Application and refinement of cross-education strength training in stroke

by

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B.Sc., Beijing University of Aeronautics and Astronautics, 2009
M.Sc., Pennsylvania State University, 2011

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

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Supervisory Committee

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Abstract

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Coordinated movements are regulated by the brain, spinal cord and sensory feedback. The interaction between the spinal cord and sensory feedback also play a significant role in facilitating plasticity and functional recovery after neural trauma. Cross-education describes training one side of the limb to enhance the strength of the homologous muscle on the contralateral side. Previous study with chronic stroke participants found significant strength gains in the more affected leg following unilateral dorsiflexion training on the less affected side, which suggested cross-education can be used to boost strength gain when training the more affected side is hard to initiate. However, there is lack of evidence showing cross-education in the arm muscles after stroke and the neural pathways mediating strength cross-education in stroke participants require further study.

The modulatory role of sensory feedback in movement control has been studied by using cutaneous stimulation as a proxy of the sensory input from skin. Mechanistic studies on neurological intact participants show that cutaneous reflex pathways are widespread in the cervical and lumbar spinal cord and have a global effect on the muscles in the non-stimulated limbs. In rehabilitation training, sensory enhancement from prolonged electrical stimulation has been used to facilitate training outcomes for those had stroke and other neurological disorders. Therefore, cutaneous pathways may be important in regulating cross-education training-induced strength gain.

The purpose of this dissertation was to explore the effects of upper limb cross-education strength training in chronic stroke participants and the role of sensory inputs in regulating intra- and interlimb neural excitability in neurologically intact participants.

In the first project (Chapter 2), we explored the efficacy of cross-education strength training in wrist extensor muscles of chronic stroke participants. Strength improvements were found bilaterally with altered excitabilities in the cutaneous pathways on the untrained side. These results show the potential role of cutaneous pathways in mediating strength transfer after unilateral strength training which led us to further explore the factors may affect the cutaneous modulation. In neurologically intact participants, we investigated the effects forearm position (Chapter 4), stimulation trigger mode and parameters (Chapter 5) on the cutaneous reflexes in the stimulated limb. Following the findings from Chapter 3, 4, and 5, the interlimb effects of self-induced sensory enhancement on the cutaneous reflexes were examined in Chapter 6.

Taken together, data from this thesis confirms the clinical application of cross-education in strength training after stroke. It addresses that exaggerated bilateral strength gains and neural plasticity can be induced following unilateral strength training on the less affected side. In addition, sensory enhancement may be applied to amplify cross-education effects in strength training.

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Chapter 1 General introduction

1.1 The neural control of human movement

Smooth, coordinated movements are regulated in the nervous system by incorporating descending commands from the brain and somatosensory afferent feedback from muscles, skin, tendons, and joints. A tripartite model consisting of the brain, spinal cord, and sensory feedback has been suggested for understanding the control properties of human movements (Zehr, 2005). Strong interaction between spinally mediated pathways and sensory input has been observed during rhythmic movements such as walking or cycling. For example, spinal reflex amplitudes can be significantly influenced by the sensory input from the skin surface or muscle (Klarner & Zehr, 2018; Zehr, 2005). The role of cortical and corticospinal pathways in bimanual interaction has also been extensively studied (Carson, 2005). However, the interaction between the spinal cord and somatosensory feedback during discrete movement is less studied.

In a neurologically intact state, each component of this tripartite system interacts with the other two parts extensively to fine-tune muscle activities during various tasks and under perturbations. Following neurotrauma, such as stroke, the pathways around the lesion site are impaired. However, spinal neural network and somatosensory afferent pathways are morphologically intact. Several studies have shown that sensory enhancement may facilitate motor function training for those who have neurological disorders (Jung et al., 2017; Sheffler & Chae, 2007). In addition, strength and motor function of the more affected limb can be improved by activating intact interlimb neural networks. Therefore, enhancing the interaction between spinal neural networks and sensory input may further amplify rehabilitation training outcomes.

This review will first discuss the current findings on interlimb neural network and sensory stimulation in movement control and rehabilitation training. To understand the regulatory role of sensory input in interlimb neural connectivity, questions arising from current findings are discussed which lead to the objectives of this dissertation.

1.2 Spinal cord and somatosensory input in interlimb movement control

1.2.1 Spinal interlimb neural connection in movement control

The role of the spinal cord in regulating interlimb movement has been extensively studied in locomotor tasks. Studies from lower animals and humans show many similarities in interlimb regulation during locomotion (Zehr et al., 2016). Patterned muscle activities in each limb during walking or cycling are regulated by neural networks called central pattern generators (Duysens & Van de Crommert, 1998; Grillner & Wallen, 1985). Evidence from decerebrated animal models shows that rhythmic locomotor movement can be modulated with minimal supraspinal input (Guertin et al., 1995; LaBella et al., 1992; Andersson et al., 1978). Indirect evidence from human studies (see reviews in Klarner & Zehr, 2018) suggests that central pattern generators, probably mainly located in the spinal cord, are evolutionally conserved. By measuring spinally-mediated pathways, phase-dependent modulation is observed in multiple limb muscles. Such phase-dependent spinal modulation is also preserved in other rhythmic movements such as stepping and arm and leg cycling which suggest cutaneous pathways play a role in regulating coordinated interlimb movement during locomotion (Zehr et al., 2007).

During discrete movements, such as holding an object or manipulating tools, interlimb neural coupling is less obvious since each arm can perform independent movements. Many studies show voluntary muscle contraction on one side can affect the motor outputs and neural excitability on the opposite side. For example, resistance training in one limb can increase the strength on the opposite side (Zhou, 2000); simultaneous bilateral contraction reduces maximal force produced in each limb during unilateral contraction (Ohtsuki, 1983). The role of the spinal cord in regulating discrete tasks has been observed in a few studies. For example, reinforced reciprocal inhibition from wrist extensor to flexor (Delwaide et al.,1988) and reduced Hoffmann (H)-reflex amplitude in wrist flexor (Hortobagyi et al., 2003) when the contralateral arm was performing voluntary movements. The existing evidence suggests even when one side of the body is at rest, interlimb neural networks are not completely silent and movement from one side of the body can affect neural excitability on the contralateral side.

1.2.2 Interaction between the spinal cord and somatosensory feedback

The effects of somatosensory feedback on motorneuronal excitability can be measured through cutaneous reflexes which are evoked by stimulating the skin surface or nerve branches innervating the skin. Cutaneous pathways are polysynaptic, and typical cutaneous reflexes in human muscles include an inhibitory response around 50-70 ms post-stimulation (early latency reflex) followed by a facilitatory response around 70-120 ms post-stimulation (middle latency reflex).

Cutaneous nerve stimulation has been used as a proxy to assess neural excitability during various motor tasks. The existing evidence shows that cutaneous reflexes modulate differentially between rhythmic and discrete tasks. Cutaneous pathways have widespread effects and sensory input has a global effect on spinal excitability and muscle activities in both stimulated and non-stimulated limbs (Zehr et al., 2001).

Phase-dependent and nerve-specific responses to cutaneous stimulation are observed during rhythmic movements. Stimulation to the tibial, sural and superficial peroneal nerve at the foot during walking produced differential functional responses in lower leg muscles (Duysens et al., 1992; Wezel et al., 1997; Zehr et al., 1997; Zehr & Stein, 1999). Highly organized muscle responses can also be induced by stimulating the cutaneous receptors in different regions of the foot with location-specific neuromechanical responses around the ankle (Klarner et al., 2017; Zehr et al., 2014). This confirms that sensory input from the dorsal and plantar surfaces of the feet play specific roles in modulating muscle activities during walking. Input from foot dorsum evokes more general responses to the perturbation while input from foot sole sculpting the movement in response to changes in the ground. Overall, the feet act as sensory antennae during locomotion steering foot position in response to perturbation from the environment (Zehr et al., 2014).

During discrete tasks, cutaneous reflex amplitudes show less nerve-specificity. When stimulation was applied to the sural, tibial or superficial peroneal nerve respectively during standing, inhibitory reflexes were evoked in the leg muscles regardless of which nerve was being stimulated (Komiyama et al., 2000). Komiyama and colleagues suggest that since maintenance of posture is of primary importance during standing, overall inhibitory reflexes among multiple muscles may act as a “shock absorber" to reduce the perturbation to the center of mass and decrease the stiffness around knee and ankle joints. Such task-dependent cutaneous reflex modulation is also present in the upper limb. Nakajima et al. (2006) measured cutaneous reflexes in intrinsic hand muscle when stimulation was applied to the thumb, index finger or little finger when each finger performed isometric flexion individually or during a pinch grip task. Larger amplitudes of the second excitatory response (E2, peak latency ~60-90ms) in the abductor digit minimi were found during pinch grip which may assist the maintenance of a steady grip. At the same window of latency, Evans and colleagues (1989) also observed task-dependent reflexes in each individual finger between isolated finger movement and handgrip. These results suggest during discrete tasks, cutaneous reflexes are sensitive to behavioral context (Nakajima et al., 2006).

The interlimb effects of cutaneous stimulation have been observed in many studies. Haridas and Zehr (2003) found phase-dependent modulation in muscles of the non-stimulated limbs when stimulation was applied to the superficial radial nerve at the wrist or superficial peroneal nerve at the ankle during walking. During static muscle contraction in a seated position, stimulation to the superficial radial nerve at the wrist or superficial peroneal nerve at the ankle evoked large muscle response in both arms and legs (Zehr & Chua, 2000). Stimulation to the ulnar nerve (Meinck & Piesiur-Strehlow, 1981) or median nerve (Kagamihara et al., 2003) at the wrist facilitated the soleus H-reflex in the leg. By stimulating the median nerve on one side of the wrist, Delwaide et al. (1991) found reinforced reciprocal inhibition from wrist extensor to flexor on the contralateral side. Altered neural excitabilities in the non-stimulated limbs indicate a widespread interlimb neural network in the spinal cord and sensory stimulation has global effects on the spinally-mediated reflexes. For those with impaired motor function on one side of the body due to neurotrauma, cutaneous stimulation from the less affected limb may be able to normalize the neural excitabilities on the more affected limb.

1.3 Clinical application of interlimb neural connection and sensory enhancement

1.3.1 Cross-education in post-stroke strength training

Stroke is one of the leading causes of disability in Canada. About 60% of stroke survivors are left with some disability that requires rehabilitation training (Heart and Stroke Foundation, 2017). Following stroke, damage around the lesion sites leads to loss of supraspinal inputs to spinal motor neurons and interneural networks contralateral to the lesion, as well as altered excitability in spinal and supraspinal pathways. Strength and motor impairments are found bilaterally and greatly amplified on the contralesional side producing a neurophysiologically more affected (so-called paretic) and less affected (so-called non-paretic) side (Barzi & Zehr, 2008; Dragert & Zehr, 2013).

It used to be falsely believed that strength training should be avoided after stroke (Bobath, 1990). Yet, the efficacy of post-stroke strength training has been confirmed repeatedly (Ada et al., 2006; Patten et al., 2004). In addition, training-induced improvements can occur many years after injury (Sun et al., 2015; Ward et al., 2019). However, strength training in the more affected limb may be difficult to implement if there is too much weakness or if muscle tone (spasticity or clonus) is too high. A phenomenon called "cross-education" describes training one side to increase the strength or function in the homologous muscle on the untrained, contralateral side (Scripture et al., 1894). Since it was first recorded by Edward Scripture, evidence of cross-education has been found following strength training in different target muscles, ranging from finger abductor (Yue & Cole, 1992), to wrist flexors (Farthing & Chilibeck, 2003), and ankle plantar- and dorsiflexor muscles (Dragert & Zehr, 2011; Shima et al., 2002). A few studies suggest cross-education can induce bilateral strength gains and neural plasticity in chronic stroke participants by training their less affected side. In a study from Dragert and Zehr (2013), chronic (> 6 months post-lesion) stroke participants completed 6 weeks of dorsiflexion resistance training with the less affected leg using 5 sets of 5 maximal contractions in each session, 3 sessions per week. Significant improvements in dorsiflexion strength were found in both trained and untrained legs. Changes in reciprocal inhibition from soleus to tibialis anterior muscle were observed on the untrained side which indicates increased contralateral sensitivity of Ia inhibitory interneurons. Urbin and colleagues (Urbin et al., 2015) found increased wrist range of motion in six stroke participants (≥ 4 months post stroke) following 16 sessions of dynamic wrist extension training on the LA side. Two participants exhibited increased voluntary muscle activity including one participant whose motor evoked potentials were unobtainable prior to the intervention. These results confirm that neural plasticity can be induced in chronic stroke participants through high-intensity training on the contralateral, less affected side.

Compared to neurologically intact participants, stronger strength transfer is induced in the clinical populations. A meta-analysis from Green and Gabriel (2018) indicate that in neurologically intact participants, strength gain in the untrained side was 18% in young and 15% in older adults; in clinical population including stroke, neuromuscular disorders, and osteoarthritis participants, the increase is 29%. Larger strength gain in clinical population suggest cross-education can be used to boost the strength of the more affected limb when training the more affected side is hard to initiate. Farthing and Zehr (2014) proposed that the asymmetry of cross-education training could be exploited to offset asymmetrical deficits from injury or neurological impairment.

1.3.2 Sensory enhancement in amplifying motor outputs

With much evidence showing the significant effects of sensory feedback in regulating movements, sensory enhancement has been used in rehabilitation to facilitate training outcomes.

One commonly used method in generating sensory enhancement is prolonged electrical stimulation. The efficacy of transcutaneous electrical stimulation (TENS) in improving hand motor function (Celnik et al., 2007, 2009; Conforto et al., 2010), walking speed (Ng & Hui-Chan, 2007), and alleviating spasticity have been confirmed with stroke participants in many studies. Studies show two hours of electrical stimulation to the median nerve on the more affected hand improves functional performance (Conforto et al., 2010; Koesler et al., 2009). Celnik et al. (2007) and Ng et al. (2007) found amplified training outcome in the hand and leg respectively if participants received transcutaneous electrical stimulation before a training intervention. Besides stimulating the cutaneous nerves directly, sensory stimulation applied over the skin can also induce functional improvement. By using a "mesh glove" to provide whole hand stimulation, Dimitrijevic and colleagues (1996) found two to ten months of daily intervention increased muscle activity in wrist extensors in chronic stroke participants. Similar findings were seen in the lower limb. Tyson et al. (2013) used “sock electrodes” to stimulate the more affected feet in chronic stroke participants. With only one session of intervention, balance performance, walking speed, plantarflexor strength and plantar proprioception were all significantly improved.

1.3.3 Potential application of sensory enhancement in cross-education

For people with stroke, amplifying strength gains in the untrained limb could optimize the training timeline and facilitate targeted training on the more affected side. With the benefits of sensory stimulation observed in clinical populations, several studies investigated the effects of sensory enhancement on cross-education strength.

In a study by Hortobagyi and colleagues (1999), participants performed 6 weeks of strength training in the left quadriceps. Those trained with electrical stimulation-induced contraction showed higher strength gain in the untrained leg compared to the group performed voluntary contraction. This suggests afferent input from the skin and muscle has an additive effect in cross-education of strength (Hortobagyi et al., 1999). The interlimb effects of prolonged stimulation were observed in several studies. Veldman et al. (2018, 2016) found 20 mins of sensory stimulation improved skill acquisition, consolidation, and interlimb transfer in a visuomotor tracking task performed through wrist flexion and extension. Hamilton et al. (2018) found stimulation-induced bicep brachii muscle contractions increased motor neuron activity of the contralateral biceps brachii during isometric contraction. The modulatory role of sensory enhancement in strength cross-education training was confirmed by Barss and Zehr(2016). In this study, unilateral wrist extension was performed with or without randomly applied sensory enhancement on the superficial radial nerve. However, less strength transfer was seen in those receiving randomly applied sensory enhancement. Although this finding is opposite to the hypothesis, it addresses the importance of sensory enhancement in cross-education training and suggests the non-synchronized sensory volley and voluntary contraction may alleviate the cross-education effects. It is likely that timed sensory stimulation during muscle contraction can amplify the effects of cross-education training.

1.4 Spinal interlimb connection in the upper limb

The above evidence shows the potential of combining interlimb neural connections and sensory input in post-stroke rehabilitation. However, how sensory input affects interlimb pathways in the upper limb during discrete movement is less studied. To better understand which type of sensory enhancement is more effective in amplifying cross-education effects, the role of sensory input in interlimb spinal excitability needs to be further studied. Based on the current findings from the lower limb, there are several factors that may affect the cutaneous pathways in the upper limb.

1.4.1 The effects of stimulation trigger methods and timing

Several studies show the excitability in cutaneous pathways may be affected by trigger methods. Baken and colleagues (2006) found reduced reflex amplitudes when cutaneous stimulation was triggered by participants themselves during walking. Reduced sensation and muscle responses following self-generated stimuli have been described as “central cancellation” by Blakemore and colleagues (1998, 1999). In those studies, attenuated activity in the somatosensory cortex was observed following self-generated tactile stimuli. The authors suggest that since the sensory consequence of self-generated stimulation can be predicted, reduced neural excitability allows a more sensitive neural network to respond to sensory perturbation from the environment.

1.4.2 The effects of joint position on cutaneous pathways

Altered spinal excitability was observed with changes in joint position. Reduced H-reflex amplitudes are seen in leg extensor muscles when body position changes from lying to sitting to standing (Angulo-Kinzler 1998; Capaday & Stein, 1987; Goulart et l., 2000; Koceja, 1993) and in the flexor carpi radials muscle when the forearm changes from prone to supine positions (Baldissera et al. 2000). These findings suggest Ia presynaptic inhibition can be modulation by body position. Some studies proposed that the origin of phase-dependent cutaneous reflex modulation during walking is altered cutaneous and proprioceptive input related to loading. Bastiannse and colleague found that larger cutaneous reflex in the soleus and medial gastrocnemius when walking with body unloading (Bastiaanse et al., 2000). The role of load-related feedback was confirmed by Nakajima et al. (2008). In this study, participants were walking on the treadmill passively with body weight fully supported, no phase modulation was seen in the leg muscles following cutaneous stimulation to the superficial peroneal nerve or distal tibial nerve.

1.4.3 The effects of stimulation parameters on spinal excitability

Differential neural adaptation was observed when prolonged sensory stimulation delivered with different parameters. Chipchase and colleagues (2011) found sensory stimulation below the motor threshold reduced corticomotor responsiveness of the stimulated muscle and its antagonist regardless of the stimulation frequency (10Hz VS 100 Hz). Different conclusions were drawn from a review by Leseman et al. (2015). Leseman suggested that the effect of stimulation is a combination of frequency, duration, and intensity. Decreasing one factor requires increasing the strength of another parameter in order to not diminish the overall effect.

1.5 Thesis objectives and research studies overview

To explore the role of spinal interlimb neural network and sensory feedback in cross-education strength training, the three main objectives of this thesis are to: 1) explore the application of cross-education strength training in the arm muscles after stroke; 2) investigate the modulation of cutaneous reflexes in the arm muscles during static contraction; and 3) investigate the effects of sensory enhancement on interlimb cutaneous pathways.

To study the effects of cross-education training on the arm muscles of chronic stroke participants, twenty-four participants completed five weeks wrist extension training using their less affected arm in the study from Chapter 2. Maximum wrist extension force was compared before and after the training on both arms. To investigate training-induced neural plasticity, corticospinal and spinal pathway excitabilities were measured before and after the training. Cutaneous reflexes from median nerve and superficial radial nerve stimulation were measured in the wrist extensors of both arms. Reciprocal inhibition from the wrist flexors to extensors were also tested bilaterally to determine whether training can reduce the co-contraction between agonist and antagonist muscles during wrist extension. To explore training-induced changes in the motor cortex of each hemisphere and the projections from each hemisphere to the ipsi- and contra-lateral wrist extensor, cortical silent period, transcallosal inhibition, short-interval intracortical inhibition, and intracortical facilitation were measured.

One of the main findings from Chapter 2 is significantly improved wrist extension strength in both arms. Greater strength gains were observed compared to neurologically intact participants. Together with the findings from other interventional studies utilizing the less affected limb to promote the function of the untrained limb (Dragert & Zehr, 2013; Kaupp et al., 2018; Klarner et al., 2016), a novel hypothesis was proposed in Chapter 3 suggesting that chronic stroke populations are more responsive to training stimuli. By activating the morphologically intact interlimb neural pathways, amplified strength gain and neural plasticity can be induced in chronic stroke participants.

Another main finding from Chapter 2 is cutaneous reflex modulation on the untrained side is normalized to the less affected side, this suggests that sensory input arising from the voluntary contraction may contribute to the strength transfer following unilateral training and the effects of cross-education training may be amplified by manipulating the sensory input participant received during training. To better understand the modulation of cutaneous pathways in the upper limb and refine the cross-education strength training methods, a few studies were performed with neurologically intact participants. Chapter 4 explored the effects of wrist position on cutaneous reflexes and reciprocal inhibition amplitudes in the wrist extensor muscle at different levels of muscle activity. To understand how concurred sensory and voluntary contraction affect cutaneous reflex pathways, Chapter 5 compared cutaneous reflex amplitudes when stimulation was triggered by participants themselves and by a computer program. Meanwhile, to investigate the effects of stimulation parameters on spinal excitability, brief reflex stimulation, and prolonged sensory enhancement were delivered, respectively.

To explore the potential of sensory enhancement in amplifying cross-education effects, Chapter 6 examined the interaction between enhanced sensory feedback and interlimb neural networks. Cutaneous reflexes were measured bilaterally following a train of sensory enhancement applied on the contralateral arm during wrist extension contraction.

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Chapter 2 Unilateral wrist extension training after stroke improves strength and neural plasticity in both arms.[1]

2.1 Abstract

Stroke induces bilateral neurological impairment and muscle weakness yielding neurologically more (MA; paretic) and less affected (LA; non-paretic) sides. “Cross-education” refers to training one side of the body to increase strength in the same muscles on the untrained side. Past work showed dorsiflexion training of the LA side produced bilateral strength increases after stroke. The current study explored the presence and extent of cross-education after arm strength training in chronic stroke.

Twenty-four chronic stroke participants completed 5 weeks of maximal wrist extension training using their LA arm. Maximal voluntary contraction force, arm motor impairment and functional performance were measured before and after training. Both spinal cord plasticity (n=12: reciprocal inhibition and cutaneous reflexes, University of Victoria) and cortical plasticity (n=12: cortical silent period, short-interval intracortical inhibition, intracortical facilitation and transcallosal inhibition, University of British Columbia) were assessed. Five weeks after training, 20 participants completed a follow-up maximal wrist extension retention test.

LA wrist extension force increased 42% and MA by 35%. Strength gains were maintained in the follow-up test. Clinically meaningful increases in Fugl-Meyer scores were noted in 4 participants. Muscle activation was correlated with cutaneous reflex amplitudes after training in the MA arm. LA cortical silent period and transcallosal inhibition from both hemispheres significantly decreased after training.

This study shows that high-intensity training with the neurologically less affected “non-paretic” arm can improve strength bilaterally and alter both spinal and cortical plasticity. The extent to which this plasticity can be enhanced or functionally exploited remains to be examined.

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2.2 Introduction

Stroke-induced neural damage leads to loss of inputs to motor neurons on the contralesional side as well as altered intra-cortical communication. Strength and sensorimotor functions are impaired bilaterally and asymmetrically which present as paretic, neurologically more affected (MA) side and non-paretic, less affected (LA) side (Dragert & Zehr, 2013; Zehr & Loadman, 2012). The benefits of post-stroke strength training have been well recognized (Ada et al, 2006). Patten and colleagues completed a systematic review emphasizing strength training after stroke is useful and does not exacerbate spasticity, or reduce joint range of motion (Patten 2004). However, directly training the MA side is often extremely difficult for those with severe muscle weakness or limited joint range of motion.

Training one side of the body to increase strength in the same muscles on the untrained sides (“cross-education”) was first reported in 1894 (Scripture et al, 1894) and can occur in both arm and leg muscles of neurologically intact participants (Yue & Cole, 1992; Dragert & Zehr, 2011; Hortobagy et al, 1997). According to the “restoring symmetry hypothesis”, Farthing and Zehr proposed that cross-education training, an asymmetrical intervention, should be applied to offset asymmetrical neuromuscular deficits after stroke (Farthing & Zehr, 2014).

After stroke, cross-education training with the LA leg can facilitate dorsiflexion strength gains on the MA side. Significantly improved voluntary strength (~30%) and tibialis anterior muscle activation in the MA ankle with improved walking ability were found after 6 weeks of dorsiflexion training using the LA side (Dragert & Zehr, 2013). In addition, Urbin et al. found 16 sessions of wrist extension training on the LA side increased active wrist range of motion on the MA side and altered corticospinal plasticity (Urbin et al, 2015).

Studies clearly indicate that unilateral training affects neural pathways bilaterally at both spinal and cortical level (Dragert & Zehr, 2011, 2013; Hortobagyi et al., 2011; Latella et al, 2012; Lee & Carroll, 2007). Altered excitability in spinal pathways that project to the contralateral side has been assessed by changes in H-reflex amplitudes and extent of reciprocal inhibition (Dragert & Zehr, 2011, 2013). Dragert and Zehr (2011) reported that dorsiflexion training altered soleus H-reflex amplitudes in neurologically intact participants and enhanced reciprocal inhibition from soleus to tibialis anterior muscle on the untrained sides in individuals with stroke (Dragert & Zehr, 2013). Reduced inhibition in the cortical and corticospinal pathways have also been recorded following unilateral training (Hortobagyi et al., 2011; Latella et al., 2012). Strong correlation between strength transfer and decreased interhemispheric inhibition were seen following unilateral strength training in dorsal interosseous muscle suggesting cross education may affect by the adaptations in interhemispheric inhibition from the trained to the non-trained primary motor cortex (Hortobagyi et al., 2011). Although training-induced neural adaption has been found in both spinal and cortical pathways in neurologically intact participants, less is known about neural adaption following upper limb cross-education training in stroke.

Resistance training-induced improvements in balance and gait performance (Flansbjer et al. 2012; Flansbjer et al. 2008; Yang et al. 2006), and reduced arm motor impairment (Winstein et al., 2004) are noted when the MA side is trained. Unilateral strength training in the ankle can improve strength and these changes may have the potential to transfer to improve function in chronic stroke participants (Dragert and Zehr 2013). However, whether MA arm strength training-induced functional changes could transfer to the untrained side in individuals with chronic stroke has not been tested.

To explore whether unilateral wrist extension could induce cross-education in strength, spinal and cortical plasticity, and motor function after stroke, 24 chronic stroke participants completed a 5-week maximal wrist extension intervention using the LA arm. We hypothesized that unilateral resistance training with the less-affected wrist would improve strength, produce neural adaptation at spinal and cortical levels and induce clinically meaningful changes bilaterally after stroke.

2.3 Methods

2.3.1Participants

Twenty-four participants with chronic (> 6 months post lesion) stroke and associated arm weakness were recruited, detailed participants’ information was provided in Table 2.1. Twelve participants trained at the University of Victoria (UVIC) and 12 at the University of British Columbia (UBC). The protocol was approved by the University of Victoria Human Research Ethics Board (protocol number: 07-480-04d) and University of British Columbia Clinical Research Ethics Board (protocol number: H15-00055）in accordance with Declaration of Helsinki. Written informed consent was obtained before data collection.

2.3.2 Control Procedures

The current study utilized a within-subject multiple baseline design (Butefisch et al, 1995). Three baseline tests (PRE1, PRE2 and PRE3; separated by 4-7 days) and one post-test (POST, within one week after training) were performed. Maximal wrist extension strength, spinal and cortical plasticity, and clinical assessments were performed at PRE1-3 and POST. Retention of strength gains was assessed in follow up tests with wrist maximal extension force and Wolf Motor Function Test (WMFT) measured 5 weeks after the last training session.

Although this multiple baseline design requires more time and labor, it has been validated as a replacement of the control group (Butefisch et al., 1995; Dragert & Zehr, 2011, 2013, Klarner et al., 2014, 2016a, 2016b, Kaupp et al., 2018), allows participants to create a reliable baseline and act as their own control, and ensures all receive treatment. To evaluate individual subject data, a 95% confidence interval (95%CI) of the wrist extension force was calculated from the 3 baselines and those whose POST value was outside this range were defined as a responder (Klarner et al., 2016a).

2.3.3 Training protocol

Five weeks of training were completed with 3 sessions (one in lab, two at home) per week consisting of 5 sets × 5 reps × 5 s maximal wrist extension contractions in the LA arm (3s breaks between contractions and 2 min breaks between sets) (Dragert & Zehr, 2011, 2013; Barss et al, 2017;). Before training, a warm-up session with 3 sets × 5 rep × 5 sec 50% maximal wrist extension contraction were completed. Training was performed with the participant seated in a comfortable position with LA arm strapped to the customized training device to ensure the wrist angle was constant during contraction

(Figure 2.1 A). When training at home, standardized audio instructions were provided with cueing of when to contract and relax during warm up and training, as well as verbal encouragement to ensure the instruction and timing were consistent between sessions. To ensure participants followed protocol when training at home, each training device included a load cell to record contractions and a micro SD card to save the data. Data from the training device were recorded and analyzed for those training at UVIC. Training devices were piloted with two neurologically intact volunteers prior to data collection. The full training protocol was completed to ensure the device was comfortable and easy to use through the training. To test the reliability of the training devices, load cell readings were recorded by adding and removing standard weights across 5 different days. High reliability was suggested based on significant intraclass correlation for all the devices (Pearson correlation >0.98, p=0.000).

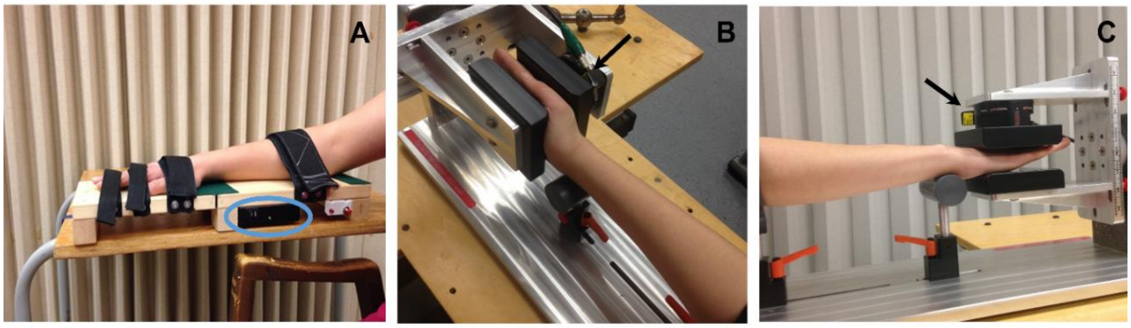

Figure 2. 1 A: Customized strength training device. Participants aligned the wrist crease to the middle of the training device at the hinge. A load cell was installed underneath. Blue circle indicates the compartment with data acquisition circuit, battery and micro SD. B and C: MVC force at wrist horizontal (B) and vertical (C) positions. Black arrow indicates force sensor.

2.3.4 Measures of strength (n=24, participants from UVIC and UBC)

During PRE, POST and follow-up tests, participants were seated comfortably with forearm and wrist supported in a customized device (Figure 2.1 B, 2.1 C). Maximal voluntary contraction (MVC) wrist extension force was measured with the wrist at horizontal (pronated) and vertical (mid-supinated) positions bilaterally using a 6-axis force sensor (ATI, Industrial Automation Gamma DAQ F/T Transducer, Apex, NC, USA). MVC force was calculated from a 10ms window around the peak with custom written MATLAB programs (Version R2013b, The Mathworks, Natick, MA, USA).

During training, wrist extension force was measured by a load cell and recorded on a Micro SD card on the training device (Figure 2.1A). Data were analyzed with a customized LabVIEW program for those training at UVIC (n=12). If the load cell reading showed a quick increase with a clear plateau >3s, that trial was considered as a "qualified" MVC. According to the training protocol described in the previous section, a total of 375 MVC (5 reps × 5 sets × 3 sessions × 5 weeks) were intended to be completed by each participant. The average number of "qualified" MVC for the 12 participants at UVIC was 288±65.

2.3.5 Measures of spinal plasticity (n=12, participants from UVIC)

Electromyography (EMG) of extensor (ECR) and flexor carpi radialis (FCR) muscles was recorded using disposable surface electrodes (Thought Technology Ltd., Quebec, Canada). EMG was amplified (×5000), bandpass filtered from 100 to 300 Hz (GRASS P511, Astromed-Grass Inc.) and sampled at 2000 Hz through a customized LabVIEW program (National Instruments, Austin, TX). Maximal EMG in ECR muscle (EMG_{MAX}) during wrist extension was determined on both sides, reciprocal inhibition and cutaneous reflexes were examined at four contraction levels (10%, 15%, 25% and 50% EMG_{MAX} of the same arm).

Reciprocal inhibition from wrist flexors to extensors and cutaneous reflexes evoked by median (MED) and superficial radial (SR) nerve stimulation were assessed bilaterally with similar procedures as found in previous studies (Thompson et al, 2008; Zehr & Kido, 2001; Kido et al, 2004). Reciprocal inhibition was evoked by a single 1.0 ms pulse applied over the median nerve just above the elbow under the curve of the biceps brachii. Stimulation intensity was set at 1.2 times the threshold that evoked a direct muscle response (M-wave motor threshold) in FCR. For cutaneous reflexes, trains of 5×1.0 ms pulses at 300 Hz were applied to the superficial SR or MED nerves at the wrist. Intensity was set as 2 times radiating threshold (RT), the lowest intensity at which a sensation of radiating paresthesia could be evoked in the innervation territory of the nerve, while not considered noxious by study participants.

Twenty data sweeps were collected and sampled by triggering pseudo-randomly every 1.5–3 s (reciprocal inhibition) or 2–3 s (cutaneous reflexes). Target EMG was presented on a computer screen during each trial so participants could match targets between stimulations. Since most participants could not generate four distinct levels of wrist extension contraction on their MA sides, two to three trials were performed with different ECR background EMG.

Typical muscle responses from reciprocal inhibition and cutaneous reflexes trials are presented in Figure 2.2. Reciprocal inhibition was calculated as the difference between the mean background EMG and the mean of a 10ms window around the post-stimulus minima with a latency to the peak of the response of ~30-40 ms. Early latency cutaneous reflexes were analyzed as the difference between the mean background EMG and the mean of a 10ms window around post-stimulation minima at ~50-75 ms latency.

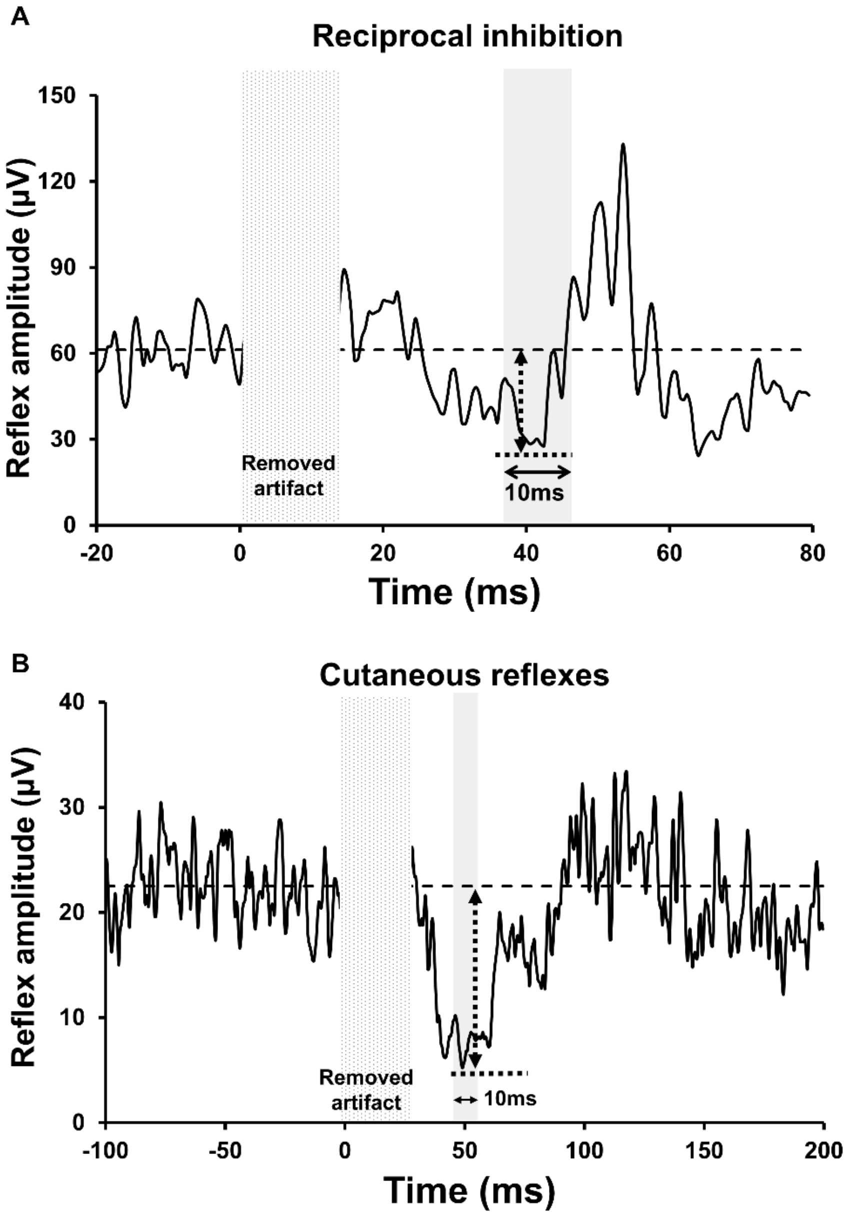

Figure 2. 2 Typical muscle responses for reciprocal inhibition (A) and cutaneous reflex (B) trials with stimulation artifact removed (blank area in figures). A. Shaded area indicates the reciprocal inhibition response measured at latency to the largest effect, a 10ms window around the lowest value that was used for data analysis at the latency around 30ms-40ms. There was a 20 ms window of background EMG data recorded before stimulation onset. The average value of the pre-stimulation background EMG was presented as a long dash line. B. Dark grey area indicates the early latency cutaneous reflex, a 10ms window around the lowest value that was used for data analysis at the latency around 50ms-75ms. There

was a 100 ms window of data recorded before stimulation onset. The average value of the pre-stimulation background EMG was presented as a long dash line.

2.3.6 Measures of cortical plasticity (n=12, participants from UBC)

Cortical silent period (CSP), transcallosal inhibition (TCI), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were measured during PRE, POST and follow-up test.

As described previously (Mang et al., 2015), CSP and TCI were elicited by single-pulse TMS with a Magstim 200^2 stimulator unit and a figure-of-eight coil (70mm, P/N 9790, Magstim Co. Ltd., Whitland, Carmarthenshire, UK) at a frequency of 0.25 Hz. CSP was measured as the prolonged decrease in ECR EMG following a motor evoked potential (MEP). During TCI trails, participants produced 50% maximum grip contraction ipsilateral to the stimulation. Ten TMS stimulations at 150% resting motor threshold were delivered over the ECR motor cortex representation to elicit ipsilateral silent period (iSP). Mean and minimum EMG amplitude during the iSP (iSP-mean, iSP-max) from both contralesional (CL) and ipsilesional (IL) side were measured. The normalized iSP-mean was calculated as iSP-mean/pre-stimulus.

SICI and ICF were evoked by paired-pulse TMS(Chen et al., 1998; Kujirai et al., 1993). SICI was defined as the suppression of the MEP evoked by a subthreshold conditioning stimulus and a suprathreshold test stimulus with a 2ms interval. ICF is a period of increased intracortical excitability in response to conditioning stimulus and test stimulus with a 12 ms interval. The amplitude of conditioning stimulation was set at 80% active motor threshold and the test stimulus was set at the necessary stimulus intensity to consistently evoke an MEP with an amplitude of 0.3-0.5 mV in ECR. Ten test stimuli, 10 SICI, and 10 ICF stimulations were delivered in a pseudo-randomized order. The percentages of SICI and ICF to unconditioned test stimuli MEP were calculated. All TMS data analyzed offline with custom MATLAB program. SICI and ICF were evoked on the ipsilesional sides of four participants during one baseline test. Therefore, only these four PRE and POST datasets were used for statistical analysis.

2.3.7 Clinical Measurements

The Fugl-Myer Upper Extremity (FM-UE) assessment indexed arm motor impairment in the MA arm for all participants (n=24) before and after training. FM-UE assessment has been commonly used in measuring motor impairment during stroke recovery (Gladstone et al, 2002). Here, FM-UE assessed joint movement from four sections: upper extremity (36 points), wrist (10 points), hand (14 points) and coordination/speed (6 points) using a 3-point scale with higher scores indicating less motor impairment (max score 66).

To evaluate arm motor function, the Wolf Motor Function Test (WMFT) (Wolf et al, 2001) were performed by the 12 participants at UBC. Due to time constraints, an abbreviated version of the Wolf Motor Function Test (abb-WMFT) were performed by the 12 participants at UIVC. The abb-WMFT included three tasks: pick up a can (gross motor), pick up a paper clip (fine motor) and fold a towel (functional task); both arms are tested during the WMFT. Performance time of each task was converted to rate of performance (Hodics et al., 2012) :

$$\text{Rate of Performance} = 60\ (\text{s}) \,/\, \text{Performance Time (s)}$$

The rates of performance were averaged among the tasks and compared statistically between PRE and POST. Participant information and clinical baseline measurements are in Table 1.

Table 2. 1 Individual participant characteristics and clinical assessment baseline.

Participant ID	Gender	MA Side	PSD (mo)	Full WMFT (MA)	Full WMFT (LA)	abb-WMFT (MA)	abb-WMFT (LA)	FM-UE (66)
UBC01	F	L	68	23	78	1	48	39
UBC02	F	R	34	18	78	5	56	11
UBC03	M	L	110	7	83	0	51	9
UBC04	F	R	181	15	43	0	43	28
UBC05	M	L	185	10	58	2	42	20
UBC06	M	L	100	38	57	22	35	48

UBC07	M	L	137	99	104	52	65	60
UBC08	M	R	137	66	123	45	82	54
UBC09	M	R	302	3	76	0	55	5
UBC10	M	R	64	51	60	30	42	54
UBC11	M	R	125	5	70	0	49	5
UBC12	M	R	195	3	74	0	51	11
UVIC01	M	R	32	na	na	0	24	22
UVIC02	F	L	96	na	na	0	28	5
UVIC03	M	R	71	na	na	0	21	63
UVIC04	M	L	90	na	na	17	25	2
UVIC05	M	L	120	na	na	0	19	55
UVIC06	M	R	94	na	na	8	25	37
UVIC07	F	L	160	na	na	17	23	3
UVIC08	M	L	231	na	na	0	25	22
UVIC09	M	L	75	na	na	0	22	15
UVIC10	F	R	249	na	na	0	29	10
UVIC11	M	R	132	na	na	0	22	11
UVIC12	M	L	93	na	na	8	22	40

MA, more-affected; LA, less-affected; na, data not available; PSD, post-stroke duration; Full WMFT: full Wolf Motor Function Tests; abb-WMFT, abbreviate Wolf Motor Function Test rate; FM-UE: Fugl-Meyer Upper Extremity assessment, with a total score of 66.

2.3.8 Statistical analysis

One-way repeated measures analyses of variance (rmANOVA) were performed (SPSS 20, Chicago, IL) to assess whether force changes over time. If there was no significant difference between PRE1, PRE2 and PRE3, baseline data were averaged to one PRE value. (Klarner et al., 2016a, 2016b). To test whether strength improved significantly after training, the main effect of TIME was tested for PRE and POST force data (n=24). To test whether the strength gains were retained after training, one-way rmANOVA was performed to test the main effect of TIME on PRE, POST and follow-up force data (n=20).

To assess the strength changes for individual participants, a 95% confidence interval (95%CI) was calculated from the 3 baseline tests with maximal of 9 MVC wrist extension contractions. If the averaged post-test strength outside the range of 95% CI, the strength improvement was considered significant and that participant was defined as a responder.

For reciprocal inhibition and cutaneous reflexes (n=12), linear regression analyses between baseline EMG and reflex amplitudes were performed and Pearson r values calculated for each pool of paired data (df = n-1). For significant linear relation, the slope and y-intercept were compared between PRE and POST data, with critical t distribution values (df = n1+ n2 - 4) used to establish significance (Dragert & Zehr, 2013).

CSP from the contralesional side (n=12), SICI and ICF values on each hemisphere (contralesional: n=12 and ipsilesional n=4) were examined across time (PRE, POST, follow-up) by one-way rmANOVA. Two-way rmANOVA with the main effect of Time and Hemisphere (CL, IL) was used for TCI measurements (n = 12). Correlation analysis was performed between the percentage change in strength gain and TMS measures for the responders.

Paired t-tests were used to compare averaged rate of performance in abb-WMFT, full-WMFT and the Fugl-Meyer between PRE and POST tests. Statistical significance was set at $p \leq 0.05$.

2.4 Results

2.4.1Force measurements

Wrist extension force significantly increased by 42% ($F_{(1,23)} = 5.603, p=0.027$) and 35% ($F_{(1,23)} = 4.510, p=0.045$) on the LA and MA sides in the trained wrist horizontal position . Paired t-test showed that the percent gain did not differ between the two arms. A significant main effect of Time was found in the 20 participants comparing PRE, POST and follow-up ($F_{(1,23)} = 4.484, p=0.018$). No significant difference between POST and follow-up suggests maintained strength. Strength improvement in the wrist horizontal position did not transfer to wrist vertical position for either hand. Figure 2.3 shows the averaged maximal wrist extension force during PRE, POST and follow-up tests. Force measurements for each participant are presented in Table 2.2.

Table 2. 2 Individual participant wrist extension strength (wrist horizontal position) during PRE, POST and follow-up test.

Participant ID	*LA PRE (N)*	*LA POST (N)*	*LA Follow-up (N)*	*MA PRE (N)*	*MA POST (N)*	*MA Follow-up (N)*	*Responder*	
							LA	*MA*
UBC01	16.86	32.36	N/A	6.70	4.37	N/A	Y	N
UBC02	58.19	30.51	12.67	7.05	13.28	7.05	N	
UBC03	17.66	39.19	N/A	14.12	38.10	N/A	Y	Y
UBC04	23.96	39.13	27.92	5.60	18.55	18.48	Y	Y
UBC05	22.94	48.65	58.10	28.89	46.55	21.87	Y	Y
UBC06	17.47	59.67	30.77	54.74	112.98	105.29	Y	Y
UBC07	27.66	61.56	59.78	80.33	77.48	46.19	Y	N
UBC08	151.45	89.15	N/A	62.90	108.05	N/A	N	
UBC09	39.62	77.87	66.38	8.53	11.23	3.9	Y	Y
UBC10	73.19	83.96	48.41	28.61	30.78	33.76	Y	N
UBC11	88.77	98.53	128.85	13.69	18.66	6.25	N	
UBC12	50.38	70.94	N/A	1.98	7.36	N/A	Y	Y
UVIC01	125.98	138.88	115.79	15.22	19.54	40.88	Y	N
UVIC02	62.65	30.93	46.63	-4.16	1.05	1.51	N	
UVIC03	41.08	32.95	40.81	48.99	51.12	49.35	N	
UVIC04	68.28	104.81	53.31	N/A	N/A	N/A	Y	N/A
UVIC05	65.35	74.10	102.69	32.54	39.72	48.35	Y	Y
UVIC06	84.04	99.53	97.78	10.53	15.90	11.93	Y	Y
UVIC07	32.95	39.16	45.52	3.84	3.53	2.44	Y	N
UVIC08	77.88	129.44	139.36	-0.94	-0.46	10.94	Y	N
UVIC09	75.35	89.65	75.58	6.43	5.99	N/A	N	

UVIC10	46.49	80.28	78.66	1.87	-0.30	29.17	Y	N
UVIC11	130.16	159.35	132.66	31.53	0.43	9.66	Y	N
UVIC12	35.47	22.17	44.11	15.81	25.61	37.53	N	

MA, more-affected; LA, less-affected; N/A, data not available; N/A cells: participant UBC01, UBC03, UBC08, UBC12 were not able to visit the lab for the strength follow-up test; participant UVIC 04, 09 developed severe spasticity in the elbow joint on the MA side, thus the MA arm could not fit in the force measurement device for all or parts of the strength tests. For "responder" Y and N indicate whether or not each participant had strength adaptations for LA or MA side. Participant UVIC06 's MA side strength could not be obtained during the POST test, therefore the MA side result is listed as N/A.

Single subject analysis showed that wrist extension force in 17 of 24 participants significantly improved in the trained arm. These 17 participants were considered LA responder. Within the17 LA responders, strength transfer occurred in 8 participants, which were determined as MA responder. Fifteen LA responders completed the follow-up tests and showed strength maintenance in 8 with only 3 MA responders.

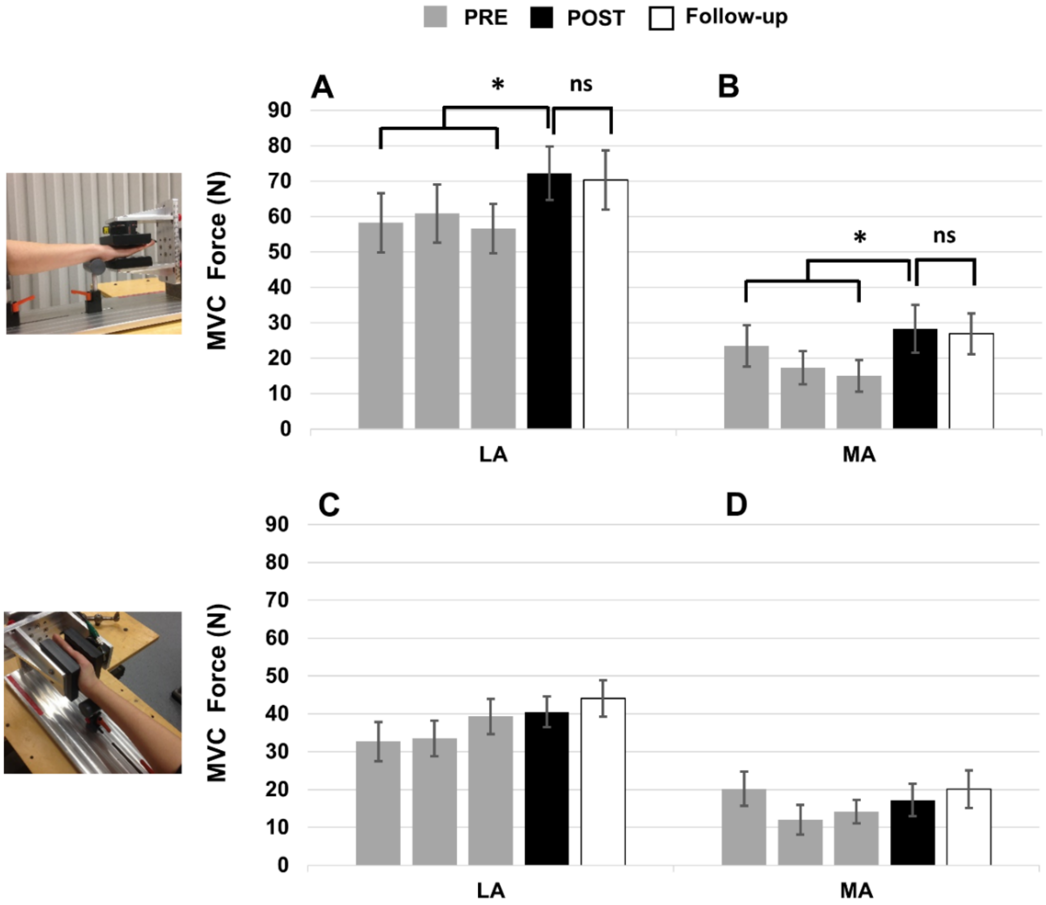

Figure 2. 3 Wrist extension MVC force at PRE, POST and follow-up at wrist horizontal (A & B) and vertical (C & D) positions. Grey, black and white bars represent force amplitude at PRE (n=24), POST (n=24) and follow-up (n=20), respectively. Each bar represents mean +/- one standard error of the mean. * indicates significant difference ($p<0.05$). ns represents there is no significant effect.

2.4.2 Spinal plasticity measurements – UVIC

Significant correlation between background EMG and reciprocal inhibition was found on the LA side before and after training with no differences between linear regression slopes (Figure 2.4). Early latency cutaneous reflexes from MED and SR nerve stimulation were also significantly correlated with background EMG in the LA arm (see Figure 2.5).

On the MA side, significant correlation was found in the early latency SR cutaneous reflexes during PRE and POST tests, and early latency MED cutaneous reflexes during PRE. A significantly decreased linear regression slope was found in the SR cutaneous response after training (t = 2.34, t_{crit} = 1.99, p=0.02).

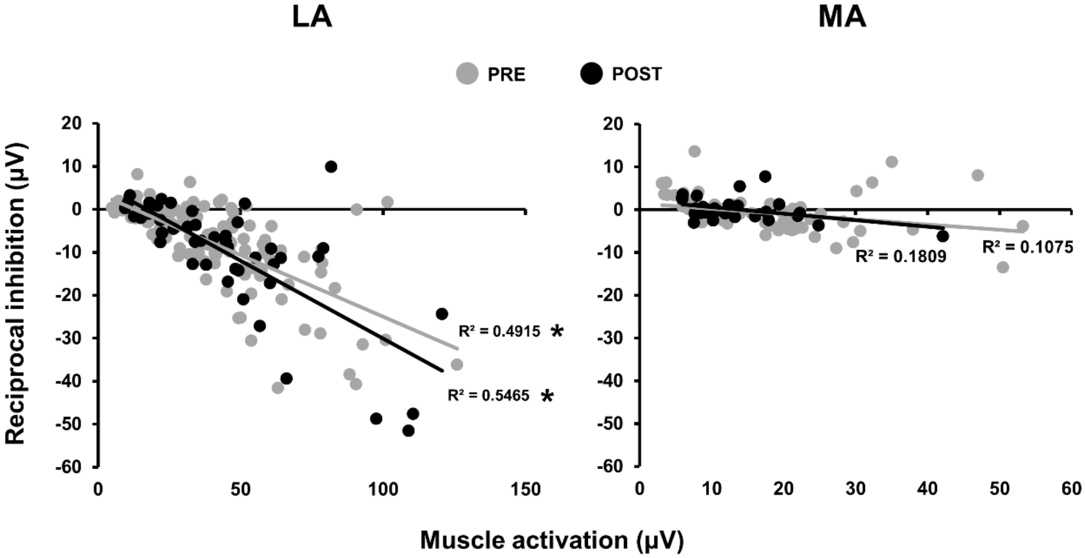

Figure 2. 4 Reciprocal inhibition evoked at different background muscle activation levels. Linear regression analyses and Pearson r values were calculated for each best-fit line. Grey and black dots represent reflex amplitudes at PRE and POST tests respectively. * indicates significant linear correlation. X-axis represents background ECR muscle activation. Y-axis represents reciprocal inhibition amplitudes.

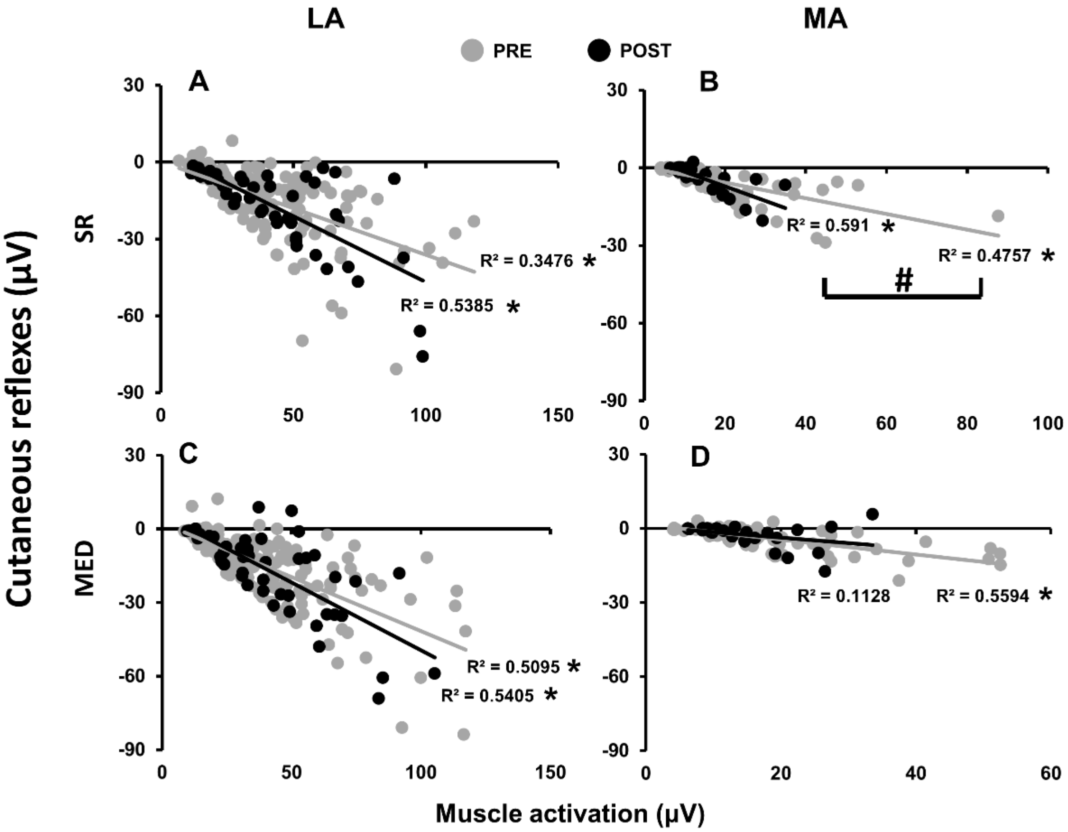

Figure 2. 5 Cutaneous reflexes evoked from superficial radial (SR; A & B) and median (MED; C & D) nerves at different background muscle activation levels. Data from less (LA) and more (MA) affected arms (n=12 participants) are shown at left and right, respectively. Grey and black dots represent reflex amplitude at PRE and POST, respectively. Linear regression analyses were performed and Pearson r values were calculated for each best-fit line. * indicates significant linear correlation. # indicates significant difference between linear regression slopes. X-axis represents background ECR muscle activation. Y-axis represents cutaneous reflexes amplitudes.

2.4.3 Cortical plasticity measurements – UBC

CSP duration decreased by 12% (*p* = 0.018) in the contralesional hemisphere (LA side) after training (Figure 2.6). No visible CSP was elicited during baseline tests in the ipsilesional hemisphere. Percentage change in CSP and strength of the LA responder were not correlated (Pearson r=0.374, n=9).

Increased normalized iSP-mean (iSP-mean/pre-stimulus) was noted (*p* = 0.023) with 1% and 3% changes in the contralesional and ipsilesional hemisphere respectively indicating reduced transcallosal inhibition (Figure 2.6). However, no significant effects of Hemisphere, Time, or Hemisphere x Time interaction showed between PRE to POST and follow-up tests (n=9, with three participants did not complete the follow-up TMS test). Correlation analysis showed no relationship between changes in normalized iSP-mean and strength for LA (Pearson r=0.205, n=9) or MA responders (Pearson r=0.334, n=6)

SICI and ICF were only generated in 4 participants during the PRE tests. No significant change occurred in either SICI or ICF after training. Results of the statistical analysis for strength and cortical plasticity are presented in Table 3.

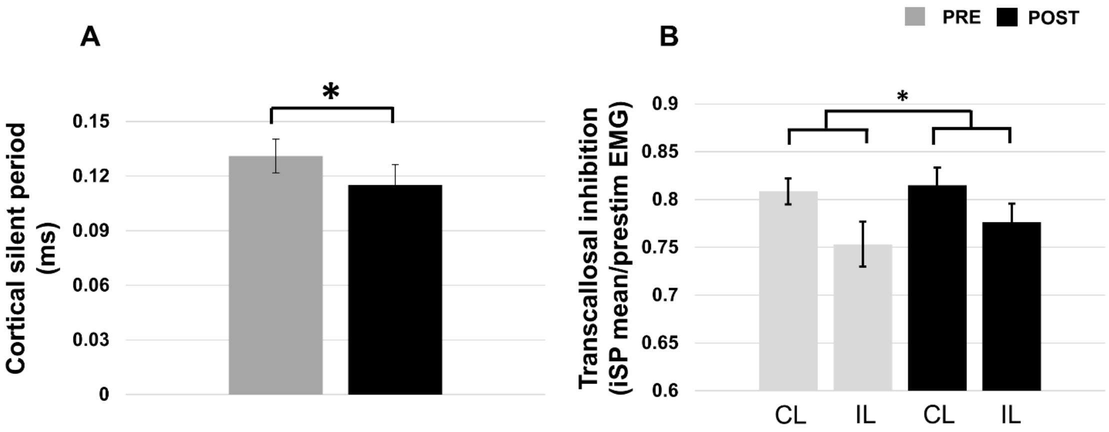

Figure 2. 6 Cortical silent period (CSP; Panel A) on the ipsilesional (IL) side. Transcallosal inhibition (Panel B) on both contralesional (CL) and IL sides. Grey and black bars represent PRE and POST tests results (n=12). Each bar represents mean +/- one standard error of the mean. * indicates significant difference (p<0.05).

2.4.4 Clinical measurements

Clinical function improved and motor impairment decreased after training. FM Upper Extremity score increased from 26.2±20.6 to 28.7±20.3 (mean ± standard deviation) after training (p = 0.001). Abb-WMFT rate increased from 37.7±16.6 to 42.5±18.8 in the LA arm (n=24, p = 0.032), but there were no significant changes (from 8.7±14.8 to 10.6±16.8, p = 0.059) in the MA arm. The full WMFT rate (n = 12; all performed at the UBC) showed significant improvement from 28.1±30.1 to 34.7±33.1 (p = 0.004) on the MA side. Results of the statistical analysis for clinical measurements are presented in Table 4.

Table 2. 3 Statistical analysis results for the strength and TMS measurements.

Measure	n	Pre (Mean(SD))	Post (Mean(SD))	*p*-value	Cohen's D
LA Strength (N)	24	59.74 (36.97)	72.20 (37.20)	0.027*	0.34
MA Strength (N)	23	20.64 (22.33)	28.24 (32.52)	0.045*	0.27
CSP (ms)	12	0.13 (0.03)	0.11 (0.03)	0.018*	0.45
TCI (normalized iSP)	12	0.78 (0.08)	0.82 (0.06)	0.023*	0.5

MA, more-affected; LA, less-affected; CSP, cortical silent period; TCI, transcallosal inhibition;

Table 2. 4 Statistical analysis results for the clinical measurements.

Measure	n	Pre (Mean(SD))	Post (Mean(SD))	*p*-value	Cohen's D
FM-UE	24	26.2 (20.1)	28.7 (19.9)	0.000*	0.13
WMFT rate LA	12	75.2 (21.6)	86.0 (22.9)	0.055	0.61
WMFT rate MA	12	28.1 (30.1)	34.7 (33.1)	0.004*	0.21
abbr-WMFT LA	24	37.7 (16.3)	42.5 (18.4)	0.032*	0.27
abbr-WMFT MA	24	8.7 (14.5)	10.6 (16.5)	0.059	0.12

FM-UE: Fugl-Myer Upper Extremities assessment; WMFT: full Wolf Motor Function Tests; abb-WMFT, abbreviate Wolf Motor Function Test rate.MA, more-affected; LA, less-affected; na, data not available;

2.5 Discussion

Unilateral wrist extension strength training of the non-paretic, less affected side can improve muscle strength bilaterally in chronic stroke. Training-induced neural adaptation was found in spinal and cortical pathways on both sides. We show here that strength gains and neural adaptation can be induced by high-intensity strength training even in individuals with chronic stroke.

2.5.1 Cross-education and strength gains

Similar percentage gains in strength were seen between arms (~42% and ~35% in LA and MA). Dorsiflexion cross-education training after stroke showed similar results between legs (~34 % and ~31 % in LA and MA) (Dragert & Zehr, 2013). Yet, in neurologically intact participants, cross-education strength gains on the untrained side is only ~8% on average (Munn et al. 2004) and ~9% for the upper limb (Manca et al. 2017). This suggests that unilateral training of the LA limb can not only be used to "boost" strength in the MA arm after stroke, and that relative gains are amplified as compared to non-stroke controls.

Training-induced strength gains were retained in both arms 5 weeks after training: 8 of the 17 LA and 3 of the 8 MA responders maintained their strength gains. Dragert and Zehr (2013) categorized 4 of the total sample of 19 (~21%) as non-responders (no strength gain on the trained side) after dorsiflexion training (Dragert & Zehr, 2013), while here we categorized 7 of 24 (~ 29%) as non-responders. The slightly higher proportion of non-responders in the current study may suggest that a similar dose of cross-education in the arm does not induce as strong of an effect as in the leg for stroke participants. This could relate to differences in functional coupling between the arms compared to the legs. In a recent review by Halperin et al.(2015), the authors suggested non-local muscle fatigue is more likely to occur in the non-training lower limb muscles compared to the upper limb. Also, the strength of neural coupling between the legs is stronger than the arms as seen in rhythmic locomotor tasks (Zehr et al., 2016). To fully utilize neural connections between arms, on-going high-intensity strength training should be applied in chronic stroke rehabilitation training.

We also found strength gain only transferred at the trained position (wrist horizontal) during wrist extension in accordance with "specificity of training" (Sale & MacDougall, 1981; Zhou, 2000). Several studies show that different wrist and forearm positions affect grip strength and muscle activation (Mogk & Keir, 2003; Richards et al, 1996; Terrell & Purswell, 1976), Baldissera and colleagues found FCR H-reflex amplitudes decreased when the forearm position was changed from pronation to supination position. They suggested that the muscle afferent pathway (as assessed by the H-reflex) to FCR motor neurons is influenced by changes in afferent feedback accompanying forearm rotation (Baldissera et al, 2000). Zehr suggested that sensory feedback may be part of the ensemble signaling associated with the cross-education effect (Zehr, 2006). Thus, it is possible that that changes in wrist position affected sensory feedback and muscle activation in both wrist extensors and flexors thus emphasizing task-specific transfer.

It is worth noting that the average post-lesion duration was 144±72 months for the less affected side responders and 158±66 months for the more affected side responders. The bilateral strength improvement found here further debunks the myth that stroke recovery plateaus three- to six-months after lesion, a concept commonly believed by many of those with stroke and often still taught to clinical professionals (Sun et al. 2015). Cross-education strength induced neural plasticity and clinical translation will be discussed in the following sections. The results from this study emphasize the idea that there is no time limit in stroke rehabilitation.

2.5.2 Spinal cord plasticity

Regression slopes between SR cutaneous reflex amplitudes and background EMG decreased with stronger inhibition in the MA arm indicating the excitability of cutaneous pathway was normalized to the LA side after training. Others have shown training-induced neural adaptation in spinal-mediated reflex pathways (Zehr, 2002; Zehr, 2006). Enhanced soleus H-reflexes were found in the untrained side in neurologically intact participants after dorsiflexion cross-education training (Dragert & Zehr, 2011). Altered reciprocal inhibition amplitudes (suggesting increased sensitivity to descending voluntary commands) were found in untrained MA TA muscle after stroke (Dragert & Zehr, 2013). Here, such correlation between reciprocal inhibition amplitude and background EMG was absent on the MA arm suggesting weaker excitability in the reciprocal inhibition pathway after stroke.

Altered SR (innervates dorsum of the hand) but not MED (innervates palm) cutaneous reflex amplitudes were found which may be related to sensory input from the mechanical action of the straps on the hand during wrist extension. Sensory input plays a critical role in the motor function recovery after stroke (Nudo et al 2000; Celnik et al. 2007) and the excitabilities of cutaneous pathways can be altered through training (Zehr, 2006). Studies in neurologically intact participants showed strength training with sensory electrical stimulation induced higher strength gains on the untrained side (Hortobagyi et al. 1999). In a short-term intervention study, unilateral voluntary contraction, sensory electrical stimulation or contraction combined with sensory stimulation produced altered amplitudes of H-reflexes and motor evoked potential on the contralateral sides differentially (Hortobagyi et al., 2003). These observations suggest enhanced sensory input modulates larger neural adaptation compared to performing voluntary contraction alone. Veldman and colleagues explored whether adding electrical stimulation to unilateral motor practice could amplify inter-limb transfer. Results suggested that outcomes from sensory electrical stimulation may depend on clinical status since the effects are much less (6 %) in healthy compared to stroke participants 27 % (Veldman et al., 2015). Further research is needed to understand whether enhanced sensory input could facilitate the cross-education effect of strength training after stroke.

2.5.3 Cortical plasticity

Significant decreases were found in TCI from both hemispheres and in CSP from the LA side after training. Reduced CSP on the LA side is similar to results after cross-education training in neurologically intact participants. Kidgell and colleagues found that four weeks of unilateral wrist flexion training decreased CSP duration significantly bilaterally which caused less inhibitory input to the motor neuron pool and increased net excitability of the corticospinal tract (Kidgell et al., 2015). Since the first 50ms of the CSP duration is believed to be controlled by spinal mechanisms while the reductions after 100ms are assumed to cause by supraspinal inhibition (Inghilleri et al.,1993) and the CSP duration seen in our participants was reduced from 131 ms to 115 ms, we assume that the training-induced reduction in CSP was primarily due to cortical factors. Although we found lack of correlation between the percentages of strength gain and changes in CSP and TCI measurements , previous studies showed that progressive decrease in CSP duration and stronger inhibition CL-iSP were associated with improvement in motor outcome for stroke participants (Brouwer & Schryburt-brown, 2006; Classen et al., 1997; Harris-Love et al. 2016). Our group results here suggest CSP and TCI may play important roles in increasing bilateral strength and motor function in stroke rehabilitation.

Paired-pulse TMS induced SICI has been used to examine $GABA_A$ mediated intracotical inhibition. People with stroke usually show deficient SICI modulation in the primary motor cortex due to the lesion(Harris-love et al, 2016; Shimizu et al., 2002). Here, we did not find decreased SICI which has been seen in other cross-education studies in neurologically intact individuals (Kidgell et al., 2015; Goodwill et al. 2012). This may due to the small sample size since SICI was only evoked in four participants. However, considering the strength gain at the POST test, lack of significant changes in SICI may indicate cross-education can utilize the intact cortical pathway inducing bilateral strength gain and without involving $GABA_A$ mediated inhibitory pathways.

2.5.4 Clinical translation

Training-induced neural plasticity was also reflected in clinical measurements. FM score increased 2.5 ± 3.1 points (mean ± standard deviation) with 4 participants showing ≥ 5 points increase suggesting reduced impairment in the MA arm and was maintained at follow-up. Although the minimal clinically important difference ranges from 4.25 to 7.25 (Page et al., 2012), the current study had more severe stroke participants with an average PRE FM score of 26.2 compared to 39.2 in the previous study(Page et al., 2012). In functional tests, abb-WMFT rate (n=24) improved significantly in the LA arm. Full WMFT (n=12, with 9 responders) performance time decreased by 1.5s (standard deviation: 1.8s) on the MA side, in the range of minimal clinically important difference of 1.5 to 2s (Lin et al., 2009). This strength training protocol shows the potential to reduce impairment and improve motor function in the arm even for severely affected stroke participants. To induce clinically significant changes, higher training intensity and/or longer training durations may be required in stroke participants with severe impairment.

2.5.5 Summary

This study for the first time shows bilateral neuromuscular and strength gains in arm muscles can be induced in chronic stroke by training the less affected side only. Neural adaptations in spinal and cortical pathways demonstrate functional neural plasticity can occur even years after stroke using high-intensity training. These results further debunk the myth that stroke recovery plateaus three- to six-months after lesion and emphasize the idea that there is no time limit in stroke rehabilitation. However, response variability between participants suggests that to induce and maintain cross-education between arm muscles may require higher intensity and on-going training in stroke participants.

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Chapter 3: Training-induced neural plasticity and strength are amplified after stroke[2]

3.1 Abstract

Following stroke, sensorimotor brain networks and descending regulation are compromised but spinal interlimb neural connections remain morphologically intact. After cross-education strength and locomotion training, amplified neural plasticity and functional responses are observed in chronic stroke compared to neurologically intact participants. We hypothesize that post-stroke neuroplasticity is amplified because of the involvement of interlimb neural connections that persist from our quadrupedal ancestry.

3.2 Introduction

Following stroke, neuronal damage leads to loss of supraspinal inputs to spinal motor neurons. The excitability in spinal and supraspinal pathways are also affected. Functionally, stroke-induced alterations in the nervous system result in inadequate motor unit recruitment, impaired coordination, and weakened muscle contractions. Strength and motor impairments are found bilaterally and are large on the contralesional side producing neurophysiologically more affected (so-called paretic) and less affected (so-called non-paretic) sides (Dragert & Zehr, 2013b; Zehr & Loadman, 2012).

Training-induced neuroplastic corticospinal, propriospinal and spinal adaptations play important roles in regulating strength gain (Adkins et al., 2006; Carroll et al., 2002; Selvanayagam et al., 2011). When translating observations from strength training in the general population to those with neurotraumatic injury, there can be reduced efficacy due to alterations in the neurological integrity of pathways subserving the adaptations themselves (Zehr & Loadman, 2012). Strength and functional training focusing on the more affected side may be hard to initiate because of muscle weakness and spasticity.

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This has contributed to the idea that the nervous system after injury may represent "fallow ground" with temporally limited and blunted adaptive responses(Sun et al., 2015).

Previous observations of human locomotor movements suggest spinal and propriospinal interlimb quadrupedal neural linkages are conserved in humans (Zehr et al., 2009). These linkages remain intact and accessible after stroke (Farthing & Zehr, 2014). Therefore, it is possible that neural excitability and muscle strength on the MA side can be modulated by training the less affected limbs and activating the intact neural pathways below the lesion site. Strength based cross-education rehabilitation interventions (Dragert & Zehr, 2013b; Sun et al., 2018) show large gains and normalized modulation of reflexes in chronic stroke participants after training with the less affected side. Spinal neural plasticity with improved performances in Timed Up-and-Go, 10-meter walking and 6-min walking tests were found after arm or arm and leg cycling training (Kaupp et al., 2018; Klarner et al., 2016a, 2016b). Neural adaptation in the untrained limbs along with larger percentage increases in cross-education strength indicate amplified neural plasticity in chronic stroke participants compared to that found in the neurologically intact.

It appears that interlimb neural networks may, in fact, be more rather than less responsive to training stimuli after injury. We suggest that the nervous system after stroke represents a fertile ground for adaptive training responses. Our hypothesis is that post-stroke adaptive neural plasticity is amplified in response to physical training stimuli compared to the intact and uninjured nervous system. By activating interlimb neural connections evolutionarily conserved from our quadrupedal ancestors (Klarner & Zehr, 2018; Zehr et al., 2016), amplified neuroplasticity can be induced and promote the strength and function in the untrained limbs in those with chronic stroke.

The core concept of our hypothesis is contained in Figure 3.1 where the nervous system is represented as a tree. Damage to the tree caused by a lightning strike is the analog of the effects of stroke on the brain. The lightning strike may damage parts of the tree and result in withered branches (Figure 3.1 B &C), yet the roots and trunk remain intact. Thus, watering and fertilizing (ie. training) not only nourish the intact parts but also boost the regrowth of the damaged branches. The entire tree can flourish again and move closer to the state before damage. Returning to the nervous system, by utilizing intact neural network after stroke, continuous training of the less affected limb can promote significant strength gain in the more affected limbs.

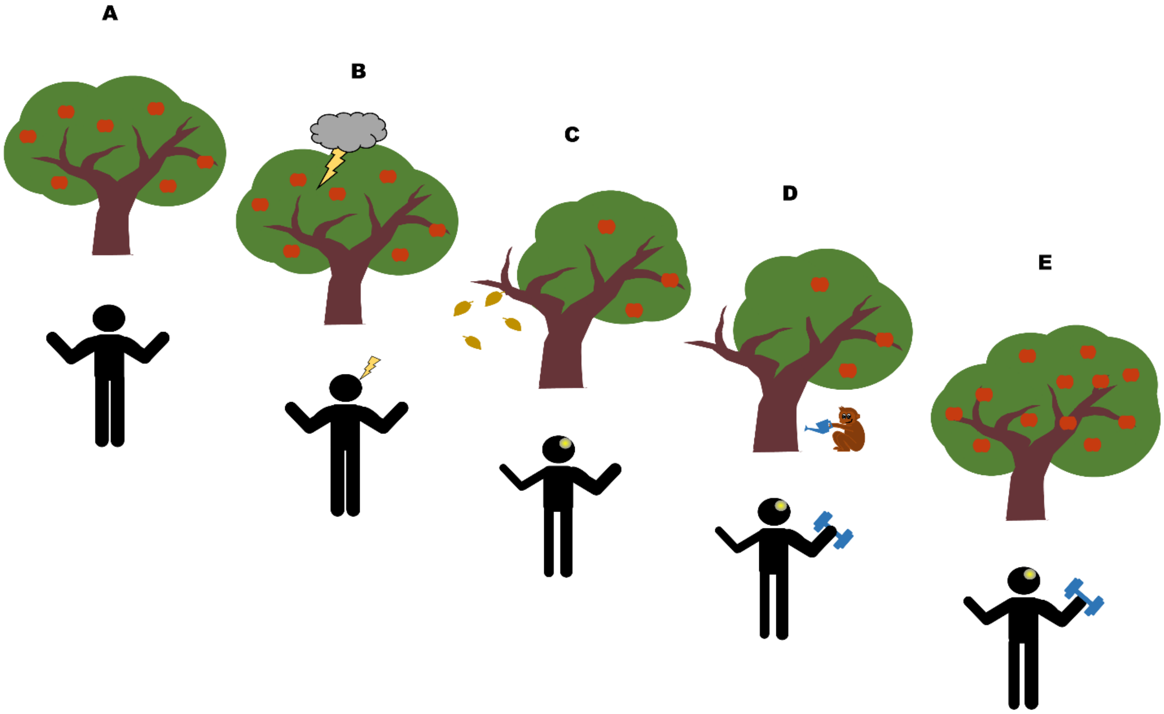

Figure 3. 1 Regrowth of a tree after a lightning strike as a metaphor for recovery of function stroke. The flourishing tree represents the intact nervous system before lesion, (A). A lightning strike on the tree results in broken and withered branches (B and C). However, since the trunk and root remain intact, continuous watering and fertilizing the tree helps the withered branches to regrow (D and E). In the nervous system, strength in the contralesional limbs is reduced dramatically in the first few months after lesion (C). However, by unitizing the interlimb neural networks conserved from our quadrupedal ancestors (represented by the monkey watering the tree), neural plasticity can be induced across the body even years after lesion (D and E).

3.3 Neural plasticity in post-stroke strength training: *bilateral strength gain from unilateral strength training*

Compared to neurologically intact participants, larger strength improvement and significant neural plasticity are found in people with stroke following various training approaches. Commonly used strength training methods focusing on the more affected side include progressive resistance training (PRT; training with progressively increased resistance, usually 70% or more of maximal strength (Hakkennes & Keating, 2005)) and constraint-induced movement therapy (CIMT; training the more affected side extensively with the movement of the less affected limb constrained through a sling 90% of the waking hours (Taub et al., 2002). Although it used to be mistakenly believed that strenuous activity on the more affected side may reinforce spasticity after stroke and must be avoided (Bobath, 1990), experiments show that training can actually reduce spasticity and effectively improve muscle strength in the more affected side after stroke (Morris et al., 2004; Patten et al., 2004). In addition, compared to the general population, systematic reviews on PRT show large effect sizes (0.98, 95% confidence interval 0.67 to 1.29) on strength gains for stroke participants (Dorsch et al., 2018) and modest effects of PRT on the general elderly population (0.68, 95% confidence interval 0.52 to 0.84) (Latham et al., 2004), this suggests that PRT has stronger effects after neurological damage arising from stroke.

Although the benefits of strength training on the more affected side have been confirmed in many studies (Ada et al., 2006; Patten et al., 2004), directly training the more affected side is not always possible and is hard to initiate for those with spasticity and muscle weakness. For those with asymmetrical weakness and immobility after stroke, training the less-affected side can be used to boost the strength of the more affected side and improve functional symmetry (Farthing & Zehr, 2014). “Cross-education” describes training muscles on one side of the body to improve strength or motor skill in the contralateral untrained limb. Since it was first described by Edward Scripture in 1894 (Scripture et al., 1894), evidence of cross-education has been found following strength training in both upper and lower limb muscles (Munn et al., 2004). In a meta-analysis with a total of 96 cross-education training studies included, Green and Gabriel (2018) found 29% of strength gain on the untrained side in those with stroke, neuromuscular disorder, and osteoarthrosis, which was higher than the 18% increase in able-bodied young adults and 15% increase in older adults. In chronic stroke participants, Dragert and Zehr found 6 weeks of dorsiflexion training with the less affected side improved strength by 34% and 31% in the trained and untrained legs and 15 out of 19 participants showed significant strength gains on the untrained side after training (Dragert & Zehr, 2013b). In contrast, with the same training protocol in neurologically intact participants, five weeks of unilateral ankle dorsiflexion training increased dorsiflexion strength only by 14.7% and 8.4% on the trained and untrained ankle respectively (Dragert & Zehr, 2011). Sun et al. found 5 weeks of training in chronic stroke improved wrist extension force by 42% and 35% in the trained and untrained side respectively and significant improvements found in the more affected arm were maintained for at least 5 weeks after training (Sun et al., 2018). The average cross-education strength increase in neurologically intact participants is 17% (Green & Gabriel, 2018). A comparison of these strength gains in stroke and neurologically intact participants after cross-education training is summarized in Figure 3.2, where larger strength gains are observed bilaterally in arms and legs in stroke participants.

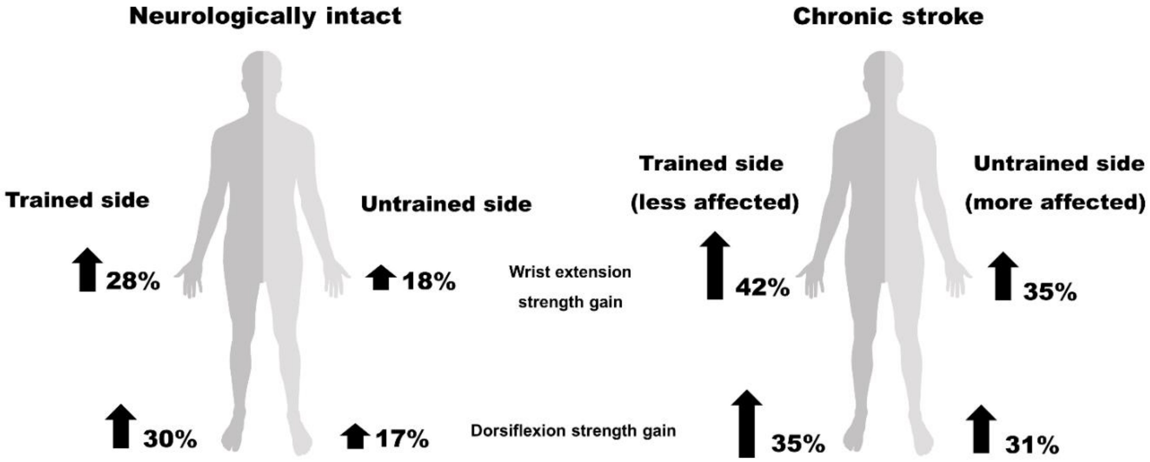

Figure 3. 2 Unilateral wrist extension and ankle dorsiflexion training produce amplified increases in strength after stroke. Compared to neurologically intact, chronic stroke participants show larger strength gains on both trained (less affected) and untrained (more affected) sides. Percentages of the strength gain in chronic stroke participants are obtained from the studies of Dragert and Zehr (Dragert & Zehr, 2013b) and Sun et al. (Sun et al.,

2018). Data from neurologically intact participants are from the meta-analysis by Green and Gabriel (Green & Gabriel, 2018)

By measuring force change during unilateral handgrip training, Barss et al. found significant strength gain on the untrained side occurred around the 15th session of training in neurologically intact participants (Barss et al., 2018). In the studies from Dragert and Zehr (Dragert & Zehr, 2013b) and Sun et al. (Sun et al., 2018), a total of 15 and 18 sessions of training were performed respectively. There is also evidence showing that 12 sessions of elbow extension can significantly improve joint torque in the untrained arm in stroke participants (Ehrensberger et al., 2019). While there are only a few studies currently showing strength cross-education in stroke participants, larger strength gain following similar doses of training compared to neurologically intact participants suggest post-stroke neural network is actually more responsive to the training stimuli.

Along with strength improvement, unilateral training altered neural excitability in both spinal and corticospinal pathways on the untrained side after stroke. Dragert and Zehr found the size of reciprocal inhibition was greater with the same background muscle activities in both legs, which suggests reduced hyperexcitability after training (Dragert & Zehr, 2013a). Following wrist extension training, the slope of the regression line between early latency cutaneous reflexes and background EMG was steeper on the more affected side indicating cutaneous pathway excitability was normalized to that found on the less affected side. Modulation in the cortical and corticospinal pathways was observed as reduced transcallosal inhibition and reduced cortical silent period from the contralesional side (Sun et al., 2018). (Figure 3.3)

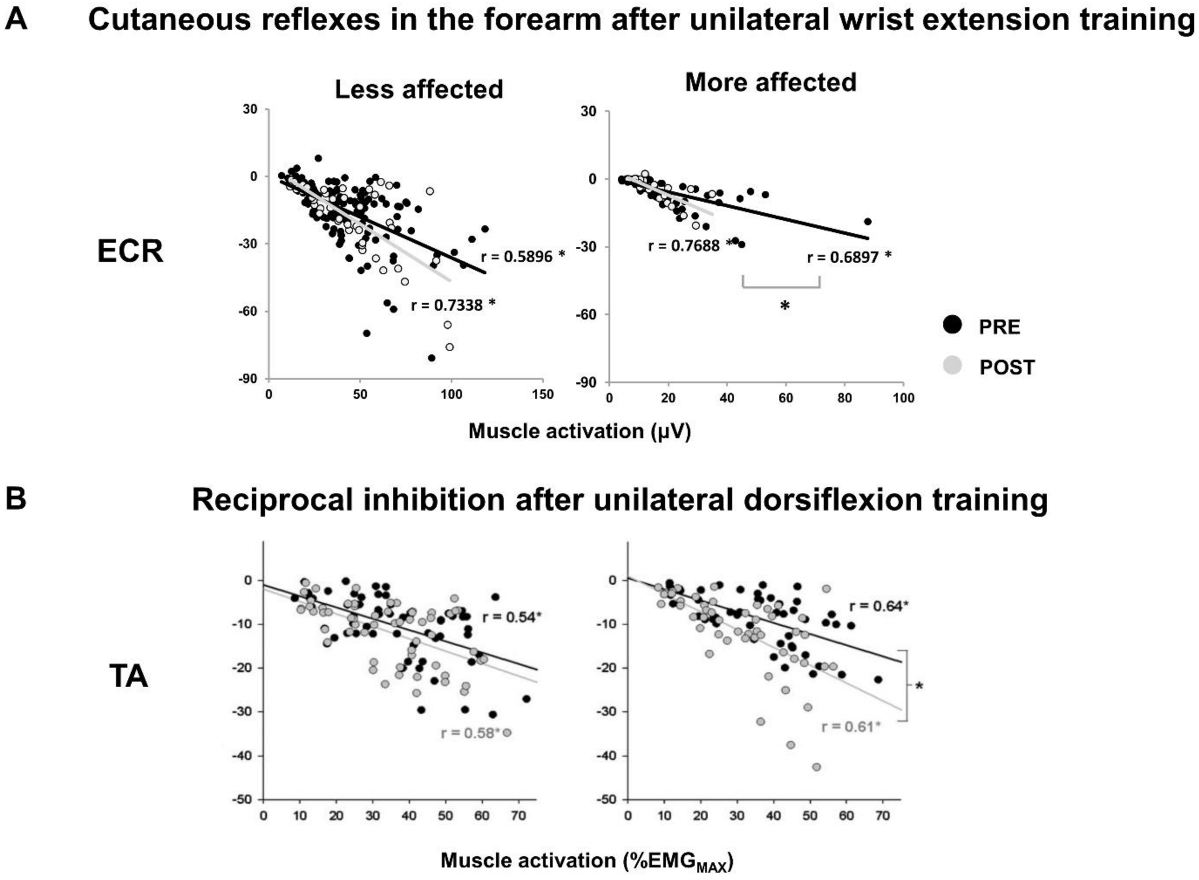

Figure 3. 3 Normalization of spinal interneuronal excitability after cross-education training. A: Normalized cutaneous reflexes in extensor carpi radials (ECR) evoked from superficial radial nerve stimulation (SR) at different background muscle activation levels. Black and grey dots represent reflex amplitude before (PRE) and after (POST) training, respectively. B: Normalized reciprocal inhibition in tibialis anterior (TA) muscle. Black and grey dots represent reflex amplitudes before (PRE) and after (POST) training. Data from less (LA) and more (MA) affected arms are shown at left and right, respectively. Linear regression analyses were performed and Pearson r values were calculated for each best-fit line. * indicates significant linear correlation. # indicates significant difference between linear regression slopes. X-axis represents background muscle activation (%EMG$_{MAX}$). Y-axis represents reflexes amplitudes. Data adapted from (Dragert & Zehr, 2013b; Sun et al., 2018).

Neural plasticity induced by cross-education training has been found at different regions of the nervous system in neurologically intact participants. A meta-analysis from

Manca et al. (2018) found reduced short interval cortical inhibition and cortical silent period in the pooled results suggesting unilateral strength training affects intracortical inhibition and $GABA_A$ergic excitability in the motor cortex of the untrained hemisphere. In chronic stroke participants, neural plasticity was not seen in these two corticospinal pathways, but changes in spinally mediated reflexes and transcallosal inhibition pathways suggest bilateral strength gain and plastic adaption in the remaining intact neural pathways can be induced (Dragert & Zehr, 2013b; Sun et al., 2018). Spinal neural plasticity was observed after strength training using ankle and wrist muscles in stroke participants (Dragert & Zehr, 2013b; Sun et al., 2018). Thus, it is likely that interlimb neural connections at the spinal level are involved in mediating cross-education of strength after supraspinal lesion.

With all the benefits of unilateral strength training in bilateral strength gain and neural plasticity, we suggest that cross-education strength training should be considered complementary to traditional training approaches focusing on functional improvement of the more affected side. The concept of training the less affected side could be used to "boost" the more affected side strength when the muscle weakness prevents training directly. After the more affected side gained enough strength to initiate the movement, targeted strength or functional training should be focused on the more affected side.

3.4 Neural plasticity in post-stroke locomotor training: *arms can give legs a helping hand*

Reduced descending input affect walking function and post-stroke quality of life. Previous studies suggest that both arms and legs share common neural control elements during rhythmic movements such as walking and cycling (Zehr, 2005). By utilizing these common interlimb neural connection, walking functions can be facilitated by other rhythmic movements such as arm cycling or arm and leg cycling after lesion.

Strong neural and mechanical linkages between the arms and legs were observed in human during locomotion although our arms play less direct roles in propulsion during walking. Besides stabilizing the torso from rotating (Elftman, 1939), rhythmic arm movements also regulate lumbar spinal cord excitability and muscle activation in the legs. Huang and Ferris investigated the neural coupling between the upper and lower limbs when participants exercised on a recumbent stepper where arm and leg movements were mechanically coupled. Arm movements during recumbent stepping enhanced muscle activity in the leg and these facilitatory effects increased when arms moved against higher resistance (Huang & Ferris, 2004) or at a higher frequency (Kao & Ferris, 2005). Interlimb neural coupling between the arms and legs was also found in other rhythmic tasks, such as walking and arm and leg cycling, with significant phase-dependent reflexes in the leg muscles evoked from sensory stimulation to the arm (Zehr et al., 2007).

After stroke, neural interlimb connections between the arms and legs are preserved. A single session of arm cycling exercise can alter the spinal excitability for the legs (Barzi & Zehr, 2008; Zehr & Loadman, 2012). Such neural connections can be applied in locomotion rehabilitation by incorporating arm and leg rhythmic movements. Klarner et al. (2016a, 2016b) found 6 weeks of moderate arm and leg cycling training with chronic stroke participants results in increased strength and range of motion in the more affected ankle. In addition, phase-dependent modulation of lower limb muscle activation and cutaneous reflexes were observed during walking indicating that interlimb neural network regulation is normalized to the neurologically intact state. Since the exercise intensity was moderate (participants reported their rate of perceived exertion between 3 and 5), trained induced neural plasticity and functional gain are mainly due to the active rhythmic interlimb movement. Although walking was not directly trained and participants were seated during all the training sessions, arm-leg cycling training can transfer to improvement in untrained walking performance. This supports the hypothesis that rhythmic movements are regulated by common core neural networks (Zehr, 2005).

The power of rhythmic movements in amplifying leg muscle activation and walking ability is further confirmed by a study from Kaupp et al (2018). By performing just arm cycling exercise for 5 weeks, 3 times per week for 30mins, significant improvements were found in chronic stroke participants’ Timed Up-and-Go, 10-meter walk, and 6-minute walk tests. In addition, arm cycling increased tibialis anterior muscle activation on the more affected side and normalized cutaneous reflexes in both legs (Figure 3.4). Such neural adaption is important in assisting with weak dorsiflexion to help improve efficiency and prevent stumbling or falling after stroke (Zehr & Loadman, 2012). Related outcomes have recently been shown after arm cycling training in incomplete spinal cord injury (Zhou et al., 2018).

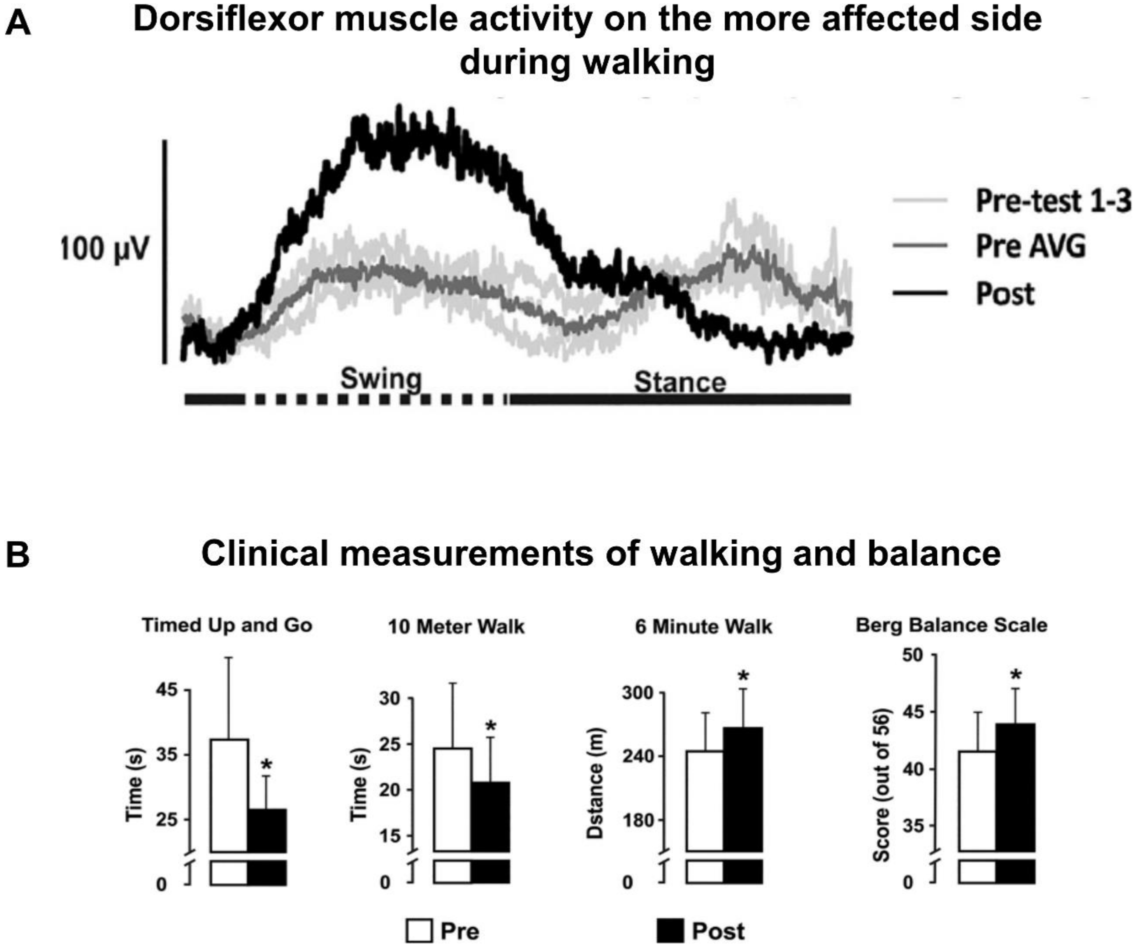

Figure 3. 4 Normalized tibialis anterior muscle activity and walking performance after arm cycling training in stroke. (From Kaupp at al. (Kaupp et al., 2018)) A: An EMG recordings of tibialis anterior (TA) muscle on the more affected side from one participant. Light gray traces are before with the dark gray trace indicating the untrained average, and the black trace is the result after training. B: Improved performance in walking and balance tests. Before (open bars) and after (filled bars) training data from the group for the Timed Up and Go, 10-Meter Walk, 6-Minute Walk, and Berg Balance Scale. Data adapted from (Kaupp et al., 2018).

A more responsive neural network was also observed following spinal cord injury. Thompson and colleagues found down-conditioning soleus H-reflex can modulate plantarflexor muscle activation and improve walking symmetry in spinal cord injured participants (Thompson & Wolpaw, 2015) but not in neurologically intact (Makihara et al., 2014). These results suggest guiding the plasticity has more profound effects on the functions and reflex modulation of the other muscles after neurotrauma (Thompson & Wolpaw, 2015).

In neurologically intact participants, the effects of rhythmic arm movement training on walking function have not been recorded. The modulatory role of arm cycling on the leg muscle activities is largely dependent on the functional state of the leg. Without active cyclic movement in the leg, arm cycling does produce subtle effects in cutaneous reflex modulation in the legs (Balter & Zehr, 2006). By comparison, the findings from Kaupp et al. (2018) present amplified neural plasticity in chronic stroke participants, arm cycling alone can activate the neural networks that regulate leg movements and significantly improve performance in walking tests.

3.5 Quadrupedal neural pathways mediating amplified neural plasticity?

Both cross-education strength training and arm cycling training alter reflex modulation at different sites of the central nervous system suggesting widespread adaptive mechanisms in the nervous system. We speculate that amplified strength gain and neural plasticity in the untrained limbs are achieved by activating evolutionarily conserved interlimb neural networks (Bobath, 1990). In quadrupedal locomotion, all 4 limbs are directly engaged in locomotor patterning and the production of propulsive force. Injury to one limb usually compromises but does not prevent locomotion. In such cases, the remaining 3 intact limbs are subjected to training stresses of increased loading and forced use. Strong neural and biomechanical interlimb coupling would enable quadrupedal animals to continue behaviors such as hunting for food or running away from predators while healing the injured limb. Actively using the non-injured limb may tap into the circuitry underlying cross-education effects to result in more rapid recovery of function in the injured limb.

Without any injury or neural damage, activity of interlimb neural networks between all four limbs in bipedal humans is subliminal and seems less obvious since we can easily perform independent uni- or bimanual motor tasks. However, the human nervous system shares many similarities with quadrupedal animals in regulating interlimb movements (Zehr et al., 2016). Considering interlimb neuromechanical interaction during locomotion from an evolutionary perspective (Zehr et al., 2016), substantial evidence shows that neural control mechanisms in rhythmic movement such as walking, running and cycling in human are similar to those in quadrupedal animals. Coordinated and smooth interlimb movements during locomotion are regulated by the same spinal neural networks (central pattern generator, CPG) for both human and other quadrupedal animals (Klarner & Zehr, 2018; Zehr et al., 2016). It should be noted that the human interlimb neural modulation is not only preserved between the legs to regulate locomotion but also exists between the upper and lower limbs, as well as the ipsilateral and contralateral side during non-locomotor tasks. For example, sensory stimulation to the arm during walking (Haridas & Zehr, 2003) or rhythmic arm movement (Frigon, 2004) affects spinal excitability for leg muscles as shown by altered H-reflex and cutaneous reflex amplitudes. Movement or strength training on one side of the body can also change the H-reflex and reciprocal inhibition amplitudes on the contralateral side (Delwaide et al., 1988; Dragert & Zehr, 2011).

Following stroke, neural damage affects the excitabilities in the cortical and corticospinal pathways associated with the lesion. However, neural circuits below the lesion site, including reticulospinal, propriospinal and other spinal neural pathways are usually morphologically intact. Studies on spinal cord injured participants and decerebrate animals provided compelling evidence that interlimb movement can be modulated by the neural network resides in the spinal cord with minimal supraspinal descending input (Sherrington, 1904; Yang et al., 1998). With reduced descending input after stroke, the remaining morphologically intact spinal neural pathways play a more critical role in regulating movements as well as facilitating neural rehabilitation. Evidence from animal models show reticulospinal (Zaaimi et al., 2012) and propriospinal (Juvin et al., 2012) pathways subserving some of the functional recoveries and regulating interlimb coordination after corticospinal lesion.

After stroke, both cross-education strength training and arm cycling training tap into the remaining interlimb neural networks by actively training with the less affected limbs. The fact that spinal excitability can be altered through these training methods in chronic stroke participants (Dragert & Zehr, 2013b; Kaupp et al., 2018; Klarner et al., 2016b, 2016a; Sun et al., 2018) confirms the contribution of interlimb neural network in mediating training-induced strength and functional improvement. We suggest that, in a manner similar to a quadruped coping with the injured limb by relying more on the unaffected limbs, ongoing activation on the less affected limb in stroke serves as the training stimulus leading to enhanced restoration of function after injury without directly involving the target muscles. It is tempting to speculate on underlying mechanisms of adaptation here, and our hypothesis would be best explained by strengthening of weakened connections and unmasking of underlying and previously silent connections (Taub et al., 2002).

A compelling, recent and relevant experiment using a murine model involved mapping the area of cervical gray matter reinnervation by sprouting corticospinal axons contralesional to a stroke lesion created by photothrombosis (Kaiser et al., 2019). RNA profiles of the reinnervated area using whole-genome sequencing revealed differentially expressed genes involved in tissue repair related to outgrowth of neurites. The conclusion from this work was that spinal gray matter denervated as a result of cortical lesion “represents a growth-promoting environment for sprouting corticospinal fibers originating from the contralesional motor cortex” (Kaiser et al., 2019). Should such processes remain operational in the human this could explain a large portion of the amplified neuroplastic training response seen after stroke.

Jon Wolpaw (2018) proposed a “negotiated equilibrium” model to explain the activity induced spinal plasticity found in reduced animal and human studies. This model emphasizes that plasticity in the brain induces and maintains that in the spinal cord. The brain and spinal cord plasticity combine to produce and preserve satisfactory performance by defining a set of key features for each behavior. One prediction of this model is “if the spinal plasticity that produces a new behavior also improves an old behavior, the magnitude of this plasticity is likely to be enhanced because it will be driven by two of the participants in the negotiation, the new behavior and the old”. This approach and framework may be directly related to our hypothesis that neural plasticity is amplified after stroke. Future studies should approach research questions from efforts grounded in these perspectives.

3.6 Summary

We hypothesize that neural plasticity is amplified, not diminished, after stroke. Greater strength gains and neural plasticity can be induced by activating the preserved interlimb neural network without directly involving the target muscles. For those with chronic stroke, conventional strength or locomotion training methods may not be easy to apply due to lack of muscle strength and coordination on the more affected side. Cross-education strength training, arm cycling and arm and leg cycling exercise provide an easily applied training paradigm to boost the strength and function of the more affected limbs. Taken together with other rehabilitation training modalities, strengthening and training methods engaging as many limbs as possible may help to achieve continuous strength and functional improvement can be achieved by the community based chronic stroke population.

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Chapter 4 Effects of wrist position on reciprocal inhibition and cutaneous reflex amplitudes in forearm muscles[3]

4.1 Abstract

In the leg, amplitudes of cutaneous reflexes and reciprocal inhibition are significantly affected by joint and limb position. Comparatively little is known about such modulation in the arm. In this study, amplitudes of reciprocal inhibition (from median nerve stimulation near elbow) and cutaneous reflexes (from median or superficial radial nerve stimulation at the wrist) were measured in forearm muscle extensor carpi radialis with the hand pronated or neutral during graded voluntary activation. Significant correlations with muscle activation were found for reciprocal inhibition and cutaneous reflex amplitudes at both positions. Only cutaneous reflexes from superficial radial nerve were modulated by wrist position. This study reveals that effect of limb position is nerve-specific in cutaneous reflexes and not significant on reciprocal inhibition in the arm. This has implications for measurement and study design in those who have mobility and motor activation challenges (e.g. neurotrauma) that affect hand function.

4.2 Introduction

Human spinal excitability has been studied by measuring amplitudes of cutaneous and muscle afferent (Hoffmann (H-)) reflexes and reciprocal inhibition during different motor tasks. Amplitudes of these evoked responses reflect the excitability in different spinal-mediated neural pathways, but can all be modulated by factors such as task and background muscle activation. Some studies also suggest joint and limb position can affect reflex amplitudes.

Significant effects of joint and limb position on H-reflex amplitude have been observed in both arm and leg muscles. Baldissera et al. measured flexor carpi radialis

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(FCR) H-reflex amplitudes at five different joint positions between wrist pronated and supinated positions (Baldissera et al., 2000). With controlled stimulus inputs (evoking similar efferent motor response amplitudes), FCR H-reflex amplitudes decreased when the wrist was rotated from the pronated to the supinated position. The mechanisms of this change are not clear but the authors suggested it may be due to the ensemble altered afferent input at different positions. Effects of limb position on modulation of H-reflex amplitudes were also found in leg muscles. Soleus H-reflex amplitudes decreased when changing posture from lying to sitting, to standing due to increased pre-synaptic inhibition at the Ia afferent alphamotoneuronal synapse (Angulo-Kinzler et al., 1998; Goulart et al., 2000; Koceja et al.,1993; Mynark & Koceja, 1997).

Currently, the extent to which joint position may modulate reciprocal inhibition and cutaneous reflex amplitudes is not well understood, especially in arm muscles. Although reciprocal inhibition and cutaneous reflexes are mediated by different spinal pathways from H-reflex, altered afferent feedback from different joint positions may affect reflex amplitude. Evans et al. found altered middle or late latency cutaneous responses in first dorsal interosseous muscle during finger isometric contraction and grip task (Evans et al., 1989). Similar results were also found in the late-latency cutaneous response in other hand muscles by Nakajima et al. (2006). Those results suggested the modulation of cutaneous reflex amplitudes is sensitive to behavioral context. It is possible that upper limb joint position could affect cutaneous reflex amplitudes in arm muscles. Compared to other spinal mediated reflexes, the modulation of reciprocal inhibition between arm muscles have received less attention. Several studies found reciprocal inhibition of the tibialis anterior muscle to soleus muscle is modulated by the posture of the task. During dorsiflexion, a stronger inhibitory effect was found while standing compared to sitting (Kasai et al., 1998). With the same background muscle activation, the amount of inhibition decreased from standing to walking to running (Kido et al., 2004). Although the effects of joint position on reflex amplitudes were not the main research question for those studies, these results suggest that altered joint position and associated changes in afferent feedback may modulate motor output demands of the task (Kasai et al., 1998), which is reflected in excitabilities in cutaneous reflexes and reciprocal inhibition pathways.

Modulation of excitability in neural pathways is commonly measured at different levels of muscle contraction. During static tasks, reflex amplitudes scale almost linearly with motor neuron recruitment from the targeted pool. This type of regulation was defined as “automatic gain compensation”(Matthews, 1986), and was suggested to ensure reflexes are scaled to the motor output during specific non-locomotor motor tasks. By comparing the relation between background muscle activation and reflex amplitudes, the modulation of neural excitabilities during different motor tasks (Stein & Capaday, 1988), pathological conditions (Thompson, et al., 2008) or intervention (Dragert & Zehr, 2013) can be studied.

Background muscle activation changes amplitudes for H-reflex (Burke e al., 1989; Matthews, 1986a), reciprocal inhibition (Crone & Nielsen, 1988; Kido et al., 2004; Shindo et al., 1984; Tanaka, 1974) and cutaneous reflexes (Duysens et al., 1993; Zehr & Kido, 2001) in the leg. In clinical populations where motor output is compromised, such as after stroke or incomplete spinal cord injury, participants may be unable to perform refined motor tasks at certain joint positions and may require adaptation of the experimental approach (Kaupp et al., 2018; Zehr et al., 2012). Therefore, investigating the potential effects of joint position on reciprocal inhibition and cutaneous reflexes in the arm muscle will not only reveal the modulation mechanisms in the upper limb neural pathway but also has critical application for control in clinical studies.

The purpose of this study was to explore the effects of wrist position and level of muscle activation on reciprocal inhibition and cutaneous reflex amplitudes in wrist extensor carpi radialis (ECR) muscle. We hypothesized that joint position would have similar effects on reciprocal inhibition and cutaneous reflex amplitudes

4.3 Methods

4.3.1 Participants

In accordance with the Declaration of Helsinki, twelve healthy, young (24± 1.8 years old) participants without any neurological impairment or muscular injuries in their upper limbs participated with written in a protocol approved by the Human Research Ethics Board at the University of Victoria.

4.3.2 Electromyography (EMG)

EMG data from extensor (ECR) and flexor carpi radialis (FCR) and biceps and triceps brachii muscles were collected the right arm of each participant. After cleansing the skin with rubbing alcohol swabs, disposable surface electrodes (Thought Technology Ltd., Quebec, Canada) were placed in bipolar configuration over the target muscle bellies. EMG signals were amplified (×5000), bandpass filtered using a 1st order filter from 100 to 300 Hz (GRASS P511, Astromed-Grass Inc.) and sampled at 2000 Hz through a customized LabVIEW program (National Instruments, Austin, TX). This procedure involves some signal loss at lower frequencies but allows for effective amplifier response during evoked potential studies (Kaupp et al., 2018; Zehr & Kido, 2001; Zehr et al., 2012).

4.3.3 Electrical stimulation

In both reciprocal inhibition and cutaneous reflexes trials, stimulation was applied using a Grass 88 stimulator with SIU5 stimulus isolation and CCU1 constant current units (Grass Instruments, Astro-Med, Inc. West Warwick, RI, US). The method for evoking reciprocal inhibition was similar to earlier studies which stimulated the antagonist muscle nerve and measured the difference between the background and conditioned EMG in the target muscle (Capaday et al., 1990; Thompson et al., 2008). Stimulation was applied to the median nerve just above the elbow under the curve of the biceps brachii with a single 1.0ms pulse. To ensure stimulation was non-noxious, the intensity was set at 1.2 times motor threshold, defined as the lowest stimulation amplitude that evoked a direct muscle response (M-wave) in FCR. In cutaneous reflexes trials, trains of 5×1.0ms pulse at 300 Hz were applied to the superficial radial (SR) and median (MED) nerves at the wrist with the intensity set as 2 times radiating threshold (RT) which evoked clear reflexes while not considered to be noxious by the subjects (Zehr & Chua, 2000; Zehr et al., 1997). RT was defined as the lowest intensity at which a sensation of radiating paresthesia could be evoked in the innervation territory of the nerve. Here, MED nerve innervates the lateral portion of the palm (thumb, index, and half of the middle finger), and SR nerve innervating the dorsal surface of the hand towards the index finger and thumb. Stimulation electrode locations and experimental set-up were illustrated in Figure 1. For both reciprocal inhibition and cutaneous reflex trials, 20 sweeps of stimulation were applied in each trial.

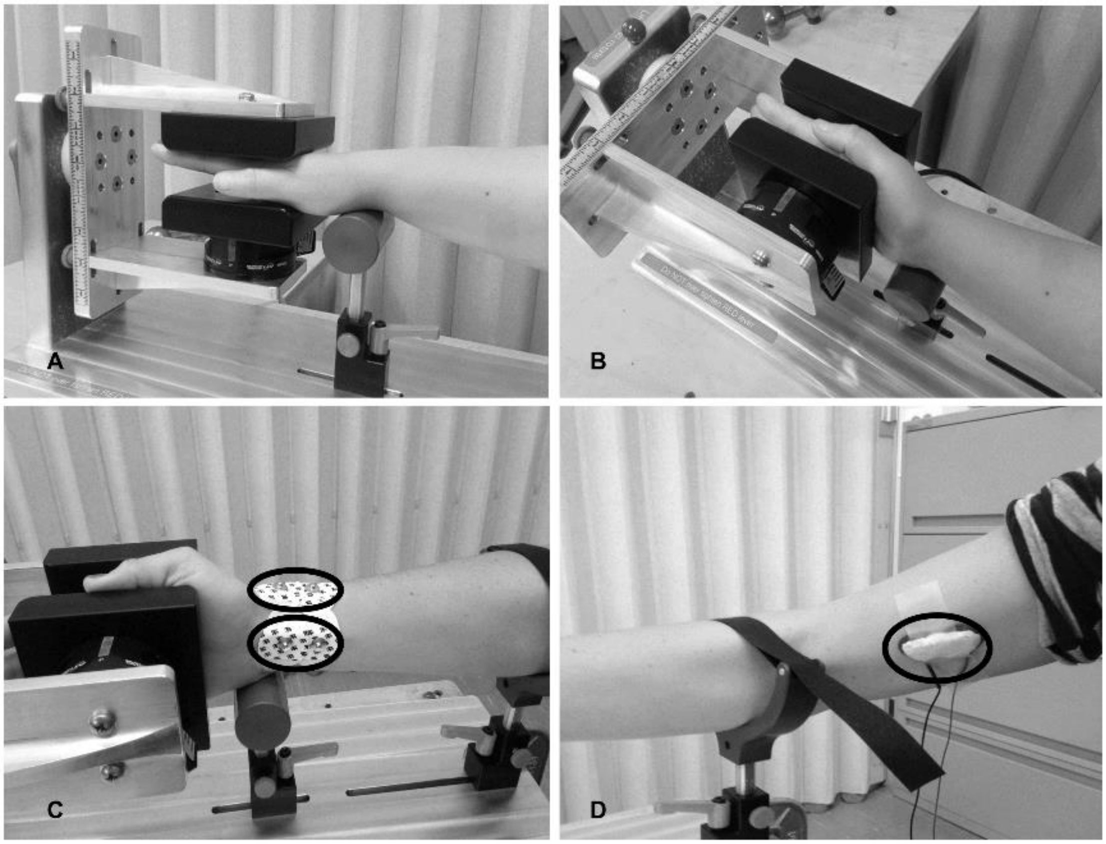

Figure 4. 1 Experimental set-up and stimulation locations. A and B illustrate the pronated and neutral wrist positions used during measurements. C and D show the stimulation locations during the test. The top circle in C indicates the superficial radial (SR) nerve stimulation location, the bottom one indicated the median nerve (MED) stimulation location. The black circle in D indicates the stimulation location for evoking reciprocal inhibition (RI).

4.3.4 Procedures

Participants were seated in a chair with back support. The right forearm and wrist were supported and constrained with straps to a customized device which helped maintain shoulder extension at ~140 and elbow flexion at ~50 degrees. Muscle activation during maximal contraction (EMG_{MAX}) in wrist extension was measured at two different wrist positions, pronated and neutral, over 2 attempts (1min break in between, EMG_{MAX} was held for 3-5s). During the EMG_{MAX} test, ECR muscle activity was rectified and averaged using a custom-written LabVIEW program. The averaged values were presented as bar graphs and updated every 25ms. Participants were instructed to do wrist extension with maximal effort to generate an ECR EMG signal as large as possible. According to each participant's ECR muscle $EMG_{MAX,}$ feedback was presented on the computer screen and four attempted contraction levels (10%, 15%, 25% and 50 of EMG_{MAX}) were calculated for each wrist position. During the reciprocal inhibition and cutaneous reflexes trials, twenty sweeps of data were triggered pseudo-randomly every 1.5–3s (reciprocal inhibition trials) or 2–3s (cutaneous reflex trials). Both responses were examined under two wrist positions and four different levels of muscle contraction in ECR. During each trial, the corresponding contraction level was presented as a target with the ECR EMG bar graph feedback. Participants were required to attempt to match their ECR EMG to the target between stimulations. FCR, biceps, and triceps brachii muscle EMG levels were monitored by the experimenter to ensure there was no co-contraction during the test.

4.3.5 EMG and reflex analysis

All the EMG data were analyzed offline with customized MATLAB programs (Version R2011b, The Mathworks, Natick, MA, USA). EMG signals were rectified and low-pass filtered using 4th order Butterworth filters at 100Hz. Muscle activation during maximal contraction (EMG_{MAX}) was calculated as the average over a 10ms window around the peak of each trial. The mean of two attempts was used for each participants EMG_{MAX} for each joint position.

Figure 4.2 shows typical responses to reciprocal inhibition and cutaneous stimulation. Reciprocal inhibition was measured as the difference between the mean pre-stimulus background EMG_{MAX} (from a 20ms window before stimulation onset) and the mean of the maximum inhibition (from a 10ms window around the post-stimulus minima with a latency ~30ms). Cutaneous reflexes were determined as the difference between EMG amplitudes during the early latency window (50-75ms post-stimulation) and prestimulus background EMG. Net cutaneous reflexes were determined from the average cumulative reflex EMG after 150 ms ($ACRE_{150}$). All reflex variables were normalized to the ECR EMG_{MAX} for each participant obtained from the corresponding joint position condition.

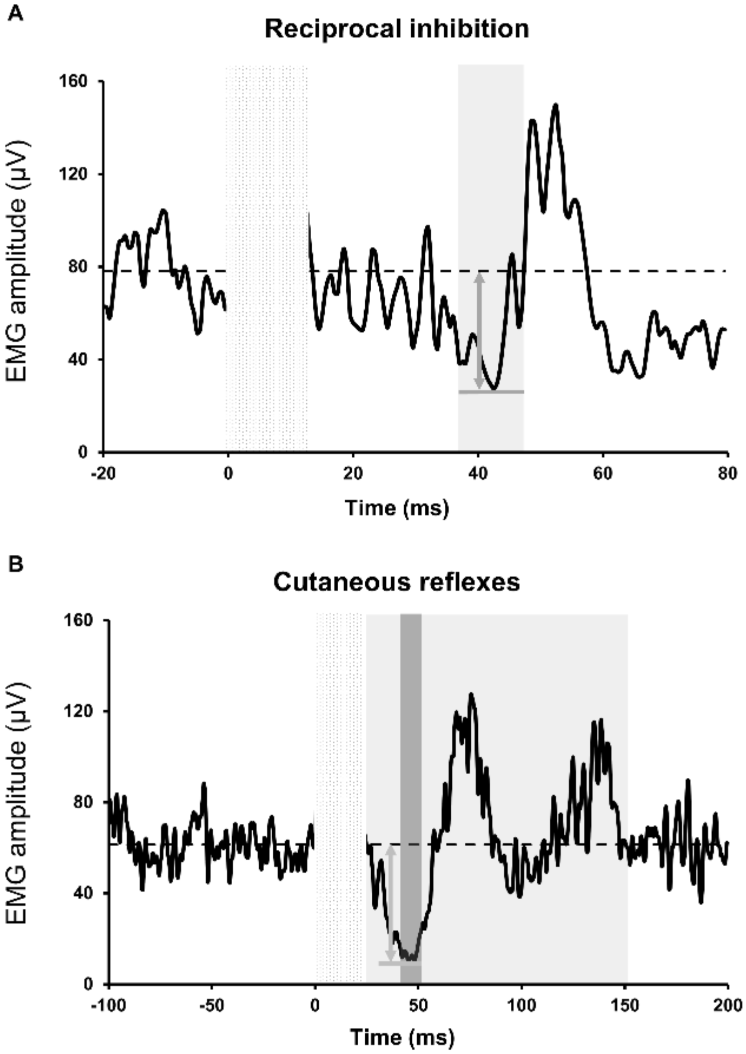

Figure 4. 2 Typical muscle responses during reciprocal inhibition and cutaneous stimulation trial. A. Typical muscle response to reciprocal inhibition. The stimulation artifact was removed from the graph. There was a 20ms window of data recorded before stimulation onset. Shaded area indicates the RI response, a 10ms window around the lowest value that was used for data analysis at the latency around 30ms-40ms. B. Typical cutaneous reflexes. The stimulation artifact was removed from the graph. There was a 100 ms window of data recorded before stimulation onset. Dark grey area indicates the early latency cutaneous reflex, a 10ms window around the lowest value that was used for data analysis at the latency around 50ms-75ms. Light grey indicates the area used for calculating net reflex, which is averaged cumulative reflex EMG in a 150ms window.

4.3.6 Statistics

Mixed linear model analysis was performed using commercial statistical software (SPSS 20, Chicago, IL) to evaluate the effects of the wrist joint position and background EMG on reflex amplitudes. Paired t-tests were used to compare the EMG_{MAX} between joint positions for each participant. The level of statistical significance was set as $p \leq 0.05$.

4.4 Results

4.4.1 EMG_{MAX}

Figure 4.3 shows average EMG_{MAX} of ECR muscle during wrist extension. There was a significant effect of joint position ($p=0.019$). Averaged EMG_{MAX} at wrist pronated position (154.69±51.23 µV) was 19% higher compared to the neutral position (129.79±58.51 µV). Eight out of twelve participants showed higher EMG_{MAX} with the wrist pronated position.

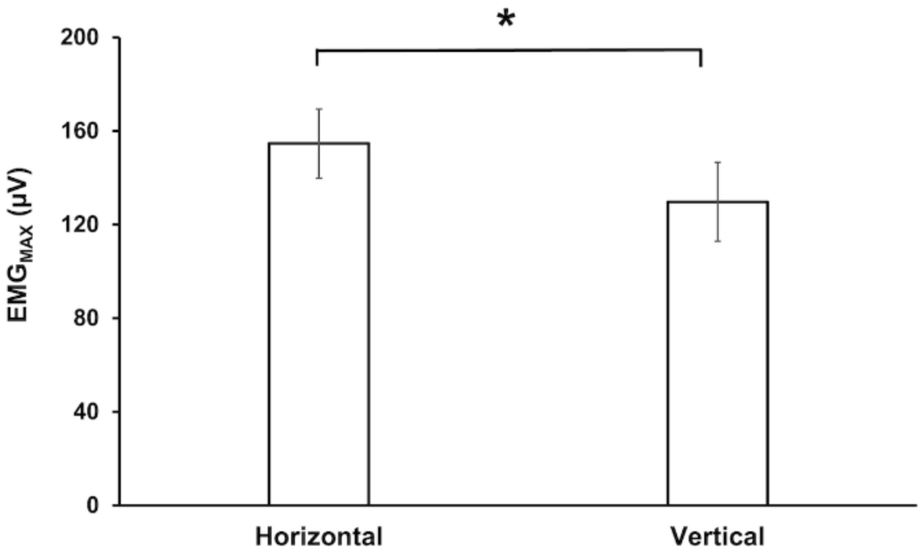

Figure 4. 3 Maximal muscle activation (EMG_{MAX}) of extensor carpi radials (ECR) during extension at two different wrist joint positions. EMG_{MAX} at pronated position (154.69±51.23 µV) was significantly higher compared to neutral position (129.79±58.51 µV). Data was averaged across 12 participants and each bar represents the mean +/- one standard error of the mean, * indicates significant difference ($p<0.05$).

4.4.2 Reciprocal inhibition

The normalized amplitudes of reciprocal inhibition (% of ECR EMG_{MAX}) for all conditions are presented in Fig4. Larger ($p=0.046$) inhibition was found at higher muscle activations for both joint positions. Average inhibited EMG amplitude decreased from 0.4% to -13% at wrist pronated position, and from 0.0% to -8% at wrist neutral position. There was no significant effect of joint position or interaction effect (Figure 4.4).

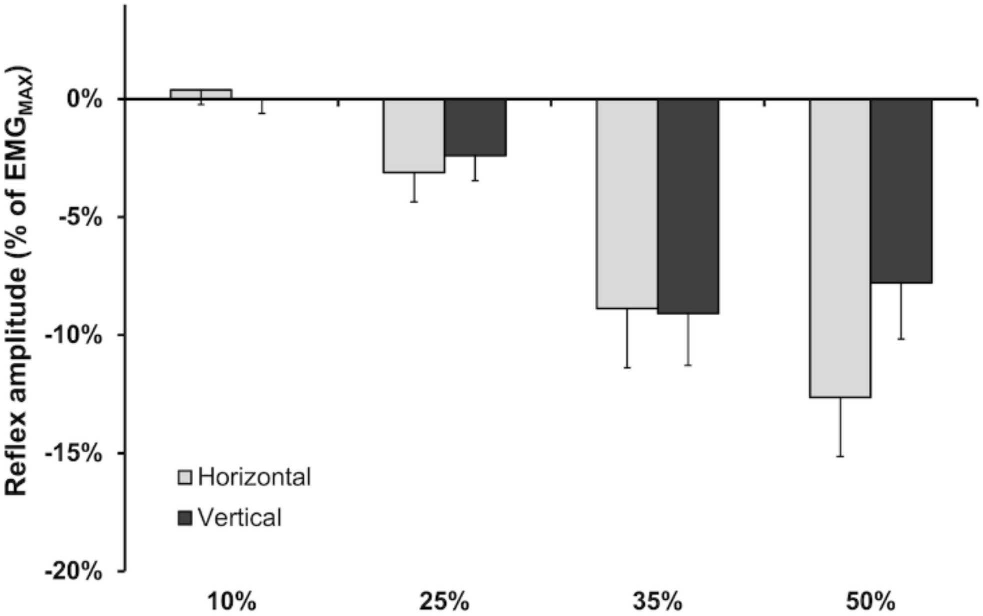

Figure 4. 4 Amplitudes of reciprocal inhibition at different levels of ECR muscle activity. The inhibitory amplitude was larger with higher background EMG. The X-axis represents four different levels of background ECR muscle activation at 10%, 25%, 35% and 50% of EMGMAX under the corresponding wrist position. The Y-axis represents the percentage of reflex amplitude to the EMG$_{MAX}$ of ECR muscle. Dark grey bars represent reflex amplitudes at wrist neutral position, light grey bars represent reflex amplitudes at wrist pronated position. Data were averaged across 12 participants and each bar represents mean +/- one standard error of the mean.

4.4.3 Cutaneous reflexes

Early latency and net reflex amplitudes for MED cutaneous reflexes are shown in Fig 5A and 5B, respectively. While no effect of wrist position was found, at both wrist joint positions early latency reflexes (p=0.027) and net reflexes (p=0.047) were significantly reduced with increasing background muscle activation. With increased background muscle activation, the normalized early latency MED cutaneous reflex amplitudes changed from 3.4% to -4.8% at the pronated position and 2.2% to –6.4% at the neutral position (Figure 4.5A). Net reflex amplitudes decreased from 0.3% to -2.6% and from 0.6% to -1.2% at wrist pronated and neutral positions, respectively (Figure 4.5

B). No interaction between background muscle activation and joint position was observed (early latency reflex: p=0.818; net reflex p=0.907).

For SR nerve cutaneous reflexes, the size of the inhibition at early latency (p=0.019) and net reflexes (p=0.000) were greater with larger background muscle activation, but no significant effect of wrist position was found for early latency reflexes. Decreased early latency reflex amplitudes were found at wrist neutral position (from -1.5% to -16.4%, Figure 4.6A). However, the effect of wrist position was only significant for net reflex amplitudes (p=0.013) and the size of inhibition was greater when the wrist was pronate, which decreased from 0.0% to -3.7% with increased background muscle activation, as shown in Figure 4.6B. No intearaction effect was observed (early latency reflex: p=0.064; net reflex p=0.533).

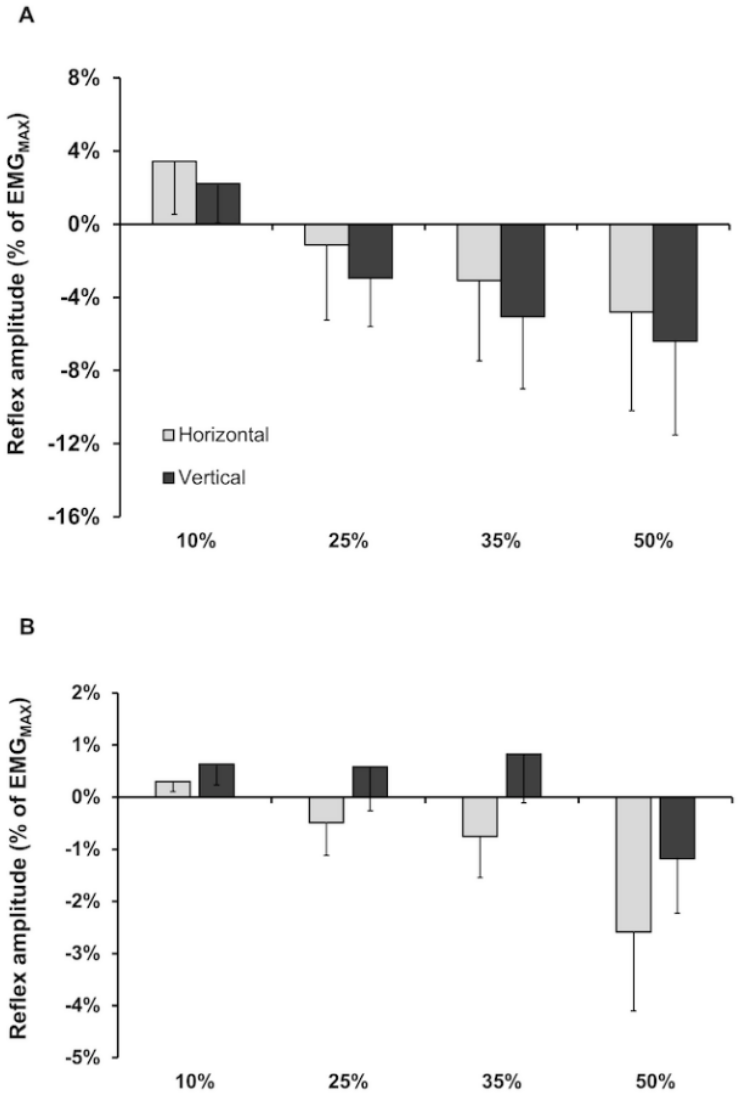

Figure 4. 5 Effect of muscle activation level and wrist joint position on (A) early latency and (B) net reflex of median nerve cutaneous reflexes. The X-axis represents four different levels of background ECR muscle activation at 10%, 25%, 35% and 50% of EMG_{MAX} under the corresponding wrist position. The Y-axis represents the percentage of reflex amplitude to the EMG_{MAX} of ECR muscle. Dark grey bars represent reflex amplitudes at wrist neutral position, light grey bars represent reflex amplitudes at wrist pronated position. Data were averaged across 12 participants and each bar represents mean +/- one standard error of the mean.

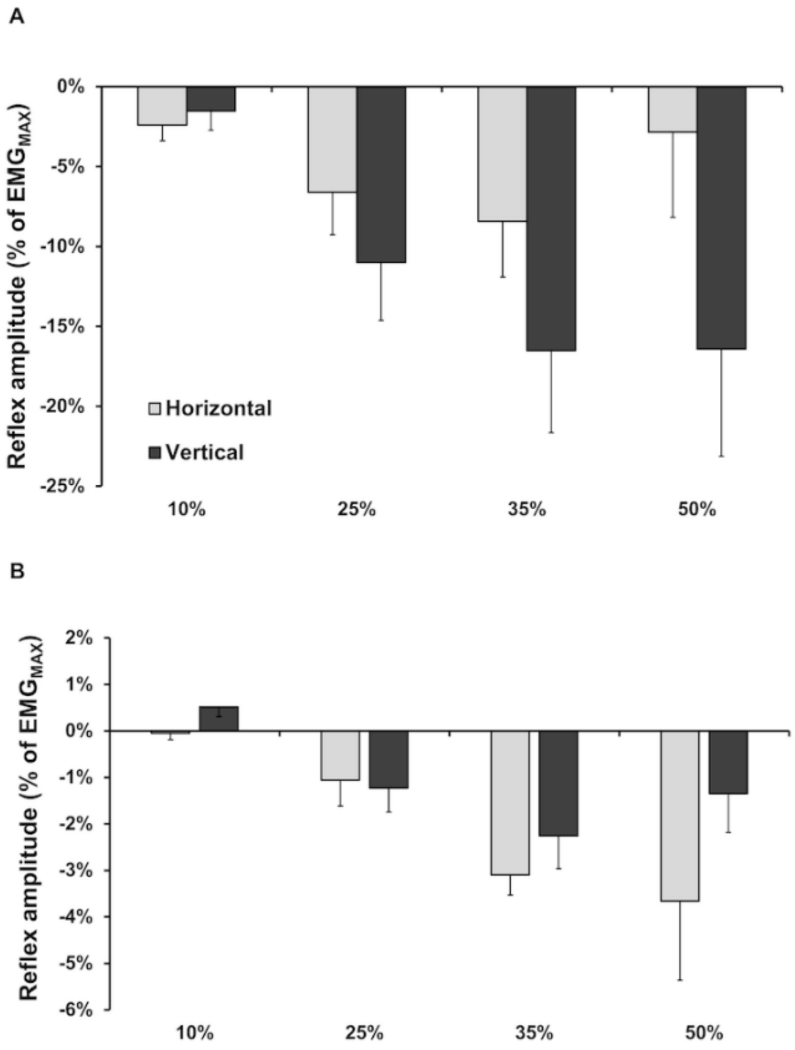

Figure 4. 6 Effect of muscle activation level and wrist joint position on (A) early latency and (B) net reflex of superficial radial nerve cutaneous reflexes. The X-axis represents four different levels of background ECR muscle activation at 10%, 25%, 35% and 50% of EMG$_{MAX}$ at the corresponding wrist position. The Y-axis represents the percentage of reflex amplitude to the EMG$_{MAX}$ of ECR muscle. Dark grey bars represent reflex amplitudes at wrist neutral position, light grey bars represent reflex amplitudes at wrist pronated position. Data were averaged across 12 participants and each bar represents mean +/- one standard error of the mean.

4.5 Discussion

The main purpose of this study was to explore the effect of joint position on modulation of reciprocal inhibition and cutaneous reflex amplitudes at different levels of muscle contraction. Both reciprocal inhibition and cutaneous amplitudes scaled with increasing muscle activation levels while the effect of wrist position was observed only for cutaneous reflexes evoked from SR nerve.

4.5.1 Modulation with joint position

Joint position modulated spinally-mediated reflexes in several previous studies. Soleus H-reflex amplitude decreased when posture changed from lying to sitting to standing (Angulo-Kinzler et al., 1998; Goulart et al., 2000), likely due to changes in Ia presynaptic inhibition (PSI). Baldissera et al found H-reflex amplitudes in FCR muscle were lower when the forearm was supinated compared to pronated (Baldissera et al., 2000). They suggested that the H-reflex pathway to FCR motor neuron is influenced by the changes in the afferent feedback accompanying forearm rotation. The mechanisms were not clearly identified, but putative excitatory contribution of the homonymous stretch reflex should be ruled out since the FCR muscle length is shorter in pronation than in supination. These results are unlikely due to effects from Golgi tendon receptors since all the tests were performed with muscles relaxed.

Here we did not find a significant effect of joint position on reciprocal inhibition amplitude from FCR to ECR muscle. There is evidence suggesting that the inhibitory reflex (~30-40ms latency) we investigated is mediated via a disynaptic spinal pathway since the Ia reciprocal inhibitory interneuron innervates the α-motor neuron directly (Day et al., 1984). As PSI does not affect α-motor neuron excitability directly(Stein, 1995), it is possible that due to different neural pathways, the effect of joint position on reciprocal inhibition is not as strong as it is on PSI. Lack of joint position effects has been found for reciprocal inhibition of lower limb muscles. Kido et al. compared reciprocal inhibition in soleus and tibialis anterior muscles during standing and walking and found a weaker task-dependency but a stronger speed-dependence in reciprocal inhibition (Kido et al., 2004). Although this study was not designed to test the effect of ankle joint angle on soleus H-reflex specifically, the authors did compare the reciprocal inhibition at matched EMG level during standing and walking, as well as the inhibition amplitudes across 16 phases in the gait cycle. No significant differences were found between all those variables. These results suggest that ankle joint angle also has little effect on the level of reciprocal inhibition between TA and SOL muscles.

Somewhat unexpectedly, we found cutaneous reflexes from the two nerve sites were modulated differentially with wrist position. SR cutaneous reflexes showed significantly increased inhibitory net reflex amplitudes at the wrist pronated position while amplitudes were relatively unchanged for MED cutaneous reflexes. Previous studies suggest cutaneous reflex amplitudes are highly task-dependent and nerve-specific in both arm and leg muscles. Depending upon the motor task, such as standing vs. walking (Komiyama et al., 2000), static vs. arm cycling (Zehr & Kido, 2001) or static vs. leg cycling (Zehr et al., 2001), cutaneous reflex amplitudes change dramatically at similar EMG levels. Differential reflex modulation was found in the same muscle when stimulating the nerves that innervated different skin area (Evans et al., 1989; Duysens et al., 1993; Haridas & Zehr, 2003; Nakajima et al., 2006). These types of task- and nerve-dependency of cutaneous reflexes have their functional significance and has been discussed in previous studies, especially in locomotion tasks (Zehr & Stein, 1999). In manual tasks, Evans et al, tested cutaneous reflexes from first dorsal interosseous muscle while performing isolated finger or grip maneuvers in eight different tasks (Evans et al., 1989). Long-latency excitatory responses were significantly lower during isolated finger tasks. Similar results were found by Nakajima and colleagues (Nakajima et al., 2006) when comparing long latency cutaneous reflexes in intrinsic human hand muscles while performing isometric abduction with different fingers and when producing a pincer grip task. Results showed that the magnitude of peak EMG around ~60–90ms latency was larger when the stimulation was applied to the homotopic digit that performed the motor task. Although not the explicit focus of their work, we interpret these earlier findings as indicators that cutaneous reflex modulation is stronger in muscles that are more functionally relevant for the task performed.

It is possible that the different joint positions used here could induce biomechanical and afferent input changes. Horri et al. examined five wrist muscle tendons at different joint angles and positions in cadavers and found the moment arm of extensor carpi ulnaris tendon significantly decreased when the forearm rotated from neutral to pronated positions (Horii et al., 1993). Rugy et al. found an increase in FCR activity and a decrease in flexor carpi ulnaris (FCU) activity as the forearm rotated from supinated to pronated position (de Rugy et al., 2012). They suggested that different joint positions might not only induce biomechanical changes but also tuned the motor commands to the muscles around the joint.

Here, differences in cutaneous reflex modulation could be due to the specific sensation and muscle functions MED and SR nerve generated and their relation to the motor task. Activation of SR nerve generates sensations in the dorsum of the hand, back of the thumb, index and middle finger. On the contrary, at the level of the wrist, the MED nerve innervates the skin of the palm side of the thumb, index and middle finger as well as the thumb flexor muscles. While participants contracted their ECR muscle at the required level, stimulation at SR nerve produced sensation within the muscles directly involved in the task. Additionally, different from the purely cutaneous sensory SR nerve, MED is a mixed nerve with both muscle and cutaneous sensory afferents and motor fibers. Studies showed that electrical stimulation in mixed nerve and cutaneous nerve activate different motor cortical areas (Kaukoranta et al., 1986). Since the afferent feedback from these two nerves convey through different ascending pathway, it is likely that different afferent composition between MED and SR cutaneous stimulation may affect the spinal interneuronal networks differently, this despite some common activity during rhythmic motor output (Zehr & Kido, 2001). Therefore, the functional difference between MED and SR nerve may relate to their different modulations such that SR cutaneous reflex amplitude during wrist extension task is likely more sensitively modulated by changes in the wrist joint position.

Higher EMG_{MAX} in ECR muscle and stronger inhibitory net reflex in SR cutaneous reflexes were found at the wrist pronated position. It is possible that altered EMG_{MAX} was a methodological confound caused by the displacement of electrodes on ECR muscle fibers with change in wrist position. However, since all the reflex amplitudes were normalized to the EMG_{MAX} at the corresponding position this potential confound is unlikely. In addition, the effects of possible movement of the surface EMG between wrist pronation and supination position have been excluded in Baldissera and colleagues' study. A control experiment were performed by using wire electrode in FCR muscle which confirm that changes in H-reflex amplitudes related to altered wrist position (Baldissera et al., 2000).

We suggest that altered sensory feedback at different wrist position plays a major role in modulating ECR motor neuron excitability and SR cutaneous reflex amplitudes. One possible source of change in afferent input is load-related feedback. Although the forearm and wrist were supported during this experiment, extending the wrist at the pronated position requires wrist extensors to contract to overcome the weight of the hand. Studies in leg muscles showed that load-related sensory inputs play important role in locomotor and postural control (Duysens et al., 2000). Walking with partial or whole body weight support can alter the phasic cutaneous reflexes modulation in the lower leg muscle (Bastiaanse et al., 2000; Nakajima et al., 2008). Bastiaanse et al also found load-dependent background muscle activity in leg extensor muscles during walking. In these studies, load-related sensory input was changed by changing total body weight (e.g. using body weight support to remove weight) or by applying external loads, but not by changing joint position. There is lack of corresponding investigations on the effects of load-related afference on cutaneous reflexes in the arm muscles during static task.

Despite that, we suggest that our results correspond with the above studies in leg muscles implying that load-related afferent input may play a role in the modulation of spinal interneuron excitability in the upper limb.

4.5.2 Modulation with muscle activation

Reciprocal inhibition and cutaneous reflexes amplitudes were both enhanced with increased ECR muscle activation. Proportional increases in reflex amplitudes with background activation was first emphasized by Marsden et al by measuring stretch reflexes in flexor policis longus muscle during thumb movement. Marsden and colleagues defined this phenomenon as "automatic gain compensation" where reflex gain increases in proportion to the number of active motor neurons. This functionally ensures that reflexes remain appropriately scaled to the motor task (Marsden et al., 1976;

Marsden et al., 1972). Matthews provided more examples of automatic gain compensation during tendon vibration induced force and inhibitory reflex in elbow flexors. Matthews suggested that reflex regulation without automatic gain compensation would tend to be too powerful when pre-existing muscle contraction was weak, and too feeble when muscle contraction was strong (Matthews, 1986). Here, muscle activation level had a significant effect on the amplitude of both reciprocal inhibition and cutaneous reflex in ECR muscles regardless of joint position. As different from rhythmic or locomotion movement (Haridas & Zehr, 2003; Zehr & Kido, 2001), this background EMG dependency suggests that during static contraction, background muscle activation affects interneuronal excitability relatively equally and makes a strong contribution to reflex amplitudes.

4.6 Conclusion

Joint position has a significant effect on SR but not MED cutaneous reflexes in ECR muscle. This effect of joint position in cutaneous reflex amplitude is thus nerve-specific. Amplitudes of cutaneous reflexes in arm muscles are likely more sensitive modulated in task-related muscles. As with related observations in the leg, amplitudes of reciprocal inhibition and cutaneous reflexes increased with background EMG in forearm muscles during tonic contraction regardless of joint position. In future studies that investigate the modulation of neural pathways, the effect of wrist joint position should be considered when measuring maximum muscle activation and SR cutaneous reflexes. Changes in joint wrist position have less effect on reciprocal inhibition and MED cutaneous reflexes amplitudes, which has relevance for choosing tools and approaches for assessments in clinical populations with limited upper limb range of motion and motor output.

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Chapter 5 Enhanced sensory stimulation modulates cutaneous reflexes in arm muscles during self-triggered or prolonged stimulation[4]

5.1 Abstract

Somatosensory feedback plays important roles in regulating all animal movement. This is widely studied using cutaneous electrical stimulation paradigms but the importance of mode (self or externally triggered) and duration (brief or sustained) of stimulation is unclear. Some research suggests that cutaneous reflex amplitudes are reduced when stimulation is self-triggered instead of externally triggered. Altered spinal excitability and motor output are also observed following sustained stimulation with various parameters. This study investigated the muscle responses following cutaneous stimulation with different combinations of trigger methods and stimulation durations.

Fifteen neurologically intact participants were recruited. Cutaneous reflexes in the extensor carpi radialis (ECR) were evoked with brief (15ms, 300Hz) or sustained (300ms, 50Hz) stimulation trains. Stimulation was applied to the superficial radial or median nerve at the wrist and triggered by: 1) a computer program (random-triggered); 2) muscle contraction (EMG-triggered); 3) the participant pressing a button (button-triggered). During each condition, isometric contractions were performed with ECR muscle activity maintained at 10, 25, 35, and 50% of maximal voluntary contraction.

Stronger inhibitory reflexes were found following brief superficial radial nerve stimulation was EMG-triggered. This suggests that modulation of cutaneous reflex excitability is specific to the timing when sensory ‘cues’ are applied during muscle contraction. No difference was observed following sustained stimulation applied to the superficial radial nerve suggesting brief and sustained stimulation affect the cutaneous pathways differentially. Nerve-specific responses were found between superficial radial and median nerve stimulation. For example, greater inhibition was induced by EMG-triggered sustained stimulation to the median nerve. These observations are critical in

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moving beyond pathway phenomenology toward targeted sensory enhancement and amplified motor output in rehabilitation and training.

5.2 Introduction

The regulatory role of somatosensory input in motor control has been extensively studied by measuring cutaneous reflex amplitudes in various muscles across the body. Some research suggests muscle responses can be affected by the stimulation trigger methods, such as self-triggered versus externally triggered. Baken et al.(2006) found reduced cutaneous reflex amplitudes in leg muscles during walking when the sural nerve (innervates to the lateral side of the foot) stimulation was triggered by participants pressing a button compared to randomly triggered by the computer program. Baken and colleagues suggested altered reflex amplitudes following self-triggered stimulation may be caused by premotor neuronal inhibitory effects on the cutaneous reflex pathways. This is similar to the central cancellation of self-generated tickle sensations (Blakemore et al., 1998) where reduced sensation and somatosensory cortex activity were observed when tactile stimuli were generated by the participants. It was proposed that sensory prediction from the voluntary movement attenuates the sensation from a self-generated movement. This enables us to distinguish more important sensory inputs such as a perturbation stimulus from the environment.

Cutaneous reflexes are modulated task-dependently with differential reflex amplitudes observed between rhythmic and discrete movements. During rhythmic movement, cutaneous reflexes are phase-dependent and nerve-specific (Zehr et al., 1997; Zehr & Kido, 2001). In contrast, nerve-specific muscle responses are absent during non-rhythmic task such as standing (Komiyama et al., 2000). In addition, cutaneous reflex amplitudes are proportional to the background muscle activation (Sun & Zehr, 2018) during static contraction, but not during rhythmic tasks (Zehr & Haridas, 2003). Considering the differential neural control mechanisms between rhythmic and non-rhythmic movement, whether cutaneous reflex pathway excitability can be affected by self-triggered stimulation during static contraction is unknown.

Besides using cutaneous reflex stimulation to evaluate spinal excitability, electrical sensory stimulation has been used to facilitate motor function after neurotrauma such as stroke (Celnik et al., 2007; Conforto et al., 2007; Conforto et al., 2010). Significantly improved hand dexterity (Zoghi & Galea, 2017) and coordinated and stable gait initiation (Dutta et al., 2009) are observed when neuromuscular electrical stimulation was triggered by participant's own muscle activation. Considering the similarity between electrical stimulation on the peripheral nerve and muscle, it is reasonable to predict that self-triggered sensory stimulation during voluntary movement should alter neural excitability differentially compared to random triggered sensory stimulation.

Previous studies suggest changes in sensory stimulation parameters can alter spinal and corticospinal excitabilities differentially. Mang and colleagues (2010) found significantly increased motor evoked potentials in tibialis anterior following common peroneal nerve stimulation at 100 but not 10, 50 or 200 Hz stimulation. In interventional studies with stroke participants, a wide range of stimulation frequencies have been used according to a systematic review by Laufer and Elboim-Gabyzon (2011). However, the effects of stimulation parameters on neural plasticity and training results are incompletely understood and confusing. Fraser et al. (2002) found motor evoked potential amplitudes increased at lower frequencies (1 and 5 Hz) but decreased at higher frequencies (10, 20, 40 Hz). With various results observed and to better understand how sensory stimulation parameters affect the nervous system, it is necessary to study how cutaneous pathways are modulated with different stimulation parameters.

To leverage directly from prior work using cutaneous nerve stimulation and to better understand application characteristics, the purpose of this descriptive study was to investigate the effects of simulation trigger mode and parameters on spinal excitability. As a proxy of spinal cord excitability, cutaneous reflexes were measured in the extensor carpi radialis (ECR) following stimulation to the superficial radial and median nerve with different trigger modes (self-trigger and random trigger) and frequencies (high-frequency reflex stimulation and low-frequency sustained stimulation).

5.3 Methods

5.3.1 Participants

Fifteen young adults (age: 23 ± 1.7 years; height: 172.8 ± 9.0 cm; weight: 69.2 ± 6.7 kg) without any neurological impairment or muscular injury were recruited. The protocol was approved by the Human Research Ethics Board at the University of Victoria (protocol number HREB 07-480-04d). Written informed consent was obtained before data collection.

5.3.2 Electromyography (EMG)

EMG from ECR and flexor carpi radialis (FCR) was measured in the right arm. After cleansing the skin with alcohol swabs, disposable surface electrodes (Thought Technology Ltd., Quebec, Canada) were placed in bipolar configuration over the target muscle bellies. EMG signals were amplified (×5000), bandpass filtered from 100 to 300 Hz (GRASS P511, Astromed-Grass Inc.) and sampled at 2000 Hz through a customized LabVIEW program (National Instruments, Austin, TX).

5.3.3 Stimulation

Stimulation parameters, trigger methods and stimulated nerve of each condition are presented in Table 1.

Table 5. 1 Overview of experimental protocol.

	Trigger methods	**Stimulated nerve**	**Contraction level**
Reflex stimulation (15ms 300Hz)	random-trigger	MED	Graded contraction at 10%, 25%, 35% and 50% EMG_{MVC}
		SR	
	EMG-trigger	MED	
		SR	
	button-trigger	SR	
	random-trigger	MED	

Sustained stimulation (300ms 50Hz)		SR	
	EMG-trigger	MED	
		SR	
	button-trigger	SR	

Stimulation trigger methods, stimulated nerve and muscle contraction levels during each condition are presented in separate columns. SR, superficial radial nerve; MED, median nerve.

Responses in the ECR muscle were evoked by stimulating the superficial radial nerve or median nerve at the wrist in separate trials with 1) reflex stimulation, a 15ms train at 300Hz; and 2) sustained stimulation, a 300ms train at 50Hz. The frequency and duration of reflex stimulation have been used as a standard stimulation to evoke cutaneous reflexes in many previous studies (Zehr & Chua, 2000; Zehr & Kido, 2001). The intensity of reflex stimulation was set at 2× radiating threshold (RT), which was defined as the lowest intensity at which a sensation of radiating paresthesia could be evoked in the innervation territory of the nerve (Zehr et al., 1997). This protocol has been used previously to evoke cutaneous reflexes in arm muscles (Zehr & Chua, 2000; Zehr & Kido, 2001). Sustained stimulation was set as 1.2× RT to provide a strong yet tolerable sensation. Such sustained stimulation was used to provide sensory enhancement during fatiguing exercise which altered spinal excitability and enhanced performance (Pearcey et al., 2017).

Both types of stimulation were delivered using GRASS 88 stimulators with SIU5 stimulus isolation and CCU1 constant current units (Grass Instruments, Astro-Med, Inc. West Warwick, RI, US). In the random-triggered condition, stimulation was delivered by a customized LabVIEW program with an interval of 1.5-3 s while the participant maintained ECR muscle activity at the target level. In the EMG-triggered condition, stimulation was triggered 1s after the participant's ECR muscle activity reached the target level.

To ensure any difference observed between EMG-triggered and random-trigger conditions were caused by the different trigger modes instead of prolonged isometric contraction during the random trigger condition, we added another trigger mode, button-trigger. In the button-triggered condition, participants maintained their ECR muscle activity at the target level on the tested arm, while stimulation was delivered by the participant pressing a button using the other hand. Participants were instructed to press the button when they were ready but could not do so unless 2 seconds had elapsed following the prior stimulation.

Twelve of 15 participants were able to complete the additional condition, 3 participants could not return to the lab.

5.3.4 Procedures

Participants were seated in a comfortable position with the forearm strapped on a customized device to ensure there was no wrist or forearm movement during contractions. Muscle activation during maximal voluntary contraction (EMG_{MVC}) in wrist extension was measured over 2 attempts interleaved by 1 minute of rest. During each trial, ECR muscle activity was rectified and averaged over a 25ms moving average window using a custom-written LabVIEW program. Participants were instructed to generate and hold maximal contractions for 3-5s. Rectified and averaged EMG was presented on the computer screen as visual feedback.

For each condition, isometric wrist extension was performed with ECR muscle activity maintained at 10%, 25%, 35% and 50% of EMG_{MVC} in four separate trials. During each trial, ECR muscle activity was assessed using a 100 ms moving averaged window and presented on the computer screen with the contraction target. To ensure sufficient pre- and post-stimulation data ware acquired in the EMG-triggered conditions, stimulation was delivered 1s after ECR muscle activity reached the target, and participants were asked to maintain the contraction for 500ms after the stimulation stopped. Visual feedback that indicated contraction target, when to maintain the contraction and when to relax was provided. There was at least 1 minute rest between each trial to avoid fatigue and participants were allowed to take breaks during the trial as needed.

5.3.5 Data analysis

Data were analyzed offline using customized written MATLAB programs (Version R2011b, The Mathworks, Natick, MA, USA). For reflex stimulation, cutaneous reflexes were calculated as the difference between EMG amplitude during the early (50-75ms post-stimulation) or middle latency (75-120ms post-stimulation) window and the background EMG averaged from a 100ms window before stimulation (Zehr & Chua, 2000). Net cutaneous reflexes were determined from the average cumulative reflex EMG over 150ms (ACRE150) post-stimulation (Zehr et al., 1998). Since there was no clear early and middle latency reflexes shown following sustained stimulation, we only calculated the net reflex post stimulation to investigate possible influences of sustained sensory input to muscle activity after stimulation. Figure 5.1 shows a typical trial from reflex stimulation and sustained stimulation, respectively. All amplitudes were normalized to the ECR EMG_{MVC} for each participant.

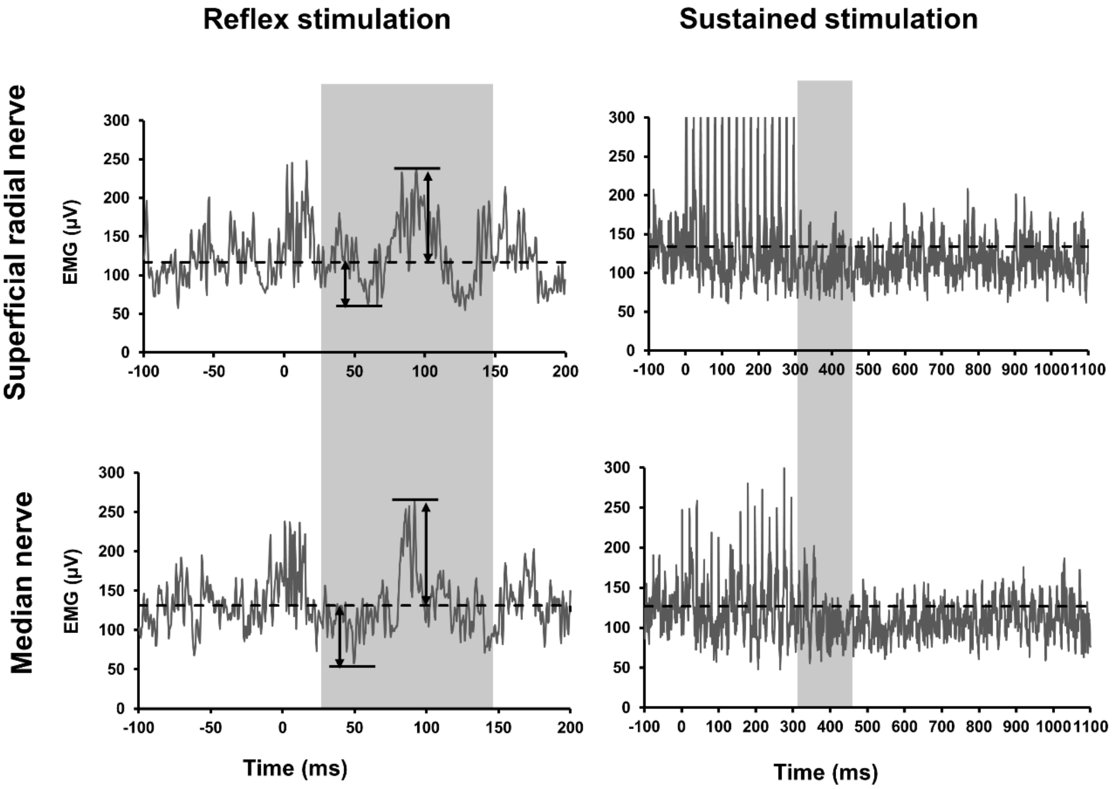

Figure 5. 1 Left column: Typical muscle activity following cutaneous reflex stimulation. The horizontal dashed line represents the average value of pre-stim EMG. Dark grey shaded areas represent the selected windows for calculating early and middle latency cutaneous reflexes, whereas light grey shaded areas represent the window used for calculating net reflexes. Right column: Typical muscle activity following sustained stimulation. The horizontal dashed line represents the average value of pre-stim EMG. The light grey shaded area represents the window used for calculating net reflexes.

5.3.6 Statistics

Statistical analysis was performed using SPSS software (IBM SPSS Statistic 20, Chicago, IL, USA). Two-way repeated measures ANOVA (rmANOVA) was used to determine the effects of condition (trigger method) and background EMG (level of muscle activity contraction) on early and middle latency amplitudes and net reflex excitability. If there was a significant effect of condition, pairwise comparisons were used to determine which condition significantly differed from the random trigger condition. Statistical significance was set at $p \leq 0.05$.

5.4 Results

5.4.1 Reflex stimulation

Dorsolateral hand surface (superficial radial nerve)

Significant effects of trigger methods were found for early latency ($F_{(2,22)} = 3.776$, $p=0.039$), middle latency ($F_{(2,22)} = 5.911$, $p=0.009$) and net reflexes ($F_{(2,22)} = 4.426$, $p=0.024$) following reflex stimulation to the superficial radial nerve (Figure 5.2). Pairwise comparisons showed significantly reduced reflex amplitudes in the EMG-triggered condition compared to the random-triggered condition at early ($p=0.004$) and middle ($p=0.006$) latency, and in net reflexes ($p=0.013$). Compared to the random-triggered condition, the button-trigger condition showed lower reflex amplitudes at middle latency only ($p=0.008$).

The effects of muscle activity were observed for early latency ($F_{(3,33)} = 24.421$, $p=0.000$), middle latency ($F_{(3,33)} = 7.533$, $p=0.001$) and net reflexes ($F_{(3,33)} = 13.284$, $p=0.000$). For both early latency and net reflexes, greater inhibitory reflexes were found at higher background EMG in all the conditions. For middle latency, facilitatory reflexes increased with background EMG.

Interaction effect between background EMG and trigger method was not significant for early latency ($F_{(6,66)} = 1.935$, $p= 0.088$), middle latency ($F_{(6,66)} = 0.927$, $p= 0.481$), or net reflexes ($F_{(6,66)} = 0.520$, $p= 0.791$).

Palmar hand surface (median nerve)

No significant difference between trigger mode was observed when cutaneous reflex stimulation was delivered to the median nerve for early ($F_{(1,14)} = 0.607$, $p=0.449$), middle latency ($F_{(1,14)} = 3.805$, $p=0.071$) or net reflexes ($F_{(1,14)} = 3.001$, $p=0.105$) (Figure 5.3). Significant effects of background EMG were found in net reflexes ($F_{(3,42)} = 11.881$, $p<0.001$) and early latency reflexes ($F_{(3,42)} = 3.365$, $p=0.027$) with greater inhibitory reflexes at higher background EMG. No interaction effect was observed for early latency

($F_{(3,42)}$ = 0.317, p= 0.813), middle latency ($F_{(3,42)}$ = 1.349, p= 0.272) or net reflexes ($F_{(3,42)}$ = 0.570 , p= 0.638).

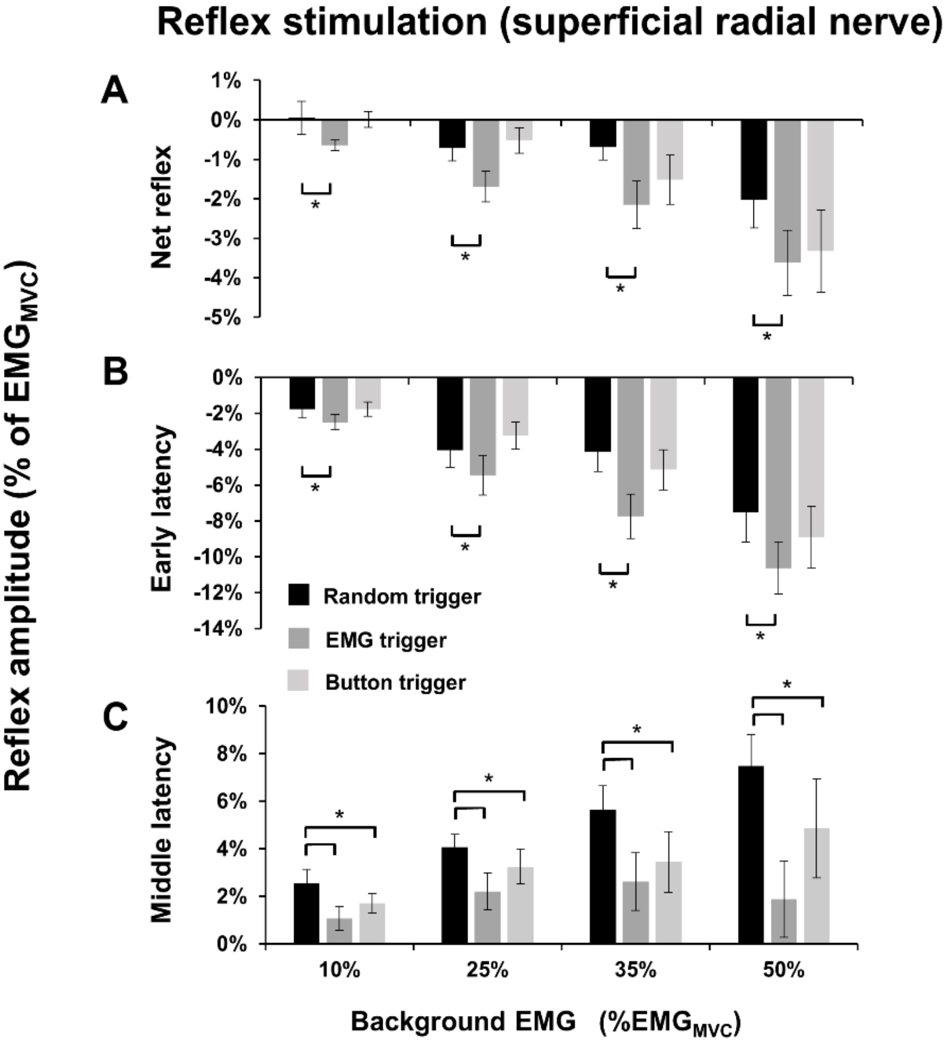

Figure 5. 2 Early latency, middle latency and net reflexes following reflex stimulation to the superficial radial nerve. The x-axis represents levels of background muscle activation. The y-axis represents reflex amplitudes. * indicates a significant difference at p<0.05.

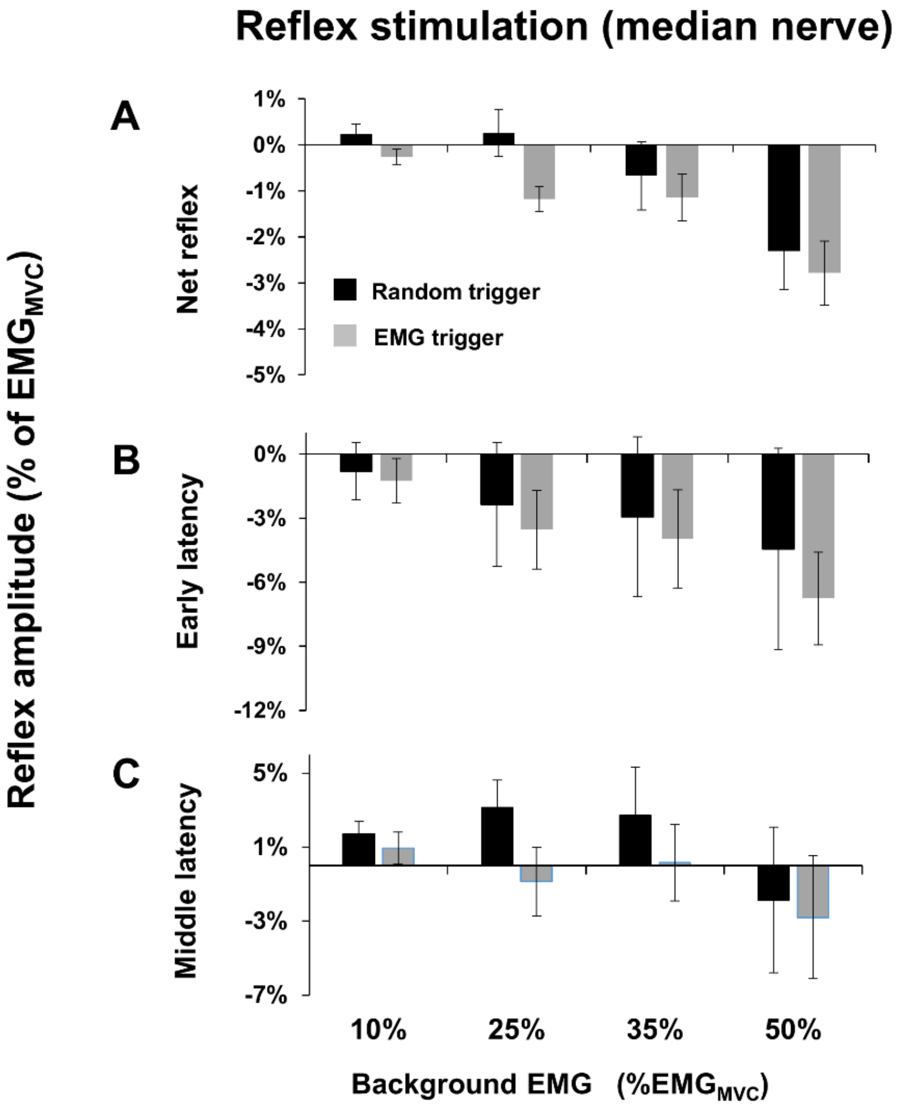

Figure 5. 3 Early latency, middle latency and net reflexes following reflex stimulation to the median nerve. The x-axis represents levels of background muscle activation. The y-axis represents reflex amplitudes. * indicates a significant difference at p<0.05.

5.4.2 Sustained stimulation

<u>*Dorsolateral hand surface (superficial radial nerve)*</u>

Following sustained stimulation on the superficial radial nerve, no significant effects of trigger methods ($F_{(2,22)} = 0.932$, p=0.409) and interaction effect ($F_{(6,66)} = 0.436$, p= 0.852) was found in the net reflex amplitude. However, inhibitory reflexes increased significantly ($F_{(3,33)} = 15.244$, p=0.000) with background EMG (Figure 5.4A).

Palmar hand surface (median nerve)

Significant effects of trigger method ($F_{(1,14)}$ = 11.552, p=0.004) and background EMG ($F_{(3,42)}$ = 8.509, p=0.000), as well as interaction effects ($F_{(3,42)}$ = 3.246 , p= 0.031) were found following sustained stimulation to the median nerve. Greater inhibitory reflexes were observed in the EMG-triggered condition, and inhibitory reflexes increased with background EMG (Figure 5.4B).

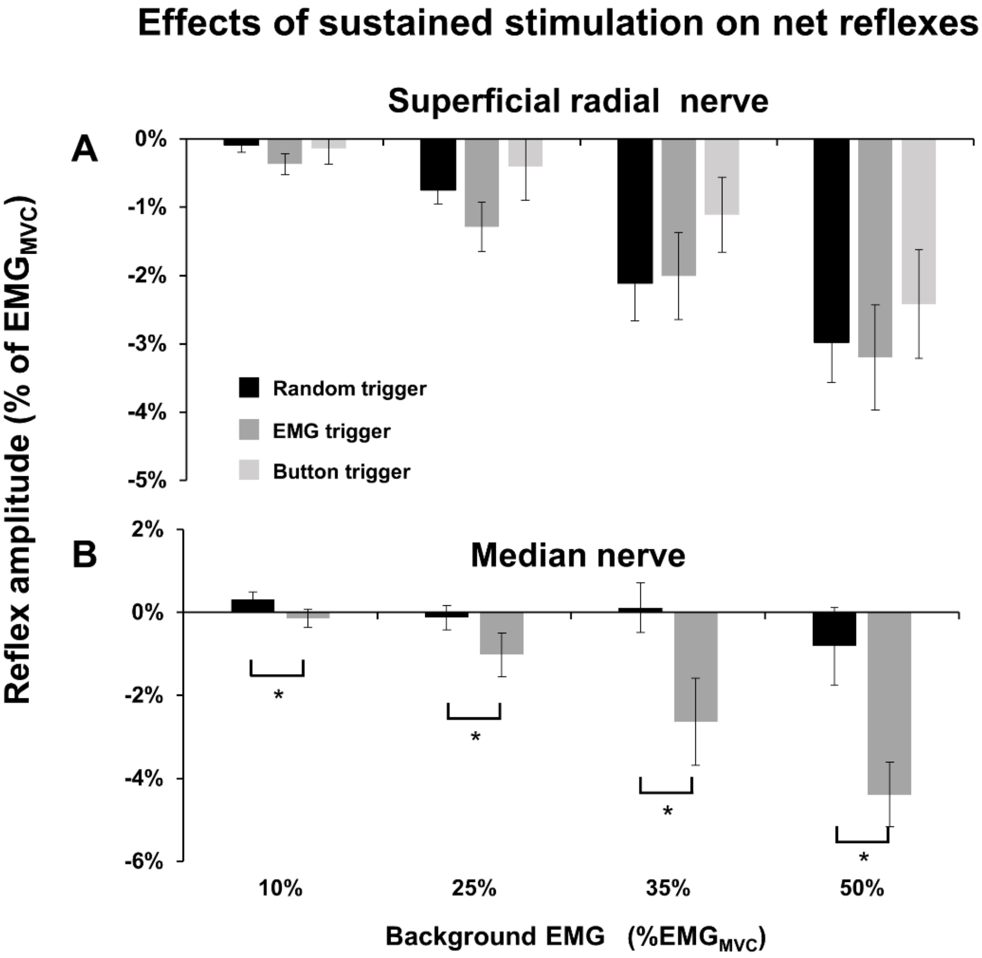

Figure 5. 4 A: Net reflexes following sustained stimulation to the superficial radial nerve. B: Net reflex following sustained stimulation to the median nerve. The x-axis represents levels of background muscle activation. The y-axis represents reflex amplitudes. * indicates a significant difference at $p<0.05$.

5.5 Discussion

This study investigated the muscle responses evoked by cutaneous stimulation of different frequencies and duration applied with different trigger modes and at different levels of muscle activation. Results revealed that reflexes are reduced when superficial radial nerve stimulation is triggered by muscle activation and that the effects of self-triggered stimulation are nerve-specific. Amplified inhibitory responses and reduced facilitatory responses were observed when reflex stimulation was applied to the superficial radial (skin contact surface in direction of contraction) but not median (skin contact surface opposed to the direction of contraction) nerve.

5.5.1 Timing of sensory prediction reduced cutaneous reflex amplitudes following EMG-triggered stimulation

EMG-triggered stimulation, a form of self-triggered stimulation, evoked greater inhibitory and smaller facilitatory reflexes when reflex stimulation was applied to the superficial radial nerve. These findings are consistent with the observations from Baken et al. (2006) who showed reduced facilitatory and enhanced inhibitory cutaneous reflexes in response to self-triggered cutaneous stimulation during walking. Attenuated sensation and muscle responses following self-generated movement (Collins et al., 1998) or tactile stimulation (Weiskrantz et al. 1971) have also been observed. Reduced sensation is likely due to less activation of somatosensory and anterior cingulate cortices (Blakemore et al., 1998). Blakemore and colleagues described such modulation as “central cancellation” of self-generated stimuli and suggested it is likely due to sensory prediction based on the internal forward model (Blakemore et al., 2000a; 2000b). Because the sensory sequence of a self-triggered stimulation can be predicted, reduced reflexes may enable a more subtle response to sensory feedback from the external environment (Baken et al., 2006).

The neural mechanisms and locus of such “central cancellation” modulation require further study but current evidence indicates both cortical and spinal cord levels. Blakemore et al. (1999) found that altered activity in the cerebellum significantly correlated with changes in the somatosensory cortex following self-triggered tactile stimulation. This suggests that the cerebellum is a source that accurately predicts the sensory consequences of a motor command and then adjusts the somatosensory cortex activity (Blackmore et al.1999). This hypothesis is further supported by the findings from Hoogkamer et al (2015), who compared the cutaneous reflex modulation in people with cerebellum lesion to a control group. Hoogkamer and colleagues found that participants with cerebellar lesions retain phase-dependent modulation but self-triggered stimulation does not attenuate the reflex amplitudes during walking. Several studies also demonstrate potential spinal mechanisms of "central cancellation". Since both early and middle latency cutaneous reflexes can be modulated independently from background EMG during walking, Baken et al. suggested that premotoneuronal modulation is likely involved in these pathways (2005). By measuring the cord dorsum potential and spinal interneuronal activity in the monkey during active wrist flexion-extension task, Seki et al. (2003) found enhanced presynaptic inhibition when sensory stimulation was applied during voluntary movement. Here, greater inhibitory early latency reflexes and reduced facilitatory middle latency reflexes confirm that self-triggered stimulation during muscle contraction can reduce the overall interneuronal excitabilities of the cutaneous pathways of the superficial radial nerve.

5.5.2 The effects of sensory prediction are stronger at the onset of muscle activation

Although stimulation was triggered by participants themselves in both the EMG-triggered and button-triggered conditions, button-triggered stimulation superficial radial nerve did not change early latency and net reflex amplitudes. Compared to the EMG-triggered condition, where stimulation was delivered 1s after ECR EMG reached the target, ECR muscle contraction was maintained at the target levels through the entire trial during the button-triggered condition. Weaker "central cancellation" in the button-triggered condition suggests the effects of sensory prediction can be influenced by the timing when stimulation is applied.

In the EMG-triggered condition, stimulation applied at the early onset of muscle contraction, sensory feedback (i.e. proprioceptive information) generated from the muscle contraction may have provided a related "sensory cue" before stimulation was delivered. Stronger self-triggered effects in the EMG-triggered condition emphasize the concept of

Hebb’s synapse theory (Hebb, 1949) since descending motor drive and associated sensory feedback are coincided. In rehabilitation training, many studies show that paired electrical stimulation and voluntary movement can significantly enhance corticospinal excitability and performance. Khaslavskaia and colleagues (2005) found that coupling the initiation of dorsiflexion with electrical stimulation on the common peroneal nerve increased amplitudes of motor evoked potentials. However, reduced corticospinal excitability was observed when the same stimulation was applied later in the sustained isometric dorsiflexion which indicates the effects of electrical stimulation depend on the concurrence of motor drive and sensory stimulation. Taylor and colleagues (2012) compared cortical excitability after ECR contractions with automated electrical stimulation, EMG-triggered stimulation, or no stimulation applied to the muscle. Significantly increased motor evoked potential amplitudes were found after EMG-triggered stimulation and voluntary activation but not the condition with automated stimulation suggesting that voluntary drive is important in enhancing the efficacy of stimulation (Taylor et al. 2012).

Here, both button-triggered and EMG-triggered stimulation modes altered middle latency reflex amplitudes. Nielsen et al. (1997) suggested that reflexes at a latency around 70-95 ms post-stimulation are at least partly mediated by a corticospinal pathway. In this study, the middle latency responses were selected from a window of 80~120 ms post-stimulation which confirm that sensory prediction from both types of self-triggered stimulation can affect cutaneous pathways excitability. However, altered early latency and net reflexes were only observed following EMG-triggered stimulation suggesting that paired sensory stimulation with voluntary movement have stronger effects on the overall excitability in cutaneous pathways. Timed sensory stimulation with muscle activation may be able to enhance the outcomes of rehabilitation practices.

5.5.3 Self-triggered effects are nerve-specific between task-relevant and task-irrelevant skin surfaces

In this study, differential reflex modulation was observed between median and superficial radial nerve stimulation. When reflex stimulation was applied to the median nerve, no self-trigger effects were observed.

Different responses from superficial radial and median nerve stimulation are likely due to the differences in sensation and muscle functions of each nerve. The median nerve innervates the palmar side of the thumb, index and middle finger as well as the thumb flexor muscles. On the contrary, the superficial radial nerve innervates the skin over the dorsum of the hand, back of the thumb, index, and middle finger. Nerve-specific reflexes have been observed in multiple arm muscles during arm cycling, Zehr and Kido (2001) found different signs of reflexes in the same muscles after stimulation applied to the median, ulnar and superficial radial nerve. Although fewer studies have investigated cutaneous reflexes in the arm muscles during static tasks, some evidence shows differential modulation when sensory stimulation is applied to the task-relevant or task-irrelevant muscle. Nakajima and colleagues (2006) compared cutaneous reflexes in intrinsic hand muscles while performing isometric abduction with different fingers and when producing a pincer grip task. Results showed larger reflex magnitudes when stimulation was applied to the homotopic digit that was performing the motor task. Sun and Zehr (2018) found ECR cutaneous reflexes evoked from superficial radial nerve were modulated by the forearm position during wrist extension, however, the effect of limb position was not observed when stimulation was applied to the median nerve. It was suggested that since sensation from superficial radial nerve stimulation is more task-relevant during wrist extension, interneuronal excitability is likely more sensitive to changes from the limb posture (Sun & Zehr, 2018). Similarly, in the current study, the cutaneous pathways of superficial radial nerve are more responsive to altered descending input or presynaptic inhibition caused by different trigger modes. More responsive cutaneous reflex modulation may help “tune” the target muscle activity. In a study from Cavallari et al., increased Ib facilitation from wrist extensors to flexors was only observed when stimulation applied to the dorsal but not the palmer surface of the finger. Cavallari and colleagues suggested that during an exploratory movement, when the wrist is extended and the back of the hand contact an object, increased Ib facilitation to the antagonist muscle may contribute to braking and regulating the wrist extension movement (Cavallari et al., 1985).

The above observation may be further applied in rehabilitation such as targeted strength training. For those who have severe weakness in the wrist extensor, cutaneous stimulation to the superficial radial nerve may facilitate activation during strength training. Previous studies also show that timed sensory feedback during voluntary movement can facilitate corticospinal (Khaslavskaia et al. 2005; Taylor et al.2012) and spinal (Pearcey et al. 2017) excitability. Here, nerve-specific cutaneous reflexes indicate timed sensory stimulation to the task-relevant skin surface may have a strong influence on the motor neuron excitability of the target muscle. Further investigation should assess whether timed stimulation on skin areas could enhance performance during functional tasks that involve multiple muscles.

5.5.4 Effects of stimulation parameters on central cancellation effects

No significant difference between trigger modes was observed following sustained stimulation to the superficial radial nerve. On the contrary, when sustained stimulation was applied to the median nerve, significantly greater inhibitory reflexes were observed in self-trigger condition.

Here, differential muscle responses between reflex stimulation and sustained stimulation were likely due to the stimulation duration. In the current literature, reflex cutaneous stimulation is commonly used as a probe to assess the spinal and cortical excitability during different motor tasks and phases of movement (Zehr & Stein, 1999). Sustained stimulation has been used in rehabilitation training to provide sensory enhancement and induces acute or chronic neural plasticity (Zehr, 2006). The effects of stimulation parameters on neural excitability are usually assessed by measuring reflex amplitudes after sensory conditioning. In a literature review from Chipchase et al. (2011), the authors compared motor evoked potential following sustained stimulation with various frequency (ranges from 1 to 150 Hz) and duration (ranges from 6 mins to 2 hours) and found differential outcomes across studies. Here, we measured responses in a 150 ms window following sustained sensory simulation. Although there is no clear early and middle latency response, reduced muscle activity (i.e. the net reflex) suggests an overall inhibitory effect when sustained stimulation was applied to the superficial radial never during wrist extension. Similar to the bi-stable behavior found in motor neurons where long-lasting motor neuron depolarization was triggered by a train of impulses (Crone et al., 1988; Hounsgaard et al., 1984), it is possible that sustained stimulation induced longer lasting excitability in the interneurons that mediate the superficial radial cutaneous pathways. Therefore, the corticospinal influence in the self-triggered condition becomes less powerful following sustained stimulation, an interpretation aligned with our finding that amplified inhibitory responses were only observed following self-triggered reflex stimulation but not sustained stimulation.

5.6 Conclusion

This study found stronger inhibitory reflexes when stimulation was self-triggered by muscle activation. This “self-triggered effect” can be influenced by the timing and the nerve that has been stimulated. These findings reveal important stimulation characteristics that will enable moving beyond studying reflex pathway phenomenology and towards exploiting their properties in functional motor enhancement in the future.

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Chapter 6: Sensory enhancement amplifies interlimb cutaneous reflexes in wrist extensor muscles[5]

6.1 Abstract

Interlimb neural connections support motor tasks such as locomotion and cross-education strength training. Somatosensory pathways that can be assessed with cutaneous reflex paradigms assist in subserving these connections. Many studies show that stimulation of cutaneous nerves elicits reflexes in muscles widespread across the body and induces neural plasticity after training.

Sensory enhancement, such as long duration trains of transcutaneous stimulation, facilitates performance during rehabilitation training or fatiguing motor tasks. Performance improvements due to sensory stimulation may be caused by altered spinal and corticospinal excitability. However, how enhanced sensory input regulates the excitability of interlimb cutaneous reflex pathways has not been studied. Our purpose was to investigate the effects of sensory enhancement on interlimb cutaneous reflexes in wrist extensor muscles.

Stimulation to provide sensory enhancement (2 s trains at 15 Hz to median or superficial radial nerves) or evoke cutaneous reflexes (15 ms trains at 300 Hz to superficial radial) was applied in different arms while participants (n=13) performed graded isometric wrist extension. Wrist extensor EMG and cutaneous reflexes were measured bilaterally.

We found amplified inhibitory reflexes in the arm receiving superficial radial and median nerve sensory enhancement with net reflex amplitudes decreased by 709.5% and 695.3% repetitively. This suggests sensory input alters neuronal excitabilities in the interlimb cutaneous pathways. These findings have potential application in facilitating

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motor function recovery through alterations in spinal cord excitability enhancing sensory input during targeted rehabilitation and sports training.

6.2 Introduction

Spinal neural connections assist in regulating muscle activity in each limb to produce smooth and coordinated movement. Somatosensory feedback is a critical factor regulating excitability in these neural networks.

Cutaneous reflexes, obtained from stimulating afferent nerves containing sensory axons (predominately Aβ but also Aδ and sometimes C fibres) and innervating specialized mechanoreceptors (Merkel disks, Pacinian and Meissner corpuscles, Ruffini endings and free nerve endings) from the skin (Zehr & Stein, 1999), have been studied as a proxy measure of the role for somatosensation in movement control. Earlier studies on cats show that cutaneous stimulation applied to one limb can evoke responses in muscles of both ipsilateral and contralateral limbs during locomotion (Duysens, 1977; Duysens & Loeb, 1980). Similarly, in humans, brief (e.g. 15 ms) high frequency (e.g. 300 Hz) stimulation trains to nerves innervating the foot evoke nerve-specific and phase-dependent responses in both stimulated (Zehr & Stein, 1999) and non-stimulated limbs (Haridas & Zehr, 2003; Tax et al., 2017; Wezel et al., 1997) during walking. Such interlimb modulation of cutaneous input has important functional roles in producing coordinated movements in response to perturbation and has been observed in all four limbs. Stimulation at the wrist induces phase-dependent muscle responses in the leg muscles with significant kinematic changes at the ankle joint during walking (Haridas & Zehr, 2003). During static tasks, cutaneous stimulation to one arm can facilitate the soleus H-reflex in the leg (Kagamihara et al., 2003) and reinforced reciprocal inhibition in the contralateral arm (Delwaide & Pepin, 1991). Stronger interlimb cutaneous reflex showed during bimanual cooperative task (Dietz et al., 2015). Zehr et al. (2001) revealed that cutaneous stimulation from the hand or foot evokes responses in muscles of all the limbs which suggests that effects of cutaneous pathways are widely distributed in the human lumbar and cervical spinal cord regardless of the type of movement. Thus, sensory input from one limb has a global effect which modulates neural excitability in all four limbs (Zehr et al., 2001).

During discrete (e.g. non-rhythmic) movements, cutaneous reflex amplitudes change proportionally with background muscle activity. This “automatic gain compensation” (Marsden et al.,1976; 1972) has been observed for stretch reflexes (Bedingham & Tatton, 1984; Marsden et al., 1976; Pruszynski et al., 2009), tendon vibration reflexes (Matthews, 1986), reciprocal inhibition and cutaneous reflexes (Sun & Zehr, 2018). This mechanism ensures the effects of reflex corrections are scaled to motor activity (Matthews, 1986). The interlimb effects of unilateral voluntary contraction are observed at cortical, corticospinal and spinal pathways in the form of altered motor evoked potentials, cervicomedullar motor-evoked potentials and H-reflex amplitudes (Hortobagyi et al., 2003), but how descending motor drive affects interlimb cutaneous pathways and reflex amplitudes in the opposite limb is not clear.

Besides using sensory stimulation as a probe to assess neural excitability, enhanced sensory feedback from prolonged cutaneous stimulation has been applied to alter neural excitability and facilitate movement recovery after neurotrauma (Lesemann et al., 2015; Zehr, 2006a). Several studies show that 30-60 mins of transcutaneous electrical stimulation to the peroneal nerve in the contralesional leg significantly improves walking function and reduces spasticity in ankle muscles (Jung et al., 2017; Sheffler & Chae, 2007). Longer duration (e.g. one session of 120 mins) sensory stimulation of the median nerve improves the reach-to-grasp performance (Koesler et al., 2009) and functional performance in Jebsen-Taylor Hand Function Test (Conforto et al., 2007) in the more affected hand.

Interlimb effects derived from sensory enhancement were observed in neurologically intact participants as increased EMG amplitudes (Hamilton et al., 2018) and improved accuracy in a visuomotor tracking task performed by flexing and extending the wrist (Veldman et al., 2018) on the non-stimulated side. In a literature review from Veldman et al., the authors proposed that the cross effects of sensory stimulation are likely due to increased excitability in the primary motor cortex ipsilateral to the side of stimulation (Veldman et al. 2014). By measuring spinal excitability during a fatigue cycling task, Pearcey et al. found sensory stimulation of the foot surface interfered with the manifestation of fatigue and could maintain spinal excitability in neurologically intact participants (Pearcey et al., 2017). Considering the widespread connectivity of cutaneous pathways affecting motor pools for all limbs, we hypothesized that targeted sensory enhancement could affect the excitability of cutaneous pathways bilaterally. Currently, how cutaneous reflex amplitudes may change after sensory enhancement has not been well studied.

The purpose of this study was to test the effects of sensory enhancement and motor activity on interlimb cutaneous pathways during static muscle contraction. As a proxy for descending motor drive, isometric wrist extension was performed at three levels of maximal EMG. In a condition-test paradigm, sensory enhancement was delivered as a prolonged (2 s) train of low frequency (15 Hz) electrical stimulation prior to a cutaneous stimulation to evoke reflexes (15 ms at 300 Hz) in the contralateral arm.

6.3 Methods

6.3.1 Participants

Thirteen neurologically intact adults (mean± standard deviation: age 26.7± 4.9 years; height 172.0 ± 9.0 cm; weight 63.1± 10.6 kg; right hand dominant =12, left hand dominant =1) participated in the study. The protocol was approved by the Human Research Ethics Board at the University of Victoria and conducted according to the declaration of Helsinki. Written informed consent was obtained before data collection.

6.3.2 Electromyography (EMG)

Muscle activity from extensor carpi radialis (ECR) and flexor carpi radialis (FCR) was measured bilaterally. After cleansing the skin with rubbing alcohol swabs, disposable surface electrodes (Thought Technology Ltd., Quebec, Canada) were placed in bipolar configuration over the target muscle bellies. EMG signals were amplified (×5000) and bandpass filtered from 100 to 300 Hz (GRASS P511, Astromed-Grass Inc.) at 2000 Hz through a customized LabVIEW program (National Instruments, Austin, TX, USA). This procedure allows for effective amplification while minimizing the stimulation artifact and has been used in many previous studies from our group (e.g. Klarner et al., 2016; Zehr & Loadman, 2012; Zehr & Kido, 2001). In this experiment, it was not possible to use feedback of EMG during sensory enhancement due to stimulation artifacts. Participants were instead instructed to maintain the same efforts of wrist extension contraction in both hands.

6.3.3 Electrical stimulation to evoke reflexes and for sensory enhancement

Stimulation to evoke cutaneous reflexes was applied over the superficial radial nerve on the dominant wrist with 1 ms pulses in a 15 ms train at 300 Hz and at 2× radiating threshold (RT, which was defined as the lowest intensity at which a sensation of radiating paresthesia could be evoked in the innervation territory of the nerve (Zehr et al. 1997)). This protocol has been used in many previous studies to evoked cutaneous reflexes in the arm muscles (Zehr & Chua, 2000; Zehr & Kido, 2001).

Stimulation for sensory enhancement was applied to the median or superficial radial nerves on the non-dominant wrist for 2 s with a 150 Hz train of 1 ms pulses. Stimulation intensity was set as 1.2× RT. These stimulation parameters have been used in previous studies (Pearcey et al. 2017) to provide strong yet tolerable sensation. To avoid any possible confounding effect of handedness, such as asymmetrical spinal excitability between the dominant and non-dominant hand (Aimonetti et al., 1999; Nativ et al., 1989), sensory enhancement was applied to the non-dominant arm and cutaneous reflexes were evoked in the dominant arm for all the participants.

Stimulation for cutaneous reflexes and sensory enhancement were delivered using two GRASS 88 stimulators with SIU5 stimulus isolation and CCU1 constant current units (Grass Instruments, Astro-Med, Inc. West Warwick, RI, US).

6.3.4 Procedures

Participants were seated with both elbows extended around 125° (where 180° is full extension) and both forearms pronated and strapped to customized devices to ensure both arms maintained the same position during data collection. Muscle activation during maximal voluntary contraction (EMG_{MVC}) for ECR was measured during 2 attempts for each arm with 1 min break in between. During the EMG_{MVC} test, ECR muscle activity was rectified and averaged over a 25 ms window using a custom-written LabVIEW program and was presented on the computer screen as visual feedback. Participants were instructed to generate and hold maximal isometric wrist extension contractions for 3-5 s.

There were six conditions in total, including two tasks and three types of sensory enhancement (Figure 6.1). To test the effects of background muscle activity, the two motor tasks included: 1) ECR muscle on the reflex-stimulated side performed graded contraction (10%, 25% and 35% of EMG_{MVC}) in three separate trials while the ECR on the sensory-enhanced side maintained 10% of EMG_{MVC}; 2) ECR muscle on the reflex-stimulated side was contracted at 10% of EMG_{MVC} while the sensory-enhanced arm perform graded ECR contraction at 10%, 25% and 35% of EMG_{MVC} in three separate trials. Considering the length of each trial, we only chose three levels of the muscle contraction with the maximal target level at 35% MVC to avoid fatigue effects.

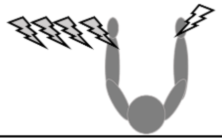
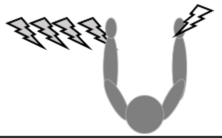
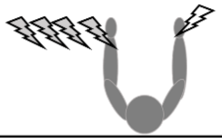
	Non-dominant arm			**Dominant arm**	
	Contraction level	Sensory enhancement		Reflex stimulation	Contraction level
Task 1	**10% EMG_{MVC}**	--		SR	**Graded contraction at 10%, 25%, 35% EMG_{MVC}**
		SR			
		MED			
Task 2	**Graded contraction at 10%, 25%, 35% EMG_{MVC}**	--		SR	**10% EMG_{MVC}**
		SR			
		MED			

Figure 6. 1 Overview of experimental protocol. Muscle contraction level and stimulation applied during each condition are presented in separate rows. Muscle contraction level and stimulated nerve (superficial radial nerve, SR; median nerve, MED) are presented in separate columns for the dominant and non-dominant arm, respectively. The single lightning bolt represents short (15 ms) duration and high (300 Hz) frequency reflex stimulation while the series of lightning bolts represent long (2 s) duration and low (15 Hz) frequency stimulation for sensory enhancement.

To test for modulation of interlimb cutaneous pathways by sensory enhancement, three sensory conditions were collected: 1) control (no sensory enhancement); 2) sensory enhancement applied on the superficial radial nerve (SR sensory); 3) sensory enhancement applied on the median nerve (MED sensory). Each condition included 15 sweeps of stimulation. These two nerves produce anatomically opposite sensation on the hand.

Superficial radial nerve stimulation generates sensation on the dorsum of the thumb and hand where is also sensory feedback produced from isometric wrist extension. On the contrary, median nerve stimulation generates sensation on the palmar side of the hand, thumb, index and middle finger which is on the opposite side of ECR muscle contraction.

During each trial, ECR EMG was averaged over a 100 ms window and presented on the computer screen with the contraction targets. Both arms performed wrist extension contraction simultaneously. After both ECR EMG channels reached (and maintained for 500 ms) the target levels, 2 s of sensory enhancement delivered to the sensory-enhanced arm. Fifty milliseconds after the sensory enhancement, a train of cutaneous reflex stimulation was applied on the SR nerve of the reflex-stimulated arm. After reflex stimulation was applied, participants maintained ECR muscle activities on both sides for 0.5 to 1 s before relaxation. Therefore, the duration of each sweep was at least 3365 ms, the time between EMG reach the target and reflex stimulation applied was 2550 ms as illustrated in Figure 6.2 (A). During sensory enhancement, participants were asked to maintain the same effort of ECR contraction in each arm. After each sweep of conditioning and test stimuli, participants were instructed to completely relax both arms and then start the next bilaterally contraction when they were ready.

Raw EMG from the ECR and FCR muscles on both arms was recorded throughout data collection trials.

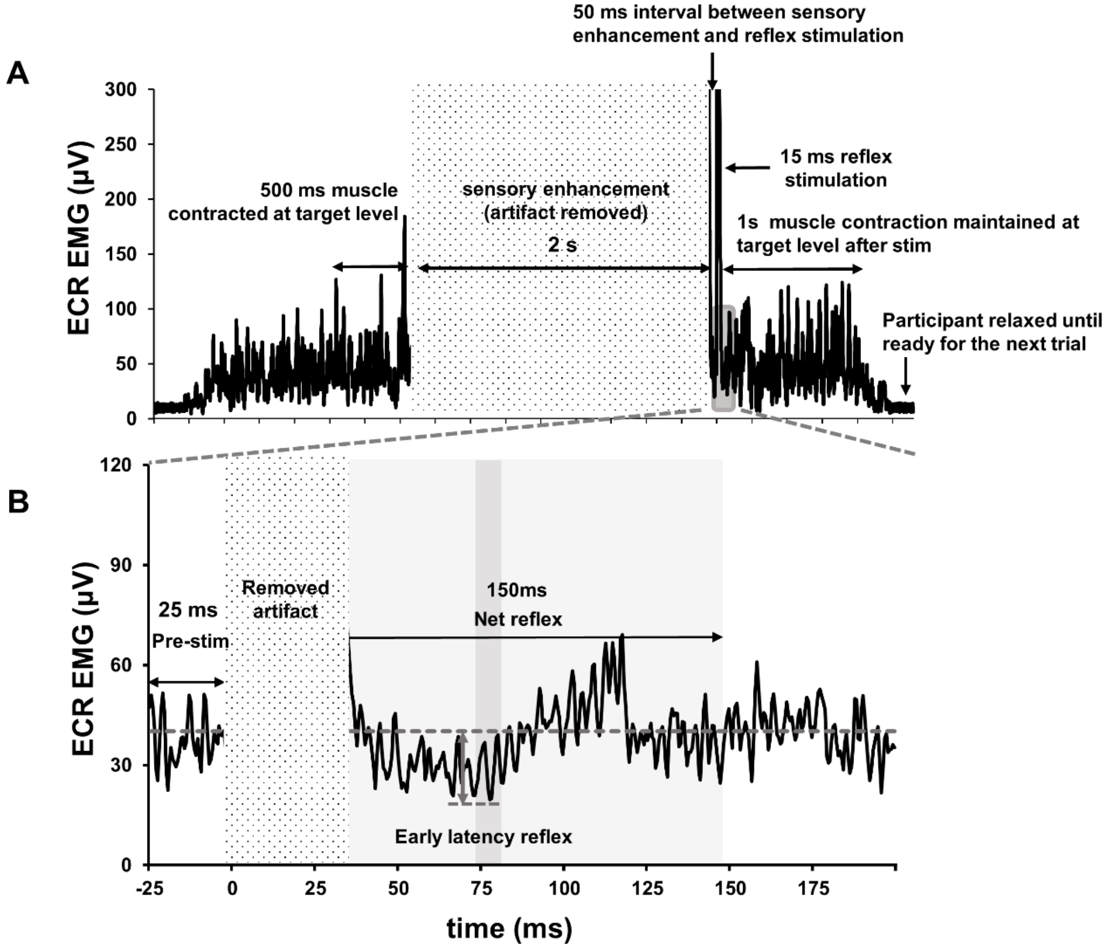


Figure 6. 2 Muscle activity during a typical trial with the windows chosen for data analysis. A: Activity of wrist extensor muscle (ECR EMG) data were rectified and low-pass filtered at 100 Hz. Artifact from the sensory enhancement was removed. The window used for cutaneous reflex analysis is indicated within the grey area. B: Data used for cutaneous reflex analysis in the same trial. The horizontal dashed line represents the average value of pre-stimulation EMG. Early latency reflex (peak response latency ~50-75 ms) is averaged over a 10ms window (dark grey) centered around the lowest value. Net reflex is the accumulated average value in the 150ms window (light grey) post stimulation period.

6.3.5 Data analysis

Cutaneous reflexes were analyzed using a custom-written MATLAB program (Version R2011b, The Mathworks, Natick, MA, USA). Stimulus artifact was removed from the reflex trace and data were then low-pass filtered at 30 Hz using a dual-pass, fourthorder Butterworth filter. Early latency cutaneous reflexes were calculated as the difference between the background EMG and the average of a 10ms window centered around the post-stimulation minima at ~50-75 ms latency (Baken et al., 2005; Zehr & Chua, 2000; Zehr & Kido, 2001), which are mainly mediated by spinal mechanisms. To determine the overall effects of cutaneous stimulation without voluntary response, net reflexes were determined as the average cumulative reflex EMG over 150 ms post-stimulation (Zehr et al.,1997; Zehr et al. 1998). Background EMG was calculated as the average EMG across a 25 ms pre-stimulus window (Figure 6.3 B). Before performing statistical analyses, early latency and net reflex amplitudes were normalized to the EMG_{MVC} of the corresponding ECR muscle.

For reference, cutaneous reflex traces during task 1 and task 2 from a single participant are presented in Figure 6.3 and 6.4, respectively.

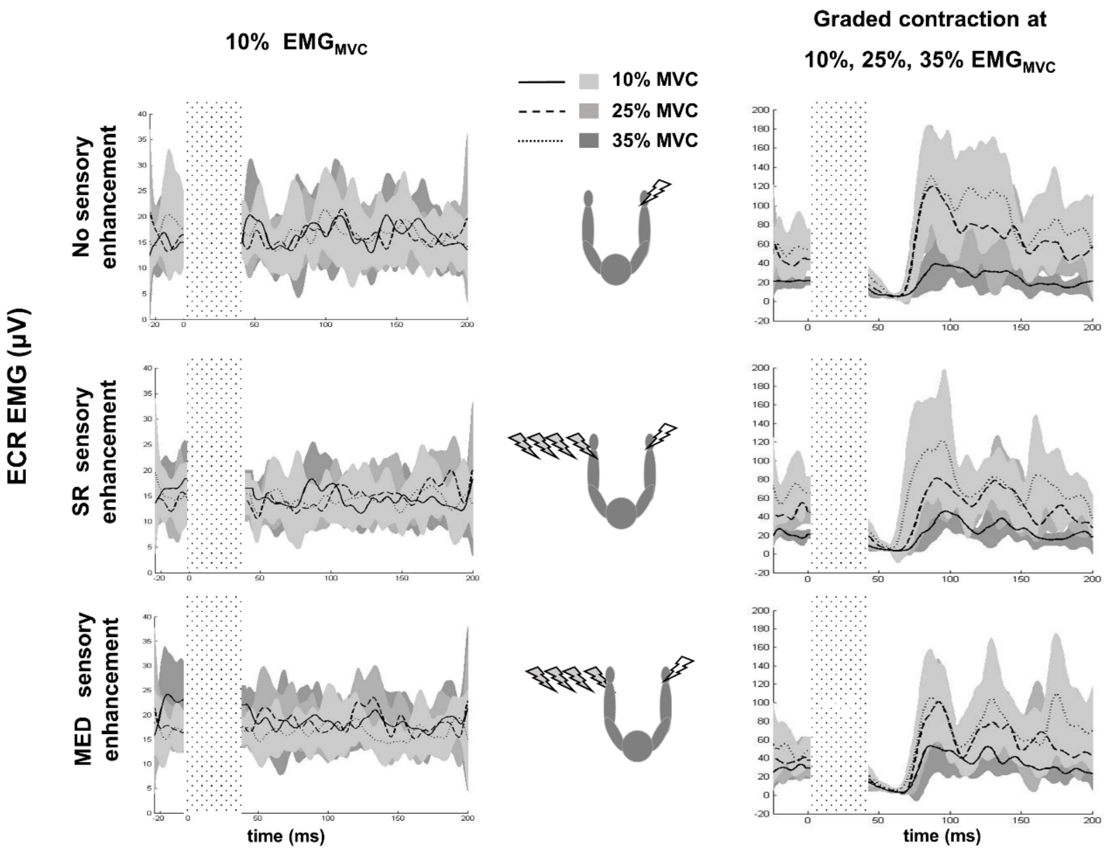


Figure 6. 3: EMG traces of an individual participant at each condition during Task 1 (sensory enhanced arm performed 10% MVC_{EMG} contraction, reflex stimulated arm

performed graded contraction). Solid, dashed and dotted lines are the average across 15 sweeps of cutaneous stimulation when reflex stimulated arm contracted at 10%, 25% and 35% of MVC. Shaded areas represent the standard deviations of 15 sweeps at each contraction level. Stimulation artifacts were removed.

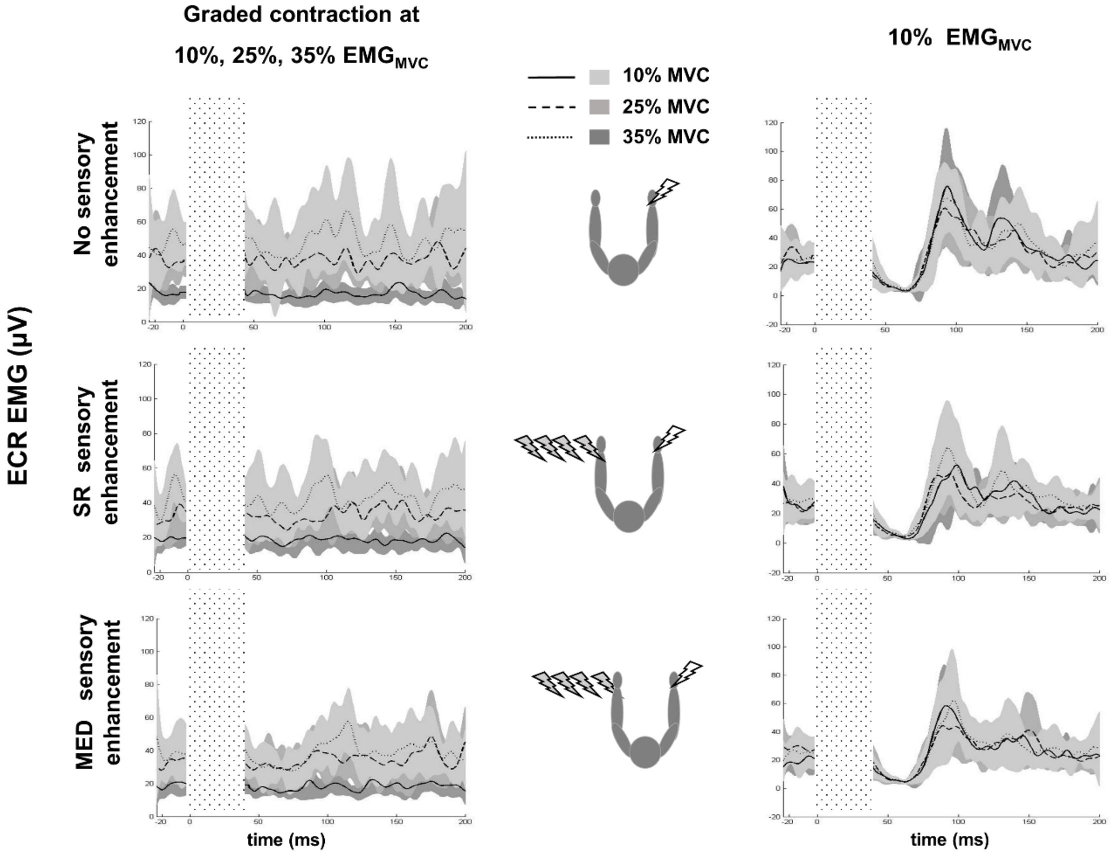


Figure 6. 4: EMG traces of an individual participant at each condition during Task 2 (sensory enhanced arm performed graded contraction, reflex stimulated arm performed 10% MVC contraction). Solid, dashed and dotted lines are the average across 15 sweeps of cutaneous stimulation when sensory enhancement arm contracted at 10%, 25% and 35% of MVC. Shaded areas represent the standard deviations of 15 sweeps at each contraction level. Stimulation artifacts were removed.

6.3.6 Statistics

Statistical analysis was performed using SPSS software (IBM SPSS Statistic 20, Chicago, IL, USA). To test the effects of condition (sensory enhancement) and background

EMG (level of muscle contraction), two-way repeated measure ANOVA (rmANOVA) were performed for early latency and net reflex data. If there was a significant effect of condition, pairwise comparisons were used to determine which condition significantly differed from the no enhancement condition.

To assess linear correlation between reflex amplitudes and background EMG in each condition, linear regression analyses were performed and Pearson r values calculated for each pool of paired data (df = n-1). When significant linear relations were identified, the slope and y-intercepts were compared between sensory conditions (control, SR sensory, MED sensory), with critical t distribution values (df = n1+ n2 - 4) used to establish significance (Dragert & Zehr, 2013). Statistical significance was set at $p \leq 0.05$.

6.4 Results

6.4.1 Task 1: Reflex-stimulated arm performing graded contraction: larger net reflex in the sensory-enhanced arm.

Sensory enhancement from the contralateral arm did not affect the reflex amplitudes in the reflex-stimulated arm. No significant effects of condition was observed for early latency ($F_{(2,24)} = 0.417$, p=0.664) and net reflexes ($F_{(2,24)} = 0.379$, p=0.689). However, significant effects of background EMG were found in early latency ($F_{(2,24)} = 80.695$, p=0.000) and net reflexes ($F_{(2,24)} = 30.597$, p=0.000) (Figure 6.5B, 6.5D). The amplitude of inhibition was significantly correlated with background EMG for both early latency and net reflexes (see Table 6.1). Pairwise comparisons and effect size between levels of muscle activity are presented in Table 6.2. No interaction effect was observed for both early latency ($F_{(4, 48)} = 1.019$, p=0.407) and net reflexes ($F_{(4,48)} = 1.11$, p=0.363) in the reflex stimulated arm.

In the sensory-enhanced arm, greater inhibitory net reflex were observed in the conditions with sensory enhancement ($F_{(2,24)} = 8.928$, p=0.001, Figure 6.5A). Pairwise comparisons indicated significant differences between control and the conditions with enhanced sensory input from SR nerve (p=0.000) and MED nerve (p=0.006) stimulation with reflex amplitudes decreased by 810.4% and 766.3% respectively. Graded muscle contraction in the reflex-stimulated arm did not affect interlimb cutaneous reflex amplitudes in the sensory-enhanced arm (early latency reflex: $F_{(2,24)} = 0.266$, p=0.769; net reflex: $F_{(2,24)} = 1.619$, p=0.219). Interaction effects were observed for early latency ($F_{(4,48)} = 2.658$, p=0.044) and net reflexes ($F_{(4,48)} = 3.341$, p=0.017).

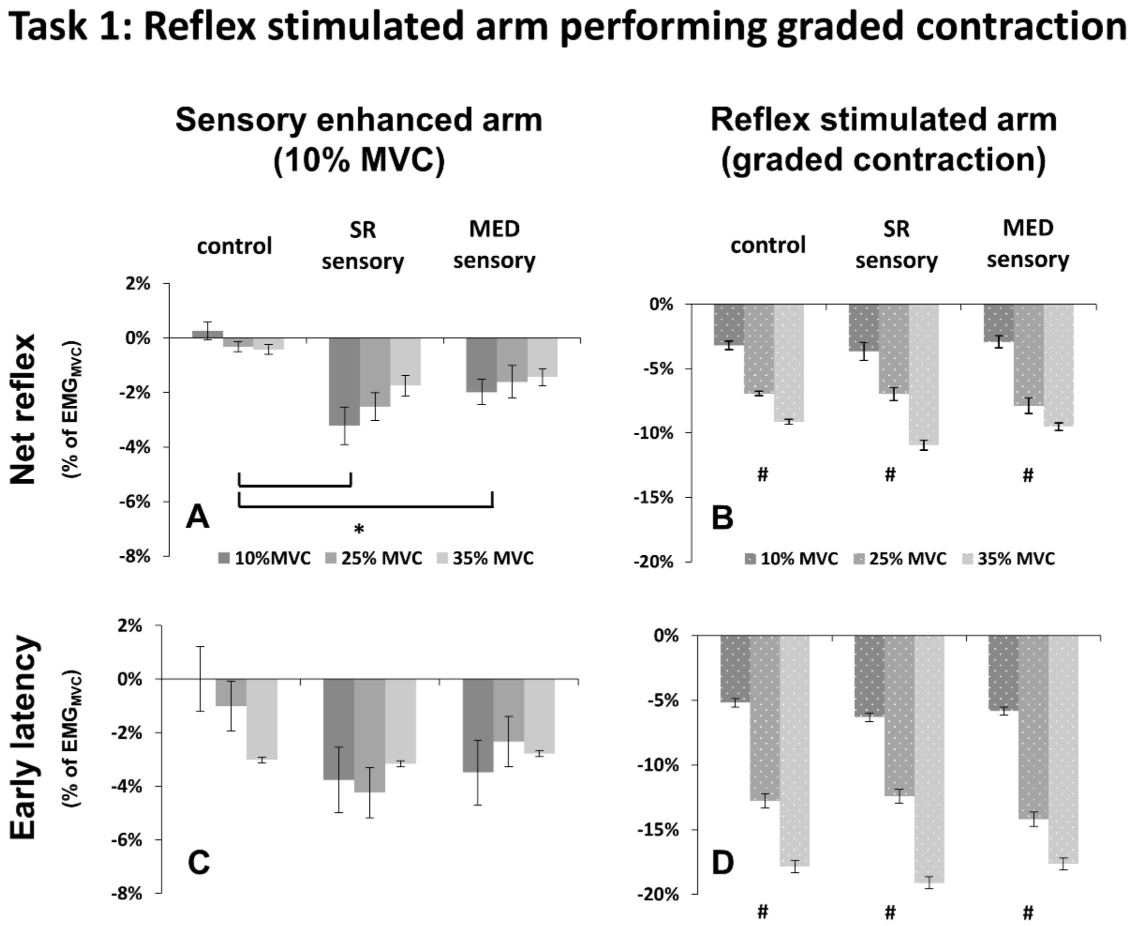


Figure 6. 5 Significant effects of sensory enhancement and background muscle activity on early latency and net reflex amplitudes with the reflex stimulated arm performing graded contraction (Task 1). A and C (solid bar graphs): Results from the sensory-enhanced arm. B and D (patterned bar graphs): Results from the reflex stimulated arm. For all panels, the y-axis represents normalized reflex amplitudes, and the x-axis represents different conditions. Different shades in each bar graph represent the level of muscle contraction performed in the reflex stimulated arm. * represents significant effects of condition at p<0.05. # represents significant effects of background muscle activity at p<0.05.

Table 6. 1 Resulting of Pearson-r values from linear correlation analysis between reflex amplitudes and background muscle activity.

		Sensory-enhanced arm			**Reflex-stimulated arm**		
		Control	**SR**	**MED**	**Control**	**SR**	**MED**
Task 1	Net reflex	r=0.298	r=0.118	r=0.000	**r=0.643***	**r=0.720***	**r=0.707***
	Early latency	r=0.122	r=0.000	r=0.031	**r=0.879***	**r=0.876***	**r=0.877***
Task 2	Net reflex	r=0.315	r=0.137	r=0.443	r=0.045	r=0.167	r=0.063
	Early latency	r=0.219	r=0.434	r=0.453	r=0.077	r=0.167	r=0.316

n=13, degree of freedom =11, * indicates significant linear correlation at p<0.05.

Table 6. 2 Results of pairwise comparisons and effect size calculation (Cohen's D) between levels of background muscle activity for the reflex-stimulated arm during task 1.

Task 1 Reflex-stimulated arm				
		10% VS 25% MVC	**25% VS 35% MVC**	**10% VS 35% MVC**
Net reflex	p-value	**0.000***	**0.001***	**0.000***
	Cohen'D	1.065	0.489	1.486
Early latency	p-value	**0.000***	**0.000***	**0.000***
	Cohen'D	1.802	0.823	2.426

Task 2 Sensory-enhanced arm				
		10% VS 25% MVC	**25% VS 35% MVC**	**10% VS 35% MVC**
Net reflex	p-value	0.121	**0.002***	0.063

	Cohen’D	0.345	0.325	0.708
Early latency	p-value	0.075	0.164	**0.016***
	Cohen’D	0.308	0.284	0.597

Table 6. 3 Results of pairwise comparisons and effect size calculation (Cohen’s D) between levels of background muscle activity for the sensory-enhanced arm during task 2.

6.4.2 Task 2: Sensory-enhanced arm performing graded contraction: reflex amplitudes altered with motor drive and sensory enhancement.

In the sensory-enhanced arm, significant effects of condition were also seen in early latency ($F_{(2,24)}$ = 4.232, p=0.027) and net reflex amplitudes ($F_{(2,24)}$ = 5.523, p=0.011). Pair-wise comparisons showed greater inhibitory early latency and net reflex amplitudes following sensory enhancement from SR (early latency reflexes: p=0.035, net reflexes: p=0.005; reflex amplitudes decreased 362.8% and 1154.1% on average, respectively) or MED nerve (early latency reflexes: p=0.01, net reflexes: p=0.015; reflex amplitudes decreased 425.9% and 1157.4% on average, respectively). Early latency ($F_{(2,24)}$ = 4.645, p=0.02) and net reflex ($F_{(2,24)}$ = 7.14, p=0.004) amplitudes were also modulated by background EMG but no significant linear correlation was observed (Figure 6A, 6C; Table 6.1). Pairwise comparisons and effect size between levels of muscle activity were presented in Table 6.3. No interaction effect was observed for both early latency ($F_{(4,48)}$ = 0.647, p=0.632) and net reflexes ($F_{(4,48)}$ = 0.638, p=0.638) in the sensory enhanced arm.

Sensory enhancement and graded background EMG did not affect early latency ($F_{(2,24)}$ = 1.933, p=1.167; $F_{(2,24)}$ = 2.629, p=0.093) and net reflex amplitudes ($F_{(2,24)}$ = 2.244, p=1.128; $F_{(2,24)}$ = 2.403, p=0.112) in the reflex-stimulated (contralateral side) arm (Figure 6B, 6D).

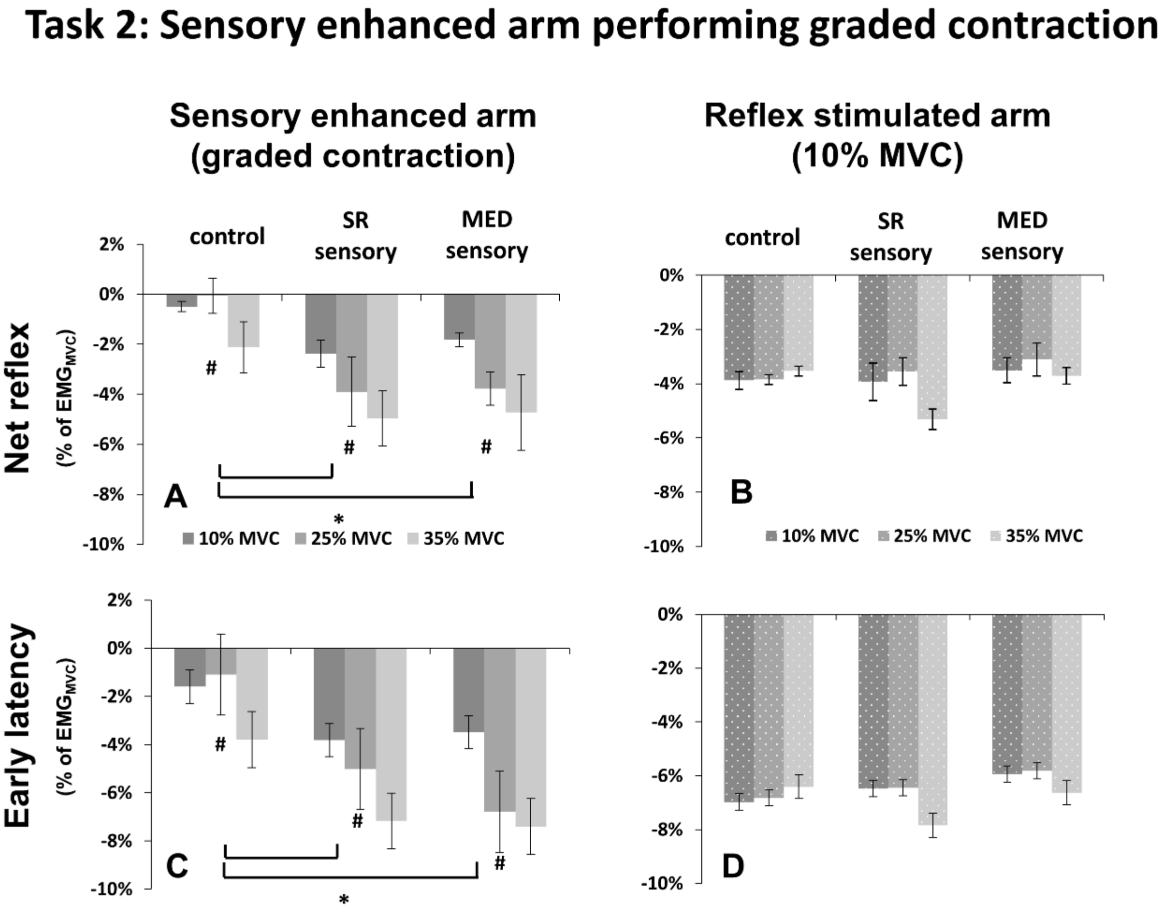


Figure 6. 6 Effects of sensory enhancement and background muscle activity on early latency and net reflex amplitudes with the sensory enhanced arm performing graded contraction (Task 2). A and C (solid bar graphs): Results from the sensory-enhanced arm. B and D (patterned bar graphs): Result from the reflex-stimulated arm. For all the panels, the y-axis represents normalized reflex amplitudes, x-axis represent different conditions. Different shades in each bar graph represent the level of muscle contraction performed in the sensory-enhanced arm. * represents significant effects of condition at $p<0.05$. # represents significant effects of background muscle activity at $p<0.05$.

6.5 Discussion

This study investigated the effects of enhanced sensory input and descending motor drive on excitability of interlimb cutaneous reflex pathways. The results show that sensory enhancement amplified interlimb interneuronal excitability and these effects are regulated independently from the descending voluntary motor drive to the contralateral arm. These results suggest sensory enhancement promotes the overall excitability of interlimb pathways which could be applied as a useful background effect to help alter motor neuron excitability to facilitate therapeutic motor function training.

6.5.1 Effects of sensory enhancement on interlimb cutaneous reflexes

In the current study, stronger inhibitory net reflexes were observed in the sensory-enhanced arm but not in the contralateral, reflex-stimulated arm. These results suggest sensory enhancement has strong local effects to increase interneuronal excitability mediating cutaneous pathways in the ipsilateral but not the contralateral arm. Compared to the strength of interlimb neural connection between the legs, "less" neural coupling has been observed between the arms during rhythmic tasks (Carroll et al. 2005; Collins et al., 1993; Hundza & Zehr, 2006; McIllroy et al., 1992; Vasudevan & Zehr, 2011). During arm cycling, phase-dependent modulation of cutaneous reflexes in the cycling arms is highly conserved and unaffected by the movement pattern (in phase or out of phase) (Carroll et al., 2005), movement amplitude (crank length) (Hundza & Zehr, 2006) and cycling frequency (Vasudevan & Zehr, 2011) in the contralateral arm. Here, reflex amplitudes in the reflex-stimulated arm were not influenced by the sensory enhancement from the contralateral arm. Our results show that, during a static task, cutaneous pathways are also modulated independently between the arms.

Amplified inhibitory interlimb reflexes were observed following sensory enhancement from either median or superficial radial nerve stimulation (Figure 6.5A; Figure 6.6A). There are many similarities between interlimb somatosensory networks for muscles of the arms and legs which are expressed during rhythmic tasks (Zehr et al 2016). In the leg, cutaneous stimulation applied to different areas of the skin can evoke nerve-specific responses with functional significance in perturbation responses (Klarner et al., 2017; Zehr et al., 1997; Zehr et al., 2014). Median nerve and superficial radial nerve stimulation generate sensation on the opposing palmar and dorsal surfaces of the hand respectively, nerve-specific cutaneous reflexes were seen in the arm muscles during arm cycling (Zehr & Kido, 2001) and wrist extension contractions (Sun & Zehr, 2018). Altered H-reflex amplitudes were also found in the flexor carpi radialis muscle when sensory conditioning was applied to the opposite surfaces of the hand (Cavallari et al., 1985). Here, sensory enhancement from median and superficial radial nerves similarly affected the excitability in the cutaneous pathways. Absence of nerve-specific cutaneous reflexes may due to the task requirement. It has been observed during standing that, regardless of which nerve was stimulated, leg muscles all showed similar (suppressive) net reflexes (Komiyama et al., 2000). Komiyama et al. suggested that, since the maintenance of posture is of primary importance during standing, a global suppressive response in the leg muscle might act like a non-specific “shock absorber” to minimize perturbations to the center of mass. Such task-dependent reflex modulation was not only observed between rhythmic and discrete tasks but also emerged during different discrete tasks (Evans et al., 1989; Gibbs et al., 1995; Nakajima et al., 2006). Reduced facilitatory reflexes were observed in the hand muscles during holding an object compared to isolated finger movement (Evans et al., 1989) as well as in the leg muscles when maintaining a standing posture compared to voluntarily contracting each target muscle (Gibbs et al., 1995). Nakajima and colleagues (2006) suggest cutaneous reflex modulation is highly sensitive to the behavior context. Reflex amplitudes may be affected by the task requirements, such as isolated muscle contraction or stabilizing a postural orientation.

In the current study, participants were required to maintain the level of muscle contraction in both arms. Differential muscle responses between unimanual and bimanual grasping task responses were shown after mechanical perturbation (Ohki et al., 2002; Ohki et al., 1999). Some studies also demonstrate that when two arms are dynamically coupled, such as when holding a tray (Dimitriou et al., 2012) or opening a bottle (Dietz et al., 2015), perturbation evoked stronger reflexes in contralateral arm compared to when two arms performing independent static tasks. Stronger interlimb reflexes indicate shared cutaneous input during cooperative bimanual tasks (Dietz 2015). Although in the current study static muscle contractions were performed independently in each arm, reinforced interlimb cutaneous reflexes suggest that spinal interlimb neural connection can be amplified through sensory enhancement even in independent bimanual tasks.

6.5.2 Effects of muscle contraction level on the interlimb cutaneous reflexes

Cutaneous reflex amplitudes in the ECR muscles increased with background EMG when performing graded contraction. Many years ago, Marsden and his colleagues defined this phenomenon as "automatic gain compensation" where reflex amplitudes increase in proportion to the background muscle activity (Marsden et al., 1976, 1972). Since graded background muscle activity serves as a proxy of descending motor drive, "automatic gain compensation" ensures the muscle response is scaled to the motor neuron activation required during the task (Bedingham & Tatton, 1984; Marsden et al., 1976, 1972; Matthews, 1986). Such background EMG dependency of cutaneous reflexes was also found in the upper limb during static contraction (Sun & Zehr, 2018). Our findings confirm the modulatory role of muscle activation in cutaneous reflexes. In addition, such modulation is only significant in the ipsilateral arm, increasing muscle activation in one arm does not affect cutaneous reflex amplitudes on the contralateral side.

To our knowledge, the effects of muscle activation on the contralateral cutaneous reflexes during static contraction have not been recorded. However, voluntary muscle contraction altering neural excitability has been observed in both corticospinal and spinal pathways on the contralateral side. Delwaide and colleagues showed that voluntary movement in the contralateral arm reinforced reciprocal inhibition from wrist extensor to flexor with unchanged wrist flexor H-reflex amplitudes (Delwaide et al., 1988). After stimulating cutaneous and mixed nerves separately, Delwaide et al. proposed that interlimb modulation in reciprocal inhibition is mainly mediated by the interneurons activated by the Ia fibers on the contralateral side (Delwaide & Pepin, 1991). Hamilton et al. (2018) found stimulation-induced bicep brachii muscle contraction increased motor neuron activity of the contralateral biceps brachii during isometric contraction. However, such enhancement was not observed when electrical stimulation was applied simultaneously with voluntary contraction in the stimulated arm. These results are consistent with the findings from Hortobagyi et al. (2003) where evoked contractions in wrist flexor muscle increased spinal excitability. There were larger H-reflex amplitudes on the contralateral arm but voluntary muscle contraction or voluntary contraction combined with stimulation-evoked contraction reduced H-reflex amplitudes on the contralateral side. Hortobagyi et al. suggested that descending input during voluntary movement may be associated with strong presynaptic inhibition from Ia afferents observed on the contralateral side (2003). These previous studies all indicate that descending input from voluntary contraction may not directly facilitate the motor neuron excitability on the contralateral side. Here, graded muscle contraction did not affect cutaneous reflex amplitudes on the contralateral side (Figure 6.5A, 6.5C, Figure 6.6B, 6.6D) suggesting interlimb cutaneous pathways are also modulated independently from the descending input. However, concurrent voluntary contraction and sensory enhancement can facilitate interlimb modulation from cutaneous stimulation.

6.6 Conclusion

Sensory enhancement applied during muscle contraction amplifies interneuronal excitability in interlimb cutaneous pathways during a static task. This reinforcement is modulated independently from motor neuron excitabilities on the contralateral side. We suggest that sensory enhancement may be applied in rehabilitation training after spinal cord injury and stroke. For example, we have used strength cross-education training in both arms (Sun et al., 2018) and legs (Dragert & Zehr, 2013) in chronic stroke to reveal strong interlimb effects and large strength and functional gains (Farthing & Zehr, 2014; Sun & Zehr, 2019). Combining such training approaches with background changes in interneuronal excitability (e.g. to enhance activity in weak and suppress activity in hyperactive muscles) using sensory enhancement could augment strength recovery after stroke and other neurological conditions(Sun & Zehr, 2019) .

6.7 References

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Chapter 7: General conclusions

Coordinated movements are regulated by a tripartite system consisting of the brain, spinal cord and sensory feedback (Zehr, 2005; Zehr & Duysens, 2004). Following stroke, cortical neurons and networks around the lesion site are affected, making the interaction between the spinal neural networks and sensory feedback become more important in movement control and functional recovery. This thesis focused on the application of cross-education training in stroke participants and the role of somatosensory input in regulating upper limb neural excitability and refine cross-education strength training. Three objectives were addressed:

1) The first objective was to explore the clinical application of interlimb neural connections in strength training after stroke. Chapter 2 investigated cross-education effects following wrist extension training in the less affected arm of stroke participants. Based on the findings from Chapter 2 and previous interventional studies with people after stroke, Chapter 3 proposed a novel hypothesis suggesting interlimb neural networks are more responsive to training stimuli after stroke. Amplified strength gain and neural plasticity can be induced by activating the morphologically intact interlimb spinal pathways. The rest of the thesis further studied the application of sensory feedback in future use for enhancing the cross-education effects.

2) The second objective was to investigate the modulation of cutaneous reflexes in the arm muscles during static contraction. Chapter 4 studied the effects of wrist joint position on spinally-mediated reflexes in wrist extensor during isometric contraction. Chapter 5 focused on the effects of stimulation modes on the excitability of cutaneous pathways. Cutaneous reflexes in the wrist extensor muscles were measured following stimulation with different trigger methods and stimulation parameters.

3) The third objective was to investigate the effects of sensory enhancement on interlimb cutaneous pathways. In Chapter 6, sensory enhancement and cutaneous stimulation were applied to the opposite arms and interlimb cutaneous reflexes were measured.

This thesis provides knowledge about the role of sensory feedback in regulating spinal excitability. It also shows the potential of using spinally-mediated interlimb neural networks and sensory enhancement in post-stroke rehabilitation. The following section is a summary of the main findings from each chapter. Directions for future studies are also proposed.

7.1 Objective 1: Explore the application of cross-education strength training in the arm muscles after stroke

The effects of unilateral strength training on bilateral strength gains were observed in chronic stroke participants in Chapter 2. Twenty-four participants completed 5 weeks of wrist extension training on the less affected arm. Significant strength gains were observed in both arms with altered neural plasticity at both corticospinal and spinal levels. Consistent with the findings from Dragert and Zehr (2013), larger percentages of strength gain were observed in chronic stroke participants compared to neurologically intact participants (Green & Gabriel, 2018). Together with other studies (Dragert & Zehr, 2013; Kaupp et al., 2018; Klarner et al., 2016a, 2016b), chronic stroke participants show amplified training-induced neural plasticity. To further discuss this phenomenon, a review paper was completed in Chapter 3. It summarized current findings from cross-education strength training and arm and leg cycling interventions. A novel hypothesis was proposed that neural plasticity is amplified after stroke. By activating morphologically intact spinal pathways preserved from our quadrupedal ancestry, amplified strength gains and neural plasticity can be induced in those with chronic stroke.

Besides bilateral strength gains, Chapter 2 also showed that the slope of linear correlation between cutaneous reflex amplitudes and background muscle activity were changed in the untrained arm, which indicates normalized reflex function in cutaneous pathways. Due to the mechanical action of the straps, participants received sensory feedback from the back of the hand during isometric contraction. Therefore, it is likely that sensory input during voluntary contraction and altered cutaneous pathway excitability play roles in mediating strength cross-education.

For people with stroke, amplified strength cross-education in the untrained limb could optimize training timeline and facilitate targeted training on the more affected side. Many studies showed sensory stimulation can facilitate rehabilitation training outcomes

(Conforto et al., 2007; Jung et al., 2017; Koesler et al., 2009). It is possible that strength cross-education may be amplified by enhancing sensory input during training. However, the interaction between spinally-mediated reflex pathways and sensory input during discrete tasks are less studied in the arms. To better understand how sensory feedback affects spinal excitability and how cross-education strength training can be refined in future studies, the following two objectives were achieved.

7.2 Objective 2: Investigate the modulation of cutaneous reflexes in the arm muscles during static contraction

Chapter 2 suggest cutaneous pathways may mediate strength cross-education following unilateral wrist extension training. Previous studies show differential modulation in spinally-mediated reflexes between discrete and rhythmic tasks. To expand our knowledge about cutaneous reflex modulation in the arm muscles during static contraction, cutaneous reflexes were measured in the wrist extensor muscles at different wrist joint positions (Chapter 4), with different trigger methods (Chapter 5) and stimulation parameters (Chapter 5).

Nerve-specific reflexes were found in both Chapter 4 and 5. Joint position and trigger method have significant effects on reflex amplitudes when stimulation is applied to the task-relevant nerve. Chapter 4 investigated the effects of wrist position on cutaneous reflex and reciprocal inhibition amplitudes in wrist extensors during isometric wrist extension. Stimulation was applied to the superficial radial and median nerve at two wrist positions, pronated and neutral, respectively. Stronger inhibitory reflexes evoked at wrist pronated position when stimulation was applied to superficial radial never. Similarly, in Chapter 5, “self-triggered” effects were observed when reflex stimulation was applied to the superficial radial nerve but not the median nerve.

During rhythmic tasks, sensory stimulation applied at different skin areas on the foot induce nerve-specific muscle responses which are critical in maintaining balance and avoiding perturbation. This nerve-specificity suggests our nervous system can cope with various perturbations from the external environment (Klarner et al., 2017; Zehr et al., 2014; Zehr & Stein, 1999). Few studies have investigated the cutaneous reflexes modulation during discrete tasks in the upper limb, but existing evidence shows larger reflex amplitudes when stimulation was applied to the homotopic digit that was performing the task (Nakajima et al., 2006). Here, superficial radial nerve produced sensory feedback on the back of the hand, which directly relates to the sensory feedback produced during isometric wrist extension. Chapter 4 and 5 suggest that during discrete movement, joint position and sensory prediction play significant roles in modulating the excitability in task-relevant cutaneous pathways.

In Chapter 4, stronger inhibitory reflexes were evoked when stimulation was applied at wrist pronated position compared to the neutral position. This suggests stronger interneuronal excitability in the superficial radial pathways at the wrist pronation position. One possible source of this change is altered load-related feedback. Some studies showed that walking with partial or whole body weight support can alter cutaneous reflex modulation in the lower leg muscles (Bastiaanse et al., 2000; Nakajima et al., 2008). However, there is no study comparing the cutaneous reflexes in arm muscles during static contraction with different loading conditions. Further studies are needed to identify the source that causes differential neural excitability at different joint positions. It is worth noting that, in Chapter 2, cross-education effects only occurred at wrist pronated position (trained position) and superficial radial nerve cutaneous reflexes were normalized in the untrained arm after training. Results from Chapter 4 provide more evidence supporting the role of cutaneous pathways in strength cross-education.

Chapter 5 compared cutaneous reflexes in wrist extensor muscles following different trigger methods and stimulation parameters. Consistent with the findings from Baken et al. (2006), reduced facilitatory reflexes were observed at middle latency when stimulation was triggered by participants' muscle activity or by participant pressing a button. Significantly stronger inhibitory reflexes were also found in early latency and net reflexes when stimulation was triggered by wrist extensor muscle activity. Since wrist contraction may provide a "sensory cue" before the stimulation is delivered, these results suggest task-relevant sensory feedback applied at the early onset of muscle contraction can amplify the overall inhibitory effects in cutaneous pathways. It has been shown in previous studies that paired electrical stimulation with voluntary contraction enhanced corticospinal excitability with increased motor evoked potentials of the target muscle

(Khaslavskaia & Sinkjaer, 2005; Taylor et al., 2012). Here, altered early latency cutaneous reflexes suggest that concurred task-relevant sensory feedback and voluntary contraction increased spinally-mediated cutaneous pathway excitability as well.

In Chapter 5, “self-triggered” effects were absent following prolonged stimulation on the superficial radial nerve, which suggests that reflex stimulation and prolonged stimulation affect the interneuronal excitability of cutaneous pathways differentially. The effects of stimulation parameters on neural excitability are not clear in the current literature (Chipchase et al., 2011). Here, sensory feedback generated from reflex stimulation approximates perturbation while prolonged stimulation provides sensory enhancement. Similar to the bi-stable behavior found in motor neurons, where long-lasting motor neuron depolarization was triggered by a train of impulses (Crone et al., 1988; Hounsgaard et al., 1984), it is possible that prolonged stimulation induced longer lasting excitability in the interneurons that mediate the superficial radial cutaneous pathways. Therefore the cutaneous pathways becomes less responsive to the corticospinal influence induced by self-triggered stimulation.

7.3 Objective 3: Investigate the effects of sensory enhancement on interlimb cutaneous reflexes.

Results from Chapter 4 and 5 suggest cutaneous reflexes can be affected by joint position, trigger methods and stimulation parameters when stimulation was applied to the task-relevant nerve. To further explore the interlimb effects of sensory feedback on spinal excitability, Chapter 6 measured cutaneous reflexes following sensory enhancement and reflex stimulation applied on the opposite arms during wrist extensor contraction on both sides. Stronger inhibitory interlimb reflexes were found in the arm that received the sensory enhancement and this effect is not nerve-specific. Sensory enhancement applied to the superficial radial and median nerve both amplified overall interneuronal excitability in interlimb cutaneous pathways. Stimulation applied on these two nerves evoked differential responses under different joint positions (Chapter 4), trigger methods and parameters (Chapter 5). Here, the absence of nerve-specificity is likely due to different task requirements. In the previous chapters, wrist extension was performed in the tested arm only, while in Chapter 6, both arm contacted at the same time and maintaining a stable contraction in both arms became the goal of the task. The absence of nerve-specific cutaneous reflexes was also observed in leg muscles during standing (Komiyama et al., 2000). Komiyama et al. suggested that, since the maintenance of posture is of primary importance during standing, a global suppressive response in the leg muscle might act like a non-specific "shock absorber" to minimize perturbations to the center of mass. Here, stronger inhibitory cutaneous reflexes following both types of sensory enhancement may minimize the external influences as detected by exterorecepters.

Chapter 6 also found the effects of sensory enhancement are somewhat insensitive to descending motor drive. Graded contraction in either sensory enhanced arm or reflex stimulated arm did not affect cutaneous reflexes on the contralateral side. This finding is consistent with other studies showing voluntary contraction does not directly facilitate the spinal excitability on the contralateral side (Hamilton et al., 2018; Hortobagyi et al., 2003). It confirms that interlimb cutaneous pathways can modulate independently from the descending input. However, concurrent voluntary contraction and sensory enhancement can facilitate interlimb modulation from cutaneous stimulation.

7.4 Limitations of the studies

There are several limitations in this thesis. In Chapter 2, spinal and corticospinal plasticity were measured in 12 different participants recruited at UVIC and UBC respectively. In addition, cortical silent period, short-interval intracortical inhibition and intracortical facilitation could not be elicited in the ipsilesional hemisphere (more affected side) for a majority of the 12 participants recruited at UBC. More information about training-induced neural plasticity in the corticospinal pathways may be revealed with all neurophysiological tests performed in all the participants. Another limitation from Chapter 2 is that the progress of strength change in the more affected arm was not measured. The time course of interlimb strength transfer has been studied in neurologically intact participants (Barss et al., 2018). Measuring this time course in chronic stroke participants will be important to understand the potential cause of low strength gain in the non-responders and to optimize training timeline for future studies.

7.5 Future directions

In this thesis, cross-education training-induced strength gains and neural plasticity suggest that interlimb neural networks are preserved in chronic stroke participants. To fully exploit these interlimb neural connections in rehabilitation training, the regulatory role of sensory feedback in intra- and interlimb cutaneous reflexes was explored in several studies. Cutaneous stimulation has been commonly used as a probe to access spinal excitability. The findings from this thesis are critical in moving beyond pathway phenomenology toward targeted sensory enhancement and amplified motor output in rehabilitation and training. Future research should focus on validating and optimizing the effects of sensory enhancement in rehabilitation training for clinical populations.

Sensory enhancement in amplifying neural connectivity

My findings show that: 1) sensory enhancement applied during muscle contraction amplifies the overall excitability in interlimb cutaneous pathways; and, 2) strength cross-education is at least partially mediated by cutaneous pathways in chronic stroke participants. In line with the finding from Barss (2016) where unsynchronized sensory stimulation with muscle contraction canceled cross-education effects from unilateral wrist extension training. The next step is to confirm that strength cross-education can be amplified in with timed sensory enhancement. In addition, more studies are needed to explore the optimal sensory enhancement protocol. For example: whether the sensory enhancement should be applied unilaterally or bilaterally; what are the effective and tolerable stimulation parameters for interventional training with stroke participants; and where is the best location to apply sensory enhancement when training different muscles.

Community-based training program

The acute and long-term benefits of high-intensity rehabilitation training have been confirmed in those with chronic stroke (Sun et al., 2015; Ward et al., 2019). However, most of the chronic stroke population are community-based with limited access to clinical rehabilitation facilities. An easily implemented training protocol is important to ensure continuous training for stroke population after discharged from the hospital. In Chapter 2, we used a simple and portable strength training device which allowed participants to perform unilateral wrist extension training at home with minimal assistance. But in Chapter 6, sensory enhancement was delivered through an electrical stimulator and customized computer programs which are commonly used in research settings. How to incorporate a commercially available electrical stimulator in cross-education training with adjustable stimulation parameters and correctly timing requires further study.

7.6 Conclusions:

Overall, this thesis studied the application of cross-education strength training after stroke and the regulatory role of sensory input in spinally-mediated reflex pathways. The results show post-stroke strength gain and neural plasticity can be induced by activating spinal interlimb neural pathways and timed sensory enhancement may amplify the cross-education effects. Future studies should focus on the application of sensory enhancement in clinical population's cross-education training.

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