THE ROLE OF THE ARMS IN THE REHABILITATION OF WALKING AFTER INCOMPLETE SPINAL CORD INJURY

by

RUI ZHOU

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Centre for Neuroscience
University of Alberta

Abstract

The overall goal of this dissertation was to develop a novel rehabilitative intervention to improve walking after incomplete spinal cord injury (iSCI). It is widely known that arm movement modulates leg activity and improves the efficiency of gait. However, gait-specific rehabilitation interventions focused on the lower limbs often neglect the involvement the arms, and primarily focus on gait-specific leg training only such as locomotor training, for restoring walking after injury or disease. To date, the effect of arms in the rehabilitation of walking after neural disorders has not been investigated. As a pilot study, I introduced a non-gait-specific rehabilitation strategy that involves simultaneous arm and leg cycling, assisted by functional electrical stimulation (FES), on improving walking in people with chronic iSCI. Specifically, I compared the training outcomes with those from study participants trained with leg cycling only. I investigated the effect of 1) non-gait-specific training and 2) active arm involvement during training on changes in overground walking capacity. Overall, both cycling training interventions resulted in substantial improvements in walking capacity after chronic iSCI; more importantly, participants trained with combined arm&leg cycling had better improvement in walking speed, distance, spatiotemporal parameters of gait, consistency of joint coordination and regulation of muscle EMG activity, relative to those in participants trained with leg cycling only. This indicated that active involvement of the arms simultaneously with the legs, produces better training improvements in rehabilitation for walking than engaging the legs alone.

I also investigated the changes to the spinal and corticospinal pathways as a function of training. I found that spinal cervico-lumbar connectivity in people with chronic iSCI was impaired, exemplified by the absence of modulation of H-reflexes during rhythmic movements.

Nonetheless, I found that the modulation could be restored, to some extent, through cycling training. I also found that dynamic arm movement strongly facilitated the corticospinal pathway to the legs in participants with intact nervous system, but this facilitation was abolished after iSCI. Although there are improvements in the corticospinal pathway after both modes of cycling training, the improvement was only significant in the participants trained with combined arm and leg cycling. Therefore, actively engaging the arms during training can significantly improve the strength of the corticospinal pathway to the legs.

To the best of my knowledge, this was the first study systematically identified the role of the arms in the rehabilitation of walking after iSCI. The findings collectively suggest that FES-assisted arm and leg cycling could provide larger improvements in overground walking capacity than paradigms focusing on leg training only. This work also provided evidence that supports the translation of rhythmic non-gait-specific training, such as cycling, to improvements in overground walking. The outcomes of this work may be instrumental in the development of future rehabilitation interventions after neural disorders.

Preface

The training and assessments of five SCI participants in the arm and leg cycling training group were part of Laura Alvarado's project for a master degree. I was responsible for designing the experiments and collecting the data for all the other participants. I also performed the data analysis for all participants. The literature review, results and discussion in all chapters are my original work.

This thesis is an original work by Rui Zhou. No part of this thesis has been published except in abstract forms. A version of Chapter 2 has been submitted as Zhou R, Alvarado L, Ogilvie R, Chong SL, Shaw O, Mushahwar VK, "The role of the arms in the rehabilitation of walking after spinal cord injury", to a peer-reviewed journal. A version of Chapter 3 has been submitted as Zhou R, Assh J, Alvarado L, Chong SL, Mushahwar VK, "The effect of cervico-lumbar coupling on spinal reflexes during cycling after incomplete spinal cord injury", to a peer-reviewed journal. A version of Chapter 4 has been submitted as Zhou R, Alvarado L, Kim S, Chong SL, Mushahwar VK, "Modulation of corticospinal input to the Legs by arm and leg cycling in people with incomplete spinal cord injury", to a peer-reviewed journal. My contributions in all three submitted manuscripts included conception and design of research, performing experiments, analyzing data, interpreting results of experiments, preparing figures, drafting manuscripts, and editing and revising manuscripts.

The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Functional electrical stimulation training to restore arm and leg function after spinal cord injury or stroke", No. Pro00001577, Date: July 21, 2009.

To mom, a role model who teaches me vision, wisdom, courage, tenacity and optimism!

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List of Abbreviations

A&L	Arm and leg cycling
ACC	Angular coefficient of correspondence
ACLS	Arm cycling, leg static
ADL	Activities of daily living
AIS	American Spinal Injury Association Impairment Scale
ALC	Both arm and leg cycling
ALS	Both arm and leg static
ASLC	Arm static, leg cycling
BWS	Body weight supported
CNS	Central nervous system
CPG	Central pattern generator
EMG	Electromyogram
FCR	Flexor carpi radialis
FES	Functional electrical stimulation
FF	Fast fatigable
FIM	Functional independence measure
FR	Fatigue resistant
Gastr	Gastrocnemius
Gluts	Gluteus
Hams	Hamstrings
H*half*	50% of the maximal H-reflex
H*int*	X-axis intercept of the fitted regression of the H-reflex curve
H*max*	Maximal H-reflex
H*slope*	Fitted slope of the H-reflex curve
IADL	Instrumental Activities of Daily Living Scale
iSCI	Incomplete spinal cord injury
ISNCSCI	International Standards for Neurological Classifications of Spinal Cord Injury
Leg	Leg cycling

MAS	Modified Ashworth Scales
MCID	Minimal clinically important difference
MEP	Motor evoke potential
MEP	Motor evoked potential
MEP*max*	Maximal MEP amplitude
MID	Minimal important difference
M*int*	X-axis intercept of the fitted regression of the M-reflex curve
MLR	Mesencephalic locomotor region
M*max*	Maximal M-wave
MRF	Medullary reticular formation
MS	Multiple sclerosis
M*slope*	Fitted slope of the M-wave curve
MSO	Maximal stimulator output
MVA	Motor vehicle accident
MVC	Maximal voluntary contraction
MVC*iso*	Isometric maximal voluntary contraction
MVC*task*	Maximal rectified cycling EMG
NI	Neurologically intact
NSCISC	National Spinal Cord Injury Statistical Center
PF	Pattern formation
PLS	Pontomedullary locomotor strip
PSFS	Penn Spasm Frequency Scale
Quads	Quadriceps
RCT	Randomized controlled trial
RG	Rhythm generator
RMS	Root mean square
SCI	Spinal cord injury
SCIM	Spinal Cord Independence Measure
SOL	Soleus
SP	Superficial peroneal
SS	Scapular stabilizers

SW/ST	Swing time/stance time
TMS	Transcranial magnetic stimulation
TMS	Transcranial magnetic stimulation
Tri	Triceps
VL	Vastus lateralis
VO2max	Maximal oxygen consumption
WE	Wrist extensors

Chapter 1. Introduction

1.1 Walking

1.1.1 Control of walking

Walking is a complex task that relies on the integration of multiple inputs. In particular, in quadrupeds, locomotion is generated and regulated by interactions between supraspinal inputs, spinal networks in the cervical and lumbar cord that are connected through propriospinal pathways, as well as sensory feedback from the periphery (Rossignol et al., 2006). Similar interactions have been described for walking in human infants (Yang et al., 1998) and adults (Dietz, 1992). Supraspinal input initiates walking, while the basic alternating locomotor rhythm is produced by spinal circuits, and fine-tuned by sensory feedback (Nielsen, 2003; Yang and Gorassini, 2006).

1.1.2 Central pattern generator (CPG)

Rhythmic locomotion, generated by the spinal circuits without supraspinal and peripheral inputs, was first discovered in animal experiments with spinalization and decerebration in the late 19th century. Sherrington first observed that a rhythmic flexion-extension movement of the limbs could be accomplished by an integrated reflex action in decerebrate and spinalized animals (Sherrington, 1898; 1910). Brown in 1911 demonstrated the ability to produce rhythmic locomotor activity in deafferented and spinalized cats, and provided strong evidence that the oscillatory circuitry resides within the spinal cord (Brown, 1911). A 'half-center' model, which underpins the alternating intralimb flexor-extensor activity, was later proposed by him (Brown, 1914). The 'half-center' model was further supported by more empirical evidence from a series of seminal experiments of mammalian locomotion (Shik and Orlovskii, 1965; Jankowska et al., 1967a; Stein et al., 1995). For example, Jankowska and Lundburg and their colleagues recorded from intracellular spinal motoneurons during L-DOPA induced locomotion in spinalized cats, in the absence of sensory stimulation (Jankowska et al., 1967b; 1967a). They found strong rhythmic and reciprocal activation of the interneurons. Their findings suggested that intrinsic interneuronal populations within the spinal cord produced the alternating activity patterns in flexor and extensor motoneurons (Jankowska et al., 1967a; 1967b). Based on this early evidence, understanding of motoneuronal activity during locomotion was further developed. In 1970s, Griller et al. developed the 'half-centre' idea into an architecture of separate unit burst generators

that controls subsets of motoneurons to produce delicate patterns of oscillatory output at the correct instance (Grillner and Zangger, 1975; McCrea and Rybak, 2008; Grillner, 2011). They renamed the intrinsic factor in the spinal cord as the 'central pattern generator (CPG).' Different conceptual models of the locomotor CPG were proposed, including the ring model (Shik and Orlovsky, 1976) and three-phasic generator (Orlovskiĭ et al., 1999). In a more recent model, Rybak et al. suggested that the mammalian locomotor CPG consists of a half-centre rhythm generator (RF) layer and a pattern formation (PF) layer (Rybak et al., 2006). In this model, the phase of rhythmic oscillation is generated at the RF layer, while the PF layer modulates the excitability of neuronal populations to adapt to changes in tasks.

Rhythmic locomotor-like activity produced by CPGs was found in lamprey, and mammals, including rats, cats, rabbits and dogs (Grillner et al., 1998; Grillner, 2011). However, those invasive experimental preparations were difficult to replicate in humans; therefore, the existence of a locomotor CPG in humans can only be explained using indirect evidence. Involuntary leg stepping-like rhythmic movement was observed in a human with incomplete cervical injury, evoked by extending his hips (Calancie et al., 1994). The observation provided evidence of a rhythmic generator for stepping in humans; however, because the injury was incomplete, both descending inputs and afferents may have contributed for the stepping movement. Dimitrijevic et al. (1998) became the first to successfully demonstrate the presence of a spinal CPG in humans (Dimitrijevic et al., 1998). In their experiments, locomotor-like electromyogram (EMG) activity was induced by epidural stimulation in people with complete motor and sensory loss due to spinal cord injury (SCI). Therefore, the locomotor pattern is likely to have been elicited only within the spinal circuitry due to the loss of supraspinal control. Additional corroborating evidence of involuntary alternating muscle activation patterns in the lower extremity in people with complete SCI were also reported (Calancie et al., 1996; Nadeau et al., 2010).

1.1.3 Descending input

Although the locomotor CPG in the spinal cord produces rhythmic locomotor-like pattern (Forssberg et al., 1980a; 1980b), the initiation of locomotion originates at the brainstem level (Whelan, 1996). Shik et al. first discovered that the mesencephlic locomotor region (MLR) in

cats, the region in the brainstem that contains neurons producing locomotion-like activities (Whelan, 1996), has projection relays to interneurons in the spinal cord (Shik et al., 1966; 1969). Additionally, the pontomedullary locomotor strip (PLS) and medullary reticular formation (MRF) also project to spinal cord (along the dorsolateral funiculus). Because they could elicit locomotion when stimulated, they could also be considered as locomotor regions (Whelan, 1996). These locomotor regions receive inputs from the forebrain and lead to the production of complex motor behaviors. Apart from the initiation of locomotion, descending inputs to the spinal cord circuitry is important to modulate the rhythmic pattern during locomotion, including cycle durations, locomotor speed and phase transitions during the gait cycle (Armstrong, 1988; Yakovenko et al., 2005). Also, a lesion to the corticospinal tract in cats could lead to foot drop during walking (Drew et al., 2002), indicating the crucial influence of descending input during locomotion. Furthermore, damage to the subcortical area, such as the cerebellum, could also result in over-shooting of the toe trajectory in rats during precision motor tasks (Aoki et al., 2013). In humans, there is an even greater role and higher dependency on descending input during walking. For example, one piece of anatomical evidence is that the corticomotoneuronal (single synapse between cortex and motoneurons) projection to the arm and leg muscles is only found in humans and primates that are close to human (Petersen et al., 2003). As a phylogenic development thought to be responsible for greater dexterity and higher volitional control, this shows that humans have a more developed cortical control of movement. Moreover, many experiments have provided evidence that the transmission in the corticospinal pathway is modulated in humans during walking or cycling, using transcranial magnetic stimulation (TMS) (Schubert et al., 1997; Petersen et al., 1998; Capaday et al., 1999; Pyndt and Nielsen, 2003; Carroll et al., 2006). The motor evoke potential (MEP), elicited by TMS, is considered to largely represent the integrity and excitability of the corticospinal tract (Nardone et al., 2014). Petersen (1998) reported that part of the modulation of the MEP in the leg muscle during walking was caused by the change in excitability of direct corticospinal projections to the spinal motoneurons (Petersen et al., 1998). Also, MEPs in the soleus muscle (ankle plantarflexor) evoked by TMS are large in the stance phase of the gait cycle and absent in the swing phase, while the MEPs in the tibialis anterior muscle (ankle dorsiflexor) are enhanced during the swing phase of walking (Capaday et al., 1999). Furthermore, lesions of the supraspinal motor pathway (e.g., pyramidal tract) can lead to more severe and lasting functional deficits in humans than in animals (Nielsen,

2003). The extent of sparing in the corticospinal tract after SCI could determine the formation of plastic sprouting and detour circuits below the injury in primates, which may be correlated with motor recovery, such as in walking and reaching tasks (Rosenzweig et al., 2010; Friedli et al., 2015). Therefore, it is believed that there are more extensive roles for descending input in the control of movement in primates and humans, compared to other animals. To date, there is extensive evidence of supraspinal regulation to the legs during various tasks of locomotion in humans (Schubert et al., 1997; Pyndt and Nielsen, 2003; Carroll et al., 2006).

1.1.4 Sensory feedback

Rhythmic locomotion can still be produced after the loss of sensory afferents, such as after dorsal rhizotomy (Goldberger, 1977; Grillner and Zangger, 1984). But while the CPG in the spinal cord sets the timing of background oscillation for rhythmic alternating muscle activation, sensory feedback may greatly influence this basic pattern by regulating the excitability and locomotor drive to the specific motoneuronal pools required for the task. In spinalized cats, afferents from the hindlimb strongly influence phase transition during walking. For example, group Ib afferents from the ankle extensors during the stance phase of walking inhibit the flexor burst activity (Pearson et al., 1992). Those afferent inputs provide force feedback and lead to a reinforcement of extensor activities while the leg is loaded (Whelan et al., 1995). Furthermore, stance-to-swing phase transition is initiated if the hip is fully extended at the end of the stance phase and consequently initiates limb flexion (Grillner and Rossignol, 1978). Similarly, spindle afferents (group Ia and II) from the lengthened limb flexor muscles can inhibit the generation of extensor activity in order to facilitate the initiation of the swing phase (Hiebert et al., 1996). Based on those observations, a set of 'If-then' rules were developed (Prochazka, 1993; McVea et al., 2005; Prochazka, 2010). Those rules were widely adopted in control systems for walking to determine the occurrence of state transitions, as well as to provide reflexive-like response to perturbations (Prochazka, 1993; McVea et al., 2005; Prochazka, 2010).

In addition to proprioceptive afferent inputs, cutaneous input is also important for modulating locomotion. Cats with cutaneous nerve denervation of the hind feet can still walk normally on a treadmill, with the main deficit only occurring during precision walking (Bouyer and Rossignol, 2003a; 2003b). However, the regained normal treadmill walking was then replaced by a deficit

of paw dragging in the same cats after spinalization. In contrast, those spinalized cats that had intact cutaneous nerves recovered proper foot placement while walking on the treadmill (Belanger et al., 1996). Therefore, cutaneous input appears to be crucial for the recovery of locomotion after damage to the central nervous system (CNS). Furthermore, studies on the modulation of cutaneous reflexes revealed the indispensable role of cutaneous afferents in responding to external stimuli and in fine-tuning the locomotor tasks. This modulation is also phase-dependent. For example, in humans, stimulation of the tibial nerve (innervating the plantar surface of the foot) during walking can facilitate ankle flexion at the stance phase to transit into swing phase, but reversely, it can reinforce the ankle extensor at the late stage of swing in order to quickly place the foot on the ground (Duysens et al., 1992; Zehr et al., 1997). Similarly, if the stimulation was delivered to the superficial peroneal (SP) nerve (innervating the dorsum of the foot), it could suppress the TA activity in early swing (e.g., stumbling corrective response) (Zehr et al., 1997); and if the stimulation was applied to the lateral part of the foot, it could result in an ankle dorsiflexion and eversion (Duysens et al., 1992). Therefore, the site of the cutaneous stimulus and the phase during the gait cycle when it occurs can largely determine the types of reflex responses, all of which are aimed at preventing further contact with the stimulus (Forssberg et al., 1975; Rossignol et al., 2006). Taken together, sensory inputs dynamically modify the basic rhythmic pattern of locomotion, correct the positioning of feet, and respond to obstacles on a step-by-step basis (Rossignol et al., 2006).

1.1.5 Arm and leg neural coupling during locomotion

In both quadrupedal animals and humans, it is suggested that a common neural control is shared across various types of rhythmic locomotion (Zehr, 2005). Specifically, the neural control of rhythmic human movement, such as walking, cycling, crawling and swimming (Wannier et al., 2001; Zehr, 2005; Zehr et al., 2007a), is suggested to be under a common neural control mechanism at the spinal level called ‘common core’ (Zehr, 2005). The ‘common core’ consists of an elementary block of oscillatory neurons that produce rhythmic motor output (e.g., locomotor CPG), and the interneuronal reflex pathway that mediates the general pattern of rhythmic activity for specific motor tasks. Furthermore, the interaction between the segmental locomotor CPGs coordinates the arms and legs during rhythmic movement (Zehr et al., 2009), forming a connection between limb oscillators. Both ascending and descending pathways are

shown to underpin the linkage between the cervical and lumbar networks (Gernandt and Megiran, 1961; Miller et al., 1975; Skinner et al., 1980; Nathan et al., 1996; Dietz, 2002a). Across different locomotor tasks, the frequency within each locomotor task remains consistent, but the coordination between arm and leg movement may vary between tasks, suggesting that the strength of the linkage is influenced by different limb movements (Wannier et al., 2001). It also suggested that the supraspinal and sensory feedback sculpt the activity in the 'common core' oscillator, and regulate the locomotor drive for behavioral needs (Zehr, 2005).

Arm and leg coordination is also reflected in the modulation of the spinal reflexes during rhythmic limb movements (Baldissera et al., 1998; Haridas and Zehr, 2003; Zehr et al., 2007c; Phadke et al., 2010). The stimulation to upper limb nerves can influence muscle activation in the lower limbs during or after rhythmic activity, and vice versa (Kearney and Chan, 1979; 1981; Delwaide and Crenna, 1984; Sarica and Ertekin, 1985; Zehr and Kido, 2001). In early studies of arm-leg spinal coupling, significant SOL H-reflex facilitation when the ipsilateral upper limb was forward (shoulder flexion) or suppression when the ipsilateral upper limb was backwards (shoulder extension) were reported, and the degree of suppression was proportional to the speed of arm swing (Delwaide et al., 1977; Hiraoka, 2001). Rhythmic arm cycling was shown to suppress the H-reflex amplitude in the remote leg muscle (Frigon et al., 2004; Nakajima et al., 2013); similarly, a suppression of the FCR H-reflex during rhythmic leg cycling was also reported in healthy humans (Zehr et al., 2007c). This modulation of reflex amplitude during rhythmic movement of the remote limb pair, namely task-dependent modulation, was attributed to an interaction between the locomotor generator and peripheral inputs (Schneider et al., 2000; Loadman and Zehr, 2007). Specifically, a subcortical or spinal contribution was demonstrated for gating the excitability of reflex pathways, likely through long propriospinal neurons that connect cervical and lumbar CPGs (Jankowska et al., 1974; Dietz et al., 2001).

1.1.6 The role of arms in walking

Humans swing their arms in opposition to the legs while walking and running. Similar to quadrupedal locomotion, synchronized rhythmic movements between the arms (forelimbs) and legs (hindlimbs) is a main characteristic feature that involves inter-segmental coordination within the spinal cord (Skinner and Mulloney, 1998; Hill, 2003), during human gait (Dietz, 2002a;

2011).

Reciprocal arm swinging during walking counter-balances the longitudinal rotational force and trunk torques induced by the lower body (Collins et al., 2001; Li et al., 2001; Collins et al., 2009), reduces torso and head rotation (Pontzer et al., 2009), reduces vertical displacement of the centre of mass and ground reaction moments (Hinrichs, 1990; Umberger, 2008; Collins et al., 2009), optimizes walking stability (Ortega et al., 2008), decreases energetic cost (Ortega et al., 2008; Umberger, 2008; Collins et al., 2009), and plays an important role in the recovery from a perturbation (Bruijn et al., 2010; Misiaszek et al., 2016). Various models were developed to explain the passive dynamic properties of arm swing during walking. For example, Jackson et al. (1978) first used a double pendulum model to predict the movement patterns of arm swing during walking based on shoulder accelerations and muscle torques (Jackson et al., 1978); however, the idea of using pendulum behavior to resemble arm movement during walking was later challenged (Gutnik et al., 2005). Also, passive dynamic walkers, with artificial arms attached to the shoulder with a hinge to mimic free-swinging arms during walking, allowed the investigations of the effect of arm swing on many mechanical effects (Collins et al., 2001; 2009).

However, arm swing during locomotion cannot be only explained as the consequence of passive mechanics. Muscles in the arms and shoulders are actively involved in walking (Ballesteros et al., 1965; Kuhtz-Buschbeck and Jing, 2012; Meyns et al., 2013). In persons with an intact nervous system, arm muscle activity was studied during different gait conditions, including walking with natural arm swing, with arms volitionally held still, with the arms immobilized and attached to the trunk, as well as with arm swing at opposite-to-normal reciprocal phasing (Kuhtz-Buschbeck and Jing, 2012). The activation patterns in the arm muscles during walking were not only observed in active arm swing conditions, but persisted even when the arms were immobilized. Therefore, a central motor mechanism, likely the spinal neuronal networks generating the rhythmic locomotor activity in arm muscles, contributes to active arm swing (Ballesteros et al., 1965; Kuhtz-Buschbeck and Jing, 2012).

Propriospinal pathways couple cervical and lumbar networks for arm-leg coordination during locomotion (Zehr and Duysens, 2004; Falgairolle et al., 2006). If the arm-leg spinal coupling is

impaired after neural disorders, altered neural activity is observed, resulting in a reduced magnitude and increased asymmetry of arm swing (Lewek et al., 2010), or altered arm-leg coordination during walking (Tester et al., 2012). Rhythmic arm movement also shapes the leg activity. For example, fast and active upper limb rhythmic movement can augment the EMG activity in the leg (Kao and Ferris, 2005). Also, locomotor-like reciprocal arm swing can markedly modulate the EMG activity and spinal reflexes of leg muscles (Massaad et al., 2014; Ogawa et al., 2015) . Those results suggest that arm movement can modulate neuromuscular recruitment of leg muscles during stepping. Recent evidence also indicated a direct contribution from the motor cortex to muscles in the arm that control arm swing during walking (Barthelemy and Nielsen, 2010).

The neural and mechanical differences between various arm tasks were compared, including arm cycling and arm swing with and without walking (Klimstra et al., 2009). Neural and mechanical differences between tasks were observed, such as different anatomical anchor positions of arms and elbow kinematics alongside differential muscle activation patterns. But importantly, 95% of the variability of the EMG and kinematic data from all arm tasks could be explained by the first few principal analysis components, suggesting a common motor control across different rhythmic arm movements (Klimstra et al., 2009). Therefore, a basic rhythmic pattern was conserved and shared between arm cycling and swinging, while also influenced by afferent feedback and supraspinal input to adapt to various tasks.

1.2 Spinal cord injury (SCI)

The spinal cord is the lower portion of the CNS with essential functions: innervating muscles for voluntary and reflex movement, as well as receiving sensory information from the skin, joints, and the muscles of trunk and limbs (Kandel et al., 2000). Via synaptic connections to motoneurons, sensory neurons and interneurons in the spinal cord, central and peripheral systems are integrated (Kandel et al., 2000). Injuries to the spinal cord could interrupt those connections and result in permanent deficits in the person's sensory and motor functions as well as autonomic regulation. Depending on where the injury sites are, people with SCI can have paraplegia (injury at the thoracic, or lumbar, or sacral level) or tetraplegia (injury at the cervical level). The injury

can be complete or incomplete, depending on the extent of the loss of ability to connect and modulate the spinal segments and brain through ascending and descending pathways.

1.2.1 Prevalence, incidence and cost

In the 'Spinal cord injury (SCI) facts and figures at a glance' updated by the National Spinal Cord Injury Statistical Center (NSCISC) in 2016, there are approximately 12,500 new SCI cases each year in the US (National Spinal Cord Injury Statistical Center, 2016). Based on most recent statistics, there are 240,000 to 337,000 persons living with SCI in the US (National Spinal Cord Injury Statistical Center, 2016). In Canada, the prevalence of SCI, including traumatic and non-traumatic origins of injury, is 2525 per million population in 2010 (Noonan et al., 2012; World Health Organization and The International Spinal Cord Society, 2014), with approximately 85,556 persons living with SCI. The World Health Organization defines the SCI as a significant public health issue and the personal and social impacts of the injury are considerable (World Health Organization and The International Spinal Cord Society, 2014). Almost half of the injuries occur in people between 16 and 30 years of age (48.9%), while 10.7% of all injuries occur at age 60 or older in the US; therefore, the resulting physical disability and financial burden of care can be overwhelming and devastating (National Spinal Cord Injury Statistical Center, 2014). Depending on the age at injury and the severity of injury, the estimated lifetime costs can range from more than 1million US dollars to almost 5 million dollars per person (Cao et al., 2011; Krueger et al., 2013; National Spinal Cord Injury Statistical Center, 2016). With traumatic SCI in Canada alone, the annual direct and indirect costs are $2.67 billion and are associated with hospitalizations, health care practitioner visits, attendant care, equipment and home modifications, and other cost drivers (Krueger et al., 2013). Costs of SCI are higher when compared to other comparable conditions such as dementia, multiple sclerosis and cerebral palsy (World Health Organization and The International Spinal Cord Society, 2014).

Moreover, due to the impairment in physical mobility and other accompanying secondary compilations after SCI, many persons are facing unemployment. NSCISC reported a 44.5% unemployment rate even 20 years after injury (National Spinal Cord Injury Statistical Center, 2014). Berkowitz (1998) also found that 66% of people with SCI are no longer working or not looking for work with the most common reason being 'physically unable' (Berkowitz, 1998;

Priebe et al., 2007). With the large number out of the labor force and not contributing to the economy, as well as the requirement of lifelong assistance, there is a large financial cost to the society. In addition to all the economic aspects, the SCI is a debilitating disease that significantly impacts the quality of life of the persons and their families (Tate et al., 2002). Therefore, it is of great importance to help increase the independence in activities of daily living and further improve the quality of their life.

1.2.2 Stage of a spinal cord injury

A SCI can be divided in three stages: acute, intermediate and late.
In the acute stage, inflammatory reactions dominate, including edema, hyperemia and hemorrhage (Nesathurai, 2000). The changes occur in the vessels and capillaries, causing disruption in blood flow; therefore, resulting in ischemia at the lesion site. As the ischemia progresses, additional axonal and neuronal necrosis in the surrounding white matter can occur (Becker and McDonald, 2012). The presence of edema and hemorrhage, as well as the variable amount of parenchyma affected by them, has been directly correlated with the prognosis and initial neural deficit (Bondurant et al., 1990; Flanders et al., 1990).

Compression due to swelling of the cord, as well as bone and ligament fragments can also damage the neurons and axons at the lesion site, resulting in a disruption to multiple levels of the neuraxis (Becker and McDonald, 2012). Moreover, the cell membranes become highly permeable, and influxes of ions are disrupted. As a result of that, released glutamate and sudden influx of calcium can evoke further damage, such as producing free radicals that attack other cellular components (Becker and Mcdonald, 2012). Excitatory amino acids increase in the extracellular environment, initiating excitotoxicity which results in secondary loss of intact nerve fibers, neurons and oligodendrocytes in the vicinity, and demyelination and fragmentation (Becker and Mcdonald, 2012). Macrophages start the process of phagocytosis to remove the necrotic debris while forming a central cavity; a few days after, glia cell proliferation peaks, forming form the astrocytic fibers between the necrotic cavity and intact tissue (Popovich et al., 1997; Nesathurai, 2000). Initial ‘spinal shock’ occurs immediately after injury, exhibiting hyporeflexia likely due to the loss of neuromodulators regulating the excitability in the spinal cord (Onifer et al., 2011). After the first 1-3 days post-injury, reflexes begin to return as a

compensatory change, in the form of denervation supersensitivity (increased neuronal firing in response to neurotransmitters, known to occur in denervated neurons in central and peripheral nervous system) associated with upregulation of neurotransmitter receptors (Ko et al., 1999; Ditunno et al., 2004).

The intermediate stage happens a few weeks post injury. By then, the edema has resolved and atrophy of the cord can be observed (Nesathurai, 2000). A few months post-injury, the injury progresses into the late stage, where scar tissue is present and nerve root regeneration occurs in most cases (Nesathurai, 2000). Plasticity following the injury starts to develop, while various growth associated genes, neurotrophic (Fouad and Tse, 2008) and outgrowth-inhibitory factors (Schwab and Caroni, 1988; Becker and McDonald, 2012) are involved. While axonal reconnect or sprout new collaterals, new synapses are established and strengthened, causing alterations in the spared neural circuitries (Fouad and Tse, 2008; Onifer et al., 2011). Hyperreflexia occurs in the intermediate stage and develops into spasticity in the late stage.

Clinical assessment of SCI is typically described by the American Spinal Injury Association Impairment Scale (AIS), which evaluates physical impairment (Kirshblum et al., 2011), as defined by the International Standards for Neurological Classifications of SCI (ISNCSCI). The AIS includes neurological assessments of 10 key myotomes (motor score, grade 0-5) and 28 dermatomes (sensory score, grade 0-2) bilaterally. Based on the lesion level and the AIS motor and sensory scores, the person is considered to have a complete or incomplete SCI, with an AIS grade ranging from A (motor and sensory complete) to E (motor and sensory function are normal).

1.2.3 Relationship of injury level to functional outcomes

The relationship between the injury level and associated functional impairment has been well established (Welch et al., 1986; Consortium for Spinal Cord Medicine and Paralyzed Veterans of America, 1999). Typically, people with C1-C3/C4 level spinal injury need ventilator assistance (Lanig and Peterson, 2000), and are fully dependent in activities of daily living (ADL). For injury levels from C5-T1, motor and sensory functional loss in elbow flexion, wrist extension, elbow extension, finger flexion and abduction (5 out of the 10 myotomes in AIS motor

assessment) is anticipated. Decreasing dependency on assistance in ADL is seen as the injury level moves caudally (Burns et al., 2012). Individuals with injuries below T1 are considered functionally independent in the use of wheelchair, and sitting balance progressively improves with injuries at lower thoracic levels (Burns et al., 2012). Similarly, in the lumbosacral spinal region, the muscles in the lower limb are affected proximal-distally as the injury level occurs caudally. The key muscles at each spinal level between L2 to S1 are hip flexors, knee extensors, ankle dorsiflexors, long toe extensors and ankle plantar flexors (the other 5 myotomes in AIS motor assessment), respectively.

In addition to sensorimotor functional impairment, damage to the autonomic nervous system is present in people with SCI, including cardiac, vasomotor, and bowel and bladder functions (Curt and Ellaway, 2012). For example, individuals with cervical lesions would have complete loss of supraspinal sympathoexcitatory control, while persons with a lesion between T1 and T5 would have partial preservation (West et al., 2012). The impairment of descending sympathetic nervous control leads to cardiac and vasomotor dysfunction, which could result in abnormal cardiovascular responses and hypotension in people with a high level SCI (Claydon et al., 2006; West et al., 2012). During exercise, impaired cardiovascular control could influence cardiac output of the heart and vasodilatation in muscles that are active (Dela et al., 2003). Moreover, because the injury disrupts the spinal pathway to sympathetic preganglionic neurons, as well as parasympathetic ganglia at the sacral level (Curt and Ellaway, 2012), up to 90% of persons with SCI at or above the T6 level could have autonomic dysreflexia (Consortium for Spinal Cord Medicine, 2002; Krassioukov et al., 2009), a life-threatening emergency mainly triggered by noxious stimuli from below the level of injury, which leads to unstable blood pressure (Cragg and Krassioukov, 2012).

The difference in functional loss owing to a wide range of injury levels has naturally led to a variety of interventions for targeted recovery, including those for regaining arm and hand function, autonomic function, and walking restoration (Anderson, 2004).

1.2.4 Current treatment paradigms

Different therapeutic paradigms aimed at treating various aspects of the injury are undertaken, ranging from protecting against secondary damage after SCI (Schwartz and Fehlings, 2001), to augmenting plasticity and regeneration (Baptiste and Fehlings, 2007), and recovery of function (Fouad and Tetzlaff, 2012). These paradigms include neuroprotection, neuroregeneration and neurorehabilitation (Sandrow-Feinberg and Houlé, 2015). Neuroprotection focuses on protecting the spared neural tissue immediately following the injury, to prevent secondary damage and expansion of the injury (Gonzalez et al., 2003; Baptiste and Fehlings, 2007; Kocsis, 2009). The approaches include surgical decompression after acute SCI (Fehlings et al., 2012), immunomodulation to reduce the inflammatory response (Schwartz et al., 1999; Ohtaki et al., 2008), or applying functional blockade to ion channels or molecules to aid in axonal conduction (e.g., block exposed potassium channel to facilitate propagation of action potential in demyelinated axons) (Deforge et al., 2004). These approaches have all provided benefits in protecting the integrity of the injured spinal cord and promoted axonal regeneration. Neuroregeneration, such as cell-mediated repair using stem cells and intraspinal transplants, targets the lesion site to facilitate nerve growth (Sandrow-Feinberg and Houlé, 2015). These interventions involve eliminating inhibitory growth factors (Fournier et al., 2003; Buchli and Schwab, 2005; Fawcett et al., 2012) or introducing neurotrophic factors (Bradbury et al., 1999; Cai et al., 2001; Dietz and Curt, 2012), providing a growth supportive environment for growth and bridging the lesion site (Bunge and Pearse, 2003; Feron et al., 2005). Neurorehabilitation focuses on enhancing neural plasticity, to facilitate functional recovery through repetitive and continuous training interventions over time in people with SCI (Fouad and Tetzlaff, 2012). The mechanisms underlying rehabilitation-induced recovery are composed of a wide range of adaptive changes, including up-regulation of growth factors, regulation of spinal circuitry, axonal sprouting, reorganization in the cortical map and changes in neuronal properties (Fouad and Tetzlaff, 2012). It should be noted that the treatment paradigms could be combined to treat the injury from various aspects and ultimately promote functional recovery (Oudega et al., 2012; Sandrow-Feinberg and Houlé, 2015); however, the following discussion will only focus on neurorehabilitation after SCI.

1.2.5 Impairment of walking after SCI

One of the most common impairments after SCI is abnormal walking function, including alteration in spatiotemporal measures, joint kinematics, and weakness in muscle activation (Pépin et al., 2003b; Awai and Curt, 2014). People with SCI generally spend more time and take smaller steps during walking, due to reduced coordination, leg paresis and impaired balance (Dietz et al., 1995; Van Hedel et al., 2009). Similar to other conditions causing chronic paralysis, such as stroke, peope with SCI also have reduced swing time, prolonged stance time, and dependency on the stronger leg as a compensatory strategy (Balasubramanian et al., 2007).

Kinematic alterations are observed in people with SCI, such as reduced range of motion, decreased consistency in joint range of motion, increased knee flexion and reduced hip extension during stance (van der Salm et al., 2005; Ditunno and Scivoletto, 2009; Pérez-Nombela et al., 2013). Hip kinematics is essential for generating appropriate locomotor patterns in humans (Dietz and Harkema, 2004). Impaired hip flexion during walking, often accompanied with limited knee flexion, could result in stiff-legged gait and impaired foot clearance (Piazza and Delp, 1996; Riley and Kerrigan, 1998). During swing, the knee flexion is often excessively larger than normal values, indicating an impaired range of motion of the knee joint. Furthermore, insufficient ankle dorsiflexion or persistent plantar flexion during the swing phase results in reduced toe elevation, and thus poor foot clearance during gait (van der Salm et al., 2005; Ditunno and Scivoletto, 2009).

In addition to the altered joint angles, muscle EMG activity during walking also deviates from normal values throughout the gait cycle (Forssberg et al., 1980b; Pépin et al., 2003b). Grasso et al. (2004) reported that even when the foot end-point trajectory in SCI participants seemed similar to that of intact participants, their muscle EMG activity differed greatly from normal values (Grasso et al., 2004; Meyns et al., 2014). They suggested that people with lesioned CNS rely on the preservation in the neuromuscular system to develop compensatory strategies for walking. Those strategies, which are not necessarily seen in the intact system, result in altered muscle regulation or intersegmental joint trajectories, although the endpoint trajectory may resemble the normal pattern (Grasso et al., 2004). Locomotor training has been shown to

improve the muscle EMG amplitude and phase patterns in people with SCI (Dobkin et al., 1995; Gorassini et al., 2008).

Spasticity could also be a significant factor affecting motor performance in people with SCI. Joint velocity during ambulation is limited by the degree of spasticity, which is a velocity-dependent phenomenon (Krawetz and Nance, 1996). Although previous studies of oral baclofen treatment did not demonstrate changes in walking in ambulatory participants with spasticity, there was an increased angular velocity and enlarged range of movement in knee flexion and ankle dorsiflexion after treatment (Corston et al., 1981). A recent study involved a combination of Tizanidine and locomotor treadmill training, and demonstrated significant improvements in walking speed and the strength of ankle dorsiflexor muscle (Duffell et al., 2015). Spasticity management could be an important factor to be considered in gait rehabilitation.

Lastly, compared to people with an intact nervous system, the slower walking also accompanies higher rate of oxygen consumption and larger energy expenditure in people with SCI (Waters et al., 1993). The increased energy cost can be even further differentiated amongst SCI people using different types of walking aid (Ulkar et al., 2003). The observations suggest that people with SCI walk slower and less efficiently. Therefore, improving the metabolic response associated with walking could also bring many benefits to people with SCI, such as greater cardiorespiratory capacity and improved body composition (Buchholz et al., 2009).

1.3 Interventions for improving walking after SCI

Restoration of ambulatory function is one of the top priorities for functional recovery in people with SCI (Anderson, 2004; Ditunno et al., 2008). In Barbeau's review in 2003, a model of recovery of walking following SCI was discussed (Barbeau, 2003). To achieve functional recovery of walking, efficient interaction between the locomotor training approaches and functional prerequisites of posture and walking, such as walking speed, walking aids and locomotion demands, is required (Barbeau, 2003). In the following section, I will briefly discuss current rehabilitative training therapies for locomotor functions, as well as suggest new directions for future treatment regimes.

1.3.1 Physical therapy for compensatory walking recovery

The spinal cord used to be considered as hard-wired and incapable of repairing itself after injury (Forssberg and Svartengren, 1983; Behrman et al., 2006). In light of such understanding, a compensatory model is commonly applied in rehabilitation, focusing on training people with SCI to adapt, not remediate, the disability in functional tasks (American Physical Therapy Association, 2002; Behrman et al., 2006). Clinical decisions are made based on the extent of functional loss, and prescribed to patients aiming to find alternative strategies through preserved parts of the body (Harkema et al., 2012a). Therefore, by setting walking as a functional goal after SCI, the compensatory strategy targets the muscle strength for walking function, and therefore can fail to produce a holistic change in gait (Behrman et al., 2006). The typical areas of focus for compensatory training include strengthening voluntary muscle control, learning new motor strategies to complete daily functional tasks, and effectively incorporating assistive devices or braces to compensate for paretic body parts and loss of upright mobility (Behrman et al., 2006; Somers, 2009). However, this could lead to secondary complications such as arm overuse from subsequently bearing body weight on assistive devices (Waters et al., 1993). Also, the support provided to arms during walking could result in more asymmetric leg kinematics and decreased muscle EMG activity (Visintin and Barbeau, 1994). Moreover, a forward-leaning trunk without arm swing could restrict the range of motion at the hips, which reduces the production of ground reaction force and increases metabolic cost (Collins et al., 2009).

Unlike the compensatory training strategy, the emerging ‘recovery model’ focuses on recovery of function (Behrman et al., 2006). For example, in neurorehabilitation, gait training is used to promote proper plasticity in the CNS. With the goal of training the nervous system for a motor task, the training repetitively engages the intrinsic network for stepping movement and facilitates the necessary inputs to the neural circuitry (Harkema et al., 2012a). A shift from compensatory strategy to a ‘recovery model’ has become popular in clinical settings. Some of these ‘recovery model’-based training paradigms are discussed in the next few sections.

1.3.2 Task-specific exercise as a commonly used therapy

Neurorehabilitative training, such as exercise, is a type of non-invasive therapy often prescribed or recommended to persons with SCI. Benefits from repetitive physical exercise have been shown in increasing muscle hypertrophy, restoring motor and sensory function, up-regulating the plasticity-related neurotrophic factors (e.g., brain-derived neurotrophic factor), reducing neuropathic pain, and demonstrating significant improvements in metabolism (Gorgey et al., 2012b). One widely accepted theory is that exercise encourages the formation of targeted synaptic connections and prunes the inactive ones through disuse, which further leads to use-oriented neural circuit reorganization. This 'use it or lose it' theory is based on the Hebbian synaptic strengthening model (Hebb, 2002). Through repetitive task-specific training exercise, neural reorganization is facilitated through repeating a targeted task. This approach is now used clinically to promote walking in the form of activity-based rehabilitation, including overground training, body-weight-supported treadmill locomotor training and robotic-assisted treadmill locomotor training. These active exercise paradigms have been shown to regulate plasticity at multiple levels of the neuraxis including cortical maps, descending supraspinal motor pathways, spinal cord circuitry and sensorimotor functions in the periphery (Fouad and Tse, 2008; Fouad and Tetzlaff, 2012). In the context of this dissertation, gait-specific training interventions are referred to as 'locomotor training interventions focused on the lower limbs.'

Task-specific walking training was first developed in research studies using cats with fully or partially transected spinal cord. In those models, the lumbar networks in the spinal cord were repetitively exposed and trained under afferent inputs from the hindlimbs at appropriate phases during locomotion. Over a period of time, training eventually resulted in the production of a coherent and organized stepping pattern (Forssberg et al., 1980a; 1980b; Barbeau and Rossignol, 1987; Rossignol et al., 1996; Van de Crommert et al., 1998). The improved locomotor pattern produced by training was retained after the training stopped, without showing significant loss up to 12 weeks post-training (de Leon et al., 1999). Studies of the motor unit properties showed that the oxidative properties of muscle fibers were relatively unaffected after training, indicating that the training-induced improvements in walking were attributable to plasticity in the neural networks developed through training (Roy and Acosta, 1986; Roy et al., 1998; Wolpaw and Tennissen, 2001). However, those studies suggested that exercise may only improve

performance in the trained task, and perhaps even reduce the ability to perform other motor activities. De Leon et al. (1998) showed that cats with complete thoracic SCI trained to stand improved their standing but did not walk well on the treadmill, whereas animals trained to walk did worse in standing (Edgerton et al., 1997; de Leon et al., 1998a; 1998b; Edgerton et al., 2001). The adaptive plasticity of spinal circuitry was likely attributable to this behavioral difference, since no difference in strength or contractile properties in hindlimb muscles were found between the groups of cats trained to step and those trained to stand (Roy and Acosta, 1986; Roy et al., 1998; 1999). Similarly, swimming as a locomotor training model improved the hind limb step pattern in rats with thoracic spinal cord contusion injury (Magnuson et al., 2009). However, because the animals were trained in an environment where the loading forces were not comparable to overground locomotion, they failed to improve the ability to bear weight (Magnuson et al., 2009). It has been proposed that after SCI, activity-dependent plasticity entails changes in both spinal and supraspinal neuronal reorganization, which probably depend on a certain level of appropriately timed afferent inputs occurring through the locomotor training (Rossignol, 2006).

A comparable idea of locomotor training in cats was then translated to clinical use (Finch et al., 1991; Wernig and Müller, 1992). Repeated exposure to the locomotor activity over a period of weeks or months, can lead to significant improvements in muscle activation, EMG activity profile and ambulatory capacity in people with SCI (Dietz, 1992). In the next few sections, several of the currently most commonly used locomotor training therapies in rehabilitation of walking will be discussed.

1.3.3 Body weight supported (BWS) locomotor training

As with experimental animals, walking function in humans after SCI can be improved, to an extent, through repetitive gait training paradigms. Among those paradigms, BWS treadmill training is one of the most studied and widespread rehabilitation interventions. A harness attached to an overhead lift supports the partial or full weight of the patients, which reduces the demand from the patients for bearing their full weight and maintaining balance/posture. Therefore, the provision of BWS allows even people with complete motor paralysis to perform the stepping training. BWS can either fully counteract the weight or dynamically accommodate

part of the weight during the step cycles (Behrman et al., 2006; Dobkin et al., 2006). As training continues, the participant usually develops the ability to support more bodyweight. Manual assistance to the legs is often provided by at least 2 (up to 3 or 4) physical therapists, especially at the beginning of training, to complete the gait cycles before the participant develops enough motor control for balancing and stepping.

In Behrman et al. (2000)'s report on case studies of locomotor training after SCI in humans, several aspects that were learnt from animal research studies were discussed and recommended for optimizing the locomotor training in humans (Behrman and Harkema, 2000). Those recommendations include: maximize the phasic sensory information such as weight loading during stance, ensure sufficient hip extension and unloading before swing, and provide assistance to facilitate the swing phase as well as maintain a normal walking speed during training (Dietz et al., 1995; Behrman and Harkema, 2000). Taken together, BWS treadmill locomotor training combined with manual assistance allows persons with SCI to practice rhythmic reciprocal stepping at a speed that replicates the normal speed, while ensuring that appropriate phasic afferent inputs are generated. BWS treadmill locomotor training also allowed the training to occur while reducing the risks of falling compared to traditional overground training (Behrman and Harkema, 2000; Dobkin et al., 2006).

Studies showed that people with SCI were able to translate the gain from the BWS treadmill training to improvements in overground locomotor abilities (Wernig and Müller, 1992; Wernig et al., 1995; Hicks et al., 2005; Thomas and Gorassini, 2005; Winchester et al., 2009; Lorenz et al., 2012; Harkema et al., 2012b). However, these improvements in overground walking were only found in people with incomplete lesions. There is no evidence demonstrating that BWS treadmill training can produce functional ambulation in people with complete SCI, although their activation of muscle EMG activity are improved and regulated (Dietz et al., 1995; 1998; Wirz, 2001). Although treadmill walking has the advantage of assisting foot propulsion and leg extension, as well as providing high rhythmic input to the legs, overground walking also has many advantages. It not only allows the use of assistive devices, which replicates a more 'real' modality of daily walking, but also places a large demand on balance, muscle strength and voluntary control, such as effort for step initiation and forward progression (Field-Fote and

Roach, 2011), during ambulation. Overall, evidence has shown that there are significant differences in heart rate and walking performance such as EMG activity and kinematic patterns between treadmill and overground walking (Murray et al., 1985; Alton et al., 1998). Some groups have introduced hybrid training therapies by combining BWS treadmill and overground training together or using BWS in overground training directly in rehabilitative training after SCI, and the resulting improvements in the balance scale, lower extremity motor scores and walking speed were significant (Postans et al., 2004; Alexeeva et al., 2011; Field-Fote and Roach, 2011; Harkema et al., 2012b).

1.3.4 Robotic-assisted locomotor training

In physical therapy, overground walking or BWS treadmill locomotor training requires demanding physical labor from several therapists to provide assistance. A type of automated locomotor training instrumentation was therefore developed. The computerized and motor-driven exoskeleton/orthosis can passively carry the legs, and therefore produce stepping movements resembling normal human gait (Colombo et al., 2000; Hesse and Uhlenbrock, 2000; Hornby et al., 2005; Kubota et al., 2013). Various instrumentations are currently used in the clinical settings such as the Lokomat (Hocoma AG, Switzerland) and Gait trainer (RehaStim, Germany).

In people with complete SCI, an orthosis-driven stepping with high percentage of body unloading was not sufficient to generate activation in leg muscles (Dietz et al., 2002). Furthermore, the continuous passive assistance and guidance during the task could even reduce motor performance and retention (Winstein et al., 1994). Evidence from participants with incomplete SCI (iSCI) and neurologically intact participants showed that passively-assisted movements decrease voluntary muscle activity and decreases plastic changes in the nervous system (Lotze, 2003; Israel et al., 2006). Although the robotic-assisted devices reduce the physical demands on the therapists, there was no evidence that participants gained greater improvements in walking than other interventions (Swinnen et al., 2010). In fact, walking improvements in people with chronic iSCI through robotic-assisted walking training were either not significant or much smaller than other gait-specific training interventions, including BWS treadmill locomotor training and overground locomotor training (Field-Fote and Roach, 2011; Knikou, 2013). It has also been argued that the control trajectory, involving a fixed trajectory

through which the participants' legs are passively driven by the powered orthosis, eliminates voluntary engagement, an essential component for the rehabilitation in humans (Yang and Gorassini, 2006). For example, when participants were asked to maximize their walking effort during robotic-assisted stepping, their hip flexor EMG activity increased and became closer to the level seen during therapist-assisted walking (Israel et al., 2006). Therefore, modifications have been developed to improve the current robotic-assisted methods. Biofeedback was added to the exoskeleton/orthosis to facilitate volitional engagement during training (Lam et al., 2006; Lünenburger et al., 2007; Lam et al., 2008b). Also, a modified cable-driven locomotor trainer was introduced which allows for kinematic error (Wu et al., 2011; 2012). The modified robotic training systems have produced significant improvements in overground walking speed and balance in people with iSCI relative to pre-training; and appear to be more effective than the BWS treadmill training for the higher functioning individuals (Wu et al., 2012). Moreover, robotic use combined with overground training provided better clinical performance than overground training only, including higher lower limb motor scores and higher scores in the functional independence measure (FIM)-locomotor scale (Esclarín-Ruz et al., 2014). Collectively, those methods encouraged the participants to be more actively engaged, and drive motor learning during training.

1.3.5 Skilled walking training

As an alternative intervention to repetitive stepping training, skilled walking has recently been introduced to the rehabilitation realm, and is also based on the idea of task-specific training. The amount of damage to the corticospinal tract was reported to be correlated with functional improvements in skilled walking in animals, such as walking on a horizontal ladder (Carmel et al., 2014) or avoiding obstacles (Drew et al., 2008). A pilot study was conducted with 4 chronic iSCI participants in an intervention with alternating phases of 'skilled walking/BWS treadmill locomotor training' (Musselman et al., 2009). The skilled walking training included various tasks important for daily walking, such as climbing stairs and stepping over obstacles. Walking endurance and skilled walking tasks were improved with both training types (Musselman et al., 2009). In a later study from the same research group, 22 iSCI participants were recruited for a pilot randomized clinical trial, with a crossover design to compare the effectiveness between skilled walking and BWS treadmill training (Yang et al., 2014). Both training interventions had

significant improvements in walking, with bigger improvements in walking distance and self-selected walking speed occurring after BWS treadmill training; however, it was argued that the total steps performed in skilled training were less than that in the BWS treadmill locomotor training intervention, which could critically influence post-training walking performance (Yang et al., 2014). Nonetheless, the emerging evidence indicates that training on walking skills may also effectively improve walking functions after SCI, although further investigation is required to understand the difference between skilled walking training and other modes of repetitive stepping trainings.

1.3.6 Cycling exercise for lower limbs

While the majority of locomotor training therapies focus on gait rehabilitation, such as the BWS locomotor training, leg cycling is also currently utilized as a treatment intervention in people with SCI, but mainly for increasing cardiovascular health (Davis et al., 1990; Nóbrega et al., 1994; Claydon et al., 2006; Cragg et al., 2013), improving body composition and metabolic response (Hooker et al., 1992a; Griffin et al., 2009; Gorgey et al., 2012a), and reversing muscle atrophy (Baldi et al., 1998; Dudley et al., 1999; Scremin et al., 1999).

The magnitudes and durations of activation in the rectus femoris and semitendinosus muscles during cycling are similar to those during treadmill or overground walking (Prosser et al., 2011). Therefore, the activation patterns in the leg muscles could be similar between the cycling and walking tasks. Similarly, despite differences in movement kinematics, commonality in neural regulation (e.g., background EMG activity) was also seen in various types of rhythmic arm and leg movement, including walking, arm and leg cycling, and arm-assisted recumbent stepping (Zehr et al., 2007a). In comparisons of leg cycling training and locomotor training in people with iSCI, substantially improved spinal reflex regulation was observed after both types of training (Kiser et al., 2005; Phadke et al., 2009; Knikou and Mummidisetty, 2014). Given the similarity and common neural control across cycling and walking, a potential role of leg cycling in walking rehabilitation could be recommended. However, currently, only scarce evidence exists showing benefits of leg cycling training for the restoration of gait function, especially after SCI (Kuhn et al., 2014; Yaşar et al., 2015). Because of the weakness in leg muscles, leg cycling training is usually combined with external assistance, often function electrical stimulation (FES).

1.4 Functional electrical stimulation (FES)

1.4.1 What is FES and its application in rehabilitation

By applying electrical charges to the extracellular environment to depolarize the cell membrane, FES can artificially activate excitable tissues (Merrill et al., 2005). For example, motor units are recruited with the application of FES and leading to muscle contraction (Gater et al., 2011). Contrary to the order of natural recruitment of motor units during volitional exercise (Henneman et al., 1965), larger size motor units are first depolarized using FES due to their low impedance. Therefore, large sized fast fatigable (FF) and fast fatigue resistant (FR) motor units are recruited before small sized slow motor units. Correspondingly, the FF and FR motor units produce large amounts of force but also fatigue quickly, while the small units can provide low but sustained activation because of their high oxidative capacity. How to optimize the FES parameters and stimulating paradigm to reduce the rapid fatigue and declining power output, and to ultimately improve the efficacy of stimulation, has been of great interest to researchers (Eser et al., 2003; Gorgey and Dudley, 2008; Duffell et al., 2009; Lou et al., 2016). Nonetheless, FES therapies have expanded to a wide variety of areas in rehabilitation, including cardiac and diaphragmatic pacing, pain management, truncal stability, bone and muscle health improvement, and functional restoration (Gater et al., 2011).

Specifically, in the rehabilitation of gait function after neural disorders, the application of FES has been widely developed and primarily focused on assisting muscle contractions during functional motor tasks. Liberson et al. first started to use electrical stimulation to assist in walking in the early 1960s (Liberson et al., 1961). They applied single channel stimulation to the peroneal nerve which effectively improved foot drop during the swing phase in people with hemiplegia (Liberson et al., 1961). This approach, and the later commercialized therapeutic products derived from the same idea (e.g., WalkAide®, Bioness L300), facilitate the activities during swing phase. This application is suitable for participants with higher function who are able to maintain their balance during single limb support during gait. Different products for lower extremity FES that involved more complex systems have also been developed to support people with greater demands of assistance, including implanted functional neuromuscular

stimulation systems (Triolo et al., 1996; Davis et al., 2001) and systems for FES-orthotic hybrid ambulation (e.g., Parastep®). Those systems have demonstrated the capability to restore standing and limited walking in persons with complete loss of lower extremity motor function, but were associated with high energy expenditure (Spadone et al., 2003).

1.4.2 FES-assisted exercises after SCI

In addition to providing assistance to lost functions, FES has been demonstrated as an effective and practical tool in rehabilitative exercises after paralysis. Many studies have suggested the effectiveness of FES-assisted gait training in improving walking function in the SCI population (Granat et al., 1993; Wieler et al., 1999; Thrasher et al., 2005; Kapadia et al., 2014). The training intervention mostly involved applying the stimulation to the common peroneal nerve, and/or to the main lower limb flexor/extensor muscles, for at least 30 minutes, 2-5 times/week up to ~4 months (Klose et al., 1997; Postans et al., 2004; Thrasher et al., 2005; Field-Fote and Roach, 2011). Longitudinal effects of FES use were also assessed in home-based regimen for people with SCI, who were encouraged to use the stimulator 'as much as possible' or 'at least half an hour each day' for several months to years (Granat et al., 1993; Wieler et al., 1999; Ladouceur and Barbeau, 2000a; 2000b). All of those studies have shown significant improvements in walking such as spatiotemporal measures and physiological cost after use of FES in exercise or daily activities. Furthermore, retention of the improvements was also observed in follow-up experiments. Retention effect in walking such as speed was found even after the foot-drop stimulator was turned off (Everaert et al., 2010) and could last for days or weeks. Along with the changes in walking performance, long-term use of FES use in daily activity could also produce significant improvement in the excitability of corticospinal pathway in people with non-progressive neural disorders (e.g., stroke) (Everaert et al., 2010).

In addition to implementation in gait training, FES is also very often combined with leg cycling exercises. Many long-term inactivity-associated adaptations after SCI were shown to be improved or reversed through FES-assisted leg cycling training (Mohr et al., 1997). Participants with SCI who were assigned to FES leg cycling as a regular rehabilitation modality showed greater muscle strength than the control participants who were assigned to 'standard of care' (Sadowsky et al., 2013). After a few weeks of FES leg cycling training in people with complete

SCI, the stimulated muscles were more resistant to fatigue and the work output was greater (Gerrits et al., 2000). Moreover, in a randomized controlled trial with acute motor complete SCI participants, the loss of body lean mass was effectively prevented after 3 or 6 months of FES leg cycling training, compared to the control group (Baldi et al., 1998). Similarly, FES cycling training could effectively produce muscle hypertrophy in people with acute incomplete SCI (Kuhn et al., 2014). In chronically paralyzed muscles after SCI, longitudinal FES-assisted exercise training could also produce significant increases in cross-section areas of muscle bulk (or muscle fiber) (Dudley et al., 1999; Scremin et al., 1999; Crameri et al., 2002; Kern et al., 2010a; 2010b). Other significant improvements as a result of FES-assisted leg cycling were also observed, including increase in the ratio of muscle to adipose tissue (Scremin et al., 1999), increase in bone mineral density (Dolbow et al., 2011), increase in capillary density (Crameri et al., 2002), and reduction in type II fibers (Crameri et al., 2002) which suggests a reversed post-injury shift in the oxidative properties.

It is important to note that, even given the widely established understanding of therapeutic effects through FES-assisted leg cycling, there are only very few studies that assessed the effect of cycling training on the improvement in gait function, especially after SCI (Kuhn *et al.*, 2014; Yaşar *et al.*, 2015). As aforementioned, the primary focus of gait rehabilitation is through task-specific training, in this case walking or stepping training. With a 'common core' neural control across various types of rhythmic locomotion including walking and cycling, there is a potential that the training effect on the common neural control network through one type of locomotion training can be translated into improvements in another type. Therefore, rehabilitative therapies to improve walking may also be performed through non-gait-specific training such as cycling (Dietz et al., 2001; Dietz, 2002a; Zehr, 2005). In the following chapters of this dissertation, existing evidence of non-gait-specific training intervention for improving walking functions is discussed.

1.5 The role of the arms in rehabilitation

In a study of locomotor training for people with SCI, Dietz et al. reported that people whose injury levels are higher (severe cervical injury) have more 'normal' locomotor patterns after

training than individuals with a mid-thoracic lesion. This suggests that the preserved neuronal circuits between the cervical and thoracolumbar levels could have important therapeutic implications in rehabilitation (Dietz, 2002a; 2011). In the intact nervous system, arms and legs interact and modulate each other during rhythmic movement through spinal cervico-lumbar coupling (Kearney and Chan, 1979; 1981; Delwaide and Crenna, 1984; Sarica and Ertekin, 1985; Zehr and Kido, 2001). Evidence suggests that the cervico-lumbar connections still exist, although weaker, after being interrupted by neural disorders (Calancie, 1991; 2002; Barzi and Zehr, 2008; Zehr and Loadman, 2012; Mezzarane et al., 2014). In people with SCI, the arm-leg reflexes became evident after ~6months after injury, indicating the development of new synaptic connections in the spinal cord areas innervating the upper and lower extremities following the injury (Calancie, 2002).

Coordinated arm and leg movement is also preserved in people with neural disorders. The coordination often occurs with an abnormal/altered pattern, although it seems more regulated in high-functioning individuals (Stephenson et al., 2009; Tester et al., 2012). The abnormal pattern is likely due to the impaired spinal cervico-lumbar coupling and supraspinal regulation after neural injury, which changes the motoneuronal excitability and alters the interneuronal pathways (Klarner et al., 2014). Nonetheless, the coordination between arms and legs during movement can still be improved. For example, arm swing during walking was associated with greater lower extremity motor scores and walking independence in people with SCI (Tester et al., 2011). After 9 weeks of BWS locomotor training, half of the participants with SCI who did not have arm swing at baseline integrated arm swing during walking (Tester et al., 2011). Despite the understanding of arm and leg coordination and neural connection, only a few studies suggested the effect of arm involvement in gait rehabilitation after SCI or other neural disorders (Behrman and Harkema, 2000; Schalow, 2003; Stephenson et al., 2010; Krasovsky et al., 2012; Tester et al., 2012). In Visintin and Barbeau's study (1994), people with iSCI showed better gait symmetry and more normal EMG activity (e.g., more normal TA EMG during the swing phase) when arm swing was allowed during BWS treadmill training (Visintin and Barbeau, 1994). Unlike the over-compensating muscle activities in the hip, knee and ankle flexion when participants were allowed to use parallel bars, a more normal gait pattern emerged when walking without parallel bars (Visintin and Barbeau, 1994). Similarly, in people with stroke, the activity

of extensor muscles during stance and the dorsiflexors during swing, were larger with free arm swing than when the individuals held onto the handrails during treadmill walking (Stephenson et al., 2010). The facilitation to leg muscle activity introduced by active arm movement during locomotion was also reported in other studies (Ferris et al., 2006; Ogawa et al., 2015). However, to date, there is no systematic evidence of the effect of active arm involvement in the rehabilitation to improve walking after neural disorders. In the rest of the dissertation, I will discuss a new rehabilitation intervention that actively and simultaneously combines arm and leg movement in the training, in order to improve walking function after SCI. This is a pilot study that, for the first time, systematically identifies the role of the arms in the rehabilitation of walking in people with neural disorders.

1.6 Summary and thesis outline

The overall goal of this project was to investigate the use of a novel rehabilitation intervention that actively involves the arms and legs for the improvement of walking after neural disorders, such as SCI. While walking, humans swing their arms rhythmically along with the legs, an action that increases the metabolic efficiency and improves stability during walking. This arm-leg coordination involves neuronal pathways between cervical and lumbar locomotor regions in the spinal cord. Despite the importance of this connectivity to walking, current rehabilitation protocols do not involve the arms for improving ambulation; instead, they primarily focus on restoring leg function through gait-specific leg training, for example, BWS treadmill training or overground walking training. Although gait training may be effective, it is highly labor-intensive. It requires a large staff-to-client ratio (involving as many as 4 staff members to 1 client), making it a very costly rehabilitation regime. Therefore, cycling training, which has less requirements for physical assistance, was used in the study.

In this study, I proposed that a FES-assisted arm and leg cycling paradigm would provide larger improvements in overground walking capacity than those produced by paradigms focused on training the legs alone. The objectives of this research work were to investigate whether the training: 1) regulates leg function and improves independent walking; 2) improves the spinal circuitry (e.g., cervico-lumbar spinal connection and excitability of the lumbar cord) for

locomotion; and 3) modulates corticospinal transmission and strengthens the residual corticospinal connection after iSCI.

Chapter 2 of this dissertation introduces a 12-week training study consisting of two groups: an arm and leg cycling group and a leg cycling group. FES was used to assist the participants to complete the cycling task as needed. The changes in walking as a function of training were assessed using clinical, electrophysiological and biomechanical measures. This study suggested that the prevailing dogma of 'gait-specific' rehabilitation to improve walking might not be necessary. More importantly, for the first time, it provided systematic evidence of the arm's essential role in the recovery of walking.

In Chapter 3, participants with intact nervous system (NI) and with iSCI were recruited to investigate the cervico-lumbar spinal connection after SCI and how it changes after training. Furthermore, the H-reflex in the soleus muscle before and after 12 weeks of training was also investigated, to understand the change in excitability of the lumbar cord as a function of training. This project provided evidence regarding the disruptive effect of iSCI on the connectivity between the cervical and lumbar regions of the spinal cord. It also showed that the cervico-lumbar spinal connection could be restored to some extent through training, and the activity in the lumbar cord could be substantially regulated through combined arm and leg cycling training.

In Chapter 4, changes in corticospinal excitability as a result of arm and/or leg cycling were assessed using TMS. Participants and participants with NI and iSCI were recruited. The excitability of the corticospinal pathway to the leg muscle before and after training was also assessed in the arm and leg cycling group and the leg cycling group. Collectively, the results appeared to confirm that active engagement of the arms could facilitate corticospinal transmission and increase the excitability of the corticospinal pathway after training.

In Chapter 5, the significance of the findings and their potential future translation to the clinic are discussed, along with the limitation of the studies. The dissertation, for the first time, systematically identified the influence of arm movement in the rehabilitation for walking. The

new knowledge gained from this study may allow for the design of more effective rehabilitation paradigms that enhance walking restoration and regulation after neural injury or disease.

In Appendix 1, an experiment that investigated the change in aerobic capacity (maximal oxygen uptake) as a function of training is discussed. Two participants from the arm and leg cycling group and six participants from the leg cycling group completed the experiment. Although the sample size was limited and unbalanced between groups, the results suggest that there may be improvement in aerobic capacity after 12 weeks of cycling training, and the amount of improvement seems to be similar between the two groups. This experiment provides preliminary findings of the changes in aerobic capacity as a function of cycling training. More importantly, the findings may suggest that the better improvements in walking function found in the group trained with combined arm and leg cycling, may not be due to a better improvement in cardiorespiratory function.

Chapter 2. The Effect of Arm and Leg Cycling on the Rehabilitation of Walking after Incomplete Spinal Cord Injury

Zhou R[1], Alvarado L[1], Ogilvie R[2], Chong SL[2], Shaw O[2], Mushahwar VK[1, 2]

1. Neuroscience & Mental Health Institute, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada
2. Division of Physical Medicine & Rehabilitation, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada

2.1 Introduction

Spinal cord injury (SCI) leads to a partial or complete loss of motor, sensory and autonomic function below the level of the lesion. Amongst the lost functions, restoring walking is one of the top desires of people with paraplegia (Anderson, 2004; Ditunno et al., 2008). In general, rehabilitation paradigms to improve ambulatory capacity after incomplete SCI (iSCI) aim to strengthen muscle activation and regulate plasticity at multiple levels of the neuraxis (Field-Fote, 2001). Most of the current interventions focus on progressively developing a 'normal' locomotor pattern through physical therapy, body-weight supported (BWS) locomotor training, functional electrical stimulation (FES)-assisted gait training or robotic-assisted training (Dietz, 1992; Wernig and Müller, 1992; Wernig, 2006; Mehrholz et al., 2012; Morawietz and Moffat, 2013). Nonetheless, various rhythmic motor tasks, such as walking and cycling, are controlled by a 'common central nervous network;' thus suggesting that non-gait-specific rehabilitation training therapies may improve walking (Dietz et al., 2001; Dietz, 2002a; Zehr, 2005). The use of cycling as an intervention in rehabilitation has been recommended in the past. For example, leg cycling exercises have a positive effect on cardiovascular variables (Davis et al., 1990; Nóbrega et al., 1994), body composition (Griffin *et al.*, 2009) and spinal reflexes (Motl et al., 2003; Phadke et al., 2009); however, evidence of benefits of cycling training in improving gait function, especially after SCI, remains scarce (Kuhn *et al.*, 2014; Yaşar *et al.*, 2015).

Furthermore, walking is more than just rhythmic movements of the legs; it also involves coordination of the leg movements with those of the arms. Arm activity can significantly modulate the neural activity of the legs in various types of rhythmic locomotion (Balter and Zehr, 2007; Zehr et al., 2007a; Massaad et al., 2014), even after neural disorders. Kawashima et al. (2008) suggested that both passive and active upper limb movements significantly shape leg muscle activity in study participants with incomplete SCI (iSCI) whose cervico-lumbar neural connections were partially preserved (Kawashima et al., 2008). Despite this knowledge, only a few research groups have discussed the relevance of the arms in the rehabilitation of walking after SCI. Facilitating reciprocal arm swing was recommended to maintain symmetrical arm-leg kinematics during locomotor training (Behrman and Harkema, 2000). Tester et al. (2011) encouraged coordinated, reciprocal arm movement during locomotor training to promote arm swing (Tester *et al.*, 2011), and suggested that proprioceptive input provided to the arms during

swing might be relevant to walking recovery post-iSCI. Nonetheless, to the best of our knowledge, there are no systematic studies that have actively involved the arms in rehabilitation interventions for improving walking.

In this project, we proposed the use of simultaneous arm and leg cycling as a rehabilitation strategy to improve ambulation. The study was conducted in people with chronic iSCI and included two groups, an arm and leg cycling group and a leg only cycling group, and investigated: 1) the extent of transfer of recumbent cycling into improvements in upright overground walking; and 2) the role of the arms in the improvement of walking. We hypothesized that coordinated phasic sensory and motor activation during a rhythmic non-gait-specific cycling training paradigm would improve walking speed, distance and quality of walking (e.g., joint kinematics, muscle EMG activity and coordination during walking) in people with iSCI. We also hypothesized that active engagement of the arms during training would provide better recovery of walking function than training without arm engagement. The results suggest that cycling does indeed transfer into improvements in overground walking. Moreover, active engagement of the arms simultaneously with the legs leads to larger improvements in walking than training of the legs alone. Preliminary results were previously published in abstracts (Wong et al., 2012a; 2012b).

2.2 Methods

A total of 19 people participated in the study. Of those, 13 had a chronic iSCI (>2yrs) with injury levels between C4 and T12. All participants with iSCI were classified as C or D according to the American Spinal Injury Association Impairment Scale (AIS) (Maynard *et al.*, 1997; Waring *et al.*, 2010). Six participants had an intact nervous system and were recruited to obtain normative biomechanical data. The study protocol and inclusion criteria were approved by the University of Alberta Human Research Ethics Board and all participants signed a consent form prior to the initiation of experimental procedures.

All participants with iSCI were capable of ambulating for short distances with varying levels of assistance **(Table 2.1),** and had residual innervation to the main muscles of the arms and legs.

Exclusion criteria were: damage to the nervous system other than the spinal cord; impaired mental capacity or currently taking antidepressants; history of epilepsy; spinal injury level below T12; complete denervation of the main muscles of the arms or legs; and other medical contraindications to cycling training.

I. Training

Two training interventions were used for the participants with iSCI in this longitudinal study: arm and leg cycling (A&L) and leg only cycling (Leg), with 8 participants in each group. FES was applied to various muscles of the arms and legs, as needed, to assist in completing the cycling task. Of the 8 participants in each group, S1A, S4A and S5A **(Table 2.1)** participated in the A&L group first, and then participated in the Leg group 23, 48, and 44 months later, respectively (S1L, S6L, S7L). This period, which was substantially longer than regular washout periods in cross-over designs in studies of gait rehabilitation (Postans et al., 2004; Yang et al., 2014), ensured washout of carry-over effects from the A&L training prior to initiating the leg only training.

The training set-up was composed of arm/leg FES ergometers to activate the arms and/or the legs simultaneously and generate arm/leg movements resembling the coordination present during natural walking. Five types of ergometers were used based on the participants' training group, comfort, maximal power output of the ergometers, and availability of the equipment. For the A&L group we used, 1) a custom-adpated arm and leg FES ergometer (THERA-vital, Medica Medizintechnik, Hochdorf, Germany; ERGYS 2, and Therapeutic Alliances, Inc. Fairborn OH, USA); 2) arm and leg Berkel Bike (Berkel, the Netherlands); 3) RT-200 arm and leg cycling ergometer (Restorative Therapies, Inc. MD, USA). For the Leg group we used, 1) RT-300 leg cycling ergometer (Restorative Therapies, Inc. MD, USA); and 2) ERGYS 2 FES ergometer (Therapeutic Alliances, Inc. Fai, born OH, USA). The training equipment provided computerized FES, delivered through surface electrodes to various muscles, as needed, in order to assist movement and enable active cycling.

Table 2.1. Characteristics of participants with iSCI in the A&L and Leg training groups.

Name	Age	Sex	Injury Level	Origin of Injury	Years post-Injury	Primary Mode of Mobility*	Walking Test Assistance	Ergometer	Group	Muscles with stimulation#
S1A	45	M	T10	Trauma/MVA	8	Crutches	Crutches	In house	A&L	Quads, Hams, Gluts
S2A	58	M	C5-C6	Trauma/MVA	36	Walker	Walker	In house	A&L	Quads, Hams, Gluts
S3A	61	M	C3-C5	Trauma	2	Powered Chair	Walker	RT 200	A&L	Quads, Hams, TA, SS, Tri
S4A	50	M	C6-C7	Trauma/MVA	13	Wheelchair	Crutches+ Walkaide®	Berkel	A&L	Quads, Hams, Gluts
S5A	49	F	T2-T4	Disc Protrusion /Surgery	6	Wheelchair	Walker	In house	A&L	Quads, Hams, Gluts
S6A	44	M	T12	Trauma /Sports	2	Wheelchair	Crutches	RT200+ Berkel	A&L	Hams, Gluts, TA
S7A	58	M	C4-C5	Trauma/Fall	3	Powered Chair	Cane	RT 200	A&L	Quads, Hams, Gluts
S8A	74	M	C4-C5	Trauma/MVA	3	Walker	No Assistive Device	RT 200	A&L	Quads, Hams, SS, WE
S1L	48	M	T10	Trauma/MVA	11	Crutches	Crutches	ERGYS	Leg	Quads, Hams, Gluts
S2L	36	F	C5-C7	Trauma/MVA	2	Wheelchair	Cane	RT 300	Leg	Quads, Hams, TA, Gastr
S3L	54	M	T4-T5	Disc Protrusion /Sports	4	Wheelchair	Walker	RT 300	Leg	Quads, Hams, Gluts
S4L	41	F	C6-C7	Trauma/MVA	7	Powered Chair	Walker	ERGYS	Leg	Quads, Hams, Gluts
S5L	62	M	C4-C5	Trauma/MVA	44	Cane	Cane	RT 300	Leg	Quads, Hams, Gluts
S6L	53	F	T2-T4	Surgery	10	Wheelchair	Walker	ERGYS	Leg	Quads, Hams, Gluts
S7L	54	M	C6-C7	Trauma/MVA	17	Wheelchair	Crutches+ Walkaide®	ERGYS	Leg	Quads, Hams, Gluts
S8L	30	F	C5-C6	Trauma/MVA	3	Wheelchair	Walker	ERGYS	Leg	Quads, Hams, Gluts

*****The primary mode of mobility was defined according to the assistive device the participant used in coming to the laboratory for the daily training sessions.

#Quads: Quadriceps; Hams: Hamstrings; Gluts: Gluteus; TA: Tibialis anterior; Gastr: Gastrocnemius; SS: Scapular stabilizers (rhomboids and supraspinatus); Tri: Triceps; WE: Wrist extensors

The main flexor and extensor muscles stimulated included the quadriceps, hamstrings, gluteus maximus, tibialis anterior, gastrocnemius, wrist extensors and scapular stabilizers (rhomboids and supraspinatus). For both A&L and Leg groups, the FES was only applied to muscles that the cycling task would otherwise fail or become very difficult to complete. In the A&L group, no FES was applied to the arms if the myotomes in the arms had an AIS score of at least 4 and the participant was able to move the arm crank by him/herself. Participants in the A&L group were encouraged to constantly and actively engage their arms in the cycling. Stimulation was composed of a rectangular biphasic waveform with 150-450 μsec pulse width, and was delivered at a frequency of 30-40 Hz. The maximal stimulation intensity was customized to each participant and set to the highest level that produced muscle contractions with tolerated sensation. Threshold stimulation level was set to the minimal level of stimulation that produced a visible muscle contraction. Stimulation intensity was automatically modulated between threshold and maximal intensity to facilitate cycling.

The target speed of cycling was set to one level above the maximal speed that each volunteer was able to cycle at with no assistance or FES, and was retained constant throughout the training. The cycling resistance on the ergometer was progressively increased throughout the training sessions in order to challenge the participants, ensure their voluntary engagement in the exercises and enhance the sensory feedback to the spinal networks. Training took place 1 hour a day, 5 days a week for 12 weeks, for a total 60 hours.

II. Assessments

Assessments including clinical and biomechanical tests were performed before, during and after the training period. Assessments of walking speed and distance were conducted every three weeks throughout the period of training, whereas other clinical and biomechanical evaluations were performed every six weeks. No FES assistance was provided during any of the assessments. To establish a reliable baseline measure, all assessments were performed two to three times prior to the initiation of training, and the results were averaged.

Clinical assessments:

1) Walking speed and endurance: The 10-meter walking test along a straight path was performed

to assess the participants' maximal waking speed (Lam et al., 2008a). To assess endurance, the 6-minute walking test was conducted on an 18.54 meter-long oblong track and the walking distance at a self-selected speed during this time period was measured (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Jackson *et al.*, 2008).

2) Assessment of motor and sensory function: A trained physical therapist performed the motor and sensory evaluation for the myotomes and dermatomes of the upper and lower extremities across all participants using the AIS (Kirshblum *et al.*, 2011), as defined by the International Standards for Neurological Classifications of SCI (ISNCSCI).

3) Balance: Balance was assessed using the Berg Balance Scale (Berg *et al.*, 1995; Lemay and Nadeau, 2010; Wirz *et al.*, 2010). This was performed by one of the experimenters and confirmed by a trained physiotherapist.

Biomechanical assessments:

To assess the changes in participants' gait due to training, biomechanical assessments were conducted prior to the initiation of the training, and repeated after 6 and 12 weeks of training. Biomechanical assessments were also performed on 6 neurologically intact subjects (age between 20-50 years) to provide a reference of norm activity.

All participants were instructed to walk on a 6 meter-long straight track at their preferred speed. Participants with iSCI used self-selected assistive devices during the walking. A Vicon motion capture system with eight infrared cameras was used for kinematic data collection at a sampling rate of 100 frames per second. All reflective markers were consistently placed on the bony joints in accordance with a full body model 'PlugInGait' (Vicon Motion Systems Ltd., Oxford, UK). Kinematic data were recorded by Vicon Workstation (version 5.2.9) and Nexus (version 1.7.3).

To assess muscle activation patterns during walking, surface electromyography (EMG) signals were recorded from four muscle groups on each side: soleus (SOL), tibialis anterior (TA), rectus femoris (RF) and biceps femoris (BF) through an AMT-8 EMG Wire Telemetry System (10-1000Hz; Bortec Biomedical Ltd., AB, Canada). EMG data were sampled at either 2 or 2.4 kHz,

and pre-amplified with a gain of 500. Kinematic and EMG data were collected synchronously during walking.

Due to the heterogeneity and asymmetry of the lesion location, all kinematic and EMG data collected from participants with iSCI were analyzed for the more affected (weaker) side or less affected (stronger) side, based on the AIS lower extremity motor score obtained pre-training. If the motor score on both sides was identical, the side with the poorer performance in the biomechanical assessment was considered as the weaker side. The number of trials obtained per assessment session varied depending on the subject's ability to walk during the session, and ranged from 12 to 45 steps per side.

1) Kinematic data analysis:
All kinematic data were pre-processed with the 'Pipeline' operation module in the Vicon system, including filling marker trajectory gaps and applying Woltring filtering. Gait events, such as heel strike and toe lift, were manually detected in each trial. Kinematic data obtained from both sides during each step were normalized to the duration of the gait cycle (0-100%) from heel strike to the next heel strike on the ipsilateral side.

Spatiotemporal measures and joint motions
Polygon analysis software (Vicon Motion Systems Ltd., Oxford, UK) was used to calculate average spatiotemporal kinematic parameters including: preferred walking speed, stride length, step length, stride time, step time, single support time, double support time, swing time, stance time and swing time/stance time (SW/ST) ratio. The symmetry of those parameters was calculated based on the weaker side/stronger side ratio (Field-Fote et al., 2005; Patterson et al., 2010). For statistical purposes, this ratio was reversed when needed to avoid the results being skew by values <1 (Patterson et al., 2010). For defining joint angles, the anatomical neutral position was used as the frame of reference in the sagittal plane. Therefore, flexion resulted in positive joint angles and extension in negative joint angles. Joint motion data were quantified throughout the gait cycle using similar parameters to those reported by Gil-Agudo *et al.* (Gil-Agudo *et al.*, 2011).

Hip-Knee cyclogram

A vector coding technique was used to evaluate the intralimb coordination of the hip and knee angles (Tepavac and Field-Fote, 2001). Hip-knee cyclograms illustrated the angular positions of the two joints within each gait cycle. Vector analysis quantified the regularity of consecutive steps by calculating the coefficient of correspondence (ACC) of the overall variability of the hip-knee coupling across all step cycles on each side. The regularity has values between 0 and 1, with 1 meaning that all cycles are identical and 0 meaning no correspondence between cyclograms of consecutive steps. The x-axis and y-axis of the cyclogram represent the range of motion of knee and hip joint, respectively. The area inside the hip-knee cyclogram was calculated. This method is sensitive to changes in kinematic variables in people with iSCI and after locomotor training (Field-Fote and Tepavac, 2002; Awai and Curt, 2014).

2) Analysis of EMG activity

The EMG signals were filtered using a 20-500 Hz band pass filter which was effective in removing motion artifacts (Winter et al., 1980; De Luca et al., 2010). The EMG signals were then rectified and low-pass filtered with a second order Butterworth filter with cutoff frequency of 6 Hz. Similar to the kinematic data, all EMG signals were diced to the gait cycles such that heel strike to the consecutive heel strike was considered as 100% stride time.

The minimal rectified EMG activity in each gait cycle was considered the no-activation level, and subsequently subtracted from all EMG values to eliminate offset. For each muscle, the root-mean-square (RMS) of the peak EMG signals from all the gait cycles was considered as the maximal EMG value of the muscle. All EMG values from this muscle were then normalized to this maximal value, and expressed as a percentage of the normalization value.

Magnitude and phase components:

In order to quantify the EMG activity patterns and assess changes with training, we implemented an EMG metric method described by Ricamato & Hidler (Ricamato and Hidler, 2005). This method compares EMG patterns generated during the gait cycle, and was validated for assessing locomotor EMG amplitude and timing properties in subjects with intact nervous system (Ricamato and Hidler, 2005). It can also be used in people with stroke or SCI for quantifying

within-subject gait training performance, and identifying their difference from normative gait-related EMG profiles (Schück et al., 2012). The metric contains two components: a magnitude component and a phase component with values ranging from 0 to 1. The magnitude component is "rewarded" in the metric when the recorded muscle EMG is active (≥~15% of the maximal EMG signal) in the portion of the gait cycle where the norm EMG activity should be 'on,' or when the no-activation period occurs during the gait cycle where the norm EMG activity should be 'off.' Otherwise, the metric "penalizes" the magnitude component in conditions opposite to the norm EMG pattern for a given muscle.

Similarly, the phase component examines the similarity of the timing properties between the recorded EMG and the norm activity. The maximal phase component (value of 1) suggests an exact match in both active and inactive phasing between the recorded EMG pattern and the norm. For comparison with normative EMG activity, the on-off patterns of EMG activity for various muscles were determined based on those in the NI subjects.

Intra-leg EMG burst activation:

To further quantify the timing of when the EMG activity occurred within a gait cycle, the onset and offset of the EMG burst were identified by visual inspection, for each muscle for a given participant and across all testing sessions. The time span between the onset and offset was calculated as the active contraction duration of the muscle, expressed in percentage of the cycle.

Inter-leg coordination:

In order to measure inter-leg coordination, we calculated the onset of EMG activity in the homologous muscle of the left and right leg (e.g., left TA and right TA) during the gait cycle and determined the phase difference. Inter-leg co-activation was also analyzed as the overlap of active contraction of the homologous muscle pair during the gait cycle.

III. Statistical Analysis

Statistical tests were performed to identify the time effect as a function of training, and the group difference between the two training groups (A&L and Leg). All statistical tests, except circular statistics, were performed using SPSS 23 (SPSS Inc., Chicago, IL, USA). Normality of data

distribution was first tested using the Shapiro-Wilk test. Comparisons of the pre-training, baseline measures and demographic characteristics between the A&L and Leg groups were performed using independent t-test or Mann–Whitney U test based on the test of normality.

The primary outcome measures were changes in the 10-meter and 6-minute overground walking tests. A two-factor mixed ANOVA was performed with a *post-hoc* test using Bonferroni correction if the main effect or interaction was significant. The two factors contained one independent factor representing the training group (A&L, Leg) and one dependent factor representing the repeated measures over time (e.g., pre-training, 3, 6, 9, 12 weeks post-training). The studentized residuals were also determined when running the two-way mixed ANOVA for primary outcome measures, and the values greater than ±3 were considered outliers (Stevens, 1984).

The post-training change refers to the difference between pre- and post-training value of each outcome measure normalized to its value at pre-training. A pairwise comparison of the 12-week post-training change was conducted between the A&L and Leg group for each outcome measure. In all cases, pre-to-post training paired comparisons were also used to illustrate the training effect within each group. Based on the test of normality, paired t-test or Wilcoxon signed-rank test was used for the pre-to-post training paired comparisons. With the outcome measure that was significantly different between the two groups at pre-training, ANCOVA was applied to compare the group difference in the 12-week post-training change with the pre-training measure as the covariate.

The Pearson's product-moment correlation (r) was performed to determine the relationship between walking performance (speed and distance) and the clinical outcome measures (AIS and Balance scores). A multiple regression was run to predict walking performance from all clinical measures and to determine the overall R^2, which represents the percentage in the change of walking performance explained by the clinical measures.

Circular statistics was applied to all degree-related measures in the kinematic and EMG tests, using the software package Oriana (version 4) (Kovach Computing Services, Anglesey, Wales).

Those measures included all the joint angular motions, as well as the phase differences in the EMG activity measured in the inter-leg coordination analysis. For each measure, a paired comparison between pre- and post-training was conducted using Hotelling's paired test. Pre-training and 12 week post-training data were also compared to measures obtained from intact individuals using Watson-Williams F-test (Zar, 2010), respectively.

Results are presented as 'mean ± 1x standard error' (unless otherwise indicated) for continuous data and 'median (75% pententile)/mean ± 1x standard error' for ordinal data. The statistical p-value regarding the training effect over time is expressed as 'Time p,' while the group effect is expressed as 'Group p.' Statistical differences with $p \leq 0.05$ were considered siginificant.

2.3 Results

Across all paticipants, there was an overall improvement with 12 weeks of cycling training in overground walking speed, overground walking distance, sensory and motor function, and balance, as well as regulation in leg muscle activation and joint motion. The group trained with arm and leg cycling demonstrated substantially larger improvements in most of the outcome measures, compared to the group with leg only cycling.

Dermographic characteristics:

Thirteen participants with iSCI completed the study with three participating in both the A&L and Leg groups, resulting in 8 people in each group. Most of the participants had cervical lesions of traumatic origin (**Table 2.1**) and were AIS grade D. The age of participants in the two groups (A&L (mean ± standard deviation): 55 ± 10 yrs; Leg (mean ± standard deviation): 47 ± 11 yrs) was similar (p=0.16). Moreover, the particpants in the A&L and Leg groups had a similar range of time span post-injury, ranging from 2 to nearly 40 years (A&L (mean ± standard deviation): 9 ± 12 yrs; Leg (mean ± standard deviation):12 ± 14 yrs; p=0.44).

The status of functional ambulation at the pre-training stage of the participants with iSCI is detailed in **Table 2.1**. All participants prior to training were able to complete the primary measures: 10-meter and 6-minute overground walking tests. To ensure that the three participants

who attended both training groups did not have carry-over effects from the previous training paradigm, their 10-meter walking speed and 6-minute walking distance prior to the start of both training paradigms were compared and determined to be similar. Thereon, the two groups of participants were considered to be independent from each other.

Training sessions:

All participants completed 60 hours of training. The training intructions were consistently applied to ensure full physical engagement with the exception of one person (S8A) in the A&L group. This participant had a history of vasovagal syncope; therefore, a clearance letter was attained from his family physician prior to enrollment in the study. Nonetheless, the training intensity for S8A was maintained at 'low' to 'moderate' level, and his training sessions were interrupted as soon as his heart rate increased above ~60% of his maximal heart rate, calculated based on his age. Due to S8A's inconsistent training relative to other participants, his results were ultimately excluded from the analyses.

The cumulative miles cycled in each training session were reported by the equipment for six participants in the A&L group and eight participants in the Leg group. The miles were calculated based on the revolutions per minute (RPM) for the leg cycling portion and cycling duration. The cumulative miles can be considered a measure of training intensity solely based on the participants' leg activity, regardless of training group. The A&L group cycled an average of 9.46 ± 0.79 miles by the end of the first training session, and the Leg group cycled an average of 8.43 ± 0.74 miles at **(Fig. 2.1A),** suggesting a similar level of leg function and physical fitness between groups at the onset of training. After 60 training sessions, the cumulative miles were still similar between the two groups (A&L: 654.94 ± 45.21 miles; Leg: 563.98 ± 45.41 miles) **(Fig. 2.1B);** thus both groups received a similar intensity of leg training ($p=0.19$).

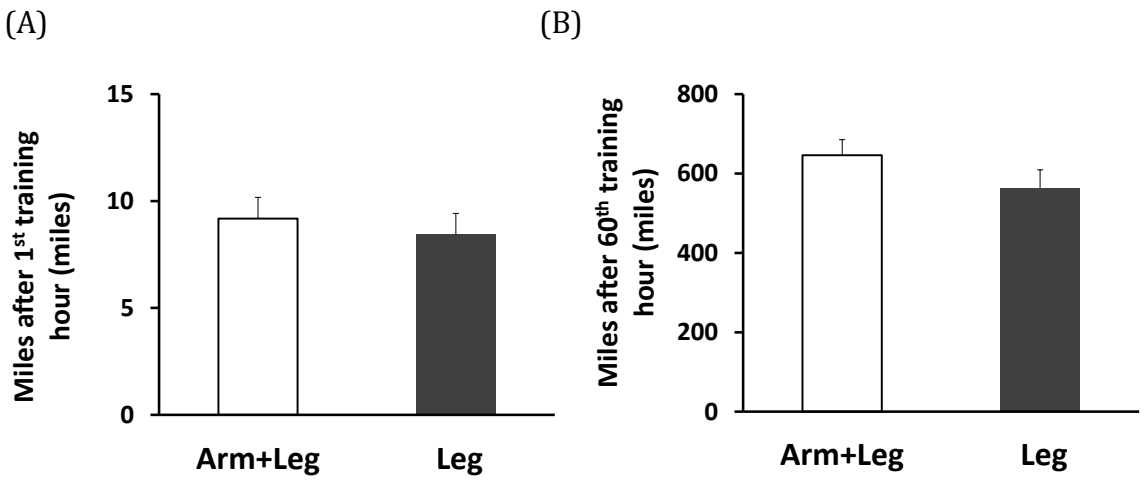


Figure 2.1. Cumulative miles after training.

(A) Cumulative miles of the A&L and Leg groups after the first training hour, and (B) after 60 hours of training (A&L: n=6; Leg: n=8).

Ten-meter and six-minute walking tests:

The A&L and Leg groups had similar pre-training, baseline measures in the 10-meter walking test (A&L: 0.45 ± 0.078 m/s; Leg: 0.50 ± 0.078 m/s; $p>0.05$). A significant increase occurred in walking speed after training regardless of group (Time $p<0.0005$) **(Fig. 2.2A).** Post-hoc analysis showed that walking speed at 6, 9 and 12 weeks of training was significantly faster than walking speed pre-training, indicating an improvement in walking speed as early as 6 weeks after the initiation of training. Specifically, within each group, there was a significant increase in average speed by 0.27 ± 0.072 m/s after 12 weeks of training in the A&L group (Time $p=0.007$) and 0.092 ± 0.022 m/s in the Leg group (Time $p=0.040$).

Each participant's increase in walking speed was then normalized to their pre-training measure. Because S7A became an outlier after the normalization, his percent change was removed from the A&L group. ANOVA analysis showed significant increase in the change of walking speed as a function of training (Time $p<0.0005$) and a group difference was found (Group $p=0.040$) **(Fig. 2.2B).** A comparison between the two groups at each of the assessment time points showed that the A&L group had a significantly larger change in walking speed than that in the Leg group at the 6th week of training (A&L: 35.45 ± 9.07%, Leg: 15.25 ± 4.52%; Group $p=0.029$) and after 12

weeks of training (A&L: 50.11 ± 13.67%, Leg: 19.40 ± 4.55%; Group p=0.034) **(Fig. 2.2B).** This suggests that the A&L group outperformed the Leg group early on in the training, and continued to have larger improvements until the cessation of training.

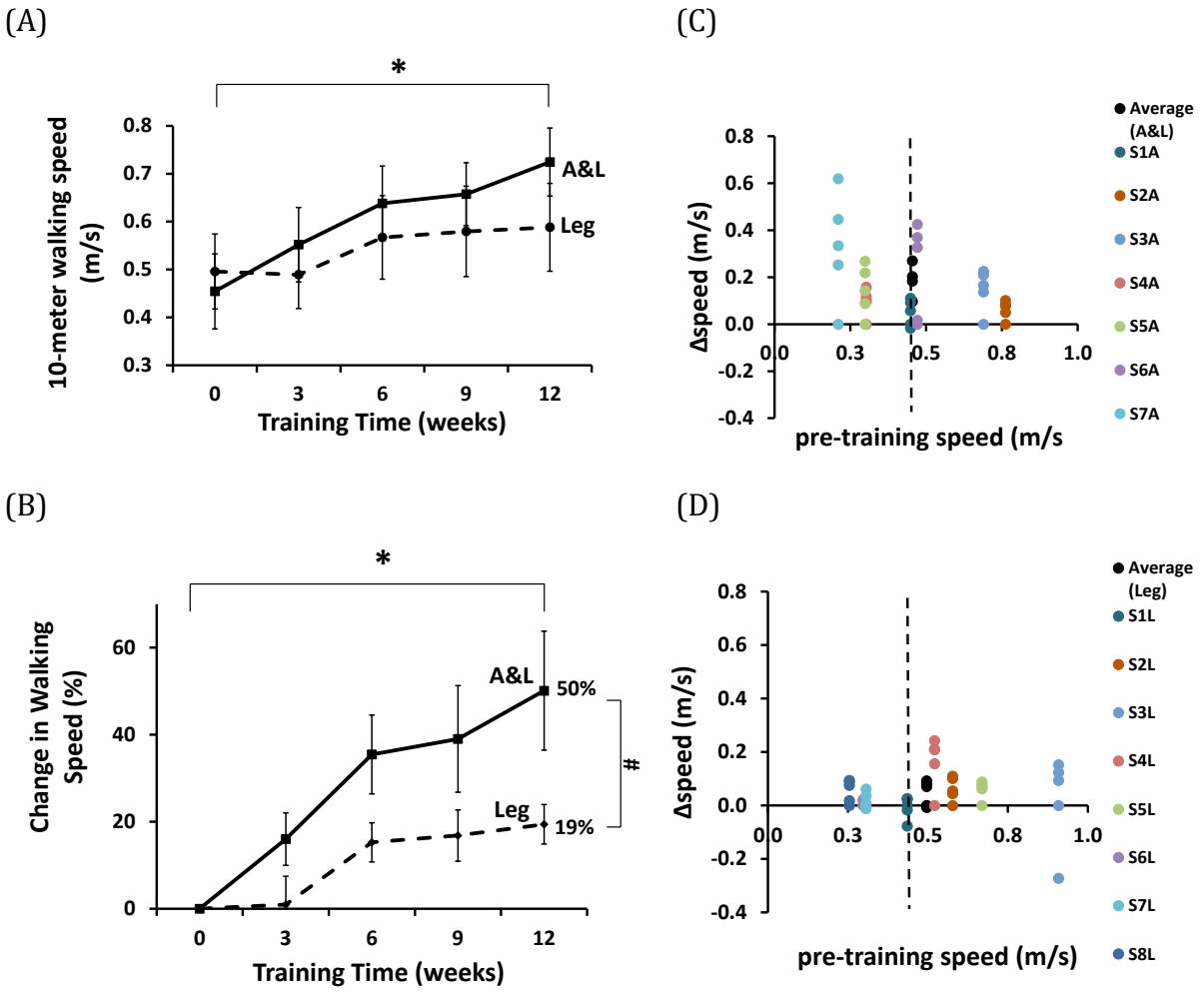


Figure 2.2. 10-meter walking speed.

(A) 10-meter walking speed in both iSCI groups throughout training (A&L: n=7; Leg: n=8). (B) Change (%) in 10-meter walking speed in both iSCI groups throughout training (A&L: n=6 – outlier removed; Leg: n=8). Absolute change (m/s) in walking speed of individual participants within the (C) A&L group and (D) Leg group. Each color represents a participant, whereas different dots of the same color represent the changes in speed compared to pre-training measured at different assessments for a given participant. Dashed line indicates a walking speed of 0.45m/s at pre-training. *significant difference over time ($p \leq 0.05$). #significant difference between the two groups ($p \leq 0.05$).

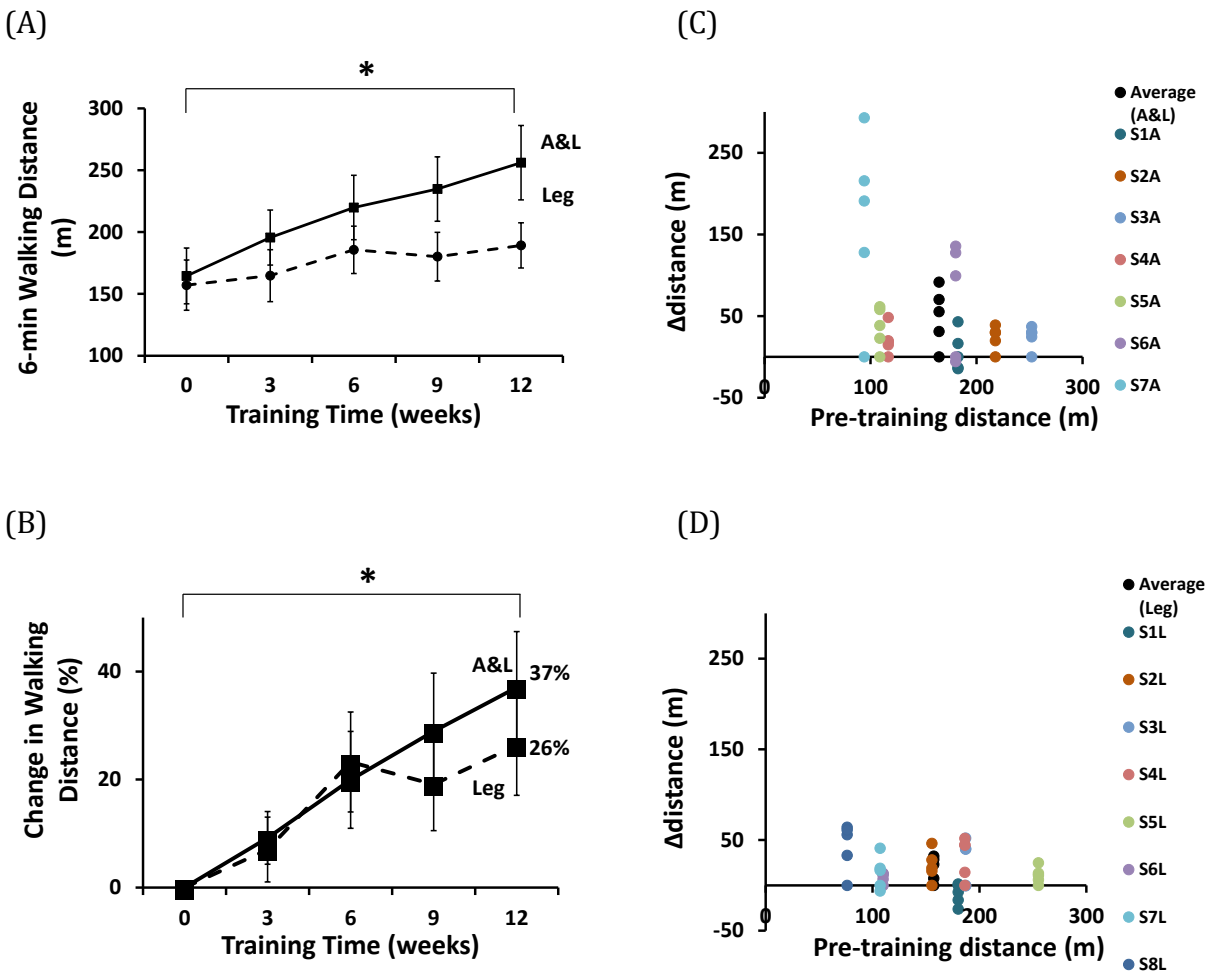


Figure 2.3. 6-minute walking distance.

(A) 6-minute walking distance in both iSCI groups throughout training (A&L: n=7; Leg: n=8). (B) Change (%) in 6-minute walking distance in both iSCI groups throughout training (A&L: n=6 – outlier removed; Leg: n=8). Absolute change (m) in walking distance of individual participants within the (C) A&L group and (D) Leg group. Each color represents a participant, whereas different dots of the same color represent the change in distance compared to pre-training measured at different assessment times for a given participant. *significant difference over time ($p \leq 0.05$).

Figures 2.2C, D show the progression in walking speed for individual participants throughout the course of training. A walking speed of ~0.45 m/s (indicated by the vertical dashed line) is considered to be the minimal speed for outdoor mobility as a community walker (Perry *et al.*, 1995; Van Hedel *et al.*, 2009). Both groups had half of the participants below (low-function) and half above (high-function) that speed level prior to the initiation of training. In both high-

function and low-function populations of the A&L group, the absolute improvements in walking speed relative to pre-training were consistently larger than those in the same population of the Leg group. This suggests that for people with various levels of ambulatory impairment, paradigms involving the arms along with the legs could result in better performance than those not involving the arms.

The pre-training, baseline measures in the 6-minute walking distance were similar between the two groups (A&L:164.52 ± 22.59 m; Leg: 157.07 ± 20.34 m; $p>0.05$) **(Fig. 2.3A).** Walking distance improved signicantly over training (Time $p=0.002$) **(Fig. 2.3A).** Within group analysis revealed significant improvements in walking distance in the A&L group (increase of 91.58 ± 36.24 m; Time $p=0.043$) and the Leg group (increase of 32.12 ± 8.74 m; Time $p<0.0005$). After removing the outlier (S7A), both groups had significant increases in the change of walking distance over training ($p\leq0.019$), while the A&L group had a substantially larger percent change in walking distance (37.05 ± 10.34%) than that in the Leg group (26.31 ± 9.24%) 12 weeks after training, but the difference between the two groups was not significant (Group $p=0.67$) **(Fig. 2.3B).** Similarly, the absolute improvements in walking distance relative to pre-training levels in the A&L group were consistently larger than those in the Leg group **(Fig. 2.3C, D).**

Motor and sensory scores:

Both groups had similar pre-training AIS motor scores (A&L: 71(91)/76.21 ± 5.64; Leg: 91(92)/82.00 ± 5.34; Group $p=0.467$). Most participants showed an increase in motor score after training. Post-training scores averaged 83.29 ± 3.70 and 87.75 ± 4.39 in the A&L and Leg groups, respectively. There were significant improvements in AIS motor scores as a function of training regardless of group (Time $p<0.0005$). Within group analysis also showed substantial and significant improvement in the A&L ($p=0.075$) and Leg group ($p=0.006$), respectively **(Fig. 2.4A, B).** However, there was no significant difference in improvements beween groups (Group $p=0.38$).

The AIS motor score was then divided into upper extremity motor score (UEMS) and lower extremity motor score (LEMS), and compared between the two groups. There was a significant increase in UEMS as a function of training in both groups, but no significant difference between

groups (Time p=0.022, Group p=0.656). The A&L group had an average increase of 9.14 ± 5.58% and the Leg group 3.37 ± 1.03% post-training in the UEMS. There was also a significant increase in the LEMS score in both groups as a function of training but no signicant difference between the groups (Time p<0.0005, Group p=0.30). The average increase in LEMS was 14.01 ± 5.58% and 14.20 ± 5.66% for the A&L and Leg groups, respectively. Within individual groups, significant pre-to-post training effect was also found in both the A&L group (Time p=0.05) and Leg group (Time p=0.008) **(Fig. 2.4C, D).**

To better understand the LEMS, we also investigated the amount of change in LEMS on the weaker and stronger side after training. Both groups demonstrated similar improvement on each side. On the stronger side, a post-training improvement in LEMS of 9.89 ± 4.88% was observed in the A&L group and 8.24 ± 2.27% in the Leg group. Interesingly, LEMS on the weaker side had a much more substantial post-training improvement, with a similar amount in both groups (A&L: 32.30 ± 17.03%; Leg: 37.30 ± 22.25%).

AIS sensory evaluations also showed significant improvements with training, but only in the A&L group (Time p=0.01). The improvements in the A&L group were 20(28)/19.50 ± 5.41 points (47.16 ± 18.36%) and those in the Leg group were 2(4)/3.00 ± 2.71 points (5.68 ± 5.04%) **(Fig. 2.5).** However, because the A&L group had significantly lower AIS sensory scores than the Leg group at the pre-training, baseline stage (A&L: 55(66)/55.07 ± 6.00, Leg: 75(88)/75.31 ± 5.97; Group p=0.033), ANCOVA was applied to assess the post-training improvements between the two groups, with the pre-training sensory scores as covariate. No significant difference between the groups was found (Group p=0.54).

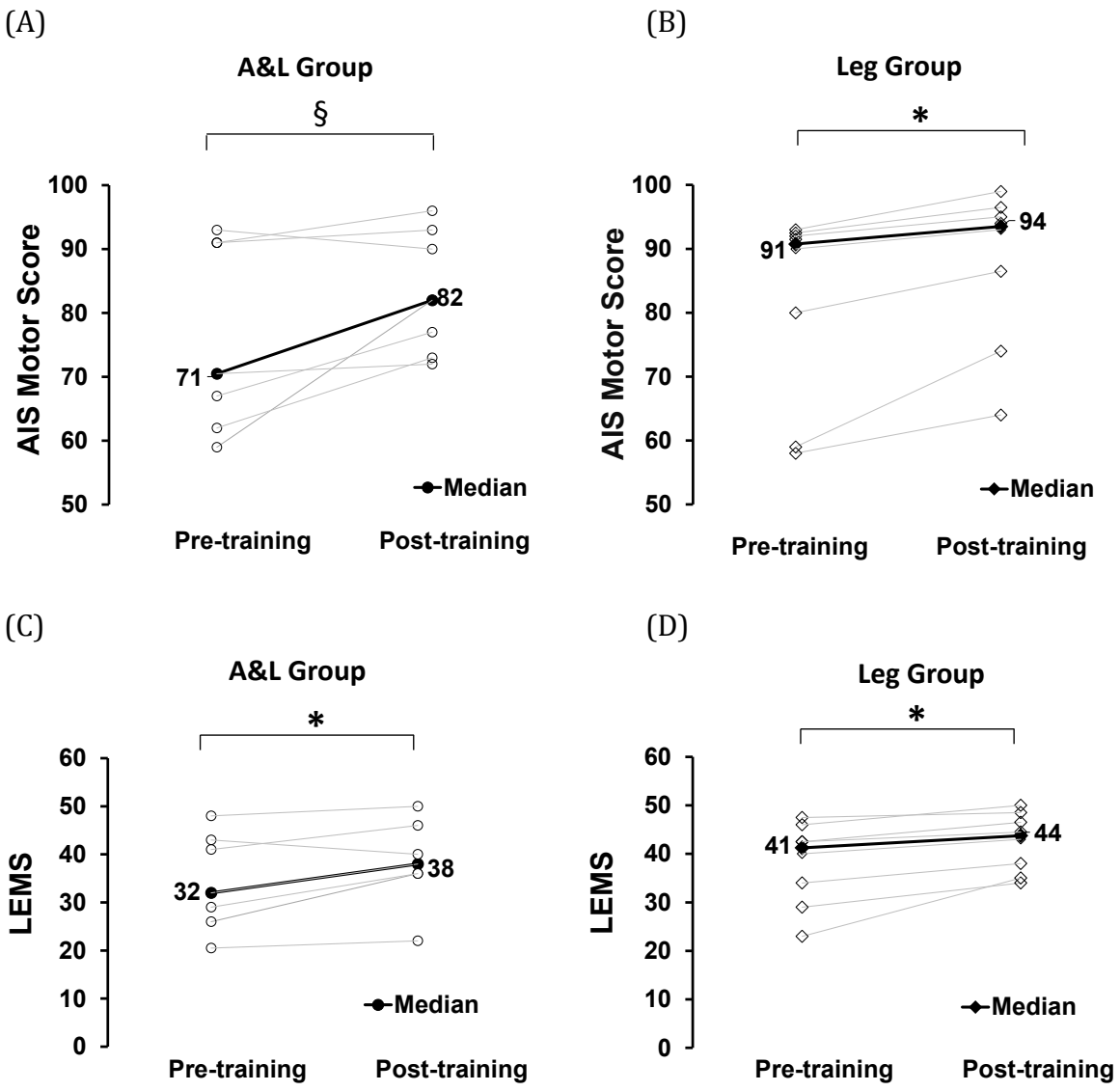


Figure 2.4. AIS motor scores.

AIS motor scores at pre-training and post-training in the (A) A&L group and the (B) Leg group (A&L: n=7; Leg: n=8). AIS LEMS at pre-training and post-training in the (C) A&L group and the (D) Leg group (A&L: n=7; Leg: n=8). *significant difference ($p \leq 0.05$); §substantial difference ($p \leq 0.1$).

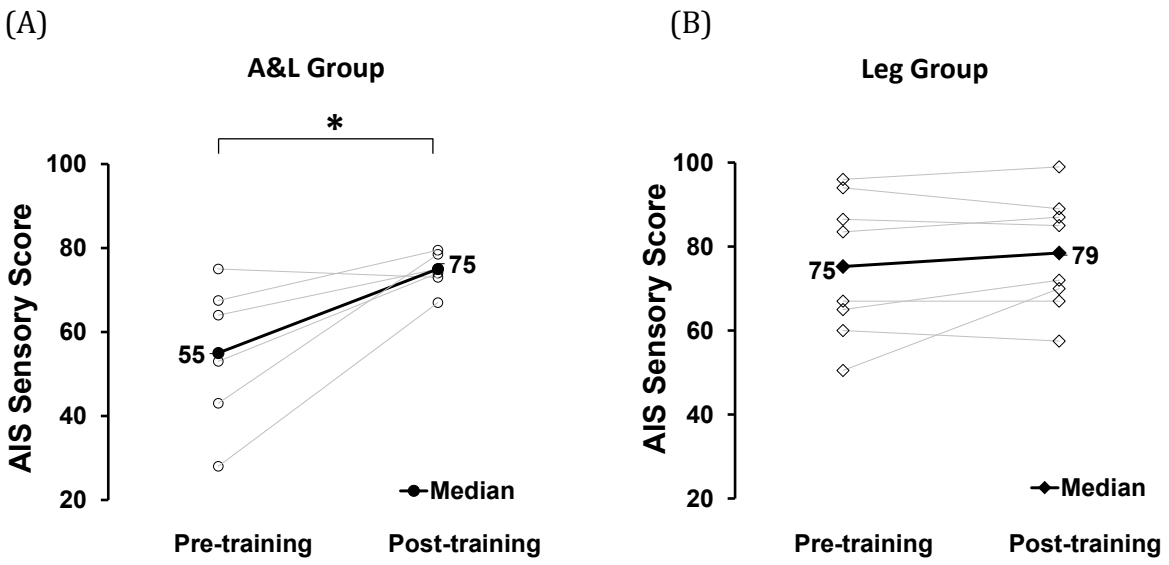


Figure 2.5. AIS sensory scores.

AIS sensory scores at pre-training and post-training in the (A) A&L group and the (B) Leg group (A&L: n=7; Leg: n=8). *significant difference ($p \leq 0.05$).

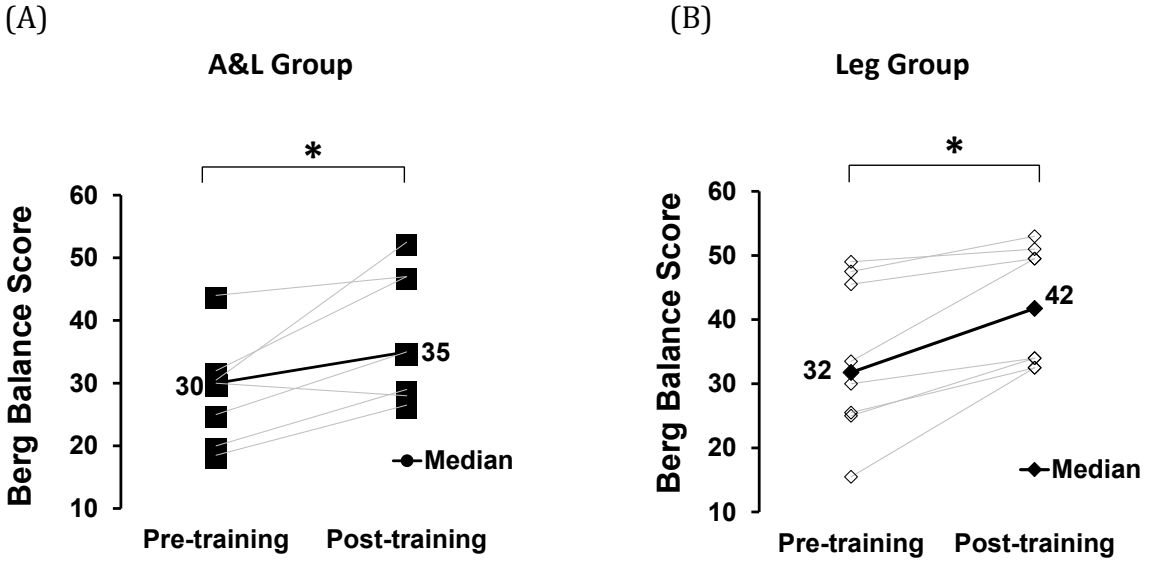


Figure 2.6. Berg Balance Scale scores.

Berg Balance Scale scores at pre-training and post-training in the (A) A&L group and the (B) Leg group (A&L: n=7; Leg: n=8). *significant difference ($p \leq 0.05$).

Balance:

There was no significant difference in pre-traning, baseline Berg Balance scores between groups (A&L: 30(31)/28.57 ± 3.25, Leg: 32(46)/33.94 ± 4.33; Group p=0.34). Post-training assessments showed changes in the Berg Balance score across participants ranging from losses of 2 points to improvements of up to 22 points in the A&L group, and 2 to 17 points in the Leg group. The score significantly increased after training by an average of 9.29 ± 2.94 in the A&L group and 8.06 ± 1.99 in the Leg group (Time p=0.001), although no difference was found between groups (Group p=0.56) **(Fig. 2.6).** Within each group, the increase in the Berg Balance score as a function of training was also significant ($p<0.05$ for each group) **(Fig. 2.6).** The amount of post-training change in the score was not significantly different between groups (A&L: 35.34 ± 10.05%, Leg: 32.33 ± 12.25%; Group p=0.86).

Correlations between walking metrics and clinical measures:

Pearson's correlation was used to assess the relationship between the post-training change in walking performance and other clinical measures in individual groups. The change in walking speed had a significantly positive correlation with the change in motor scores (r=0.79, p=0.017), but had a weak and a moderate correlation with the change in sensory (r=0.17) and balance (r=0.49) scores, respectively. Change in walking speed remained significantly correlated with the change in motor scores in the Leg group (r=0.65, p=0.042), with a moderate correlation with change in sensory (r=0.56) and balance (r=0.36) scores.

Similarly for the change in walking distance, the correlation with the change in motor scores was significant in both groups ($p<0.05$). In addition, change in walking distance was also strongly correlated with the change in Berg Balance score (A&L: r=0.59; Leg: r=0.70). The correlation with the change in sensory scores was weak for both groups.

A multiple linear regression was then run to determine how much of the change in walking performance could be explained by individual clinical measures. The R^2 value for predicting the change in walking speed by the overall model, which included the Berg Balance, AIS motor and AIS sensory scores, was 0.74 for the A&L group and 0.86 for the Leg group, a large effect size according to Cohen (Cohen, 1988). Individually, in the A&L group, the change in motor scores

explained 39.1% of the variability in the speed change, while the Berg Balance and AIS sensory scores explained 23.6% and 6.6%, respectively. In the Leg group, the percentage of change in walking speed was explained 31.5%, 13.2% and 35.4% by the change in motor, balance and sensory scores, respectively.

Similarly, with R^2 of 0.74 for the A&L and 0.75 for the Leg group, the change in motor scores and the change in Berg Balance scores explained the major variability in the change in walking distance, while the change in sensory scores only accounted for less than 5% of the change in distance.

Spatiotemporal measures:

Table 2.2 summarizes the spatiotemporal parameters for both cycling groups obtained while walking at a self-selected speed. There was no significant difference between the groups for any of the parameters at the pre-training, baseline stage. Almost all parameters became closer to the values obtained from intact participants after training. Within-group analysis showed that the A&L group improved significantly in most parameters over the course of training, while none of the parameters in the Leg group reached significance with training, except for stride length and preferred walking speed.

The average self-selected walking speed of all the iSCI participants at the pre-training, baseline stage was much lower than that of the the intact group. After training, there was an average increase of 0.17 ± 0.060 m/s in the A&L group and 0.071 ± 0.030 m/s in the Leg group. Correspondingly, the stride time was shorter and stride length was larger, which could be attributed to the reduced step time and increased step length in both groups.

For paricipants in both groups, the stronger leg had shorter swing and longer stance time than the weaker leg at pre-training, presumably to compensate and maintain gait stability. Such a relationship remained even after training; however, training substantially reduced the stance time and increased swing time in both the strong and weak legs, especially in the A&L group. Compared to the Leg group, a significantly larger post-training improvement in the SW/ST ratio (stronger side, p=0.040) and single support (weaker side, p=0.030) was found in the A&L group.

Overall, the A&L group consistently showed larger improvements than the Leg group in the spatiotemporal measures, and reached significance after training in most of them.

Similar changes in symmetry between the weaker and stronger legs were found in the two groups. Although the participants did not present asymmetry in their step length between the strong and weak legs, large improvements were found in the symmetry of swing time, stance time, and SW/ST ratio after training for both iSCI groups (ratio after training closer to 1).

Joint motion:

Figure 2.7 illustrates the joint kinematic parameters during the gait cycle. Both the A&L and Leg groups had altered joint angular motions on both the weaker and stronger sides at pre-training compared to the NI group. In general, compared to the NI group, the participants with iSCI had delayed stance-to-swing phase transition, inadequate hip extension during stance and pre-swing, limited hip flexion during swing, limited knee flexion range, excessive ankle plantar flexion, and impaired foot contact (van der Salm *et al.*, 2005). The deviation of joint kinematics from those in the NI group remained even after training in both iSCI groups, but the occurrence of phase transition significantly improved in the A&L group.

Post-training improvement was observed in the hip joint, especially in the A&L group, which had a significant change in the minimal hip angle during stance on the stronger side ($p=0.042$) and a substantial change on the weaker side ($p=0.078$) **(Fig. 2.7).** This suggested an enlarged maximal hip extension during stance in the A&L group after training. The Leg group did not have significant improvement in the hip joint after training.

Table 2.2. Summary of spatiotemporal measures for NI and both iSCI groups (values are mean ± 1x standard error).

	A&L Group (n=7)				Leg Group (n=8)				Able-bodied (n=6)
	00wk		*12wk*		*00wk*		*12wk*		
Variable	***Stronger***	***Weaker***	***Stronger***	***Weaker***	***Stronger***	***Weak***	***Stronger***	***Weak***	
Preferred Walking Speed (m/s)	0.27 ± 0.034		0.44 ± 0.083*		0.36 ± 0.060		0.43 ± 0.078*		1.17 ± 0.073
Stride Length (m)	0.74 ± 0.045		0.91 ± 0.064*		0.78 ± 0.046		0.86 ± 0.060*		1.34 ± 0.065
Stride Time (s)	3.12 ± 0.55		2.41 ± 0.40*		2.76 ± 0.54		2.56 ± 0.44		1.15 ± 0.033
Step Length (m)	0.41±0.019	0.33±0.034	0.46±0.027	0.44±0.045*	0.39±0.025	0.39±0.032	0.42±0.021	0.45±0.042	0.67 ± 0.033
Step Time (s)	1.47±0.30	1.62±0.26	1.13±0.21*	1.28±0.20*ǂ	1.34±0.26	1.44±0.29	1.20±0.19	1.34±0.24	0.57 ± 0.016
Single support in (%)	25.77±2.24	20.09±1.58	29.70±2.61§	25.73±2.64*	26.07±2.50	24.59±3.19	27.18±2.84	24.85±3.05	36.80 ± 0.41
Double support in (%)	54.33±3.80	54.28±3.78	44.68±5.07*	44.87±5.19*	50.30±5.47	49.30±5.49	48.09±5.72	47.84±5.94	26.61 ± 0.90
Swing time in (%)	20.64±1.76	25.63±2.33	25.61±2.43*	29.41±2.77§	23.63±3.32	26.12±2.62	24.73±3.07	27.31±3.15	36.59 ± 0.53
Stance time in (%)	79.36±1.76	74.37±2.33	74.39±2.43*	70.59±2.77§	76.37±9.38	73.88±7.41	75.27±8.68	72.69±8.92	63.41 ± 0.53
SW/ST ratio	0.25±0.026	0.35±0.042	0.35±0.049*ǂ	0.43±0.057§	0.33±0.18	0.36±0.13	0.34±0.16	0.39±0.17	0.58 ± 0.012
Step length symmetry	1.03 ± 0.011		1.03 ± 0.0076		1.03 ± 0.014		1.02 ± 0.011		
Swing time symmetry	1.29 ± 0.045		1.18 ± 0.049		1.30 ± 0.25		1.16 ± 0.13		
Stance time symmetry	1.08 ± 0.015		1.06 ± 0.019		1.07 ± 0.018		1.06 ± 0.021		
SW/ST ratio symmetry	1.40 ± 0.068		1.26 ± 0.072		1.40 ± 0.33		1.23 ± 0.22		

*significant difference post-training (12wk) compared to pre-training (00wk) ($p \leq 0.05$); §substantial difference at post-training (12wk) compared to pre-training (00wk) ($p \leq 0.1$); ǂsignificant difference between the A&L and Leg groups post-training ($p \leq 0.05$).

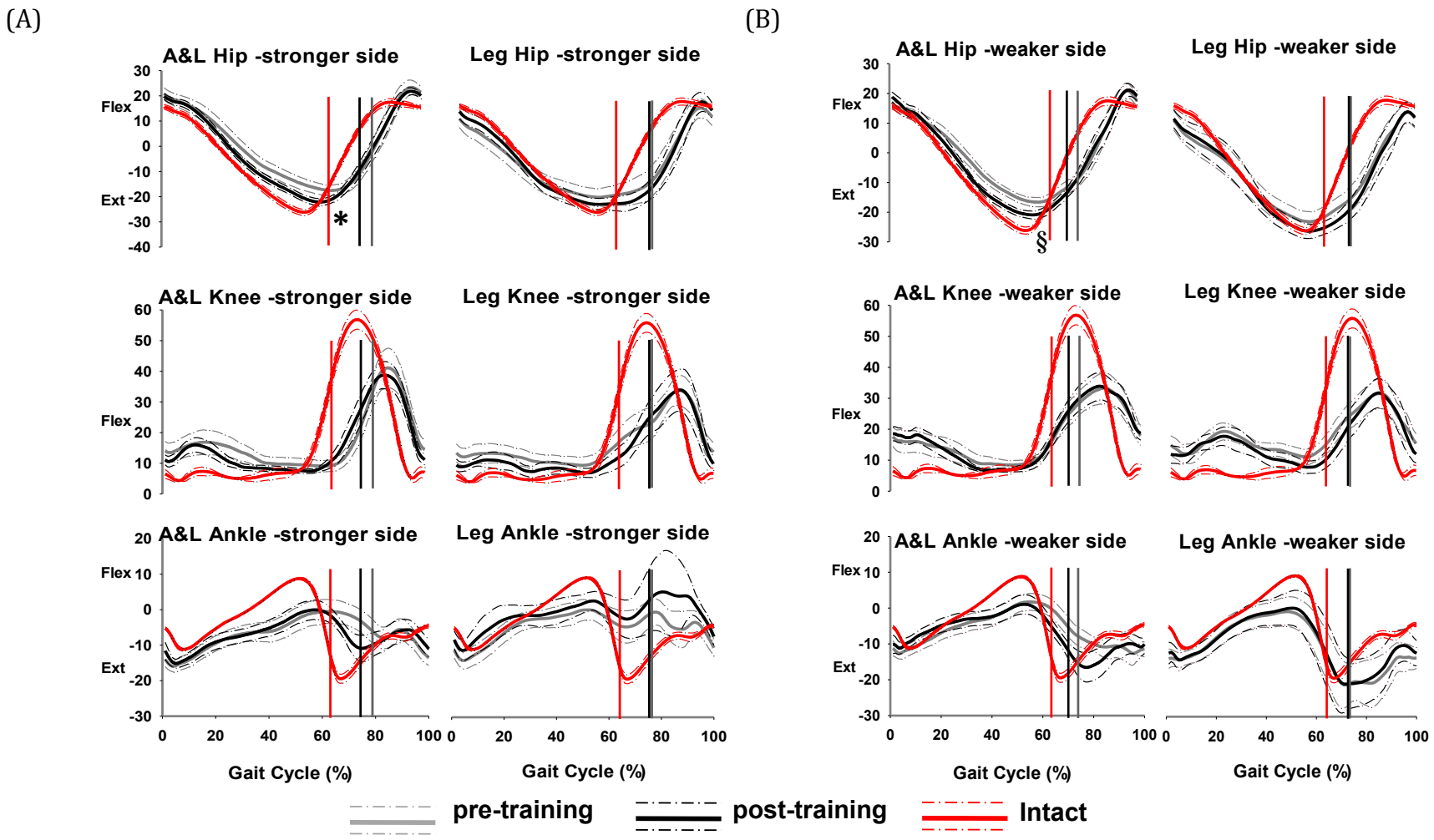


Figure 2.7. Summary of joint kinematics.

Summary of joint kinematics in NI (NI: n=6) and both iSCI groups on the (A) stronger side and (B) weaker side (A&L: n=7; Leg: n=8). The vertical lines indicate the transition from stance to swing phase. After training, the A&L group had an earlier transition to swing than the Leg group. Solid line indicates the group average, and the dash-dot line indicates the standard error. *significant difference of the minimal angle during stance after 12 weeks of training (12wk) compared to pre-training (00wk) ($p \leq 0.05$); §substantial difference of the minimal angle during stance after 12 weeks of training (12wk) compared to pre-training (00wk) ($p \leq 0.1$).

Figures 2.8A (top) shows a representative example of hip-knee cyclogram on the stronger side of a participant with iSCI (S4L). The ACC of the hip-knee cyclogram which indicates the level of hip-knee cycle consistency, did not differ significantly between the A&L and Leg group at pre-training on either the stronger leg or weaker leg (A&L: 0.47 ± 0.033 weaker side, 0.46 ± 0.035 stronger side; Leg: 0.48 ± 0.034 weaker side, 0.47 ± 0.033 stronger side) **(Fig. 2.8B).** Similarly, the area of cyclogram at pre-training, which indicates the hip-knee joint range of motion, was not significantly different between the two groups (A&L: 809.42 ± 286.53 deg^2 weaker side, 964.66 ± 237.71 deg^2 stronger side; Leg: 731.58 ± 204.00 deg^2 weaker side, 824.38 ± 194.63 deg^2 stronger side) **(Fig. 2.8C).**

Both groups had improvements on the stronger and weaker sides after training. On the stronger side, a significantly higher ACC of the hip-knee joint movement (Time p=0.016) and a larger area within the cyclogram (Time p=0.042) were found as a function of training. Within group analysis further showed that the significant change in ACC only occurred in the A&L group, by an increase of 0.057 ± 0.0086 (p=0.001), but not in the Leg group with an increase of 0.037 ± 0.031 after training (p=0.27).

Because ankle joint motions are strongly associated with foot clearance, we analyzed the toe trajectory to further examine the kinematic pattern of foot movement. **Figures 2.8A (bottom)** also shows an example of toe trajectory on the stronger side from participant S4L. At pre-training, the A&L and Leg groups had a similar value of maximal toe elevation during the gait cycle on both sides (A&L: weaker side, 0.050 ± 0.0057 m; stronger side, 0.064 ± 0.0053 m. Leg: weaker side, 0.054 ± 0.0098 m; stronger side, 0.072 ± 0.0097 m). After training, a large increase in maximal toe elevation by 14.33 ± 9.023 % on the weak side was found in the A&L group (p=0.22) and 12.53 ± 10.81 % in the Leg group (p=0.25). The increase was similar on the strong side too. No significant group difference was found.

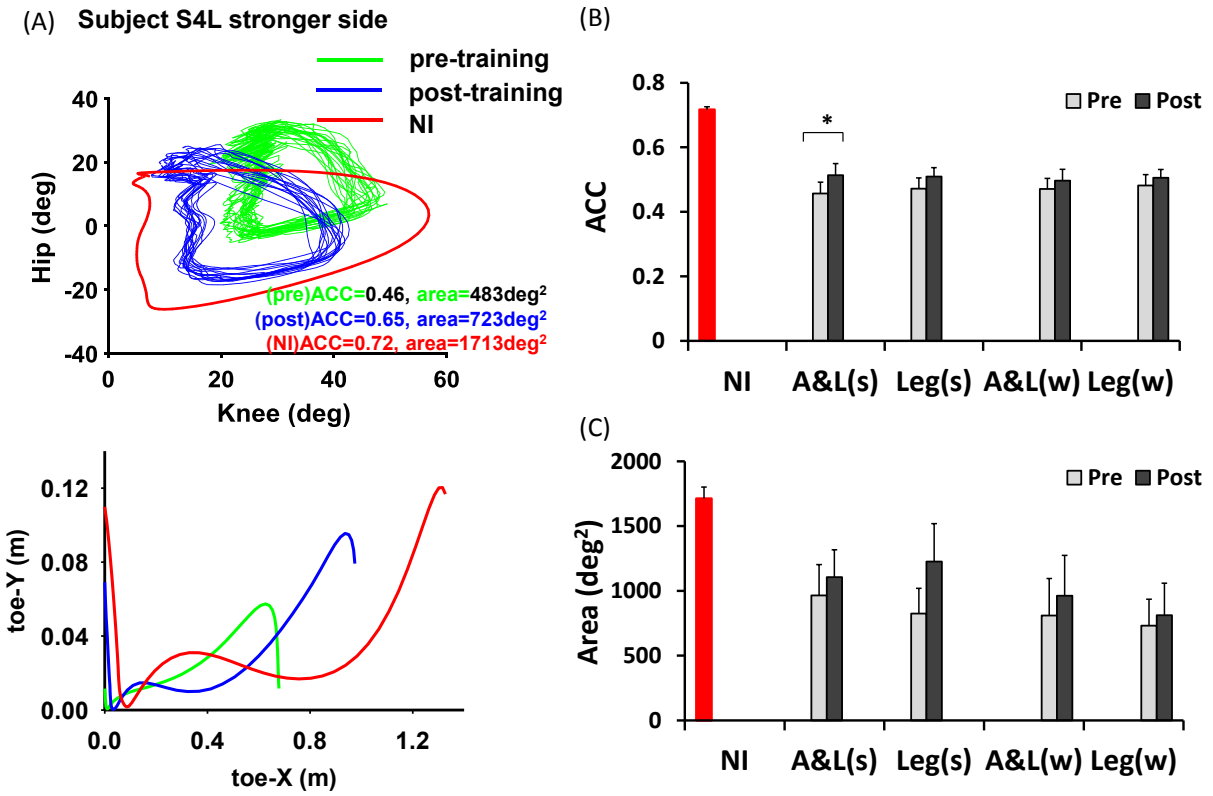


Figure 2.8. Hip-knee cyclogram and toe trajectory.

(A) Examples of the hip-knee cyclogram (top) and toe trajectory (bottom) on the stronger side during gait cycle in a participant with iSCI (S4L). Green indicates pre-training data and blue indicates post-training data. Red indicates average data in the NI group (NI: n=6). Toe-X and toe-Y indicate the horizontal and vertical toe trajectory during gait cycle, respectively. (B) ACC of the hip-knee cyclogram on the stronger (s) and weaker (w) side in the NI group (NI: n=6), and in the A&L group and the Leg group at pre-training and post-training (A&L: n=7; Leg: n=8). (C) Area of the hip-knee cyclogram on the stronger (s) and weaker (w) side in the NI group (NI: n=6), and in the A&L group and the Leg group at pre-training and post-training (A&L: n=7; Leg: n=8). *significant difference ($p \leq 0.05$).

EMG activity:

a) Intra-leg:

Both iSCI groups had similar values of magnitude and phase components of the EMG metrics at pre-training (data not shown). More regulated muscle activities of the TA and SOL muscles during walking were observed after training, but significant differences were only observed in the SOL muscle and only in the A&L group. Specifically, on the stronger side, both SOL magnitude and phase components were significantly improved (Time $p<0.005$) as a function of

training in the A&L group. Also post-training, the A&L group showed significantly larger increases in the SOL magnitude (A&L: 7.33 ± 1.33%; Leg: 0.95 ± 1.98%; p=0.029) and phase component (A&L: 10.93 ± 1.0064%; Leg: 3.50 ± 2.22%; p=0.019) components than the Leg group. Similar results were observed on the weaker side, where significantly larger values in the phase component post-training only occurred in the A&L group.

Figure 2.9 summarizes the onset and active duration of individual muscles. Overall, all muscles except the TA in the participants with iSCI had lengthened active durations relative to participants with intact nervous system. After training, both the A&L and Leg groups showed significant reductions in the active duration of SOL on the stronger side **(Fig. 2.9A, B);** however, significant changes in the SOL active duration on the weaker side were only seen in the A&L group **(Fig. 2.9C).** Furthermore, the A&L group had a significantly shorter active duration in RF on the weaker side.

b) Inter-leg:

To further understand the coordination between legs, the phase difference between the onsets as well as the co-activation of homologous muscle pairs during the gait cycle were determined. As indicated in **Figure 2.9**, for both A&L and Leg groups, the onset of each homologous muscle pair between legs (e.g., onset of LTA vs. onset of RTA) were similar before and after training. As a result, there was no significant change in the phase difference of onsets for any homologous muscle pair for both groups.

Figure 2.10 depicts the EMG co-activations of the TA and SOL muscle between the left and right legs, which are substantially larger than those in intact participants. Both iSCI groups had similar values in this measure at pre-training for both muscle pairs. After training, there was a significant reduction in LSOL vs. RSOL muscle co-activation but only in the A&L group (p=0.005). Collectively, the findings may suggest that the A&L group had better training-induced regulation in the EMG activity than the Leg group.

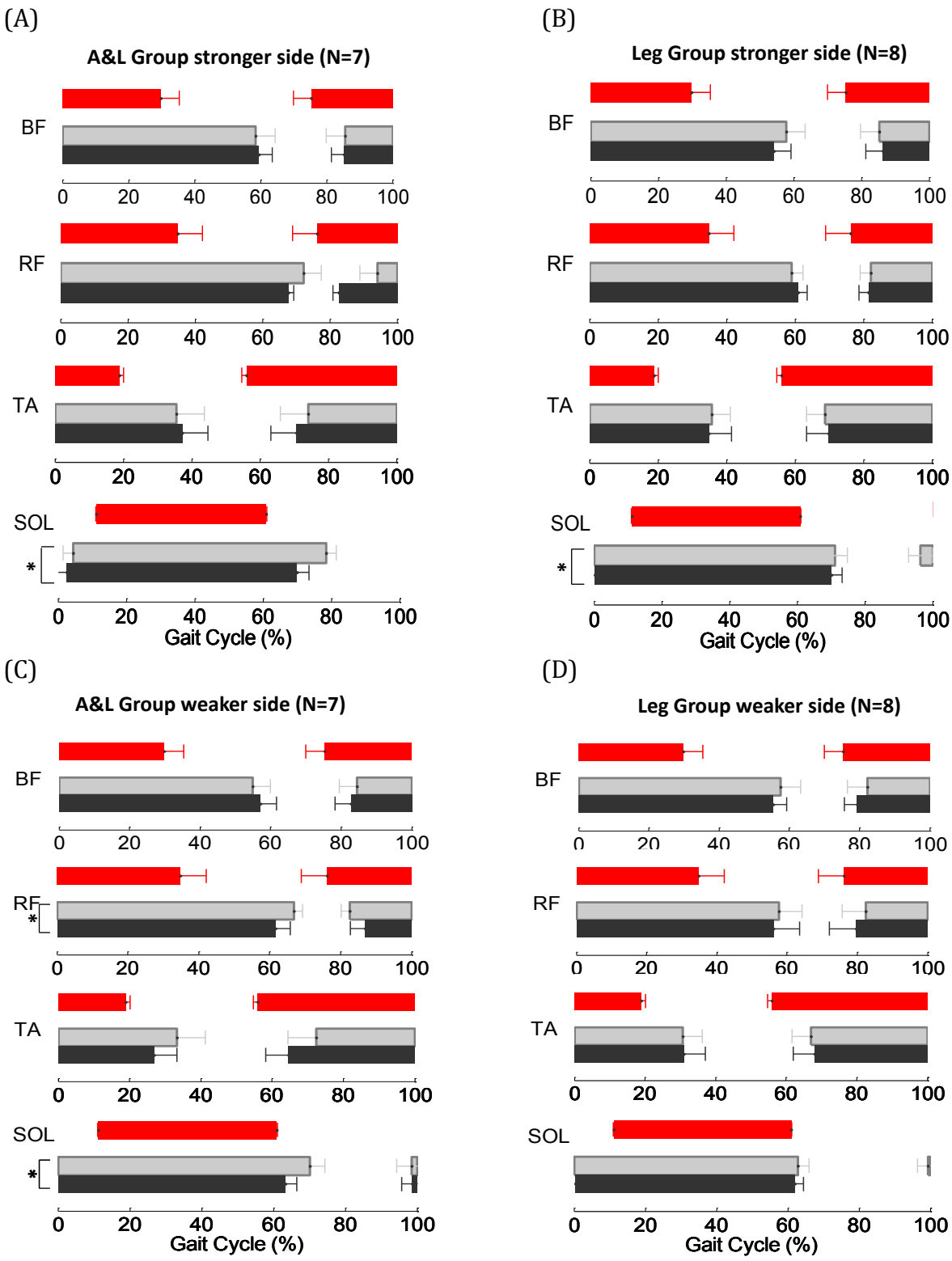


Figure 2.9. Muscle EMG activation patterns.

(A) Group data of EMG activation patterns of muscles on the stronger side in the A&L group and (B) Leg group (A&L: n=7; Leg: n=8); (C) Group data of EMG activation patterns of muscles on the weaker side in the A&L group and (D) Leg group (A&L: n=7; Leg: n=8). Gray indicates the data collected at pre-training, and black indicates the data collected at post-training. Red are the group data collected from the NI participants (NI: n=6). *significant difference ($p \leq 0.05$).

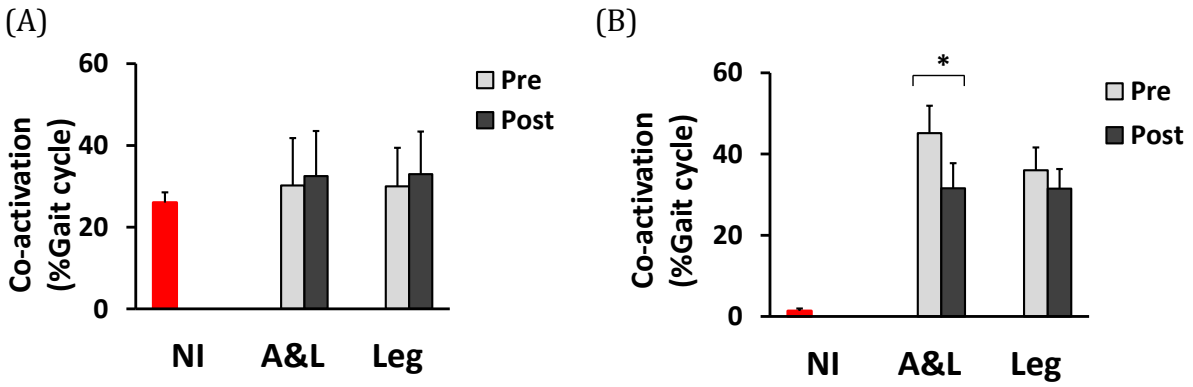


Figure 2.10. Muscle EMG co-activation.

(A) Group data of EMG co-activation of the TA muscle on the left and right leg and (B) EMG co-activation of the SOL muscle on the left and right leg (A&L: n=7; Leg: n=8). Red bars are the grouped data from the NI participants (NI: n=6). *significant difference ($p \leq 0.05$).

2.4 Discussion

The goal of this project was to explore the efficacy of non-gait-specific training for the improvement of ambulation, as well as to investigate the role of the arms in the rehabilitation of walking after iSCI. In people with quadriplegia and paraplegia, voluntary arm crank along with electrical stimulation-induced leg exercise produced improvements in metabolic, hemodynamic and cardiovascular responses (Davis et al., 1990; Hooker et al., 1992a). To the best of our knowledge, the present study is the first to investigate systematically the effects of cycling on walking, and the role of the arms in gait rehabilitation.

Overall, the main findings were: 1) Maximal overground walking speed was significantly increased in both cycling groups relative to pre-training levels, and the increases in the A&L group were significantly larger than those in the Leg group. 2) Cycling training also significantly improved walking distance relative to pre-training levels, with substantially greater increases in the A&L group. 3) Cycling training resulted in significant improvement in the AIS motor scores of the lower extremities in both groups. 4) Most spatiotemporal parameters of gait in the weaker and stronger legs significantly improved after training in the A&L group, while Leg group only

had significant improvement in the preferred walking speed and stride length. 5) A&L cycling resulted in significant improvement in the consistency of hip-knee coordination. 6) Intra- and inter-leg regulations of EMG activity, especially in the extensor muscles, were observed in both groups, but significant improvements were mostly found in the A&L group. Collectively, these findings suggest that non-gait-specific cycling training results in substantial improvements in walking capacity after chronic iSCI. Moreover, active engagement of the arms simultaneously with the legs can produce larger improvements in walking than engaging the legs alone.

Participants and training:

Among the participants in the cycling training, there was a dominance of AIS D cervical SCI, with two AIS C participants in each of the A&L and Leg groups. The participants had chronic injuries which occurred up to several decades earlier. Within each group, half of the participants had maximal walking speed above 0.45 m/s (approximate minimal walking speed for a community ambulator) and half below. Therefore, the study population had a wide range of impairment in walking function, which resulted in large variability in some of the outcome measures. Nonetheless, this range afforded the opportunity to assess, albeit qualitatively, improvements in walking metrics in "low" and "high-functioning" individuals. Regardless of initial walking capacity, the study employed a consistent protocol, including the training durations, number of hourly sessions and instructions to all participants (except S8A), which allowed direct comparison between the cycling groups.

Cycling to improve walking speed and distance:

Regardless of training group, there were significant improvements in the 10-meter walking speed and 6-minute walking distance after training in all study participants. This included the "high functioning" individuals who also showed positive increases in walking metrics, indicating that a ceiling effect in walking capacity had not been reached, as has also been suggested by others (Kuerzi *et al.*, 2010). Furthermore, in the A&L group, the "low functioning" participants showed substantially larger improvements in walking metrics than "low functioning" participants in the Leg group. Nonetheless, we found that in both A&L and Leg groups, the post-training increases in maximal walking speed were higher than the minimal important difference (MID) (0.06 m/s) in the SCI population (Musselman, 2014). More importantly, with an average post-training

increase of 0.27 m/s in the A&L group, the improvement of walking speed in this group have exceeded the minimally clinically important difference (MCID) (approxiamately 0.11-0.16 m/s) (Forrest et al., 2014). The results showed that repetitive cycling training of the arms and legs or legs alone can translate into significantly faster overground walking speed and longer walking distance. This observation challenged the widely accepted motor learning principles of task specificity in the rehabilitation of walking (Edgerton et al., 1997; Behrman and Harkema, 2000; Mastos et al., 2007). As an elementary building block on which the rhythmic movements are based, a core subcortical network shares commonalities in neural control of rhythmic activities across various types of locomotion (Zehr and Duysens, 2004). Therefore, we believe that cycling training could improve the common elements in the spinal network that are also responsible for producing rhythmic walking. The results of the present study may provide the most direct evidence of that to date.

One source of contribution to the improvement in post-training walking could be the change in muscle strength. Previous studies in participants with chronic SCI showed that for both the weaker and stronger sides, muscle strengh (particularly hip muscles) was strongly correlated with walking speed, distance and independence of walking (Kim et al., 2004; DiPiro et al., 2015b). Yang et al. (2011) suggested that preserved strength in key muscle groups could allow for improvement in walking speed after locomotor training in people with iSCI (Yang *et al.*, 2011). Nonetheless, an improvement in the strength of leg muscles may not necessarily result in improved walking capacity (Wirz *et al.*, 2006; Yang *et al.*, 2011). In the present study, the two groups had a similar range and average of AIS motor scores pre-training, especially for the lower extremities. Regardless of training group, we oberserved a similar and significant improvement in the motor scores post-training, as well as a strong correlation between the change in motor scores and change in walking speed or distance. Therefore, increased muscle strength in the lower extremities was likely contributing to the improvement in both groups, but does not necessarily explain the larger increases in walking speed and distance in the A&L group. Moreover, it is possbile that A&L cycling training has engaged more trunk muscles than the Leg cycling only, which could partically account for an improvement in balance and ultimately, walking stability. Nonetheless, both groups had similar significant improvements in the Berg

Balance score after training; therefore, this too may not explain the larger improvements seen in the A&L group, given that similar post-training changes in balance were seen in the two groups.

The repetitive cycling movements throughout training likely increased the magnitude and regulation of afferent feedback to spinal and supraspinal circuitry, an input that is essential for the development of neural plasticity for locomotion (Van de Crommert et al., 1998; Behrman et al., 2006; Rossignol, 2006). The assistance of repetitive FES is also important to develop use-driven adaptations which lead to neural development (Gary *et al.*, 2011; Sadowsky *et al.*, 2013). Collectively, this could explain the significant increase in AIS sensory scores post-training; however, it may not explain the change in walking speed and distance, especially in the A&L group, given the weak correlation between sensory scores and walking metrics.

Linkage between rhythmic upper limb and lower limb movement produces coordinated movement in animals and humans (Miller et al., 1975; Ferris et al., 2006). Studies of cervico-lumbar modulation of reflexes have supported that rhythmic arm movement could sculpt leg muscle activation, even after SCI (Frigon et al., 2004; Hiraoka and Iwata, 2006; Loadman and Zehr, 2007; Zehr et al., 2007b; Kawashima et al., 2008), suggesting that arm movement changes the excitability in the lower limbs, likely through central pattern generator (CPG)-driven modulation. Therefore, we postulate that arm cycling along with rhythmic leg cycling exercises, may have introduced a facilitation to the leg locomotor activities (Zhou et al., 2016c). We suggest that through repetitive faciliation over the course of training, neural interaction between arm and leg during rhythmic locomotor-like movement was enhanced, as well as the spinal circuitry related to the production of leg activities (Zehr et al., 2007b; Ogawa et al., 2015). For example, coupled recumbent arm and leg stepping showed that self-driven arm activation significantly facilitates neuromuscular activation of the legs, and the faciliation is graded by the the level of exertion in the upper limbs (Huang and Ferris, 2004; Kao and Ferris, 2005). Therefore, the facilitaton induced by coupled arm and leg exercise in this study might contribute to the substantially larger amount of change in walking speed and walking distance in the A&L group than the Leg group post-training (Zhou et al., 2016c).

Cycling to improve the quality of walking:

Spatiotemporal measures during walking:

People with SCI generally walk slowly and take small steps (Pépin et al., 2003a; 2003b). In the present study, both A&L and Leg groups started with a preferred walking speed below 0.4 m/s **(Table 2.2),** but reached a level above 0.4 m/s after training, suggesting a clinically functional change in their ambulation. Also, significant increases in stride length in both iSCI groups after training could be associated with an improvement in walking speed (De Quervain *et al.*, 1996).

Similar to other chronic types of hemiparesis (e.g., stroke, central cord syndrome), the SCI participants in both groups showed reduced swing time, prolonged stance time, and a dependency on the stronger leg before training (Balasubramanian *et al.*, 2007; Gil-Agudo *et al.*, 2013). After training, the A&L group achieved significant post-training improvements in most of the spatiotemporal measures, including faster speed, larger steps, increased swing time and decreased stance time, which indicated better dynamic balance and walking control. Importantly, the A&L group had significantly larger improvement in the SW/ST ratio post-training than the Leg group. As an indicator of balance control and having strong correlations with speed (Bowen *et al.*, 2001; Shin *et al.*, 2011), the increase in the SW/ST ratio, together with the shortened single and double support time in the A&L group, could contribute to the better walking performance in this group. Furthermore, although not statistically significant, swing time symmetry and SW/ST ratio symmetry in both groups were substantially changed towards normal (value of 1), suggesting improved coordination between the legs (Patterson et al., 2010).

Joint kinematics during walking:

Reduced range of motion and abnormal motion at the joints are some of the limitations of walking speed in people with SCI (Pépin et al., 2003b). For example, reduced range of motion of the hip and knee in SCI participants at pre-training could limit step length or result in a stiff-legged gait and impaired foot clearance (Piazza and Delp, 1996; Riley and Kerrigan, 1998). Although the joint kinematics remained abnormal after training compared to neurologically intact participants, both groups with iSCI showed improved range of motion at the hip joint (e.g., hip extension) post-training **(Fig. 2.7).** One reason could be the stimulation-assisted contraction of the gluteal muscles during cycling training, which reinforced the function of hip extension

(Triolo *et al.*, 2001). However, only the A&L group reached a significant level of difference in hip extension after training, perhaps through a more regulated neural network that adapted the proprioceptive feedback during training (Dietz, 2002b). Inadequate hip extension during stance could also reduce stability since the centre of mass could move too far forward increasing the risk of falling (van der Salm *et al.*, 2005). Therefore, significantly enlarged hip extension may at least partially explain the larger improvement in post-training walking speed, distance and spatiotemporal paramters in the A&L group. Furthermore, both groups demonstrated higher consistency and larger area within the hip-knee cyclgram after training **(Fig. 2.8),** with significantly higher consistency found only in the A&L group. Awai et al. (2014) suggested that the distorted cyclogram after SCI may not only originate from motor deficits, but could also be associated with limited access to supraspinal control and impaired sensory feedback (Awai and Curt, 2014). Therefore, we speculate that the improved consistency and range of motion in intra-leg joint coordination could rise from enhanced descending input and modulation from peripheral feedback through training. The significant improvement in joint consistency observed in the A&L group could be due to a better regulation of the preserved neuromuscular system by active arm involvement during training.

Inadequate anke dorsiflexion and excessive ankle plantarflexion indicate an inefficient movement strategy (van der Salm *et al.*, 2005), which reduces toe elevation during gait (Ditunno and Scivoletto, 2009). Training did not reduce the excessive ankle plantar flexion or increase dorsiflexion in the iSCI groups. One of the reasons could be the lack of stimulation of the TA muscle. Only one participant in each group had TA muscle stimualtion in their training (S6A, S2L). Therefore, the average strength of TA muscle in both groups may have not reached a significant difference after training, and therefore failed to provide adequate dorsi-flexion. However, improvements in the maximal toe elevation still noticeably occurred on the weaker side in both groups after training.

Muscle activies during walking:

Modifying muscle activity towards a more regulated pattern after locomotor training was related to the improvement in walking performance, such as speed, distance, walking independence and accurate foot positioning in space (Dietz *et al.*, 1994; 1995; 1998; Nymark *et al.*, 1998). The

findings in our study suggest that muscle activity can also be regulated through cycling training. Better regulation was observed in the A&L group which also had larger improvements in walking.

After chronic SCI, extensor msucles are excessively active through the gait cycle (Forssberg et al., 1980b; Pépin et al., 2003b). After training, better intra- and inter-leg regulation in the SOL muscle was found in the A&L group relative to that in the Leg group. Consistent with the findings in the present study, Gorassini et al. (2008) found substantial reduction in prolonged extensor muscle activity, although not in SOL, during treadmill walking in chronic iSCI participants (Gorassini *et al.*, 2008). The difference could be partially due to the differences in EMG activity and kinematic patterns between treadmill and overground walking (Murray et al., 1985; Alton et al., 1998). Moreover, in their study, the EMG activity was averaged from the left and right legs. In the present study, after separating the analysis into weaker and stronger sides **(Fig. 2.9),** we found in the A&L group a significantly shorter RF activation on the weaker side after training, and correspondingly a substantial increase in RF activation during swing phase on the stronger side. This could be the associated compensatory change on the stronger side with the increased walking speed post-training (Forssberg et al., 1980b). It also suggests that in order to adapt to a new motor learning strategy, the stronger leg may take a more compensatory role. As an emerging focus in rehabilition locomotor training (Lam et al., 2008b; 2009), enhancing the flexor muscle activity during swing phase, such as RF, could help improve gait speed (Pépin et al., 2003a) and obstacle avoidance (Ladouceur *et al.*, 2003). Therefore, a new motor strategy after A&L training could also contribute to the better walking function in this group.

In Visintin and Barbeau's study (1994), people with iSCI showed better gait symmetry and more normal EMG activity, when the parallel bars were removed to allow arm swing during BWS treadmill training (Visintin and Barbeau, 1994). Unlike the over-compensation of muscle activity in the hip, knee, and ankle flexion seen when participants used parallel bars for support during walking, a more normal gait pattern emerged after the bars were removed. Similar observations were found in people with stroke, with an increased activity in extensor muscles during stance, as well as in the dorsiflexors during swing, when arms freely swinging compared to when arms holding onto the handrails (Stephenson et al., 2010). Further neurological analysis should be

conducted to investigate the changes in the nervous system for leg activity induced by movement of arms (Zhou et al., 2016a; 2016c).

The role of the arms in rehabilitation:

Rehabilitation strategies to improve ambulation have to date focused on restoring leg functions through physical therapies and gait-specific locomotor training. Systematic reviews on recent studies of novel gait-specific locomotor training protocols focused on the lowerlimb to enhance functional ambulation in people with SCI can be found in (Morawietz and Moffat, 2013; Lam et al., 2014). The present study provided longitudinal and systematic evidence to support the application of non-gait-specific training in rehabilitation for ambulation. Furthermore, for the first time, this study demonstrated better improvements in walking when actively engaging the arms in rehablitation.

We compared our findings with published studies that have incorporated locomotor training focused on the lower limbs in chronic (at least ≥7 month post-injury) AIS C or/and D SCI participants, such as (Alexeeva et al., 2011; Field-Fote and Roach, 2011; Yang et al., 2011; Harkema et al., 2012b; Yang et al., 2014) **(Fig. 2.11)**. In our study, there was an increase of 0.27 ± 0.072 m/s in post-training walking speed in the A&L group and 0.092 ± 0.022 m/s in the Leg group. The reported increase in speed in other training studies were 0.14 m/s (Yang *et al.*, 2011), ~0.04-0.07 m/s (Yang *et al.*, 2014), 0.10-0.16 m/s (Alexeeva *et al.*, 2011), 0.09-0.11 m/s (Harkema et al., 2012b), and 0.01-0.09 m/s (Field-Fote and Roach, 2011) **(Fig. 2.11A)**. With regard to the change in walking distance, the A&L group increased by 91.58 ± 36.24 m and the Leg group increased by 32.12 ± 8.74 m post-training in the present study. Reported walking increases after locomotor training were 24-44 m (Harkema et al., 2012b) and ~10-30 m (Yang *et al.*, 2014) **(Fig. 2.11B)**. Interestingly, comparison of these results suggests that the improvements in the Leg cycling group in the present study were similar to those obtained with the above gait-specific training paradigms which largely focused the legs. In some of the studies, arm swing was encouraged during treadmill locomotor training (Thomas and Gorassini, 2005; Field-Fote and Roach, 2011; Tester et al., 2011; Yang et al., 2011), but not systematically monitored and the support of parallel bars were always provided. Furthermore, in the trainings that involved walking with assitive devices, the arms were supporting a large proportion of body weight of the

participants, instead of producing rhythmic movement. Therefore, stystemtically engaging active and rhythmic arm movement in gait rehabilitation, as shown in the present study, could be the key to the nearly doubled improvements in walking metrics. The result suggests that the rhythmic arm movement can play a very significant role in the rehabiltiation of walking. Nonetheless, it is important to interpret these comparisons with caution due to the limited number of participants in the present study. Also, all of our participants were capable of completing the 10-meter and 6-min walking tests at pre-training, suggesting that on average, they may have been higher functioning than participants in the other studies.

The routine use of the systems for leg cycling and simultaneous arm and leg cyling in this study demonstrated that the equipment is safe, reliable and easy to use. The occurrence of adverse events was low during the study period. Adverse events included muscle soreness after the first few training sessions or sometimes when cycling resistance was increased, but this usually disappeared in a few days. One participant developed skin allergy to the hydrogel electrodes (e.g., PALS® platinum electrodes, Axelgaard Co., CA, USA) used for FES during training, in which case the electrodes were replaced with hypoallergenic gel electrodes (e.g., PALS® blue gel electrodes, Axelgaard Co., CA, USA) and the allergy subsided. None of the participants dropped out of the sudy because of adverse events. The majority of participants found the training apparatus comfortable and easy to use. A distinctive difference between this cycling training intervention and clinical rehabilitation may be a substantial reduction in therapist labor intensity. For example, gait-specific locomotor training therapies, especially treadmill locomotor training, were suggested to have several personnel to assist in the training session (Behrman and Harkema, 2000; Morrison and Backus, 2007). In this study, only one person was needed for the entire process of preparation, set-up (e.g. set up stimulation paramenters, apply electrodes) and supervising the cycling training. The length of gait-specific locomotor training sessions is often limited by therapist fatigue rather than the patient (Van Hedel and Dietz, 2010). A complete hour of locomotor training within a clinical session is highly uncommon. Cycling training could provide meaningfully long durations of training per session since manual assistance from the therapists is not required to facilitate the cycling. For example, no manual assistance was provided to the participants during training throughout the present study. Therefore, the findings from the present study could lead to an effective intervention for gait rehabilitation. Cycling

intervention may be readily implemented in clinical care since ergometers are common devices in rehabilitation centers. Lastly, the equipment required for the cycling, especially the leg ergometers, are becoming more and more available in rehabilitation clinic, although only a few rehabilitation clinics or community centres have arm-leg-coupled cycling equipment similar to that used in the A&L group in the present study. Furthermore, it is not common for such institutions to have therapists capable of providing the type of controlled FES required for FES-assissted cycling training sessions. Because the present study was based on a selective group of people with SCI (AIS C or D), future studies should explore the general efficacy of the proposed A&L cycling intervention in a broader population of people with SCI, as well as other neural injuries or diseases, including stroke, cerebral palsy and multiple sclerosis.

2.5 Other Contributions

Active engagement of the arms in training may also result in better cardiovascular function and larger aerobic capacity after iSCI. Improved fitness and metabolic response in people with iSCI as a result of training has been reported for various types of rehabilitation interventions, including BWS locomotor training (de Carvalho et al., 2006; Alexeeva et al., 2011; Kressler et al., 2013), leg cycling training (Faghri et al., 1992; Yaşar et al., 2015), arm cycling training (Warburton et al., 2007), and combined arm and leg cycling/stepping training (Nagle et al., 1984; Heesterbeek et al., 2005; Thijssen et al., 2005; DiPiro et al., 2015a). Although more evidence is needed, hybrid exercise that combines the arms and legs may provide relatively greater cardiorespiratory stress than separate leg exercise or arm exercise for persons with SCI, which ultimately results in greater improvement in fitness (Nagle et al., 1984; Krauss et al., 1993; Mutton et al., 1997; Verellen et al., 2007; Hettinga and Andrews, 2008). In the present study, the greater increase in walking capacity in the A&L group may partially be due to better improvement in fitness. Nonetheless, the improvements in the regulation of muscle activity during walking may be the result of improvements in descending and spinal mechanisms (Zhou et al., 2016a; 2016c) which are not directly driven by changes in fitness.

Patterned electrical stimulation was delivered to various muscles in the present study. This repetitive stimulation is important to develop use-driven adaptations which lead to neural

development (Gary *et al.*, 2011; Sadowsky *et al.*, 2013). Stimulation of the common peroneal nerve at physiologically relevant frequencies along with sensory feedback during stepping, was crucial for inducing short-term plasticity in a spinal circuit (Perez *et al.*, 2003). Sensory inputs evoked byelectrical stimulation might also have a short-term effect on cortical excitability (Kaelin-Lang *et al.*, 2002). Moreover, increase in muscle strength was found in muscles targeted by submotor threshold stimulation in longitudinal training studies (Hoffman and Field-Fote, 2007; Field-Fote, 2009). Therefore, the training paradigms in this study may have augmented the activation of afferents, parellelling with the mechanical events of muscle contraction, to enhance the sensorimotor integration at the spinal and supraspinal levels (Dobkin, 2003). Ultimately, FES-assited muscle contraction can regulate neural activity and enhance sensory feedback, both of which may have contributed to the significant improvements in the sensory test.

2.6 Limitations

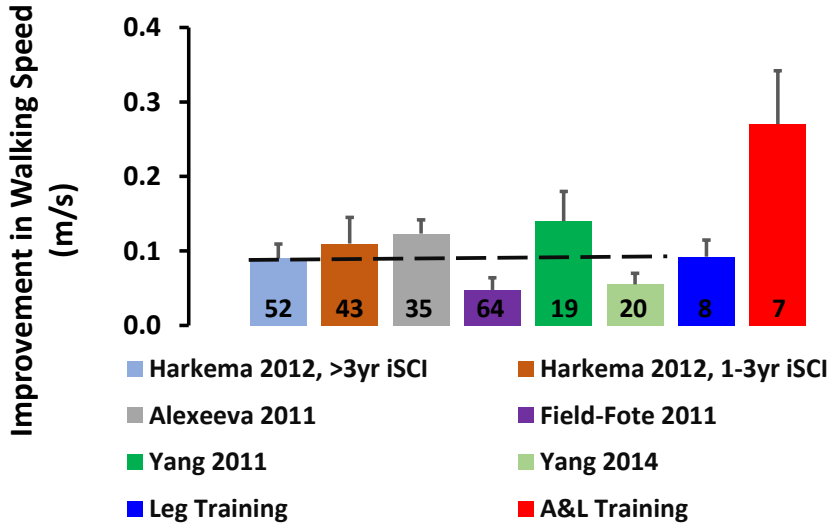
As a pilot study, a small sample size of participants was recruited in each training group. The participants in this study also account for a selective subpopulation of people with SCI (chronic iSCI with AIS grade C or D). Future studies should investigate the generalized efficacy of the training invervention in people with SCI, as well as other neurological injuries and diseases, such as stroke and cerebral palsy. Furthermore, while similar participant demographics and training durations to the present study were considered when selecting locomotor training studies to compare the improvements in walking to, a direct comparison can be made in future studies by adding a new control group of treadmill or overground locomotion training to the study. Because the experimenters were not blinded to the training groups nor the outcome measures, a bias in the comparison of assessment between groups could be unintentionally introduced. A double-blinded study design is encouraged in future investigations.

2.7 Conclusion

This study proposed a new rehabilitation intervention that actively involves the arms and legs in cycling for the improvement of walking after SCI. We suggest that an FES-assisted arm and leg cycling paradigm could provide larger improvements in overground walking capacity than paradigms focusing on leg training only. Evidence was also presented supporting the translation

of rhythmic non-gait-specific training to improvements in walking capacity, gait metrics and the neural regulation of walking.

(A)



(B)

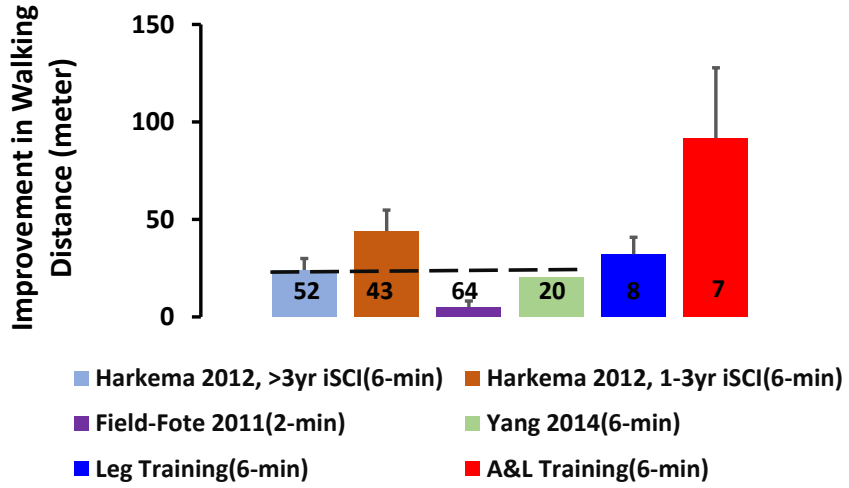


Figure 2.11. Comparisons of the improvement in walking.

(A) A comparison of the improvement in walking speed (m/s) among recent studies of novel locomotor training protocols focused on the lower limbs, as well and the two cycling groups in the present study. (B) A comparison of the improvement in walking distance (m) among recent studies of novel locomotor training protocols focused on the lower limbs and the two cycling groups in the present study. Figures were created based on the reported values in the referred literature. Values are expressed as mean ± standard error. Horizontal dashed line indicates the average improvements across the recent studies. Sample size for each study is indicated in the bar. 6-min and 2-min indicate that the walking distance was obtained from a 6-min walking test and 2-min walking test, respectively.

Chapter 3. The Effect of Cervico-lumbar Coupling on Spinal Reflexes during Cycling after Incomplete Spinal Cord Injury

Zhou R[1], Assh J[2], Alvarado L[1], Chong SL[2], Mushahwar VK[1, 2]

1. Neuroscience & Mental Health Institute, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada
2. Division of Physical Medicine & Rehabilitation, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada

3.1 Introduction

Cervico-lumbar coupling was first demonstrated in animal experiments in the 1970s and 80s (Miller et al., 1975; Yamaguchi, 1986). In quadrupedal animals, there are clear functional interconnections between the locomotor networks for the forelimbs and hindlimbs, providing interlimb coordination (Ballion et al., 2001; Juvin et al., 2005). The forelimbs can modulate neural networks engaged in hindlimb locomotor activity; e.g., initiating step-like movements in the suspended hindlimbs of intact dogs (Shik and Orlovskii, 1965). The frequency of forelimb activation can also dominantly regulate the duration of the locomotor cycle of the hindlimbs in decerebrated animals (Akay et al., 2006). In postnatal rats, the forelimbs mature earlier than the hindlimbs and are mainly used for movement in the environment at the early stage (Altman and Sudarshan, 1975; Clarac et al., 1998; Brocard et al., 1999). However, other evidence has challenged the dominant influence of the forelimbs in stepping performance (Ballion et al., 2001; Gerasimenko et al., 2009). Studies in animals and humans have suggested that the lumbar cord could also regulate the excitability of the cervical cord. Lumbar central pattern generators (CPGs) in isolated neonatal rat spinal cords generated a greater influence on cervical CPGs than the other way around (Juvin et al., 2005; Gordon et al., 2008; Juvin et al., 2012). Also in humans, the cadence of leg cycling was not affected by alterations in arm cadence, but involuntary changes in the cadence of arm cycling were seen when leg cycling cadence changed (Sakamoto et al., 2007). Taken together, the interaction between cervical and lumbar spinal networks is dynamic and bidirectional, as both rostrocaudal and caudorostral effects were observed (Gordon et al., 2008).

Mechanisms underlying the neural control of quadrupedal locomotion are conserved in humans (Dietz, 2002a; 2011), and studies on spinal reflexes in humans may shed some light on the underlying arm-leg spinal coupling (Kearney and Chan, 1979; 1981; Delwaide and Crenna, 1984; Sarica and Ertekin, 1985; Zehr and Kido, 2001). For example, modulation of spinal reflexes in the arms/legs was studied during rhythmic movements of the legs/arms, and a generalized suppression of reflex excitability was found in people with an intact nervous system (Zehr et al., 2001; Frigon et al., 2004; Loadman and Zehr, 2007; Zehr et al., 2007c; Hundza and Zehr, 2008; Sosnoff and Motl, 2010; Nakajima et al., 2013). This modulation suggested an intersegmental linkage between the cervical and lumbar cord through propriospinal connections

(Nathan and Smith, 1959; Dietz, 2002a; Ferris et al., 2006).

A few studies have also looked into the cervico-lumbar connection after neural disorders such as stroke (Barzi and Zehr, 2008; Zehr and Loadman, 2012; Mezzarane et al., 2014), Parkinson's disease (Dietz, 2011) and multiple sclerosis (MS) (Motl et al., 2007; Sosnoff et al., 2009; Sosnoff and Motl, 2010). The cervico-lumbar connection was still preserved after these neural disorders. For example, the H-reflex in the leg muscle was still modulated by arm movement in people with stroke (Barzi and Zehr, 2008). In cases with a direct injury to the spinal pathway such as SCI, Calancie et al. showed that the cervico-lumbar connection becomes widespread and less inhibited (Calancie, 1991; 2002). It however remains unclear how rhythmic movements of the upper and/or lower limbs affect the cervico-lumbar connection after SCI.

In this study, we investigated the effect of incomplete SCI (iSCI) on the modulation of the cervico-lumbar coupling. We compared the modulation of the H-reflex in an arm or leg muscle during rhythmic cycling of the remote limb pair. The comparison was conducted in neurologically intact (NI) volunteers and volunteers with incomplete SCI (iSCI). We hypothesized that the H-reflex would be suppressed during cycling of the remote limb pair in NI participants. We also hypothesized that the suppression of the H-reflex would be substantially altered after an incomplete spinal cord lesion.

In the second part of the study, we assessed the effect of electrical stimulation-assisted cycling training on regulating the modulation of cervico-lumbar connectivity as well as general spinal excitability. In a previous study (Wong et al., 2012a; 2012b; Zhou et al., 2016b), we demonstrated that a rehabilitation paradigm involving cycling of the legs results in improvements in overground walking, balance, and sensory and motor scores in people with iSCI. The improvements in walking speed and distance were similar to those reported by gait-specific locomotor rehabilitation interventions focused on the lower limbs for improving ambulation (Zhou et al., 2016b). We also demonstrated that actively engaging the arms simultaneously with the legs during cycling, may produce even larger improvements in all measured walking metrics. In the present study, we investigated the effect of cycling training on cervico-lumbar coupling. We hypothesized that inhibition of neural activity in the lumbar spinal networks by rhythmic arm

movements would be enhanced after cycling training. We then examined the influence of active arm engagement during cycling on the excitability of the lumbar networks of the spinal cord by assessing in detail the effect of the two training paradigms (arm and leg cycling, legs only cycling) on changes in the H-reflex of the soleus muscle.

3.2 Methods

All experimental protocols were approved by the University of Alberta Human Research Ethics Board and participants signed consent forms prior to the initiation of the study.

Participants

A total of 17 neurologically intact (NI) adults (age: 26 ± 10 yrs (mean ± standard deviation); sex: 12 females, 5 males) and 16 adults with iSCI participated in the studies. All NI participants and 10 of the participants with iSCI took part of experiments focused on investigating spinal cervico-lumbar coupling during rhythmic movements by assessing the extent of reflex modulation **(Study 1).** Eleven participants with iSCI first underwent electrical stimulation assisted-cycling training either of the legs alone (Leg), or the arms and legs simultaneously (A&L). The effect of training on spinal cervico-lumbar coupling was then assessed **(Study 2).**

Study 1: Cervico-lumbar coupling during rhythmic movements

The demographic information of participants with iSCI in this study are summarized in **Table 3.1.** The injury level in the participants was between C4 and T10 and the severity of injury was classified as C or D according to the American Spinal Injury Association Impairment Scale (AIS) (Maynard et al., 1997; Waring et al., 2010), as defined by the International Standards for Neurological Classifications of SCI (ISNCSCI). The total AIS motor score was determined by summing the upper extremity and lower extremity motor scores on both sides. The side with higher AIS motor scores (e.g., stronger side) was chosen to be the experimental side. None of the participants with iSCI were undergoing any rehabilitation training interventions at the time of their participation. Exclusion criteria were: damage to the nervous system other than the spinal cord; impaired mental capacity or currently taking antidepressants; spinal injury level below T12; and other medical contraindications to cycling.

Table 3.1. Characteristics of participants with iSCI in Study 1.

Subject	Age	Sex	Origin of Injury	Years post-injury	Level of injury	Primary mode of mobility*	UEMS	LEMS
S1	68	M	Trauma/Sports	9	C4-5	Cane	48	48
S2	53	F	Surgery	10	T2-T4	Wheelchair	50	42
S3	51	M	Trauma/MVA	14	T10	Crutches	50	41
S4	54	M	Trauma/MVA	17	C6-7	Wheelchair	29	31
S5	71	M	Trauma/Sports	27	C4-5	Walking poles	48	42
S6	62	M	Trauma/MVA	44	C4-5	Cane	45	48
S7	58	M	Trauma/Fall	3	C4-5	Powered chair	33	26
S8	30	F	Trauma/MVA	3	C5-6	Wheelchair	36	26
S9	27	F	Trauma/MVA	7	C6-7	Wheelchair	44	33
S10	63	M	Trauma	1	C4-5	Wheelchair	38	44

*The primary mode of mobility was defined according to the assistive device the participant used in coming to the laboratory for the experiment.

Experimental Protocol

The NI and iSCI participants completed two parts of the experiment. In the first part, the role of leg cycling in modulating the amplitude of the flexor carpi radialis (FCR) H-reflex was examined. Specifically, we studied the regulation of the FCR H-reflex amplitude when the legs were cycling and when the legs were statically placed at 4 different positions within a cycling revolution. In the second part, we applied similar procedures to examine the effect of arm cycling on the amplitude of the soleus (SOL) H-reflex. Ten NI participants completed each part of the experiment. Participants with iSCI completed both parts of the experiment in two half days that were spaced less than a month apart.

Table 3.2. Characteristics of participants with iSCI participating in the A&L and Leg training groups in Study 2.

Name (XX)*	Age	Sex	Injury Level	Origin of Injury	Years post-Injury	Primary Mode of Mobility	Ergometer	Group	Muscles with stimulation[#]
S1A (S3)	45	M	T10	Trauma/MVA	8	Crutches	Custom-adapted	A&L	Quads, Hams, Gluts
S2A	58	M	C5-C6	Trauma/MVA	36	Walker	Custom-adapted	A&L	Quads, Hams, Gluts
S3A	61	M	C3-C5	Trauma	2	Powered Chair	RT 200	A&L	Quads, Hams, TA, SS, Tri
S4A (S4)	50	M	C6-C7	Trauma/MVA	13	Wheelchair	Berkel	A&L	Quads, Hams, Gluts
S5A (S2)	49	F	T2-T4	Disc Protrusion /Surgery	6	Wheelchair	Custom-adapted	A&L	Quads, Hams, Gluts
S6A (S7)	58	M	C4-C5	Trauma/Fall	3	Powered Chair	RT 200	A&L	Quads, Hams, Gluts
S1L (S3)	48	M	T10	Trauma/MVA	11	Crutches	ERGYS	Leg	Quads, Hams, Gluts
S2L	36	F	C5-C7	Trauma/MVA	2	Wheelchair	RT 300	Leg	Quads, Hams, TA, Gastr
S3L	54	M	T4-T5	Disc Protrusion /Sports	4	Wheelchair	RT 300	Leg	Quads, Hams, Gluts
S4L	41	F	C6-C7	Trauma/MVA	7	Powered Chair	ERGYS	Leg	Quads, Hams, Gluts
S5L (S6)	62	M	C4-C5	Trauma/MVA	44	Cane	RT 300	Leg	Quads, Hams, Gluts
S6L (S2)	53	F	T2-T4	Surgery	10	Wheelchair	ERGYS	Leg	Quads, Hams, Gluts
S7L (S4)	54	M	C6-C7	Trauma/MVA	17	Wheelchair	ERGYS	Leg	Quads, Hams, Gluts
S8L (S8)	30	F	C5-C6	Trauma/MVA	3	Wheelchair	ERGYS	Leg	Quads, Hams, Gluts

*The name in parentheses identifies the participants who also participated in Study 1 **(Table 3.1);**
#Quads: Quadriceps; Hams: Hamstrings; Gluts: Gluteus; TA: Tibialis anterior; Gastr: Gastrocnemius; SS: Scapular stabilizers (rhomboids and supraspinatus); Tri: Triceps;
MVA: motor vehicle accident.

Flexor Carpi Radialis H-reflex

Participants sat in a custom-adapted arm/leg cycling ergometer (THERA-vital, Medica Medizintechnik, Hochdorf, Germany; and ERGYS 2, Therapeutic Alliances, Inc. Fairborn OH, USA) with fixed back support, and the feet strapped in the foot pedals. The arm and leg compartments of the ergometer were not mechanically linked, but the left and right arm cranks (as well as the left and right foot pedals) were coupled and out-of-phase by 180°. Experiments were conducted on the left arm for all NI participants and on the stronger side for iSCI participants. Each participant had the experimental arm strapped in a fixed position (10-35° shoulder flexion, 40-45° shoulder abduction, 70° shoulder horizontal abduction, 130-140° elbow flexion) with the palm supinated and resting on the testing table **(Fig. 3.1A).** The participants were instructed to maintain this arm position for the duration of the experiment. The cycle of the foot pedal on the experimental side was divided into 4 phases, referenced as 0, 90, 180 and 270°, with 180° being the top dead centre. The FCR H-reflex was elicited while the legs were held statically at these positions or while they cycled through them.

To elicit the FCR H-reflex, the skin was cleaned and stimulating electrodes were positioned over the median nerve, 1 cm proximal to the medial epicondyle of the humerus near the cubital fossa. Bipolar stimuli (1 ms pulse width) were delivered using a constant current stimulator (DS7A; Digitimer, Hertfordshire, UK). Electromyographic (EMG) signals were recorded using Ag-AgCl electrodes placed on the belly of the FCR muscle.

An FCR M-wave–H-reflex recruitment curve (M-H recruitment curve) was then obtained for each participant with the participants' foot on the experimental side resting at 0° and the other foot at 180°. The M-H recruitment curve was obtained with FCR at rest as well as with FCR activated to 10% of its maximal isometric voluntary contraction (MVC). To obtain the MVC, the participants were asked to perform 3 maximal isometric contractions of wrist flexion, with the induced force measured by a transducer attached to the arm (Neurolog, Hertfordshire, UK). A voltage level equivalent to 10% MVC force was displayed on an oscilloscope for visual feedback during the experiment. The M-H recruitment curves were acquired by stimulating the median nerve at different intensities (from the level evoking no activity to the level evoking the maximal M-wave (M*max*)). To investigate the potential facilitation or suppression of the H-reflex induced

by experimental conditions, the stimulating level that evoked 50% (H*half*) of the maximal H-reflex (H*max*) on the ascending limb of each recruitment curve was selected for all the experimental trials (Meinck, 1980).

To ensure that the stimulation intensity always evoked H*half* immediately before starting a testing condition in participants with iSCI, we collected multiple M-H recruitment curves (in 8 of the 10 participants) throughout the experiment. The M-H recruitment curves were collected at three salient time points: before the leg static condition, after the leg static condition/immediately before the leg cycling condition, and after the leg cycling condition/end of the experiment. At each time point, two M-H recruitment curves were collected, one with FCR at rest and the other with FCR at 10% MVC. During the collection of the M-H recruitment curves, the participants' foot on the experimental side rested at the 0° position and the other foot at the 180° position.

To assess the phasic modulation of the amplitude of the FCR H-reflex by the legs, 10 (for NI participants) or 6 (for iSCI participants) stimuli to the median nerve evoking H*half* were delivered while the legs were at each of the 4 foot reference positions. To investigate the difference in the effect on FCR H-reflex between stationary and dynamic leg conditions, the experiment started with the stationary leg condition first, followed by the leg cycling condition. During the leg stationary trials, the foot pedal on the experimental side was randomly placed at each of the 4 phases, and the stimuli to the median nerve were manually triggered with 5 to 7 s intervals between the stimuli. During the leg cycling trials, participants cycled at 50% of their peak personal cycling speed. The peak personal cycling speed was defined as the speed at which a participant can cycle for a minute at his/her maximal power output. Stimuli were delivered automatically to the median nerve during leg cycling when the foot pedal of the same side passed one of the 4 phases (±5° variation). Stimuli to the median nerve for all participants during the leg cycling trials were delivered every 3 to 6 rotations, which ensured that the time interval between stimuli was approximately 5 - 7 s. All leg stationary and cycling trials were performed when the FCR muscle was quiescent or maintained at a tonic isometric wrist flexion equivalent to 10% MVC.

Soleus H-reflex

Participants sat in the same arm/leg cycling ergometer with feet secured in the foot pedals. The hip angle was maintained at ~90° and knee angle was ~110°. The testing was conducted on the same side as in the FCR H-reflex experiment. After the skin was cleaned with alcohol, stimulating electrodes were placed at the posterior tibial nerve in the popliteal fossa on the experimental side to evoke the SOL H-reflex.

To examine the effect of rhythmic arm movement on the amplitude of the SOL H-reflex, the posterior tibial nerve was stimulated under arm stationary and cycling conditions. The cycle of the arm cranks was also divided into 4 phases and referenced as 0, 90 (~15° shoulder flexion, the most extended shoulder position), 180 and 270° (~60° shoulder flexion, the most flexed shoulder position) **(Fig. 3.1C).** Similarly, M-H recruitment curves were obtained with the SOL at rest and at 10% MVC for each participant, while the ipsilateral foot was maintained at the 0° position. The MVC of each participant was an average of 3 maximal isometric contractions of plantar flexion. The stimuli evoking the SOL H*half* were applied to all subsequent experimental trials. To ensure the consistency of the stimuli, M-H recruitment curves were also collected (with SOL at rest and when activated to 10% of its MVC) before the arm static condition, before the arm cycling condition and at the end of the experiment (in 8 of the 10 participants with iSCI). During the collection of M-H recruitment curves, the ipsilateral arm rested at the 180° position and the other arm at the 0° position.

The experiment always started with the stationary arm condition first, followed by the arm cycling condition. Ten (for NI participants) or 6 (for iSCI participants) stimuli were delivered to elicit the SOL H-reflex when the ipsilateral arm was passively placed at, or cycling through, one of the 4 arm phases. The order of the phases was randomized during the static arm trials. In the arm cycling trials, participants cycled the arm cranks at 50% of their personal peak arm cycling speed. All arm stationary and cycling trials were performed when SOL was either quiescent or tonically plantar flexed at 10% MVC.

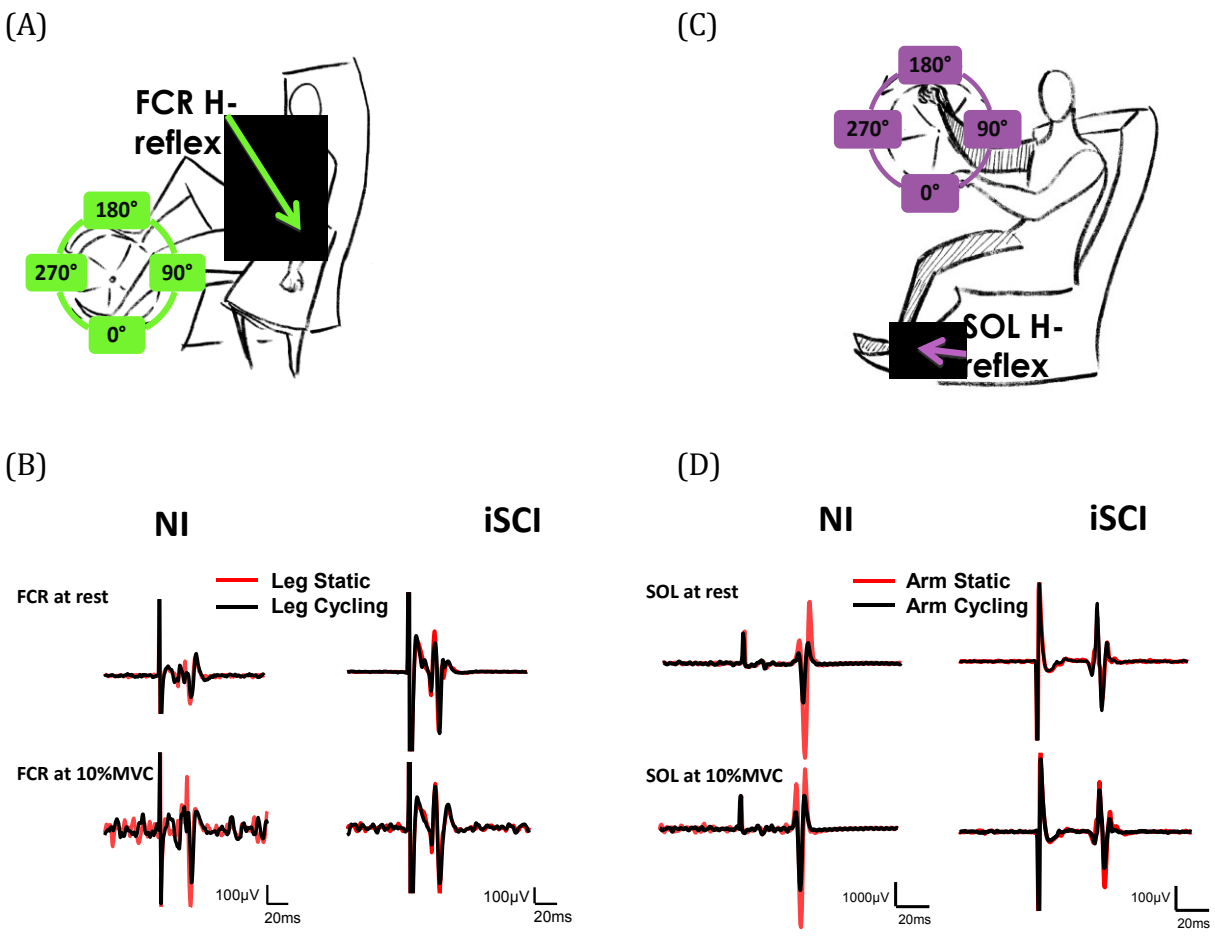


Figure 3.1. Experimental set-up and example traces for Study 1.

(A) Experimental set-up for assessing FCR H-reflex modulation through leg cycling. (B) Example traces of the FCR H-reflex during leg static **(red)** and cycling **(black)** conditions from an NI and an iSCI participant; (C) Experimental set-up for assessing SOL H-reflex modulation during arm cycling; (D) Example traces of the SOL H-reflex during arm static **(red)** and cycling **(black)** conditions from an NI and an iSCI participant. The scale of amplitude and time are indicated for both top and bottom traces in (C) and (D).

Data Acquisition and Analysis

All EMG signals were amplified and band-pass filtered from 20 to 1000 Hz. Signals were then digitized (CED 1401; CED Ltd., Cambridge, UK) at a sampling frequency of 2000 Hz using Spike 2 software (CED Ltd., Cambridge, UK). A window including 100 ms pre-stimulus and 300 ms post-stimulus activity was selected to analyze for all stimuli within an arm/leg position. The background (pre-stim) EMG activity was calculated as the mean of activity over the 100 ms prior

to the stimulus and averaged across stimuli. The peak-to-peak amplitudes of the evoked H-reflex and M-wave were also calculated and averaged over the 10 (NI) or 6 (iSCI) stimuli per leg/arm position. The averaged H-reflex and M-wave were then normalized to the M*max* from the recruitment curve obtained immediately prior to the testing condition.

Statistics

Statistical comparisons were performed separately for FCR and SOL H-reflexes using SPSS 23 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was first tested using Shapiro-Wilk test. A three-factor repeated measure ANOVA was performed to find the significance of the main effect and interactions amongst the factors, including movement (cycling, stationary), phases (0, 90, 180, 270°) and muscle facilitation (muscle at rest, muscle at 10% MVC). The corrected Bonferroni *post-hoc* test was used to further identify significance. A separate two-factor repeated measure ANOVA (three time points throughout the experiment × muscle facilitation) was also performed to examine whether there was a significant difference in the M*max* or H*max* collected at the beginning, middle and end of the experiment session.

Study 2: Effect of cycling training on cervico-lumbar coupling and spinal excitability after iSCI

The characteristics of the 11 volunteers with iSCI who participated in this study are summarized in **Table 3.2.** Participants were classified as AIS C or D, with spinal cord injury levels between C4 and T12. Two training interventions were conducted: arm and leg cycling (A&L) and legs only cycling (Leg). Three participants underwent the A&L training first (A1, A4 and A5), and after a 'washout period' of 23 - 40 months, underwent Leg training (L1, L7 and L6). The duration of the washout period ensured the absence of training carry-over effects. These participants were treated as independent participants in separate groups in the statistical analysis (A&L, n=6; Leg, n=8).

The training paradigm was previously discussed (Zhou et al., 2016b). Briefly, training took place one hour per day, 5 days per week for 12 weeks. The training entailed either simultaneous arm and leg cycling or leg cycling only. In both training modalities, electrical stimulation was applied to various muscles, as needed, to assist with the cycling movements. Different ergometer systems

were used depending on participant comfort and availability of equipment. These included: 1) a custom-adapted arm and leg FES ergometer (THERA-vital, Medica Medizintechnik, Hochdorf, Germany; ERGYS 2, and Therapeutic Alliances, Inc. Fairborn OH, USA); 2) arm and leg Berkel Bike (Berkel, the Netherlands); 3) RT-200 arm and leg cycling ergometer (Restorative Therapies, Inc. MD, USA); 4) RT-300 leg cycling ergometer (Restorative Therapies, Inc. MD, USA); and 5) ERGYS 2 FES ergometer (Therapeutic Alliances, Inc. Fai, born OH, USA).

The effect of training on spinal networks was evaluated in two ways. First, changes in cervico-lumbar coupling were examined per- and post-training; and second, changes in the M-H recruitment curves in SOL were assessed.

Modulation of the SOL H-reflex by rhythmic arm movements

Eight iSCI participants (A&L group: S2A, S3A, S5A, S6A; and Leg group: S5L, S6L, S7L, S8L) participated in this part of the study. Three of the participants performed the experiment with the SOL at rest while the other 5 participants performed the experiment with the SOL both at rest and activated to 10% of its MVC. The experimental protocol was similar to that described in Study 1 above.

M-H recruitment curves of the SOL muscle

All 6 A&L participants and 8 Leg participants completed this part of the study. The side with lower AIS motor scores was chosen to be the experimental side, unless the H-reflex could not be elicited from that side, in which case the side with higher motor scores became the experimental side. During these assessments, the participants sat in a custom-built chair with the knee joint of the experimental leg flexed to ~100° relative to horizontal, hip joint extended to ~110° and ankle joint extended to ~5°.

Electrical pulses, 1 ms in width, were used to stimulate the posterior tibial nerve. Stimuli of varying intensities, ranging from an intensity level triggering no activity to a level at which M*max* was elicited, were delivered in a random order. The peak-to-peak amplitudes of the evoked H-reflex and M-wave at each stimulus intensity were measured and normalized relative to the M*max*. An M-H recruitment curve of the SOL muscle was then constructed and the

H*max*/M*max* ratio was determined (Phadke et al., 2007; Lagerquist and Collins, 2008). To compare the M-H recruitment curves at pre-training and after 12 weeks of training, linear regression using least-sum-of-squares was fitted to the central portion (approximately 10 - 90%) of the ascending limb of the M and H curves **(e.g. Fig. 3.6A)**. A ratio of slopes (H*slope*/M*slope*) was subsequently calculated based on the fitted slopes. This method has been previously used to assess the gain of the H-reflex, which can be indicative of spinal excitability (Funase et al., 1994; Kalmar et al., 2006; Hayes et al., 2009). The x-axis (stimulus intensity) was normalized to the intensity evoking M*max*. The x-axis intercept (M*int* or H*int*) calculated from each of the regression equations, was considered as the minimal level of stimulation required for an M or H response (Ferris et al., 2001; Larsen and Voigt, 2004). The difference between the x-axis intercepts of the M and H regression equations was determined as M*int* - H*int*.

Statistics

All statistical tests were performed using SPSS 23 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was first tested using Shapiro-Wilk test. Pairwise comparisons of pre-training measures in the A&L and Leg training groups was performed using independent t-test or Mann–Whitney U test, based on the test of normality.

To assess the effect of cycling training on changes in cervico-lumbar coupling, a mixed linear model was applied to assess the effect of 4 factors (pre-/post-training, arm static/cycling, SOL at rest/at 10% MVC, and arm at 4 different phases) on the amplitude of the SOL H-reflex. The mixed linear model was also applied when the data were divided into separate comparisons (e.g., comparison of pre-training and post-training; comparison of muscle at rest and at 10% MVC).

In all measures regarding the SOL M-H recruitment curves, a comparison of pre- and post-training within each group was also performed using paired t-test or Wilcoxon signed-rank test based on the test of normality, to illustrate the training effect of individual groups.

For all comparisons, statistical differences with p values ≤ 0.05 were considered significant. Results are expressed as mean ± 1x standard error unless otherwise specified.

3.3 Results

Study 1: Cervico-lumbar coupling during rhythmic movements

I. Modulation of the H-reflex in NI participants

Representative examples of the changes in the amplitude of the peak-to-peak FCR H-reflex while the legs were static and cycling in NI participants are shown in **Fig. 3.2A (left).** Examples of the changes in the amplitude of the SOL H-reflex while the arms were static and cycling are shown in **Fig. 3.2A (right).**

Figures 3.3A, B and **C** show the average (mean ± 1x standard error) normalized H-reflex, pre-stim EMG activity and normalized M-wave of the FCR muscle, respectively, during the leg static and leg cycling conditions across all NI participants. As expected, pre-stim activity with the FCR activated to 10% of its MVC was significantly larger than the pre-stim activity with the muscle at rest ($p=0.004$) **(Fig. 3.3B).** However, the pre-stim activity was similar between the leg static and cycling conditions, and across the 4 different leg positions ($p=1.00$). The normalized M-wave amplitude **(Fig. 3.3C)** across NI participants was not significantly different ($p>0.45$) between any experimental conditions (leg movement, FCR facilitation or leg position).

The normalized FCR H-reflex amplitudes in the NI group **(Fig. 3.3A)** were significantly reduced during leg cycling compared to those during leg static ($p=0.023$), but without any significant difference among the 4 leg positions ($p=0.12$). Activation of FCR to 10% MVC tended to increase the H-reflex amplitude compared to FCR at rest ($p=0.082$). The interaction between FCR facilitation (at rest or at 10% MVC) and leg position was significant ($p<0.0005$). Further analysis showed that the significant interaction only occurred during leg cycling ($p=0.006$), but not when the legs were stationary ($p=0.46$). Specifically, leg position had a significant effect on the FCR H-reflexes during leg cycling, when the FCR was at 10% MVC ($p=0.046$).

The change in the amplitude of the FCR H-reflex during leg cycling relative to that during the leg static condition was calculated. Because leg position had no significant effect on the normalized FCR H-reflex, the change was averaged across all leg positions. There was a 26.45% decrease in the normalized amplitude of the reflex during leg cycling with the FCR at rest, and an 18.97% decrease with the FCR at 10% MVC.

Figures 3.3D, E and **F** show the average (mean ± 1x standard error) normalized H-reflex, the pre-stim EMG activity and the normalized M-wave of the SOL muscle, respectively, during the arm static and arm cycling conditions across all NI participants. Pre-stim activity **(Fig. 3.3E)** was significantly different between conditions with the SOL at rest and at 10% MVC ($p<0.0005$). However, the pre-stim activity was similar between arm movement conditions (arm static and cycling), and across all 4 arm positions ($p\geq0.42$). The normalized SOL M-wave amplitude **(Fig. 3.3F)** was not significantly different ($p\geq0.26$) between any experimental condition (arm movement, SOL facilitation, or arm positions).

The normalized SOL H-reflex amplitude **(Fig. 3.3D)** during arm cycling significantly decreased compared to that during arm static ($p=0.032$), regardless of arm position ($p=0.32$). Also, whether the SOL was at rest or at 10% MVC had no significant influence on the amplitude of the SOL H-reflex ($p=0.19$). No significant interaction between the conditions was found.

The change in the amplitude of the SOL H-reflex during arm cycling relative to that during the arm static condition was calculated. Because arm position had no significant effect on the normalized amplitude of the SOL H-reflex, the change was averaged across all arm positions. During arm cycling, there was a 23.75% decrease in the normalized amplitude of the SOL H-reflex with the SOL at rest, and a 20.31% decrease with the SOL at 10% MVC.

II. Modulation of the H-reflex in participants with iSCI

The H*max* and M*max* values obtained from the FCR M-H recruitment curves collected at 3 different time points during the experiment were averaged from 8 participants with iSCI. The facilitation of FCR (rest vs. 10% MVC) had a significant effect on M*max* ($p=0.029$) and H*max* ($p=0.043$). However, no significant difference was found in the M*max* or H*max* across all time points ($p\geq0.19$). There was also no significant change in M*max* or H*max* values obtained from the SOL M-H curves throughout the experiment ($p\geq0.60$), regardless of SOL muscle activation ($p\geq0.71$). The results indicate that M*max* and H*max* remained constant before each of the testing conditions and until the end of the experiment.

Representative examples of the changes in the amplitude of the peak-to-peak FCR H-reflex while the legs were static and cycling in participants with iSCI are shown in **Fig. 3.2B (left).** Examples of the changes in the amplitude of the SOL H-reflex while the arms were static and cycling in the same participants are shown in **Fig. 3.2B (right).** While the suppression in the amplitude of the H-reflex during leg cycling was relatively consistent amongst the NI participants **(Fig. 3.2A),** no definitive pattern could be found in the iSCI group **(Fig. 3.2B).**

Figures 3.4A, B and **C** are the average (mean ± 1x standard error) normalized H-reflex, pre-stim EMG activity and normalized M-wave of the FCR muscle, respectively, during the leg static and leg cycling conditions for the iSCI group. Significantly different pre-stim activities **(Fig. 3.4B)** between the conditions of the FCR at rest and at 10% MVC were found ($p=0.001$); however, the pre-stim activities were similar across the 4 different leg positions, and between leg static and cycling conditions ($p\geq0.27$). Similar to the NI participants, none of the experimental conditions had any significant effect on the normalized M-wave amplitude ($p\geq0.34$) **(Fig. 3.4C).**

Contrary to the observation in the NI participants, there was no significant change in the normalized amplitude of the FCR H-reflex between leg static and cycling conditions ($p=0.19$) **(Fig. 3.4A).** The effect of leg position was still not significant ($p=0.27$); however, a significant increase in the normalized H-reflex amplitude was found during the FCR at 10% MVC compared to the FCR at rest ($p=0.034$). No significant interaction between conditions was found in the iSCI group.

The change in the amplitude of the FCR H-reflex during leg cycling relative to that during the leg static condition was calculated, and the change was averaged across all leg positions. Contrary to the NI group, there was only a 6.77% decrease in the amplitude of the FCR H-reflex during leg cycling with FCR at rest, and an 11.28% increase with the FCR at 10% MVC in the iSCI group.

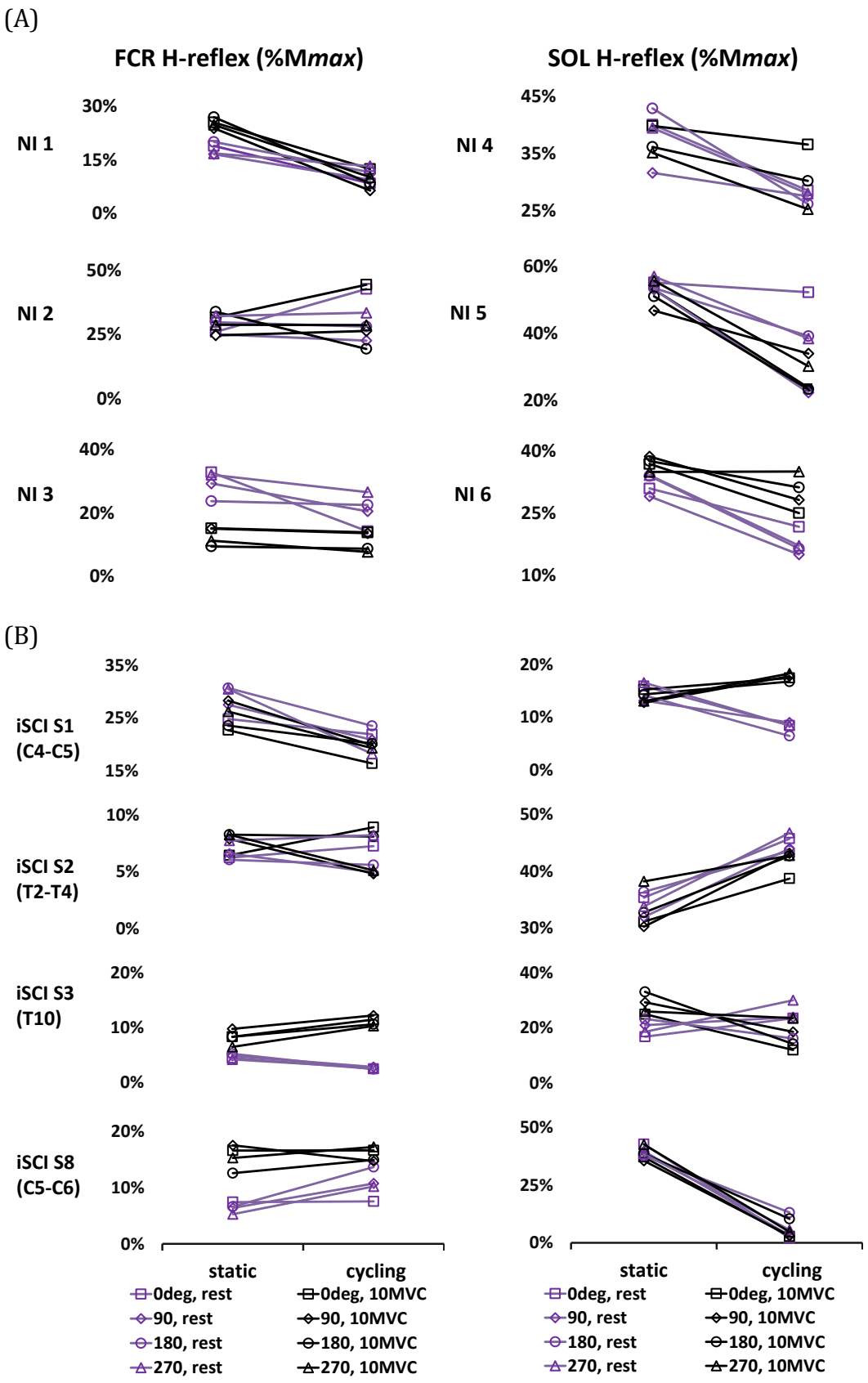


Figure 3.2. Representative patterns of H-reflex modulation.

Representative patterns of H-reflex modulation in the FCR and SOL muscle during leg and arm cycling, respectively, in (A) NI participants and (B) participants with iSCI.

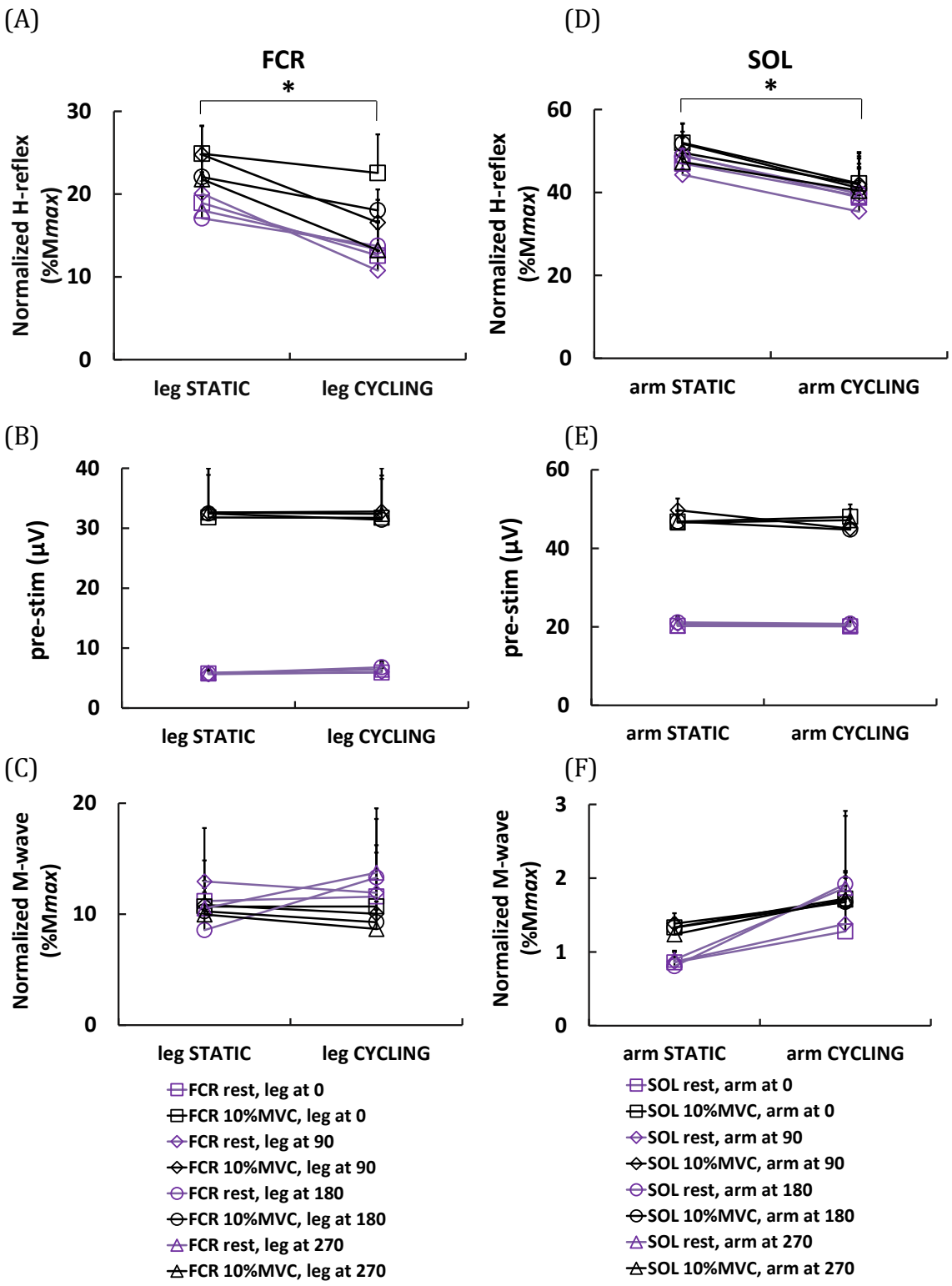


Figure 3.3. Group data in the NI group for Study 1.

(A, B, C) Group average of the normalized H-reflex amplitude, pre-stim EMG activity and normalized M-wave amplitude of the FCR muscle in the NI group, respectively (n=10). (D, E, F) Group average of the normalized H-reflex amplitude, pre-stim EMG activity and normalized M-wave amplitude of the SOL muscle in the NI group, respectively (n=10). *significant difference between static and cycling conditions ($p \leq 0.05$).

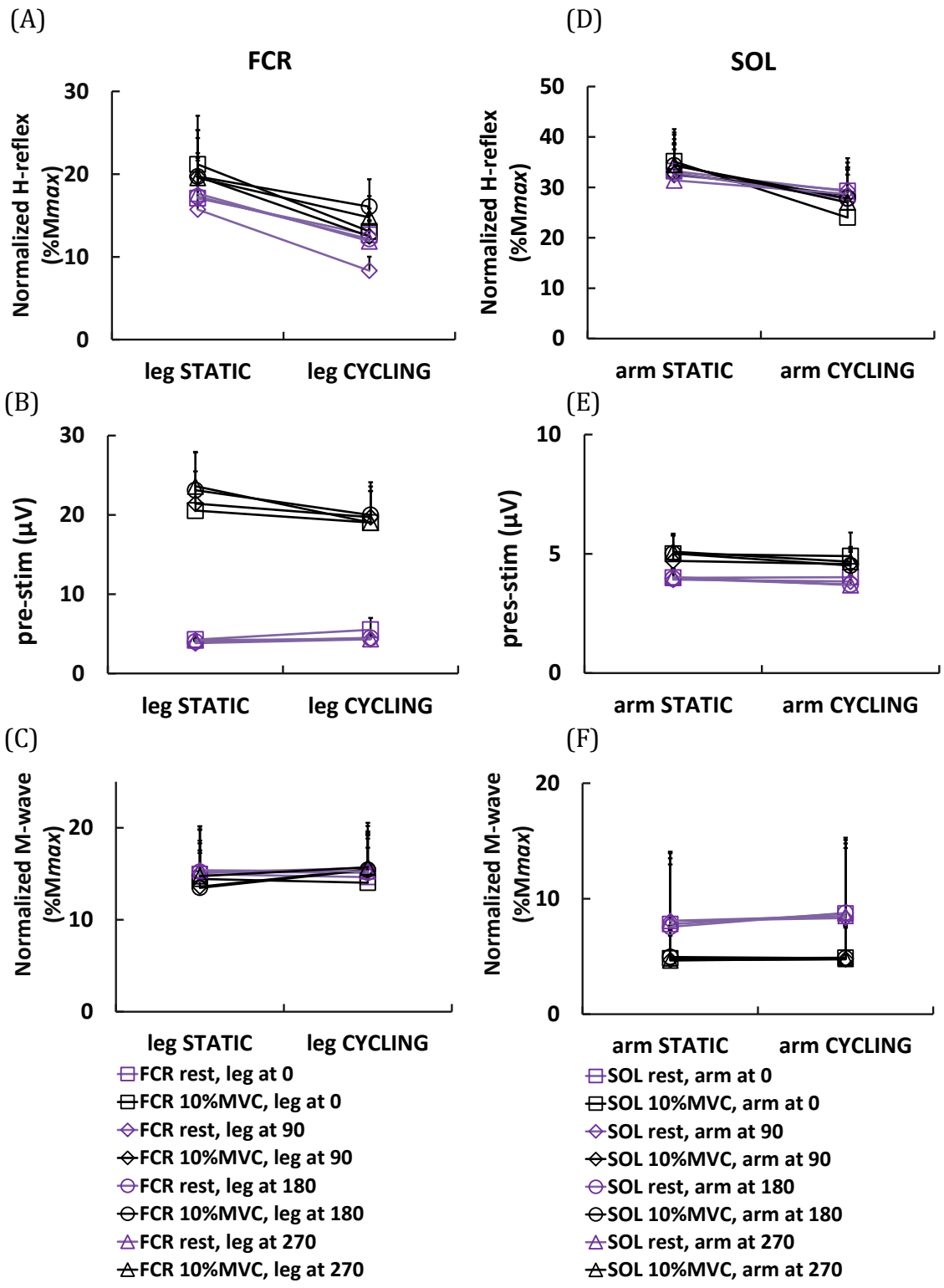


Figure 3.4. Group data in the iSCI group for Study 1.

(A, B, C) Group average of the normalized H-reflex amplitude, pre-stim EMG activity and normalized M-wave amplitude of the FCR muscle in the iSCI group, respectively (n=10). (D, E, F) Group average of the normalized H-reflex amplitude, pre-stim EMG activity and normalized M-wave amplitude of the SOL muscle in the iSCI group, respectively (n=10).

Figures 3.4D, E and **F** are the average (mean ± 1x standard error) normalized H-reflex, pre-stim EMG activity and normalized M-wave of the SOL muscle, respectively, during the arm static and arm cycling conditions across all participants with iSCI. Pre-stim activity **(Fig. 3.4E)** was significantly different between conditions with the SOL at rest and at 10%MVC ($p=0.016$) but pre-stim activity remained similar between arm movement conditions (arm static or cycling) and across all 4 arm positions ($p=1.00$). Normalized M-wave amplitude **(Fig. 3.4F)** was not significantly different between any of the experimental conditions ($p\geq0.33$).

In contrast to the finding in the NI group, there was no significant difference in the normalized amplitude of the SOL H-reflex between arm static and arm cycling ($p=0.15$), regardless of arm position ($p=0.98$) or SOL facilitation ($p=0.95$). There was also no significant interaction between conditions. The averaged change in amplitude of the SOL H-reflex across all arm positions during arm cycling and arm static showed that there was only a 6.47% decrease during arm cycling with the SOL at rest, and an 11.40% decrease with the SOL at 10%MVC.

Study 2: Effect of cycling training on cervico-lumbar coupling and spinal excitability after iSCI

In this study, we first assessed the change in cervico-lumbar connectivity after cycling training in participants with iSCI. We then investigated in more detail the effect of the different modalities of cycling training (A&L; Leg) on changes in spinal excitability. Changes in cervico-lumbar connectivity were assessed by comparing the modulation in the amplitude of the SOL H-reflex during arm static and cycling conditions pre- and post-training. The effect of the different modalities of cycling training on spinal excitability was assessed by investigating the difference in changes in the properties of the SOL H-reflex between the two training groups.

I. Effect of Cycling Training on Cervico-lumbar Connectivity

The pre-stim activity did not differ between pre-training and post-training ($p=0.96$). Moreover, there was no significant difference in the pre-stim activity between arm static and cycling ($p=0.44$), nor across all 4 arm positions ($p=0.99$). However, as expected, pre-stim activity was significantly larger with the SOL at 10% MVC relative to the SOL at rest ($p<0.0005$). The

amplitude of the SOL M-wave also remained similar across all experimental conditions (training, arm movement, SOL facilitation, or arm position) ($p \geq 0.70$). No significant interaction was found in any comparison.

Figure 3.5 shows the average (mean ± 1x standard error) amplitude of the SOL H-reflex at pre- and post-training across all participants with iSCI in this study. At pre-training, there was no significant difference in the amplitude of the SOL H-reflex between any of the experimental conditions ($p \geq 0.38$) **(Fig. 3.5A).** After 12 weeks of A&L or Leg training, a significant suppressive effect was found in the amplitude of the SOL H-reflex during arm cycling ($p=0.018$), compared to that during arm static (**Fig. 3.5B).** Furthermore, during arm cycling, the amplitude of the SOL H-reflex was significantly smaller with the muscle at 10% MVC compared to that when the SOL was at rest ($p=0.026$).

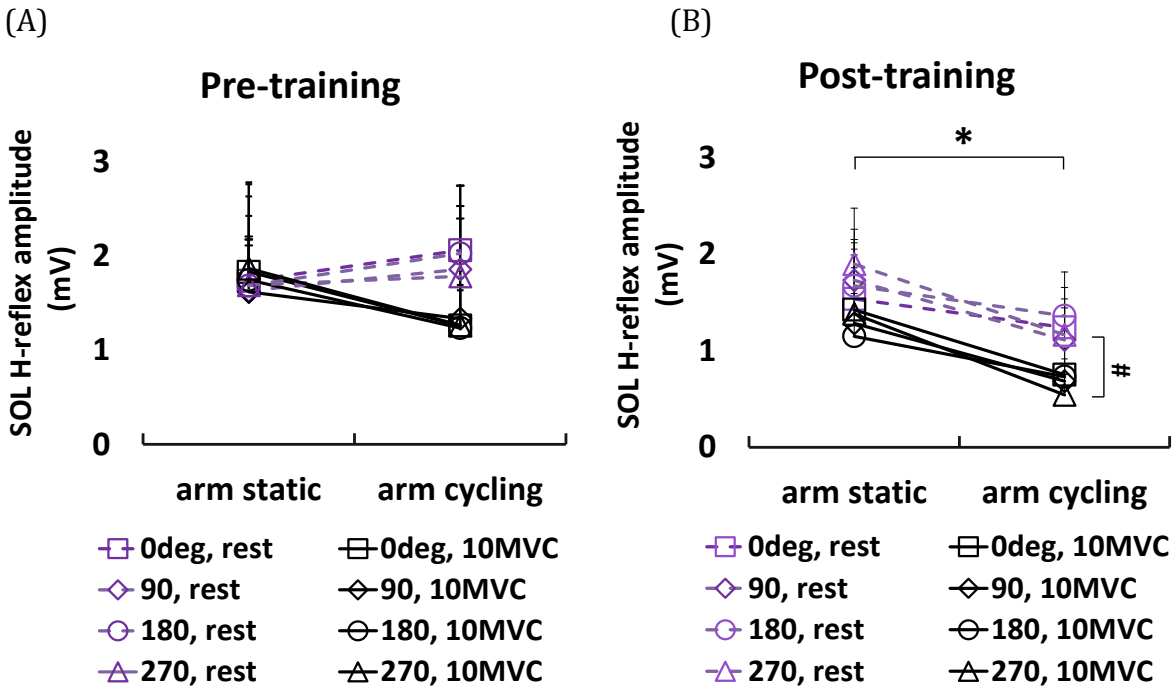


Figure 3.5. Group data in the iSCI group at pre- and post-training.

Group average of SOL H-reflex amplitude (A) at pre- and (B) post-training (n=8). *significant difference between static and cycling conditions ($p \leq 0.05$). #significant difference between the conditions with the testing muscle at rest and at 10%MVC ($p \leq 0.05$).

II. Effects of A&L and Leg Cycling Training on Spinal Excitability

A representative example of the M-H recruitment curves of the SOL muscle is shown in **Fig. 3.6A**. The slopes of the ascending limb of the H-curve and M-curve were calculated with linear regression to assess spinal excitability. At pre-training, the A&L group tended to have a lower H*slope*/M*slope* ratio than the Leg group (A&L: 1.05± 0.31; Leg: 2.50 ± 0.58), but the difference was not significant (p=0.070). There was no significant difference in the H*slope*/M*slope* ratio between pre- and post-training (p≥0.33), regardless of training group. The values of M*int* - H*int* at pre-training did not differ between the A&L group and Leg group (A&L: 17.61 ± 2.20; Leg: 13.60 ± 3.40). After training, there was a decrease in M*int* – H*int* in the A&L group, although not significant (p=0.16); but there was no change in the Leg group (p=0.97) (A&L: 13.24 ± 3.14; Leg: 13.67 ± 2.54).

The two training groups had similar H*max*/M*max* ratios at pre-training (A&L: 0.51 ± 0.11; Leg: 0.73 ± 0.070). After training, the H*max*/M*max* ratio had an average reduction of 10.68 ± 10.64% in the A&L group and 7.54 ± 4.58% in the Leg group (**Fig. 3.6B**). However, the H*max*/M*max* ratio still was not significant as a function of training within either the A&L (p=0.11) or Leg group (p=0.090). Furthermore, the absolute values of the H*max* and M*max* (results not shown) were not significantly different after training in any of the two groups, although the reduction of H*max* amplitude after training seemed more pronounced in the A&L group (p≥0.12) (**Fig. 3.6C**).

Peak-to-peak amplitude of the H*5%* was calculated and normalized to the M*max*. At pre-training, there was no significant difference in the normalized H*5%* between the A&L and Leg group (A&L: 0.45 ± 0.10; Leg: 0.55 ± 0.13). The A&L group demonstrated a greater reduction in the normalized H*5%* after training (p=0.090) compared to that in the Leg group (p=0.47). Specifically, after training 5 out of 6 participants in the A&L group had a decrease in the H*5%* by a range of 6.68 to 78.27% relative to pre-training levels, and one participant showed an increase by 3.74%. The average change in H*5%* in the 5 individuals after training was significant (p=0.052). Meanwhile, half of the participants (4 individuals) in the Leg group had a decrease in H*5%* after training and the other half showed an increase. When comparing the 5 A&L

participants with the participants in the Leg group, a significant group difference in the post-training change in H*5%* was found (p=0.044), with a reduction of 39.72% ± 12.22% in the A&L group and an increase of 3.17% ± 11.87% in the Leg group **(Fig. 3.6D).**

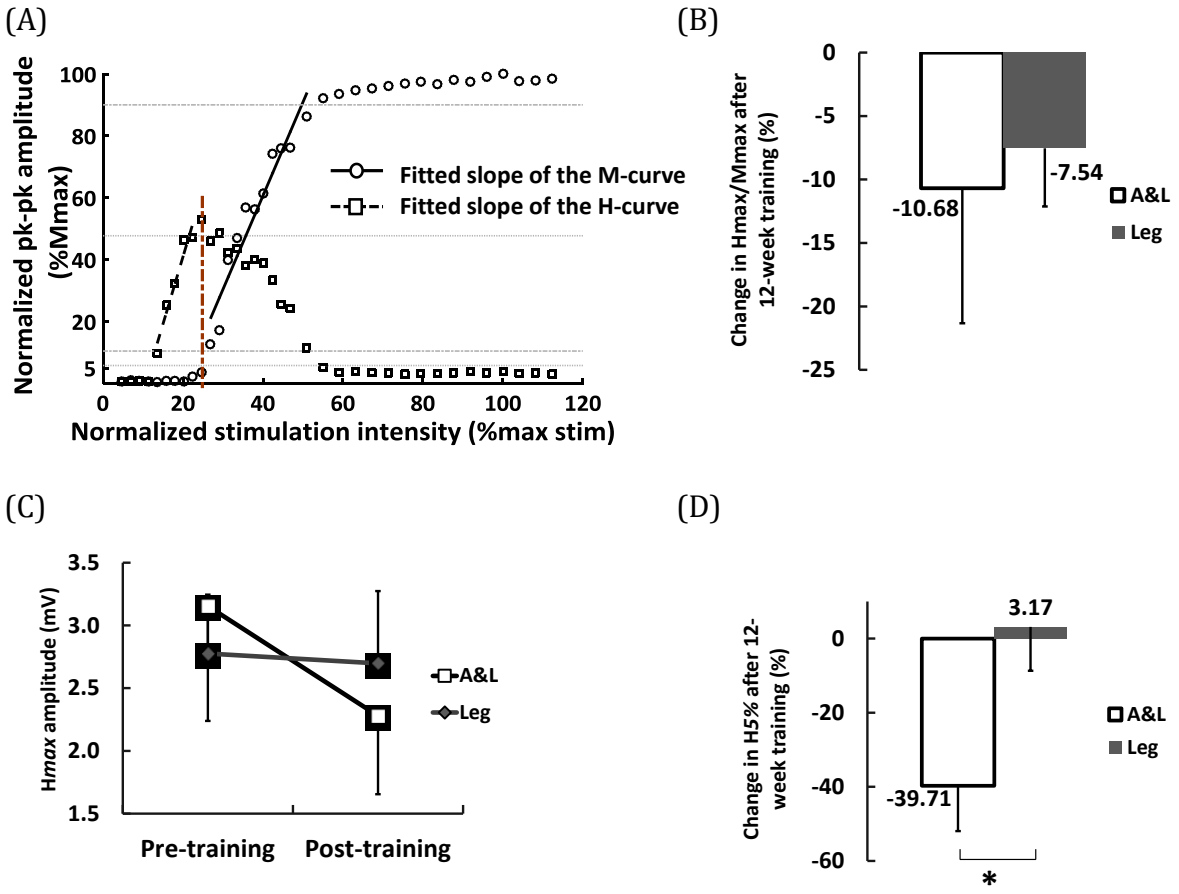


Figure 3.6. M-H recruitment curves of the SOL muscle.

(A) Example of a fitted regression lines on M- and H- recruitment curves from the a SOL muscle in a participant with iSCI; brown dash-dot line indicates the intensity that evokes 5% of the Mmax in the SOL muscle; the area between the grey lines represents the central portion (approximately 10 - 90%) of the ascending limb of the M and H curve, respectively; (B) Group change (%) in SOL H*max*/M*max* ratio in iSCI participants post-training (mean ± standard error) (A&L: n=6; Leg: n=8); (C) Group change in the H*max* amplitude of the SOL H-reflex in iSCI participants at pre- and post-training (mean ± standard error) (A&L: n=6; Leg: n=8); (D) Group change (%) in SOL H*5%* in iSCI participants post-training change (mean ± standard error) (A&L: n=5; Leg: n=8). *significant difference between A&L and Leg groups (p≤0.05).

3.4 Discussion

The goals of this project were twofold. First, we wanted to assess the neural coupling between the cervical and lumbar regions of the spinal cord in the neurologically intact system and following incomplete spinal cord injury. Second, we wanted to investigate the effect of two modes of electrical stimulation-assisted cycling on the regulation of spinal cervico-lumbar coupling and on spinal excitability.

Similar to previous reports in neurologically intact individuals, we found that rhythmic movements of the arms and legs significantly suppress the spinal reflexes of the legs and arms, respectively. We demonstrated, for the first time, that this interlimb (arm-leg) suppression of spinal reflexes is lost after iSCI, and various patterns of modulation of the H-reflex emerge. We also found, for the first time, that electrical stimulation-assisted cycling in people with iSCI may restore the reciprocal suppression in cervico-lumbar coupling. Finally, we found that rehabilitation training involving simultaneous arm and leg cycling tended to produce greater regulation of the SOL H-reflex than legs only cycling, suggesting a more effective control of spinal excitability when the arms are actively involved in the rehabilitation of walking after iSCI.

Cervico-lumbar modulation of the H-reflex during movement

Our finding of task-dependent (static, rhythmic cycling) modulation of the H-reflex through cervico-lumbar coupling in the NI participants is consistent with previous studies involving people with intact nervous system (Loadman and Zehr, 2007; Zehr et al., 2007c; Nakajima et al., 2013; Massaad et al., 2014). The modulation of H-reflex was not only observed during rhythmic movement of the upper or lower extremities in which the reflex was evoked (Crenna and Frigo, 1987; Boorman et al., 1992; McIllroy et al., 1992; Brooke et al., 1997; Zehr et al., 2003), but also during movement of the remote limb pair.

Previous studies have shown that rhythmic arm cycling or arm swing could suppress the amplitude of H-reflex in a remote leg muscle (e.g., SOL), and that this suppression is likely mediated by reinforced presynaptic inhibition in Ia lumbar afferent terminals (Gossard, 1996; Frigon et al., 2004; Nakajima et al., 2013). The suppressive effects in the H-reflex of the SOL muscle however, were not influenced by the phase or locus (unilateral or bilateral) of arm

cycling (Loadman and Zehr, 2007). Therefore, it was suggested that, compared to afferent feedback from the arms, central pattern generating circuits that regulate rhythmic arm movements have a more dominant contribution to the suppressive effect on the H-reflex (Hundza et al., 2012). Similarly, rhythmic leg cycling was also shown to suppress FCR H-reflex in humans with intact nervous systems (Zehr et al., 2007c), and this suppression is likely produced by lumbar central pattern generating networks. The cervical and lumbar circuits, coupled through long propriospinal neurons, gate the excitability of reflex pathways in order to facilitate general arm and leg coordination (Dietz et al., 2001; Huang and Ferris, 2009).

Studies of cervico-lumbar coupling during rhythmic movements were performed in people with neural disorders, such as stroke (Barzi and Zehr, 2008; Zehr and Loadman, 2012; Mezzarane et al., 2014), Parkinson's disease (Dietz, 2011) and multiple sclerosis (MS) (Sosnoff and Motl, 2010). In general, the coupling is either weakened or abolished after neural disorders (Barzi and Zehr, 2008). One study in cervical iSCI participants showed that upper limb movements significantly shape the EMG activity produced by passive, motor-driven stepping of the legs, (Kawashima et al., 2008). The study however only investigated unidirectional modulation; i.e., effect of arm cycling on the leg muscle after SCI, and the effect on arm muscle activity during rhythmic leg movement was not explored.

To the best of our knowledge, this study is the first to examine fully the change in task-dependent cervico-lumbar modulation in both directions after iSCI. As hypothesized, the amount of cervico-lumbar modulation during rhythmic movement was weakened or abolished in the participants with iSCI. On average, the suppression in H-reflex was only 1/3 to 1/2 of that in intact participants. The H-reflex in the FCR with 10% MVC activation was even facilitated during leg cycling. The patterns of cycling-induced change in the H-reflex in iSCI participants were inconsistent (**Fig. 3.2B**), likely due to variations in the heterogeneity of the disruption in cervico-lumbar pathways.

We found no directional dominance in the modulation of H-reflex through cervico-lumbar coupling in this study. In the NI participants, the average suppression in FCR H-reflex was similar to the suppression in SOL H-reflex during cycling of the remote limb pair, suggesting the

modulation is equivalent in both top-down and bottom-up directions. However, we also found a significant interaction between the background level of FCR activity and phase of leg cycling, which may suggest that the legs may have a more refined influence on the reflex activity of the arms.

In participants with iSCI, the change in H-reflex during cycling was inconsistent and no directional modulation was found. Although 8 out of 10 participants with iSCI had injury levels at or above C7 (which innervates FCR) suggesting that propriospinal cervico-lumbar connections are relatively preserved, inconsistency in the modulation of the H-reflex was still observed. This provides further evidence of the dominant contribution of rhythm generating networks (e.g., between C4 and C7) to task-dependent cervico-lumbar modulation. Descending input to rhythm generating networks could also play an important role in this coupling.

In NI participants, the level of cycling-induced suppression in the H-reflex was similar when the test muscle was at rest and when activated to 10% of its MVC. This indicates that the cervico-lumbar modulation may partially arise from the premotoneuronal level, and likely mediated by presynaptic Ia inhibition. Therefore, the absence of modulation in participants with iSCI could partially be ascribed to reduced presynaptic inhibition (Nielsen et al., 1995). Further investigation is needed to assess other possible mechanisms, such as reciprocal inhibition (Petersen et al., 1999; Dragert and Zehr, 2013) and recurrent inhibition (Shefner et al., 1992).

There was no phase-dependency in the cervico-lumbar modulation during movement for both NI and iSCI participants. As previous studies suggested, the cervico-lumbar connection might be a general and loose neural coupling (Sakamoto et al., 2006; Zehr et al., 2007c). However, part of the reason could also be because we only had 4 equally spaced phases during cycling, which might not be sensitive enough to assess the phasic effect. Domingo et al. (2013) reported that the H-reflex in stationary FCR muscle during walking was suppressed to 80% of that during leg static condition; the suppression was only phase-dependent when the gait cycle was divided into more than 4 phases (Domingo et al., 2013). Further study should consider assessing the modulation during cycling with smaller phases partitions.

Cervico-lumbar modulation of the H-reflex during movement in iSCI after training

Although absent at pre-training, suppression of SOL H-reflex during arm cycling was observed after 12 weeks of training. To the best of our knowledge, this is the first evidence in persons with SCI that cervico-lumbar modulation can be restored, to some extent, after rehabilitative training. The improvement could be due to an enhanced inhibition in the spinal circuitry. Experiments in decerebrate cats showed that during locomotion, there was an increased excitability in presynaptic inhibitory pathways, which can be activated by supraspinal (reticular formation) and peripheral sensory inputs (Sirois et al., 2013). Cycling training may have strengthened presynaptic inhibition in the participants with iSCI, likely through repetitively engaging descending and sensory input during cycling.

Changes in M-H curve properties in iSCI participants after training

To compare the effect of training modality on the inhibition of spinal excitability, we investigated the change in properties of the SOL H-reflex in the A&L and Leg groups. Various changes in H-reflex after exercise training were reported in animals and humans with SCI (Phadke et al., 2009; Shields et al., 2011; Bose et al., 2012; Knikou and Mummidisetty, 2014). Following a single bout of overground walking training, the H*max*/M*max* ratio significantly decreased in people with iSCI (Trimble et al., 2001). In cats with complete SCI at the T13 level, a decrease in monosynaptic excitation was observed after 3-4 weeks of treadmill training (Cote et al., 2003). In other populations, such as persons with multiple sclerosis, instant reduction in the H*max*/M*max* ratio was seen after a single bout of arm cycling or leg cycling also showed (Sosnoff and Motl, 2010). Collectively, these findings suggested improved segmental reflex excitability after training.

In our study, we did not find significant changes in the slopes or thresholds of the H-M recruitment curves after training in either group. However, there was a reduction in the H*max*/M*max* ratio after training in both groups, indicating an overall reduction in hyperexcitability of the lumbar cord, and potentially spasticity (Faist et al., 1994; Aymard et al., 2000). Interestingly, a substantial reduction in H*max*, H*5%*, and M*int* – H*int* only occurred in the A&L group. Therefore, training modalities that engage larger proportions of the neuraxis may lead to better regulation of spinal networks.

3.5 Limitations

Although the present study demonstrated a restoration of cervico-lumbar coupling in people with chronic iSCI as a result of cycling training, it is still unclear if the extent of restoration is different between A&L and Leg cycling due to the small number of participants. Similarly, with 6 participants in the A&L group and 8 participants in the Leg group, only a trend of training effect on the SOL M-H curve properties was observed within each group. Given the heterogeneity in the iSCI population in this study, a large variability in the pattern of H-reflex was found (e.g. **Fig. 3.2B**). A larger sample size of participants and a subgroup assessment of cervical and thoracic injury should be considered in the future.

3.6 Clinical Implications

Taken collectively, the results of this study demonstrate that the modulation in cervico-lumbar coupling reemerges after cycling exercise in people with iSCI. This may partly underlie the significant improvements in overground walking after cycling exercise (Zhou et al., 2016b). Interestingly, the improvements in walking seen after leg cycling were similar to those obtained by locomotor rehabilitation paradigms that focus primarily on the legs (Zhou et al., 2016b). It therefore may be the case that these paradigms also contribute to enhancements in the regulation of cervico-lumbar coupling during coordinated arm and leg movement (Tester et al., 2011).

Arm and leg cycling may capitalize on the cervico-lumbar coupling more effectively resulting in better regulation of lumbar reflexes. It also significantly enhances the corticospinal drive to the legs (Zhou et al., 2016a). The improvements in motor control at the spinal and corticospinal levels produced by this training modality may very well explain the significantly larger improvements in walking compared leg training only (Wong et al., 2012a; 2012b; Zhou et al., 2016b). Therefore, actively including the arms in rehabilitation interventions for the improvement of walking is recommended.

Chapter 4. The Modulation of Corticospinal Input to the Legs by Arm and Leg Cycling in People with Incomplete Spinal Cord Injury

Zhou R[1], Alvarado L[1], Kim S[2], Chong SL[2], Mushahwar VK[1, 2]

1. Neuroscience & Mental Health Institute, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada
2. Division of Physical Medicine & Rehabilitation, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada

4.1 Introduction

In humans, like all quadrupeds, arms and legs are coupled and their activity is coordinated during various types of rhythmic locomotion such as walking, cycling and swimming (Wannier et al., 2001; Zehr, 2005; Zehr et al., 2007a). In these locomotor tasks, the coupling of arms and legs is supported by 'common core' control (Zehr, 2005). A 'common core' network is postulated to consist of the central pattern generator (CPG) that produces rhythmic motor outputs, and the interaction between segmental CPGs through ascending and descending spinal pathways to coordinate the movements of the arms and legs (Zehr and Duysens, 2004). Rhythmic motor activity is also dynamically modulated by descending input from supraspinal centers and peripheral feedback arising during various functional tasks. Particularly, descending input has an essential role in locomotion (Yang and Gorassini, 2006) and disruption to descending pathways (e.g., corticospinal pathway) could lead to deficits in or altered patterns of movement. For example, locomotor velocity, cycle durations and phase transitions can be influenced by impaired descending input to the spinal cord (Armstrong, 1988; Yakovenko et al., 2005). Lesioning of the corticospinal tract in cats can lead to paw-drag during walking and inability to modify the walking pattern to step over obstacles (Drew et al., 2002). In humans, there are even more extensive roles and greater dependency on descending input in the control of locomotion (Nielsen, 2003; Lemon and Griffiths, 2005; Yang and Gorassini, 2006). However, how the descending input, particularly the corticospinal input, dynamically interacts with the 'common core' network during rhythmic arm and leg movement is still largely unknown.

Although the coupling of arms and legs is present in various types of locomotion, to date, most investigations have focused on the regulation of cortical control to either the legs or the arms separately during movement (Schubert et al., 1997; Bonnard et al., 2002; Pyndt and Nielsen, 2003; Carroll et al., 2006). For example, cortical input was shown to be closely linked with motor circuits that control dorsiflexor muscle activity during human walking and cycling (Capaday et al., 1999). Part of the modulation of leg activity during walking is caused directly by changes in the excitability of corticospinal projections to spinal motoneurons (Petersen et al., 1998; Pyndt and Nielsen, 2003). Similarly, changes to corticospinal excitability in various arm muscles during arm cycling have been reported, indicating a direct contribution from the motor cortex to the activity of arm muscles (Carroll et al., 2006; Forman et al., 2014). While those

studies supported that arm or leg movement can modulate the corticospinal pathway to muscles in the respective limbs, movement of the remote limb pair may also influence the corticospinal input in these limbs.

In healthy humans, motor evoked potentials (MEPs) elicited in the flexor carpi radialis muscle were facilitated during leg cycling compared to when the legs were static, indicating greater corticospinal excitability of the arm muscle during leg movement (Zehr et al., 2007c). Also, Barthelemy et al. (2010) reported that using subthreshold-transcranial magnetic stimulation (TMS), which likely only activates intracortical inhibitory interneurons, causes suppression in the posterior deltoid muscle during walking and during tonic contraction at similar levels of EMG activity (Barthelemy and Nielsen, 2010). Their findings suggested an active corticospinal contribution to the ongoing EMG activity in arm muscles, but did not illustrate the functional significance of arm and/or leg movement in influencing the corticospinal contribution (Blouin and Fitzpatrick, 2010).

Understanding how arm-leg movement influences the corticospinal pathway can help develop more effective training paradigms in neurorehabilitation. Given the evidence that arms and legs are functionally linked during locomotion and are subject to common neural control during various rhythmic tasks, it is surprising that current rehabilitation paradigms for walking focus only on the legs (Alexeeva et al., 2011; Field-Fote and Roach, 2011; Harkema et al., 2012b; Yang et al., 2014). We proposed that actively engaging the arms along with the legs in rehabilitation training paradigms may result in better recovery of walking capacity after incomplete spinal cord injury (iSCI), and demonstrated that training consisting of simultaneous arm and leg cycling may produce larger improvements in walking metrics compared to leg cycling as well as other rehabilitation interventions that focus on the legs only (Zhou et al., 2016b). We also demonstrated that the spinal cervico-lumbar coupling may be reinforced after cycling training, and that active engagement of the arms in training may result in better regulation of spinal excitability after iSCI (Zhou et al., 2016c). However, to date, modulation of the corticospinal drive to the legs during combined arm and leg rhythmic movements remains unclear. Moreover, the effect of combined arm and leg training on the enhancement of corticospinal drive to the legs after neural disorders in unknown.

In the present study, we investigated the modulation of the corticospinal drive to the legs by active rhythmic arm movements, and the effect of combined arm and leg cycling training on strengthening the corticospinal pathway to the legs in people with iSCI. Specifically, we first compared the corticospinal drive to a leg muscle when the arms and legs were stationary and during rhythmic cycling in neurologically intact (NI) people and in people with chronic iSCI. We hypothesized that the amplitude of the MEPs in the leg muscle would be facilitated during cycling, and that the extent of facilitation would be in an increasing order from arm cycling to leg cycling to combined arm and leg cycling. In people with iSCI, we hypothesized that this modulation would either be reduced relative to NI participants, or completely abolished. We then investigated the changes in the corticospinal pathway produced by two 12 week-long rehabilitation paradigms (simultaneous arm and leg cycling vs. legs only cycling) in people with iSCI. We hypothesized that the corticospinal pathway to the leg muscles would be enhanced after both training interventions; however, the group with combined arm and leg cycling would have larger improvements compared to the legs only cycling group.

4.2 Methods

All experimental protocols were approved by the Research Ethics Board at the University of Alberta. The experimental procedures were explained to all study participants prior to the start of the experiment and an informed written consent of their participation was obtained.

Participants

Fourteen participants with no history of neurological conditions or disorders (6 male, 8 female) and ranging in age from 20 to 49 years (mean ± standard deviation: 33 ± 8 years) were recruited to the study. A total of 18 participants with chronic iSCI were also recruited. All NI participants and 9 participants with iSCI completed experiments that focused on assessing the modulation of the corticospinal drive to the legs during rhythmic arm and/or leg movements **(Study 1).** Twelve participants with iSCI first underwent functional electrical stimulation (FES)-assisted cycling training either of the legs alone (Leg), or the arms and legs simultaneously (A&L), and the effect of training on the corticospinal pathway was assessed **(Study 2).**

Study 1: Modulation of the corticospinal pathway during cycling

The demographic information of participants with chronic iSCI in this study are summarized in **Table 4.1.** The spinal cord injury levels were between C4 and T8 and were classified as C or D according to the American Spinal Injury Association Impairment Scale (AIS) (Maynard et al., 1997; Waring et al., 2010), as defined by the International Standards for Neurological Classifications of SCI (ISNCSCI). None of the iSCI participants was undergoing any rehabilitation training interventions at the time of their participation, and all except one were able to walk for 10 m at a self-selected speed with an assistive device. Exclusion criteria were: damage to the nervous system other than the spinal cord; impaired mental capacity or currently taking antidepressants; has implanted medical devices; spinal injury level below T12; and other medical contraindications to cycling or transcranial magnetic stimulation (TMS).

Electromyography Setup

Surface electromyography (EMG) signals were recorded from the vastus lateralis (VL) muscle using bipolar electrodes after the area of the skin surface was cleaned. The electrodes were connected to an AMT-8 EMG Wire Telemetry System (Bortec biomedical Ltd., Calgary, Canada). The EMG signals were amplified and band pass filtered between 30 and 1000 Hz and digitized at a sampling rate of 2000 Hz. The VL EMG signals were rectified and displayed on an oscilloscope for visual feedback throughout the experiment.

EMG activity pattern during cycling

The participants were seated in a custom-adapted ergometer that combined stationery ergometers with arm and leg cycling components (THERA-vital, Medica Medizintechnik, Hochdorf, Germany; ERGYS 2, and Therapeutic Alliances, Inc. Fairborn OH, USA) (**Fig. 4.1A**). The participants' feet were strapped in the foot pedals of the bike, while the hands held onto the arm cranks. The arm and leg compartments were not mechanically linked, but the left and right arm cranks (as well as the left and right foot pedals) were coupled and 180° out-of-phase.

The experiment was performed on the left side for participants in the NI group and on the stronger side in the group with iSCI. To begin the experiment, participants were instructed to

perform isometric knee extension with the foot in the bottom dead centre position of the foot pedal (6 o'clock position) in order to produce EMG activity corresponding to a maximal voluntary contraction in the VL muscle (MVC*iso*). The participants then simultaneously cycled their arms and legs at a self-selected speed. The power output of the leg ergometer was adjusted to a level at which the maximal rectified VL cycling EMG burst (MVC*task*) was at 10 to 20% of the rectified MVC*iso*. This power output was then maintained throughout the experiment. Upon determination of the power output, the VL EMG activity during 10 consecutive cycling revolutions was collected and averaged. Using this EMG pattern, 4 phases within a cycling revolution where the VL muscle was quiescent, at peak (MVC*task*), rising (~50% MVC*task*) and descending (~50% MVC*task*) activities were determined (**Fig. 4.1D**). Each phase indicated the ipsilateral position of the foot pedal during a cycling revolution. The corresponding ipsilateral arm crank position was set to be 180° out-of-phase.

Table 4.1. Characteristics of participants with iSCI in Study 1.

Subject	Age	Sex	Origin of Injury	Years post-injury	Level of injury	Primary mode of mobility*	Preferred 10-m walking speed (m/s)
S1	52	F	Surgery	9	T2-T4	Wheelchair	0.13
S2	53	M	Trauma/MVA	16	C6-7	Wheelchair	0.12
S3	41	M	Aneurysm	3	T5-6	None	0.31
S4	70	M	Trauma/Sports	26	C4-5	Walking poles	0.14
S5	75	F	Spinal Compression	1	C7-T1	Walker	0.15
S6	69	M	Spinal Dura Fistula	20	T6-8	Wheelchair	n/a
S7	61	M	Trauma/MVA	43	C4-5	Cane	0.17
S8	62	M	Trauma/MVA	40	C5-6	Walker	0.24
S9	67	M	Trauma/Sports	8	C4-5	Cane	0.21

*The primary mode of mobility was defined according to the assistive device the participant used in coming to the laboratory for the experiment; n/a: subject was not able to walk.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) was applied to the contralateral motor cortex using a

monophasic, single pulse stimulator (Magstim2002, Magstim Company Ltd., Carmarthenshire, UK) connected to a double cone coil. The motor cortical area that most consistently produced the largest VL MEP upon stimulation was determined and marked. Experimenters ensured that the coil position was aligned with the marker throughout the experiment. Participants were instructed to perform isometric knee extension in order to contract the VL muscle to reach an equivalent level of MVC*task* prior to each stimulus. The stimulation intensity increased, in increments of 5% maximal stimulator output (MSO), from a level that produced no activity to a level above that producing maximal MEP amplitude (MEP*max*). At each level of MSO, three stimuli were delivered and the MEP peak-to-peak amplitude was averaged. A VL MEP recruitment curve was then constructed and the intensity that produced ~50% of MEP*max* was determined and used for all trials.

Data Collection

A total of four conditions were investigated in this study: 1) arm static, leg cycling (ASLC); 2) arm cycling, leg static (ACLS); 3) both arm and leg cycling (ALC), and 4) both arm and leg static (ALS). The order of conditions was randomized. Both arm and leg cycling were produced voluntarily with no external assistance or use of FES. In each condition, 10 (for NI participants) or 6 (for iSCI participants) stimuli were delivered at each of the 4 phases of VL EMG activity within the cycling revolution. During cycling trials, the stimuli were delivered every 5 revolutions. During static trials, stimuli were delivered every 4 to 6 s while the participants performed a tonic contraction equivalent to the VL muscle activity at the same phase during cycling.

1) ASLC. The participants cycled their legs at the same self-selected speed during which the phases of VL EMG activity within a cycling revolution were identified. In each trial, the TMS pulse was triggered automatically to evoke a VL MEP when the foot pedal cycled through one of positions corresponding to one of the phases of VL EMG activity, using custom-written software. The arms were relaxed with the ipsilateral arm held at a position that was 180° out-of-phase from the leg position during which the TMS pulse was delivered.

2) ACLS. The experimental leg was fixed at a position corresponding to one of the 4 phases of

VL EMG activity with the contralateral leg at 180° out-of-phase. Participants were instructed to cycle their arms at the same speed as in the leg cycling trials, and to activate the VL muscle in the experimental leg to the same EMG level for that phase during leg cycling. TMS pulses were delivered automatically to evoke VL MEPs when the ipsilateral arm crank cycled through the predetermined arm position.

3) ALC. Participants were asked to actively cycle their arms and legs together at the same speed in a coordinated fashion. The speed was the same as during other cycling trials. TMS pulses were delivered when the experimental leg passed one of the 4 phases of VL EMG activity every 5 rotations.

4) ALS. Participants' legs remained stationary with the experimental leg positioned at locations corresponding to each of the 4 phases of the VL EMG activity. The contralateral leg and the ipsilateral arm were fixed at positions that were 180° out-of-phase from the experimental leg. Stimuli were delivered with VL either relaxed or tonically active to levels matching the EMG activity at the same phase during leg cycling

Data Analysis

Data were analyzed off-line using custom-written Matlab programs (Matlab R2015, The MathWorks Inc., MA, USA). The EMG activity was averaged over 100ms (leg static trials: ALS, ACLS) or 25ms (leg cycling trials: ALC, ASLC) immediately prior to the TMS pulse for each trial. The root-mean-square (RMS) of the average EMG activity from the sweeps in each phase within each condition was then determined. The RMS value represented the background pre-stimulus EMG activity (pre-stim). The MEP in the VL muscle was identified within a post-stimulus time window that was selected by visual inspection, and applied to all trials obtained from a given participant. The average peak-to-peak MEP amplitude across all 10 or 6 stimuli at each phase within each condition was calculated. The pre-stim value and MEP amplitude were then normalized to MVC*task.*

To identify the effect of arm cycling on the modulation of the corticospinal drive to VL, a two-factor repeated measure ANOVA (conditions × phases) was performed on the normalized MEP

amplitude and normalized pre-stim values using SPSS 23 (SPSS Inc., Chicago, IL, USA) and Fisher's LSD *post-hoc* test. The Pearson's product moment correlation coefficient (r) was used to establish the relationship between the pre-stim and MEP values.

Study 2: Effect of cycling training on the excitability of corticospinal pathway after iSCI

The characteristics of the 12 volunteers with chronic iSCI who participated in various parts of this study are summarized in **Table 4.2.** Participants were classified as AIS C or D with the spinal cord injury level between C3 and T12. Two 12 week-long training interventions were conducted: electrical stimulation-assisted arm and leg cycling and electrical stimulation-assisted leg cycling (Zhou et al., 2016b). Three participants underwent the A&L training first (A1, A4 and A5), and after a 'washout period' of 23 - 40 months underwent Leg training (L1, L7 and L6). The long wash-out period ensured the absence of potential carry-over training effects; therefore, these participants were treated as independent participants in separate groups (A&L, n=7; Leg, n=8).

The training protocol was previously described in detail (Zhou et al., 2016b). Briefly, training took place one hour per day, 5 days per week for 12 weeks. In both training modalities, FES was applied to the muscles as needed to assist in completing the cycling movements. Based on the training intervention, participant comfort and availability of equipment, different ergometer systems were used, including: 1) a custom-adapted arm and leg FES ergometer (THERA-vital, Medica Medizintechnik, Hochdorf, Germany; ERGYS 2, and Therapeutic Alliances, Inc. Fairborn OH, USA); 2) arm and leg Berkel Bike (Berkel, the Netherlands); 3) RT-200 arm and leg cycling ergometer (Restorative Therapies, Inc. MD, USA); 4) RT-300 leg cycling ergometer (Restorative Therapies, Inc. MD, USA); and 5) ERGYS 2 FES ergometer (Therapeutic Alliances, Inc. Fai, born OH, USA).

Table 4.2. Characteristics of participants with iSCI participating in the A&L and Leg training groups in Study 2.

Name (XX)*	Age	Sex	Injury Level	Origin of Injury	Years post-Injury	Primary Mode of Mobility	Ergometer	Group	Muscles with stimulation#
S1A	45	M	T10	Trauma/MVA	8	Crutches	Custom-adapted	A&L	Quads, Hams, Gluts
S2A (S8)	58	M	C5-C6	Trauma/MVA	36	Walker	Custom-adapted	A&L	Quads, Hams, Gluts
S3A	61	M	C3-C5	Trauma	2	Powered Chair	RT 200	A&L	Quads, Hams, TA, SS, Tri
S4A (S2)	50	M	C6-C7	Trauma/MVA	13	Wheelchair	Berkel	A&L	Quads, Hams, Gluts
S5A (S1)	49	F	T2-T4	Disc Protrusion /Surgery	6	Wheelchair	Custom-adapted	A&L	Quads, Hams, Gluts
S6A	58	M	C4-C5	Trauma/Fall	3	Powered Chair	RT 200	A&L	Quads, Hams, Gluts
S7A	74	M	C4-C5	Trauma/MVA	3	Walker	RT 200	A&L	Quads, Hams, SS, WE
S1L	48	M	T10	Trauma/MVA	11	Crutches	ERGYS	Leg	Quads, Hams, Gluts
S2L	36	F	C5-C7	Trauma/MVA	2	Wheelchair	RT 300	Leg	Quads, Hams, TA, Gastr
S3L	54	M	T4-T5	Disc Protrusion /Sports	4	Wheelchair	RT 300	Leg	Quads, Hams, Gluts
S4L	41	F	C6-C7	Trauma/MVA	7	Powered Chair	ERGYS	Leg	Quads, Hams, Gluts
S5L (S7)	62	M	C4-C5	Trauma/MVA	44	Cane	RT 300	Leg	Quads, Hams, Gluts
S6L (S1)	53	F	T2-T4	Surgery	10	Wheelchair	ERGYS	Leg	Quads, Hams, Gluts
S7L (S2)	54	M	C6-C7	Trauma/MVA	17	Wheelchair	ERGYS	Leg	Quads, Hams, Gluts
S8L	30	F	C5-C6	Trauma/MVA	3	Wheelchair	ERGYS	Leg	Quads, Hams, Gluts

*The name in parentheses identifies the participants who also participated in Study 1 **(Table 4.1)***;*
#Quads: Quadriceps; Hams: Hamstrings; Gluts: Gluteus; TA: Tibialis anterior; Gastr: Gastrocnemius; SS: Scapular stabilizers (rhomboids and supraspinatus); Tri: Triceps; WE: Wrist extensors**;**
MVA: motor vehicle accident.

The effect of cycling training on the corticospinal drive was examined by assessing the changes in the modulation of VL MEP during arm and/or leg cycling after training. Moreover, the effect of training modality on changes in the characteristics of the MEP recruitment curves in the tibialis anterior muscle before and after training was investigated.

Transcranial Magnetic Stimulation and Data Collection

I) MEP of the VL muscle during cycling after training

The experimental protocol in *Study 1* was replicated here to investigate the modulation of VL MEP during arm and/or leg cycling before and after training. Four iSCI participants in the Leg group (L5, L6, L7, L8) participated in this part of the study.

II) MEP of the tibialis anterior (TA) muscle after training

Assessment of the MEPs in TA was conducted before and after training. All participants in both training groups completed this experiment. During the assessments, participants sat in a custom-made chair with the knee joint flexed to ~100°, hip joint flexed to ~110°, and the ankle joint plantar flexed to ~5°. Surface EMG signals were recorded from the TA muscle on the experimental side using bipolar electrodes. The experimental side was the side with the lower AIS motor scores at the time of assessment before training, unless the MEP could not be consistently obtained from that side. The electrodes were connected to an AMT-8 EMG Wire Telemetry System (Bortec biomedical Ltd., Calgary, Canada). The EMG signals were amplified and band pass filtered between 30 and 1000 Hz and digitized at a sampling rate of 2000 Hz.

TMS through a double cone coil was used to stimulate the contralateral motor cortex. The area that most consistently produced the largest TA MEP was marked and stimuli were delivered to that region through the experiment. The stimulation intensity was increased in increments of 5% maximal stimulator output (MSO) from a level below threshold for producing a TA MEP, to a level at which the amplitude of the MEP plateaued or the stimulator reached near 100% MSO or when a participant can no longer endure the intensity of stimulation. Five TMS pulses were delivered with 6-7 s interstimulus interval per intensity level. Typically, stimulation intensities ranged from 30 to 85% of MSO. Participants were instructed to contract their TA muscle by performing isometric ankle dorsiflexion, and the stimulus was not delivered until the induced

force reached a horizontal line on the oscilloscope that matched 20% of maximal voluntary contraction (MVC) of the TA muscle. To obtain the MVC, the participants were asked to perform three maximal isometric contractions of ankle dorsiflexion on the experimental side, with the induced force measured by a transducer attached to the foot (Neurolog, Hertfordshire, UK). During post-training assessments, the background contraction of the TA muscle at 20% MVC was matched to the levels obtained at pre-training.

Data Analysis

The pre-stim EMG activity for a given TMS pulse was the average EMG activity over a 100ms window prior to stimulation. To ensure a uniform level of pre-stim activity across all trials, EMG sweeps with pre-stim EMG activity that was more than 2x standard deviations from the grouped pre-stim EMG activity from all sweeps were discarded. The peak-to-peak amplitude for the MEP response was measured within a time window post-stimulus that was set manually for each participant. The pre-stim activity and peak-to-peak MEP amplitude were averaged from all sweeps per stimulation intensity. A TA MEP recruitment curve was then constructed by plotting the MEP amplitude against the corresponding stimulation intensity. MEP*max* was then determined as the largest MEP amplitude of the recruitment curve (**Fig. 4.4D**). A fourth-parameter Boltzman sigmoidal function was used to fit the recruitment curve (**Fig. 4.4D**) (Devanne et al., 1997; Carroll et al., 2001; Thomas and Gorassini, 2005). Two measures were extracted from the fitted curve: the intensity required to obtain 50% of the MEP*max* (S50 in units of %MSO); and the peak slope of the function (in units of μV/%MSO) which indicates the maximal rate of increase in MEP magnitude with stimulus intensity. Following the methods of Carroll et al., the peak slope of the function was defined as its tangent at S50 (Carroll et al., 2001).

All statistical tests were performed using SPSS 23 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was first tested using Shapiro-Wilk test. The pre-training assessment measures between the A&L and Leg groups were compared using independent t-test or Mann–Whitney U test, depending on the normality test.

To determine the effect of training on the modulation of the corticospinal drive to VL, a three-

factor repeated measure ANOVA (training × conditions × phases) was performed followed by Fisher's LSD *post-hoc* test. Repeated measure ANOVA was also applied separately when the data divided into pre-training and post-training.

To determine the training effect and group difference on all measures regarding MEP recruitment curves in the TA muscle, a two-way mixed ANOVA (group, time) was performed with a *post hoc* Bonferroni correction. Additionally, paired t-test or Wilcoxon signed-rank test was used depending on the test of normality, to assess training effect within individual groups. Post-training change in each outcome measure was compared between training groups, using independent t-test or Mann–Whitney U test, based on the test of normality.

For all statistical analyses, differences with $p \leq 0.05$ were considered siginificant. All results are presented as mean ± 1x standard error unless otherwise indicated.

4.3 Results

Study 1: Modulation of Corticospinal Input to the Legs during Arm and Leg Cycling

Examples of rectified VL EMG activity (mean ± standard deviation) during leg cycling from an NI and iSCI participant are shown in **Fig. 4.1D**. The EMG activity was collected at the beginning of the experiment (without using electrical stimulation in participants with iSCI), in order to determine the EMG activity phases during which the TMS pulses will be delivered. The phases of VL EMG activity used in this study were: 'baseline,' 'mid-rising,' 'peak,' and 'mid-descending.' The TMS intensity evoking 50% MEP*max* in VL was held constant across all EMG activity phases during all arm/leg static and cycling conditions. **Figures 4.1B** and **C** show example traces of VL MEP obtained during arm static/cycling and during leg static/cycling conditions from an NI participant and a participant with iSCI, respectively.

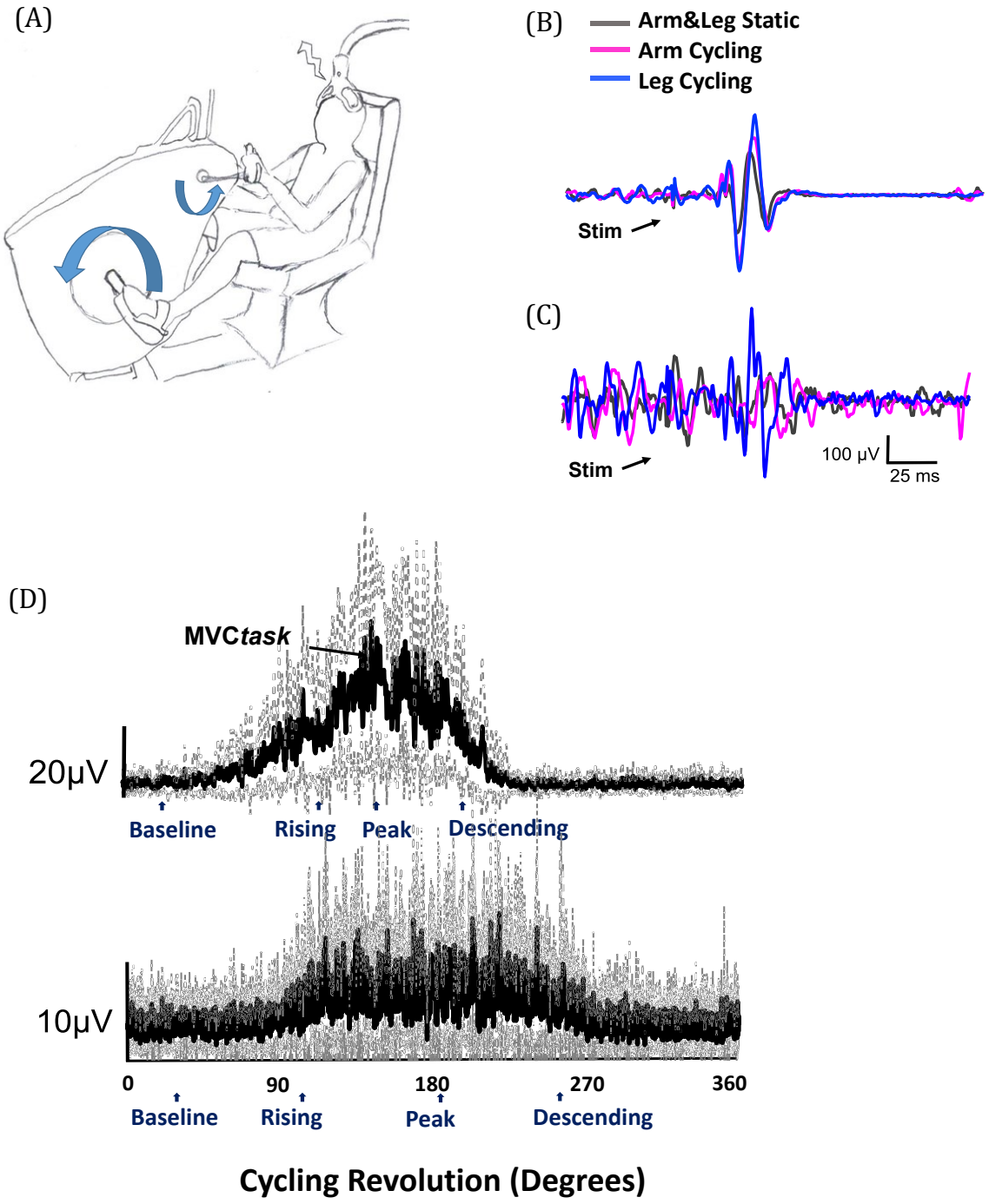


Figure 4.1. Experimental set-up and example trace for Study 1.

(A) Experimental set-up for Study 1. Examples of single MEP trace from the VL muscle during arm&leg static, arm cycling, and leg cycling conditions, respectively, in (B) an NI and (C) an iSCI participant. (D) Examples of the rectified EMG pattern from the VL muscle during one cycling revolution from an NI participant (top) and an iSCI participant (bottom). Black and grey lines represent the average and standard deviation of the EMG activity, respectively.

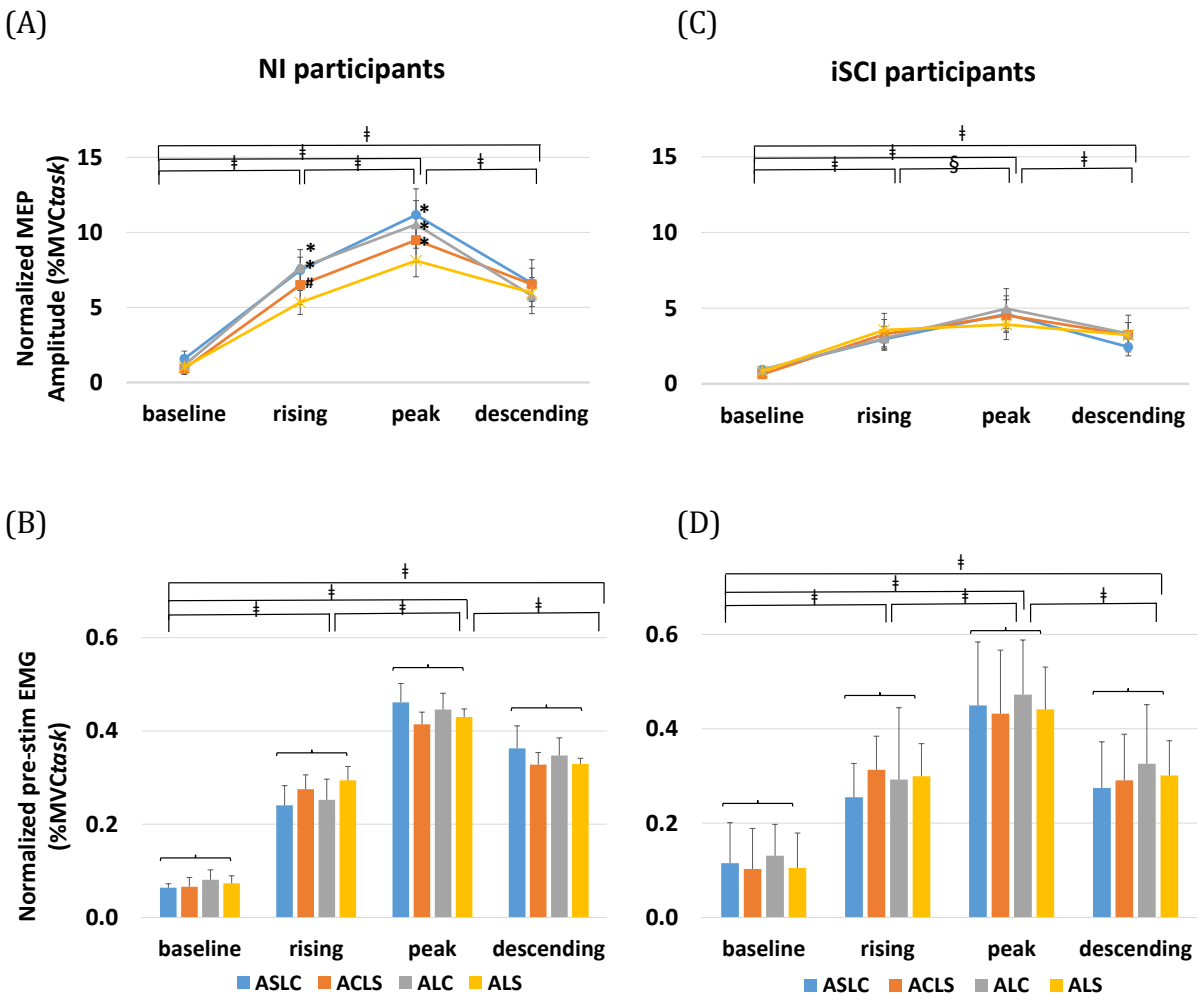


Figure 4.2. Group data in the NI and iSCI group for Study 1.

(A) Group data for normalized MEP amplitude of the VL muscle in NI participants (NI: n=14) and (C) iSCI participants (iSCI: n=9). Group data for normalized pre-stim EMG activity of the VL muscle in (B) NI participants (NI: n=14) and (D) iSCI participants (iSCI: n=9). * indicates significant difference from the ALS condition ($p \leq 0.05$). # indicates substantial difference from the ALS condition ($p \leq 0.1$). ǂ indicates significant difference between two phases ($p \leq 0.05$). § indicates substantial difference between two phases ($p \leq 0.07$). Values are expressed as average ± standard error.

Figure 4.2 shows the group average of normalized VL MEP amplitude **(Fig. 4.2 A, C)** and normalized VL pre-stim activity **(Fig. 4.2B, D)** for each of the arm/leg static and cycling conditions across all EMG activity phases for NI and iSCI participants. Not surprisingly, for both

the NI and iSCI groups, the pre-stim EMG activity was significantly different between any two phases (intact participants: $p \leq 0.003$; participants with iSCI: $p \leq 0.004$) except between the 'rising' and 'descending' phases intact participants: $p \geq 0.1$; participants with iSCI: $p \geq 0.7$). However, within each VL EMG activity phase, the pre-stim activity did not significantly differ between conditions in either the NI ($p \geq 0.4$) or the iSCI ($p \geq 0.2$) group.

In the NI group, there were significant differences in normalized MEP amplitudes across conditions ($p=0.01$) and phases ($p<0.0005$), with no significant interaction. Because the normalized MEP amplitude was significantly correlated with the level of pre-stim activity ($p<0.0005$, $r=0.6$), we analyzed the difference in normalized MEP amplitude among conditions during individual phases. During the 'rising' phase, MEP amplitudes in both leg cycling conditions (ALC: 7.64 ± 1.21, $p=0.01$; and ASLC: 7.48 ± 0.87, $p=0.01$) were significantly larger than that in the ALS condition (ALS: 5.33 ± 0.80). The MEP amplitude in the ACLS condition (6.50 ± 1.31) during this phase was substantially, but not significantly, different from ALS ($p=0.1$). During the 'peak' phase, the normalized MEP amplitude of the ALS condition (8.12 ± 1.08) was significantly smaller than the amplitude in the other three conditions (ALC: 10.53 ± 1.59, $p=0.03$; ASLC: 11.16 ± 1.74, $p=0.03$; ACLS: 9.49 ± 1.48, $p=0.03$). No significant difference between conditions was found during the 'baseline' and 'descending' phases.

In contrast, no significant difference in the normalized MEP amplitude across conditions was found in the iSCI group ($p=0.7$). Normalized MEP amplitudes in the iSCI group were substantially smaller than those in the NI group during the same EMG phase **(Fig. 4.2 A, C)**, even though the group average of normalized pre-stim activity was similar between the two groups (**Fig. 4.2B, D).** Similar to the NI group, the normalized MEP amplitude was significantly correlated with pre-stim activity ($p<0.0005$, $r=0.6$) **(Fig. 4.2C).** Nonetheless, within a phase of EMG activity, there were no significant differences in the MEP amplitude between any arm/leg static and cycling conditions.

We also calculated the onset latency in the VL MEP at each condition across all EMG phases for the NI and iSCI group. No significant difference was found in the MEP latency across conditions (NI: $p=0.3$; iSCI: $p=0.5$) or across phases (NI: $p=0.2$; iSCI: $p=0.2$). However, the group average

of MEP latency in the iSCI group (34.28 ± 0.96 ms) was much longer ($p<0.0005$) than the latency in the NI participants (20.26 ± 0.77 ms)

Study 2: Training Effect on the Modulation of Corticospinal Pathway

I) MEP of the VL muscle during cycling after training

Figure 4.3 shows the group average of normalized MEP amplitude and normalized pre-stim activity of the VL muscle from four iSCI participants at pre- and post-training. Pre-stim activity was not different among conditions ($p=0.3$), or between pre- and post-training ($p=0.8$) **Fig. 4.3B, D.** The pre-stim activity however was significantly different between the 4 phases of VL EMG activity ($p<0.0005$).

Overall, the normalized MEP amplitude **(Fig. 4.3A, C)** was not significantly different before and after training ($p=0.9$), although it was significantly different across the 4 phases of EMG activity ($p<0.0005$). After 12 weeks of training (leg cycling), the effect of conditions on the normalized MEP amplitude remained non-significant ($p=0.3$); however, cycling seemed to facilitate the MEP amplitude to a small extent (**Fig. 4.3C**).

II) MEP of the TA muscle after training

At pre-training, the A&L group and Leg group had a similar TA MEP*max*, with a comparable level of background contraction at 20%MVC (A&L: MEP*max* = 417.60 ± 131.08 μV, pre-stim = 19.32 ± 4.09 μV; Leg: MEP*max* = 479.33 ± 140.12 μV, pre-stim = 16.69 ± 5.27 μV). There was a significant increase in the MEP*max* after training only in the A&L group, with an average increase of 0.22 ± 0.12 mV ($p=0.02$) (**Fig. 4.4B**). The average post-training change in the A&L group (44.77 ± 18.50%) was substantially larger than that in the Leg group (19.39 ± 11.15%) **(Fig. 4.4C).**

The pre-stim EMG activity of the TA muscle was similar before and after training for both A&L and Leg groups (A&L at pre: 19.32 ± 4.09 μV, at post: 20.02 ± 3.71 μV, $p=0.7$; Leg at pre: 16.69 ± 5.27 μV, at post: 17.68 ± 5.89 μV; $p=0.5$). The pre-stim activity was also similar between both groups at pre-training and at post-training. MEP onset latency was also similar between the two groups at pre-training (A&L: 38.39 ± 1.11ms; Leg: 35.57 ± 2.58ms; $p=0.4$), and remained

similar after 12 weeks of training regardless of group (p=0.2).

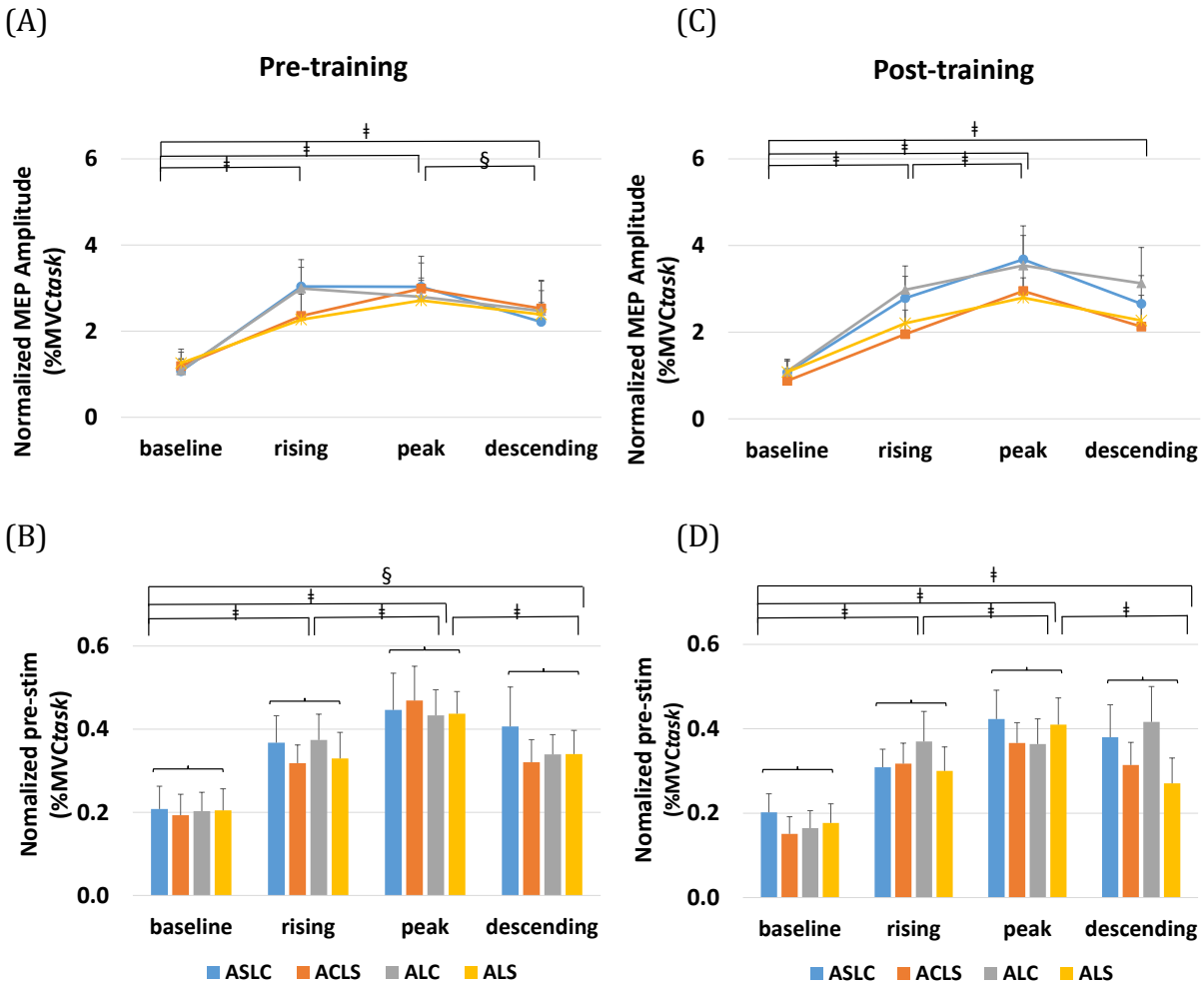


Figure 4.3. Group data of iSCI participants at pre- and post-training.

(A) Group data for normalized MEP amplitude of the VL muscle in four iSCI participants from the Leg group at pre- and (C) post-training (iSCI: n=4). Group data for normalized pre-stim EMG activity of the VL muscle in iSCI participants at (B) pre- and (D) post-training (iSCI: n=4). ǂ indicates significant difference between two phases ($p \leq 0.05$). § indicates substantial difference between two phases ($p \leq 0.1$). Values are expressed as average ± standard error.

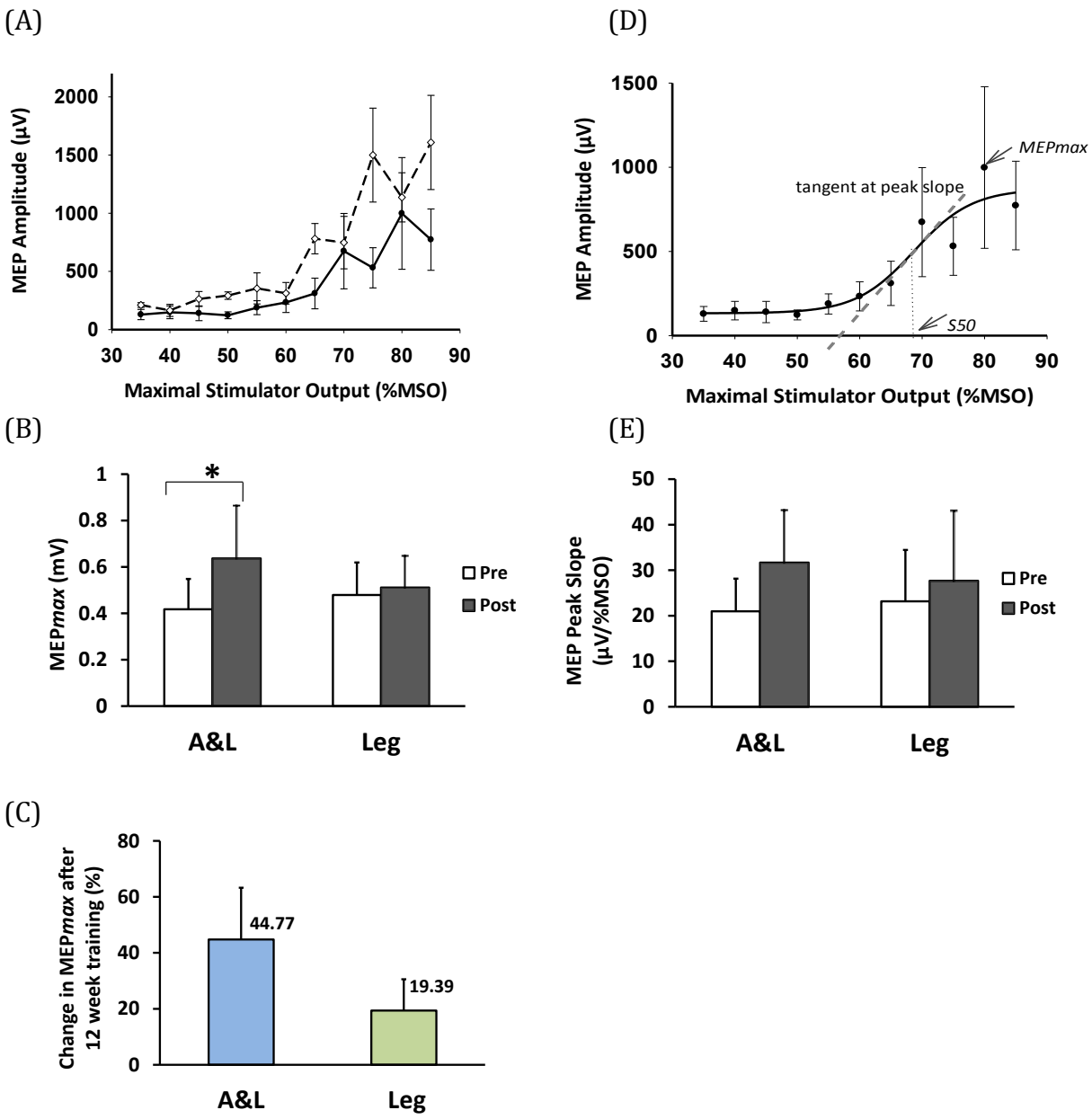


Figure 4.4. MEP recruitment curves.

(A) Examples of the MEP recruitment curve (mean± standard deviation) at pre- and post-training from an iSCI participant. (B) Group average of MEP*max* at pre- and post-training (A&L: n=7; Leg: n=8). (C) Post-training change in MEP*max* in the A&L and Leg group (A&L: n=7; Leg: n=8). (D) An example of the MEP recruitment curve (mean± standard deviation) and parameters from the fitted function from an iSCI participant. (E) Group average of the peak slope at pre- and post-training (A&L: n=7; Leg: n=8). * indicates significant difference ($p \leq 0.05$). Values are expressed as average ± standard error.

The S50 and peak slope, which were extracted from the fitted recruitment curve**,** can indicate changes in the MEP excitability. Both A&L and Leg groups had similar values of those two measures at pre-training **(**A&L: S50, 65.79 ± 2.80 %MSO; peak slope, 20.98 ± 7.17 μV/%MSO; Leg: S50, 66.77 ± 5.77 %MSO; peak slope, 23.16 ± 11.30 μV/%MSO**)**. After training, S50 remained the same (p=0.8), regardless of group. The A&L group appeared to have a larger post-training change (increase of 10.69 ± 13.63 μV/%MSO) in the peak slope compared to the Leg group (increase of 4.50 ± 16.60 μV/%MSO) **(Fig. 4.4E);** however, this difference was not statistically significant (p=0.5).

4.4 Discussion

The findings from this study suggest that, in an intact nervous system, rhythmic leg movements strongly modulate the corticospinal pathway to the legs. Interestingly, arm cycling alone may also facilitate the corticospinal transmission to the legs, and this facilitation can be close in magnitude to that provided by leg cycling.

The findings also demonstrate that after iSCI, arm and/or leg movement-related facilitation to the corticospinal pathway may be abolished. However, leg cycling training may restore some facilitation. Furthermore, a rehabilitation training strategy involving simultaneous arm and leg cycling may produce greater MEP increases in the TA muscle than legs only cycling, indicating a better improvement in the strength of corticospinal connectivity.

Modulation of Corticospinal Input to the Legs during Leg Cycling

MEP amplitude of the leg muscle has been found to be significantly modulated during walking and cycling in people with intact nervous system (Schubert et al., 1997; Capaday et al., 1999; Pyndt and Nielsen, 2003; Sidhu et al., 2012). The modulation was explained by the changing excitability of the corticospinal projections to motoneurons during movement (Pyndt and Nielsen, 2003). Specifically, MEP amplitude is facilitated as the background EMG of active muscles increases, suggesting adaptation in the corticospinal excitability to dynamically changing motor tasks (Shadmehr and Mussa-Ivaldi, 1994; Zabukovec et al., 2013). The findings

from the intact participants in the present study are in conformity with those previous studies.

The significantly greater MEP amplitude at the 'rising' and 'peak' stages of EMG activity during cycling, compared to that during the leg static condition, also confirms the increased corticospinal excitability during locomotion (Schubert et al., 1997; Petersen et al., 1998). On the other hand, normalized VL MEP amplitudes were not different among all conditions at the 'descending' phase even though the EMG activity was similar to that in the 'rising' phase. Other indirect pathways could also influence MEP amplitude, including interneurons in the spinal cord receiving corticospinal inputs. These pathways contribute to differences in the MEP modulation during various tasks (Nielsen et al., 1999). Also, recruitment gain (recruitment gradation) of the motoneuron pool, which is associated with the responsiveness of the pool, could still be different even at a similar background EMG activity during various tasks (Kernell and Hultborn, 1990; Nielsen and Kagamihara, 1993; Barthelemy and Nielsen, 2010). Therefore, even though at a similar background EMG activity, the 'rising' and 'descending' phases might have different recruitment gains of the motoneuronal pool and different excitability of interneuronal pathways. These could ultimately influence the descending synaptic inputs to the motoneurons.

Modulation of Corticospinal Input to the Legs during Arm Cycling

Our study, for the first time, investigated the effect of arm movement on modulating the corticospinal input to the leg muscle in humans. The facilitation in MEP amplitude induced by arm cycling had a comparable influence to leg cycling on corticospinal transmission to the leg. This modulation could be attributed to both cortical and spinal mechanisms (Zhou et al., 2016c). Modulation of arm-leg coordination through spinal intersegmental linkage has been suggested in previous studies (Dietz, 2002a). The linkage, composed of propriospinal pathways, connects the cervical and lumbar locomotor networks in the spinal cord. In neonate rats, after a rostral hemi-lesion of the spinal cord between C1 and T3 and contralateral hem-lesion between T5 and L1, excitation of the propriospinal neurons promoted locomotor-like activity that supplemented the ineffective drive from the brainstem (Cowley et al., 2008). The results suggested that propriospinal neurons could transmit descending locomotor commands. Experiments during human walking also found that corticospinal input interacted with spinal inhibitory interneurons, to modulate the postsynaptic potentials mediated by propriospinal-like interneurons (Iglesias et

al., 2008). Therefore, corticospinal input can be transmitted, and possibly modulated along propriospinal pathways. Furthermore, in studies investigating the effect of arm cycling on modulating the spinal reflex in a leg muscle, the cervical locomotor network was a dominant source responsible for the modulation of leg activity (Hundza et al., 2012; Zhou et al., 2016c). Therefore, the arm cycling-induced facilitation of the MEP to the leg in this study may be at least partially attributed to the excitation of cervical networks, which might augment the corticospinal transmission to the leg.

Intracortical mechanisms may also be involved in modulating corticospinal excitability during coordinated arm and leg movement in humans (Debaere et al., 2001). Although anatomical connections between the representations of arm and leg muscles in the primary motor cortex (M1) have not been established, overlap of arm and leg areas was found in secondary motor areas that provide input to M1 (Brown et al., 1991; Fink et al., 1997; Byblow et al., 2007). For example, premotor cortex and supplementary motor areas facilitated corticomotor pathways during hand-foot coordination (Byblow et al., 2007). Also, M1 output could facilitate wrist movements that were isodirectional to foot movement (Baldissera et al., 2002). Together along with other similar evidence (Borroni et al., 2004; Muraoka et al., 2015; Nakagawa et al., 2015), it is suggested that intracortical excitability can be modulated during a coordinated arm-leg movement. Therefore, in the present study, cortical mechanisms may have also contributed to MEP facilitation during arm and/or leg cycling.

Furthermore, in the NI participants, we found that the amount of change in MEP amplitude during ALC was not equal to the algebraic sum of the change during ASLC and ACLS. In fact, the change during ALC was similar to the change during ASLC or ACLS. Previous evidence suggested that MEP amplitude is susceptible to the background contracting level, as well as the state of the muscle (Liepert et al., 2001; Van Hedel et al., 2007; Reis et al., 2008). For example, different force levels or tasks of the testing muscle could lead to the differences in the MEP response (Diehl et al., 2006; Van Hedel et al., 2007; Reis et al., 2008). In this study, the maximal background contraction of the VL muscle was fixed at a low contraction level (10-20% MVC*iso*). It is unclear whether the contraction level could potentially saturate or impede the modulation of corticospinal transmission when combining movements of arms and legs.

Modulation of Corticospinal Input to the Legs during Cycling after SCI

Importantly, this study demonstrated that iSCI abolished the modulation of corticospinal drive during rhythmic movements of both the arms and legs. This is likely due to impairment in supraspinal regulation and/or loss of cervico-lumbar coupling in the spinal cord (Kato et al., 1984; Cowley et al., 2014; Klarner et al., 2014; Zhou et al., 2016c).

After SCI, corticospinal projections sprout extensively above and below the lesion (Fouad et al., 2001; Rosenzweig et al., 2010). These corticospinal collaterals, relayed by long propriospinal neurons, travel to segments away from the lesion site, and form new intraspinal circuits (Bareyre et al., 2004). The reorganization of descending and propriospinal connections may contribute to the plasticity in functional motor recovery after SCI (Courtine et al., 2008). For example, the spinal region caudal to an injury in people with SCI, could contribute to the facilitation of residual corticospinal output (Bunday et al., 2013). In the present study, the significantly longer latencies of VL MEP in participants with iSCI compared to NI participants indicated the formation of new polysynaptic connections after injury. Interestingly, the MEP latencies in both NI and iSCI participants were independent of experimental conditions or phases of cycling EMG activity. The similar central motor conduction time across conditions suggests the involvement of a similar central motor pathway.

After 12 weeks of leg cycling training, the VL MEP amplitude seemed to increase during leg cycling compared to leg static conditions in four participants with iSCI in the Leg group; however, this increase was not significant. This may suggest that leg cycling training may have strengthened corticospinal transmission to the legs. However, arm-cycling-induced facilitation was not found in those participants after training. This could be due to the absence of active arm involvement during their training. Because of the limited sample size in this part of the experiment, it remains unclear how training could affect the modulation of the corticospinal pathway during arm and/or leg cycling in people with iSCI.

Changes in Corticospinal Pathway after Training

A significant increase in TA MEP*max* was found in the A&L group after 12 weeks of training,

but not in the Leg group, indicating that adding arms to the training produced more effective enhancement of the corticospinal pathway after SCI.

In people with neural disorders, it has been shown that MEP*max* could be increased after a long-term training intervention, such as through locomotor training (Thomas and Gorassini, 2005; Zewdie et al., 2015) or over repeated FES use (Everaert et al., 2010). Our results demonstrated that cycling training could also increase MEP*max*, but that was significant only in the A&L group. The amplitude of MEP represents the integrity of the corticospinal tract, the cortical and spinal excitability, as well as the peripheral pathway to the muscle (Nardone et al., 2014). Therefore, significantly increased MEP*max* suggests an improved connectivity and excitability of the corticospinal pathway in the A&L group. Furthermore, the A&L group appeared to have a greater increase, although not significant, in the peak slope than that in the Leg group. These results confirmed our hypothesis that active arm engagement could produce greater improvement in the corticospinal pathway.

4.5 Limitations

In the present study, we assessed the change in MEP amplitude of the VL muscle during cycling on 4 participants with iSCI from the Leg group, at pre- and post-training. However, the finding did not reach a statistically significant difference. It may be because the sample size was too small to be adequate enough for detecting the change as a result of training, especially given the heterogeneity of this population. Therefore, more participants are required in order to assess the training effect on impaired modulation of corticospinal input to the legs after SCI. Moreover, it is unclear how the observation would change if those participants had actively involved the arms in their training.

4.6 Clinical Implications

The MEP was reported to predict and be associated with the improvement in leg motor functions and ambulatory capacity after SCI (Curt and Dietz, 1999; Petersen et al., 2012; Barthelemy et al., 2013). For example, MEP amplitude could be indicative of faster walking speed and longer walking distance for individuals with chronic SCI (Barthelemy et al., 2013). Moreover, both

MEP amplitude and latency were correlated with the degree of foot drop in people with SCI (Barthelemy et al., 2010). Therefore, corticospinal transmission is important during human gait, and thus its recovery is beneficial in neurorehabilitation. In this study, we also found strong correlations between MEP*max* and walking speed before and after training (data not shown).

Our earlier study suggested a novel rehabilitation intervention to improve walking function in people after iSCI, by actively and simultaneously engaging arm and leg movement in training (A&L) (Zhou et al., 2016b). A significantly better improvement in walking function was found in the A&L group compared to training with leg cycling only (Zhou et al., 2016b). In the present study, A&L participants have also demonstrated a substantially larger improvement in corticospinal pathway compared to the Leg group. As observed from the NI participants, arm cycling alone could significantly increase the MEP amplitude in the leg. Therefore, active engagement of the arms in training may have strengthened both cortical and propriospinal connections (Zhou et al., 2016c), leading to better transmission of the corticospinal input and ultimately a better walking capacity (Zhou et al., 2016b). This work provides support for the need to engage the arms actively in lower limb rehabilitation for people with neural disorders, such as SCI, for a better neural regulation and restoration of leg function.

Chapter 5. General Discussion

5.1 Summary and significance

The overall goal of my project was to investigate a novel approach for the rehabilitation of walking after neural disorders. The approach focused on actively engaging the arms simultaneously with the legs in a cycling training paradigm. We assessed the effect of the intervention on walking capacity in people with chronic iSCI. We compared the primary outcome measures, walking speed and distance, between two training paradigms in people with iSCI: electrical stimulation-assisted arm and leg cycling (A&L) and electrical stimulation-assisted leg cycling (Leg). The results of this novel intervention have confirmed the hypotheses: 1) a rhythmic non-gait-specific cycling training paradigm can improve overground walking speed, distance and quality of walking (joint kinematics and regulation of muscle EMG activity during walking) in people with iSCI; and 2) the improvement in walking function after Leg training is similar to that obtained with gait-specific training interventions focused on the lower limbs; however, A&L training can provide even better recovery in walking function. This study has challenged the dogma of task-specificity in rehabilitative training (Edgerton et al., 1997; Behrman and Harkema, 2000; Mastos et al., 2007). More importantly, although arm involvement in gait rehabilitation after neural disorders has been recommended previously (Behrman and Harkema, 2000; Stephenson et al., 2010; Meyns et al., 2011), this is the first study that systematically investigated the role of arms in a longitudinal rehabilitation intervention program to improve walking function after a neural disorder.

To further investigate the neural adaptation after SCI and more importantly, the underlying neural mechanisms underpinning the improvements in walking capacity as a function of training, we first performed cross-sectional experiments to understand the changes to the spinal and supraspinal pathways in people with iSCI. Specifically, we studied the cervico-lumbar coupling and the modulation of the corticospinal transmission during rhythmic arm and/or leg movement in volunteers with intact nervous system and in untrained iSCI participants. Results showed a weaker or even abolished spinal and supraspinal modulation during movement in iSCI participants. In light of the findings, we investigated the training-induced change to the spinal and supraspinal pathway and found improvements in both A&L and Leg groups. In particular, the cervico-lumbar spinal regulation was restored to some extent after cycling training, and the excitability of the lumbar network was also more regulated, especially in the A&L group.

Similarly, the corticospinal connectivity was strengthened after training, but only the A&L group showed a statistically significant improvement. This study provides evidence that cycling training could regulate and improve the impaired neural activity in people with SCI at both spinal and corticospinal levels, which likely contributed to the improved walking function achieved in the present study. The findings consistently demonstrated, for the first time, that non-gait specific rhythmic training can be effective in improving overground walking capacity. They also systematically demonstrated, for the first time, that engaging the arms actively in lower limb rehabilitation can provide better regulation of the nervous system and more effective restoration of leg function.

5.2 Limitations

As a pilot investigation, we recognize that there are a number of limitations in the studies of this dissertation. Firstly, the sample sizes were limited in these studies, which resulted in large variations and reduced statistical power in the analysis of various outcome measures. We focused on a selected subpopulation of participants (chronic iSCI with AIS grade of C or D), and the range of injury levels among participants was wide (from C3-4 to T12). Therefore, the conclusions may not be generalized to the entire population of SCI. Secondly, there were only two types of training interventions: combined arm and leg cycling, and leg cycling only. Because a control group of gait-specific training was not included, we were not able to compare directly the efficacy of cycling training and gait-specific training in restoring walking functions. Similarly, adding a group of participants who only trained with arm cycling could add further evidence to identify the role of the arms in the rehabilitation of walking. Lastly, examiners in this study were not blinded to the interventions, assessment procedures or results; a matter that could introduce unintentional bias in subjective clinical measures. These limitations are acknowledged by the researchers, and suggestions for future studies are made with the limitations taken into account (See **5.4**).

5.3 Translation to clinical care

Among the different areas in health care for persons with SCI, the need for physical therapy and rehabilitation is in large and constant demand (Christopher Dana Reeve foundation, 2009), and

the cost of which can be exorbitant (Ong et al., 2015). During gait-specific rehabilitative training, especially treadmill locomotor training, the client often requires physical assistance from 3-4 physical therapists/staff members, to maintain the stability at the hips and to help move his/her legs over the treadmill belt to simulate walking. Therefore, the labor-intensive modality of locomotor training accounts for a large amount of the cost in rehabilitation. According to a report of the financial feasibility of locomotor training in 2007, gait training is the most commonly billed procedure during visits for rehabilitation (Morrison and Backus, 2007). Based on the report, with a typical delivery model of one physical therapist, two physical therapy technicians, and one volunteer, the cost of personnel accounts for 85% of the direct cost, and the average cost of personnel is USD 102.09 per visit for a 1.25 hour session (Morrison and Backus, 2007). Therefore, because cycling training only requires one staff member to prepare, set up and supervise the training per client, the implementation of this cycling intervention is likely to cut at least 67% of the personnel cost compared to locomotor training.

Furthermore, the equipment required for cycling training, especially leg cycling ergometers, are common in rehabilitation facilities, but currently, their main use is for improving cardiovascular health and averting muscle atrophy. For example, there are at least 13 RT arm and/or leg ergometers (Restorative Therapies, Inc. MD, USA) in Alberta, at different clinics and community centers for public use (information based on a personal communication with the Western Canada distributor). Therefore, the implementation of the leg cycling intervention in clinics does not introduce an extra equipment cost. However, it is important to note that, the market share for the arm and leg combined ergometer is still extremely small (~5%). Therefore, implementation of the combined arm and leg cycling intervention may still require a new purchase or in-house adaptation of existing equipment at most facilities.

5.4 Future directions

5.4.1 Additional measures

In the present study, I attempted to capture training-induced changes from as many aspects as possible, but there were still some measures or functions not systematically monitored.

For example, autonomic functions were not examined in the study. Depending on the level and severity of the injury, autonomic dysfunctions can alter cardiovascular function and bladder, bowel and thermoregulation in people with SCI (Juknis et al., 2012). A direct connection between exercise and bladder or bowel function after SCI is not established; however, from anecdotal evidence and post-training interviews with the participants from both training groups, a large number of them reported noticeably better control and voiding of the bladder, and/or an improvement in bowel routine (refer to **Appendix 2** for the interview questions). Regarding cardiovascular function, in the present study, only two participants from the A&L group and six participants from the Leg group completed an aerobic test to measure maximal oxygen uptake before and after training (refer to **Appendix 1** for details of the experiment). The results allowed me to assess the changes in fitness and aerobic capacity as a result of training. However, I could not perform a quantitative analysis on the difference of training-induced fitness between groups due to the limited and unbalanced sample size. Moreover, I did not consistently document the participants' blood pressure, heart rate and metabolic response during training; therefore, I was not able to quantify the training intensity by the level of cardiovascular stress (ACSM, 2013). An ongoing clinical trial, 'CHOICES' (ClinicalTrials.gov Identifier: NCT01718977), is investigating whether BWS treadmill locomotor training has beneficial effects, especially on cardiovascular health, over arm cycling training in people with SCI. However, these two training interventions only focus on separate arm and leg exercises. A study investigating how combined arm and leg cycling training influences cardiovascular adaptations in people with SCI can provide new understanding in the design of rehabilitative interventions with a greater efficacy and better health outcome.

Spasticity was not directly measured in the present study. Instead, I performed experiments using the H-reflex in arm and leg muscles, which may indirectly explain changes in the excitability of the spinal cord with training (Wolpaw and Tennissen, 2001; Misiaszek, 2003). However, the reported evidence on the changes to the reflex after SCI and whether they are an accurate estimate for spasticity is inconsistent (Ashby et al., 1974; Taylor et al., 1984; Little and Halar, 1985; Thompson et al., 1992; Faist et al., 1994; Schindler-Ivens and Shields, 2004). Clinical measures of spasticity can be included in future studies to quantify the changes over training, such as using the Modified Ashworth Scales (MAS) for muscle tone and the Penn Spasm

Frequency Scale (PSFS) for spasms (Hsieh et al., 2008). But interestingly, some participants in the present study have reported a reduction in spasticity during their post-training interviews, regardless of training group. An exceptional example is participant S3L, who was prescribed an implanted baclofen pump prior to the start of his training; but immediately after 12 weeks of cycling training, he was diagnosed as 'almost no spasticity' and 'no need to implant the baclofen pump' by his physiatrist.

Quality of life and daily functions were reported to be significantly higher in the groups with cycling training compared to the control group (assigned to 'standard of care') in people with SCI (Sadowsky et al., 2013). Therefore, self-reported questionnaires for quality of life from the participants in future studies can be a valuable measure of the well-being of the participants (e.g., Medical Outcome Study 36-Item Short-Form Health Survey (McHorney et al., 1993)). Clinical measures that evaluate the basic function and independence of participants should also be included, such as the FIM score or Instrumental Activities of Daily Living scale (IADL), especially measures validated for the SCI population (e.g., Spinal Cord Independence Measure (SCIM) (Catz et al., 2001a; 2001b)).

Lastly, exercise training has also shown improvements in body composition, bone density, distribution of muscle fiber type, stress and pain levels in people with SCI (Ditor et al., 2003; Hicks et al., 2003; Dolbow et al., 2011; Gorgey et al., 2012a; 2012b), which can all be important measures to examine the effect of training from a variety of aspects.

5.4.2 Patterns of the training paradigm

A natural pattern of arm and leg coordination was encouraged during arm and leg cycling training in the present study. Specifically, the movement between the arms and legs was reciprocal (180° out-of-phase) and had a 1:1 arm to leg frequency ratio. Previous understandings of arm and leg coordination were mostly established based on moving the ipsilateral arm and leg in anti-phase, as is the case with the arms swinging in opposition to the legs during walking or crawl swimming (Wannier et al., 2001). Although rhythmic arm movement influences leg activity through neural coupling, the natural locomotor-like anti-phase arm swing is more effective than ipsilateral or bilateral in-phase swing in modulating the motor output of the legs

(Massaad et al., 2014). FES-assisted rowing intervention has been shown to improve aerobic fitness, bone density, muscle strength and body composition (Gibbons et al., 2014; Kim et al., 2014; Gibbons et al., 2016); however, the efficacy of FES-assisted rowing training in improving overground walking capacity is still unclear. Furthermore, unlike in walking or cycling, the movement of arms and legs are maintained at an in-phase manner. A study that compares the effect on walking function with the arms actively engaged along with the legs, in walking/stepping training, cycling training and rowing training, will provide important understanding about how a natural pattern of arm and leg coordination may influence the recovery of walking.

In the present study, participants completed one hour of cycling training every weekday for 12 weeks. Although an effective intensity of rehabilitation for restoring walking is not established, there is evidence that aerobic training performed at a moderate to vigorous intensity (3 days/week for 2 months), could improve cardiovascular fitness, musculoskeletal fitness, oxidative metabolism and exercise tolerance (Warburton et al., 2007). It should also be noted that a 2-week FES-assisted leg cycling training in people with multiple sclerosis did not significantly change either the walking speed or muscle strength (Szecsi et al., 2009), suggesting that an effective intensity and duration of training for improving walking should be further explored.

5.4.3 Design of a randomized controlled trial (RCT)

As a pilot investigation, the present study demonstrated improvements in walking function through leg cycling training, and the magnitude of improvement could be equivalent to that obtained from gait-specific locomotor rehabilitation. Also, compared to leg cycling only, active involvement of arms during training showed better improvement in restoring and regulating walking. To calculate the effect size within the A&L group and Leg group in the present study, the equation below was used (Musselman, 2014):

$$\text{Effect size} = \frac{Mean_{post} - Mean_{pre}}{\sqrt{(S_{pre}^2 + S_{post}^2)/2}} \qquad \text{Eq. 1}$$

Where $Mean_{pre}$ is the average value of pre-training measure, $Mean_{post}$ is the average value of post-training measure, S_{pre}^2 is the variance of pre-training measure, and S_{post}^2 is the variance of post-training measure. Based on the data in the present study, the effect size is determined to be 1.4 in the A&L group and 0.4 in the Leg group for 10-meter walking speed, representing a strong and moderate change as a function of training (Cohen, 1988), respectively. Correspondingly, it also indicates a great clinical significance (Jacobson and Truax, 1991), since an effect size of 0.2 has been considered as the minimally important difference (Samsa et al., 1999; Crosby et al., 2003). Similarly, the effect size is 1.3 in the A&L group and 0.6 in the Leg group for the 6-minute walking distance. Based on these results from this pilot study, I am able to expand the research question to a larger scale, and make recommendations regarding the design of a randomized controlled trial (RCT) to evaluate the efficacy of different training interventions in the SCI population. A few suggested designs are listed below:

1) An RCT to compare combined arm and leg cycling and leg cycling. To design a randomized controlled trial with blinded assessors, walking speed and distance are selected as primary measures. The sample size to achieve a significant difference between the two groups is estimated based on the values from the present study. With power of 0.8 and a confidence level of 0.05, a sample size of 14 participants in each group would be needed for a difference of 31% between groups and a standard deviation of 28% in the change of 10-meter walking speed after training (or 14 participants in each group based on a group difference of 0.18 ± 0.16 m/s in the increase of walking speed). Similarly, in the change of 6-minute walking distance, a sample size of 89 participants in each group for a difference of 11% between groups and a standard deviation of 25% is determined to achieve a power of 0.8 (or 24 participants in each group based on a group difference of 59.46 ± 72.03 m in the increase of walking distance). Collectively, with an estimate of 10% dropout rate, at least 26 participants in each group are suggested to be included in an RCT study in order to reach a statistically strong power in walking performance (speed and distance) in the SCI population. According to the prevalence rate of SCI in Canada, 2525 per million population in 2010 (Noonan et al., 2012), there are approximately 85,556 persons with SCI. Correspondingly, there are ~10,100 people with SCI in the province of Alberta given a provincial population of approximately 4 million (Government of Alberta, 2015). Among those people, incomplete SCI is the most frequent neurological category, approximately 66%, while

complete SCI constitutes 34% of the population (National Spinal Cord Injury Statistical Center, 2016). Therefore, there could potentially be 6,666 individuals in Alberta with incomplete motor and/or sensory function. However, the number may still be small to fulfill the required number of participants for the RCT study within Alberta, in which case a multi-center collaboration will be needed.

2) Although the present study only investigated the training effect in people with chronic injury, it will be of great interest to study whether there is a difference in training effect between persons with acute (< 1yr post-injury) and chronic (≥ 1yr post-injury) SCI. Along with spontaneous recovery, the responsiveness to rehabilitative training could be facilitated owing to augmented neural plasticity in the early stage post-injury (Battistuzzo et al., 2012; Fouad and Tetzlaff, 2012). An RCT design can include 4 randomized blocks, including A&L training and acute SCI, A&L training and chronic SCI, Leg training and acute SCI, and Leg training and chronic SCI. Assuming at least 26 participants are still needed for each group, the recruitment of the participants with acute SCI can be challenging, given the annual SCI incidence of 109 per million in Canada (traumatic and non-traumatic origin combined) (Noonan et al., 2012). Therefore, a multi-center collaboration across provinces/states for the RCT would be needed.

3) A gait-specific training intervention was not included in the present study. A direct comparison of the efficacy between different interventions, including A&L cycling, Leg cycling only, and gait-specific training focused on the lower limbs (e.g., BWS treadmill locomotor training, overground walking, walking with FES assistance) would be important for changing clinical practice. Systematic reviews of gait-specific training to enhance functional ambulation in people with SCI have suggested that there is no superiority of one intervention over another (Mehrholz et al., 2012; Morawietz and Moffat, 2013). Therefore, I averaged the reported values of improvement in walking speed from multiple research studies that involved gait-specific locomotor training focused on the lower limbs (see **Chapter 2 Discussion**). The calculated average was 0.09 m/s, which was equivalent to the improvement observed in the Leg group in the present study. Therefore, it is less likely that there is a difference in improving walking speed between Leg cycling training and gait-specific locomotor training interventions, although this comparison still needs to be tested. A similar sample size to the one proposed for the comparison

between the A&L and Leg training may be needed to demonstrate a significant training difference between combined arm and leg cycling and gait-specific training in an RCT study.

4) Other factors are also important to be considered in a large clinical trial for improving ambulation. For example, a control group of iSCI participants who receives a training intervention that only involves rhythmic arm movement should also be added in order to identify more directly the effect of arm training on restoring ambulation. Also, due to the heterogeneity of the SCI population, a subgroup assessment of the training effect in persons with quadriplegia and paraplegia, or persons with complete and incomplete injury should be considered. Furthermore, the combined arm and leg cycling training is applicable to a wide range of neurological conditions. Although the present study used iSCI as a model, future studies should also explore the efficacy of this intervention in other populations, such as persons after stroke, cerebral palsy or multiple sclerosis.

Appendix 1. The Changes in Aerobic Capacity after Cycling Training

6.1 Introduction

Wheel-chair dependency and physical inactivity, which are major risk factors for cardiovascular disease and premature mortality, are highly prevalent in people with SCI (Jacobs and Nash, 2004; Myers et al., 2007; Warburton et al., 2014). Daily routine activities involve low levels of intensity and are insufficient to maintain the cardiovascular fitness in people with SCI (Hoffman, 1986). The lack of activity further leads to possible cardiovascular complications and deleterious metabolic alterations (Bravo et al., 2004; Manns et al., 2005; Nelson et al., 2007). Therefore, exercise interventions are often needed to mitigate the health risks associated with cardiovascular and other chronic diseases after SCI (Buchholz et al., 2009; Warburton et al., 2014).

Because of injury-induced muscle weakness and reduction in voluntary drive, BWS and/or FES are often used to assist with leg exercise in people with SCI (Hooker et al., 1992b; Alexeeva et al., 2011; Kressler et al., 2013; Yaşar et al., 2015). The commonly used forms of exercise for SCI participants include BWS treadmill or overground walking, leg cycling, and exercises in the upper limbs such as wheelchair propulsion or arm crank cycling. FES can be used to assist in any of these exercises. The reported increases in aerobic capacity from different forms of exercise were approximately 20%-30%, but increases of more than 50% were also seen (Hoffman, 1986; DiCarlo, 1988; Faghri et al., 1992; de Carvalho et al., 2006; Warburton et al., 2007; Alexeeva et al., 2011; Kressler et al., 2013).

When comparing arm and leg exercises separately in healthy humans, arm cycling produces only ~80% of the maximal aerobic power produced by leg exercise, due to the relatively smaller mass of the arm muscles (Nagle et al., 1984; Franklin, 1985). However, this difference is smaller, and sometimes even reversed, in persons with SCI (Hettinga and Andrews, 2008). In a study comparing the difference in physiological responses to arm and leg exercise in people with SCI, there was a consistently higher peak heart rate and faster rate of adjusting to oxygen uptake during incremental voluntary arm exercise, compared to those during FES-assisted leg cycling (Barstow et al., 2000). The findings suggest that the weakness and deconditioning of leg muscles after injury could compromise the aerobic benefits of exercise involving the legs alone. However, it is still unclear whether upper-extremity training alone could lead to positive central adaptation in aerobic capacity or body composition after SCI (Hoffman, 1986; Fisher et al.,

2015). Therefore, hybrid exercise that combines the arms and legs may provide relatively greater cardiorespiratory stress than separate leg exercise or arm exercise for persons with SCI, although the evidence is still under debate (Krauss et al., 1993; Mutton et al., 1997; Raymond et al., 1997; Phillips and Burkett, 1998; Verellen et al., 2007; Hettinga and Andrews, 2008).

In Chapter 2, I demonstrated that actively engaging the arms along with the legs in rehabilitation training paradigms may result in better recovery of walking capacity compared to legs only training after iSCI. In Chapters 3 and 4, I found that the activity in spinal lumbar networks and the excitability of corticospinal pathway to the legs may be better improved after arm and leg cycling training. Therefore, active engagement of the arms in training may also result in better neural regulation after iSCI. In this study, I investigated the changes in aerobic capacity as a function of cycling training in both groups, by using maximal oxygen consumption (VO2max). I also compared the difference in post-training changes in VO2max between the A&L and Leg groups. However, because of the small sample size in this experiment, the conclusions regarding group differences are observational and do not involve statistical analysis.

6.2 Methods

The characteristics of the participants and details of the training protocol are described in Chapter 2. The test of VO2max was performed before training, at the 6th week after the initiation of training and at the conclusion of training. Two participants from the A&L group and 6 participants from the Leg group completed the test. To avoid the influence of fatigue and food intake, the VO2 test was always performed first thing in the morning on the testing day. Participants were instructed not to exercise before completing the test, and had only taken light breakfast with no caffeine, nicotine or alcohol prior to the start of the test. Expired gas was collected through a mouthpiece (Oxycon mobile, CareFusion, CA, US). The turbine and gas analyzer were calibrated before the test started. The breath-by-breath metabolic response was continuously analyzed using an indirect open-circuit calorimeter system (Oxycon mobile, CareFusion, CA, US). During the test, participants were instructed to perform leg cycling on the leg ergometer (ERGY) with no external assistance, while the arms relaxed on the armrests. The test started with 2 minutes of resting, followed by leg cycling at 0 W power output of the

ergometer. The test usually lasted 8-12 minutes with the power output of leg ergometer increasing at the end of every minute. The increments in power output remained approximately consistent throughout the test. The participants were also asked to rate their perceived exertion of their lower extremity and their cardiorespiratory intensity, both according to the Borg exertion scale (Borg, 1982), at the end of each minute of cycling. The experiment ended when any of the Borg score for either parameter reached 17-19 ('very hard, difficult to continue to exercise'). Heart rate was monitored via a polar belt and transmitted wirelessly to the data collection unit. The consumption of oxygen was averaged from the last 30-second period at each intensity of power output. The highest oxygen uptake was regarded as VO2max and the corresponding power output of the leg ergometer was considered as peak power output (in units of W). The post-training change was calculated as the difference between pre- and post-training value of the outcome measure, normalized to its value at pre-training. Values are expressed as mean ± 1x standard error unless otherwise specified.

Statistical tests were performed to identify the time effect as a function of training after combining participants from both training groups (A&L and Leg), using SPSS 23 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was first tested using the Shapiro-Wilk test. Paired t-test or Wilcoxon signed-rank test was used for the pre-to-post training comparisons, based on the test of normality. Because of the small sample size, participants from A&L and Leg groups were combined for the statistical analysis of change in VO2max as a function of training. The Pearson's product-moment correlation was performed to determine the relationship between walking performance (speed and distance) and VO2max.

6.3 Results

The average age of participants who completed the aerobic test was similar between the two groups (A&L: 51±10 years; Leg: 45±11 years (mean ± standard deviation)). The values of VO2max at pre-training varied between the two groups. As illustrated in **Fig. 6.1A**, participants in the Leg group had relatively lower levels of VO2max compared to the two participants in the A&L group. The magnitude of increase in VO2max after training had a large variability amongst participants in both groups. With an average increase of 29 ± 26% in the A&L group and 14 ±

6% in the Leg group (**Fig. 6.1B**), the VO2max in the A&L group remained higher than that in the Leg group after training (Post-training: A&L, 22.24±2.55 ml/kg/min; Leg, 11.94±1.77 ml/kg/min). When combining participants from both groups, there was no significant change in VO2max as a function of training (p=0.29). However, after training, the levels of the peak power output where the VO2max was collected increased in both groups **(Fig. 6.1C)**.

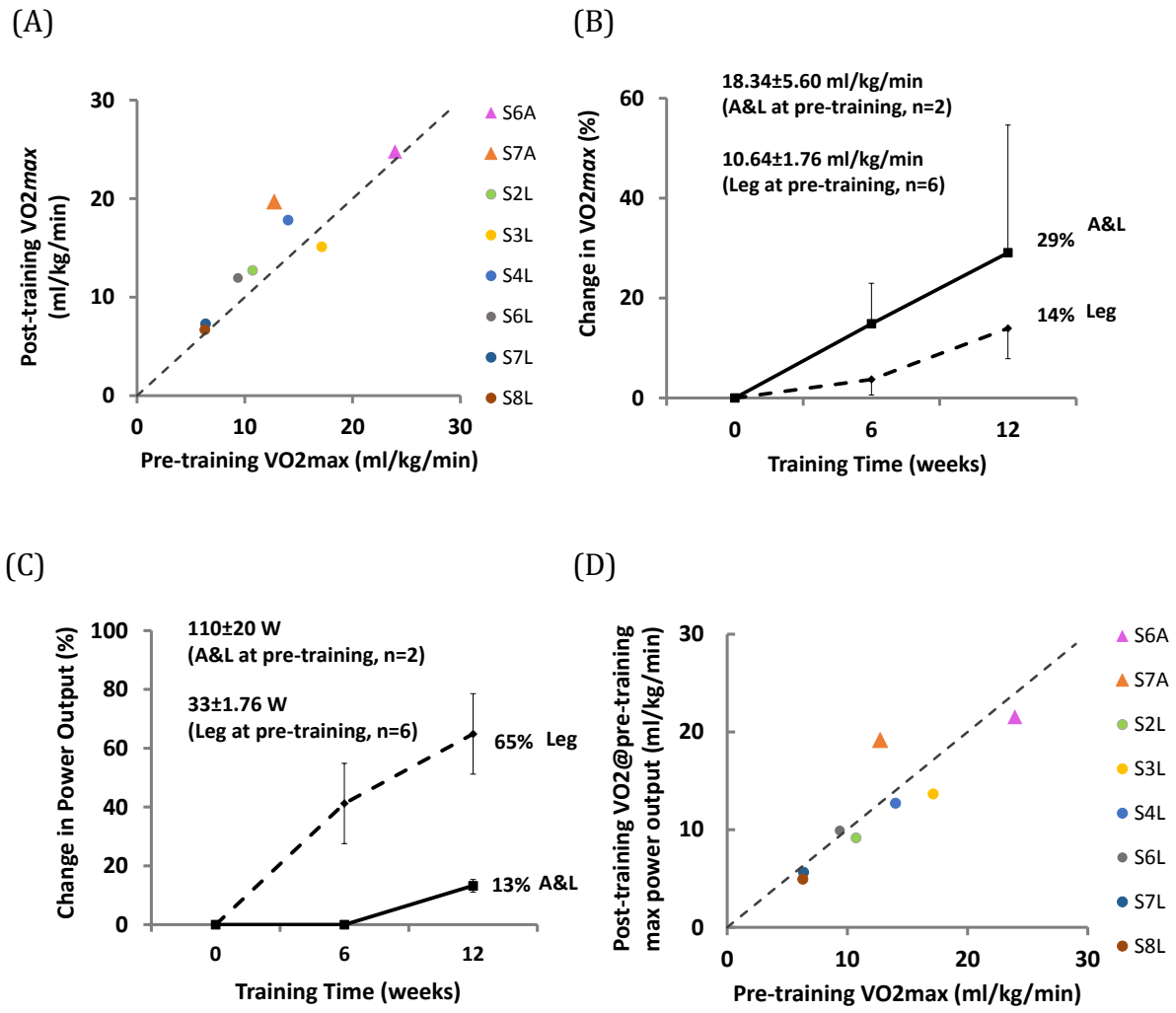


Figure 6.1. VO2max and power output.

(A) Individual results of VO2max for iSCI participants in both training groups. (B) Group average of post-training change in VO2max for the two iSCI groups. (C) Group average of post-training change in peak power output for the two iSCI groups. (D) Individual results of VO2max at pre-training and VO2 collected at an equivalent level of pre-training peak power output at post-training from the iSCI participants in both groups. Values were expressed as group average ± standard error.

In order to assess exercise efficiency, in the experiment at post-training, the oxygen uptake (VO2) collected at a level equivalent to the peak power output at pre-training, was also determined. This value was then compared to pre-training VO2max for each individual **(Fig. 6.1D)**. In general, there was a non-significant reduction in oxygen uptake at post-training compared to pre-training (p=0.678).

As **Fig. 6.2A** and **B** indicate, the VO2max was strongly correlated with walking speed and distance in participants from both groups at pre-training. After training, the change in walking speed and distance was only strongly correlated with the change in VO2max within the A&L group, but not that in the Leg group **(Fig. 6.2C, D)**. However, the difference may be because there were only two participants in the A&L group. When combining the participants from both groups, the correlation was moderate **(Fig. 6.2E, F)**.

6.4 Discussion

In this study, after combining participants from both groups, there was a trend of increase in VO2max and improved exercise efficiency after training; however, the changes were not significant. Also, with large variations in post-training changes, A&L and Leg participants seemed to have a similar change in VO2max as a function of training; however, Leg participants had a larger increase in peak power output after training, likely because the values at pre-training were relatively smaller than those in the A&L group.

Aerobic power (cardiorespiratory capacity) can be directly determined by measuring the VO2max during exercise (Davis, 1995). In the present study, the test was performed through leg cycling exercise without external assistance. Due to the weakness of the muscles, the legs often fatigued before reaching the intensity of exercise inducing a maximal cardiorespiratory stress in the participants. As a result, the average increase in VO2max after training in the present study seemed to be on the lower end, compared to the values reported from other training studies that

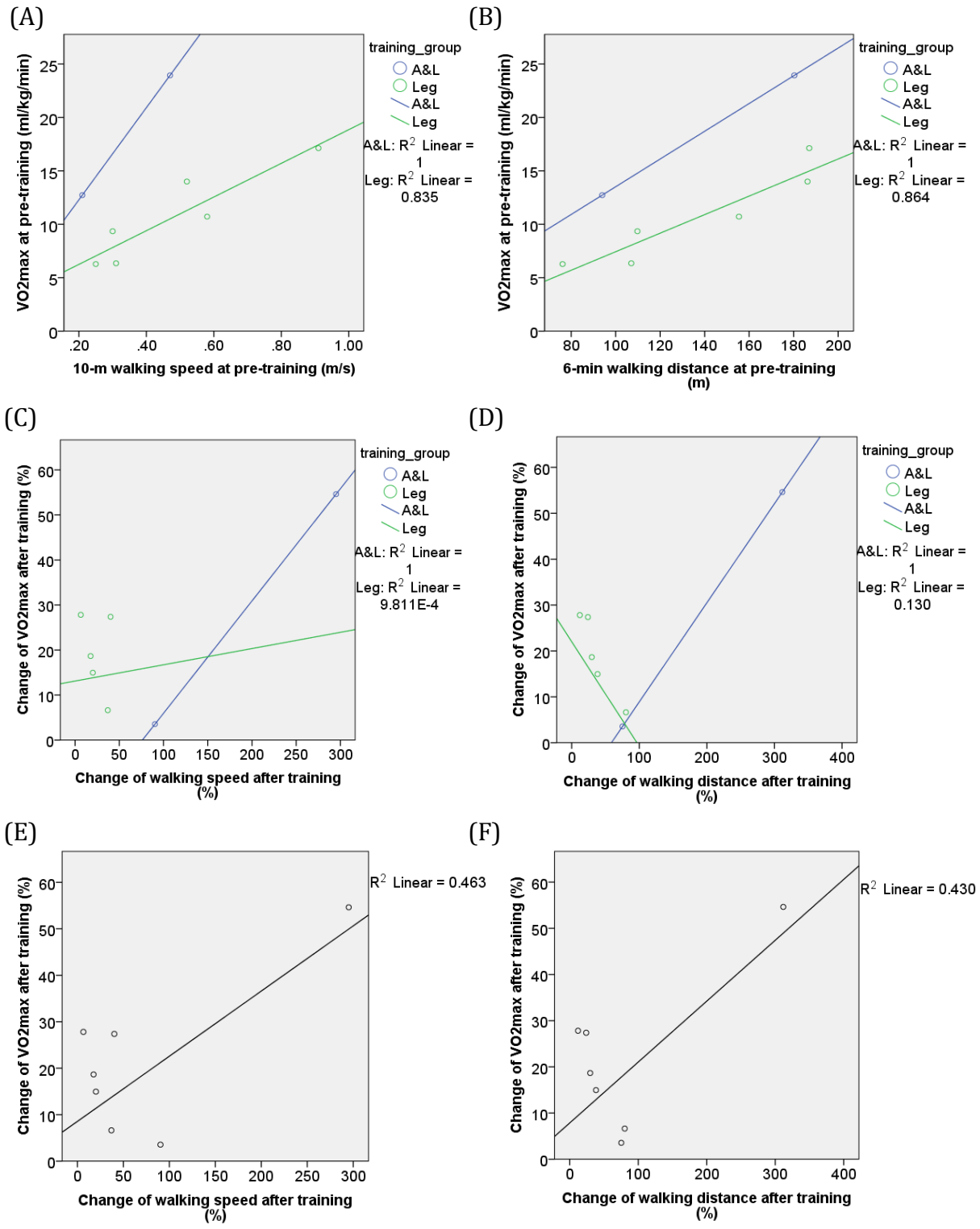


Figure 6.2. Correlations between the VO2max and walking.

(A) Correlation between the VO2max and 10-meter walking speed and (B) 6-min walking distance at pre-training in both groups. (C) Correlation between post-training change in VO2max and change in 10-meter walking speed in both groups. (D) Correlation between post-training change in VO2max and change in 6-min walking distance in both groups. Correlation between change in VO2max after training and change in (E) 10-meter walking speed and (F) 6-min walking distance after training in all participants with iSCI, regardless of group.

conducted the aerobic tests through arm cranking or FES-assisted leg locomotion (Faghri et al., 1992; Jacobs et al., 1997; de Carvalho et al., 2006; Alexeeva et al., 2011; Stoller et al., 2015). Furthermore, VO2max at post-training was still far below the values from the age-matched population with intact nervous systems (ACSM, 2013). Also, autonomic dysfunction in heart rate regulation could occur in people with lesion levels above T6 (West *et al.*, 2012), which could also limit their peak work outputs and oxygen delivery to the active muscles (Hoffman, 1986; Alexeeva et al., 2011). Therefore, it is important to note that the VO2max in the present study may not reflect the oxygen uptake under the most stressed cardiorespiratory condition. However, unassisted leg cycling provided a comparable condition across individuals. For example, leg cycling was a component of training in both groups; therefore, its use in the aerobic tests eliminated the potential effect of training task-specificity as it recruited the same limb musculature and induced similar metabolic stimuli.

Despite the significant improvements in walking speed and distance after training in both A&L and Leg groups (Chapter 2), significant change in aerobic capacity was not found. Similar results were also reported in other training studies with iSCI participants using various gait rehabilitation interventions (Alexeeva *et al.*, 2011; Kressler *et al.*, 2013). My findings showed that VO2max was significantly correlated with walking performance before training. Moreover, the change in VO2max was moderately correlated with the changes in walking function after training. It should be noted that the relationship between the change in aerobic capacity and improvement in walking over training is still largely unclear, as conflicting observations have been reported based on various types and intensities of training interventions (Ulkar et al., 2003; Alexeeva et al., 2011; Kressler et al., 2013; Yaşar et al., 2015). Qualitatively, the change in VO2max after training was not different between the A&L and Leg groups. Although the sample size in this experiment is severely limited, the findings may, with great caution, indicate that the larger improvements in walking function seen in the A&L group after training are not attributable to a larger aerobic capacity in this group.

Appendix 2. Interview Questions at Post-Training

General Questions:

- How would you describe your overall experience with this research study?
- How would you describe your satisfaction or dissatisfaction with the training provided by this study?
- Has the time commitment required by this study proven onerous for you?
- Do you have any comments you'd like to share about our assessment procedures for:
    - Transcranial Magnetic Stimulation
    - H Reflex Testing
    - Clinical Walking
    - Instrumented Gait Analysis
- Do you have any comments about the reimbursement provided by this study?
- Do you have any comments on the quality of lab facilities (including change rooms, chairs, overall comfort / cleanliness)?

Questions Regarding the Changes throughout Training:

- Over the course of this study, describe any changes you have experienced?
- Have you noticed changes in your walking ability? How would you describe those changes?
    - Pattern? Speed? Distance?
- Any change in your balance? Coordination?
- Any change in your muscular strength?
- Any change in your sensation?
- Any change in your spasticity?
- Any change in your endurance?
    - Your cardiovascular health?
- Any change in your autonomic function?
    - Bowel and bladder function?
- Your skin health in areas of stimulation and your circulation?
- How have any changes you've noticed impacted your quality of life? (e.g., change your habits, improve ambulation, be able to involve in more activities in the community, etc.).
- Have you changed your medication or dosage of the medication?
- Personally, did the involvement of your arms in the training make a difference? (for A&L participants only)
- Would you recommend this exercise protocol to other people?

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