.

This highlights another key area of interest in the clinical assessment of motor performance, which is functional walking ability. Direct measures in this category are the 10m walking test, where time and number of steps it takes a patient to walk 10m is recorded, and the 6min walking test, where distance travelled by a patient while walking for six minutes is recorded. Such time and distance values have the benefit of being entirely objective and precise in nature. During the implementation of either of these tests, a clinician can also rank a patient's walking ability using Functional Ambulation Categories (Holden et al. 1984). These categories range from 0 (non-functional ambulation) to 5 (independent ambulation on both level and non-level surfaces/stairs/inclines), and have been correlated to multiple temporal distance measures of gait while also showing high inter-rater reliability (Holden et al. 1984).

Balance is a universal component to appropriate execution of many motor tasks, including activities of daily living such as walking. Some broad-spectrum clinical measures have incorporated an assessment of balance into their evaluation (e.g. (Fugl-Meyer et al. 1975; Verheyden et al. 2004)), but there are also well-established standalone tests, such as the Berg Balance Scale (Berg et al. 1992). This test assesses balance through observation of 14 functional tasks of progressive complexity (e.g. standing, standing with eyes closed, transferring from sitting to standing, etc.). Each task is scored from 0 to 4 using a detailed scale, and then all scores are summed (maximum score = 56). The test itself is strongly correlated with functional and motor performance in stroke patients (Berg et al. 1992; Blum and Korner-Bitensky 2008), and has high intra- and

inter-rater reliability (Blum and Korner-Bitensky 2008). However, it has also been reported to suffer from floor and ceiling effects, such that it may not detect meaningful changes for patients with either severe or mild balance impairment (Blum and Korner-Bitensky 2008). To address this shortcoming, it may be useful to employ additional balance measures in conjunction with this test.

A relatively simple measure that provides a combined assessment of balance and gait maneuvers used in everyday life is the Timed Up and Go test (Podsiadlo and Richardson 1991). For this timed test, a patient rises from a standard arm chair and walks for 3m; then they pivot, return to the chair and sit down again. The test reflects and standardizes many basic mobility maneuvers (Podsiadlo and Richardson 1991; Mikulic et al. 1976), such as moving from sitting to standing, while being a quick and practical test. The measure also has the added benefits of a time score; that is, being a precise and objective means of following functional change over time. As a test of physical mobility, scores correlate well with gait speed and more formal balance tests, as well as other validated surveys and indices of functional capacity during activities of daily living (Podsiadlo and Richardson 1991; Mahoney and Barthel 1965). The test also has good intra- and inter-rater reliability (Podsiadlo and Richardson 1991).

The Timed Up and Go Test is a simple example of a broad evaluative tool of motor function, with other clinical measures taking even more comprehensive approaches. Such methods assess multiple categories of motor impairment under separate test subsections. The Fugl-Meyer scale is an example of such a test (Fugl-Meyer et al. 1975). This is a stroke-specific impairment index that measures level of sensorimotor recovery in patients suffering from hemiplegia (Gladstone et al. 2002). It has five

separate sections, which include motor and sensory function, balance, joint range of motion and joint pain. Each section has a list of items that are each scored on a 3-point scale (0, cannot perform; 1, performs partially; or 2, performs fully). Items across sections are then summed to generate a total Fugl-Meyer score (maximum = 226). The evaluation of motor function is probably the most widely applied feature of this test, and includes measures of movement, coordination and (stretch) reflex action across joints in both the upper and lower limbs. While the entire Fugl-Meyer scale and all subsections have excellent intra- and inter-rater reliability, other shortcomings are present within some test domains. For example, the motor domain has been shown to suffer from ceiling effects, and has also been criticized for its heavy weighting on arm over leg function (Gladstone et al. 2002). Thus, studies that wish to specifically evaluate lower limb function and/or patients with mild impairments for change would be wise to include additional measures beyond the Fugl-Meyer alone (Gladstone et al. 2002). The original Fugl-Meyer test was also reported to have poor validity in items that measure sitting balance (Malouin et al. 1994), with slight modifications to scoring for these items able to address this concern (Blum and Korner-Bitensky 2008). Even with these limitations, the use of the Fugl-Meyer is still recommended in evaluation of post-stroke motor impairment (Gladstone et al. 2002).

Another example of a broad evaluative tool of motor function is the Brunnstrom Stages of Recovery (Brunnstrom 1966). This is a classification system based on observation of degree of spasticity, synergies and voluntary movement. Patients are grouped into a stage of recovery on an incremental scale that progresses from patient flaccidity and inability to move voluntarily (stage 1), to voluntary control of movement in

the presence of spasticity (stage 3), to normal joint movements and disappearance of spasticity (stage 6) (Brunnstrom 1966; Naghdi et al. 2010). Different limbs and/or body parts are often classified and reported separately; e.g. upper vs. lower limbs, leg vs. foot, etc. (Barzi and Zehr 2008; Zehr and Loadman 2012). The test has been found to be a valid measure of motor ability (Naghdi et al. 2010). However, similar to the modified Ashworth Scale previously described, the gross nature of these categories results in a lack of precision, and thus an increased likelihood that subtle changes over time may not be detected.

Finally, it is important to note that the above clinical methods, even those that include multiple functional tests, are not necessarily well-suited to the evaluation of post-stroke muscle weakness in the context of training interventions. Indeed, it has been suggested that such clinical tests, including the Fugl-Meyer, do not challenge muscles sufficiently in their measures of motor performance to provide an accurate indicator for strength (Bohannon 2007). Thus, to accurately assess the effects of strength training on functional change post-stroke, additional measures are likely required beyond the standard tools employed by clinicians. These may include more complex muscular force output and gait kinematics techniques, which are more common within motor control experimental research settings.

1.5.3 Potential of remote motor signalling in post-stroke re-training

A number of potential functional applications of remote motor signalling have been discussed in previous sections, with many tied to rehabilitation following neurotrauma. Some of these applications will be summarized here with a focus on the lower leg.

First, the previously described suppressive effect of arm cycling on lower leg reflex excitability (Barzi and Zehr 2008) may have direct applications in post-stroke motor retraining, alone or in combination with lower leg rhythmic movement (Zehr et al. 2009; Ferris et al. 2006). For example, a paradigm that employed repeated arm cycling bouts may over time reduce post-stroke hyperexcitability of ankle extensor motoneurons (Kreisel 2006; Faist et al. 1994). This reduction may translate into more normalized muscle activation patterns during lower leg movement, such as walking and activities of daily living, and also allow more effective dorsiflexor action at the ankle. No work to date has evaluated the efficacy of this approach.

Second, the cross-education phenomenon (i.e. signalling between limb pairs) has potential for motor re-training applications where patients are unable to appropriately exercise one limb (Lee and Carroll 2007; Farthing 2009). One-sided dorsiflexor weakness is common post-stroke (Patten et al. 2004), and is a major contributor to dysfunctional gait patterns (Zehr and Loadman 2012; Dobkin 2003). Therefore, it is of interest whether the cross-education effect persists following stroke, and if so, whether targeted dorsiflexor resistance training on the less-affected side can induce strength gains in the hemiparetic leg to improve execution of functional motor tasks. Such training is specifically applicable to patients who suffer from severe hemiparesis; i.e. weakness so substantial in the more-affected leg that it precludes sufficient muscle activation to induce a training effect under conventional training approaches (Olsen 1989). In such cases, increasing muscle activation in the target limb via alternative signalling routes may help to establish the baseline of strength needed to begin successful within-limb training.

No work has evaluated the application of cross-education in this context; further, it is unknown whether such crossed strength gains would result in improved functional outcomes. However, support for functional transfer is provided by post-stroke strength training investigations that noted improvement in various indices of functional outcome (Patten et al. 2004; Hill et al. 2012; Stoykov et al. 2009). Moreover, promising findings come from a recent study that employed a post-stroke mirror therapy paradigm (Sutbeyaz et al. 2007). In this work, unilateral dorsiflexion training sessions were completed in the less-affected leg while a mirror was positioned between the legs to display the training leg's movements to the subject. Mirror training induced significant improvement in clinical measures of motor recovery (Brunnstrom Stages of Recovery (Brunnstrom 1966)) and motor functioning (motor items of the FIM, or Functional Independence Measure, instrument (Keith et al. 1987)) (Sutbeyaz et al. 2007). Unfortunately no quantitative measures of neural excitability or force output were taken, and thus the true level and type of gains achieved in this study are unclear. However, the study's training paradigm shares many similarities to the post-stroke cross-education paradigm proposed above; thus, its translation of dorsiflexor trained movement to improved functional outcomes bodes favorably for the application of cross-education in the ankle flexor muscles following stroke.

An additional aspect of remote neural signalling that may play a role in the two applications described above is that of motor coordination between functional antagonist muscle groups (i.e. signalling within a limb). As previously described, a combination of post-stroke unilateral dorsiflexor weakness (Patten et al. 2004) and plantarflexor hyperexcitability (Thompson et al. 2009) often leads to disordered gait. Altering one or

both of these neural signalling issues, through resistance and/or remote movement training, may lead to a change in the reciprocal signalling patterns between these muscle groups. That is, the core circuitry that is reciprocal activation of ankle flexors and extensors during walking may be an underlying determinant of observed functional improvements.

1.6 Thesis objectives

The primary focus of this thesis was to better our understanding of neural interlimb connections associated with motor coordination. Specifically of interest were the modulatory projections to ankle flexor and extensor muscles induced by remote rhythmic arm movement or contralateral resistance training. Further, the final aim of this work was to apply these earlier observations in the context of a post-stroke rehabilitation paradigm, aimed at normalizing muscle activation patterns within the more-affected limb. Thus, the objectives of this thesis were as follows:

- To evaluate modulation patterns of spinal excitability within functional antagonists of the lower limb that arise from remote motor activity (rhythmic arm movement), through assessment of
 1. Ia afferent (i.e. Hoffmann reflex) pathways that affect a single muscle. Since a general effect of rhythmic arm cycling on leg reflex activity was previously speculated (Frigon 2004), it was hypothesized that rhythmic arm movement similarly modulates H-reflex amplitude in both the ankle flexor (SOL) and extensor (TA) muscles.

2. Ia inhibitory interneuronal (short latency reciprocal inhibition) pathways that affect coordination at a single joint. It was hypothesized that arm cycling would increase RI between both muscle groups, but that movement conditioning would vary depending on stimulus intensity used to evoke the reflex response (Kido et al. 2004). Thus, we predicted a global descending influence of rhythmic arm movement on RI in the lower limb.
- To determine whether remote motor activity modulatory effects, i.e. unilateral resistance training and the cross-education phenomenon, can be elicited in the ankle dorsiflexor muscles, and to assess spinal plasticity associated with adaptations to training in functional antagonist muscle pairs. It was hypothesized that the training paradigm would increase dorsiflexion strength bilaterally and facilitate trained TA H-reflex excitability concurrent with reduced SOL H-reflex excitability in the trained limb. Based on previous speculation of supraspinal loci of muscular crossed effects (Lagerquist et al. 2006b), it was also hypothesized that TA and SOL spinal reflex excitability would remain unchanged in the untrained limb.
 - To evaluate the efficacy of a post-stroke unilateral resistance training paradigm that builds on observations of remote modulatory effects (cross-education) to strengthen dorsiflexion in the more-affected leg. It was hypothesized that maximal dorsiflexion force and TA muscle activation (EMG_{max}) would increase bilaterally following the intervention. Building on previous findings in neurologically intact participants (see Chapter 4), bilateral changes in spinal excitability were also predicted, seen as increased gain of spinal interneuronal excitability to the TA muscles and measured as

a change in the slope of the relationship between reciprocal inhibition and muscle activation.

1.7 References

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2. Rhythmic arm cycling modulates Hoffmann reflex excitability differentially in the ankle flexor and extensor muscles¹

2.1 Abstract

Rhythmic arm movement significantly suppresses H-reflex amplitude in the soleus (SOL) muscle. This is evidence of neural linkages between the arms and legs which can be exploited during locomotion and have been ascribed to the descending effects of CPGs for arm cycling. However, the generalizability of the effects of arm movement on reflex excitability within the lower leg musculature has not been confirmed, as findings have been limited solely to the ankle extensor group. Here we tested the hypothesis that rhythmic arm movement similarly modulates H-reflex amplitude in both the ankle flexors and extensors by observing responses in the SOL and tibialis anterior (TA) muscles. SOL and TA H-reflex recruitment curves were recorded bilaterally during control and 1Hz arm cycling conditions. Our results showed significant suppression in H-reflex amplitude (H_{max}) in the SOL muscle in both the dominant and non-dominant legs during arm movement. However, results also revealed an unpredicted bidirectional (i.e. either suppression or facilitation) modulation of TA reflex amplitude that was not present in the SOL muscle. These findings suggest a differential regulation of ankle flexor and extensor H-reflex responses during rhythmic arm movement. This may be the result of differences in CPG output to the flexors and extensors during rhythmic movement, as well as increased involvement of cortical drive to the flexors relative to the extensors during rhythmic movement. These findings may be pertinent to future investigation of

¹ Dragert K, Zehr EP (2009) Rhythmic arm cycling modulates Hoffmann reflex excitability differentially in the ankle flexor and extensor muscles. *Neurosci Lett* 450:235-238.

rehabilitative therapies that involve facilitative modulation of ankle flexor motor responses.

2.2 Introduction

There is evidence for neural coordination mechanisms in humans that regulate rhythmic activity between the arms and legs (reviewed in (Dietz 2002; Zehr and Duysens 2004)). For example, it has been suggested that arm to leg coordination patterns result from the activity of coupled neural central pattern generators (CPGs) similar to the coordination of fore- and hindlimbs during quadrupedal locomotion (Wannier et al. 2001). Such activation has been attributed to neural linkages between cervical and lumbosacral networks in the spinal cord (Gernandt and Megirian 1961). Recent work in our laboratory has revealed interlimb modulation of reflex excitability in the legs caused by rhythmic movement of the arms (Balter and Zehr 2007; Frigon 2004; Loadman and Zehr 2007; Zehr et al. 2007a). Rhythmic arm cycling was found to contribute to cutaneous reflex modulation patterns to functionally support the action of the legs (Balter and Zehr 2007). Arm movement was also found to significantly suppress H-reflex amplitude in the soleus muscle (Frigon 2004; Loadman and Zehr 2007; Zehr et al. 2007a). Such modulation has been attributed to overflow of upper limb CPG activity to lower limb spinal networks via descending pathways (Frigon 2004; Zehr and Duysens 2004), and provides additional evidence of neural linkages between the arms and legs. From these and other findings, it has been suggested that rhythmic arm movement affects leg reflex activity during walking (Frigon 2004; Haridas and Zehr 2003; Zehr and Duysens 2004). However, the generalizability of the observed effects of rhythmic arm

movement on reflex excitability within the lower leg musculature has not been confirmed, as findings have been limited to the soleus (SOL) muscle, an ankle extensor. Of specific interest is whether similar effects are present in the tibialis anterior (TA) muscle, an ankle flexor and the functional antagonist to the SOL. Such information would further our understanding of the descending regulation of motor output involved in locomotor movement execution.

Since we previously speculated a general effect of rhythmic arm cycling on leg reflex activity (Frigon 2004), in this study we tested the hypothesis that rhythmic arm movement similarly modulates H-reflex amplitude in both the ankle flexors and extensors by observing responses in the SOL and TA muscles. Similar modulation of H-reflex amplitude in both muscle groups induced by arm movement would suggest that the effects of upper limb rhythmic movement are broadly generalizable across different functional muscle groups within the lower leg. Alternatively, CPG output is known to be differentially specified for leg flexors and extensors in reduced animal preparations during locomotion (reviewed in (Rossignol et al. 2006)). The presence of differential effects of arm movement on H-reflex amplitude in the ankle flexors and extensors would suggest muscle-specific signaling patterns elicited by rhythmic arm movement to the lower limbs.

2.3 Methods

Thirty-six subjects (14 men, 22 women) participated in a protocol that was approved by the University of Victoria Human Research Ethics Committee and

performed according to the Declaration of Helsinki. Within this sample, there were four subjects for whom it was not possible to elicit either SOL or TA reflex responses (two for each group), thus reducing the sample size to thirty-four for both muscle groups. Leg dominance was determined by asking participants which leg they preferred to use when kicking a ball (Lagerquist et al. 2006). H-reflexes were generated bilaterally under both static control and arm cycling conditions. Participants were seated in a back-supported chair with ankle, knee and hip angles maintained at approximately 100, 120 and 90 degrees, respectively. Clockwise bilateral arm cycling was performed on an instrumented arm cycle ergometer, with its handles coupled 180° out of phase (Balter and Zehr 2007; Frigon 2004; Loadman and Zehr 2007; Zehr et al. 2007b). During control trials, a constant arm position was maintained where the right elbow was fully extended, and during arm cycling trials a cycling frequency of 1Hz was maintained. EMG was recorded using surface electrodes applied in bipolar configuration over the SOL, TA, vastus lateralis (VL), and posterior and anterior deltoid muscles (PD and AD, respectively). EMG signals were amplified (GRASS P511, AstroMed) and band pass filtered from either 100 to 1000 Hz (SOL, TA) or 100 to 300 Hz (VL, PD, AD). The output was sent to the A/D interface (National Instruments, Austin, TX.) and the computer sampled at 5000 Hz. All trials were performed while a tonic low-level contraction (~10-15% MVC) was maintained by the muscles in which reflexes were evoked for that trial. H-reflexes were elicited and recorded following procedures previously described (Frigon 2004; Zehr et al. 2007a; Zehr et al. 2007b). Briefly, bipolar stimulation (0.5ms pulse) was delivered pseudo-randomly every 2-5s using either Digitimer (Medtel, NSW, Australia) constant current stimulators (model DS7A), or a Grass S88 stimulator connected to a SIU5

isolation unit and a CCU1 constant current unit (AstroMed Grass, Inc.). Stimulating electrodes were placed over the posterior tibial nerve at the popliteal fossae (SOL muscle), and over the common peroneal nerve at the fibular head (TA muscle). M-wave and H-reflex recruitment curves were constructed for each condition using 40 sweeps while stimulation current was concurrently measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL.; also custom built current monitors). This allowed for the detection of the H-reflex and M-wave through all ranges of amplitude. For example, H-reflex data was obtained from its threshold up to a maximum on the rising edge of the curve and then along the descending edge until it became completely occluded, and the M-wave data was obtained from its threshold up to a maximum plateau value. To obtain a clear depiction of the recruitment curve, the sweeps initially concentrated on the rising edge of the H-reflex curve, and were then collected along the full distribution of the curve.

Peak to peak amplitudes of M- and H-waves from the single unrectified sweeps of EMG were calculated offline with custom written software (Matlab, Nantick). For each subject, M-waves and H-reflexes were normalized to the corresponding M_{\max} to reduce inter-subject variability. Average H_{\max} was calculated from the three largest peak to peak H-reflexes, which occurred with an M-wave of ~10-15% of M_{\max} for SOL, and ~24-34% M_{\max} for TA reflexes. Utilizing STATISTICA software, 2-way analysis of variance (ANOVA) and a-priori planned comparison testing were used to identify significance of effects ($p \leq 0.05$).

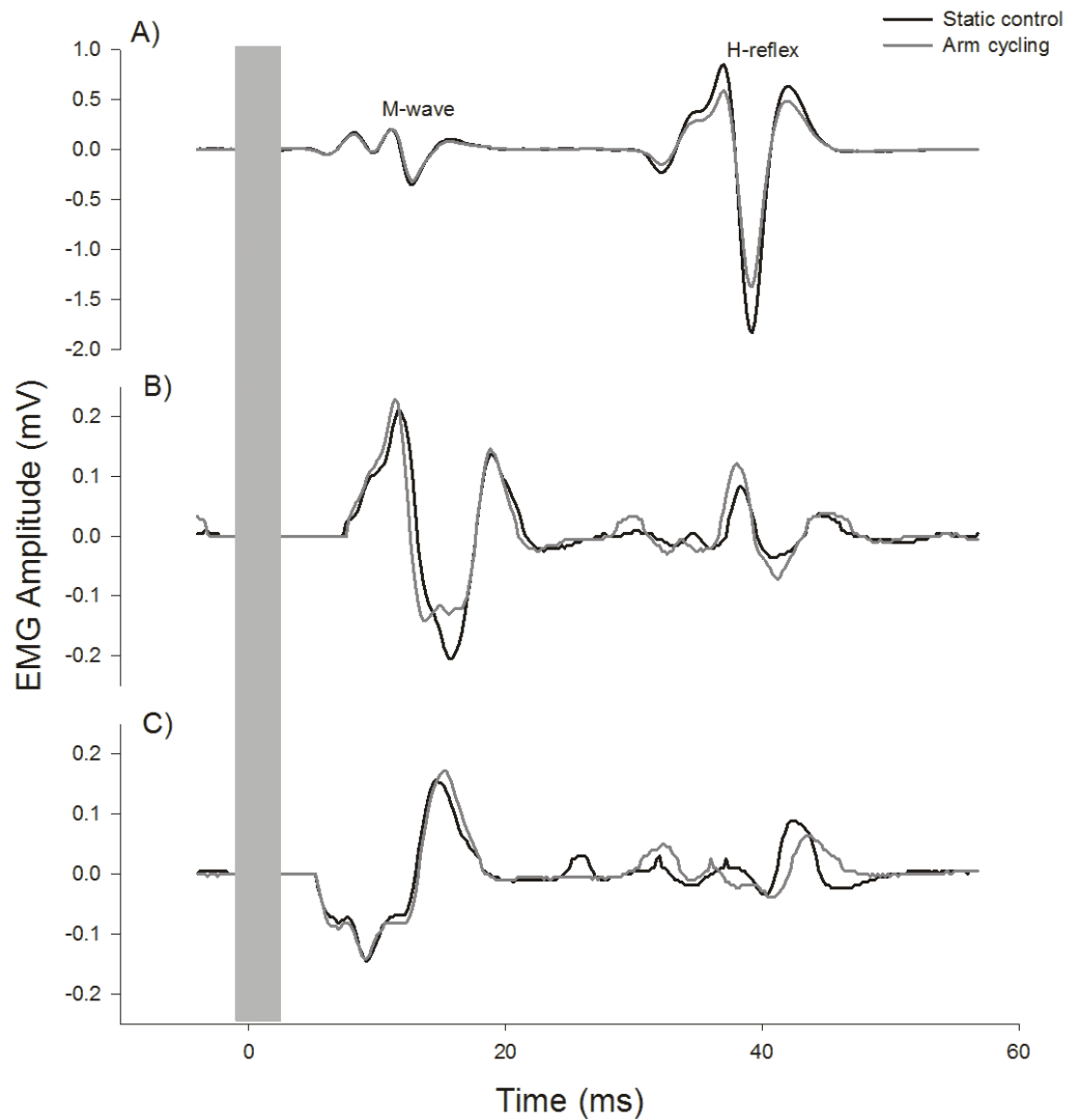


Figure 2.1: Single subject H-reflex recruitment curve (ascending limb) data during static activity and arm cycling for the SOL (A) and TA muscle (B, C). Arm cycling suppressed reflex amplitudes in SOL (A). In TA, during arm cycling a bidirectional reflex response was observed as either facilitation (B) or suppression (C). Data are single sweeps taken from the dominant legs of three different subjects. The grey bar represents the stimulus artefact which has been removed from the sweeps.

2.4 Results

The results of this research were as predicted for the SOL muscle, where arm cycling significantly suppressed H-reflex amplitude bilaterally. However, experimental results revealed a bidirectional (i.e. either suppression or facilitation) reflex response to arm movement in the TA muscle in both legs. Fig. 2.1 a, b and c show single 90ms sweeps of data taken at H_{\max} for the SOL and TA muscles on the dominant side from sample H-reflex recruitment curves. It is clear in the Fig. 2.1a example from the dominant leg that arm cycling suppressed H_{\max} in the SOL muscle. Across subjects, planned comparison testing revealed that SOL H_{\max} was significantly suppressed during arm cycling in both the dominant and non-dominant legs by 14.5 and 14.7%, respectively (Fig. 2.2a, black bars; $p < 0.01$ for both legs). In the TA muscle responses were smaller, with TA H_{\max} on the dominant side significantly suppressed (5.0%; $p = 0.04$) during arm cycling, and with no significant change present on the non-dominant side ($p = 0.12$) (Fig. 2.2a, grey bars). However, of interest are the antonymous effects of arm cycling on TA H-reflex amplitude for the two sample subjects shown (see Fig. 2.1b, c). Upon further investigation of these results, an unanticipated bidirectional reflex response was revealed in both the dominant and non-dominant leg data that was not present in the SOL muscle. Thus, subsequent to our initial analysis, TA data were divided into facilitatory (dominant $n = 13$; non-dominant $n = 17$) and suppressive (dominant $n = 21$; non-dominant $n = 17$) reflex response groups for further analysis. Planned comparison testing of these groups showed a significant change from control in both legs (see Fig. 2.2b; $p < 0.01$ for all groups tested). In the facilitatory response group, H-reflex amplitude increased by 18.2% and 14.3% in the dominant and non-dominant leg, respectively (Fig 2.2b, light grey bars),

and in the suppressive response group responses were suppressed by 19.3% and 19.5% in the dominant and non-dominant leg, respectively (Fig. 2.2b, dark grey bars). These results were not apparent when all subject data was grouped together, as the differential effects in the data cancelled out any obvious change in H-reflex amplitude. Further, upon inspection of SOL data, no evidence for bidirectional effects was found. Overall, a similarly specified modulatory effect (i.e. ~15-20% change) was observed in both the TA and SOL muscles.

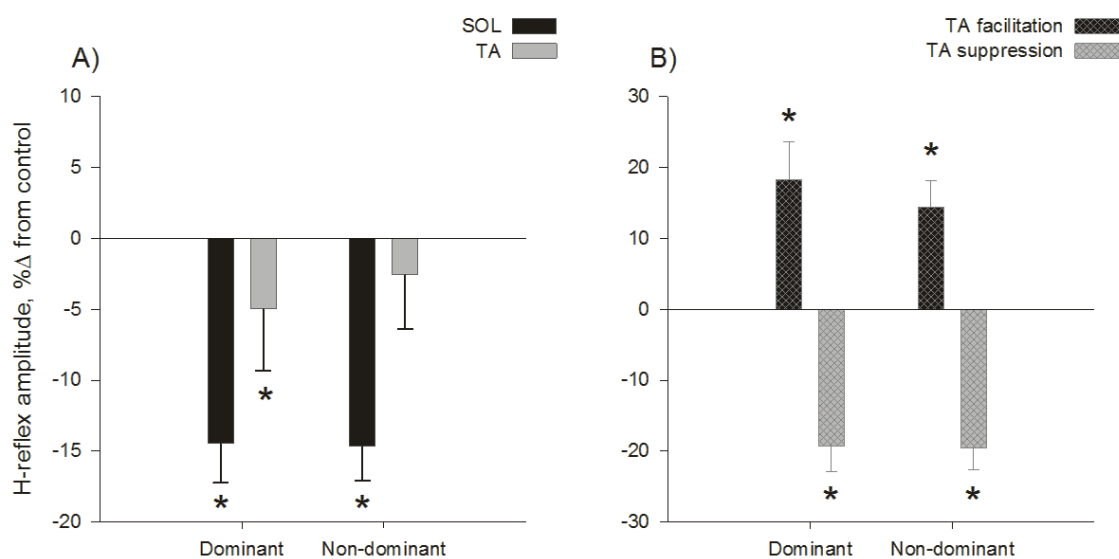


Figure 2.2: Group data for H_{max} during arm cycling condition, displayed as percent change from control for SOL and TA muscles in the dominant and non-dominant legs. A) Combined group data for SOL and TA ($n = 34$). In SOL (black bars), arm cycling significantly suppressed H_{max} in both legs. In TA (grey bars), combined data showed a significant suppression in the dominant leg during arm cycling, but no significant change in the non-dominant leg. B) TA data sorted into facilitation (dominant $n = 13$; non-dominant $n = 17$; dark grey hatched bars) and suppression responses (dominant $n = 21$; non-dominant $n = 17$; light grey bars). Significant change from static was observed across these groups. Data are given means \pm S.E.; $p \leq 0.05$ (indicated by *).

In an attempt to discern any other relationships in the TA data, we further categorized participants based on response symmetry/asymmetry (i.e. having either the same or differing responses in either leg) and direction of reflex modulation observed (i.e. facilitative or suppressive). This categorization broke down as symmetric suppression (n=12), symmetric facilitation (n=8), asymmetric suppression (DOM) with facilitation (NON) (n=9), and facilitation (DOM) with suppression (NON) (n=5). However, a chi-square analysis performed on the resulting groups showed no differences in the frequency of observation between symmetric/asymmetric groups.

For all trials M-wave amplitudes, background TA and SOL muscle EMG levels (i.e. antagonist muscle activity), as well as EMG levels within the muscles tested were well controlled. There were no significant differences across conditions for these parameters. Contraction level in test muscles ranged from 12 to 14%MVC.

It is worth noting that there was no significant difference observed in H-reflex response between the dominant and non-dominant limbs for either muscle group tested. Based on data collection procedures from a single limb, the conclusions of many previous studies have relied on the assumption of reflex symmetry within homologous muscle groups (Balter and Zehr 2007; Frigon 2004; Brooke et al. 1997a; Brooke et al. 1997b; Capaday et al. 1999). However, it is only recently that bilateral H-reflex responses observed during rhythmic movement conditions have been reported (Balter and Zehr 2007; Mezzarane and Kohn 2002), and those studies were limited to the SOL muscle. Within our parameter of interest (H_{max}), our findings confirm this previous assumption of

homologous muscle reflex symmetry between limbs in both the ankle flexors and extensors.

2.5 Discussion

The novel finding of this study reveals differential effects of rhythmic arm movement on ankle flexor and extensor H-reflex responses. Such reflex modulation differs from predictions made based on results in other research, such as the notion that arm swing forms a background of general bias regulation, i.e. suppression, in reflex excitability (Frigon 2004). Brooke et al. (1997b) also suggested that similar modulation of reflex responses exists between the TA and SOL muscle groups (in the form of conditioned Ia autogenic pathways), given their observation of suppressed TA H-reflex response during passive leg movement. The bidirectional effect in TA contrasts with SOL muscle response observed in this study, which agrees with previous findings (Frigon 2004; Loadman and Zehr 2007; Zehr et al. 2007a). Based on observations in the cat, it has been suggested that CPG output is differentially modulated for leg flexors and extensors during rhythmic movement such as locomotion (Rossignol et al. 2006). For example, differences are known to exist in the phase dependence and sources of group I excitation to flexor and extensor motoneurons in the cat during fictive locomotion, suggesting that these motoneurons are excited by separate groups of interneurons (Quevedo et al. 2000). Further, previous research in humans has described a disparity in cortical influence on resulting motor response between ankle flexors and extensors during movement (Bawa et al. 2002; Capaday et al. 1999; Schubert et al. 1997). Capaday et al. (1999) suggested that during walking the corticospinal tract is more closely linked with

segmental motor circuits that control the TA muscle than with those controlling the SOL muscle. Also, Bawa et al. (2002) observed the corticomotoneuronal connections to the TA motoneuron pool to be very strong, while similar connections to the SOL, although still present, to be generally weak. Given these earlier findings, we interpret the observed bidirectional H-reflex modulation in the TA during rhythmic arm movement as further evidence for differential regulation between the ankle flexors and extensors, perhaps due in part to a reduction in spinally-mediated drive as well as increased involvement of cortical drive to the ankle flexors during rhythmic movement relative to the extensors.

Interestingly, similar bidirectional modulation to that reported here has been observed in cutaneous reflexes during rhythmic movement (Balter and Zehr 2007; Zehr and Duysens 2004). Whether such effects are the result of a similar regulatory pathway or drive is unclear. Also, it is unknown whether similar modulatory effects of arm movement can be observed for both types of evoked responses within the same individual (e.g. observation of both suppressive H- and suppressive cutaneous reflex responses in the TA muscle during arm cycling). This may be an interesting avenue for future investigation.

In terms of functional implications of our findings, we suggest that they may be relevant to future clinical research. For example, up or down-regulation of post-trauma reflex activity may be applicable in rehabilitative settings for optimal motor recovery. We recently reported that the suppressive effect of rhythmic arm cycling on SOL H-reflex amplitude is partially maintained in both the more and less affected legs of stroke

participants with reflex hyperactivity (Barzi and Zehr 2008). This indicates that the neural activity related to arm cycling can still access interlimb pathways in this population, and thus it has the potential to be exploited in rehabilitative interventions aimed at modifying reflex activity in ankle muscles (Barzi and Zehr 2008). The extent to which this affects flexor muscles generally and facilitatory TA reflex modulation specifically, remains to be seen. However, the potential for such a finding to build towards improved treatment of chronic ankle flexor weakness warrants further investigation in this field.

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3. Differential modulation of reciprocal inhibition in ankle muscles during rhythmic arm cycling²

3.1 Abstract

Interlimb neural linkages relay activity related to rhythmic arm movement to the lumbar spinal cord. This is detected by modulated reflex amplitudes in muscles remote from the rhythmic movement. Improved understanding of modulation in ankle flexor and extensor muscles due to rhythmic arm movement can be gained using modulation of spinal excitability as a probe. The modulatory effect of rhythmic arm movement on Ia reciprocal inhibition (RI) between functional antagonists at the ankle has not been studied. We investigated the influence of rhythmic arm cycling on short latency (~55 ms post-stimulus) RI between ankle flexor (tibialis anterior, TA) and extensor (soleus, SOL) muscles at varying (0.9, 1.0, 1.2, 1.5 and 2.0x motor threshold (MT)) stimulus intensities. We hypothesized that arm cycling would increase RI between antagonists, but that movement conditioning would vary depending on stimulus intensity used to evoke the RI response. Amplitude of RI deduced from suppression of ongoing EMG activity was compared in static and arm cycling conditions. Arm cycling significantly ($p < 0.05$) increased RI in SOL at 1.0xMT, but had no effect in TA at any stimulus intensity ($p > 0.05$). Descending signals arising from rhythmic arm movement significantly alter transmission in RI pathways between ankle flexor and extensor muscles differentially. This may be due to differences in descending supraspinal inputs to ankle flexors vs. extensors, and could be related to functional requirements during locomotion.

² Dragert K, Zehr EP (2012) Differential modulation of reciprocal inhibition in ankle muscles during rhythmic arm cycling. *Neurosci Lett*. DOI 10.1016/j.neulet.2012.11.038; 10.1016/j.neulet.2012.11.038

3.2 Introduction

Neural linkages contribute to rhythmic action between the arms and legs in humans (Dietz and Michel 2009; Dietz 2002; Zehr and Duysens 2004). These coordination patterns have been attributed to output from supraspinal and spinal centers, which links activity between cervical and lumbrosacral spinal networks related to locomotor control (Dietz and Michel 2009; Gernandt and Megirian 1961; Zehr et al. 2009). Extensive documentation of modulation of reflex excitability in the lumbar spinal cord has been revealed using remote rhythmic arm movement (Mezzarane et al. 2011; Balter and Zehr 2007; Dragert and Zehr 2009; Zehr et al. 2007; Loadman and Zehr 2007; Frigon 2004). Such movement modulates cutaneous (Balter and Zehr 2007) and Hoffmann (H-) reflex amplitudes (Mezzarane et al. 2011; Dragert and Zehr 2009; Loadman and Zehr 2007; Frigon 2004) in a phasic pattern (de Ruyter et al. 2010). Interestingly, we previously observed a differential effect of rhythmic arm cycling on H-reflexes in ankle flexor and extensor muscles (Dragert and Zehr 2009). This suggested an asymmetry in the extent to which descending influences modulate lumbar cord excitability for flexor and extensor muscles.

From these and other findings, it has been suggested that rhythmic arm movement affects motor output of the legs during locomotion (Zehr and Duysens 2004; Frigon 2004; Ferris et al. 2006; Haridas and Zehr 2003). In the case of the H-reflex, a dominant mechanism is activation of the Ia presynaptic inhibitory interneuron, which alters transmission in the Ia afferent-alpha motoneuronal pathway (Frigon 2004). The extent to

which other lumbar interneuronal networks are activated by rhythmic arm movement requires further study.

Improved understanding of the descending pathways and lower limb spinal networks involved in remote modulation may be gained through the study of additional pathways, such as those involving the Ia reciprocal inhibitory interneuron. The sensitivity of reciprocal inhibition (RI) between the ankle flexor and extensor muscles to modulation during rhythmic leg movement has been demonstrated previously (Kido et al. 2004; Petersen et al. 1999). However, the impact of remote rhythmic movement on these responses has not yet been studied.

To further our knowledge of the descending regulation of locomotor coordination, we investigated the modulatory effect of rhythmic arm cycling on reciprocal inhibition between ankle flexor (tibialis anterior, TA) and extensor (soleus, SOL) muscles at varying stimulus intensities. We hypothesized that arm cycling would increase RI between both muscle groups, but that this movement conditioning would vary depending on stimulus intensity used to evoke the reflex response (Kido et al. 2004). Thus, we predicted a global descending influence of rhythmic arm movement on RI in the lower limb. This prediction was consistent with speculation that the Ia interneurons mediating reciprocal inhibition would be altered by arm cycling in a similar fashion to Ia presynaptic inhibition (Frigon 2004).

3.3 Materials and methods

Twelve subjects (7 women, 5 men) participated in a protocol approved by the University of Victoria Human Research Ethics Committee and performed according to the Declaration of Helsinki. SOL RI data were not collected for one subject, thus reducing the sample size to eleven for this muscle group. RI was recorded from the left leg of all subjects, and evoked under both static control and arm cycling conditions. Participants were seated in a back-supported chair with ankle, knee and hip angles maintained at approximately 100, 120 and 90 degrees, respectively. Clockwise bilateral arm cycling was performed on an instrumented arm cycle ergometer, with handles coupled 180° out of phase (Dragert and Zehr 2009; Frigon 2004). During control trials a constant arm position was maintained where the right elbow was fully extended, and during arm cycling trials a cycling frequency of 1Hz was maintained, with stimulation delivered when the left arm was in the 3 o'clock position (Dragert and Zehr 2009). EMG was recorded using surface electrodes applied in bipolar configuration over the SOL, TA, vastus lateralis (VL), and posterior and anterior deltoid muscles (PD and AD, respectively). EMG signals were amplified (GRASS P511, AstroMed) and band-pass filtered from 100 to 1000Hz (SOL, TA for RI conditioning stimulus) or 100 to 300Hz (VL, PD, AD; SOL, TA for MVC and RI trial recordings). Output was sent to the A/D interface (National Instruments, Austin, TX.) and sampled at 2000Hz. Maximum voluntary isometric contraction (MVC) trials were collected for TA and SOL muscles over 3 to 5sec, with maximal muscle activation calculated offline using custom written software. RI was then evoked while a low-level tonic contraction (~10%MVC) was maintained in the muscle in which RI was evoked, with visual oscilloscope feedback on contraction level provided. RI was elicited and recorded following procedures previously

described (Kido et al. 2004). Bipolar stimulation (0.5ms pulse) was delivered pseudo-randomly every 2-3sec using a Digitimer (model DS7A, Medtel, NSW, Australia) constant current stimulator. Stimulating electrodes were placed over the posterior tibial nerve at the popliteal fossae (SOL muscle), and over the common peroneal nerve at the fibular head (TA muscle). RI was observed as depression of EMG activity produced by antagonist muscle-nerve stimulation (Kido et al. 2004; Capaday et al. 1990; Thompson et al. 2009). For example, during TA RI recordings a conditioning stimulus was applied to the tibial nerve to evoke a SOL motor (M-) wave response, and RI was observed in the TA as depressed ongoing EMG activity post-stimulus. Stimulus intensity was set relative to the observed motor threshold (MT), with intensities of 0.9, 1.0, 1.2, 1.5 and 2.0xMT employed in pseudo-random order for both static and arm movement conditions.

For each RI trial, 20 sweeps were recorded with a duration of 300ms each (100ms pre-stimulus), and average rectified EMG traces were analyzed offline using custom written software (Matlab, Nantick). The mean 'peak' EMG depression over a 10ms interval was chosen by visual inspection and computed (Kido et al. 2004). We focused on short-latency (group Ia afferent) RI and used the first depression post-stimulus (latency to peak suppression = $54.7\text{ms} \pm 5.9$). Background mean pre-stimulus EMG for each trial was subtracted from this RI amplitude, followed by normalization to the corresponding MVC.

Utilizing SPSS software, a-priori planned contrasts were first completed to evaluate the effect of movement condition on RI response at each stimulus intensity. This was based on the prediction that the impact of movement conditioning would vary

depending on stimulus intensity used to evoke the response, similar to that observed previously in the SOL muscle during standing vs. walking (Kido et al. 2004). Two-way analysis of variance (ANOVA) tests were also run, to identify significant main effects of movement and stimulus intensity on the amplitude and latency of reciprocal inhibition and on the agonist and antagonist background EMG. Where applicable, Least Significant Difference (LSD) tests were performed post-hoc on significant main effects (i.e. presence of a significant F value). For this test, a modified t-test is employed that replaces the standard pooled variance estimate with the calculated MS_{error} value from the ANOVA test (Howell 2004). Significance was set at $p \leq 0.05$.

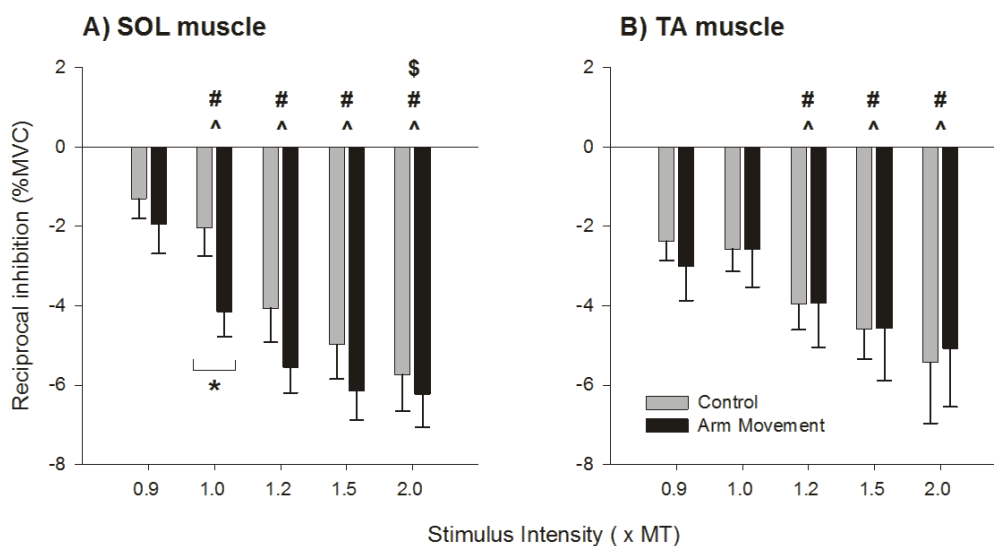


Figure 3.1: Group EMG data for all conditions and stimulus intensities in SOL (A) and TA muscles (B). Values are across subject means of the subtracted response from the average prestimulus EMG, normalized to maximal voluntary contraction (MVC). A) In SOL, size of reciprocal inhibition (RI) was graded relative to stimulus intensity: RI at 0.9 x motor threshold (MT) was reduced relative to all other stimulus intensities ($p < 0.05$, indicated by ^); RI at 1.0xMT was less than 1.2, 1.5 and 2.0xMT ($p < 0.05$, indicated by #); and RI at 1.2xMT was less than RI at 2.0xMT ($p < 0.05$, indicated by \$). Further, the extent of RI was enhanced by arm movement in SOL at 1.0 x MT ($p < 0.05$; indicated by *). B) In TA, similar scaling of reflex response occurred based on stimulus intensity: RI at both 0.9 and 1.0xMT were reduced compared to 1.2, 1.5 and 2.0xMT ($p < 0.05$, indicated by ^ and #, respectively). No differences between conditions were detected in TA at any stimulus intensity ($p > 0.05$).

3.4 Results

Results revealed novel information on differences in remote modulatory effects of movement to the ankle flexor and extensor muscles, while reinforcing the influence of stimulus intensity on resulting inhibitory response. Interestingly, a significant main effect of movement was detected in SOL ($p=0.047$) but not in TA ($p=0.954$). In SOL, planned comparisons revealed that RI was significantly larger during movement compared to control at $1.0 \times \text{MT}$ ($p=0.005$; see Figure 3.1a, 3.2a). No significant differences between control and movement condition RI were detected at any other stimulus intensity ($p>0.05$), though a similar pattern of larger RI response during movement was visible across stimulus intensities (see Figure 3.1a). This is unlike the TA muscle, where planned comparison testing showed no significant effects of movement at any stimulus intensity ($p>0.05$; see Figure 3.1b, 3.2b).

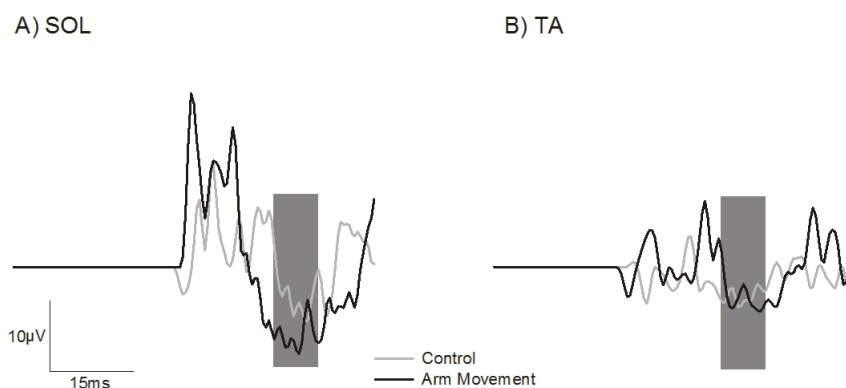


Figure 3.2: Single subject EMG traces for control and arm cycling conditions at a stimulus intensity of $1.0 \times \text{MT}$ in SOL (A) and TA muscles (B). Data are one individual's 20-sweep EMG average for that trial. EMG data are normalized to each trial's prestimulus average. The approximate RI window is shown for each muscle. For clarity, stimulus artifact has been removed.

The amplitude of RI was graded relative to stimulus intensity. Statistical results showed a significant main effect of stimulus intensity on RI for both SOL and TA muscles ($p < 0.001$ and $p = 0.009$, respectively). In SOL, post-hoc LSD results revealed a clear scaling effect relative to stimulus intensity: RI at 0.9xMT was significantly smaller compared to all other stimulus intensities ($p = 0.02$ for 1.0xMT; $p = 0.001$ for 1.2xMT; and $p < 0.0001$ for both 1.5 and 2.0xMT); RI at 1.0xMT was also significantly smaller compared to 1.2, 1.5 and 2.0xMT ($p = 0.004$, 0.003, and 0.001, respectively); and RI at 1.2xMT was significantly smaller compared to 2.0xMT ($p = 0.02$). No differences were detected between RI at 1.5 and 2.0xMT ($p > 0.05$; see Figure 3.1a). Though less robust in TA, a general scaling pattern of reflex size based on stimulus intensity was also apparent in this muscle: compared to 1.2, 1.5 and 2.0xMT, RI at 0.9xMT was significantly smaller ($p = 0.001$, 0.004, and 0.02, respectively), as was RI at 1.0xMT ($p = 0.006$, 0.002, and 0.01, respectively). No differences were detected between RI at 0.9 and 1.0xMT, nor between RI at 1.2, 1.5 and 2.0xMT ($p > 0.05$; see Figure 3.1b).

Reliability of methodological technique was confirmed through evaluation of background agonist and antagonist muscle prestimulus EMG levels. No significant differences were observed between stimulus intensities or movement conditions for either SOL or TA ($p > 0.05$). Mean agonist activation levels for SOL and TA RI were 11.7%MVC (± 2.3) and 11.4%MVC (± 2.7), respectively, while mean antagonist activation levels were 2.2%MVC (± 3.8) and 9.9%MVC (± 8.9), respectively. Furthermore, latency of RI was found to be consistent across conditions and stimulus intensities, with no significant differences detected for either muscle group ($p > 0.05$).

Mean response latencies for SOL and TA RI were 54.5ms (± 4.1) and 54.9ms (± 7.2), respectively.

3.5 Discussion

We show that the influence of descending signals arising from rhythmic arm movement significantly alters transmission in reciprocal inhibitory pathways from ankle flexor to extensor muscles. This extends our understanding of remote movement modulation on spinal excitation beyond previously identified effects in cutaneous and Ia afferent pathways. Interestingly, rhythmic arm movement appears to alter excitability in the core circuitry that comprises the interaction between functional agonist/antagonist pairs. Contrary to our expectations, this effect was asymmetrical and appeared only in the extensor SOL and not the ankle flexor TA.

A modulatory effect of arm movement to increase RI emerged in SOL at 1.0xMT. This finding expands the observation of descending effects of rhythmic arm movement to a fundamental neural component of locomotion; that is, the reciprocating inhibitory signals between lower limb antagonist muscle pairs, long recognized for their impact in coordinated movement execution (e.g. (Sherrington 1913)). The mechanism of this coordination between rhythmic arm movement and SOL RI cannot be fully deduced from our methodology. However, it is worth noting related modulation by contralateral movement previously reported between the arms (Delwaide et al. 1988). Both passive and voluntary contralateral arm movements were found to increase the amplitude of RI in the opposite flexor carpi radialis muscle. Taken together, these effects were attributed to

Ia interneuron facilitation via segmental Ia afferent fibers originating within the mobilized arm (Delwaide et al. 1988). This supposition was later reinforced using remote stimulation to effect contralateral RI response (Delwaide and Pepin 1991). The current results extend this concept of remote limb movement modulating RI from a contralateral effect to an arm-to-leg conditioning effect. Whether a common signaling source invokes reinforcement of RI within (e.g. from arm to arm) as well as between limb (e.g. from arm to leg) pairs is unknown.

Unlike the clear observations of movement-induced modulation of RI in the extensor SOL, no effect was seen in flexor TA at any stimulus intensity. This is contrary to our hypothesis of a global descending influence of remote movement on RI in the lower limb, based on previous observations of increased RI in the SOL and TA during walking (Kido et al. 2004). It is likely that this arises due to different signalling pathways activated with remote (e.g. arm to leg) vs. local (leg to leg) limb movement. Instead, our findings are consistent with our prior report of differential effects of arm movement on H-reflex amplitude modulation in ankle flexor and extensors (Dragert and Zehr 2009). Thus, they provide further evidence of muscle-specific signaling patterns elicited by rhythmic arm movement to the lower limbs. Differences in descending effects of rhythmic arm movement on flexor and extensor muscles may be related to increased levels of cortical drive to the ankle flexors compared to the extensors during rhythmic movement (Bawa et al. 2002; Capaday et al. 1999; Dragert and Zehr 2011). This suggestion fits with the proposed mechanisms underlying SOL RI enhancement. Thus, it appears that descending motoneuronal signals originating from higher spinal centers

impact SOL Ia inhibitory interneuron excitation more strongly than in the TA, where instead cortically-based descending inputs dominate. The end result is differential modulatory effects of remote limb movement within this agonist/antagonist muscle pair, and a bias towards reinforcement of dorsiflexion.

Similar to other studies, RI was scaled relative to stimulus intensity in both muscle groups, with larger stimulus intensities leading to a greater depression of EMG activity and thus a larger response (Kido et al. 2004; Petersen et al. 1999; Capaday et al. 1990), the so-called “automatic gain compensation” of Matthews (Matthews 1986) (see Figure 3.1). The present work builds on these previous studies, such that multiple stimulus intensities, including sub- and supra-motor threshold, were investigated for their impact on remote movement conditioning. Our comprehensive approach clearly shows the similar effect of stimulus intensity on RI across lower limb muscle groups. It also demonstrates the lack of movement-induced modulatory response in TA, irrespective of stimulus intensity. This is helpful information, given previous concerns raised in the literature that stimulus intensity may impact the ability to observe conditioning effects on RI (e.g. (Petersen et al. 1998)). Indeed, significant modulation of SOL RI response in the present work was seen only at 1.0xMT.

While the current findings do not directly reflect the motor patterns of walking, they provide further insight into the influence of the arms on the legs during a reflexively similar rhythmic locomotor activity (Balter and Zehr 2007; Zehr et al. 2007). We have shown that arm movement leads to RI reinforcement in the plantarflexors, and suggest

that rhythmic arm cycling may access spinal networks related to locomotor control that have asymmetrical outputs to functional antagonists. If active during whole body locomotion, this could ensure adequate dorsiflexion and foot clearance in the swing phase of gait, which would align with previous reports of increased inhibition from dorsi- to plantarflexors during this walking phase (Petersen et al. 1999). More in-depth study (e.g. assessing the presence of phasic modulation found at different positions, extent of plastic adaptation) of this interlimb RI effect is warranted, and will aid in extrapolating specifics on its action and possible extended functional role during walking.

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4. Bilateral neuromuscular plasticity from unilateral training of the ankle dorsiflexors³

4.1 Abstract

Training a muscle group in one limb yields strength gains bilaterally – the so-called cross-education effect. However, to date there has been little study of the targeted application of this phenomenon in a manner relevant to clinical rehabilitation. For example, it may be applicable post-stroke, where hemiparesis leads to ankle flexor weakness. The purpose of this study was to examine the effects of high-intensity unilateral dorsiflexion resistance training on agonist (tibialis anterior, TA) and antagonist (plantarflexor soleus, SOL) muscular strength and H-reflex excitability in the trained and untrained limbs. Ankle flexor and extensor torque, as well as SOL and TA H-reflexes evoked during low-level contraction, were measured before and after five weeks of dorsiflexion training (n = 19). As a result of the intervention, dorsiflexor maximal voluntary isometric contraction force (MVIC) significantly increased ($p < 0.05$) in both the trained and untrained limbs by 14.7% and 8.4%, respectively. No changes in plantarflexor MVIC force were observed in either limb. Significant changes in H-reflex excitability threshold were also detected: $H_{@thresh}$ significantly increased in the trained TA and SOL; and $H_{@max}$ decreased in both SOL muscles. These findings reveal that muscular crossed effects can be obtained in the ankle dorsiflexor muscles, and provide novel information on agonist and antagonist spinal adaptations that accompany unilateral training. It is possible that the ability to strengthen the ankle dorsiflexors bilaterally could

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be applied in post-stroke rehabilitation, where ankle flexor weakness could be counteracted via dorsiflexor training in the less affected limb.

4.2 Introduction

High intensity resistance training is a robust and well-established method of evoking muscular adaptation. Within 6 weeks of resistance training, there is an increase in strength that occurs in the absence of functionally significant myogenic changes and is therefore attributable to adaptation in the nervous system (Abe et al. 2000; Moritani and deVries 1979; for reviews, see Bird et al. 2005; Folland and Williams 2007). Such gains may be especially applicable in a rehabilitative setting, where short-term resistance training could be used to improve muscular strength and functional ability in individuals suffering from neuromuscular deficits (Taylor et al. 2005).

Recently, measurement of spinal reflex excitability (using the Hoffmann (H-) reflex) has allowed for estimation of spinal cord neural plasticity during resistance training (Aagaard et al. 2002; Lagerquist et al. 2006b). Resistance training may alter alpha-motoneuron pool excitability as well as the level of presynaptic inhibition (PSI) of Ia afferent transmission, leading to modulated H-reflex amplitude (Aagaard 2003; Lagerquist et al. 2006b; Zehr 2006). Thus, when paired with observed strength gains, change in amplitude may reveal information on spinal mechanisms underlying these gains. Given that spinal afferent feedback from a muscle reinforces targeted muscle activation (i.e. positively supports the trained movement), it stands to reason that this

feedback should increase with targeted training. Indeed, such findings have been noted previously (Aagaard et al. 2002; Holtermann et al. 2007; Lagerquist et al. 2006b).

In addition to adaptations in the trained limb, neural adaptations associated with unilateral resistance training have been found to cause strength gains in the untrained limb. This phenomenon was originally described by Scripture et al. (1894) as cross-education and has also been referred to as a muscular crossed effect (Carroll et al. 2006; Lee and Carroll 2007; Scripture et al. 1894; Zhou 2000). Cross-education has been shown to occur in neurologically intact subjects following short-term (i.e. 4-6 weeks) high-intensity unilateral resistance training (Munn et al. 2005). It is currently uncertain where the adaptations occur in the nervous system and both spinal and supraspinal factors have been proposed. It was recently shown that despite bilateral gains in plantarflexion strength (i.e. training adaptation in the soleus muscle, SOL) after 5-weeks of unilateral training, H-reflex amplitudes were increased only in the SOL muscle of the trained limb (Lagerquist et al. 2006b). These findings were suggested to have arisen due to different loci for the adaptations in the trained and untrained leg. Both spinal and supraspinal contributions were suggested for the trained leg, but only supraspinal contribution within the untrained leg (Carroll et al. 2006; Lagerquist et al. 2006b).

It is of interest to determine whether similar reflex adaptation and strength gains can be made in other muscles, particularly those of direct relevance for locomotor control and which are typically affected by neurotrauma such as the tibialis anterior (TA) muscle. This ankle dorsiflexor muscle plays a significant role in appropriate movement execution

during walking, and its weakness contributes to inappropriate ankle movement during gait in various clinical groups (Sackley et al. 2009). Earlier research has evaluated changes in strength and spinal cord excitability following various dorsiflexion training paradigms (Christie and Kamen 2010; Van Cutsem et al. 1998), but have not included observation of TA H-reflex responses. Further, while increased spinal reflex excitability following training has been observed in the SOL muscle, differences in descending drive to the ankle dorsiflexors and plantarflexors during acute movement have been noted previously (Capaday et al. 1999; Dragert and Zehr 2009; Rossignol et al. 2006; Schubert et al. 1997). Thus, it is uncertain whether observations for SOL spinal reflex adaptation following resistance training are broadly applicable within the lower limb.

Another aspect of training-induced reflex adaptation that has been neglected in the literature is the study of reflex response in the muscle group antagonistic to the trained movement. No work to date has investigated antagonist H-reflex adaptation following resistance training. Given the nature of reciprocal inhibition between the ankle flexor and extensor muscles (e.g. Tanaka 1974) and the clear observation that SOL H-reflexes amplitudes are reduced during dorsiflexion movement (Morita et al. 2001), it could be reasoned that antagonist (SOL) H-reflex amplitudes evoked at rest or low-level contraction should be concurrently reduced following a period of dorsiflexor resistance training. However, this hypothesis has not been confirmed. Further, while agonist spinal reflex changes have been downplayed as a locus for the muscular crossed effect, it is unknown whether a reduced antagonist reflex response contributes to strength increases in the untrained agonist muscle following unilateral training. Previous work by Carolan

and Cafarelli (1992) found that unilateral isometric resistance training lead to significantly reduced antagonist muscle activation (measured via EMG recordings) in both the trained and untrained lower limbs. However, this finding has not been universal, with a number of studies failing to detect any change in antagonist co-activation following agonist resistance training (Aagaard et al. 2000; Colson et al. 1999; Hakkinen et al. 1998; Hortobagyi et al. 1996; Reeves et al. 2005). Further, no study to date has built on the findings of Carolan and Cafarelli (1992) to determine what, if any, changes in antagonist Ia afferent excitability may accompany enhanced agonist force production. Such research may help to resolve the discrepancies between past findings, while also expanding our understanding of the specific neural mechanisms that underlie the muscular crossed effect.

The purpose of this study was to investigate the effects of a 5-week high-intensity unilateral dorsiflexion resistance training program on agonist (TA) and antagonist (SOL) maximal muscular strength and H-reflex excitability during tonic low-level contraction in the trained and untrained limbs. H-reflex recruitment curves were used to probe for training-induced spinal cord plasticity. Using a recruitment curve approach allows for sampling a variety of motor unit sizes contributing to the compound H-reflex (Buchthal and Schmalbruch 1970), which may be more sensitive to subtle changes occurring in different populations. Interestingly, recent work that monitored a single H-reflex size following plantarflexor resistance training found no cross-education of spinal excitability (Fimland et al. 2009). Such a finding further highlights the need for a broader reflex sampling window when investigating potential training adaptations. Thus, we

investigated a set of parameters extracted from the recruitment curves to assess possible differential training-induced plasticity affecting a range of H-reflex amplitudes, which has not been evaluated previously following a resistance training intervention.

We hypothesized that the present training paradigm would increase dorsiflexion strength bilaterally and facilitate trained TA H-reflex excitability concurrent with reduced SOL H-reflex excitability in the trained limb. Since we previously speculated supraspinal loci of muscular crossed effects (Lagerquist et al. 2006b), we hypothesized that TA and SOL spinal reflex excitability would remain unchanged in the untrained limb. The ankle dorsiflexors were targeted because of the important functional role subserved during locomotion. We aimed to observe responses in a neurologically intact subject group as an initial step toward application of a similar training paradigm in a clinical group.

4.3 Materials and methods

4.3.1 Participants

Nineteen participants (eight men and 11 women), aged 23 to 52 years and with no known history of neurological impairment, were involved in this study. Participants provided informed written consent to a protocol approved by the University of Victoria Human Research Ethics Committee and performed according to the Declaration of Helsinki.

4.3.2 Experimental design

The study used a repeated-measures (pre/post-test) quasi-experimental design, with all participants completing a right-ankle dorsiflexion training program. For some participants, it was not possible to elicit either SOL or TA reflex responses in one or both legs (including subjects whose TA recruitment curve data were unsuitable for inclusion; see Results, Change in Reflex Excitability). Further, exclusion of some data sets was required and, for clarity, sample size is provided for each method undertaken.

To confirm reliability of baseline measures, including familiarization to experimental procedures, the first 14 subjects recruited for the study participated in two “baseline” experimental sessions over a period of one to two weeks, with at least two days between sessions. During these sessions, maximal voluntary isometric contraction (MVIC) (dorsiflexion and plantarflexion torque $n = 11$) and static H-reflex recruitment curve measurements were taken (right TA $n = 6$, left TA $n = 4$; right and left SOL $n = 13$). Reflexes were sampled while a tonic low-level contraction was maintained in the muscle group in which reflexes were evoked for that trial (calculated grand mean: $12.8 \pm 3.7\%$ MVIC). The data from these two sessions were analyzed, and no significant differences were observed for any variables tested in either leg ($p > 0.05$; data not shown). Thus, reliability of single session baseline testing was confirmed, and baseline measures were established for the remaining participants during one experimental session only. Subjects who completed two baseline sessions had data from their second session (i.e. the session closest to onset of the intervention) used for post-training comparison. Following baseline measurement, participants completed an isometric resistance training protocol. Post-training data were collected within three days of the final training session.

Across the study, environmental conditions (i.e. temperature, noise, lighting, subject position) during training and data collection were kept as constant as possible, including session time of day as per recommendations from Lagerquist et al. (2006a) and Zehr (2002).

4.3.3 Training protocol

Training sessions were completed with participants in a seated position with ankle, knee and hip angles maintained at angles consistent to that specified during data collection. A simple custom-built foot brace that immobilized the foot during contraction and ensured a constant ankle angle during and across training sessions was fit to each participant. Participants trained in 25 minute sessions, three days a week for five weeks. This training duration is similar to that used in previous investigations of neural adaptation associated with resistance training (e.g. Geertsen et al. 2008; Lagerquist et al. 2006b), and has been suggested to preclude significant morphological myogenic adaptations as a contributor to any observed strength gains (Abe et al. 2000; Bird et al. 2005; Moritani and deVries, 1979). Training sessions involved a warm-up of three sets of five repetitions of unilateral, submaximal (~50% MVC), isometric dorsiflexion contractions separated by two minute rest periods (Lagerquist et al. 2006b). Following warm-up, participants completed five sets of five isometric repetitions held for five seconds at maximal voluntary effort. A two second rest interval was provided between contractions and a two minute rest interval between sets. Similar to previous unilateral training studies, subjects were instructed and reminded repeatedly throughout the training

sessions to keep the untrained leg relaxed (Munn et al. 2005), as well as to relax the SOL and VL muscles in the trained leg to minimize co-contraction and heteronymous effects.

4.3.4 Data collection protocol

Participants were seated in a custom-fitted chair designed to minimize trunk and leg movement, with ankle, knee and hip angles maintained at approximately 100, 120 and 90 degrees, respectively (Frigon et al. 2004; Lagerquist et al. 2006b; Loadman and Zehr 2007). Following a brief isometric warm-up, MVIC measurements were taken in both legs for both muscle groups. Static H-reflex recruitment curves were then generated and recorded bilaterally in the presence of tonic low-level contraction (Dragert and Zehr 2009; Frigon et al. 2004; Loadman and Zehr 2007; Zehr et al. 2007b). During H-reflex trials, a constant arm position was maintained to control for impact on lower limb reflex response (Dragert and Zehr, 2009; Frigon et al. 2004; Loadman and Zehr 2007). All data were recorded using custom-written LABVIEW virtual instruments (National Instruments, Austin, TX).

4.4 MVIC

Subjects were given three attempts (2 minutes rest between each) for achieving both dorsiflexion and plantarflexion MVIC (held 3 to 5 seconds) for each leg separately. Maximum forces produced during dorsi- and plantarflexor contractions were measured via a load cell (Omegadyne Ltd. Model 101-500) and converted to torque at the ankle. MVIC for each leg was taken as the average of the greatest torque values generated over the three trials for each muscle observed (n = 18 and 19 for dorsi- and plantarflexor torque, respectively).

4.5 EMG recordings

EMG was recorded using surface electrodes applied in bipolar configuration over the SOL, TA, and vastus lateralis muscles (VL). Using anatomical landmarks, EMG and stimulation electrodes were placed by the same experimenter for all sessions to control for variation in pre-post test electrode positioning, and data collected and analyzed from the two baseline sessions confirmed reliable EMG and H-reflex recordings prior to the intervention. EMG signals were amplified (GRASS P511, AstroMed) and band pass filtered from 100 to 1000 Hz (SOL, TA) or 100 to 300 Hz (VL). The output was sent to the A/D interface (National Instruments, Austin, TX.) and the computer sampled at 5000 Hz. All trials were performed while a tonic low-level contraction (~10-15% MVIC) was maintained by the muscles (either SOL or TA) in which reflexes were evoked for that trial. To assist in maintaining a constant EMG level during recruitment curve acquisition, subjects were provided visual feedback of their contraction level on an analogue oscilloscope.

H-reflexes were elicited and recorded following procedures previously described (Frigon et al. 2004; Loadman and Zehr 2007; Zehr et al. 2007b). Briefly, bipolar stimulation (0.5ms pulse) was delivered pseudo-randomly every 2-5s using either Digitimer (model DS7A, Medtel, NSW, Australia) constant current stimulator, or a Grass S88 stimulator connected to a SIU5 isolation unit and a CCU1 constant current unit (AstroMed Grass, Inc.). Stimulating electrodes were placed over the posterior tibial nerve at the popliteal fossae (SOL muscle), and over the common peroneal nerve at the fibular

head (TA muscle). M-wave and H-reflex recruitment curves were constructed for each condition using 40 sweeps while stimulation current was concurrently measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL. and also custom-built current monitors).

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). For each subject, M-waves and H-reflexes were normalized to the corresponding M_{\max} (with H-reflex data consequently expressed as a percentage of M_{\max}) to reduce inter-subject variability. 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 (Klimstra and Zehr 2008; Zehr et al. 2007b; Zehr et al. 2007c).

As part of the curve fitting procedure, average H_{\max} and M_{\max} were calculated from the three largest H-reflexes and M-waves, respectively. Then, from the curve fit analysis, other variables analyzed included the following: 50% H_{\max} ; H-reflex threshold (H_{thresh}), i.e. the initial H-reflex response detected at the lowest current intensity; and H_{slope} , i.e. the slope of the ascending limb of the recruitment curve at 50% of the H_{\max} value (Klimstra and Zehr 2008; Loadman and Zehr 2007; Zehr et al. 2007b).

Further, predicted “fitted curve” values were also calculated, as described elsewhere (Klimstra and Zehr 2008). Briefly, the current intensities coincident with the H-reflex variables taken from the pre-training recruitment curves were used as inputs to

the equations describing the post-intervention recruitment curves. This procedure allowed for comparison of reflex amplitudes at the same relative current intensities pre- and post-training, which has the largest sensitivity for detecting training-induced plasticity. That is, the presence or absence of shifts in the recruitment curve at different normalized stimulus intensities could be investigated, and therefore motor units with different recruitment thresholds evaluated for change in sensitivity. This is similar in practice to our previous use of this procedure in examining H-reflex amplitudes in control situations and when conditioned by rhythmic movement (Zehr et al. 2007b, Zehr et al. 2007c). To differentiate the description of the reflex variables taken from the fitted curves from the standard recruitment curve variables, they are described as “@” the value from control.

The following predicted values were analyzed: $H_{@thresh}$, reflecting recruitment of the lowest threshold motor units; $H_{@max}$, reflecting recruitment of the highest threshold motor units; and $H_{@50\%}$, reflecting intermediary threshold units (Buchthal and Schmalbruch 1970). For the variables to which it applied, the pre-intervention H-reflex value was compared to both its post-intervention equivalent as well as the predicted $H_{@}$ value; for example, pre-intervention H_{thresh} was contrasted against post-intervention H_{thresh} and $H_{@thresh}$ in separate analyses.

4.6 Statistics

Utilizing STATISTICA software (version 6.1, StatSoft, Tulsa, OK), paired t-tests were used to identify significant effects of isometric resistance training on the variables of interest. Right and left leg data were analyzed separately. In the trained limb, we

predicted increased dorsiflexor strength, as well as facilitated TA and suppressed SOL H-reflex amplitudes during the respective TA and SOL recruitment curve trials. Further, while dorsiflexor strength was predicted to increase in the untrained limb, TA and SOL spinal reflex excitability were expected to remain unchanged in this limb. To establish that an accurate goodness of fit had been achieved for the fitted recruitment curves, we employed a minimum critical value for Pearson product-moment correlation coefficient (r) for data inclusion (Sheskin 2004). Based on the directional alternate hypothesis of $p > 0$ for this variable, the critical value for a one-tailed test at $p \leq 0.05$, $df = 38$, was set at $r = 0.2642$ (Sheskin 2004).

For hypotheses where direction of change was predicted, one-tailed paired t-tests were performed (i.e. H-reflex response in the right leg and TA force in both legs). For all other variables, two-tailed tests were completed. Statistical significance was set at $p \leq 0.05$.

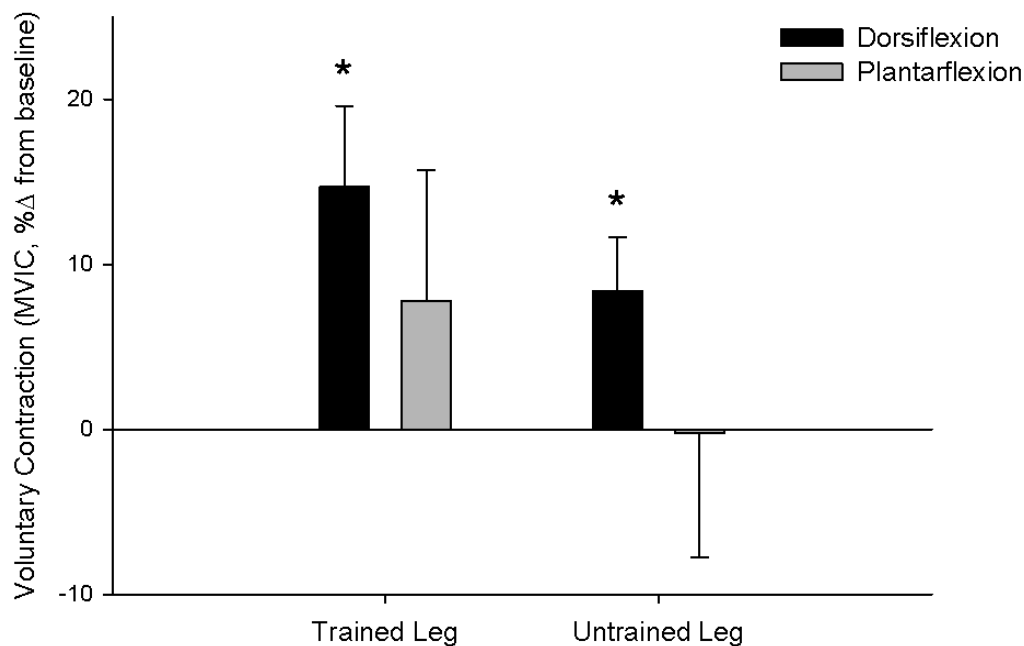


Figure 4.1: Dorsiflexion training increased strength bilaterally. Grand mean maximal voluntary isometric contraction (MVIC) data are displayed as percent change from baseline and post-intervention measures in the trained and untrained legs. In the dorsiflexors (black bars), mean data showed a significantly increased MVIC in both the trained and untrained legs (Cohen's $d = 0.25$ and 0.33 for the trained and untrained leg, respectively). In the plantarflexors (grey bars), no significant change was detected in either leg (Cohen's $d = 0.17$ and 0.12 for the trained and untrained leg, respectively). Data are means \pm S.E. * indicates differences pre-post at $p \leq 0.05$.

4.7 Results

4.7.1 Strength gains arising from training

The strength training intervention yielded significant increases in dorsiflexion MVIC bilaterally. Following the intervention, dorsiflexor MVIC increased by 14.7% in the trained limb ($p = 0.006$), and by 8.4% in the untrained limb ($p = 0.015$) compared to pre-training measures (see Table 4.1, Figure 4.1). These observed changes were also compared between limbs, from which it was determined that the relative gain did not significantly differ between the trained and untrained side ($p = 0.52$; data not shown).

Plantarflexor MVIC remained unchanged in both the trained and untrained limbs ($p = 0.52$ and $p = 0.54$, respectively).

Muscle Group	Variable	n	Untrained Leg		P	d	n	Trained Leg		P	d
			Pre-Intervention	Post-Intervention				Pre-Intervention	Post-Intervention		
SOL	MVIC (Nm)	19	29.50 (11.34)	28.05 (12.83)	0.54	0.12	19	37.54 (9.87)	39.49 (13.44)	0.52	0.17
	Pre-stim EMG (%MVIC)	19	12.81 (3.87)	12.27 (2.55)	0.60	0.16	19	12.67 (3.51)	12.30 (2.35)	0.68	0.12
	ANT Bkg EMG (%M _{max})	11	0.03 (0.01)	0.02 (0.008)	0.41	0.33	9	0.03 (0.03)	0.06 (0.05)	0.60	0.68
	M _{max} (mV)	19	7.94 (2.87)	7.42 (3.06)	0.32	0.18	19	8.92 (3.46)	8.05 (2.62)	0.11	0.28
	H _{max} (%M _{max})	19	51.89 (14.39)	49.69 (15.25)	0.28	0.15	19	51.37 (16.02)	48.72 (20.22)	0.12	0.15
	H _{slope}	19	4.11 (2.62)	3.35 (2.63)	0.15	0.29	19	4.51 (4.11)	3.23 (1.99)	0.08	0.40
	H _{@thresh} (%M _{max})	19	6.20 (1.73)	12.75 (15.42)	0.09	0.60	19	6.11 (1.89)	16.63 (15.82)	0.004*	0.93
	H _{@50%} (%M _{max})	19	26.04 (7.26)	19.09 (17.45)	0.17	0.52	19	25.74 (8.05)	28.04 (18.05)	0.26	0.16
	H _{@max} (%M _{max})	19	45.68 (12.66)	28.92 (18.75)	0.006*	1.05	19	45.22 (14.10)	40.27 (18.35)	0.03*	0.30
	TA	MVIC (Nm)	18	23.07 (6.92)	24.99 (8.41)	0.02*	0.25	18	23.22 (8.09)	25.78 (7.51)	0.006*
Pre-stim EMG (%MVIC)		11	13.22 (5.67)	12.91 (2.25)	0.83	0.07	9	11.78 (2.34)	12.46 (1.40)	0.38	0.35
ANT Bkg EMG (%M _{max})		19	0.32 (0.14)	0.35 (0.23)	0.55	0.19	19	0.20 (0.16)	0.11 (0.09)	0.02*	0.70
M _{max} (mV)		11	2.93 (1.39)	2.99 (1.56)	0.85	0.04	9	2.66 (1.24)	2.81 (2.00)	0.40	0.09
H _{max} (%M _{max})		11	13.93 (6.34)	14.93 (6.82)	0.67	0.15	9	12.20 (4.73)	15.78 (6.43)	0.13	0.64
H _{slope}		11	0.67 (0.72)	0.36 (0.25)	0.22	0.56	9	0.49 (0.48)	0.47 (0.22)	0.45	0.06
H _{@thresh} (%M _{max})		11	1.76 (0.90)	3.55 (2.64)	0.08	0.91	9	1.84 (0.73)	4.40 (3.28)	0.03*	1.08
H _{@50%} (%M _{max})		11	6.95 (3.20)	5.93 (3.04)	0.37	0.33	9	6.10 (2.37)	6.90 (4.08)	0.35	0.24
H _{@max} (%M _{max})		11	12.40 (5.48)	10.53 (6.01)	0.43	0.33	9	10.75 (4.16)	12.89 (7.89)	0.26	0.34

Table 4.1: Group data of trained and untrained leg for SOL and TA MVIC, pre-stimulus agonist and antagonist EMG, M_{max} and H-reflex measures.

Values are means (SD). MVIC, maximal voluntary isometric contraction; ANT Bkg EMG, pre-stimulus antagonist muscle background EMG during opposing muscle's H-reflex trial; M_{max}, maximal M waveform, in millivolts (mV); H_{max}, maximal H waveform, as a percentage of M_{max} (%M_{max}); H_{slope}, slope of the ascending limb of the H-reflex recruitment curve; H_@, predicted fitted curve value; P, probability level; d, Cohen's effect size. *Significant at $P \leq 0.05$

4.7.2 Change in reflex excitability

To determine the goodness of fit between the recruitment curve data collected and the generated sigmoid curve, Pearson Product-moment correlation coefficient (r) values were calculated for each trial, and data sets were required to meet or exceed a criterion value of $r = 0.2642$ for inclusion. Values for SOL trials displayed a large degree of covariance, with a grand mean (calculated via Fisher z-transform processing) of 0.92 and

0.95 for the right and left legs, respectively. Response variability in TA recruitment curve data points gave rise to a weaker fit to the generated curves, with grand means of 0.46 for both right and left legs. Further, a poor fit for pre- and/or post-intervention TA data points led to the exclusion of some subjects' TA H-reflex data from further analysis. The final sample sizes for reflex analyses were as follows: $n = 9$ and 11 for trained and untrained TA, respectively, and $n = 19$ for both SOL muscles.

Following the intervention, significant changes in H-reflex recruitment curve parameters were seen in the trained TA and bilaterally in SOL (see Table 4.1, Figures 4.2, 4.3). $H_{@thresh}$ was significantly increased in the trained TA and SOL ($p = 0.03$ and 0.004 , respectively). Further, $H_{@max}$ was significantly decreased bilaterally in the SOL ($p = 0.03$ and $p = 0.006$ in the trained and untrained legs, respectively; see Table 4.1, Figures 4.2, 4.3). There were no other significant changes from pre-training H-reflex measures ($p > 0.05$; see Table 4.1).

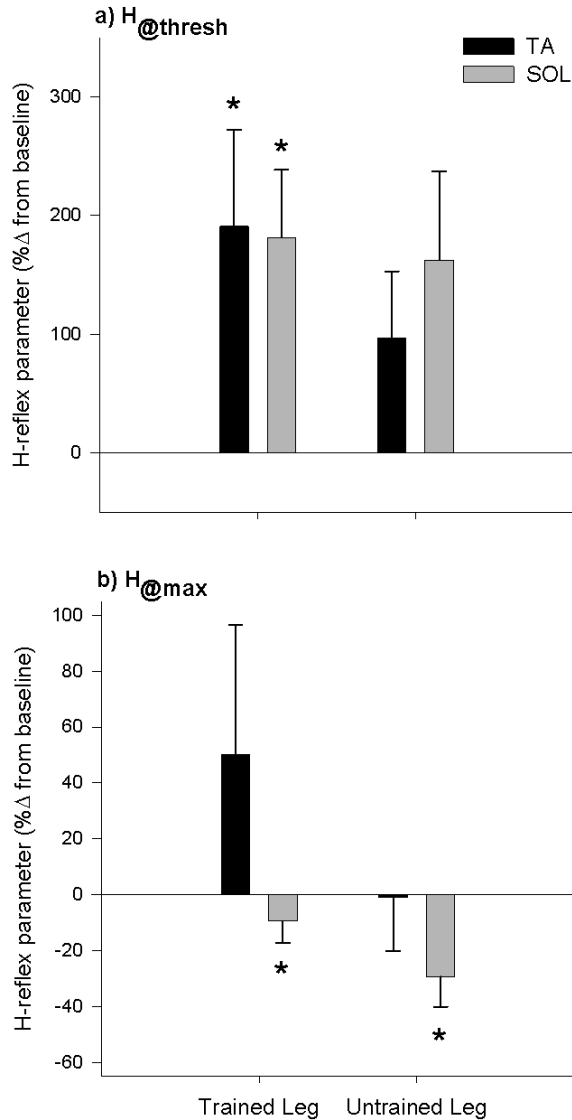


Figure 4.2: Dorsiflexion training altered TA and SOL H-reflex recruitment curve parameters bilaterally. Grand mean $H_{@thresh}$ (a) and $H_{@max}$ (b) recruitment curve data (collected during 10-15% MVIC of the muscle group in which reflexes were evoked) are displayed as percent change from baseline, i.e. zero, and post-intervention measures in the trained and untrained legs. a) Mean $H_{@thresh}$ data significantly increased post-intervention in the trained TA (black bars; Cohen's $d = 1.08$ and 0.91 for the trained and untrained leg, respectively) and in the trained SOL (grey bars; Cohen's $d = 0.93$ and 0.60 for the trained and untrained leg, respectively). Note that these $H_{@thresh}$ values are small, and thus the post-intervention increase appears as a very large percent change from baseline. b) Mean $H_{@max}$ data significantly decreased post-intervention bilaterally in SOL (Cohen's $d = 0.30$ and 1.05 for the trained and untrained leg, respectively). Data are means \pm S.E. * indicates differences pre-post at $p \leq 0.05$.

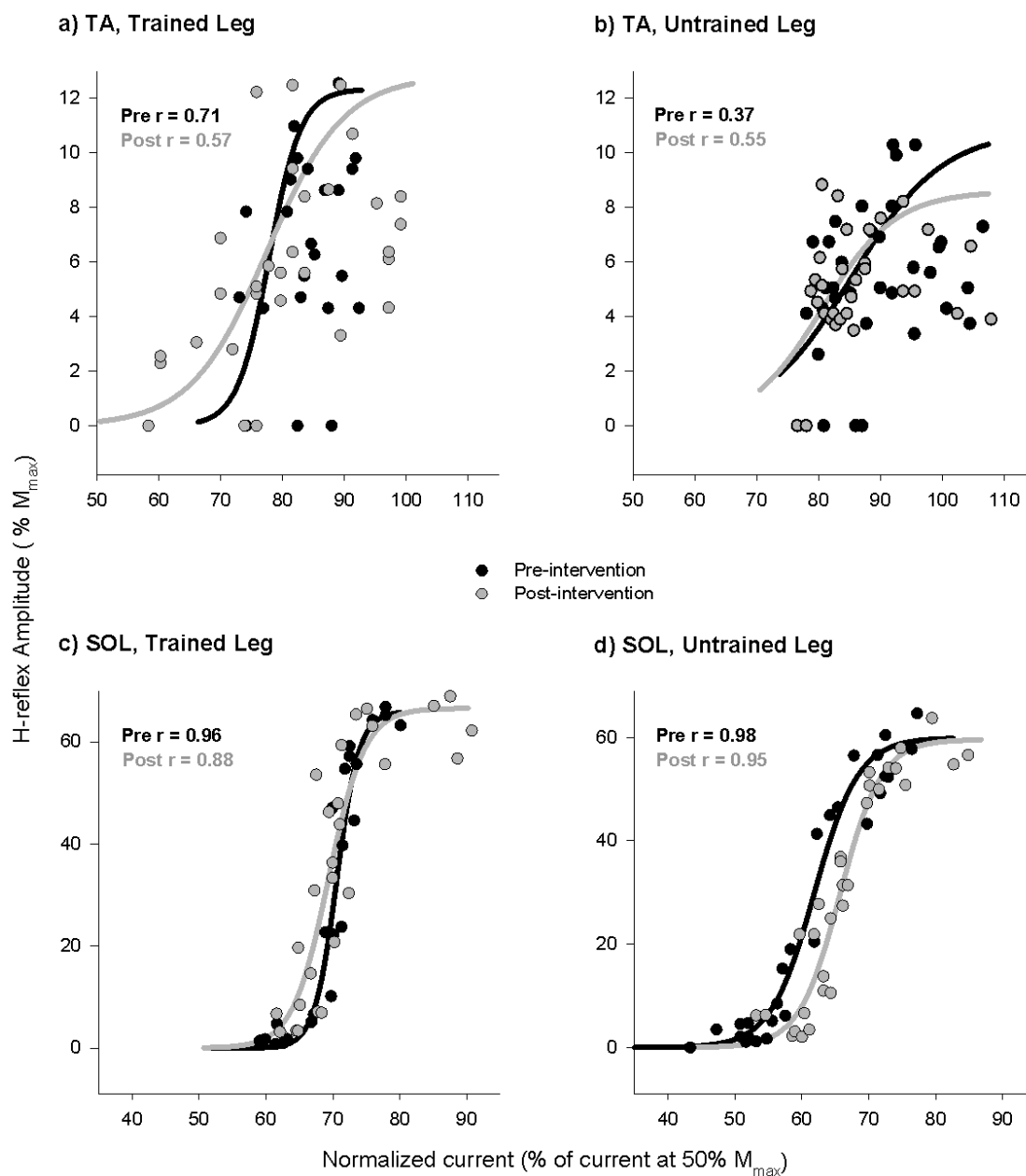


Figure 4.3: Example recruitment curve data taken from individual subjects pre- and post-intervention (black and grey lines/circles, respectively). The fitted lines correspond to the best-fit sigmoidal representation of the data, based on the recorded H-reflex data points displayed. The goodness of the lines' fits to their respective points is reported as Pearson product moment correlation coefficient (r) values within the figure. EMG data are normalized to the maximum M-wave amplitude (M_{max}) for that trial, and corresponding current values are normalized to current at 50% of M_{max} .

4.7.3 Background EMG

For pre / post-intervention session comparison, maximal M-wave amplitude, EMG levels within the target and antagonist muscles were well controlled (see Table 4.1). Significant differences were detected in trained leg TA background EMG during SOL H-reflex trials, with EMG activity significantly decreased post-intervention ($p = 0.02$; see Table 4.1). Besides this variable, there were no other differences observed during H-reflex data collection in any muscles for these parameters.

To exclude the possibility that observed increases in dorsiflexor MVIC post-intervention were at least in part due to changes in antagonist activation level, SOL background EMG during MVIC trials was compared to pre-intervention values. No significant change in SOL activation level during dorsiflexor MVIC was observed in either leg ($p > 0.05$; data not shown).

4.8 Discussion

Following five weeks of unilateral high-intensity isometric dorsiflexion training, subjects significantly increased strength in both the trained and untrained leg, thus demonstrating for the first time a muscular crossed effect in the ankle dorsiflexors. Following training, it was found that $H_{@thresh}$ significantly increased from baseline; i.e. the H-reflex amplitude evoked by threshold stimulation intensities before training was significantly enhanced after training. That is, the “foot” of the H-reflex recruitment curve was evoked at lower stimulus intensity than that required to elicit a response at pre-training baseline (see Table 4.1, Figure 4.3). Thus, while the recruitment threshold

(H_{thresh}) remained unchanged, the gain of the threshold response increased such that more low-threshold motor units were recruited. This effect was observed for the TA and SOL of the trained limb. Further, SOL $H_{\text{@max}}$ was significantly decreased in both the trained and untrained limb; i.e. at the given current value for H_{max} at baseline, the post-intervention H-reflex amplitude was reduced (see Table 4.1, Figure 4.3). This suggests that there was a reduction in excitability of the largest H-reflexes of the antagonist muscles when comparing post-intervention to pre-training baseline. We propose that these adaptations suggest the presence of subtle spinal adaptation associated with cross-education, and may also reflect generalized descending inputs on lower limb spinal response following resistance training. Furthermore, this may represent a differential effect of training on ankle dorsiflexors compared to previous work with plantarflexors. We believe our findings to be the first evidence of plastic adaptation in bilateral antagonist muscle spinal reflex output induced by unilateral training.

4.8.1 Crossed effects in the ankle dorsiflexors

The findings of this study broaden the observation of muscular crossed effects within the lower limb to the TA muscle group, an ankle dorsiflexor. The increases in strength for the trained and untrained leg were 14.7% and 8.4%, respectively, which is in agreement with recent reviews and meta-analyses on the typical anticipated magnitude of muscular crossed effects (Carroll et al. 2006; Munn et al. 2004). While previous research has observed muscular crossed effects in the upper limb flexor muscles (e.g. Farthing et al. 2005; reviewed by Carroll et al. 2006; Farthing 2009; Munn et al. 2004), this is the first study to investigate these effects in lower limb flexor muscles. Our results

demonstrate that unilateral isometric dorsiflexion training is an effective method of inducing significant strength gains in the contralateral ankle dorsiflexor muscles.

4.8.2 Generalized enhancement of spinal cord reflex excitability

The finding of increased $H_{@thresh}$ provides evidence that following unilateral dorsiflexion training, the ability to recruit motor neurons in the reflex arc is increased in the trained limb. Specifically, it appears that there is a training-induced change in either presynaptic inhibition of Ia afferent transmission or motoneuron pool excitability so that motor units are recruited into the compound H-reflex at lower stimulation intensities. It is also worth noting that while $H_{@thresh}$ in the untrained TA was not significantly increased, the calculated effect size was large ($d = 0.91$). Thus, a strong relationship pre- to post-intervention was present in this muscle group, which may merit a more greatly powered investigation than could be provided in the present work. As it stands, these observations in the untrained TA muscle, combined with the findings of significant change detected in the agonist and antagonist muscles of the trained limb, hint at modulation of spinal cord excitability that is due to a broadly applicable descending signal to the lower limbs. That is, a generalized descending signal that impacts both the trained and untrained muscle groups, i.e. whole motoneuron pool excitability, of the lower limbs could result from resistance training. However, confirmation of this suggestion is beyond the scope of the methods employed in the present work and would require direct study of descending signals (e.g. corticospinal) and their response to resistance training in the future. Further, it would be crucial to determine what impact a larger sample size may have on untrained TA H-threshold response under a similar resistance training paradigm. The inherent

variability in TA H-response, as shown presently as well as in past research (e.g. Dragert and Zehr 2009), epitomizes future challenges when undertaking such work.

4.8.3 Differential ankle dorsiflexion and plantarflexion regulation following training

Although the concept of chronic spinal reflex adaptation due to high-intensity resistance training is accepted in the literature (e.g. Aagaard 2003; Gabriel et al. 2004; Zehr 2006), evaluation of such adaptation utilizing H-reflex as a measurement tool is a recent development and has been limited to the SOL muscle, an ankle plantarflexor (Aagaard et al. 2002; Geertsens et al. 2008; Lagerquist et al. 2006b). This is the first targeted resistance training study focused on spinal reflex modulation within an ankle dorsiflexor muscle group. Variation in TA muscle reflex adaptation in this study compared to previous work from our laboratory and others highlights differences that may exist between the ankle dorsiflexor and plantarflexor muscles (Bawa et al. 2002; Capaday et al. 1999; Dragert and Zehr 2009). Differences in descending drive to these two muscle groups during short duration movement tasks have been highlighted previously (e.g. Bawa et al. 2002; Capaday et al. 1999; Dragert and Zehr 2009; Rossignol et al. 2006; Schubert et al. 1997). Studies in the cat have revealed differential modulation in spinal cord locomotor output for leg flexors and extensors during rhythmic movement (Rossignol et al. 2006). For example, flexor and extensor motoneurons are suggested to be excited by separate groups of interneurons in the cat during fictive locomotion (Quevedo et al. 2000). In humans, differences in cortical influence on ankle dorsiflexor and plantarflexor motor responses have been observed during movement (Bawa et al. 2002; Capaday et al. 1999; Schubert et al. 1997). Bawa et al. (2002) noted that

corticomotoneuronal connections to the TA motoneuron pool are very strong, while similar connections to the SOL are weaker. Further, Capaday et al. (1999) found that during walking the corticospinal tract is more closely linked with segmental motor circuits that control the TA muscle than with those controlling the SOL muscle. Recent work in our laboratory showed bidirectional H-reflex modulation in the TA during rhythmic arm movement, while SOL H-reflexes were consistently suppressed (Dragert and Zehr 2009). These findings provided additional evidence of differential regulation between the ankle dorsiflexors and plantarflexors during a short duration motor task.

When the current observations of agonist TA reflex adaptation are compared to those reported previously in the SOL following a similar training paradigm (Lagerquist et al. 2006b), it may be inferred that there is differential regulation between ankle dorsiflexors and plantarflexors following training. This could be due in part to increased involvement of cortical drive to the ankle dorsiflexors (compared to plantarflexors) during the performance of the trained coordinated task. Thus, a training paradigm that previously revealed obvious H-reflex adaptation in the SOL (Lagerquist et al. 2006b) only resulted in more subtle spinal changes in the TA in the present study. As this is the first work to report comprehensive recruitment curve data in both agonist and antagonist muscle groups bilaterally following unilateral resistance training, it is not known whether a similar $H_{@thresh}$ effect can be seen following plantarflexion training. Despite the similar training paradigm, adaptive neural plasticity in reflex pathways to TA and SOL could differ. There is currently a general consensus in the literature that the neural plasticity associated with cross-education of strength has a supraspinal locus, no matter the muscle

group trained (Carroll et al. 2006; Farthing et al. 2005; Lagerquist et al. 2006b; Lee and Carroll 2007). To directly substantiate and comprehensively describe the presence of differential regulation between these muscle groups following training, future research is needed. Bearing in mind that our study using multiple measures of H-reflex excitability has shown an effect of cross-education whereas another recent study with a single reflex measure (Fimland et al. 2009) did not, we suggest future work should include recruitment curve acquisition in both groups, and comparison of the same measures of reflex excitability in each, following similar plantarflexor training.

4.8.4 Antagonist reflex response and force output

SOL $H_{@max}$ was significantly decreased during low-intensity (10-15% MVIC) isometric plantarflexor contractions in both the trained and untrained limb. This indicates that the training intervention resulted in reduced spinal excitability of high-threshold motor units within the muscle group antagonist to the trained movement. SOL $H_{@thresh}$ was also significantly increased in the trained limb. These adaptations may be indicative of a broad amplification of motoneuron pool excitability following unilateral dorsiflexion training. The observations in SOL of the trained limb agree with our prediction, which was based on the previous study of reflex changes during acute dorsiflexion movements (Morita et al. 2001), as well as work that found significantly decreased antagonist co-activation during MVC following maximal isometric training (Carolan and Cafarelli 1992). Although no change in antagonist background EMG was detected during MVIC or H-reflex trials, our observation of modulated reflex response corroborates this previous research.

The presence of plastic neural adaptation in the untrained SOL (as evidenced by the observed change in $H_{@max}$ in this muscle) was not predicted, based on previous findings in our laboratory (Lagerquist et al. 2006b). However, our earlier study only monitored spinal activity in the agonist and homologous muscle group on the untrained side. This study is the first to quantitatively measure spinal reflex activity bilaterally in a muscle that is functionally antagonist to a trained unilateral movement. Further, recruitment curve analysis allowed for detection of subtle shifts in the curve pre- to post-intervention. This adaptation represents an indirect adaptation (Zehr 2006) arising from training.

4.8.5 Translational implications for rehabilitation

The ability to produce muscular crossed effects in the dorsiflexor muscles has important implications for gait rehabilitation, particularly in hemiparesis arising after stroke. It is well established that following stroke, the use of resistance training is a safe, effective rehabilitation method for enhancing strength and function (see reviews in Duncan et al. 2005; Morris et al. 2004; Taylor et al. 2005). The training paradigm followed in this study fits well with current aims of post-stroke motor recovery, where increased strength of the weakened ankle dorsiflexors could help counter decreased ability to dorsiflex the ankle during the swing phase of gait (Dobkin 2003). Interestingly, this functional application of cross-education is similar in effect to a recent study by Farthing et al. (2009) who found that during three weeks of unilateral immobilization, concurrent unilateral strength training performed in the free limb attenuated loss of

strength in the immobilized limb. The present findings may be relevant for cases of severe post-stroke hemi-paresis where paretic limb re-training is not initially possible, but training the less-affected limb could establish a baseline of strength on the contralateral side. Caution must be taken in extrapolating our results too far as this approach has not yet been confirmed in a clinical group. Such work is currently being explored in our laboratory.

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5. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke⁴

5.1 Abstract

Hemiparesis after stroke decreases ability to dorsiflex the more-affected ankle during walking. Increased strength would be beneficial, but the more-affected limb is often too weak to be trained. In neurologically intact participants, training one limb induces strength gains in the contralateral, untrained limb. This approach remains unexplored post-stroke. The aim of this study was to test the hypothesis that unilateral dorsiflexor high-intensity resistance training on the less-affected side increases strength and motor output bilaterally following stroke. 19 participants (84.1±77.6mo post-infarct) performed 6wks of maximal isometric dorsiflexion training using the less-affected leg. Voluntary isometric strength (dorsiflexion torque, muscle activation), reciprocal inhibition (RI), walking ability (gait speed, kinematics, EMG patterns) and clinical function were measured within 1wk before and four days following training. Post-intervention, dorsiflexion torque increased by ~31% ($p<0.05$) in the more-affected (untrained) and by ~34% ($p<0.05$) in the less-affected (trained) legs. Muscle activation significantly increased bilaterally, by ~59% and ~20% in the trained and untrained legs, respectively). Notably, 4 participants who were unable to generate functional dorsiflexion on the more-affected side before training could do so post-intervention. Significant correlations between muscle activation and size of RI were noted across muscle groups before and after training, and the relation between size of RI and level of muscle activation in the

⁴ Dragert K, Zehr EP (2012) High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. *Exp Brain Res*. DOI 10.1007/s00221-012-3351-x

more-affected tibialis anterior muscle was significantly altered by training. Thus, significant gains in voluntary strength and muscle activation on the untrained, more-affected side after stroke can be invoked through training the opposite limb. We demonstrate residual plasticity existing many months post-stroke, and suggest clinical application of the cross-education effect where training the more-affected limb is not initially possible.

5.2 Introduction

Stroke leads to weakness and impaired motor function that is expressed as hemiparesis (Patten et al. 2004) and results in more (MA) and less-affected (LA) sides (Zehr and Loadman 2012; Zehr 2011; Barzi and Zehr 2008). Post-stroke weakness is common, and is often more evident in distal vs. proximal muscle groups (Patten et al. 2004; Zehr 2011; Adams et al. 1990; Krakauer 2005). An example of such weakness is often seen at the ankle where dysfunction in plantar- and dorsiflexion is evident. Indeed, maximal dorsiflexor torque on the more-affected side has been reported to be reduced to 38% of the less-affected side after stroke (Barzi and Zehr 2008). This leg flexor muscle weakness may also be combined with excessive extensor muscle activity, which presents as hyper-excitable reflex pathways (Barzi and Zehr 2008; Thompson et al. 2009) and which can contribute to further dysfunction. Concerning functional motor tasks, lower leg weakness will impair the ability to perform tasks of daily living, including moving from sitting to standing as well as walking (Zehr and Loadman 2012; Zehr 2011; Morris et al. 2004); for example, decreased dorsiflexion during the swing phase of walking leads to slow and inefficient gait (Zehr and Loadman 2012; Dobkin 2003). From this evidence, it

can be postulated that increased dorsiflexor (tibialis anterior (TA)) strength, alone or in the presence of decreased extensor (soleus (SOL)) hyper-excitability, may improve lower limb motor ability post-stroke. Resistance training improves muscular strength and functional ability after stroke (Zehr 2011; Duncan et al. 2005; Taylor et al. 2005), and can aid in motor recovery when combined with task-specific training protocols (Duncan et al. 2005; Eng 2004). Despite that, this training is often difficult to implement in post-stroke hemiparesis. Substantial MA limb weakness may prevent sufficient activation needed to gain a training effect (Olsen 1989).

Interestingly, short-term, high intensity resistance training on one side of the body causes “crossed” strength gains in the contralateral, untrained limb (Carroll et al. 2006; Munn et al. 2004; Scripture et al. 1894). This “cross education” training effect was first described over 100 years ago by Scripture et al. (Scripture et al. 1894). Recent work in neurologically intact (NI) participants in our laboratory extended this observation to the dorsiflexors (Dragert and Zehr 2011). This paradigm could be applicable post-stroke, with the LA limb used to establish a baseline of strength on the contralateral, MA side. Currently, no study has applied cross-education after stroke.

Here we sought to leverage this well-recognized phenomenon of cross transfer of strength training between the limbs after stroke. This premise has not been directly tested, and therefore we sought to determine how effectively unilateral strength training would induce responses in the untrained, more affected limb. As such, this study was a proof of principle test of cross-education after stroke using high-intensity isometric dorsiflexion

resistance training of the LA limb. Strength, reciprocal inhibition and maximal voluntary muscle activation (EMG_{max}) of the TA and SOL muscles were used to probe for training-induced plasticity. Dorsiflexors were targeted because of their important functional role subserved during locomotion (Dragert and Zehr 2011), and the common occurrence of post-stroke lower leg weakness (Patten et al. 2004) and dorsiflexor dysfunction (Zehr and Loadman 2012; Barzi and Zehr 2008; Dobkin 2003). This clinical population presented the challenge of selecting a neural measure that was both widely and easily producible across subjects, while also allowing for assessment of the integrated neural activation patterns of TA and SOL muscles. Reciprocal inhibition (RI) was chosen for this task, as it has been used previously to quantify the balance of excitability between these functional antagonists (Kido et al. 2004) and has also been successfully evoked in patients suffering similar neurological deficits (Thompson et al. 2009; Crone et al. 1994). To assess the translational effects of this training paradigm to functional tasks, walking kinematics and muscle activation patterns were collected along with clinical measures of physical performance.

Our a-priori hypothesis was that maximal dorsiflexion force and TA muscle activation (EMG_{max}) would increase bilaterally following the intervention. Building on previous findings in neurologically intact participants (Dragert and Zehr 2011), we also predicted changes in spinal excitability bilaterally. This would be seen as increased gain of spinal interneuronal excitability to the TA muscles bilaterally, measured as a change in the slope of the relationship between reciprocal inhibition and muscle activation.

Subj. #	More Affected side	Post stroke (months)	Ashworth (leg)	Berg Balance Scale	FAC	Modified Fugl-Meyer (lower ext.)	10m Walk (sec)	Timed Up & Go (sec)
1	L	87	3	32	4	84	31.50	38.84
2	L	171	1	53	4	117	6.66	8.47
3	L	284	1	39	4	92	23.03 _c	37.91 _c
4	R	21	0	56	5	143	5.72	7.75
5	R	30	1	44	4	99	13.82	16.25
6	L	64	2	47	5	104	13.13	21.56
7	R	7	1	55	4	118	6.28	9.85
8	R	224	3	45	5	84	10.25	11.66
9	L	10	1	54	4	124	16.22	22.21
10	L	28	3	49	4	94	29.97	16.54
11	L	6	0	55	4	133	5.69	7.5
12	L	41	2	47	4	125	13.16	20.43
13	R	144	1	55	5	126	5.94	7.28
14	L	7	0	52	5	122	8.84	11.63
15	L	85	0	19	3	80	40.81 _c	63.00 _c
16	R	114	1.5	50	4	133	13.15	14.47
17	L	91	0	47	4	125	9.66	13.18
18	R	111	1	52	4	111	8.06	12.25
19	L	72	3	50	4	102	10.03	14.78
Averages (SD)								
	L:12	84 .1	1.3	47.4	4.2	109.4	14.31	18.61
	R:7	(77.6)	(1.1)	(9.2)	(0.5)	(18.0)	(9.98)	(13.86)

Table 5.1: Summary of physical characteristics and baseline clinical assessments for individual stroke participants.

L, left; R, right; MCA, middle cerebral artery; n/a, not available; ICA, internal carotid artery; PICA, posterior inferior cerebellar artery; FAC, functional ambulation category. _c: Patients who required the use of canes during their walking assessments.

5.3 Methods

5.3.1 Participants

Subject recruitment occurred through community stroke support groups, posters in medical offices/hospitals, and newspaper articles. As inclusion criteria, participants were required to be >6 months post-infarct, and have one-sided dorsiflexor weakness. The presence of such weakness was assessed through initial verbal screening (e.g. “does your foot on your more-affected side drag when you walk?”), and then confirmed on-site

by a licensed physical therapist using the Fugl-Meyer and observation during a 10m walk test (see below). Further inclusion criteria were that a participant be able to free-stand with or without assistive devices, and that they maintain their activity levels during the study. Exclusion criteria included: medications affecting muscle tone less than three months prior; and cardiovascular, musculoskeletal, respiratory, or other chronic disease comorbidities. Sample size was based on previous studies of spinal reflex adaptations to resistance training (Dragert and Zehr 2011; Geertsen et al. 2008) and post-stroke reflex excitability (Barzi and Zehr 2008; Crone et al. 2003), as well as other interventions yielding strength gains after stroke (Patten et al. 2004; Butefisch 1995; Engardt et al. 1995; Sharp and Brouwer 1997). 24 participants were recruited, in line with statistical reports that an n of 26 will specify a power of 0.80 at a large effect size and criterion value of 0.05 (Cohen 1992). During the study's implementation, five subject exclusions occurred because of self-withdrawal (n=2), injury not related to the prescribed training (n=1), or change in physical activity patterns (n=2). Data are reported for the remaining 19 subjects (15 men), aged 26 to 81 years (mean = 58.3 ± 12.2 yrs) (see Table 5.1). Informed written consent was obtained for a protocol approved by the University of Victoria Human Research Ethics Committee and performed according to the Declaration of Helsinki.

5.3.2 Experimental design

A repeated-measures (pre/post-test) design was used and all participants completed the isometric training program on their LA side. Baseline data were collected 1-2 weeks prior to the intervention across 2 laboratory visits. Post-intervention data were

collected within four days of the final training session. Across measurements laboratory conditions (i.e. temperature, noise, lighting, subject position) during data collection were kept as constant as possible, including session time of day (Lagerquist et al. 2006a; Zehr 2002).

5.3.3 Training protocol

Participants trained while seated using a simple custom-built foot brace that ensured a constant ankle angle. Training was 25 minutes per session, three days a week for six weeks (18 sessions total) (see (Dragert and Zehr 2011; Geertsen et al. 2008; Lagerquist et al. 2006b). This training period precluded significant morphological myogenic adaptations as a contributor to any observed strength gains (Bird et al. 2005; Moritani and deVries 1979; Abe et al. 2000). As employed previously, training occurred in-laboratory once each week when feedback on appropriate technique was provided (Dragert and Zehr 2011). Other sessions were completed at home, with participants contacting the laboratory immediately upon session completion. Adherence was closely monitored and all data sets came from those completing the required number of sessions on schedule.

A standardized pre-recorded audio clip provided verbal direction to participants, with commands on when to 'contract' (including promotion for maximal activation) and when to 'relax' between reps and sets. In this way contraction/relaxation timing and verbal encouragement was consistent across participants and training sessions. A single training session consisted of a warm-up (three sets of five repetitions of unilateral,

submaximal, isometric dorsiflexion contractions), followed by five sets of five maximum effort isometric repetitions held for five seconds. Rest was two seconds between contractions and two minutes between sets. These parameters follow accepted maximal strength training program practices (Bird et al. 2005). They are also similar to previous strength training studies that saw lower limb cross-education effects in neurologically intact (Dragert and Zehr 2011; Lagerquist et al. 2006b), and corroborate with previous post-stroke high-intensity training protocols in the leg (e.g. (Sharp and Brouwer 1997)). Subjects were instructed and reminded repeatedly while training to keep the untrained leg relaxed (Dragert and Zehr 2011; Munn 2005), as well as to relax the SOL and vastus lateralis (VL) muscles in the trained leg to minimize co-contraction and heteronymous effects. To confirm this, EMG recordings during training were taken from a sub-sample of participants (see Results).

5.3.4 Motor circuit data collection protocol

Similar to training sessions, participants were seated with ankle, knee and hip angles fixed at approximately 100° (i.e. slight plantarflexion), 120° and 90°, respectively (Dragert and Zehr 2011; Lagerquist et al. 2006b). Following a warm-up, maximal voluntary isometric contraction (MVIC) measurements were taken. Reciprocal inhibition (RI) was then evoked separately for each TA and SOL muscle at different levels of agonist tonic contraction. Subsequently, gait EMG and kinematics were collected. All data were recorded using custom written LABVIEW virtual instruments (National Instruments, Austin, TX).

5.3.5 Maximal voluntary isometric contraction (MVIC)

Subjects had two attempts (2min rest between each) to achieve dorsiflexion MVIC (held 3-5sec) for each leg separately. Force was measured via a load cell (Omegadyne Ltd. Model 101-500) and converted to ankle torque. Muscle activation was also recorded for these trials, and calculated offline with custom written software (Matlab, Version 7.1, The Mathworks, Natick MA USA). Maximal agonist activation (EMG_{max}) was normalized to the mean maximal motor-wave (M_{max} ; see below).

5.3.6 EMG recordings

Surface EMG electrodes were applied in bipolar configuration over SOL, TA, and VL muscles. Placement was based on anatomical landmarks for the first session and then measured and photographed. Subsequent electrode placement was based on these measures and applied by the same experimenter. EMG signals were amplified (GRASS P511, AstroMed) and band-pass filtered from 100-1000Hz (SOL, TA for RI conditioning stimulus) or 100-300Hz (VL; SOL, TA for MVIC, RI and walking trial recordings). Output was sent to the A/D interface (National Instruments, Austin, TX.) and sampled at 2000Hz.

5.3.7 Nerve stimulation

Maximal motor waves (M-wave, M_{max}) and RI were elicited and recorded following established procedures (Dragert and Zehr 2011; Kido et al. 2004). Bipolar stimulation (0.5ms pulse) was delivered pseudo-randomly every 2-5 seconds (M_{max} trials) or 2-3 seconds (RI trials) using a Digitimer (model DS7A, Medtel, UK) constant current stimulator. Electrodes were placed over the posterior tibial nerve at the popliteal fossae

(SOL), and over the common peroneal nerve at the fibular head (TA). Five M_{\max} sweeps were recorded in each muscle separately while stimulation current was measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL) and agonist contraction was maintained at $\sim 10\% \text{MVIC}$. Peak to peak M-wave amplitudes were calculated offline from single unrectified EMG sweeps using custom written software (Matlab, Version 7.1, The Mathworks, Natick MA USA), and average M_{\max} was calculated from 2-4 of the largest M-waves.

For RI trials, responses were observed as depression of EMG activity produced by antagonist muscle nerve stimulation (1.2x motor threshold) (Thompson et al. 2009; Kido et al. 2004; Capaday et al. 1990). For example, during TA RI recordings a conditioning stimulus was applied to the tibial nerve to evoke a SOL M-wave response, and RI was observed in the TA. Trials were recorded in pseudo-random order, and for each trial subjects were asked to maintain different muscle activation levels ranging from $\sim 10\text{-}50\% \text{MVIC}$ as indicated via oscilloscope by the experimenters. Depending on subject ability, up to five trials were recorded for each muscle. Fifteen 300ms sweeps were recorded for each trial (Stein and Thompson 2006).

Average rectified EMG traces were analyzed offline using custom written software (Matlab, Version 7.1, The Mathworks, Natick MA USA). At each tonic contraction level, the mean RI was calculated over a 10ms interval chosen by visual inspection centered around the largest depression post-stimulus (grand mean = $59.7\text{ms} \pm 11.1$). The mean pre-stimulus EMG for that trial was subtracted from this RI

depression and normalized by the corresponding M_{\max} . RI was then plotted against the background activation level (Kido et al. 2004; Capaday et al. 1990).

5.3.8 Walking trial

Similar to previously reported methods (Zehr and Loadman 2012; Haridas and Zehr 2003), participants walked at a self-selected (“comfortable”) speed on a motorized treadmill (Woodway USA, Waukesha, WI) with an overhead safety harness (Pneumex, Pneumex Inc, Sandpoint, ID). After establishing a steady walking pace, data were collected over a three minute trial (>120 steps). While no one wore an ankle foot orthosis (AFO) for the trial, two subjects required harness support for a percentage of their body weight pre-intervention (see Results); the remaining subjects wore the safety harness without body weight support both pre- and post-intervention. Subjects were free to use hand held railings in-front or beside them ad libitum during the trial.

Heel strike was used to define the beginning of each step cycle, and phase parameters were obtained with the use of custom-made force sensing resistors (model 1027-1001-ND, Digi-Key, Thief River Falls, MN) located under the heel and ball of foot in both shoes. In this way step cycle timing could be extrapolated in cases of unclear heel strike of the MA limb. Offline, EMG and joint kinematics data were averaged and separated into 16 phases based on step cycle (Haridas and Zehr 2003): phases 1-10 as stance; and phases 11-16 as swing. This sorting was confirmed by manual inspection of individual subject data.

EMG data were recorded as previously described from SOL and TA muscles bilaterally (see “EMG Recordings”), and quantified as amplitude in mV. Goniometers (Biometrics Inc) were used to detect joint kinematics in the MA knee (flexion/extension) and both ankles (dorsi-/plantarflexion and inversion/eversion). Three static trials (heel strike, toe off and standing with feet together) provided data for calibration of goniometer positioning and output into degrees, such that a joint’s range of motion (ROM) through the step cycle was determined. Absolute ROM ratios were also calculated from these data, using the maximum and minimum angular excursions recorded across the 16 step cycle phases.

5.3.9 Clinical measures

The same licensed physical therapist collected the following clinical measures across all subjects both pre- and post-intervention: Timed Up and Go (Podsiadlo and Richardson 1991); Timed 10m Walk; Modified Ashworth Scale (Lee et al. 1989); Functional Ambulation Category (Holden et al. 1984); Berg Balance Scale (Berg et al. 1992); and the Fugl-Meyer (Fugl-Meyer et al. 1975) . For this final measure, balance and upper limb motor components of the test were excluded, resulting in a ‘modified Fugl-Meyer’ score of the remaining components; i.e. sensation (24), pain (44), joint ROM (44), and lower extremity motor evaluation (34) (total maximum score = 146; see Table 5.1).

5.3.10 Statistics

STATISTICA software (version 6.1, StatSoft, Tulsa, OK) was used to evaluate intervention effects on variables of interest, excluding RI analyses (see below). For statistical comparisons, LA and MA limb data were analyzed separately. Statistical significance was set a-priori at $p \leq 0.05$.

Repeated Measures ANOVA were performed on gait EMG data across all walking phases to identify main effects of training on movement phase, with Scheffe's tests performed post-hoc on significant differences. For the remaining variables paired t-tests were used. We predicted increased dorsiflexor strength and muscle activation in both the trained and untrained limb, while conservatively predicting a null result for all other comparisons. For a-priori hypotheses where direction of change was predicted, one-tailed paired t-tests were performed.

For RI data, linear regression analyses were performed, Pearson r values were calculated for each pool of paired data, and this was assessed at the appropriate critical value ($df=n-1$). Data were analyzed for pre-post differences in slope and y-intercept, with critical t distribution values ($df=n_1+n_2-4$) used to establish significance (Sheskin 2004). The number of paired data points contributing to the linear regression was totaled for each muscle (one to five points per subject) and used to calculate df. Based on our directional prediction of increased gain of RI, one-tailed critical values were employed for SOL and TA slope and y-intercept comparisons (Sheskin 2004).

Participant n is specified in the following results when it differs from 19.

Variable	MA, Untrained Leg					LA, Trained Leg				
	n	Pre-intervention	Post-intervention	p	d	n	Pre-intervention	Post-intervention	p	d
Dorsiflexors / TA										
MVIC (Nm)	19	9.18 (9.05)	12.06 (9.05)	0.009*	0.60	19	12.36 (9.25)	16.50 (11.23)	0.02*	0.50
M _{max} (mV)	15	1.90 (1.07)	1.43 (0.77)	0.06	0.55	15	2.66 (1.12)	2.31 (1.23)	0.10	0.46
EMG _{max} (%M _{max})	15	3.28 (2.12)	5.22 (4.32)	0.03*	0.62	15	4.75 (1.66)	5.70 (2.42)	0.02*	0.68
Plantarflexors / SOL										
MVIC (Nm)	19	16.20 (14.01)	15.47 (9.89)	0.77	0.07	18	16.60 (13.04)	18.84 (16.95)	0.55	0.15
M _{max} (mV)	14	3.15 (2.18)	3.47 (1.81)	0.42	0.23	14	4.09 (2.32)	5.44 (3.07)	0.09	0.51
EMG _{max} (%M _{max})	14	1.49 (1.37)	1.12 (0.86)	0.22	0.38	14	2.20 (1.01)	1.94 (0.77)	0.33	0.28

Table 5.2: Group data of trained and untrained leg for dorsi-/plantarflexor MVIC, TA/SOL EMG_{max} and M_{max}.

Values are means (SD). MVIC, maximal voluntary isometric contraction, in Newton-meters (Nm); M_{max}, maximal M waveform, in millivolts (mV); EMG_{max}, maximal muscle activation, as a percentage of M_{max} (%M_{max}); P, probability level; d, Cohen's effect size. *Significant at $p \leq 0.05$.

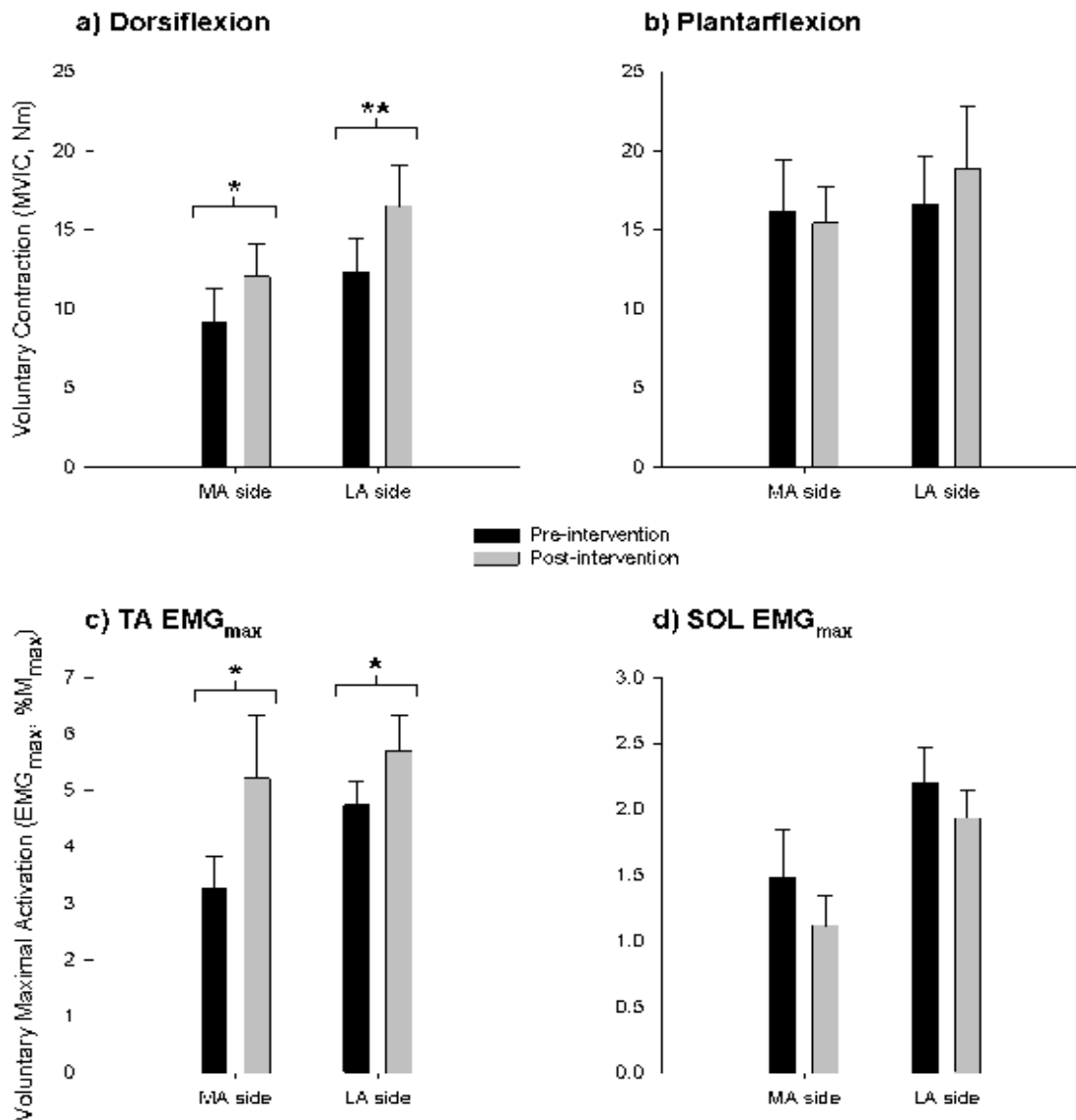


Figure 5.1: Unilateral dorsiflexion training increased strength and muscle activation bilaterally. Group mean data collected pre- (black bars) and post-intervention (gray bars) for maximal voluntary isometric contraction, MVIC (i.e. torque at the ankle, in Newton-meters, Nm) (a, b), and maximal muscle activation, EMG_{max} (expressed as % of maximal M-wave, M_{max}) (c, d). a) Dorsiflexion MVIC significantly increased on the less-affected (LA) and more-affected (MA) sides following the intervention. b) Plantarflexion MVIC showed no significant changes. c) EMG_{max} in the LA and MA TA muscles significantly increased following the intervention. d) EMG_{max} in the LA and MA SOL muscles showed no significant changes. Data are means \pm SE. *Significant at $p < 0.05$; **Significant at $P < 0.01$.

5.4 Results

5.4.1 Strength gains arising from training

Dorsiflexor MVIC increased by 33.53% in the trained, LA limb ($p=0.02$), and 31.37% in the untrained, MA limb ($p=0.009$) (see Table 5.2, Figure 5.1a, b), with no differences in the amount of increase between sides ($p=0.36$). Plantarflexor MVIC remained unchanged.

EMG_{max} increased by 20.19% in the LA TA ($p=0.02$; $n=15$) and 59.32% in the MA TA muscle ($p=0.03$; $n=15$). No significant differences were seen in SOL ($p=0.33$ and 0.22 for LA and MA, respectively; $n=14$). See Table 5.2, Figure 5.1c, d).

5.4.2 Training session EMG recordings

Data was collected from training session 14 of 18 from 6 participants. The choice of session was based around logistics of scheduling between study participants and experimental equipment / laboratory availability. Beyond this, collecting data from a later training session was beneficial in that it ensured subjects were comfortable with the training regimen, and were able to effectively complete the session as per normal in the presence of additional experimental distractions (e.g. EMG recording methods). For this training session, average LA (trained) TA activation was $89.01 \pm 4.51\%$ MVIC. Mean co-activation during these trials in the LA leg was $\sim 15.31\%$ (SOL) and 25.83% (VL) of MVIC. Co-activation in the MA (untrained) leg averaged $\sim 21.94\%$ and 27.90% of MVIC in the TA and SOL muscles, respectively.

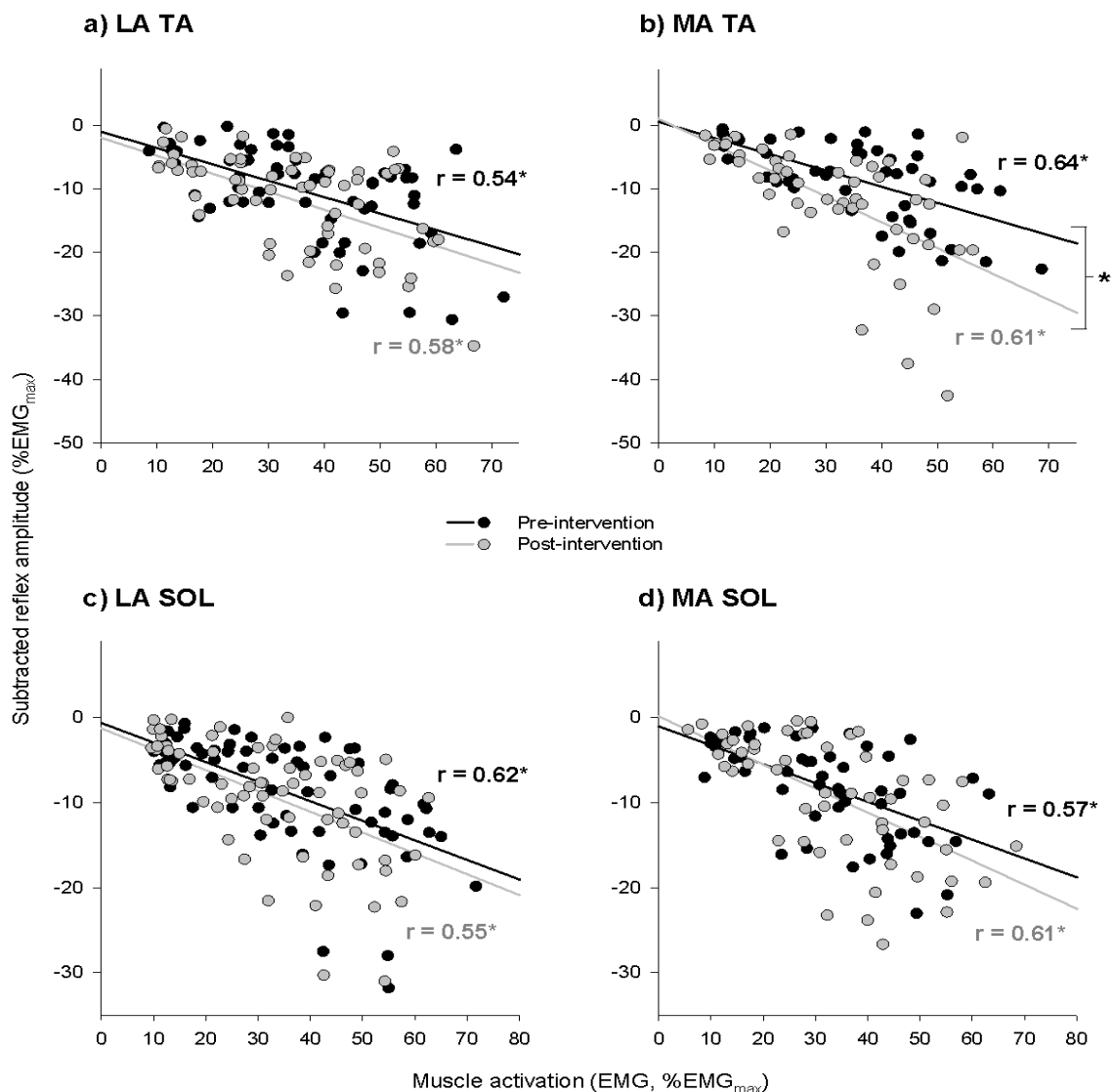


Figure 5.2: Paired values of subtracted reciprocal inhibition (RI) response and muscle activation (both normalized to EMG_{max}) are used in a linear regression analysis to produce a best-fit line for each muscle. Pre- (black) and post-intervention (gray) data are shown with calculated Pearson-Product Moment r values for each best-fit line. For all muscles, the r correlation (i.e. goodness of fit) was significant at baseline and post-intervention. a) Less-affected (LA) TA muscle; b) More-affected (MA) TA muscle, for which a significant difference in slope pre- to post-intervention was also detected; c) LA SOL muscle; d) MA SOL muscle. Data are paired points collected across subjects. *Significant at $p < 0.05$.

5.4.3 RI: Correlation with muscle activation and change in slope

There were significant correlations between size of RI and level of muscle activation across muscles ($p < 0.05$; see Figure 5.2; TA $n = 16$ (LA) & 14 (MA); SOL $n = 17$ (LA) & 14 (MA)). MA TA also showed significant change in slope pre- to post-intervention ($t = 1.74$, $t_{crit} = 1.66$, $df = 94$; see Figure 5.2b; TA $n = 59$ (LA) & 49 (MA); SOL $n = 68$ (LA) & 52 (MA)). At baseline, no significant differences were observed between slope for MA and LA TA muscles ($t = 0.031$, $t_{crit} = 1.66$, $df = 104$).

5.4.4 M_{max} and background EMG

M_{max} ($n = 15$ (TA) & 14 (SOL); see Table 5.2) remained unchanged across the experiment. To exclude the possibility that observed increases in dorsiflexor MVIC resulted from changes in antagonist activation level, SOL background EMG was compared to pre-intervention values ($n = 19$ for each limb) and no change in was observed in either leg ($p > 0.05$; data not shown).

5.4.5 Gait EMG and kinematics

Self-selected walking speed (1.59 km/hr pre vs. 1.66 km/hr post, $p = 0.15$; $n = 17$) was maintained across the experiment. Two subjects required body weight harness support: one had their whole body supported both pre and post-intervention (weight = 68kg); the other (weight = 73kg) had 20kg (27.4% of total) supported at baseline, but required no support post-intervention.

For muscle activation during walking, no differences were observed in LA TA ($p = 0.07$; $n = 17$), but significant main effects were seen in MA TA ($p = 0.03$; $n = 16$) as well

as both the LA and MA SOL ($p=0.005$ and 0.04 , respectively; $n=17$). Across all movement phases the absolute peak SOL EMG values pre- to post-intervention in the LA leg were 61.99 and $61.18\mu\text{V}$, respectively, and in the MA leg were 60.29 and $62.92\mu\text{V}$, respectively. In the TA, absolute peak EMG values pre- to post-intervention in the LA leg were 49.50 and $55.26\mu\text{V}$, respectively, and in the MA leg were 44.56 and $38.64\mu\text{V}$, respectively. A significant main effect was also seen for dorsi-plantarflexion range of motion on the LA ($p=0.04$), but not the MA side ($p=0.16$) ($n=17$ for both). Pre- to post-intervention, dorsi-plantarflexor ROM in the LA leg was $12.49\pm 7.90^\circ$ and $15.80\pm 8.44^\circ$, respectively, and in the MA leg was $14.50\pm 10.96^\circ$ and $14.83\pm 11.31^\circ$, respectively. Further examination of all significant main effects using post-hoc testing found no pre / post-intervention differences within any of the 16 bins ($p>0.05$). Visual inspection of these phased data revealed no obvious pre- to post-intervention trends or patterns, with shifts across the gait cycle appearing small in some phases and larger but more variable in others (data not shown). Thus, the impact of these observed main effects is unclear (see Discussion). Analysis of kinematics ranges ($n=17$ for MA knee flexion/extension; $n=13$ for MA ankle inversion/eversion) showed no change following the intervention ($p>0.05$; data not shown).

Variable	n	Pre-intervention	Post-intervention	p	d
Modified Ashworth (/ 5)	19	1.29 (1.10)	1.13 (1.04)	0.11	0.39
Berg Balance (/ 56)	19	47.42 (9.17)	47.17 (9.46)	0.60	0.12
FAC (/ 5)	19	4.21 (0.54)	4.32 (0.48)	0.33	-0.23
Modified Fugl-Meyer (/ 146)	19	109.37 (17.95)	109.26 (17.73)	0.94	0.02
10m Walk (sec)	19	14.31 (9.98)	14.05 (10.49)	0.77	0.07
Timed Up & Go (sec)	19	18.61 (13.86)	17.41 (12.35)	0.05*	0.59

Table 5.3: Group data of clinical measures. Values are means (SD). FAC, functional ambulation category; d, Cohen's effect size. *Significant at $p \leq 0.05$.

5.4.6 Clinical measures

Timed Up and Go was significantly reduced from 18.61 seconds to 17.41 seconds following training ($p=0.05$; see Tables 5.1, 5.3). No other changes were observed for clinical measures ($p>0.05$; see Table 5.3).

5.5 Discussion

This work shows that significant gains in voluntary strength and muscle activation in the untrained limb can be achieved by training the opposite limb in chronic stroke. Further, we report novel information on changes in spinal reflex excitability and RI within the untrained MA TA. Overall, our results demonstrate the residual plasticity that exists post-stroke, including the ability to produce a cross-education effect using a very minimalistic high-intensity strength training protocol.

5.5.1 Crossed strength and muscle activation gains in the untrained, MA dorsiflexors

Strength increases in LA (~34%) and MA (~31%) limbs are larger than previous observations in NI subjects (Carroll et al. 2006; Dragert and Zehr 2011). This could be related to the reduced pre-intervention capacity in stroke, who are often essentially “detrained” (Zehr 2011). Previous baseline measures of dorsiflexion MVIC in NI participants averaged 23.07 and 23.22Nm in the dominant and non-dominant limb, respectively (Dragert and Zehr 2011), compared with 12.36 and 9.18Nm (LA and MA limb, respectively) in the present study (see Table 5.2). This post-stroke weakness compared to age-matched controls is common in both MA and LA limbs (Patten et al. 2004; Barzi and Zehr 2008; Adams et al. 1990). Still, the magnitude of the induced effect is impressive, especially given the relatively short training duration (six weeks), the execution of the majority of training in a home setting, as well as the minimal absolute training time employed in the present paradigm. Indeed, training sessions consisted of a total isometric contraction time of only 200sec (40 repetitions), and were conducted just three days per week (18 sessions total; see Methods). A common component in many post-stroke motor rehabilitation protocols is that of high repetitions and/or lengthy training sessions (Patten et al. 2004). Thus, the fact that such strength gains were made with reduced patient time commitment may be extremely valuable from a clinical standpoint. Furthermore, these large gains were seen in a ‘chronic’ post-stroke cohort: while a single participant was 6mo post-infarct, the average was ~84mo (7yrs), with the longest duration reaching 284mo (~23yrs). Accordingly, these findings demonstrate the ability to induce neural adaptation well beyond typical post-stroke motor rehabilitation

timelines, and highlight the usefulness of home-based resistance training long after a patient has been discharged from hospital.

The observed strength gains are also notable given the variability of training response often seen within NI groups (Hubal et al. 2005) and heterogeneous stroke populations (Patten et al. 2004). Four subjects were non-responders (i.e. showed no strength change in the trained leg). The significant strength gains including these data highlights the robust nature of the training effect in both limbs. Importantly, a separate four participants who could not produce meaningful MA dorsiflexion torque at baseline were able to post-intervention. Of these participants, three met or surpassed the minimum torque level required to dorsiflex the mass of a foot based on 50th percentile averages for their sex (Huston 2009). Muscle activation (TA EMG_{max}) also significantly increased bilaterally, suggesting similar access to neuroplastic adaptation remains after stroke as in NI (Shima 2002).

5.5.2 RI alterations with training

The significant change in slope of the RI-EMG regression line in the untrained, MA TA muscle (see Figure 5.2) suggests increased sensitivity to descending motor commands associated with voluntary movement. A role for RI in the modification of contralateral motor pathways and the cross-education effect has been described previously (Lee and Carroll 2007), but the present observations are the first to reveal effects of maximal unilateral contractions on transmission in contralateral Ia inhibitory pathways. While confirming specific mechanisms is beyond the scope of this study,

repeated bouts of high-intensity unilateral dorsiflexion training could lead to increased contralateral sensitivity of the Ia inhibitory interneurons and larger suppression of alpha-motoneuron excitability (Delwaide et al. 1988; Delwaide and Pepin 1991). Further resistance training studies in NI groups are needed to substantiate or refute this point.

It is worth noting that hyper-excitability within the RI pathway was not observed in MA SOL relative to the less-affected side. This finding differs from previous reports of hyper-excitability spinal reflex pathways within this muscle group post-stroke when compared to NI controls (Barzi and Zehr 2008; Thompson et al. 2009). These past studies employed H-reflex as a neural probe; thus, this discrepancy may be accounted for by differences between RI and H-reflex pathways and relative differences in control between functional antagonists. Overall, the present observations further highlight the robust nature of agonist muscle cross-education effects and their induced adaptations within a more limited set of neural pathways.

5.6 Training session activation patterns

In many previous cross-education studies of the lower limb, participants were given instruction to keep the untrained leg from contracting during training sessions (e.g. (Lagerquist et al. 2006b; Munn 2005; Fimland et al. 2009)). Quantified measures of neural activation in the untrained side during short-term unilateral training have been previously reported for the upper limb (Carroll et al. 2008). However, we believe that this is the first work to report bilateral lower leg muscle activation during a session of a unilateral strength training intervention. Given the high-intensity of this training

paradigm, an average activation of ~89%MVIC in the trained (LA) TA muscle across a session is not surprising. In our own NI single subject observations of agonist muscle output during a similar training session, we noted average TA activation levels of ~76%MVIC (unpublished observations); one could attribute this slight variation to the fact that absolute activation levels post-stroke are much lower (see above discussion). Also of interest is co-activation within the untrained leg, where average activation levels of ~22% and ~28%MVIC were noted in the MA TA and SOL, respectively. The presence of post-stroke muscle overactivity in the form of involuntary co-contraction has been previously described in the literature (Gracies 2005); however, the level of contralateral leg muscle co-activation during unilateral activation has not been quantified in stroke or NI. With no 'untrained leg' normative data to compare the present post-stroke observations to, we can only speculate as to the impact of such training activation levels on the present crossed dorsiflexor strength gains. However, given that no significant change in MA SOL MVIC was observed post-intervention, it can be reasoned that such activation was too little to significantly contribute to the resulting strength gains seen in MA TA. Further work in both stroke and NI groups would be valuable in confirming this conjecture.

5.6.1 Gait analysis and clinical measures

While significant main effects were observed in activation of MA TA and both SOL muscles as well as LA ankle range of motion, they did not translate into a significant change in any single phase of the gait cycle. It is possible that this represents the presence of a generalized change in gait bilaterally; however, no obvious trends could

be discerned from the data, and thus it is challenging to draw conclusions from these observations. Of the clinical measures collected, the Timed Up and Go significantly improved by ~1.2 seconds. This test assesses basic functional mobility and incorporates components from a number of other specific tests (Podsiadlo and Richardson 1991). For this variable the calculated effect size was medium (0.59; see Table 5.3), indicating a reasonably sized change. Yet it has been suggested that a relative change in scores (smallest real change, SRD) exceeding 23% for this test may be required clinically (Flansbjer et al. 2005); i.e. an improvement of 4.2 seconds. However, SRD often differs from a clinician's qualitative assessment of 'clinically relevant change', for which an arbitrarily chosen minimal amount of change is deemed important (Beckerman et al. 2001). Taken together, these observations may hint at potential transfer of the cross-education effect to functional tasks, but further investigation is necessary to demonstrate truly useful impact on activities of daily living.

5.6.2 Study limitations

The main limitation of this work is our sample size (n=19). Even so, the Cohen's d effect size calculations (see Tables 5.2 & 5.3) suggest robust results. Additionally, our inclusion criteria were not restricted to a particular functional level and many of our subjects had good ability (see Table 5.1). Though these higher functioning subjects were still restricted by significant lower limb hemiparesis, our projected application for patients suffering more extensive impairment could only be assessed in the four severely affected participants.

5.7 Conclusions

Following stroke, the use of resistance training combined with task-specific motor rehabilitation protocols is a safe, effective method for enhancing strength and function (Duncan et al. 2005; Taylor et al. 2005; Eng 2004). In our 2011 paper we highlighted that the cross-education training model could have translational implications for stroke rehabilitation (Dragert and Zehr 2011). Here we report on a successful attempt to use this training model in stroke, such that unilateral strength training of the LA leg produced significant improvement in strength and muscle activation on the untrained, MA side. The potential to access these adaptations remains present many years after the infarct (e.g. ~84mo post-stroke), which demonstrates residual plasticity and efficacy of continued motor retraining beyond typical acute rehabilitation timelines. These findings may be applicable in chronic stroke, when training the MA limb is not initially possible and training the LA limb could establish a baseline of strength on the MA side. This work demonstrates proof of the principle that neuromuscular crossed-effects can be accessed post-stroke using a simple training protocol applicable in community dwellers.

5.8 References

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6. General Conclusions

The main objectives of this thesis were: 1) to explore modulation of motor output in the ankle flexor and extensor muscles induced by remote arm movement and contralateral resistance training; and 2) to apply these observations in a post-stroke resistance training paradigm, aimed at normalizing muscle activation patterns within the more-affected limb. In this way, the broader concept of a tripartite system of organization that underlies motor output (i.e. supraspinal input, spinal circuits and sensory feedback (Zehr and Duysens 2004; Zehr 2005)) has been further elucidated, to include novel information on inter- and intralimb communication and its clinical application. This section is a summary of the main findings of this thesis, and also outlines potential directions for future research in this area.

6.1 Spinal adaptation induced by remote rhythmic arm movement

As described in Chapter 1, there is strong evidence for the presence of remote modulatory effects of rhythmic arm movement on reflex response and motor output in the legs (Zehr and Duysens 2004; Ferris et al. 2006; Zehr et al. 2009). Chapters 2 and 3 provide further support of these effects, and also reveal novel information on differences in reflex modulation between antagonistic muscles in the lower leg.

Chapter 2 describes how rhythmic arm movement differentially affects H-reflex in the ankle flexor vs. extensor muscles, such that H-reflex amplitude is consistently suppressed in SOL, but may be suppressed or facilitated in TA. These findings support the presence of interlimb neural coupling, such that remote motor action (arm movement) influences lumbar spinal cord excitability. Of interest is the fact that these descending

signals impact ankle flexors and extensors differentially. This observation varies from previous suggestions of a generalized depression of lower limb reflex excitability produced by arm movement (Brooke et al. 1997; Frigon 2004). Instead, it aligns with other reports of differences in cortical influence on motor output to the ankle flexor vs. extensor muscles during movement (Bawa et al. 2002; Capaday et al. 1999; Schubert et al. 1997). Thus, these bidirectional effects in TA H-reflex can be interpreted as further evidence for differential regulation between the ankle flexors and extensors, which may be due in part to a reduction in spinally-mediated drive as well as increased involvement of cortical drive to the ankle flexors during rhythmic movement relative to the extensors (see Chapter 2). These findings illustrate one method of producing facilitative modulation of ankle flexor motor responses, which may be applicable in a clinical situation where up-regulation of reflex response is desired (Wolpaw 2012): for example, post-stroke dorsiflexor weakness (Patten et al. 2004).

Chapter 3 further highlights differential effects of arm movement on ankle flexor vs. extensor muscles. Moreover, it extends the observation of modulatory effects of rhythmic arm movement to the reciprocal inhibitory (RI) pathway in the legs, a core circuitry that comprises the interaction between functional antagonist muscle pairs. While increased RI was observed in SOL during rhythmic arm cycling, no effect of movement was seen in TA. Based on these observations and those described above (see Chapter 2), it appears that descending signals that originate from higher spinal centers impact SOL Ia inhibitory interneuron excitation more strongly than in the TA, which is instead chiefly impacted by cortically-based descending inputs. The end result is differential modulatory effects within this agonist/antagonist muscle pair, and a bias

towards reinforcement of dorsiflexion during arm movement. Interestingly, the observation of asymmetrical output to these functional antagonists aligns well with coordination requirements during walking, and supports the concept that arm movement-induced modulation may contribute to adequate dorsiflexion and foot clearance during the swing phase of gait.

6.2 Neural plasticity and the cross-education effect

Much work has highlighted the benefits of resistance training in post-stroke rehabilitation (Patten et al. 2004; Bohannon 2007; Eng 2004; Zehr 2011). Moreover, the application of remote motor activation in the form the cross-education effect has been underlined for its potential in clinical settings (Lee and Carroll 2007). Data from Chapters 4 and 5 demonstrate the ability to induce a resistance-trained cross-education effect in the previously unexplored ankle flexor muscles, both in neurologically intact and after stroke. Thus, efficacy of this remote modulatory effect for improving hemiparetic dorsiflexor weakness is shown for the first time. Further, novel spinal adaptations associated with the cross-education effect are also revealed.

Chapter 4 examined the effects of high-intensity unilateral dorsiflexion resistance training on agonist (TA) and antagonist (SOL) muscular strength and H-reflex excitability in the trained and untrained limbs of neurologically intact subjects. Post-intervention, dorsiflexor torque increased bilaterally, and significant changes in H-reflex excitability were detected in the trained ankle flexor (agonist) muscle and in both ankle extensor (antagonist) muscles. Specifically, $H_{@thresh}$ increased from baseline in SOL and TA of the trained leg, such that the foot of the reflex recruitment curve was evoked at

lower stimulus intensity than that required to elicit a response pre-intervention; i.e. more low-threshold motor units were recruited at the same stimulus intensity (Klimstra and Zehr 2008). Further, SOL $H_{@max}$ decreased bilaterally, indicative of reduced excitability of the largest H-reflexes (and thus higher threshold motor units) of the antagonist muscles post-intervention. This is the first investigation of H-reflex amplitude modulation in a functional antagonist following a resistance-trained agonist movement, and indicates a spinal contribution to the plasticity that has arisen. Furthermore, these findings suggest the presence of subtle antagonist muscle spinal adaptation associated with cross-education, and may also reflect generalized descending inputs on lower limb spinal response following resistance training (see Chapter 4). Interestingly, these observations of crossed spinal effects differ from those noted previously in SOL following unilateral plantarflexor resistance training (Lagerquist et al. 2006). Thus, these data may provide further evidence of differential descending signalling to these two muscle groups. However, it is also possible that similar motor unit-specific spinal adaptations occur in SOL but were missed previously, due to lack of H-reflex recruitment curve acquisition (Klimstra and Zehr 2008; Lagerquist et al. 2006) and observation in antagonist muscles. Importantly, these findings of crossed strength gains provide the context for investigative application of the cross-education effect within the ankle flexor muscles in a clinical setting; for example, improving one-sided weakness and/or motor dysfunction following neurotrauma.

Chapter 5 explored the application of a similar high-intensity unilateral dorsiflexion resistance training paradigm examined in Chapter 4 to a post-stroke clinical group; specifically, the efficacy of inducing strength gains in the more-affected leg via

strength training of the less-affected leg was investigated. Clinical evaluation of motor function was also assessed, as well as disynaptic RI signalling between agonist (TA) and antagonist (SOL) muscles bilaterally. Post-intervention, significant gains were seen in dorsiflexor force output and maximal muscle activation bilaterally. These findings are the first to demonstrate the ability to induce a cross-education effect post-stroke. This is especially noteworthy, given the sizeable improvements observed bilaterally and the minimal absolute training time employed to induce those improvements (see Chapter 5). Indeed, a total isometric contraction time of 200sec (40 repetitions) per session, three times per week, was found to invoke gains in dorsiflexion force output of ~31% and 34% in the more- and less-affected legs, respectively. A common component in many previous post-stroke motor rehabilitation protocols is that of high repetitions and/or lengthy training sessions (Patten et al. 2004). Thus, the fact that such strength gains can be induced with reduced patient time commitment may be extremely valuable from a clinical standpoint. Of further interest clinically are the observations of subtle changes in motor function testing post-intervention. While these changes were small (see Chapter 5), their presence provides promise for future investigations of the cross-education effect's functional application(s).

Interestingly, novel information was also revealed on spinal excitability changes associated with the cross-education effect. The slope of the RI-muscle activation relation in the untrained TA muscle was significantly altered, such that at any given level of muscle activation TA RI was larger (i.e. greater inhibition) post-intervention relative to baseline. Such crossed effects of motor output on contralateral RI agree with observations made during transient one-sided arm muscle activity (Delwaide et al. 1988; Delwaide and

Pepin 1991), and they may have similar underlying mechanisms as those suggested previously. That is, repeated bouts of high-intensity unilateral dorsiflexion training could lead to increased contralateral sensitivity of the Ia inhibitory interneurons and larger suppression of alpha-motoneuron excitability (Delwaide et al. 1988; Delwaide and Pepin 1991). This is the first work to investigate and show effects of repeated maximal unilateral contractions on transmission in contralateral Ia inhibitory pathways. Thus, it is unknown whether similar contralateral changes in RI also occur in a neurologically intact system, or if such adaptation develops only in the presence of a post-stroke spinal signalling milieu.

6.3 Future directions

The findings of this thesis point to a number of research inquiries that would be valuable to resolve in the future. The following questions are of specific interest, to build from the present work and further understanding of remote input effects on motor output:

Can a lasting change on ankle dorsiflexor motor output (e.g. spinal excitability) be induced via rhythmic arm movement training in neurologically intact and/or post-stroke?

Do bilateral H-reflex adaptations observed in TA following unilateral strength training persist in other muscles of the lower limb, such as SOL, and/or in muscles of the upper limb?

Can ‘cross-education’ strength gains also be induced in the more-affected upper limb after stroke by training the less-affected side?

Can RI signalling changes observed in the contralateral, untrained TA muscle following unilateral dorsiflexion training post-stroke also be induced in a neurologically

intact system? Are such adaptations generalizable to the untrained homologous muscle, regardless of the muscle group trained?

What are the minimal training requirements for inducing a muscular crossed effect post-stroke? Would training paradigm changes in the form of increased repetition and/or session length result in more sizeable transfer to functional motor tasks? Overall, what pattern of unilateral training would best maximize strength and functional gains?

Finally, the culmination of this thesis was implementation of the proof of principle that remote motor input, in the form of unilateral resistance training, can be successfully applied post-stroke to induce useful change in motor output. These findings may be applicable in situations where training the more-affected limb is not initially possible, so that training the less-affected limb would establish a baseline of strength on the more-affected side. Thus, the last suggestion for future research is for further work in this area: that is, clinical trials of a similar post-stroke unilateral training protocol across chronic and/or acute patients with varying levels of unilateral dorsiflexor weakness, including patients who suffer major hemiparesis.

6.4 References

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