LOCOMOTOR CONTROL AND RECOVERY AFTER HUMAN SPINAL CORD INJURY

By

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To the adults and children whose lives are affected by spinal cord injury and to my parents, loving husband, and wonderful children

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Animal studies indicate that walking and locomotor behaviors are partially controlled by oscillating spinal networks responsive to task-specific sensory input. Furthermore, the nervous system may employ a modular organization of muscle coordination to simplify control of complex behaviors. Human incomplete spinal cord injury (ISCI) alters neuromuscular control, resulting in walking disability. Although rehabilitation interventions, such as locomotor training (LT), activate the neuromuscular system below the lesion and improve walking, the effects of ISCI on locomotor control and the mechanisms underlying improved walking function remain unclear. Thus, the purpose of this research was to investigate locomotor control in adults and children with chronic ISCI.

The modular organization of muscle coordination during walking and other reciprocal lower extremity (LE) tasks was examined in control children (n=5, mean age=9 years) and children post-ISCI (n=5, age=9+/-3 years). Compared to controls, fewer modules were required to account for the variance in LE electromyograms (EMG) recorded from children post-ISCI (mean=2.11(0.71), mode=2) ($p<0.05$, one-sided). Moreover, the modules used during treadmill stepping accounted for >86% of the EMG

variance during other tasks. Consistent with studies of animals and healthy adults, these findings suggest that similar mechanisms underlie the control of varied locomotor tasks.

In a second study of these children post-ISCI, higher amplitudes of LE EMGs were recorded during reciprocal LE tasks compared to amplitudes recorded during volitional isolated joint movements ($p<0.05$). Amplitudes were greatest during treadmill stepping ($p<0.05$). Thus, similar to adults, the neuromuscular system of children post-ISCI appears responsive to task-specific sensory input with a greater capacity to generate muscle activation during weight-bearing locomotor tasks compared to volitional isolated joint movements.

In a third study, adults post-ISCI (n=8) exhibited altered muscle coordination and LE biomechanics during walking, relative to controls (n=13) ($p<0.05$). Modular control was similar across groups. Post-45-LT sessions, the mean number of modules required did not change (mean=3.81, mode=4). Post-LT, speed increased from 0.27+/-0.10m/s to 0.54+/-0.30m/s ($p<0.05$). Individual changes in muscle coordination were evident and biomechanical changes were associated with gait speed changes ($r=0.833$, $p<0.05$). These findings suggest that while modular organization is preserved post-ISCI, individual motor solutions are used to achieve gait biomechanics.

CHAPTER 1
INTRODUCTION

1.1. Rehabilitation of Walking for Individuals with Spinal Cord Injury

Regaining walking function is a primary goal of individuals with spinal cord injury (SCI) and a focus of rehabilitation interventions (Ditunno et al. 2008). More than half of individuals with SCI are diagnosed with an incomplete injury and the likelihood of regaining some degree of walking function is great (Burns et al. 1997; Scivoletto et al. 2008). However, traditional rehabilitation of walking for individuals with SCI has emphasized the use of braces, assistive devices and alternative movement strategies to compensate for sensory and motor impairments to achieve walking function (Waters et al. 1989). Individuals with SCI often walk at a slow pace and for a limited distance, relying on compensatory strategies that restrict normal movement patterns and have high energy costs (Waters et al. 1993). Traditional rehabilitation is based on a hierarchical model of motor control that attributes residual deficits after SCI to disruptions in descending cortical pathways (Fouad and Pearson 2004). Moreover, injuries are assumed to be permanent and irreparable (Finger and Almli 1985). Thus, compensations are viewed to be the only solution to afford return of function in this model.

Contemporary models of locomotor control are based on basic and translational evidence of distributed control across the neural axis. A tripartite model of neural control integrates the roles of supraspinal and spinal centers, as well as ascending afferent information in controlling walking and locomotion (Edgerton et al. 2004). Evidence of the intrinsic capacity of the lumbosacral spinal cord and neural centers below the level of a spinal cord lesion to control locomotor function and respond to task-

specific training has provided a basis for a paradigm shift in rehabilitation of walking for individuals with SCI (Behrman et al. 2006). Rehabilitation interventions for individuals with incomplete SCI (ISCI) are now striving to maximize recovery of walking with the goal of returning individuals to their pre-morbid walking status, rather than promoting reliance on external compensatory devices (Behrman and Harkema 2007). Locomotor training (LT) is the most prevalent intervention used to optimize walking recovery after SCI. LT applies principles of walking control and activity-dependent plasticity to activate the neuromuscular system below the level of a spinal cord lesion. Task-specific sensory input is enhanced during intense walking practice (Behrman and Harkema 2000, 2007). This approach is beneficial for improving walking function in individuals with motor-incomplete SCI. Following LT, individuals often recover some degree of walking function and are reported to walk faster, with less assistance, and for greater distances (Behrman and Harkema 2000; Dietz et al. 1995; Wernig et al. 1995).

The beneficial effects of LT have been reported in adults with ISCI and emerging evidence from our laboratory and others suggests that children with ISCI also may benefit from LT (Behrman et al. 2008; Fox et al. 2010; Prosser 2007). Children may be particularly responsive to LT due to their immature and developing nervous systems which may be more responsive to repetitive activation or training (Bregman and Goldberger 1983; Howland et al. 1995). Walking therefore may be restored in children with chronic or severe injuries who are not predicted to recover walking (Behrman et al. 2008). Furthermore, following SCI, children often experience severe musculoskeletal complications due to their on-going physical development (Vogel et al. 2002). Our work with children with ISCI, however, suggests that restoration of upright mobility may

reduce the incidence and severity of secondary musculoskeletal complications (Fox et al. 2010). Together, these factors are likely to positively impact a child's quality of life and successful transition to adulthood (Anderson et al. 2004).

1.2. Measurement of Walking Function

Although LT has been shown to restore or improve walking in children and adults with ISCI, it remains unclear how to determine who will likely regain walking function or will benefit from this intervention (Basso 2011). Predicting walking function and response to walking interventions in individuals with ISCI is necessary to determine rehabilitation requirements, long term care needs, health cost estimations, and vocational training. Traditionally, prediction of walking function and response to interventions is based on tests of isolated joint movement and strength (Crozier et al. 1992; Krawetz and Nance 1996). These tests, based on a hierarchical model of motor control, assess movements largely under descending supraspinal control and do not assess muscle activation that may be highly influenced by task-specific sensory input and spinal control mechanisms. Furthermore, studies examining the association between isolated joint strength and walking have assessed walking function using braces and assistive devices (Scivoletto et al. 2008). Recently, studies investigating muscle activation in adults with complete and ISCI reported that muscles which could not be activated during attempted isolated joint movements demonstrated rhythmic activation during assisted, loaded, upright stepping (Maegele et al. 2002). This suggests that tests of voluntary isolated joint motion do not reflect the capacity of the nervous system to generate rhythmic muscle activation during locomotor tasks. Furthermore, this points to the need for clinical assessments used to predict walking function to be based on recent evidence of the neuromuscular control of walking and

consider the role of task-specific sensory input and subcortical contributions to walking control (Maegele et al. 2002).

Although some rehabilitation interventions for individuals with ISCI now are focusing on recovery, measures of walking function and response to interventions continue to assess an individual's walking ability while ambulation is performed using compensatory devices and braces (Jackson et al. 2008). Walking that requires altered movement strategies, such as increased upper extremity loading and reduced hip extension, alter critical afferent information and result in diminished rhythmic motor output from neural centers (Visintin and Barbeau 1994). Walking using compensated movement strategies therefore may put the nervous system at a disadvantage and measurement under these conditions may not identify features of recovery or the capacity of the nervous system to contribute to walking control in an individual with ISCI. Thus, as a new paradigm is emerging for optimizing recovery of walking after SCI, translation of this recovery-based model has not been extended to measurement of walking recovery (rather than walking using external devices and braces to compensate for sensorimotor impairments) and assessment of associated, underlying mechanisms (Basso 2011; Behrman et al. 2006).

1.3. Introduction Summary and Aims

Elucidating mechanisms of walking and locomotor control as well as response to locomotor interventions is essential to the development of appropriate assessments and the advancement of rehabilitation interventions targeting recovery. Therefore, the over-arching goal of this dissertation is to provide evidence of the neuromuscular control mechanisms associated with locomotor control in adults and children with ISCI. Three experiments have been conducted and the findings will collectively provide insight

regarding the control of locomotion after human SCI, as well as mechanisms responsive to activity-based interventions, such as LT. The specific research aims are:

Experiment 1 Aim: Identify neuromuscular control mechanisms used during rhythmic, reciprocal lower extremity tasks in children with intact nervous systems and to determine the effect of pediatric ISCI on these mechanisms.

Experiment 2 Aim: Compare the level of activation of lower extremity muscles during volitional, isolated joint movements and rhythmic, reciprocal lower extremity tasks in children with chronic ISCI.

Experiment 3 Aim: Examine neuromuscular and biomechanical control mechanisms underlying walking recovery and response to locomotor training interventions in adults with ISCI.

The following chapter, Chapter 2, will provide the background for these experiments and will discuss basic science and translational research pertaining to locomotor control and rehabilitation of walking for individuals with ISCI. Chapter 2 will therefore provide a review of literature and serve as a foundation for the experiments.

The literature review addresses: 1) demographics and classification of human SCI, 2) the effects of impaired upright mobility in adults and children with SCI, 3) walking function after ISCI, 4) the emerging and ongoing paradigm shift in walking rehabilitation, 4) differentiating compensation from recovery, 5) locomotor training for the restoration of walking, 6) neuromuscular control of walking, 7) neural plasticity, 8) advancing rehabilitation of walking, 9) modular control of movement and locomotion, and 10) biomechanical functions associated with modular control of walking.

Chapters 3-5 present each of the three experiments: 1) Neuromuscular control across locomotor tasks in children with ISCI, 2) Activation of lower extremity muscles during voluntary movements, stepping, and other locomotor tasks in children with severe ISCI, and 3) Mechanisms of response to locomotor training in adults with motor ISCI.

CHAPTER 2
LITERATURE REVIEW

2.1. Human Spinal Cord Injury

2.1.1. Demographics and Classification of Spinal Cord Injury

More than 300,000 people in the United States are living with a spinal cord injury (SCI) and approximately 12,000 individuals are injured annually. Most SCIs are caused by traumatic events such as motor vehicle accidents, falls, violence, and participation in sports. Injuries occur primarily in young men (80%) between 16 and 30 years of age, with an average age of 40 years (National Spinal Cord Injury Statistical Center 2010). Spinal cord injuries most often occur in the cervical region of the spinal cord, resulting in tetraplegia, which is associated with sensory and motor impairments in the upper limbs, lower limbs, and trunk. Paraplegia results in approximately 40% of the cases due to injury to the thoracic, lumbar or sacral regions of the spinal cord and causes sensory and motor impairments primarily in the lower limbs and sometimes the upper extremities and trunk, depending on the level of the spinal cord lesion (i.e. thoracic SCI versus lumbar or sacral SCI) (National Spinal Cord Injury Statistical Center 2010).

Following injury, the level of the spinal cord lesion and lesion severity are classified based on the pattern of sensory and motor impairments below the level of the injury. Specifically, neurologic classification of injury is determined according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Marino et al. 2003), which were first published by the American Spinal Injury Association (ASIA) in 1982 (American Spinal Injury Association 1982). Injury classification according to the ISNCSCI is based on scores from standardized sensory and motor examinations and is used to determine an individual's rehabilitation needs

and predict neurological and functional recovery after injury (Burns et al. 1997; Crozier et al. 1992; Oleson et al. 2005; Zorner et al. 2010). The ISNCSCI is based on the segmental organization of the spinal cord and includes bilateral tests of isolated joint movement and strength in 10 key muscles in the upper and lower extremities, sensory tests (sharp/dull discrimination and light touch) of 28 dermatomes, as well as an anorectal examination to determine sensory and motor function in the S4-S5 spinal cord segments which is used to classify the injury as complete (no S4-S5 sensory or motor function) or incomplete (S4-S5 sensory or motor function) (American Spinal Injury Association 2006).

According to the ISNCSCI, SCI is classified based on the ASIA impairment scale (AIS) from A (complete SCI) to E (normal spinal cord function). An injury classified as AIS-A is defined as complete based on the absence of sensory and motor function in the S4-S5 spinal cord segments. Individuals with injuries classified as AIS B-D have incomplete injuries based on residual function in the lowest sacral segments. Persons with injuries classified as AIS B (sensory incomplete) present with residual sensory function in segments below the injury, including S4-S5. Whereas, individuals with AIS C and D injuries (motor incomplete) have impaired motor function below the injury level, with AIS C injuries resulting in the majority of muscles below the injury level with a muscle strength grade of ≤3/5 based on standardized tests of muscle strength performed while the individuals is supine. Individuals with AIS-D injuries have ≥3/5 muscle strength in key muscles below the injury. Individuals with AIS E have normal sensory and motor function. The National Spinal Cord Injury Statistical Center (2010) reports that since 2005, 38% of injuries were classified as incomplete tetraplegia, 21%

as incomplete paraplegia, and approximately 40% as AIS-A, complete SCI (National Spinal Cord injury Statistical Center 2010).

2.1.2. Secondary Complications Associated with Human Spinal Cord Injury

The AIS classification of injury and lesion level are indicative of the extent and severity of primary and secondary impairments associated with SCI. SCI causes primary impairments of sensory and motor function, as well as impairments in bowel and bladder function, the respiratory system and cardiovascular system, as well as altered sexual function. Development of secondary impairments is associated with the myriad of primary impairments affecting the individual, as well as functional limitations, reduced mobility, and psychosocial factors affecting the individual after injury (Krause et al. 2008). Secondary impairments, which commonly include osteoporosis, heterotopic ossification, urological and respiratory infection, and pressure ulcers are a major factor in an individual's overall health (New et al. 2002). Moreover, the incidence of such complications contributes to the population's overall rate of mortality and morbidity, with urinary and respiratory infections as well as cardiovascular disease being leading causes of morbidity and death after SCI (Cotton et al. 2005; DeVivo et al. 1993, 1999; Krause et al. 2008). While the life expectancy of individuals with SCI approaches normal (34.2 years for an individual injured at age 40) (National Spinal Cord injury Statistical Center 2010), lifetime healthcare costs and living expenses for individuals with paraplegia may exceed one million dollars and are estimated to be more than three million dollars for individuals with tetraplegia. Lost wages and productivity are additional costs associated with injury (Cifu et al. 1999; National Spinal Cord injury Statistical Center 2010).

Perhaps the most profound and complex consequence associated with SCI is the impact on life satisfaction and quality of life (Barker et al. 2009; Krause et al. 1997; Whiteneck et al. 2004). The International Classification of Functioning, Disability, and Health (ICF) is a useful framework for examining the numerous, complex factors associated with quality of life after SCI. The ICF was developed by the World Health Organization in 2001 to describe and classify health-related domains and relationships across health domains (World Health Organization 2002). This model may be used to depict how factors associated with SCI, such as motor impairments, reduced mobility, attitudes, and family support, may contribute to an individual's health, participation in life roles, and overall quality of life.

Compared to individuals without injury, quality of life for people with SCI is significantly poorer (Barker et al. 2009). An individual's overall health, the prevalence of secondary impairments and the ability to participate in life roles substantially influences quality of life after SCI (Barker et al. 2009; Jain et al. 2007). In fact, prevalence of secondary impairments, activity limitations, and participation restrictions are reported to be more important in determining quality of life than level or severity of injury (Barker et al. 2009). Other factors such as job opportunities and education also are important (Anderson et al. 2003).

2.1.3. Spinal Cord Injury and the Effect of Impaired Upright Mobility

A primary consequence of impaired sensory and motor function after SCI is the decreased ability to assume an upright position and ambulate which results in reliance on a wheelchair for mobility. Not only is impaired mobility associated with reduced quality of life (Jain et al. 2007), but reduced upright mobility and decreased lower extremity weight bearing further contribute to the development of secondary

impairments such as muscle atrophy, bone demineralization, joint contractures, and skin ulcers (Gelis et al. 2009; Giangregorio and McCartney 2007; Shah et al. 2006). These mobility-related impairments may lead to additional complications such as non-traumatic fractures, infections, and further mobility limitation. Given the association of secondary impairments with quality of life and mortality after SCI, reducing the prevalence of these impairments is a priority. Moreover, this highlights the detrimental effects of impaired upright mobility on health and disability after SCI. Additionally, studies examining the effect of increased lower extremity weight bearing and upright mobility suggest that the severity of these secondary musculoskeletal impairments may be reduced (Alekna et al. 2008; Jayaraman et al. 2008). Rehabilitation that incorporates daily standing or walking may attenuate bone demineralization (Alekna et al. 2008), increase muscle size and function (Jayaraman et al. 2008), and lead to beneficial effects on walking function (Gregory et al. 2007), mobility, and health.

2.1.4. Pediatric Spinal Cord Injury and the Effects of Impaired Upright Mobility

The effect of impaired upright mobility and secondary impairments is even greater in the proportion of individuals injured before adulthood. Children with SCI (<15 years) represent approximately 10% of the population of individuals with SCI (National Spinal Cord Injury Association 1995-1998). Epidemiology of pediatric SCI and the occurrence and severity of secondary impairments associated with injury vary according to the age of injury onset. Among children injured at a young age (0-5 years), boys and girls are equally likely to experience a SCI; however, a greater proportion of boys are injured during adolescence (Vitale et al. 2006; DeVivo and Vogel 2004). Pediatric SCI most often is caused by motor vehicle accidents and violence, with a high proportion of injuries associated with failure to wear a seatbelt or poor lap-belt placement (Vitale et al.

2006). Similar to adult trends, adolescents also experience sports-related injuries. Compared to the most common injuries experienced by adults, young children (≤12 years) are more likely to sustain a complete SCI or injuries resulting in paraplegia. Adolescents are more likely to sustain injuries resulting in incomplete tetraplegia (Vogel and Anderson 2003).

Although, children with SCI experience similar types of secondary complications and medical issues that affect adults with SCI, the prevalence and severity of these complications are much greater in children injured at a young age (Vogel et al. 2003). Due to ongoing growth and physical development, the inability to stand and ambulate results in severe musculoskeletal impairments, especially in children injured prior to adolescence (Bergstrom et al. 1999; Driscoll and Skinner 2008; Vogel et al. 2004). Of children injured prior to adolescence, 78% (Bergstrom et al. 1999) to 98% (Dearolf et al. 1990) develop scoliosis, with the highest incidence and most severe complications developing in children injured at a very young age (Bergstrom et al. 1999). Injury at a young age (10 years or younger) also is associated with hip subluxation/dislocation (McCarthy et al. 2004). To prevent or remediate musculoskeletal complications, children are prescribed orthotics or braces. Orthotics, such as those used to immobilize and stabilize the thoracic and lumbar spine and prevent scoliosis, further hinder a child's mobility (Chafetz et al. 2007). Additionally, to correct severe bone deformities surgical interventions often are required which are associated with high health costs and additional health risks (Driscoll and Skinner 2008).

The impairments associated with pediatric SCI as well as the secondary complications are endured across the child's lifespan (Vogel et al. 2002). Therefore

these factors not only impact their growth and development, but also their quality of life and their ability to successfully transition to adulthood (Anderson et al. 2004, 2006). For these reasons, improving upright mobility and walking function in children may have profound effects on their overall health, lead to reduced disability and such benefits may carryover to adulthood.

2.1.5. Prediction of Walking Function after Incomplete Spinal Cord Injury

Irrespective of injury severity, level of injury, or age of injury onset in adults, improving or re-gaining walking function is a primary goal of individuals with SCI (Ditunno et al. 2008). Although walking function is reported as a high priority, individuals with tetraplegia indicate their first priority is to regain arm and hand function. In contrast, sexual function is the highest priority for individuals with paraplegia (Anderson 2004). Increased bowel and bladder function also is reported to be of primary importance to all individuals with SCI (Anderson 2004; Ditunno et al. 2008).

Based on the association between mobility impairment and secondary complications, reduced quality of life, and the importance of re-gaining walking function, upright mobility skills and walking function are a major focus of rehabilitation (Anderson 2004; Ditunno et al. 2006, 2008). The prognosis for achieving functional skills, including ambulation, is based on the initial level of injury, injury severity, and voluntary strength of muscles below the spinal cord lesion level (Crozier et al. 1992; Kirshblum and O'Connor 2000; Krawetz and Nance 1996; Scivoletto et al. 2008). Therefore, compared to individuals with complete injuries, individuals with incomplete SCIs are more likely to regain sensory and motor function, achieve greater independence in performing functional tasks, and regain walking function (Burns et al. 1997; Raineteau and Schwab 2001).

Given that most adults with SCI have injuries classified as incomplete (>55%) (National Spinal Cord Injury Statistical Center 2010), a high proportion of individuals may have the potential to achieve some degree of walking function. Although reports vary, studies of walking function post-SCI indicate that of the individuals with a SCI classified as AIS C, nearly half are able to ambulate 150 feet at the time of discharge from inpatient rehabilitation and 75% of individuals with an AIS D injury regain this level of walking function (Hall et al. 1999). Although these reports suggest that walking function may be achieved by a high proportion of individuals with ISCI, outcomes are based on an individual's ability to walk a limited distance, such as 150 feet over an indoor walking pathway (Hall et al. 1999). Furthermore, 'walking' is achieved using assistive devices, lower extremity braces and orthotics, and alternative movement strategies (Burns et al. 1997; Hall et al. 1999; Scivoletto et al. 2008). Therefore upright mobility or 'walking' may be re-gained, but it is achieved using strategies that are very different from those used prior to injury.

2.1.6. Walking Function after Incomplete Spinal Cord Injury

Walking function for individuals post-SCI has traditionally been accomplished by relying on alternative movement strategies that emphasize use of the muscles above the level of the spinal cord lesion. Assistive devices, such as walkers, enable the individual to transfer a significant portion of the body weight from their lower extremities to the arms. To further compensate for sensory and motor deficits below the spinal cord lesion, lower extremity braces and orthotics are used to stabilize and support the lower extremity joints (Hussey and Stauffer 1973; Rosman and Spira 1974; Waters et al. 1989). For instance, individuals who demonstrate sufficient upper extremity strength are taught to ambulate by using lower extremity braces, such as a knee-ankle-foot

orthoses (KAFOs), and an assistive device, such as a walker. The KAFOs stabilize the knee and ankle joints and often lock the knee joint into extension to compensate for the paralyzed or weak leg muscles and prevent buckling of the knee. The walker allows the individual to transfer their body weight on to their arms and hurdle or propel their legs forward by throwing their head and trunk backward (Atrice et al. 2005; Somers 2009). This approach and similar strategies are slow, have high energy requirements, and are difficult to sustain (Merkel et al. 1984; Waters et al. 1993). Individuals often elect to, and are even encouraged, to use a wheelchair as their primary mode of locomotion (Rosman and Spira 1974).

2.1.7. Rehabilitation of Walking after ISCI

Walking strategies that rely on the use of the muscles above the spinal cord lesion to compensate for sensory and motor impairments are based on assumptions pertaining to how the nervous system controls locomotion and the response of the nervous system to injury. First, assumptions regarding the control of locomotion are based on a hierarchical model of motor control (Shumway-Cook and Woollacott 2006). This model assumes a 'top-down' control system. The cortex is thought to be the primary control center, with little contribution from 'lower' central nervous center structures. The role of the spinal cord in controlling walking or locomotion is viewed primarily as a conduit to transmit sensory and motor signals (Maynard et al. 1997), with little intrinsic capacity to control walking.

Second, this hierarchical model assumes that the central nervous system is 'hard-wired' and damage to the spinal cord is permanent and irreparable (Basso 1998). Therefore, based on these assumptions, because damage to the spinal cord disrupts descending cortical signals as well as ascending afferent information to the cortex,

regaining walking function using pre-morbid strategies is not possible. Thus, compensation is viewed as the only viable approach for improving function and walking ability after SCI (Almli and Finger 1988; Finger and Almli 1985).

2.1.8. Paradigm Shift in Rehabilitation of Walking for Individuals with SCI

Basic and translational science investigations have provided evidence of distributed control across the neural axis as well as activity dependent plasticity that can drive functional recovery after injury (Anderson et al. 1978; Edgerton et al. 2004; Grillner 1979; Wolpaw and Carp 1993). These discoveries have supported a paradigm shift in the rehabilitation of walking for individuals with SCI. (Behrman et al. 2006; Behrman and Harkema 2007). New rehabilitation approaches now focus on improving task-specific sensory input and activating spinal networks in the lumbosacral spinal cord, below the level of the lesion. Intense, repetitive practice is emphasized to promote neural plasticity and functional recovery (rather than reliance on compensations) after injury (Barbeau et al. 2006; Behrman and Harkema 2000; Wernig and Muller 1992).

Animal models of SCI and walking recovery have demonstrated the capacity of oscillating neural networks, located in the lumbo-sacral spinal cord, to control reciprocal hind limb movements during stepping (Andersson et al. 1978; Grillner 1979; Hodgson et al. 1994; Lovely et al. 1986; Rossignol et al. 1996). Furthermore, basic and translational studies indicate that these centers are responsive to afferent input associated with walking and through repetitive practice can improve motor output during stepping (Beres-Jones and Harkema 2004; de Leon et al. 1998; Dietz et al. 1995, 2002; Harkema et al. 1997; Maegele et al. 2002). Studies of human SCI demonstrate that walking control and function may be improved following repetitive training that optimizes afferent input so locomotor networks (Behrman and Harkema 2000; Dietz et al. 1995).

Moreover, evidence suggests that traditional gait interventions that focus on compensation strategies do not take advantage of the inherent capacity and plasticity of the neuromuscular system (Edgerton et al. 1991; Visintin and Barbeau 1994).

Based on this new understanding of locomotor control and evidence of activity dependent plasticity, locomotor training (LT) has emerged as a prominent rehabilitation intervention for the restoration of walking after incomplete SCI (ISCI). LT capitalizes on the intrinsic capacity of spinal cord pattern generating networks and plasticity of the neuromuscular system to restore walking, rather than promote reliance on compensations (Barbeau et al. 2006; Behrman and Harkema 2000, 2007). Studies investigating the effects of LT will be covered in Section 2.3. Additionally, the foundations of LT, neuromuscular control of walking and activity-dependent plasticity will be discussed in Sections 2.4 and 2.5.

2.2. Differentiating Compensation from Recovery

As approaches to support walking recovery have emerged in animal models and have been applied to humans with SCI, distinct terminology has surfaced to more specifically describe how a function is accomplished. Specifically, a distinction between recovery of function and compensated function has been established (Behrman et al. 2006; Behrman and Harkema 2007; Levin et al. 2008). Functional *recovery* is the reinstatement of the same or similar movement strategies that were used to perform a function prior to injury. With respect to walking, recovered walking is performed with upright posture, without devices or braces, and to the same extent (speed, distance, stepping cadence, limb kinematics) as prior to injury. Rehabilitation that strives to promote functional recovery after SCI aims to change or adapt the individual's neuromusculoskeletal system below the spinal cord lesion to perform the function,

rather than promote compensations. In contrast to recovered walking, the function of walking may be performed using compensatory movement strategies and devices. Once the devices are removed, however, the individual's capacity to perform the function is lost. Traditionally, persons with SCI have relied heavily on sensory and motor function above the lesion to use compensatory devices and alternative movement strategies to re-gain walking function.

Functional recovery has not only been distinguished from compensated function, but also from neurologic recovery (Levin et al. 2008). Neurologic recovery is the reinstatement of neural processes resulting in neural control of a function that is the same as prior to injury (Levin et al. 2008). Although the primary goal of locomotor training (LT) is to promote recovery of walking, pre-morbid walking function is likely accomplished through extensive neural reorganization, or neural compensations (Barriere et al. 2008; Basso et al. 2002; Edgerton et al. 2004; Raineteau and Schwab 2001). Injury to the spinal cord causes structural and functional changes as well as secondary changes such as altered synaptic connectivity and ischemia (Ek et al. 2010; Rowland et al. 2008). SCI therefore changes the nervous system and neurologic adaptations promoted by rehabilitation take place within this 'new' nervous system (Barriere et al. 2008; Basso et al. 2002; de Leon et al. 2001; Edgerton et al. 2007). Neural reorganization or adaptations, referred to as neural plasticity, as it relates to SCI and walking recovery will be discussed in Section 2.5.

The goal of LT is to restore pre-morbid walking function; however, individuals with SCI often require the use of assistive devices to safely ambulate at home or in the community. When assistive devices are required, the least restrictive device should be

chosen and used in a manner consistent with recovered walking (upright posture, maximal loading on the lower extremities, and walking at normal walking speeds, if possible) (Behrman et al. 2006, 2008; Behrman and Harkema 2000; Tester et al. 2010). Since devices often are used and walking may not be fully restored, recovery of walking can be viewed along a continuum. Thus, the paradigm shift in rehabilitation of walking for individuals with SCI has changed the focus and goal of rehabilitation away from compensation towards recovery. Within this framework, clinical decisions and treatment options are based on the goal of walking recovery (Behrman and Harkema 2007).

2.3. Locomotor Training to Restore Walking after SCI

2.3.1. Introduction to Locomotor Training

Locomotor training (LT) is a rehabilitation intervention based on knowledge of walking control and neural plasticity (discussed in Section 2.5) in spinal cord centers associated with walking control (Behrman and Harkema 2007). LT focuses on walking recovery by providing repetitive walking practice in a permissive environment that enhances afferent input associated with walking. Afferent input associated with specific aspects of walking, such as upright trunk posture, appropriate limb kinematics, and maximal load bearing on the lower extremities (rather than bearing weight on the arms or a device) is safely practiced using a partial body weight support system and a treadmill. Skilled trainers also may assist with stepping and trunk posture to enable step practice at normal walking speeds (Barbeau 2003; Behrman and Harkema 2007; Muir and Steeves 1997). As skills are gained and recovered in the treadmill environment, they are then practiced in the overground environment and adaptive skills needed for community ambulation are incorporated. Based on basic and translational studies, principles of LT have been described to guide clinical decision making

(Behrman and Harkema 2007). These studies and principles will be discussed in Section 2.5.

Locomotor training has demonstrated benefit for improving walking recovery in adults with both acute and chronic SCI (Behrman and Harkema 2000; Dietz et al. 1995; Dobkin et al. 2006; Wernig et al. 1995; Wernig and Muller 1992; Wirz et al. 2001). Following several weeks of daily LT, individuals have demonstrated the ability to walk a greater distance, use a less-supportive assistive devices, increase gait speed, and transfer walking skills to tasks such as stair climbing (Behrman and Harkema 2000; Dietz et al. 1995; Dobkin et al. 2006; Wernig et al. 1995; Wernig and Muller 1992; Wirz et al. 2001). Moreover, individuals with no walking or standing ability have recovered independent or assisted walking and the benefits of LT have exceeded the improvements in walking following conventional rehabilitation (Wernig et al. 1995).

The benefits of LT for enhancing walking recovery have recently emerged in three case reports of children with ISCI (Behrman et al. 2008; Fox et al. 2010; Prosser 2007). In addition to a case report of a child with sub-acute ISCI regaining walking function (Prosser 2007), a recent report from our laboratory suggests that LT also may be effective in children with chronic, severe SCI, and little to no strength or volitional control of their lower extremity joints (Behrman et al. 2008). Thus, LT may be a promising intervention to restore walking in children with ISCI. Additionally, children may be more responsive to LT due to their immature and developing nervous systems. Studies of new born kittens injured shortly after birth indicate that the immature spinal cord has great potential for repair (Bregman and Goldberger 1983 (II); Bregman and Goldberger 1983 (III)) and response to training (Bregman and Goldberger 1982; Howland et al.

1995). Furthermore, based on our follow-up case report of a child two years post-LT, the benefits of LT may be maintained in children, especially if a threshold of independent ambulation is achieved so that ongoing 'self-training' is performed (Fox et al. 2010). Additionally, the benefits of LT also may extend to improved musculoskeletal health or delay the onset of secondary musculoskeletal complications (Fox et al. 2010).

Investigations of the effects and benefits of LT for restoring human locomotion now span more than twenty years. Early efficacy studies translated principles of locomotor control and methods used in animal training to humans with complete and incomplete SCI (ISCI) (Barbeau et al. 1987) to examine the capacity of this approach for inducing stepping and walking in humans (Behrman and Harkema 2000; Dietz et al. 1995). Electromyographic (EMG) recordings were used to demonstrate phasic muscle activation in response to the task-specific afferent input associated with LT. As the benefits of LT for improving walking function after ISCI were confirmed, more recent investigations focused less on the neuromuscular responses to LT and more on the functional improvements seen after prolonged training. Thus, the use of standardized measures to assess gait function, based on speed and endurance, has been emphasized (Ditunno et al. 2006). Research also has been expanded to compare LT to traditional gait interventions and to evaluate the limitations of LT as well as variations on LT, such as training with a robotic device (rather than manual assistance from therapists of trainers) (Wirz et al. 2005), incorporating adjunctive interventions such as functional electrical stimulation (FES) (Field-Fote 2001; Field-Fote and Tapavac 2002) and skill training for the development of community ambulation (Musselman et al. 2009), and the use of LT to restore walking in children with ISCI (Behrman et al. 2008; Prosser 2007).

The following section will review the development of LT from early studies assessing acute responses to LT to a recent randomized controlled clinical trial assessing the effect of LT in adults with ISCI. Studies assessing related training approaches, such as robotic training and the use of LT with children with SCI also will be discussed. The purpose of this comprehensive review is to demonstrate the progression from emerging translational science to clinical practice. Furthermore, details from studies will be discussed to emphasize specific observations that highlight limitations in our current understanding of walking control and recovery in individuals with ISCI. Moreover, while there are specific Biologic principles underlying the application of LT and guidelines have been established for clinical application of this approach (Behrman and Harkema 2007), there is wide variation in the use of this intervention. Thus, as the literature is discussed in the following sections, it should be noted that great variation exists in how researchers have applied biologic locomotor-control principles and whether these principles were used as a framework for clinical and scientific decision-making.

2.3.2. Translational Investigations Assess Efficacy of LT

Early reports of LT described the translation of specific instrumentation and procedures from cat models of SCI to humans with SCI. Hugh Barbeau, a physical therapist and neuroscientist, first reported on the use of a system that incorporated a speed-controlled treadmill and a body weight support (BWS) apparatus which enables persons with SCI to simultaneously practice all components of locomotion (Barbeau et al. 1987). In Barbeau's description (1987) he recognized the limitations of conventional gait rehabilitation in promoting the practice of multiple components of walking, including stepping and balance control with an appropriate, upright posture. Interestingly, this

early report on the LT system also described instrumentation to record electromyography (EMG) and measure gait kinematics during treadmill walking and highlighted the potential role of adjunctive therapies (electrical stimulation, biofeedback) that could be combined with LT.

Following the preliminary studies describing the application of this novel approach, investigations of the efficacy of LT emerged. These studies were comprehensive investigations of the effect of LT on walking that incorporated measures of muscle activity (EMG), joint kinematics, as well as measures of gait speed and endurance. These investigations focused not only on LT's effect on walking function post-SCI, but also to determine if locomotor control principles identified in cat models were applicable to human locomotion. Wernig and Muller (1992) reported on eight individuals with chronic ISCI who completed daily LT for two to seven months. Five of the eight individuals demonstrated no muscle activation when strength tested in a supine position, but demonstrated phasic muscle activation during treadmill locomotion. All subjects demonstrated improved gait function as evidenced by faster walking speeds, increased endurance, and less reliance on assistive devices or physical assistance. Kinematic measures of joint angles were not evaluated pre and post training, but were used to characterize individuals' gait patterns. Lower extremity joint kinematics reflected a 'spastic gait' pattern. The EMG assessments were intriguing as Wernig and Muller (1992) described muscles that appeared paralyzed during strength tests that exhibited both co-activation and reciprocal phasic activation during treadmill locomotion. Although most subjects could not activate muscles to perform an isolated joint movement during strengths tests, all reportedly could initiate a mass extensor

multi-joint patterned movement of the lower extremities. This was likely one of the earliest descriptions of locomotor capacity based on muscle activation during walking as well the role that patterned co-activation may have in walking recovery after SCI.

In a preliminary study, Barbeau et al. (1993) further demonstrated the effects of LT in nine subjects with ISCI. All subjects exhibited increased gait speed and endurance after six weeks of training. Improvements also were reported in joint kinematics, spatiotemporal gait parameters, and timing of muscle activation during walking. One individual was highlighted as having progressed from a full-time use of a wheelchair to the ability to walk overground with forearm crutches. Examination of his gait pattern during treadmill stepping (post-training) revealed near-normal joint kinematics while stepping more consistently. Moreover, Barbeau et al. (1993) reported that fewer compensatory strategies were used, such as hip hiking. This study was one of few that assessed specific changes in gait control and the level of compensation following LT.

As studies of mammalian locomotion and the potential effects of LT were emerging, scientists aimed to determine the locomotor capacity of the injured spinal cord in humans (Dietz et al. 1995, 1998; Dobkin et al. 1995). While most of these investigations examined the immediate or short term effects of the afferent information associated with LT (Beres-Jones and Harkema 2004; Harkema et al. 1997; Maegele et al. 2002) Dietz et al. (1995) examined EMG recordings of individuals four to five weeks post complete or incomplete SCI, before and after five months of daily LT. As reported in previous investigations (Wernig et al. 1995; Wernig and Muller 1992), individuals with incomplete injuries demonstrated improved abilities to walk on the treadmill with less

body weight support (BWS). Inappropriate muscle co-activation was reduced after training and timing of muscle activation became more coordinated. In patients with complete paraplegia, Dietz et al. (1995) reported that stepping movements could be induced in the LT environment, suggesting that the neuronal mechanisms underlying human locomotion are organized similarly to that of the cat. Moreover, across the five months of training, the extensor muscles of individuals with complete SCI increased activation in response to weight bearing and loading, suggesting that the human spinal cord could also 'learn'. Similar to Wernig's observations (1992, 1995), Dietz (1995) also reported that although the subjects with incomplete paraplegia regained unsupported stepping, their ability to generate isolated muscle force did not change.

Wernig and colleagues (1995) conducted a comprehensive investigation comparing the benefits of LT (referred to by Wernig and colleagues as Laufband therapy) to conventional treatments after SCI in subjects with acute and chronic ISCI. Along with Barbeau's early reports (1987, 1993), this study was instrumental in highlighting the role of afferent input and the 'rules of locomotion' as critical elements in the training. In this study of more than 150 individuals with ISCI, walking function was classified into six groups (0-5) with 0 indicating 'wheelchair bound' and an inability to stand or walk without moderate help. A classification of 6 was indicative of walking without devices for greater than five steps. This was one of the early reports of gait categories used to classify walking ability in individuals with SCI. As seen in contemporary gait classifications, classification was based on reliance on devices, braces often were used to ambulate, and classification was unrelated to the quality of the gait pattern. The outcomes of this study demonstrated that LT (referred to as

Laufband Therapy by the authors of this study) was more effective in restoring walking function than conventional rehabilitation for individuals with acute and chronic injury. Similar to earlier reports, Wernig et al. (1992) reported that several individuals who could not activate their lower extremity muscles during 'static' isolated strength tests, recovered independent stepping and exhibited reciprocal muscle activation during stepping. Moreover, these individuals could perform multi-joint, 'generalized' lower extremity flexion or extension (Wernig et al. 1992).

2.3.3. Pilot Studies Examine Effect of LT on Clinical Outcomes

Early studies of the effect of LT and the capacity of the human spinal cord to respond to afferent input associated with training were followed by smaller pilot studies (case series) that closely examined this approach for improving walking after SCI. These reports began to merge translational evidence with more common rehabilitation measures and procedures used in clinical settings. Moreover, these pilot studies examined the effects of LT on performance of daily activities as well as self-reported perceptions of health and disability. Behrman and Harkema (2000) reported on four adults, three of whom had an ISCI, who participated in 15-85 sessions of LT. Two individuals with chronic ISCI (>3 months) experienced significant gains in walking speed and reduced reliance on devices without a concomitant increase in isolated joint strength. Self-rated handicap also decreased, as did the degree to which health status was perceived to limit physical functioning. One individual with acute ISCI (< 1 month) progressed from being unable to walk to independent ambulation with a cane. In contrast to the individuals with chronic injuries (>3 months), this individual demonstrated significant gains in strength. Across three individuals with ISCI (two with chronic injury; one with acute injury), improved walking was reported based on decreased use of

compensatory assistive devices and alternative movement strategies. These authors also reported that no braces were used during LT or tests of walking function. Furthermore, Behrman and Harkema (2000) also investigated the effect of LT on stepping function in one individual with chronic complete SCI. Following LT, this individual was able to complete 3-5 consecutive steps on the treadmill without assistance and could support 90% of her body weight. However, consistent with Dietz's (1995) report, these gains did not transfer to improved overground ambulation.

Behrman and Harkema's report (2000) described the specific training procedures for LT which involves training on the treadmill and also overground. Across both environments, similar principles to optimize task-specific afferent information were applied. Moreover, Behrman and Harkema (2000) extended the principles of LT to the selection of assistive devices, emphasizing the use of devices that promote the most normal or recovered walking pattern and a reduction in reliance on assistive devices. Although this study did not examine biomechanical changes in walking function, they extended the training paradigm to additional aspects of LT and examined the effects of improved locomotion on performance of daily skills and perceived handicap.

Protas and colleagues (2001) also conducted a pilot study to examine the effectiveness and safety of LT. Following 12 weeks (3 times per week) of LT, three individuals with chronic ISCI made significant improvements in gait speed and endurance. Improvements also were noted relative to decreased orthotic and assistive device requirements, but movement strategies or biomechanical variables were not reported. Minimal changes in isolated muscle strength were reported. Similar to Behrman and Harkema (2000), Protas (2001) assessed self-reported function and other

domains of perceived health (life satisfaction, depression). While the findings were not significant, the inclusion of these measures is indicative of the value of these aspects and insight into the potential impact of walking recovery on other areas of physical and emotional health.

2.3.4. Randomized Controlled Trial to Examine Effects of LT

As the benefits of LT were established and a new focus on walking rehabilitation after SCI was emerging, the need for standardized assessments of walking function became more apparent (Protas et al. 2001). Thus, in the early 2000s, rehabilitation scientists placed emphasis on developing standardized measures of walking and applying assessments validated in other clinical populations to examine walking in individuals with SCI (Jackson et al. 2008). Based on this, studies examining the effect of LT relied on outcomes largely based on standardized measures of gait speed (10-meter walk test (10MWT) (van Hedel et al. 2006; Rossier and Wade 2001), gait endurance (6-minute walk test (6MWT) (van Hedel et al. 2005), and an individual's use of gait devices, orthotics, and physical assistance (Walking Index for Spinal Cord Injury-version II (WISCI-II) (Ditunno et al. 2000; Ditunno and Ditunno 2001; Marganti et al. 2005).

Standardized gait assessments were the primary outcomes reported in the only multi-center randomized controlled trial conducted to examine the effectiveness of LT in individuals with SCI. Dobkin and colleagues (2006) conducted this trial to compare the effectiveness of LT to more conventional overground mobility therapy in patients with ISCI who were admitted for inpatient rehabilitation. Across six centers, 146 individuals completed 12 weeks of equal intensity of LT or conventional overground (standing, traditional walking interventions) therapy. Subjects in both groups completed 20-30

minutes of daily mobility training for 45-60 sessions and achieved similar improvements across all primary and secondary outcome measures. For this large trial the primary outcome measures were the Functional Index Measure (FIM) and overground gait speed. Secondary measures included the WISCI-II and the 6MWT and also muscle strength as assessed by the AIS lower extremity motor score (LEMS). No biomechanical or electrophysiological assessments were conducted to examine underlying changes associated with increased gait speed and endurance. However, the authors reported that improvements in walking occurred in parallel to gains in leg strength. This report is consistent with previous reports of greater changes in the LEMS in individuals with injuries for less than 3 months (Behrman and Harkema 2000; Wernig et al. 1995). Dobkin et al. (2006) also reported that individuals achieved greater improvements in gait speed and endurance if they received the interventions within four weeks of injury. Although this study was the first randomized controlled trial comparing the effectiveness of LT to conventional gait interventions, several methodological problems were identified and both intervention arms experienced greater than usual gains in walking function (Barbeau et al. 2006). Moreover, while it is useful to apply standardized assessments of gait function, nearly 150 individuals with ISCI demonstrated unprecedented gains in gait speed and endurance and no measurement of the underlying mechanisms of control were conducted. Thus, we know these individuals improved, but it is not known *how*. This leaves future studies on walking recovery with little information as to how to improve therapies or which underlying mechanisms are associated with improved walking function.

2.3.5. New and Varied Applications of LT

As the benefits of LT have been confirmed, investigations have examined the potential limitations of this approach as well as the use of adjunctive therapies to enhance the effectiveness of LT. Robot-assisted LT, LT with functional electrical stimulation (FES), and LT along with training focused on gait adaptability are three rehabilitation approaches that have emerged. Related studies will be described briefly along with specific outcomes reported in these studies examining unique aspects and applications of LT. First, the use of a driven gait orthosis or robotic device that provides external trunk support and physical stepping assistance has been explored. A recent multi-center trial examined the benefits of automated (robotic) LT for improving walking function in 20 patients with chronic ISCI. (Wirz et al. 2005) The primary measures of walking function included the 10MWT, the 6MWT, and the WISCI-II. Secondary outcomes examined impairments such as muscle strength (LEMS) and reflexes. Across the measures of walking function, participants exhibited increased gait speed and endurance when walking overground with their customary device and/ or braces. Interestingly, the authors described the use of the WISCI-II as a measure of walking capacity, but also reported that this measure did not detect changes in ambulatory function in their study population because increases in speed and endurance were independent of any change in device use or need for physical assistance. Similar to previous studies of LT (Behrman and Harkema 2000; Dietz et al. 1995; Wernig et al. 1995; Wernig and Muller 1992), the changes in speed and endurance also were independent of any changes in muscle strength (LEMS). Wirz et al. (2005) reported that changes in volitional strength likely reflect improved corticospinal function, whereas the improvements in walking may reflect plasticity in spinal centers below the spinal

cord lesion. Although the authors concluded that the use of a driven gait orthosis improved overground walking, the mechanisms underlying these gait improvements were not examined.

A second area of inquiry is the adjunctive use of functional electrical stimulation (FES) to facilitate stepping during LT (Field-Fote EC 2001; Field-Fote and Tepavac 2002) Phase-dependent FES of the common peroneal nerve is administered to elicit a flexion withdrawal reflex and enhance flexion during the swing phase of gait (Field-Fote EC 2001) The combined use of FES and LT is beneficial for increasing overground gait speed (Field-Fote 2001; Field-Fote EC and Tepavac 2002; Nooijen et al. 2009) and lower extremity coordination. Field-Fote and Tepavac (2002) examined the effect of 12-weeks of combined use of FES and LT and reported increased gait speed post training. Speed increases were associated with improved coordination, as evidenced by more consistent hip-knee joint movements and more consistent timing of knee extension onset post 12 weeks of combined training (Field-Fote and Tapavac 2002). Although this study was designed to examine motor control and improvements in gait quality post training, 12 of 14 participants completed the gait assessments using at least one lower extremity orthotic. The use of upper extremity support during the treadmill assessments was not reported. Therefore it should be recognized that although this study provided valuable information pertaining to underlying changes associated with increased gait speed post-training, improvements were assessed relative to external supports. Changes in gait function relative to pre-morbid walking ability or normal gait strategies were not examined.

A recent study that incorporated the use of FES with LT compared the effectiveness of four training approaches for improving gait speed and quality (Nooijen et al. 2009). The approaches, which included the use of a treadmill with manual assistance, the use of a treadmill and electrical stimulation, overground walking practice with electrical stimulation, and the use of a treadmill with robotic assistance all demonstrated equal benefit for improving gait speed. Gait quality was assessed while the subject walked overground at a preferred speed using their usual orthotic and assistive device. Measures of gait quality indicated that all approaches were equivalent for improving cadence, step length, stride length, step symmetry, intra limb coordination, and timing of onset of knee extension during gait. This study was unique in that it explored the effectiveness of four locomotor interventions; however, gait improvements were assessed relative to the use of assistive devices and braces. Therefore, how these 51 individuals walked relative to their pre-morbid walking ability (compared to healthy control subjects walking without devices) remains unknown (Nooijen et al. 2009). A recent follow up to this study reported the effect of these four training approaches in 74 individuals (including the 51 who were included in the previous report) (Field-Fote and Roach 2011). Outcomes were consistent with the first report in that overground gait speed increased following the application of all four locomotor interventions. Also consistent with the initial report was that participants were examined during overground walking using devices and lower extremity braces. The primary outcomes were limited to walking speed and distance, with the only other reported outcome measure was the lower extremity motor score. Although the main finding of this randomized clinical trial was that gait speed improved for all groups, gait speed

improved less than 0.1 m/second for each training group. Walking distance during two minutes was reported to be greater in the group trained overground with stimulation. However, as Basso (2011) notes in her commentary, because gait tests were conducted overground and during these tests, the use of assistive devices was permitted, this was the only group that received task-specific training (i.e. trained overground with assistive devices and also tested in this manner). Moreover, this highlights the fact that although this study purported to explore four locomotor training approaches, the training parameters were inconsistent with principles locomotor control and the use of LT (Behrman and Harkema 2007).

The third focus of studies examining the limitations of LT questions whether LT will restore the skills necessary for successful community ambulation (Musselman et al. 2009). Musselman et al. (2009) posited that LT is specific training for stepping; however, locomotor tasks that require gait adaptability, such as negotiation of curbs, ramps, and uneven surfaces, may not be successfully re-trained. Four individuals with chronic ISCI received LT and overground skill training that included practice of gait adaptability tasks. The subjects alternately participated in the interventions for a 3-month period each. Gait outcomes were determined by scores on the 6MWT, 10MWT, and a less common measure, the Emory Functional Ambulation Profile. The authors selected this measure because it includes adaptability tasks and the scoring accounts for the use of assistive devices. Although community ambulation improved most following the overground skill training, this study did not examine *how* (gait strategy) the individuals completed the walking assessments. Therefore it is not known how the benefits were achieved and how the response to the two interventions differed.

Understanding such mechanisms would provide valuable information necessary to identify the benefits and limitations of locomotor interventions. This information is critical for expanding the benefits of current training approaches and also for the development of new therapies.

2.3.6. The Effects of LT in Children with ISCI

A recent development in the application of LT for individuals with SCI is the use of this approach with children with SCI. Thus far, the benefits of LT have been described in three case reports of children with severe, ISCI (Behrman et al, 2008; Fox et al, 2010; Prosser 2007). The first published case report examining LT in a child with SCI reported the feasibility of carrying out a LT program as part of inpatient rehabilitation program and initiated LT with a five year-old, one month after injury. This child with acute ISCI made rapid gains in walking function and a concomitant improvement in leg strength. Walking function was assessed based on outcomes on standardized measures such as the WISCI II and the Functional Independence Measure for Children-II (WeeFIM II). This report indicated that it was feasible to carry out LT in a rehabilitation setting with a child. Based on improvements in the child's LEMS, functional independence, and walking function, the authors concluded that the outcomes for this child were consistent with those reported for adults with SCI (Prosser 2007).

A second case report, published by our laboratory group in 2008, described the beneficial effects of LT in a non-ambulatory child with chronic injury (16 months post injury) (Behrman et al. 2008). Following 76-sessions of LT, this child recovered a reciprocal stepping pattern that enabled him to walk independently using a reverse rolling walking. Prior to LT, this child could perform little to no volitional, isolated joint movements, but instead performed patterned multi-joint lower extremity extension

movements. Following LT and recovery of independent ambulation, his ability to control isolated joint movements and strength remained largely unchanged (Behrman et al, 2008). In our follow-up report of this child's walking recovery 2 years post LT, we reported that this child's walking ability was maintained and continued to improve (Fox et al. 2010). Two years post LT and walking recovery, the child continued to attend school full-time without the use of a wheelchair, increased his gait speed, and also used his reciprocating lower extremity movements to perform other locomotor tasks such as tricycle pedaling, stair climbing, and crawling (Fox et al. 2010). Across our two case reports of this child with chronic SCI, scores on standardized gait assessments (WISCI-II), gross motor function (Gross Motor Function Measure), as well as clinical observational analyses of the child's gait strategies and use of compensatory strategies were reported. Although the child continued to use a reverse rolling walker two years post-LT, our case reports describe the rationale for ongoing use of this device with regards to providing external support and promoting the most normal (least compensated) gait pattern. Furthermore, our reports describe the child's decreased reliance on compensatory gait deviations. Thus, our emphasis was on walking recovery and *how* the child ambulated relative to walking strategies used by children without injury (Behrman et al. 2008; Fox et al. 2010).

2.3.7. Summary of LT Applied to Adults and Children with ISCI

Studies of the effects of LT for improving walking function and recovery span more than twenty years. Early studies examined the role of afferent input associated with walking for promoting reciprocal muscle activation and stepping. As larger studies and a randomized clinical trial were conducted, the effect of LT was examined using standardized assessments of gait speed, endurance, and need for physical assistance

and devices. Recent investigations have sought to identify improvements for delivering LT (robot-assisted LT) and to enhance its effectiveness (LT and FES). Most recently, LT has been applied to children with ISCI and described in 3 case reports. While this evidence is just emerging, outcomes from these cases support the use of LT for promoting walking recovery in children with ISCI.

Although evidence supports the use of LT for improving walking function in adults and children with ISCI, it is unclear how an individual's gait function improves relative to their pre-injury ability. Specifically, what is the effect of LT on walking *recovery*? Moreover, few studies have examined underlying mechanisms associated with walking function post SCI, as well as mechanisms responsive to LT. Identification of underlying gait mechanisms and mechanisms associated with recovery is fundamental to the advancement of interventions targeting walking recovery.

Locomotor training is founded on the neural control of locomotion and clinical principals regarding its use and application to individuals with SCI is based on contemporary models of walking control. This foundational information also is the basis for examining walking control after SCI and identifying mechanisms of response associated with LT. Therefore, an in-depth review follows to discuss control of locomotion and activity dependent plasticity as a foundation for walking recovery and the application of LT.

2.4. Neuromuscular Control of Locomotion and Walking

2.4.1. Models of Walking Control Provide a Foundation for LT

The foundation of LT and the ongoing paradigm shift in the rehabilitation of walking after SCI is grounded in two models of walking control. First, the theoretical foundation of LT is based on a tripartite model of the neurological control of walking

(Behrman et al. 2006; Edgerton et al. 2004; Zehr 2005). This model recognizes the integrated roles of cortical and descending signals, spinal cord circuitry, and ascending pathways in the control of walking (Zehr 2005). Thus, control of functional overground walking is distributed across all levels of the neural axis. Second, with an aim to restore functional, goal-directed ambulation, LT is founded on a control model that specifies three neural control tasks associated with functional walking: reciprocal stepping, upright dynamic balance during stepping propulsion, and adaptability to meet environmental demands and individual goals (Barbeau 2003; Forssberg 1982).

In the presence of SCI and altered descending control, LT aims to augment the role of spinal circuitry and ascending signals for the generation of reciprocal stepping. Stepping and balance are practiced in a permissive treadmill environment. As these two subtasks (stepping and balance) are recovered, overground training is integrated and LT is performed in this environment (Behrman and Harkema 2007; Dobkin et al. 2006). As recovery is demonstrated during treadmill and overground walking, adaptability tasks that require greater cortical control, such as stopping, starting, and stepping over obstacles, are integrated (Wernig et al. 1995; Behrman and Harkema 2000).

The integration of these two models of walking control guides the application of LT. Not only are specific control tasks practiced (stepping, balance, adaptability), but each task is practiced in a manner to enhance activation of neural centers underlying walking control. The following sections will define and describe the neural control tasks associated with functional walking. Then, the neurologic control of walking relative to

the three subtasks will be discussed. Each section will discuss basic science evidence as well as translational human investigations.

2.4.2. Neural Control Sub-tasks Associated with Walking

Locomotion is a complex motor task controlled by dynamic sensorimotor interactions (Rossignol 2006) in order to initiate, terminate, and direct goal-oriented behavior under predictable and unpredictable conditions (Grillner 1979). As previously stated, walking incorporates three neural control 'subtasks' (Barbeau 2003; Forssberg 1982). First, a reciprocating stepping pattern is required to propel the body forward. In humans, the lower limbs rhythmically flex and extend to produce a coordinated stepping pattern. Second, balance and equilibrium must be maintained during stepping. Limb, head, and trunk muscles coordinate to maintain upright alignment and stability. Third, functional locomotion must be adaptable to an individual's goals and environmental demands. Moreover, balance and locomotor adaptability must be maintained under predictable and unpredictable conditions. Therefore, these control mechanisms must integrate feedback responses during unpredictable environmental challenges as well as feed-forward commands during times when adaptable changes are anticipated and goal-directed.

2.4.3. Neural Control of Stepping and Other Rhythmic, Reciprocal Locomotor Skills

Central pattern generators: The mammalian stepping pattern is characterized by rhythmic, reciprocating limb movements used during locomotion. As studied in cats and lower vertebrates, these rhythmic limb movements are largely controlled by spinal pattern generators (Grillner, 1979). Although not definitive, evidence supports the role

of these neural centers in human locomotion as well (Calancie et al. 1994; Dimitrijevic et al. 1998; Dobkin et al. 1995).

While descending supraspinal commands and peripheral sensory inputs are important to modulate output from these spinal networks, central pattern generators (CPG) are capable of rhythmic firing without sensory input. As evidence of this, fictive locomotor patterns have been studied and provide evidence that the pattern generators are able to propagate rhythmic output to flexor and extensor limb muscles (Gossard et al. 1991). Furthermore, the fictive model provides critical evidence that such patterns are produced by oscillating networks, rather than spinal reflexes (Grillner and Zangger 1975; Marder and Bucher 2001).

Although spinal networks can propagate rhythmic motor output in the absence of afferent sensory information, these neural centers are highly influenced and regulated by peripheral feedback (Gossard et al. 1991; Rossignol 2006). Studies of spinal cats and humans with spinal cord injury (SCI) have demonstrated that sensory information regarding hip position and limb loading provides critical cues to regulate the basic stepping pattern.

Afferent input from the hip joint: Hip joint and muscle afferents provide proprioceptive feedback to regulate the stance and swing phases of walking. The timing of the step cycle as well as the amplitude of flexor and extensor muscles are regulated by this afferent input (Rossignol 2006). Grillner and Rossignol (1978) reported that initiation of the swing phase could be delayed or prevented in spinalized cats when hip extension motion was limited, suggesting that movement into hip extension is a critical stimulus for swing initiation. Furthermore, muscle activity

corresponds to the amplitude of the hip joint angle. Andersson et al. (1978) demonstrated that small amplitude hip movements into flexion or extension resulted in activation of the corresponding muscle group (small amplitude hip extension resulted in hip extensor activity). Large amplitude hip extension movements, however, elicited hip flexor activity, apparently initiating swing phase activity (Andersson et al. 1978).

Studies of human locomotion further support the importance of hip joint motion. Dobkin et al. (1995) reported spontaneous hip flexion activity when the stance limb of a person with SCI moved into extension during treadmill walking. More detailed findings have been reported by Dietz et al. (2002) who investigated the influence of lower extremity joint kinematics on muscle activation in persons with complete SCI and uninjured subjects. The influence of hip, knee, and ankle joint movements was investigated using a driven gait orthosis. Dietz and colleagues (2002) reported that hip joint afferents had the most significant influence on the muscle activation pattern during stepping.

Afferent input associated with limb loading: Afferent feedback regarding limb loading is another critical afferent signal during locomotion. Limb loading may signal the limb to maintain stance and delay the onset of swing (Duysens and Pearson 1980). Furthermore, in studies of locomotor recovery after spinalization, cats demonstrated more consistent, coordinated hindlimb muscle activity when trained with appropriate limb loads (Edgerton et al. 1992).

Studies of walking recovery after human SCI also have demonstrated the significance of limb loading on the generation and modulation of rhythmic motor output (Dietz et al. 2002; Harkema et al. 1997). Harkema et al. (1997) studied the effect of

limb loading on lower leg muscle activity in persons without injury as well as individuals with complete and incomplete SCI (ISCI). During locomotor training on a treadmill, with varying levels of partial body weight support and manual assistance, muscle activity was recorded in the soleus, gastrocnemius, and tibialis anterior muscles. Activity in the lower limb muscles was significantly related to limb load in all subjects, indicating that loading is an important sensory input for modulation of locomotion.

A combination of joint kinematics and limb loading has been studied in persons with complete and incomplete SCI. Results indicate that a combination of appropriate limb loading and lower extremity kinematics, consistent with the task of walking produces alternating flexor and extensor muscle activation, even in muscles not under volitional control (Maegele et al. 2002). Furthermore, loading and kinematics influence reciprocal activation of the contralateral limb, even when the limb is stationary and unloaded (Ferris et al. 2004).

Control of other rhythmic, reciprocal locomotor tasks: In addition to propagating rhythmic motor activity for stepping and walking, spinal pattern generators also may control other rhythmic, reciprocal locomotor tasks. Basic science investigations across vertebrates suggest there is great overlap in the control across tasks (Berkowitz 2008; Earhart and Stein 2000; Forssberg et al. 1980; Mortin and Stein 1989). Inter-neuronal recordings during fictive swimming and scratching indicate shared circuitry is used to control a variety of turtle behaviors (Berkowitz 2008). Moreover, electromyogram (EMG) recordings also support shared circuitry across stepping, swimming, and scratching in the turtle (Earhart and Stein 2000) as well as stepping and galloping in the spinal kitten (Forssberg et al. 1980).

Computational approaches have recently been applied to the study of neural control mechanisms used across locomotor tasks in healthy adults (Stoloff et al. 2007; Zehr et al. 2007). Although joint kinematics vary across tasks, analyses of muscle activation patterns across upper and lower extremities suggest that walking and recumbent stepping rely on common neural networks (Stoloff et al. 2007). Additionally, Zehr et al. (2007) reported that walking, arm and leg cycling, and arm-assisted stepping also rely on similar muscle activation patterns suggesting common neural control mechanisms. Studies of quadrupedal control and interlimb coordination further support shared neural circuitry across tasks (Patrick et al. 2008; Wannier et al. 2001; Zehr 2005).

Supraspinal input associated with stepping control: Although rhythmic, reciprocal limb movements are largely controlled by central pattern generators, descending supraspinal commands are important for activating or initiating locomotion. (Note that the role of descending commands in locomotor adaptability will be addressed in a subsequent section.) The mesencephalic locomotor region (MLR) has been studied predominantly in animals, demonstrating that descending commands are relayed through this center to the central pattern generators (CPGs) via the reticulospinal neurons (Brocard and Dubuc, 2003). With inputs from corticospinal centers, the basal ganglia, and cerebellum, the MLR integrates multiple input signals for locomotor control. The reticulospinal neuronal network also is a primary center for activating and regulating pattern generation (Matsuyama et al. 2004). As reviewed by Matsuyama and colleagues (2004), multiple overlapping cortical inputs project to the reticulospinal pathway for bilateral descending control via multiple inter-neuronal

connections. Furthermore, it is suggested that this system may have functional sub-units to modulate goal directed locomotion.

Receiving input from cortical projections, the basal ganglia (BG) control critical descending commands, via the MLR, for the initiation of walking and control of postural tone during stepping. The descending command to 'release' goal-directed walking behavior comes from dis-inhibition of the basal ganglia. Input from the cortex stimulates inhibitory neurons within the striatum to dis-inhibit neurons in the pallidal layer of the BG and allows for activation of descending signals to the CPGs (Grillner et al. 2008; Takakusaki et al. 2003). Therefore connections between the BG and sensorimotor cortex integrate with other signals from the MLR and the reticulospinal pathways to initiate and modulate stepping.

Summary: This section has summarized the role of the spinal networks in generating a fundamental stepping pattern. Peripheral feedback is integrated with descending commands to regulate the step cycle as well as the pattern and amplitude of muscle activation. Descending commands are important for signaling the CPG and initiating the stepping pattern. While it is impossible to separate the neural control mechanisms based solely on their role in stepping, this section highlights several ascending and descending pathways integrated to control this neural sub-task.

2.4.4. Neural Control of Balance and Equilibrium during Locomotion

While the CPG and step generation have been studied in detail (Grillner et al. 2008), the methodology for investigating postural control is more complex and less is understood about this control task of locomotion (Deliagina et al. 2008).

Balance during locomotion is described in terms of postural orientation and equilibrium (Macpherson et al. 1997). Postural orientation is the position of the body

segments relative to each other and to the environment. Postural equilibrium refers to control of the linear and angular momentum of the body (Macpherson et al. 1997). Postural orientation may be partially controlled by spinal circuits, as demonstrated by the spinal cat's ability to maintain orientation. This control may be partially sub-served by extensor activation by spinal pathways. Body orientation also is controlled by the vestibular system. Bilateral vestibular input is directed to the reticulospinal system to send signals to postural muscles. Furthermore, the basal ganglia also play a role in regulating muscle tone for balance and equilibrium (Grillner et al. 2008). Moreover, the basal ganglia receive projections from visual pathways that also contribute to control postural orientation.

Although postural equilibrium may be partially regulated by spinal centers, as evidenced by preserved control in spinal cats, equilibrium responses to perturbations during standing are not preserved (Macpherson et al. 1997), suggesting these responses are controlled by higher centers. Deliagina et al. (2008) examined the contributions of spinal and supraspinal input for postural control (orientation) in the cat. Although studies were done in standing, as opposed to walking, they provide evidence of interactions between ascending and descending pathways that integrate to control postural orientation. Limb mechanoreceptors provide peripheral input for corrective responses while long reflex loops from supraspinal structures integrate information from visual and vestibular systems. The corticospinal system, along with other descending pathways, transmits signals to the spinal cord for corrective postural responses (Deliagina et al. 2008).

Although less is known about the specific orientation and equilibrium responses during locomotion as well as the capacity of the spinal cord to control these responses without supraspinal input (Deliagina et al. 2008), integration of control signals across the nervous system is required. Commands are integrated from peripheral, spinal, and supraspinal pathways demonstrating shared function across the neural axis.

2.4.5. Neural Control of Locomotor Adaptability

Locomotor adaptability is the ability to modify the locomotor pattern based on behavioral goals and in response to expected and unexpected environmental demands. Adaptable locomotion therefore includes a spectrum of behaviors and integration across several neural centers to modulate peripheral and descending commands.

Peripheral inputs: Basic locomotor adaptation is accomplished by spinal modulation of peripheral input. Peripheral input from cutaneous stimulation and joint receptors modulate spinal patterns in response to unexpected locomotor demands, such as changes in speed (during treadmill stepping) and obstacle negotiation (Rossignol 2006).

Studies of locomotor re-training in spinal cats demonstrate that afferent information regarding stepping speed is integrated by spinal networks to allow for modulation of the step cycle (Barbeau and Rossignol 1987). Barbeau and Rossignol (1987) investigated spinalized cats and reported their ability to adapt their stepping pattern across a range of walking speeds. Furthermore, they reported better phase coupling between the hindlimbs and amplitude of muscle activation observed at higher stepping velocities. Therefore, not only are spinal networks able to adapt the locomotor pattern to speed changes, peripheral input regarding speed also is an important stimulus for locomotor control.

Persons with complete and incomplete SCI also demonstrate integration of peripheral information regarding stepping velocities (Beres-Jones and Harkema 2004). At higher stepping speeds, such as those approximating normal walking velocities, persons with SCI demonstrated shorter step cycle durations, shortened muscle burst durations, and higher amplitude of leg muscle electromyograms (EMG).

Spinal networks also demonstrate phase dependent modulation of cutaneous inputs during locomotion (Forssberg 1979). Cutaneous input may provide feedback regarding an unexpected obstacle. Therefore, the limb response must account for the limb position and whether it is unweighted during swing, or weight bearing during stance. Cutaneous stimulation to the dorsum of the foot in intact and spinal cats during swing provokes increased flexion of the limb, as during obstacle negotiation. When a similar stimulus is provided during stance, a reflexive response of the extensor muscles is generated (Forssberg 1975). Cutaneous afferent input therefore modulates the locomotor output of the CPG to adapt the stepping pattern to unforeseen obstacles. In more recent investigations of cutaneous inputs for locomotor control, Bouyer and Rossignol (2003) studied locomotor recovery in cats after spinal transection with and without denervation to remove cutaneous limb feedback. While cats could initially adapt to the peripheral denervation, following spinal transection, weight bearing and paw placement were impaired during precision walking skills, demonstrating the importance of cutaneous feedback during locomotion after SCI.

Supraspinal control: Several supraspinal structures contribute to feed-forward locomotor adaptations. Visual input and corticospinal pathways are important for feed-forward adaptations and goal-directed modulation. Vision is critical for responses to

environmental demands, such as during anticipated obstacles or terrain changes as well as for goal-directed locomotion. Visual information is projected to the MLR to initiate stepping during goal-directed locomotor behavior and is integrated with vestibular and peripheral afferents for modifications during walking.

Corticospinal projections play an important role in cat locomotion, and likely have an even greater role in human locomotion. In cats, the rubrospinal tract shares function with the corticospinal tract in controlling locomotion. Drew et al. (2002) reported on studies of spinal cats with lesions preserving some connections in the descending corticospinal or rubrospinal tracts. These cats recovered skilled walking function, suggesting that the reticulospinal and vestibulospinal pathways were able to compensate for the damaged pathways. However, more severe lesions damaging both the rubrospinal and corticospinal tracts resulted in long-term impairments of skilled locomotor adaptability. Drew et al. (2002) postulated that the corticospinal tract plays a significant role in skilled human locomotion adaptations. While damage to this system in cats and non-human primates causes locomotor deficits, Drew et al. (2002) hypothesized that the rubrospinal system plays a greater role in these mammals and is therefore able to compensate (neuronal compensation) when the corticospinal system is damaged. In humans, however, the corticospinal system has a greater role in locomotor function, while other descending tracts have less influence. Drew et al. (2002) suggest this may partially explain why humans have significant difficulty overcoming corticospinal damage while spinal animals recover greater locomotor function.

Another important neural control center for locomotor adaptability is the cerebellum. During locomotion, afferent copies of the CPG output are sent to the cerebellum via the spinocerebellar tract and the spinoreticulocerebellar pathways (MacKay- Lyons 2002). The cerebellum compares intended movement to the actual motor output and influences motoneurons indirectly via the vestibulospinal, reticulospinal, and corticospinal pathways. A recent study in persons with cerebellar damage found that the cerebellum is important for predictive, anticipatory responses to expected locomotor adjustments (Morton and Bastian 2006). Individuals with cerebellar dysfunction did not have impaired feedback control and were able to adapt to unexpected locomotor demands.

Control of locomotor adaptability is distributed across multiple command centers, integrating peripheral inputs and descending commands for feed-forward and feedback adaptations. Thus, there is an overlap in the neural mechanisms controlling locomotor adaptation. This is not surprising considering the broad repertoire of adaptations required for functional locomotion.

2.5. Neural Plasticity

As reviewed in the previous section, basic and translational science provide evidence of the distributed neural control of walking as well as the intrinsic capacity of the spinal cord to control reciprocal stepping. Additionally, scientific evidence provides support for plasticity of spinal cord circuits and the ability of such circuits to respond or adapt to training or ‘learn’ a motor task. The following section will discuss neural plasticity and will review basic and translational studies demonstrating plasticity in spinal networks associated with locomotor control. Furthermore, these discoveries provide the foundation for locomotor training (LT) principles, specific guidelines designed to provide

a framework for clinical decision making (Behrman and Harkema 2007). This section will therefore extend the discussion to principles of LT and describe the application of these scientific discoveries to clinical practice.

2.5.1. Activity-Dependent Plasticity as a Foundation for Locomotor Training

A fundamental characteristic of the vertebrate nervous system is its ability to continually adapt its structure and processes to changes in use (Bailey and Kandel 1993; Harkema 2008; Kleim et al. 1996; Kleim and Jones 2008). This plasticity or adaptability of the nervous system as well as the ability to sustain structural and functional change (here, sustained is relative to the duration of the change in demand) is referred to in contemporary rehabilitation and scientific literature as neural plasticity (Kleim and Jones 2008). Neural plasticity occurs in response to how the nervous system is activated and even in response to how it is not activated; it is directed by the actions and use of the nervous system and therefore, may have a positive or negative impact on motor control and function (de Leon et al. 1999; Nudo 2007). Neural plasticity is not only driven by the activities that are performed, but also the degree to which they are repeated. Neural adaptation is most robust when activities are repetitively practiced (Kleim et al. 2004; Wolpaw and Herchenroder 1990). Neural plasticity in response to repetitive activity is termed ‘activity-dependent plasticity’ (Wolpaw and Tennissen 2001). Activity-dependent plasticity underlies changes in motor control, performance, and motor learning and is therefore a foundation for many rehabilitation interventions, including LT (Behrman and Harkema 2007; Harkema 2008; Hubbard et al. 2009; Kleim and Jones TA 2008; Levin et al. 2008).

The paradigm shift in the rehabilitation of walking after incomplete SCI (ISCI) is based on evidence of activity-dependent plasticity of spinal neural networks that control

rhythmic locomotion (Behrman et al. 2006; Edgerton et al. 2004; Harkema et al. 1997; Hodgson et al. 1994; Lovely et al. 1986). Although it was known that spinal cats could recover hindlimb stepping (Grillner 1975), it was not until the 1980s that the role of task-specific training to optimize activity-dependent plasticity in the spinal networks below the injury level was evident (de Leon et al. 1998; Hodgson et al. 1994; Lovely et al. 1986). An ensemble of sensory inputs critical for activation of lumbo-sacral networks below the level of the injury and enhancement of motor activity for rhythmic stepping were identified (Andersson et al. 1978; Barbeau and Rossignol 1987; Edgerton et al. 1992). Results from these experiments were translated to humans and lead to the development of LT and clinical principles (Behrman and Harkema 2007; Maegele et al. 2002).

2.5.2. Repetitive, Specific, and Ongoing Training to Optimize Plasticity and Recovery

The capacity of the spinal cord to learn a complex motor task, such as walking, became evident from studies of spinal cats that practiced treadmill stepping with their torso supported while their forelimbs stood stationary on a platform and their hind limbs were assisted with stepping on a treadmill (Barbeau and Rossignol 1987; de Leon et al. 1989; Lovely et al. 1986). Compared to untrained animals, cats who received repetitive step training were able to achieve full weight bearing earlier and could step at higher speeds (de Leon et al. 1998; Lovely et al. 1986). Step training also improved limb kinematics and increased hind limb muscle coordination and activation (de Leon et al. 1998). These studies demonstrated the effect of repetitive training on spinal control of locomotion and stepping recovery after SCI.

Although, repetitive training activates spinal networks to generate a rhythmic output for the control of stepping, task practice must be highly specific to the desired task and ongoing to achieve durable training effects. For example, Hodgson et al. (1994) demonstrated that the mammalian spinal cord can learn a specific motor task, but when subsequently trained in another task, the initially-trained skill may be lost. Stand-trained spinal cats recovered hind-limb weight bearing and standing. Following stand-training, however, 2 of 5 cats were unable to step and the remaining 3 animals could only perform slow, poorly-controlled steps. In contrast, untrained cats were able to treadmill step and step-trained cats could step at twice the speed of untrained animals. Stand-training therefore interfered with stepping recovery, even when compared to untrained control cats (Hodgson et al. 1994). Furthermore, even in animals that initially received intense step-training and recovered stepping, stepping ability diminished when practice was discontinued and also following repetitive stand training (de Leon et al. 1998). Practice of a related task, such as standing, may interfere with the acquisition and retention of stepping. Additionally, ongoing stepping practice is necessary to maintain stepping recovery (de Leon et al. 1999). Similar findings in humans support the role of specific task practice (Winstein et al. 1989) and the necessity of ongoing practice to maintain stepping performance (Wirz et al. 2001).

2.5.3. Locomotor Specific Afferent Input Enhances Activity-Dependent Plasticity

Introduction: Studies of task training and activity-dependent plasticity in mammalian lumbosacral spinal networks lead to the identification of sensory inputs associated with locomotor output and recovery. Furthermore, based on indirect evidence of a human spinal pattern generator (Bussel et al. 1996; Calancie et al. 1994; Dimitrijevic et al. 1998; Dobkin et al. 1995; Nadeau et al. 2009), translational studies

followed to determine the role of locomotor-specific afferent input in producing rhythmic locomotor output (Dietz and Harkema 2004; Dobkin et al. 1995; Harkema et al. 1997). Afferent input associated with hip joint muscle tendon length changes, limb loading, and the temporal distribution of limb loading (associated with speed changes) are sensory inputs now known to enhance motor activation during stepping. While these sensory inputs have been systematically investigated, scientists agree that an *ensemble* of appropriate sensory information is necessary to maximize rhythmic locomotor output (Edgerton et al. 2004; Harkema 2008; Maegele et al. 2002). The following section will highlight basic and clinical studies of the afferent input associated with rhythmic motor output from spinal pattern generators in animal and human models of SCI. Because these experiments provided the foundation for principles of LT, specific training principles also will be described to demonstrate translation of evidence into clinical practice.

Hip joint muscle tendon length changes: In spinal cats, afferent input associated with hip joint muscle-tendon length changes during flexion and extension movements modulates flexor and extensor muscle activation (Andersson et al. 1978; Dietz et al. 2002). Moreover, in persons with complete SCI, hip flexion activity while treadmill stepping occurs in response to hip extension movement while the limb is loaded during stance (Dobkin et al. 1995). Hip flexion or the onset of swing is further facilitated by rapid unloading of the limb as it is extended and transitions from stance to swing. Additionally, the velocity of hip extension movement in association with faster stepping is associated with increased lower extremity muscle activation (Beres-Jones and Harkema 2004). Based on these findings, LT aims to optimize stepping kinematics

and achieve hip extension during terminal stance. An upright trunk posture is promoted to ensure that the lower extremity is extended relative to upright trunk and pelvic alignment. Limb movements are timed appropriately based on a normal rate and rhythm of stepping. As the hip is extended, weight is shifted from the extended limb to the contralateral lower extremity. Hip extension and stepping are coordinated with reciprocal arm swing (Behrman and Harkema 2007).

Limb loading: Reciprocal limb loading and weight bearing during stepping are critical sensory inputs for activation of spinal locomotor networks (Edgerton et al. 1992; Lovely et al. 1986). Although not tested in their experiments, maximal limb loading was cited by de Leon and colleagues (1998) as a key ingredient in their training studies of spinal cats. Limb loading and weight bearing are associated with increased limb muscle activation and coordination during stepping in spinal animals (Edgerton et al. 1992). Adults with SCI also respond to increased limb loading with improved reciprocal activation and greater amplitude of muscle activity during limb movements (Dietz et al. 2002; Harkema et al. 1997). During LT on a treadmill with partial body weight support, soleus muscle activation, a plantar flexor muscle necessary for propulsion during stepping (Neptune et al. 2001) is modulated by the amount of lower extremity limb loading in individuals with SCI (Harkema et al. 1997). Furthermore, reduced lower extremity loading, due to upper extremity weight bearing, such as on an assistive device, results in decreased muscle activation in the lower extremities. In comparison, reduced LE loading due to partial body weight support causes a reduction in lower extremity muscle activation (Visintin and Barbeau 1994). Therefore, during LT, maximal LE loading is encouraged while upper extremity weight bearing is discouraged

(Behrman and Harkema 2007). While LT often includes partial body weight support (BWS), the guidelines suggest that 40% BWS or less should be provided or an amount necessary to enable other training variables to be maximized (e.g. upright trunk and hip extension during terminal stance). Thus, BWS contributes to a permissive environment, allowing other variables to be maximized and is only provided when necessary. Limb loading is maximized relative to each individual's stepping ability and to promote the most robust ensemble of sensory inputs during LT (Behrman and Harkema 2007).

Stepping speed: During stepping, the mammalian lumbosacral spinal cord also responds to the rate of afferent input and modulates motor output in response to changes in stepping speed (Barbeau and Rossignol 1987; Lovely et al. 1990). Moreover, higher stepping speeds and speeds that approximate normal lead to improved limb coordination and joint kinematics (Barbeau and Rossignol 1987). Similarly, humans with SCI demonstrate greater leg muscle EMG at higher stepping speeds. In persons with clinically complete SCI, muscles that were inactive during slow stepping become active at faster stepping speeds (Beres-Jones and Harkema 2004). During LT, stepping at speeds that approximate normal (0.8-1.2m/s) (Craik and Dutterer 1995). is encouraged. As discussed previously, partial BWS and stepping assistance from trainers create a permissive environment, enabling step practice at this speed while other sensory variables are simultaneously maximized (Behrman and Harkema 2000).

Summary: Early experiments of training and step recovery in spinal cats provided critical insights into the capacity of locomotor networks to respond to a complex ensemble of afferent information and adapt motor output associated with motor learning

and locomotor recovery. Translational investigations demonstrated that rhythm-generating neural networks in humans may respond similarly and therefore are amenable to adaptations promoting functional recovery. The specific physiological and biochemical mechanisms associated with locomotor recovery and activity-dependent plasticity have not been isolated and may be numerous (Edgerton et al. 2004). Following injury, plasticity in remaining spinal pathways may occur via altered synaptic connections, changes in the use of neurotransmitters (de Leon et al. 1999b; Edgerton et al. 1997a), or through non-neuronal cell types (Gomez-Pinilla et al. 2002). Isolation of biologic processes associated with activity-dependent plasticity requires ongoing investigation. Moreover, there are likely many other variables associated with plasticity and functional recovery (Tester and Howland 2008). Because plasticity is a fundamental characteristic of the nervous system and it underlies motor learning and functional recovery, rehabilitation may have profound influence. However, the specific biologic mechanisms and substrates associated with locomotor recovery are not fully understood.

2.6. Advancing Rehabilitation of Walking for Individuals with ISCI

As described in the previous sections, basic and translational studies of walking control and activity-dependent plasticity have provided a foundation for the ongoing paradigm shift in walking rehabilitation after spinal cord injury (SCI). In some clinics, rehabilitation of walking for individuals with incomplete SCI (ISCI) now emphasizes recovery of walking rather than reliance on compensations (Behrman et al. 2006). As a new paradigm has emerged and is ongoing for enhancing walking recovery after ISCI, progression of this paradigm depends on continued application of biologic principles of walking control and activity dependent plasticity (Basso 2011; Behrman et al. 2006;

Behrman and Harkema 2007). Specifically, these biologic principles must be extended to the examination of walking recovery and to the identification of mechanisms associated with recovery. Therefore, to further advance the paradigm shift in walking rehabilitation, re-consideration must be given to 1) how an individual's walking capacity or potential to re-gain walking function is determined, 2) measurement of walking function, and 3) reliance on standardized assessments of walking that are currently limited to measurement of speed, endurance, and use of a device.

2.6.1. Assessing Walking Potential after ISCI

Currently, as described in Section 2.1.5, following SCI the prognosis for regaining functional skills after SCI, including determination of walking potential, is based on tests of isolated joint control and strength (Burns et al. 1997; Crozier et al. 1992; Mulcahey et al. 2007; Oleson et al. 2005; Scivoletto et al. 2008; Zorner et al. 2010) which are used to assess residual cortical activation of lower extremity motor pools (American Spinal Injury Association 2006). Following SCI, however, rhythmic motor output during walking and activation of muscles below the spinal cord lesion depends on task-specific afferent input (Edgerton et al. 2008; Harkema 2008). Based on this, Maegele and colleagues (2002) compared the activation of lower extremity motor pools in individuals with complete and ISCI during weight bearing stepping, movements in supine simulating stepping, and during isolated lower extremity joint movements, such as those performed during tests to determine an individual's lower extremity motor score (American Spinal Injury Association 2006). Consistent with Biologic principles of locomotion, motor pool activation was greatest and more appropriate in the presence of task-specific sensory input, such as during lower extremity weight bearing and rhythmic stepping in an upright position (Maegele et al. 2002). These findings further suggest that an individual's

walking capacity should be assessed within the context of walking and in association with an appropriate, task-specific sensory ensemble. Although this evidence exists for adults with SCI, standardized assessments of locomotor capacity have not yet been adopted. Moreover, comparisons of motor pool activation in children with ISCI have not been reported, but are necessary to provide a foundation for determining appropriate examination approaches for children with ISCI.

2.6.2. Assessment of Walking Function after ISCI

Although rehabilitation of walking after SCI now emphasizes recovery of pre-morbid function, examination of walking continues to be conducted using compensatory assistive devices and braces (Field-Fote and Roach 2011). Measurement of walking function using a device or braces provides a measure of walking relative to that specific gait strategy and is based on a model of compensation (Scivoletto et al. 2008). To measure an individual's walking recovery or determine the effect of an intervention on walking recovery, walking must be assessed relative to pre-morbid walking strategies. Commonly used walking measures do not assess an individual relative to their pre-morbid gait strategy; assistive devices and braces are readily included (Jackson et al. 2008). Not only does the use of such devices change the task of walking and alter the movement strategy, but these devices also obstruct appropriate afferent input necessary for an optimal locomotor pattern and may further hamper walking control due to altered motor activation (Visintin and Barbeau 1994). Conducting assessments of walking recovery could be safely accomplished in a permissive environment that uses a treadmill and partial body weight support. Not only would this be a safe option for the patient, but this environment would provide the opportunity for sensory input associated with walking to be optimized (Behrman et al. 2005). Moreover, models of walking

control, such as Forssberg's model (1982) that focuses on the subtasks of stepping, dynamic balance, and adaptability, may be applied to provide a framework for the examination of specific features of walking recovery such as upright trunk control or reciprocal stepping (Barbeau 2003; Behrman et al. 2006; Forssberg 1982).

2.6.3. Standardized Assessments of Walking Function are Limited

Finally, as discussed in Section 2.3.4., examination of walking function in individuals with SCI emphasizes the use of standardized assessments of gait speed, gait endurance, and reliance on assistive devices and physical assistance (Jackson et al. 2008; Steeves et al. 2007). These assessments are useful in that they are standardized and allow for comparisons across individuals and populations. However, consideration should be given to what is measured and also to what is not captured by these assessments. Specifically, the commonly adopted standardized gait assessments [10 meter walk test (Rossier and Wade 2001; van Hedel et al. 2005, 2006), 6 minute walk test (Brooks et al. 2003; van Hedel et al. 2005, 2006), and the Walking Index for Spinal Cord Injury, version II (Ditunno et al. 2000; Ditunno and Ditunno 2001; Morganti et al. 2005)] assess gait speed, gait endurance, and reliance on a device or assistance, but do not provide information regarding how an individual walks, the quality of their gait pattern, or walking control relative to pre-morbid ability. Furthermore, these tests do not restrict the use of a device or brace and permit the individual to ambulate in any manner for the prescribed distance or time. As the goals of walking rehabilitation have now shifted towards recovery, it is important to consider measures of walking function that assess an individual within this framework of recovery. Thus, additional measures are needed also to examine walking function

relative to pre-morbid ability and to measure mechanisms underlying walking function and recovery (Basso 2011).

2.6.4. Mechanisms Underlying Walking Control and Recovery are Not Well-Understood

Mechanisms of walking control and recovery in individuals with SCI have been explored in a limited number of studies. Studies have sought to determine underlying mechanisms of response to locomotor interventions, such as 1) changes in muscle activation (Dietz et al. 1995; Gorassini et al. 2009; Grasso et al. 2004) and 2) lower extremity coordination (Grasso et al. 2004; Field Fote and Tepavac 2002), and 3) limiting factors associated with gait impairment post SCI (Pepin et al. 2003). In early studies examining the effect of LT, Dietz et al. (1994; 1995) examined changes in muscle activation in individuals with complete and incomplete SCI following five months of daily LT. Inappropriate muscle co-activation was reduced following training and the pattern of activation of the ankle dorsiflexors and plantarflexors became similar to the uninjured controls. In contrast to this finding of more normal muscle activation following LT, Grasso and colleagues (2004) reported that individuals with ISCI trained to step on a treadmill with partial body weight support recovered limb coordination based on more normal patterns of foot motions, but adopted individual motor solutions. Thus, recovery of walking was associated with more normal foot trajectory, but was controlled using compensated muscle activity. Grasso and colleagues (2004) suggest that following training, individuals with SCI used new strategies that were motor equivalents of normal strategies in order to control the kinematics of the foot. Furthermore, based on the reconstructed maps of motor neuron activity along the spinal cord, it was concluded that

plasticity or changes in motor pool activation were distributed across the spinal cord rather than isolated to networks in the lumbosacral spinal cord (Grasso et al. 2004).

Gorassini et al. (2009) examined changes in muscle coordination in 17 individuals with ISCI following 4-5 months of training using a treadmill and partial body weight support. Training was carried out at slow speeds to allow participants to concentrate on voluntary muscle activation during stepping. Gorassini (2009) compared electromyogram recordings in individuals who achieved a ≥ .06 m/second increase in treadmill gait speed (responders) and those who did not (non-responders). Responders demonstrated increased muscle activation in ankle dorsiflexors and hamstring muscles and decreases in burst duration and co-contraction of quadriceps and hamstring muscles. Gorassini (2009) reported that muscle activation of individuals with SCI before and after training remained vastly different from individuals without injury, supporting the notion that individual motor solutions are used to improve walking control in individuals with ISCI.

In addition to changes in muscle coordination, studies also have examined kinematic and kinetic changes associated with improved walking function (Field-Fote and Tepavac 2002; Gregory et al. 2007). Field-Fote and Tepavac (2002) examined intra-limb coordination between hip and knee movements following a training program that used partial body weight support and electrical stimulation while treadmill walking in 14 subjects with ISCI. Following 36 training sessions, gait speed and intra-limb coordination improved, demonstrating more consistent limb kinematics. Although increased recovery of joint coordination was reported and individuals were assessed during treadmill walking without an assistive device, 12 of 14 subjects used at least one

ankle orthotic and 7 subjects used bilateral orthotics (Field-Fote and Tepavac 2002). Thus, it is difficult to interpret the findings of this study relative to recovered walking.

In a study examining the effect of resistance training on locomotor recovery in three individuals with ISCI, Gregory et al. (2007) reported that increases in gait speed following resistance training were associated with increased hip joint excursion and propulsion, based on measures of anterior-posterior ground reaction forces. Increases in peak torque production of the ankle plantarflexors were presumed to be associated with gains in gait speed and propulsion (Gregory et al. 2007). Spatiotemporal features of the participants' gait pattern also improved or recovered.

Spatiotemporal characteristics of walking, such as step length and frequency, may be limiting factors in the maximal walking speed of individuals post SCI (Pepin et al. 2003). In a study of five individuals with ISCI, Pepin et al. (2003) compared stride length and frequency (cadence) at different walking speeds to control subjects. Across walking speeds, individuals with SCI had a significantly lower stride frequency compared with the control subjects. Maximal stride length increased as speed increased in both groups and achieved maximum in spinal cord injured subjects as they approached their fastest walking speed. Based on the findings, the authors suggested that rehabilitation interventions should emphasize improving the capacity to generate rapid alternate stepping movements in the lower extremities (Pepin et al. 2003). Examination of spatiotemporal gait characteristics provides quantitative data that characterizes an individual's gait strategy. While this is informative, it does not provide insight into the neural control strategy used by the nervous system to generate the walking pattern.

Summary: Given that few studies have examined walking control and function within the context of recovered, pre-morbid strategies, it is not clear how individuals with ISCI control walking and respond to interventions targeting recovery. Identification of mechanisms associated with walking control and recovery is necessary to explore the benefits and limitations of rehabilitation interventions and to provide a foundation for the development of new treatment strategies to enhance walking recovery. The following section will discuss neuromuscular control of natural movements and locomotion within a modular control framework. This framework is founded on basic and translational investigations of motor control (d'Avella et al. 2003; Poppele and Bosco 2003) and has recently been applied to the study of human locomotion (Clark et al. 2010). Furthermore, studies of human locomotion have explored modular control in association with biomechanical control of walking subtasks (Clark et al. 2010; Ivanenko et al. 2007; Neptune et al. 2009). Therefore this framework may be useful in identifying mechanisms associated with walking recovery and control of specific biomechanical functions.

2.7. Modular Control of Movement and Locomotion

2.7.1. Introduction to Modular Control

Neural control of locomotion requires the coordination of numerous neural commands and sensory inputs to control muscle activation across articulated limbs with multiple degrees of freedom. Studies of vertebrate locomotion and other natural behaviors indicate that the nervous system may simplify control using a modular-control framework (Bizzi et al. 1991, 2000, 2008; Giszter et al. 1993). A modular-control framework proposes that high-dimensional neuromuscular parameters involved in complex tasks are reduced or simplified to produce low-dimensional task-specific

behaviors (Ting 2007). This framework suggests that a limited set of muscle activation patterns or muscle synergies (which reflect the motor output from a module), controlled by an equally limited set of neural commands may be combined in various time and space dimensions to produce a wide array of behaviors (d'Avella et al. 2003).

Across animal and human models, modules have been consistently identified using a variety of computational approaches applied to numerous electromyogram (EMG) recordings (Ivanenko et al. 2005; Tresch et al. 2006). Furthermore, modules have been shown to be relatively consistent in their muscle composition (Clark et al. 2010; Torres-Oviedo and Ting, 2007) and timing of activation (Clark et al. 2010; Ivanenko et al. 2003, 2005). Moreover, studies of modular control suggest that the discrete activation of a module may be associated with specific biomechanical functions associated with task performance (Clark et al. 2010; Davis and Vaughan 1993; Neptune et al. 2009; Ting and Macpherson 2005). During walking in healthy adults, a set of 4-5 modules control and coordinate lower extremity movements (Clark et al. 2010; Davis and Vaughan 1993; Ivanenko et al. 2004). Each module is activated in association with biomechanical subtasks required for coordinated walking control. For instance, during late stance, the gastrocnemius and soleus muscles are co-active to support the body and propel it forward (Clark et al. 2010; Neptune et al. 2009).

Studies of vertebrate and human locomotion suggest that a modular-control framework is useful for examining neuromuscular as well as biomechanical control of locomotor behaviors. Furthermore, because modularity reflects the control scheme of the nervous system, this may be a useful framework to examine the effects of neurologic injury on locomotor control and recovery. For instance, a recent

investigation identified that the discrete activation of modules is compromised in the hemiparetic lower extremity of individuals post-stroke (Clark et al. 2010). Analysis of patterned muscle activity during walking identified fewer modules in the paretic limb compared to the non-paretic limb and the lower extremities of healthy individuals. Modular control was compromised as evidenced by merged or co-active modules which was associated with greater walking impairment. Moreover, following an intense locomotor training program, individuals post-stroke demonstrated greater walking recovery as evidenced by discrete activation of merged modules which correlated with increased gait speed and improved biomechanical characteristics of their walking pattern (Clark et al. 2009). While this investigation focused on individuals post-stroke, it is the culmination of basic and translational studies in the neural and biomechanical control of walking and therefore provides a foundation for investigating the effects of neurologic injury, such as SCI, on walking control.

The following sections will review basic science and translational investigations of modular control. Early studies in the frog model will be discussed to explain the scientific rationale for this neural control scheme. Studies of posture control in the cat and human also will be discussed. Finally, translational investigations in human locomotion will be discussed and will demonstrate the application of this neural control framework to the study of human movement.

2.7.2. Basic Science Provides a Foundation for Modular Control

Modular organization was initially studied in spinal frogs where the muscle forces evoked by spinal stimulation were mapped based on repeated stimulation to the same spinal cord location as the hind limb was moved in different positions (Bizzi et al. 1991). A map of position-dependent forces based on activation of the limb muscles was

described as a ‘force-field’ (Bizzi et al. 1991). Stimulation to different cord regions produced only a few varying force-fields and provided initial evidence that the spinal cord produces a limited set of muscle activation patterns. Giszter et al. (1993) performed experiments that verified that the force fields were not due to direct motor neuron activation or stimulation of sensory afferents. Furthermore, this work supported the concept of ‘movement’ or motor primitives as a basic element of motor behavior (Giszter et al. 1993). This theory suggested that specific muscle synergies, or co-activation of a set of muscles, produce primitive motor movements. Moreover, the synergistic activation and primitive movements were elicited without descending or afferent influences (Giszter et al. 1993).

To further examine the patterns of muscle activity, a computational approach was applied to the study of spinal modules in the frog (Tresch et al. 1999). Tresch et al. (1999) examined the patterns of muscle activation evoked by cutaneous stimulation in spinal frogs. Muscle activation patterns in response to the stimulation were evaluated using non-negative matrix factorization. This analysis revealed that a wide range of motor responses could be explained by a small set of muscle synergies and that the weighted combination of a limited set of muscle synergies could produce varied motor responses (Tresch et al. 1999). This study provided quantitative evidence of modular spinal control to activate specific, functionally related muscle synergies. The limited set of spinal commands (as evoked by stimulation) controlled the equally limited set of synergies to produce a broad repertoire of movements in the frog.

The computational algorithm (non-negative matrix factorization) applied by Tresch et al. (1999) extracts muscle synergies, or patterns of synchronous muscle activity, from

recorded electromyographical (EMG) data. An iterative mathematical process selects non-negative weighting coefficients for the set of extracted synergies and compares the reconstructed (extracted) data to the recorded EMG. The process is repeated until the error between the observed response and reconstructed response is minimized (Bizzi et al. 2008; Lee and Seung 1999; Tresch et al. 1999). d'Avella and colleagues (d'Avella et al. 2003; d'Avella and Bizzi 2005) used this computational method to explore natural motor behaviors, including kicking, jumping, and swimming in intact frogs. Moreover, they extended their computational approach to evaluate both synchronous and time-varying muscle synergy patterns. A limited set of muscle synergies adequately explained a variety of natural motor behaviors in the intact frog. Thus, across a wide variety of motor behaviors, the recorded activity in 13 hindlimb muscles of each frog could be accounted for by three to eight patterns of muscle activity that occurred either synchronously or in a specific time sequence, defined by a single timing coefficient (d'Avella et al. 2003; d'Avella and Bizzi 2005). This work extended the framework of modular control to natural behaviors under spinal and supraspinal control. Thus, this was evidence that more complex commands are organized to control a limited set of synergistic muscle patterns in intact animals engaged in wide ranging locomotor behaviors.

2.7.3. Afferent and Supraspinal Inputs to Modular Control Mechanisms

Basic science studies of frog behavior also have examined the roles of sensory feedback and supraspinal input in modular control of locomotor behaviors (Cheung et al. 2005; Drew et al. 2008; Hart and Giszter 2004). An analysis of muscle synergies in the frog before and after deafferentation demonstrated that hindlimb muscle activation during swimming and jumping behaviors could be explained by the same set of

synergies, suggesting that the behaviors were largely controlled by spinal or supraspinal mechanisms. Sensory information played a role in modulating the motor output and influenced the pattern of muscle activity. The authors reported that sensory information often caused pairs of synergies to couple or uncouple centrally organized synergies (i.e. two distinct synergies merged into a single synergy after deafferentation) (Cheung et al. 2005).

Supraspinal input from the cortex and brain stem also influences activation of modules (Drew et al. 2008; Hart and Giszter 2004). A study of motor behavior in spinal and medulopontine frogs compared the composition and temporal bursting in hindlimb muscles in the two frog preparations. Six synergistic patterns of muscle activity accounted for greater than 80% of the motor behaviors in the spinal and brainstem frogs. Greater co-activation was observed in the muscle patterns of the spinal frogs, suggesting that brainstem signals modulate modular motor output (Hart and Giszter 2004).

Recently, Drew and colleagues (2008) explored how the motor cortex might influence the activation of muscle synergies during cat locomotion. Cortical signals during visually guided movements are theorized to modify the magnitude and phase of the base locomotor pattern. Previous work by his lab suggests that there are specific subpopulations of pyramidal tract neurons that interact with spinal circuits to influence the locomotor pattern. Thus, these subpopulations may preferentially interact with specific spinal networks to influence specific locomotor synergies. During steady-state walking the influence of these commands might simply alter the magnitude and time of

activation of locomotor synergies. Whereas, more complex gait modifications might require that the composition of the synergies be adapted to the task (Drew et al. 2008).

2.7.4. Modular Control of Posture and Locomotion

As the scientific underpinnings of modular control have been established, this framework has been extended to the study of posture control (Ting 2007; Ting and Macpherson 2005; Torres-Oviedo and Ting 2007) and locomotion (Clark et al. 2010; Ivanenko et al. 2003, 2004, 2005, 2007; McGowan et al. 2010; Neptune et al. 2009). These studies have applied a variety of computational approaches, such as non-negative matrix factorization (NNMF) and principal components analysis (PCA), to examine patterns of muscle activation across numerous EMGs. Varied computational approaches have yielded consistent results (Ivanenko et al. 2005; Tresch et al. 2006). Along with varied computational approaches, differing terminology has been used to characterize the neural control scheme (modular control) and patterns of muscle activity (referred to as synergies, muscle activation patterns, modules), which are identified using various mathematical algorithms (referred to modules, factors, components). Despite these variations, results have provided increasing support for this dimensional reduction framework as well as the association between neuromuscular output and biomechanical control.

Posture Control: Ting and colleagues applied this dimensional reduction framework (high dimensional sensorimotor information reduced to low dimensional task-level control) to the study of the muscle coordination during postural responses (Ting 2007; Ting and Macpherson 2005). Initial investigations of postural responses in cats demonstrated that four muscle synergies explained greater than 95% of the muscle activation used during postural responses in 16 directions in 8-15 hindlimb muscles in

the intact cat. Furthermore, the synergies were correlated with the activation of individual basis force vectors, measured by the ground reaction forces as the cats responded to the perturbations. The authors suggested that this correlation may reflect that the muscle synergy, and thus, the neural command, was directed to specify the force of the limb in response to the postural perturbation (Ting and Macpherson 2005).

This approach was subsequently applied to the study of muscle synergies and modular control during human postural responses (Torres-Oviedo and Ting 2007). Humans use small amplitude, quickly activated ankle strategies as well as large hip and trunk motions, producing a wide array of postural responses. Torres-Oviedo and Ting (2007) applied NNMF to EMG data recorded in 16 leg and back muscles in 9 healthy subjects. Across all subjects, a few basic muscle synergies with consistent patterns of muscle activity were identified, suggesting that a general neural strategy was used to coordinate muscle activity during postural responses within and across individuals (Torres-Oviedo and Ting 2007).

The work of Ting and colleagues (Ting 2007; Ting and Macpherson 2005; Torres-Oviedo and Ting 2007) extended the foundation of modular control of complex, functional behaviors. Their studies applied a NNMF algorithm to identify co-active muscle synergies for postural control in the cat and human. Furthermore, these investigations identified relatively consistent patterns of muscle activation as well as associations between muscles synergies and biomechanical task control functions. The association between task biomechanics and modular control is a focus of the studies in human locomotor control.

Control of Locomotion: The study of modular control during human locomotion has produced a variety of findings. Ivanenko and colleagues suggest that the neuromuscular system may simplify control by specifying 'complex muscle synergies' to control for specific kinematic task variables during locomotion (Ivanenko et al. 2003, 2004, 2005, 2007) and has emphasized the consistent timing of module activation. In contrast to the notion that the nervous system activates complex muscle synergies, recent studies of human locomotion in healthy adults (Clark et al. 2010), individuals post-stroke (Bowden et al. 2009; Clark et al. 2010), and using computer simulations (McGowan et al. 2010; Neptune et al. 2009) suggest that the nervous system may rely on a set of relatively consistent muscle synergies or modules that are activated in association with biomechanical subtasks and adapted to meet altered mechanical demands during walking. Across studies, however, support is provided for the association between modular control and biomechanical task-level control.

Ivanenko and colleagues (2003, 2004) examined modular control associated with temporal and kinematic task variables by studying the effects of limb loading and gait speed on the pattern of muscle activity in healthy individuals (Ivanenko et al. 2003, 2004). Although the patterns of muscle activity varied with walking speed and level of lower extremity loading during treadmill walking, five basic temporal patterns were identified using principal components analysis (PCA). PCA is a computational technique, similar to non-negative matrix factorization, used to determine if the variability in the recorded EMG can be explained by a small set of basic components. Temporal patterns were consistent across subjects, shifting based on walking speed, but remained robust during unloading, suggesting that the neuromuscular control

variables are specified based on limb kinematics during locomotion (Ivanenko et al. 2004).

The temporal activation of complex, patterned muscle activity also remained consistent when voluntary tasks are combined with walking (Ivanenko et al. 2005). The basic temporal features of the muscle activation during walking were preserved, and the motor activity associated with the voluntary task (i.e. ball kick, obstacle negotiation, right/ left stoop) was either synchronous with muscle activation during walking, or was added as an additional temporal component (Ivanenko et al. 2005). Thus, the basic activation patterns for locomotion were preserved with the addition of a voluntary gait task. These results suggest that the motor program for the voluntary task was superimposed onto the locomotor program and did not alter its basic activation (Ivanenko et al. 2005).

Based on the notion that modular control is specified based on limb kinematics, Ivanenko and colleagues (2007) investigated a range of locomotor behaviors including running and hopping and applied PCA to examine whole limb kinematics. Two components of limb motion during locomotion, limb length and limb orientation, accounted for endpoint movement across the locomotor tasks. These results supported the researchers' view of modular control and suggest that the nervous system may control specific kinematic variables and modulate muscle patterns to meet these kinematic demands (Ivanenko et al. 2007).

2.7.5. Neurologic Injury Affects Modular Control Mechanisms

Introduction: As researchers have replicated and confirmed the evidence for a modular control strategy for varied natural behaviors, investigators are now applying this framework to examine the effect of neurologic injury such as SCI and stroke (Clark et al.

2010; Ivanenko et al. 2003). Study of modular control has lead to insight regarding how cortical or spinal cord lesions may affect the complexity of motor control and possible compensation strategies adopted by the nervous system to meet task-specific demands. Furthermore, researchers have applied this framework to better understand the effect of a locomotor intervention on neuromuscular and biomechanical control of walking (Clark et al. 2010; Ivanenko et al. 2003).

The effect of ISCI on modular control mechanisms: To investigate modular spinal control mechanisms, Ivanenko et al. (2003) studied locomotor control in uninjured persons and individuals with SCI. Individuals with complete and incomplete SCI (based on assessment after acute injury) were trained to step on a treadmill with partial body weight support and manual assistance. Training was initiated one to six months after injury and the authors reported that all participants could take independent steps during the final evaluation of walking. Kinematic and EMG data recorded in over 20 muscles were collected during walking at various speeds. Across all subjects, consistent activation of 5 temporal components, comprised of complex muscle synergies, was identified using PCA. Temporal activation had the strongest correlation with foot motion during stepping. Persons with SCI recovered the ability to step (with partial body weight support), but their patterns of muscle activity remained varied across individuals and distinct from healthy individuals. Ivanenko et al. (2003) concluded that the subjects with SCI demonstrated 'motor equivalence' based on their stepping recovery (foot trajectory) through altered or compensatory motor patterns. Furthermore, because the muscle activity across the limb and trunk muscles within all of the subjects had a similar temporal component, and because this activity was recorded in muscles below the

lesion level in persons with complete SCI, the results suggested that the temporal components were related to activity of the spinal pattern generators (Ivanenko et al. 2003).

The effect of stroke on modular control mechanisms: Clark and colleagues (2010) recently examined modular control mechanisms used during walking in healthy individuals and individuals post-stroke. NNMF was applied to EMGs recorded in 8 bilateral lower extremity muscles to examine the composition and number of modules required to explain greater than 90% of the variability in the EMG data. Compared to healthy individuals who activated 4 modules to control locomotion as well as the non-paretic limb, fewer modules (muscle synergies) were used in the hemiparetic limbs of individuals post-stroke. The number of modules identified in the hemiparetic limb was associated with walking speed and stepping symmetry. Use of fewer modules reflected a less complex motor pattern and was explained by merging of modules. Merged modules suggested that individuals post-stroke relied on the same fundamental modular organization to control locomotion, but that discrete activation of modules was impaired. The composition and timing of independent modules across all subjects was consistent and was associated with biomechanical subtasks associated with walking control. These findings corroborate results from basic science investigations that indicate that supraspinal commands influence the discrete activation of modules (Hart and Giszter 2004).

Modular control was examined in a sub-set of Clark's subjects (n=15) to investigate the underlying mechanisms associated with walking recovery (Clark et al. 2009). These subjects participated in a locomotor training program, incorporating

training on the treadmill and overground. As described above, the complexity of locomotor control in the hemiparetic leg was reduced prior to LT and in comparison to control subjects, as evidenced by fewer independent modules. Following LT, increased motor complexity was observed based on a greater number of modules in the hemiparetic limb in 40% of the subjects. Modules that were previously merged or co-activated gained discrete activation which was associated with greater walking recovery (Clark et al. 2009).

While Ivanenko and colleagues (2003, 2004) identified 5 basic activation patterns underlying locomotion, these patterns, representative of modular control, were consistent based on their temporal distribution across the gait cycle, but were less consistent with respect to their composition of muscle activation. In contrast, Clark et al. (2010) identified 4 patterns of muscle activation (modules) that were not only consistently active during the gait cycle, but also were relatively consistent in the composition of muscles within each module. The number of modules necessary to control locomotion (4 versus 5) may be influenced by the number and distribution of EMGs included in the analysis. For instance, Ivanenko (2003, 2004) studied muscle activation in up to 20 EMGs recorded from trunk and lower extremity muscles while Clark et al. (2010) investigated 8 muscles in each leg. The findings from Clark et al. (2010) are supported by previous studies of postural control which identified consistent muscle activation in association with biomechanical task demands (Torres-Oviedo and Ting 2007). Although modular activation across individuals has repeatable characteristics, muscle activation is expected based on individual gait characteristics and motor experiences.

2.7.6. Modular Control Associated with Consistent Timing of Muscle Activation and Biomechanical Control Functions during Walking

Clark and colleagues (2010) provide a useful model for investigating walking control in healthy individuals and persons with neurologic injury. Each of the 4 modules identified in healthy individuals was active during a particular region of the gait cycle and had consistent characteristics. For instance, module 1 was active primarily during early stance and consisted primarily of extensor activation from the gluteus maximus and the vastus medialis muscles. Module 2 was active during late stance and consisted primarily of ankle plantar flexor muscle activation (soleus and medial gastrocnemius). The third module was active during early stance and early swing and included activation of the tibialis anterior and rectus femoris muscles. Module 4 consisted primarily of hamstring activation and was active during late swing and early stance. Based on the timing of each module and the patterns of muscle activity, each module was active in association with biomechanical subtasks required for coordinated walking control (Clark et al. 2010).

Based on the timing of module activation, which is consistent with biomechanical subtasks of walking [such as body support during early stance (module 1), forward propulsion during late stance (module 2), ground clearance during swing (module 3), and deceleration of the limb during late swing (module 4)], a modular control strategy may represent the functional transformation of sensorimotor signals to meet biomechanical task demands (Poppele and Bosco 2003; Ting and Macpherson 2005). To further test this association, Neptune et al. (2009) used a muscle-actuated forward dynamics simulation of normal walking to assess the contribution of each module to biomechanical walking sub-tasks (Neptune et al. 2009). Findings were consistent with

previous studies of modular locomotor control and provide further evidence for modular organization of neuromuscular control to produce task-specific biomechanical functions (Neptune et al. 2009).

2.7.7. Biomechanical Functions Associated with Modular Control

Introduction: Because a modular control framework represents the nervous system's control strategy to perform complex motor tasks such as walking, this model may be useful in understanding the effect of neurologic injury on walking control and mechanisms associated with recovery and response to interventions targeting recovery. Indeed, recent investigations have applied this framework to examine the effect of stroke and SCI on walking control and have provided initial findings upon which future work can develop from. Furthermore, modular motor output is specified in association with specific biomechanical functions associated with coordinated walking. This suggests that examination of biomechanical control is not only critical, but that modular and biomechanical control variables should be studied in parallel. The following section will discuss key biomechanical functions that may be informative relative to the study of modular control of walking in individuals with SCI.

Propulsion: Forward propulsion of the body's center of mass during stance is a primary sub-task of walking and is associated with appropriate anterior-posterior ground reaction forces (Neptune et al. 2003). The ankle plantar flexors, active during late stance, have been shown to be significant contributors to forward propulsion (Neptune et al. 2001). Recent studies of modular control also have identified co-activation of the ankle plantarflexors (module 2) in association with modular activation (module 2) at this time in the gait cycle (Clark et al. 2010; Neptune et al. 2009). Furthermore, propulsion and propulsion symmetry have been associated with changes in gait speed and walking

function, both in persons with SCI (Gregory et al. 2007) and individuals post-stroke (Bowden et al. 2006; Balasubramanian et al. 2007).

Several factors, however, affect propulsion generation, such as step kinematics and muscle coordination. Because changes in muscle activation following neurologic injury can further affect propulsion, a recent study examined underlying mechanisms associated with propulsion generation in controls and individuals post-stroke (Peterson et al. 2010). Leg extension, as determined from measures of the leg angle (angle between the line from the pelvis center of mass to the foot center of mass and vertical), was determined to be a predictor of leg propulsion in control subjects and in both lower extremities in individuals post-stroke. The association between leg extension and propulsion may reflect the importance of adequate hip and knee extension during late stance (Peterson et al. 2010). Moreover, because of the importance of appropriate limb kinematics (i.e. hip extension) in walking control in individuals with SCI, leg extension also may be an important underlying mechanism for walking control post SCI.

Hip joint extension: Based on animal and translational studies, afferent input associated with adequate hip extension during terminal stance is necessary for the successful transition from stance to swing (Andersson and Grillner 1983; Calancie et al. 1994; Grillner and Rossignol 1978). This afferent input from the hip joint is critical for generating effective limb flexion at the onset of swing. Individuals with SCI often walk with a flexed posture and do not achieve adequate hip extension. This lack of hip extension may further impair muscle activation and walking function. Furthermore, in a study of high functioning individuals with ISCI, increased hip extension in terminal

stance was associated with increased gait speed following a targeted intervention (Gregory et al. 2007).

Foot trajectory: A primary goal and sub-task during swing is to clear the foot and advance the leg forward in preparation to accept the body weight as the center of mass progresses forward. Clearance of the foot during swing depends on flexion of the hip and dorsiflexion of the ankle to clear the forefoot and toes. The position of the foot during swing also has been proposed to be a control feature of walking, such that individuals post SCI may control walking by prioritizing the foot position or trajectory during swing (Ivanenko et al. 2003). Foot trajectory during swing may be an informative biomechanical measure reflecting control of this subtask. Moreover, modular control studies indicate that the hip flexors and ankle dorsiflexors are co-activated in a module during swing (Neptune et al. 2009). Thus, it may be informative to understand how control of biomechanical functions such as ground clearance during swing is related to activation of motor modules at this time in the gait cycle. Knowledge of biomechanical and neuromuscular control strategies and their associations may provide valuable insights into control of walking following SCI.

2.8. Literature Review Conclusion

Spinal cord injury (SCI) impairs the neuromuscular control of walking resulting in functional limitations and activity restrictions that lead to severe secondary complications and reduced quality of life. These effects are devastating and most severe in children with SCI. Regaining walking function is a primary goal of individuals with incomplete SCI (ISCI) and a focus of rehabilitation for individuals with incomplete injuries. Based on evidence of activity dependent plasticity and the neurobiology of locomotion, a paradigm shift has emerged and is ongoing for rehabilitation of walking for

adults with ISCI. Rehabilitation of walking for individuals with ISCI now includes therapies that aim to promote walking recovery rather than reliance on compensatory devices and braces. Locomotor training (LT) is a rehabilitation intervention that focuses on walking recovery after ISCI. LT is based on basic and translational evidence of activity dependent plasticity and the role of task-specific afferent input to enhance activation of spinal networks below the level of the spinal cord lesion. Although rehabilitation of walking for individuals with ISCI now includes interventions that target walking recovery and LT has demonstrated beneficial effects in children and adults with ISCI, the mechanisms associated with locomotor control and recovery are not well-understood. Evidence of locomotor control mechanisms and mechanisms associated with walking recovery and response to interventions is necessary to advance rehabilitation of walking and locomotor recovery for individuals with SCI.

The following chapters will describe three experiments for the examination of neuromuscular control of walking and locomotion in adults and children with ISCI. Experiments 1 and 2 examine underlying neuromuscular control mechanisms associated with walking and other locomotor tasks in children with ISCI. Experiment 3 examines neuromuscular and biomechanical control mechanisms associated with walking recovery in adults with ISCI as well as control mechanisms responsive to locomotor training.

CHAPTER 3
NEUROMUSCULAR CONTROL ACROSS LOCOMOTOR TASKS IN CHILDREN WITH INCOMPLETE SPINAL CORD INJURY

3.1. Background

Identification of neural control mechanisms is fundamental to the development of rehabilitation strategies targeting locomotor recovery after neurologic injury. Locomotion, however, is complex and requires coordination of multi-articular limbs and numerous muscles. Therefore, although the prevalence of walking impairment following neurologic injury is well documented (Barbeau et al. 1999; Gresham et al. 1975; Sturt et al. 2009) the underlying neural mechanisms associated with walking impairment have not been elucidated (Clark et al. 2010; Courtine et al. 2009; Mulroy et al. 2010; Wirz et al. 2005).

Across species, a wide variety of locomotor behaviors are controlled by oscillatory neural networks or central pattern generators (CPGs) located in the spinal cord (Grillner 1979; Grillner and Zangger 1975; Marder and Bucher 2001; Rossignol 2006; Grillner et al. 2008). Evidence supports the role of CPGs in controlling human locomotion as well (Calancie et al. 1994; Dimitrijevic et al. 1998; Dobkin et al. 1995; Nadeau et al. 2009). Furthermore, overlapping or redundant neural networks may control a variety of locomotor behaviors and rhythmic limb movements (Berkowitz 2008; Earhart and Stein 2000; Forssberg et al. 1980; Mortin and Stein 1989). For instance, shared circuitry controls stepping, swimming, and scratching in the turtle (Berkowitz 2008; Earhart and Stein 2000) and stepping and galloping in the spinal kitten (Forssberg et al. 1980). Moreover, studies of human quadrupedal control and interlimb coordination also support shared circuitry across varied locomotor tasks (Patrick et al. 2008; Wannier et al. 2001; Zehr 2005, 2007).

The complexity of controlling an extensive repertoire of motor behaviors may be simplified by the nervous system using motor primitives or a modular control framework (Bizzi et al. 2008; Hart and Giszter 2010; Ivanenko et al. 2004, 2005; Mussa-Ivaldi et al. 1994; Ting 2007; Ting and Macpherson 2005; Tresch et al.1999). This dimensional-reduction framework suggests that the control of complex tasks is reduced to a limited set of neural commands that activate an equally limited set of functional muscle synergies (Bizzi et al. 1991, 2000, 2008; Ting and Macpherson 2005; Tresch et al. 1999). A module is a functional unit of the spinal cord which specifies patterns of task-dependent motor activity (Bizzi et al. 2008). While recent evidence in the spinal frog indicates that sets of spinal interneurons form the basis of motor primitives and modular output (Hart and Giszter 2010), motor output also is dependent upon task biomechanics (Clark et al. 2010; Ivanenko et al. 2003; McGowan et al. 2010; Neptune et al. 2009; Ting and Macpherson 2005) sensory feedback (Cheung et al. 2005) and supraspinal inputs (Drew et al. 2008; Kozlov et al. 2009). Thus, a module also has been characterized as the functional transformation between sensory and motor signals and biomechanical output (Clark et al. 2010).

Computational algorithms have been used to identify motor modules or patterns of muscle activity across multiple electromyograms (EMGs) recorded during frog limb movements (Hart and Giszter 2010; Tresch et al. 1999), postural control tasks in cats (Ting and Macpherson 2005), and human locomotion (Ivanenko et al. 2004, 2005; Clark et al. 2010). Computational methods are particularly useful in studies of human locomotion where invasive approaches are not feasible. Clark et al. (2010) applied non-negative matrix factorization (NNMF) to identify a set of four motor modules that

accounted for muscle activity recorded across eight channels of lower extremity (LE) EMG in healthy adults. Modular control was consistent across subjects and the timing of peak activation of each module coincided with specific biomechanical requirements during gait. Similarly, Ivanenko et al. (2004) recorded muscle activity from 12-16 trunk and LE muscles and used principal components analysis to identify five basic muscle activation patterns associated with gait kinematics in healthy adults.

Computational approaches also have been applied to the study of neural control mechanisms used *across* locomotor tasks in healthy adults (Stoloff et al. 2007; Zehr et al. 2007). Analyses of muscle activation patterns across upper and lower extremities indicate that walking and recumbent stepping rely on common neural networks (Stoloff et al. 2007). Additionally, Zehr et al. (2007) reported that walking, arm and leg cycling and arm-assisted stepping also rely on similar muscle activation patterns (synergies) suggesting common neural control mechanisms.

Researchers examining the effect of neurologic injury on modular control of walking have identified associations between modular control and gait impairment. A reduced number of motor modules is associated with decreased gait speed (Bowden et al. 2010; Clark et al. 2010) and poor biomechanical control of walking (Clark et al. 2010) in individuals post-stroke. Furthermore, locomotor training (LT), a rehabilitation intervention that optimizes task-specific afferent input to activate CPGs and provides repetitive practice of rhythmic limb movements (Edgerton et al. 2004), may enhance walking function and improve modular control (Clark et al. 2009).

If the underlying neural control mechanisms are similar for the control of varied locomotor tasks then LT may affect the control of other locomotor behaviors.

Preliminary evidence to support this emerged in our recent report on a child with severe incomplete spinal cord injury (ISCI) who completed 76 sessions of LT and recovered reciprocal flexion and extension leg movements enabling independent ambulation with a reverse rolling walker (Behrman et al. 2008). Following LT, this child used similar movement patterns to perform other rhythmic, reciprocal tasks such as crawling, stair climbing, and tricycle pedaling. The child could not perform these skills after his ISCI and did not practice them; they emerged following his participation in LT and development of reciprocal stepping (Fox et al. 2010). Based on developing evidence of spinal control mechanisms used to control a variety of locomotor tasks, this observation may suggest that children use similar neural control mechanisms across rhythmic, reciprocal locomotor tasks and that these shared mechanisms may be preserved or restored after ISCI.

The purpose of this study was to examine neuromuscular control of rhythmic, reciprocal locomotor tasks (treadmill stepping, overground walking, stair climbing, tricycle pedaling, crawling, and supine LE flexion and extension) in children with intact nervous systems (controls) and children with ISCI. The primary hypotheses were that 1) compared to controls, children with ISCI would use fewer modules to control locomotor tasks. Reliance on fewer modules may be indicative of reduced complexity of neuromuscular control following SCI and also may suggest an inability to discretely activate modules. Although ISCI was expected to alter the modular control of locomotion, based on the preserved spinal networks below the level of the injury, an additional hypothesis was that 2) for each child (controls and with ISCI) their pattern of muscle activation would be similar across varied locomotor tasks, suggesting that

neuromuscular control is similar across tasks and that redundant mechanisms are preserved after pediatric ISCI.

3.2. Methods

Participants: Five children with intact nervous systems, hence forth referred to as 'controls', and five children with ISCI, American Spinal Injury Association Impairment Scale (AIS) C, for >1 year, ages 3-13 years (Table 3-1), participated. This age range was selected based on the development of a mature gait pattern (3 years) (Sutherland 1980). All children were medically healthy and free from musculoskeletal impairment. Inclusion criteria for the children with ISCI included clinical signs of upper motor neuron injury such as ankle clonus or positive Babinski reflex to rule out lower motor neuron injuries, such as peripheral nerve damage. Medical approval for participation was obtained for all children with ISCI. Parents provided informed consent for each child's participation and each child assented to participate in this University of Florida Institutional Review Board approved study.

General Procedures: Each child with ISCI was examined according to the American Spinal Injury Association (ASIA) International Standards for Neurological and Functional Classification of Spinal Cord Injury (American Spinal Injury Association 2006). The severity of each child's injury was classified based on the ASIA Impairment Scale (AIS) and volitional LE movement was assessed using the Lower Extremity Motor Score (LEMS) (Table 3-1) (American Spinal Injury Association 2006). Lower extremity EMGs were recorded during a variety of rhythmic, reciprocal locomotor and locomotor-like tasks which included treadmill (TM) stepping, overground (OG) walking, pedaling, supine LE flexion/extension, stair climbing, and crawling (details in the following sections). Control children independently performed all tasks while children with ISCI

often required physical assistance (Table 3-1). Two to three trials of each task were performed. The trials each were 30 to 60 seconds in duration for TM stepping, pedaling, and supine flexion/extension. Overground walking and crawling occurred on a 15-foot pathway and stair climbing used 3-4 contiguous stairs. Performance details of each locomotor task are described below.

Treadmill stepping: After becoming acquainted with TM stepping, children walked on a 2.5 foot wide, standard TM surface (Figure 3-1). All children were encouraged not to hold onto the rails and to swing their arms reciprocally. Children with ISCI wore a body weight support harness (Robertson Harnesses, Henderson, NV) attached to a fixed overhead support to unweight approximately 40% of their body weight and to prevent falls. Body weight support and assistance during TM stepping were provided in accordance with locomotor training principles and therefore emphasized upright trunk posture, appropriate LE kinematics, and rhythmic stepping with weight bearing on the LEs (Behrman and Harkema 2000).

Overground walking: Controls and ambulatory children with ISCI (n=2) walked independently across a 15-foot walkway. Children with ISCI used a reverse rolling walker (Figure 3-1).

Pedaling: Pedaling was performed at a consistent, rhythmic pace on a stationary bicycle or adapted tricycle. As needed, children with ISCI were assisted to maintain a consistent pace for the duration of each trial. Children with ISCI were secured at their waist and chest for safety. Foot straps were used to prevent their feet from slipping off the pedals (Figure 3-1).

Supine LE flexion/extension: Rhythmic, reciprocal LE flexion and extension, mimicking cycling or stepping movements, was performed in a supine position. Controls were cued to perform consistent, full-range movements. Children with ISCI received physical assistance to perform full-range LE movements at a consistent pace, for several repetitions (Figure 3-1).

Stair climbing: Children with ISCI ascended 3-4 stairs without assistive devices and therefore required assistance to maintain upright balance and ensure safety. Children independently controlled reciprocal LE flexion and extension movements to negotiate the stairs (Figure 3-1).

Crawling: Crawling was performed in a standard quadruped position (Figure 3-1). Children with ISCI were cued to maintain trunk alignment and for correct limb placement.

Data acquisition: To obtain overground gait speed and identify cycles of locomotor activity, the children were instrumented with reflective markers using the modified Helen Hayes marker set (Kadaba et al. 1989). Kinematic data were acquired with an eight-camera passive motion analysis system (Vicon Motion Systems, Los Angelos, CA). Electromyographic (EMG) data were recorded during all locomotor tasks using Ag-AgCL surface electrodes placed bilaterally on LE muscles: tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM). Electrodes were placed longitudinally over the muscle belly with an inter-electrode distance of 2.0 cm. Inter-electrode distance was decreased for smaller children to minimize cross-talk (Winter et. al. 1994) and electrodes and leads were secured with tape and medical wrap to prevent mechanical

artifact. EMG data were acquired using a synchronized, telemetry system (Konigsberg Instruments, Pasadena, CA) and sampled at ≥2000 Hz using Vicon software and saved to disk for off-line analysis.

Data analysis: Data were analyzed using customized Matlab (Mathworks Inc., Natick, MA) programs. Overground gait speed was calculated based on the trajectory of a reflective marker affixed to a bony landmark on the child's trunk, e.g. C-7 spinous process. (Overground gait speed = $\Delta d / \Delta t$, where d=distance and t=time based on the trajectory of the marker ball.) Cycles of locomotor activity were determined by visual inspection of the trajectory of the reflective markers affixed to the child's LEs. To make comparisons across tasks, locomotor cycles were consistently defined as initial contact of the LE (foot or knee) to the next consecutive contact of the same limb during TM stepping, OG walking, stair climbing, and crawling. In a similar manner, cycles of pedaling and supine LE flexion/extension were defined by each revolution of the LE, starting with the initiation of extension motion of the LE to the next subsequent onset of limb extension. Thus, each LE completed cycles of locomotor activity defined by active limb extension, such as pushing downward during pedaling or weight bearing (stance) during walking, and limb flexion, such as during the swing phase of gait.

To reduce signal noise and movement artifact, and in preparation for analysis using non-negative matrix factorization (NNMF), EMG data were high-pass filtered at 30 Hz with a zero lag fourth-order Butterworth filter, demeaned, rectified, and smoothed with a zero lag fourth-order low pass, 4 Hz, Butterworth filter. To minimize the influence of large variations in muscle activation, EMG data for each muscle were normalized to the mean value for each trial. Data were re-sampled at each 1% of the activity cycle

and divided into two bins or regions based on the flexion or extension phase of locomotor activity.

Non-negative matrix factorization: For each subject and each LE, the original EMG data (EMG_o) for each trial of locomotor activity were combined into an m x t matrix where m is the number of muscles (max=six muscles) and t is the time (t=number of cycles of activity x101 (i.e. 0-100% of the activity cycle)). A non-negative matrix factorization (NNMF) algorithm (Lee and Seung 1999; Ting and Macpherson 2005) was applied to the original m x t matrix. After the number of modules (n) is specified, the NNMF algorithm reconstructs EMG_o by iteratively populating two matrices. For all trials, n was specified to reconstruct the EMG data (EMG_r) using 1 to 5 modules.

Matrix 1 X Matrix 2= EMG_r
Matrix 1= m x n (relative weighting of each muscle within each module)
Matrix 2= n x t (activation of the module across the cycle of locomotor activity)

The NNMF algorithm permits muscles to belong to more than one module, with the weighted contribution of a muscle within a module held constant across the cycle of activity. The reconstructed data, EMG_r, was compared to the original EMG data, EMG_o, by calculating the sum of the squared errors, $(EMG_o-EMG_r)^2$. The NNMF algorithm iteratively reconstructs the data (EMG_r) until the sum of the squared errors is minimized.

Determining the number of modules to reconstruct the original EMG data: For comparison, the NNMF algorithm reconstructed the EMG data using 1, 2, 3, 4, and 5 modules. To determine how well the reconstructed model (EMG_r) adequately explained the variability in the original EMG (EMG_o), the variance accounted for (VAF) was calculated.

$$VAF=1- (EMG_o - EMG_r)^2 / EMG_o^2$$

For each subject, leg, and trial of locomotor activity, the overall VAF was calculated. The VAF also was calculated for the EMG recorded from each muscle and also for each segment (flexion or extension) of the activity cycle for each trail. Calculation of the VAF across these portions of the data allowed us to verify that the data were adequately reconstructed across all muscles and regions of the original data.

To determine the minimum number of modules required to adequately reconstruct the EMG data, the reconstructed models and VAF values for 1 to 5 modules were reviewed. The fewest number of modules such that the overall VAF was ≥90% and each individual muscle VAF and region of the locomotor cycle (flexion or extension) with a VAF≥85% was identified. Thus, 9 criteria were reviewed for each subject, leg, and trial of locomotor activity (overall VAF, VAF for 6 muscles and for flexion and extension regions of each task) (Clark et al. 2010). In some instances, the overall VAF was ≥90% but the VAF values for all muscles and regions of the data were <85%. In these cases, if the addition of another module to the reconstructed model did not increase the overall VAF more than 4%, the reconstructed model was accepted (Ting and MacPherson 2005). These criteria indicate that the addition of a module did not make a significant contribution (>4%) to the reconstructed model. Across all criteria, standards were established to ensure adequate agreement between the reconstructed EMG and the original EMG recordings.

Determination of modular control used across locomotor tasks: Once the minimum number of modules required to account for the variability in the recorded EMG was identified, a second step was performed to determine the similarity of neuromuscular control used across the locomotor tasks. For each child, the

reconstructed model (number of modules and relative weighting of each muscle within the module (Matrix 1) that adequately accounted for the variance in the EMG recorded during TM walking was used to reconstruct (calculate EMGr) the EMG data from each LE and trial of locomotor activity (OG walking, pedaling, supine flexion/extension, stair climbing, and crawling) (Torres-Oviedo et al. 2006). Thus, with Matrix 1 specified (using the muscle weights extracted from the analysis of TM walking), the NNMF algorithm reconstructed the EMG data by iteratively populating Matrix 2. The number of modules (n) was constrained to the same number that was specified in Matrix 1 and the overall VAF of this module model was calculated. Therefore, this step determined what proportion of the variance in the EMG recorded during OG walking, pedaling, supine flexion/extension, stair climbing, and crawling could be explained by the selection and relative contribution of the muscles used to control TM walking (Gizzi et al. 2011; Torres-Oviedo et al. 2006).

Statistical analysis: To determine if children with ISCI use fewer modules to control locomotor tasks (Hypothesis 1), group differences (controls to ISCI groups) in the overall number of modules used across all locomotor tasks were compared using a Wilcoxon rank-sum test. Additionally, group comparisons also examined the number of modules used during each locomotor task with the Fisher's exact test. Statistical significance was established at $P<0.05$. The relative similarity of control (selection and relative contribution of each of the six muscles) used by each child across the varied tasks (Hypothesis 2) was quantitatively assessed by calculating the VAF as described in the methods in the previous section ('Determination of modular control used across locomotor tasks'). The VAF was calculated to quantify the proportion of variance

accounted for in the EMGs recorded during the other locomotor tasks when the TM modules were used to reconstruct the EMG data (Torres-Oviedo et al. 2006).

3.3. Results

Number of modules used by controls and children with ISCI: Across all locomotor tasks, an average of 3.26 modules (SD=0.65; mode=3) was required to account for muscle activation in the LEs of control children (5 children, n=10 LEs) (Table 3-2). Four modules were required 38% of the time, 3 modules 51% of the time, and 2 modules 11% of the time (Figures 3-2, 3-3, 3-5). Across the tasks, crawling had the highest module requirement (average 3.60 modules) and supine flexion/extension required the fewest modules (average 2.90 modules).

Overall, across all tasks, fewer modules were needed to account for muscle activation in the LEs of children with ISCI (5 children, n=10 LEs) (one-sided, $P<0.05$) (Table 3-2; Figure 3-4). Across all tasks, an average of 2.11 modules (SD=0.71; mode =2) was required to account for the EMG data recorded in LEs of children with ISCI. Four modules was required 5% of the time, 3 modules 17% of the time, 2 modules 64% of the time, and 1 modules was required 14% of the time (Figure 3-5). Treadmill stepping had the highest module requirement with an average of 2.80 modules required to account for the original EMG data. Supine flexion/extension required the fewest modules, requiring an average of 1.70 modules (Table 3-2).

Module composition and timing of activation: The modules exhibited by control children during OG and TM walking displayed characteristics similar to modules identified in the LEs of healthy adults (Clark et al. 2010) and to those demonstrated in simulation studies (Neptune et al. 2009). In children whose LEs required 4 modules to account for muscle activation during walking, Module C-1a, which was active during

early stance, consisted primarily of activation of the VM and GM and to a lesser extent, RF (Figure 3-2). Module C-2a consisted mainly of activation of MG and was active during late stance. Module C-3a was composed of activation of the TA and RF and was active during early swing and late swing to early stance. Module C-4a was active during late swing to early stance and consisted of activation of the MH and to a lesser extent, TA (Figure 3-2).

In the set of 3 modules identified in the LEs of control children (Figure 3-3), two of the modules had characteristics similar to the modules in 4-module set, and one module exhibited characteristics of combined module activation. Module C-1b had characteristics of module C-1a and C-2a (Figure 3-3). This was apparent based on dual peaks in the activation timing profile (peaks in early and late stance) and representation of VM and RF (generally seen in early stance, module C-1a) combined with representation from MG (active during late stance, module C-2a). Module C-2b displayed attributes of module C-3a (TA and RF activation during early to mid swing) and module C-3b exhibited properties similar to module C-4a (identified in the 4-module set) (Figure 3-3).

In contrast to the discrete timing and task specific activation observed in the control modules, the modules identified in the children with ISCI exhibited co-activation across multiple muscles and less distinct activation timing. This was most apparent in the LEs of children who required 2 modules to account for muscle activation during OG or TM walking. Co-activation across nearly all muscles except MH was evident in module SCI-1 (Figure 3-4). This module was active during stance. Distinct from the modules used by controls, this module had strong representation from antagonist

muscles, MG and TA. The second module, module SCI-2, with a single peak of activation during swing had the highest representation from MH with smaller contributions from the other muscles (Figure 3-4).

One child, SCI-6, required 4 modules to account for his pattern of muscle activation during TM stepping. This child could not step overground and could not perform isolated LE joint movements (Table 3-4). The representation of muscles within each of the 4 modules used by this child displayed characteristics similar to those used by controls. Module 1 had strong representation from VM and RF, but was active during late stance, rather than early stance. Module 2 consisted of strong representation from the MG; however, timing of the module across the gait cycle was variable. Module 3 had strong representation from the TA and was active during late stance and early swing. The fourth module for this child consisted of MH activation and the peak of activation coincided with mid-swing (Figure 3-4).

Neuromuscular control across locomotor tasks: Across both groups of children, all LEs, and all locomotor tasks, the modules [muscle combinations and weightings (Matrix 1)] used for the control of TM stepping accounted for greater than 86% (stair climbing) of the variance in the EMG recorded during the other tasks (Table 3-2). Across the tasks of OG walking, pedaling, supine flexion/extension, and crawling, greater than 90% of the variance was explained when the TM modules were applied to the reconstruction of the EMG data recorded during the other locomotor tasks. For all tasks performed by the children with ISCI, greater than 90% of the variance was explained by the treadmill modules (Table 3-2).

3.4. Discussion

For each child with ISCI and uninjured controls, the muscle activity across six LE muscles during five reciprocating locomotor tasks could be explained by a small set of motor modules, identified using NNMF to reconstruct the EMG data. The data suggest that pediatric-onset ISCI reduces the number of modules used to control varied locomotor tasks. For each child, the pattern of muscle activity in the modules used to control TM stepping explained a high proportion of the variance in the EMG data recorded during other rhythmic, locomotor tasks. This finding was robust in all children in both groups and is consistent with previous studies in animals (Earhart and Stein 2000; Forssberg et al. 1980) and healthy adults (Stoloff et al. 2007; Wannier et al. 2001; Zehr et al. 2007). Similar modular organization suggests redundancy in the neural mechanisms used to control rhythmic limb behaviors in uninjured, healthy children and that mechanisms are preserved after ISCI.

The effect of pediatric ISCI on modular control of locomotor tasks: Consistent with the first hypothesis, fewer modules were required to explain the muscle activation in the LEs of children with ISCI performing a variety of rhythmic, reciprocal locomotor tasks compared to healthy, uninjured children. Children with ISCI most often required two modules and relied on synergistic muscle co-activation across the flexion and extension phases of each task (Figure 3-4). The use of fewer modules may indicate that the modules were co-activated, rather than discretely activated. Clark et al. (2010) reported merged or co-activated modules in the hemiparetic LE of ambulatory adults post-stroke. Reliance on fewer modules or co-active modules was associated with greater walking impairment (Clark et al. 2010).

A reduced number of modules also may reflect the damage to neural control structures and therefore reduced complexity of neural control (Hart and Giszter 2004). Specifically, each task required rhythmic, reciprocal LE flexion and extension movements largely organized by spinal pattern generators located below the level of the SCI (Dietz 2003; Edgerton et al. 2004). These neural centers, presumed to be present in humans, were likely preserved or not directly damaged, based on the location of the SCI, which was above these lumbo-sacral segments in the children with ISCI (Table 3-1). Descending input to these lumbo-sacral segments, however, was likely significantly disrupted. Basic science studies indicate that supraspinal inputs modulate the muscle activation within each module and reduced descending input results in more extensive muscle co-activation (Hart and Giszter 2004). Furthermore, the reduced LE motor scores (LEMSs) of the children with ISCI suggest that corticospinal control was severely compromised. Although this study did not assess the integrity of specific spinal tracts, damage to these pathways also may account for the children's inability to balance (i.e. they required a walker or physical assistance to maintain upright) or adapt their movements outside of the flexion and extension synergic movement patterns.

In contrast to these findings in children with ISCI, control children most often required three or four modules to account for muscle activation across varied locomotor tasks. A set of 4 or 5 motor modules is required to account for muscle activation during walking in healthy adults (Clark et al. 2010; Ivanenko et al. 2004; Neptune et al. 2009). Although several control children required 3 modules to account for activation in one or both LEs during a locomotor task, this may reflect the fact that we recorded from 6 muscles bilaterally and previous studies recorded from 8 or more muscles (Neptune et

al. 2009). The activation timing profiles of the modules used by control children during TM and OG walking were highly consistent with modular activation in healthy adults (Clark et al. 2010; Ivanenko et al. 2004; Neptune et al. 2009). Each of the four modules identified in control children was active at a specific time period in the gait cycle. Moreover, the muscles represented in each module were appropriate to meet the biomechanical demands associated with that time period in the gait cycle. This suggests that the muscles were functionally grouped to meet biomechanical task demands associated with walking (Neptune et al. 2009).

Modular organization is similar across varied locomotor tasks: Consistent with the second hypothesis, and a primary outcome of this study, is the finding that across both groups, the unique pattern of muscle activation or modular organization used for TM stepping explained a high proportion (in nearly all instances ≥90%) of the muscle activation used during OG walking, pedaling, supine flexion/extension, stair climbing and crawling. This finding is consistent with studies of vertebrate locomotion in experimental models and recent work in humans (Earhart and Stein 2000; Forssberg et al. 1980; Stoloff et al. 2007; Wannier et al. 2001). Furthermore, basic science studies suggest that similarities in modular control reflect similar neural control mechanisms used across locomotor tasks (Bizzi et al. 2000; Ting and Macpherson 2005). Moreover, a ‘common core’ of oscillatory neurons has been proposed to be the source of rhythmic, reciprocal locomotor control used in bipedal and quadrupedal tasks such as pedaling, swimming, crawling, and walking (Zehr 2005). This study supports this notion, that a common core or network of neurons rhythmically activates basic flexion and extension

patterns used to perform a variety of locomotor tasks and that these mechanisms are present in healthy, uninjured children and those with severe, chronic, ISCI.

Task-specific sensory input alters modular organization: Although all of the locomotor tasks required rhythmic, reciprocal LE movements, and the data suggest that redundant neuromuscular mechanisms underlie the control of these varied tasks, the locomotor tasks also had many unique characteristics. Each task had distinctive requirements for joint kinematics, postural stabilization, limb loading, and upper extremity use. Furthermore, the tasks varied in the degree of optic flow and vestibular input. These diverse task demands and afferent inputs may account for the variations in modular control demonstrated across the locomotor tasks. For instance, supine flexion/extension had the lowest modular requirement across both groups. This task did not require trunk stabilization or LE weight bearing. Moreover, during supine flexion/extension, the hip did not move into an extended position (Figure 3-1). Limb loading (Harkema et al. 1997) and hip joint position (Dietz et al. 2002) are two critical afferent inputs that influence and modulate motor output during locomotion (Ferris et al. 2004; Maegele et al. 2002). Absence of these locomotor-specific inputs may account for the reduced number of modules required to explain muscle activation during supine flexion/extension.

The role of locomotor-specific afferent input also may explain why children with ISCI required the greatest number of modules to account for muscle activation during TM stepping. The children with ISCI were provided partial body weight support, physical assistance and cueing to perform TM stepping. Locomotor-specific afferent input pertaining to LE loading, limb kinematics, stepping speed, and reciprocal arm

movements was enhanced during TM stepping (Behrman and Harkema 2007). This ensemble of task-specific sensory inputs regulates neuromuscular activation during walking (Maegele et al. 2002) and may have contributed to the activation of additional modules and a more complex locomotor output. This was most apparent in the child, SCI-6, who exhibited very little motor activation in muscles below his injury and required 4 modules to account for muscle activation during TM stepping. This child had a LEMS of 0/50 and tests of voluntary movement indicated that he could only perform slight contractions of his hip flexor muscles and slight toe movements. During all locomotor tasks, he required nearly full assistance to complete the tasks. Based on these factors, his muscle activation during TM stepping may primarily reflect the influence of task-specific afferent input on spinal centers below his spinal cord lesion (Dietz and Harkema 2004; Harkema 2008; Maegele et al. 2002). Furthermore, given that the other children with ISCI exhibited greater co-activation and required fewer modules, this also may reflect the impact of altered (rather than nearly absent, as in SCI-6) descending input on the modular organization of muscle coordination.

In contrast to this robust sensory experience associated with TM stepping, children who walked overground relied on a reverse rolling walker, walked at slower speeds, and used alternative movement strategies which altered limb and trunk kinematics. Furthermore, use of a rolling walker partially unloaded the LEs and transferred weight from the LEs to the upper extremities. Thus, the afferent input associated with OG walking in the children with ISCI was less consistent with healthy-coordinated walking (compared to TM stepping) and likely altered or degraded the motor activation during

this task (Beres-Jones and Harkema 2004; Maegele et al. 2002; Phadke et al. 2007; Visintin and Barbeau 1994).

Methodological considerations: Modular control mechanisms were investigated in a small sample of control children and children with ISCI. The modular organization exhibited by each child with ISCI was likely influenced by numerous factors that we did not control for, including those pertaining to the child's injury (e.g. etiology, age at the time of injury), motor experiences prior to and following injury, and rehabilitation experiences (Edgerton 2004). Indeed, the children with ISCI had diverse injuries and motor experiences. For instance, two of five children were injured as infants and never developed walking prior to injury. Two children were injured secondary to traumatic accidents and a third child had an ISCI caused by a surgical resection of a spinal tumor. Of the two children who walked OG with a rolling walker, one was injured as an infant and the other had a traumatic injury at 3.5 years. Interestingly, both children recovered walking more than a year after injury (SCI-1, 16 months post injury; SCI-5, more than 5 years post injury) and following several months of LT (Behrman et al. 2008). Moreover, both children required 2 modules to account for the activation in each of their LEs (n=4 LEs, each required 2 modules) (Figure 3-4). Therefore, despite a small sample size, the diversity of injuries and motor experiences represented within the sample of children with ISCI may indicate that the findings of reduced modular control in the children with ISCI and similar muscle activation patterns used across tasks may be even more meaningful and point to the effects of injury and shared neural control mechanisms.

The outcomes from this study may be influenced by the number of EMGs that was recorded from. A greater number of EMGs would increase the specificity of outcomes

in terms of understanding neuromuscular coordination across a greater proportion of the muscles. However, because the same number of EMG recordings was conducted in the controls and children with ISCI, we would expect the relative proportion of modules between the two groups to remain the same even if the number of EMGs was increased. Moreover, it is not expected that this would change the overall finding of a reduced number of modules in children with ISCI. Recording from a greater number of muscles would perhaps enable more direct comparisons of these results with previous studies that recorded from 8 or more muscles (Clark et al. 2010; Ivanenko et al. 2004).

Clinical application: Identification of fewer modules required to account for the muscle activation across locomotor tasks in children with ISCI provides evidence of the effect of ISCI on neuromuscular control mechanisms. Identifying mechanisms associated with locomotor control is critical for the development of rehabilitation interventions designed to restore walking and locomotion after pediatric-onset ISCI. Furthermore, the use of shared neuromuscular mechanisms across varied locomotor tasks suggests that current training paradigms that activate spinal neural networks (Edgerton et al. 2004) may have benefits that extend to a variety of tasks. Locomotor training is a therapeutic intervention that aims to restore walking by optimizing afferent input to spinal networks and promoting activity-dependent plasticity (Edgerton et al. 2008). The beneficial effects of this intervention have recently been reported in 2 children with ISCI, across 3 case reports (Behrman et al. 2008; Fox et al. 2010, Prosser et al. 2007). Our prior report of a non-ambulatory child with chronic, severe ISCI who recovered reciprocal stepping, enabling independent ambulation with a rolling walker suggests that LT may be effective for activating the neuromuscular system below the

level of the lesion in children with ISCI (Behrman et al. 2008). Furthermore, this child's walking recovery was associated with recovery of other locomotor tasks such as crawling, pedaling, and stair climbing (Fox et al. 2010). Together, these reports suggest that retraining neuromuscular control of walking through repetitive, task-specific practice provided by LT may result in improved limb reciprocation for walking as well as other locomotor tasks. Although similar mechanisms for the control of rhythmic, reciprocal tasks have been reported in healthy adults (Stoloff et al. 2007; Zehr et al. 2007), future studies should assess these findings in adults with ISCI. Furthermore, investigators examining the effects of locomotor training or therapies activating the neuromuscular system below the spinal cord lesion should consider outcome measures that capture the therapeutic effects across varied locomotor tasks. These steps may lead to the refinement of current rehabilitation interventions as well as the development of adjunctive therapies that further enhance walking and locomotor recovery after SCI.

3.5. Tables and Figures

Table 3-1. Subject demographics and task participation for controls (C1-C5) and children with incomplete spinal cord injury (ISCI).

Subject	Age (yrs)	Injury level	Etiology	Age of injury (yrs)	LEMS	OG gait speed (m/s)	TM speed (m/s)	Pedal	Supine flex/ex	Stair climb	Crawl
C-1	9					0.88	0.78	X	X	---	X
C-2	6					1.21	0.78	X	X	---	X
C-3	7					2.03	0.72	X	X	---	X
C-4	13					0.81	0.72	X	X	X	X
C-5 (F)	8					0.90	0.33	X	X	X	X
Avg.	9					1.17	0.67				
SD	4					0.51	0.19				
SCI-1	9	C7	GSW	3.5	4/50	0.57	0.56	X	X	X	X
SCI-4	12	T4-T8	Tumor Rsx	8.5	0/50*	----	0.58	X	X	---	X
SCI-5	7	C4-7	Unknown*	6 mo	4/50	0.36	0.83	X	X	X	X
SCI-6	12	T10	MVA	10.5	0/50*	----	0.64	X	X	---	---
SCI-7	3	C1-T6	Tr. Myelitis	5 mo	0/50*	----	0.89	X	X	---	---
Avg.	9					0.47	0.70				
SD	3					0.15	0.15				

Notes: One female (F) participated. Ages are reported in years (yrs) or months (mo). The Lower Extremity Motor Score (LEMS) is based on voluntary isolated joint strength in five bilateral muscles. Asterisks (*) indicate an inability to perform isolated joint movements in the standardized position (American Spinal Injury Association 2006). Overground (OG) and treadmill (TM) gait speeds are reported. An 'X' indicates the child performed the task indicated (Pedaling (Pedal), supine lower extremity flexion/extension (Supine flex/ex), stair climbing (stair climb) and crawling (crawl). Dashed lines (---) indicate that the task was not performed or EMGs were not usable. Average (Avg.) and standard deviations (SD) are reported. Etiologies of the spinal cord injuries are reported as gunshot wound (GSW), unknown* and suspected cause of transverse myelitis or trauma secondary to motor vehicle accident (MVA), surgical re-section secondary to tumor (Tumor Rsx) and transverse myelitis (Tr. Myelitis)

Table 3-2. Average number of modules required to account for EMG activation in each locomotor task.

	Number of modules required to reconstruct EMG data (SD)		Overall VAF: EMG data reconstructed with treadmill module muscle weightings (SD)	
	Control children	Children with ISCI	Control children	Children with ISCI
TM step	3.40 (0.52)	2.80 (0.79)		
OG walk	3.30 (0.48)	*2.00 (0.00)	92.95 (4.29)	94.58 (0.98)
Pedaling	3.22 (0.97)	1.80 (0.63)	91.85 (4.15)	95.29 (3.35)
Supine flex/ex	2.90 (0.74)	1.70 (0.48)	92.06 (6.46)	94.93 (2.30)
Stair climb	3.00 (0.00)	2.25 (0.50)	86.57 (4.97)	90.59 (3.63)
Crawl	3.60 (0.52)	*2.25 (0.50)	91.42 (6.39)	90.66 (4.00)
AVERAGE	3.26 (0.65)	*2.11 (0.71)	91.63 (5.29)	93.88 (3.37)
Mode	3.00	2.00		

Notes: Standard deviations (SD) are indicated. Average percent of the variance accounted for (VAF) when the muscle activations for treadmill stepping were used to reconstruct the EMG data recorded during other locomotor tasks. Values are indicated for treadmill stepping (TM step) overground walking (OG walk), pedaling, supine flexion/extension (supine flex/ex), stair climbing (stair climb) and crawling (crawl). The number of modules used by children with ISCI was lower than number required by control children (*P< 0.05, one-sided) overall and for overground walking (*P<0.05) and crawling (*P<0.05).

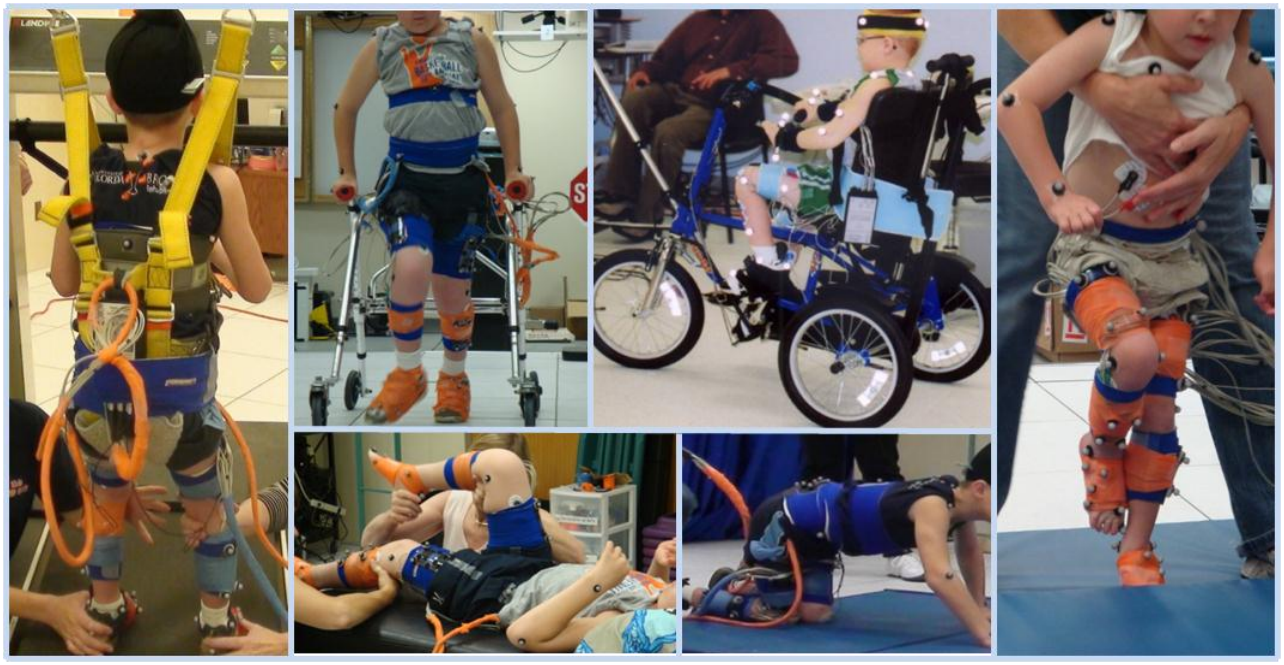

Figure 3-1. Children with incomplete spinal cord injury performing locomotor tasks: treadmill stepping, overground walking, supine flexion/extension, tricycle pedaling, crawling and stair climbing. Photos are courtesy of the author.

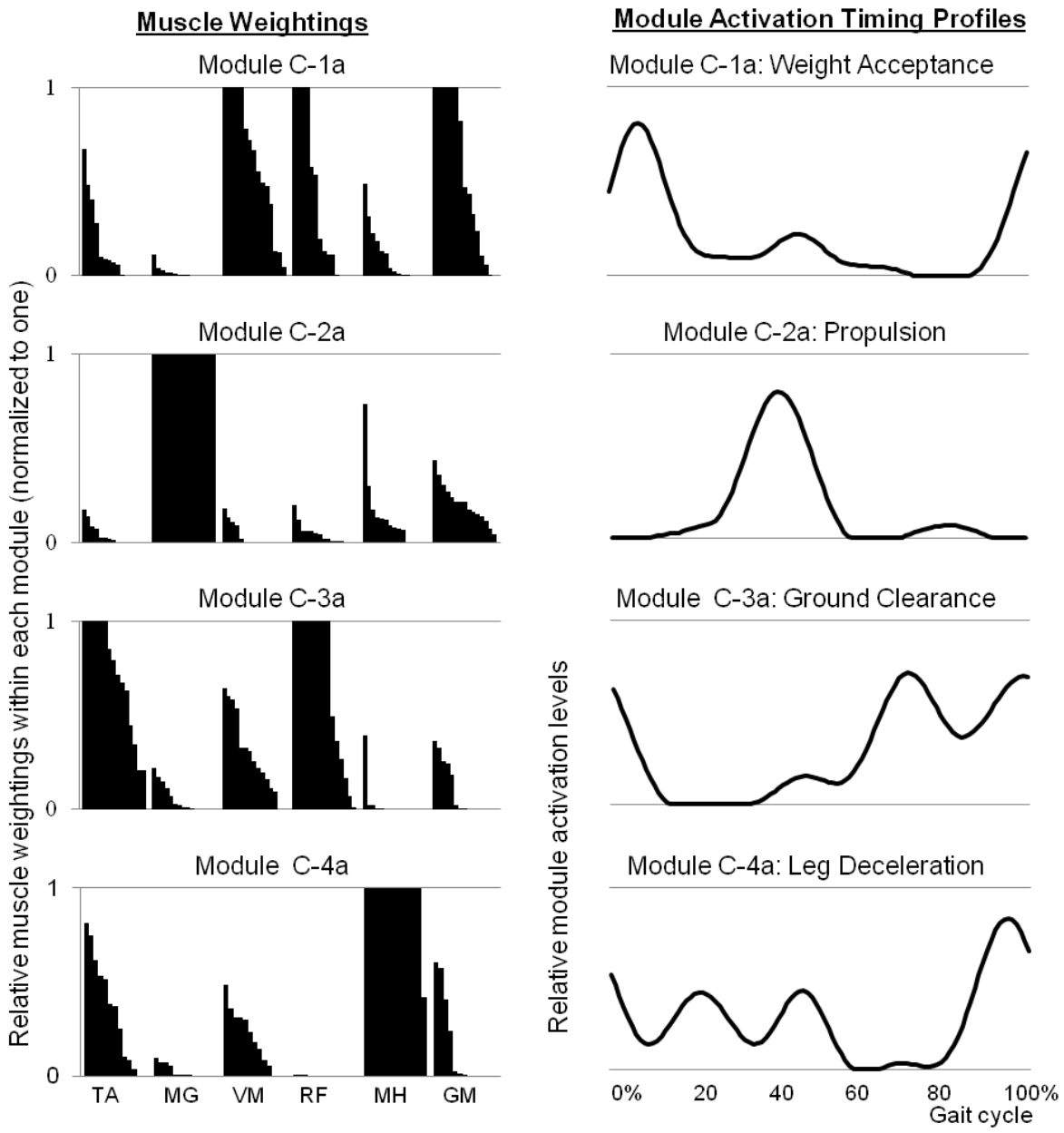

Figure 3-2. Muscle module weightings and timing profiles for overground walking in control children using 4 modules. Muscle weightings for the 10 lower extremities in the control children are shown for the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM) muscles. Black bars represent the relative activation of each muscle in the module. The weighting for the muscle with the greatest activation is set to one. Activation timing profiles indicate the relative level of activation of a module across the gait cycle (0-100%). Each module was active at a distinct time point consistent with key biomechanical demands for overground walking (Clark et al. 2010; Neptune et al. 2009).

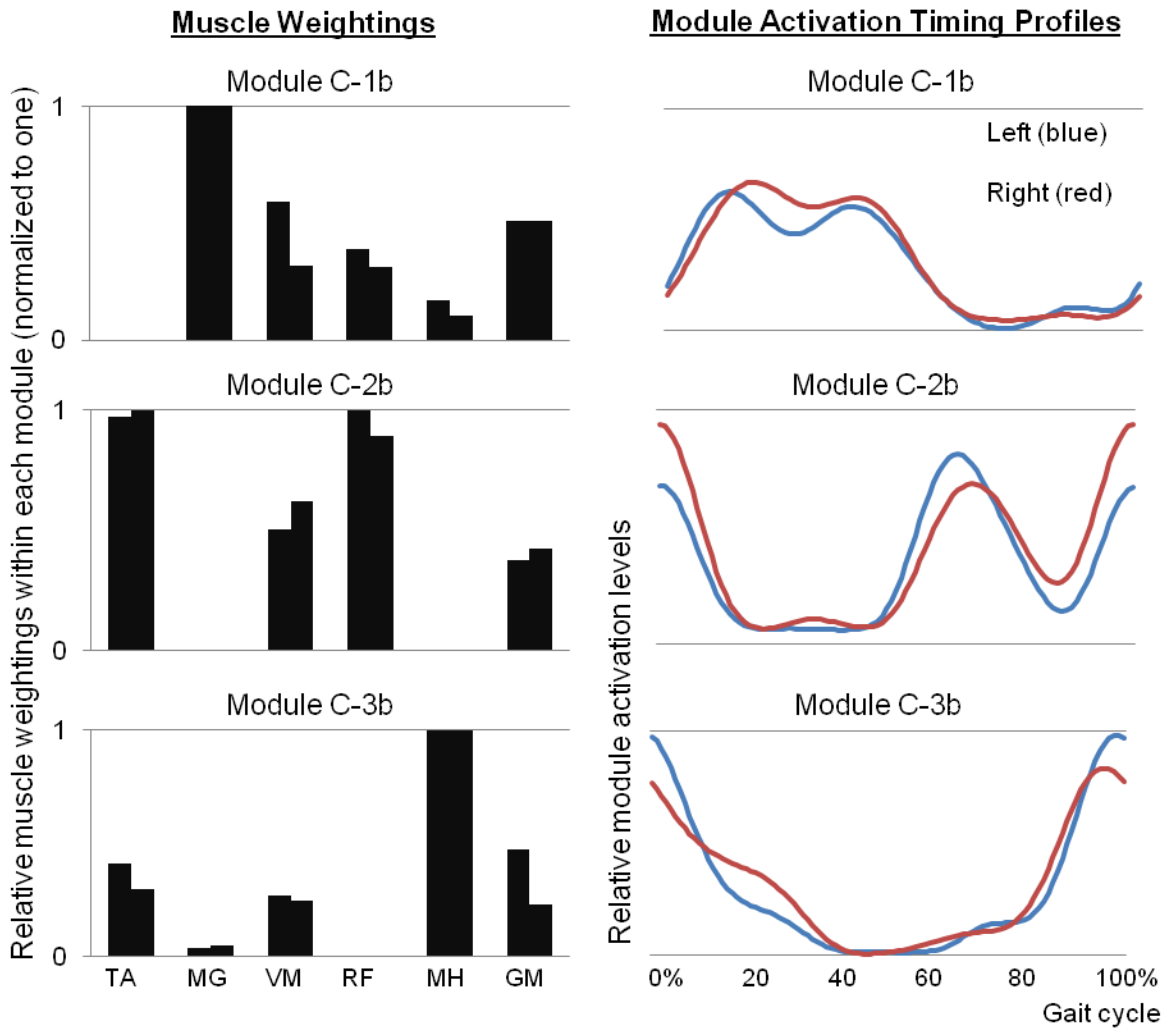

Figure 3-3. Muscle module weightings and timing profiles for treadmill stepping in one control child using 3 modules. Muscle weightings for both lower extremities for tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM) are represented. Black bars represent the relative activation of each muscle in the module. The weighting for the muscle with the greatest activation is set to one. Activation timing profiles indicate the relative level of activation of each module across the gait cycle (0-100%).

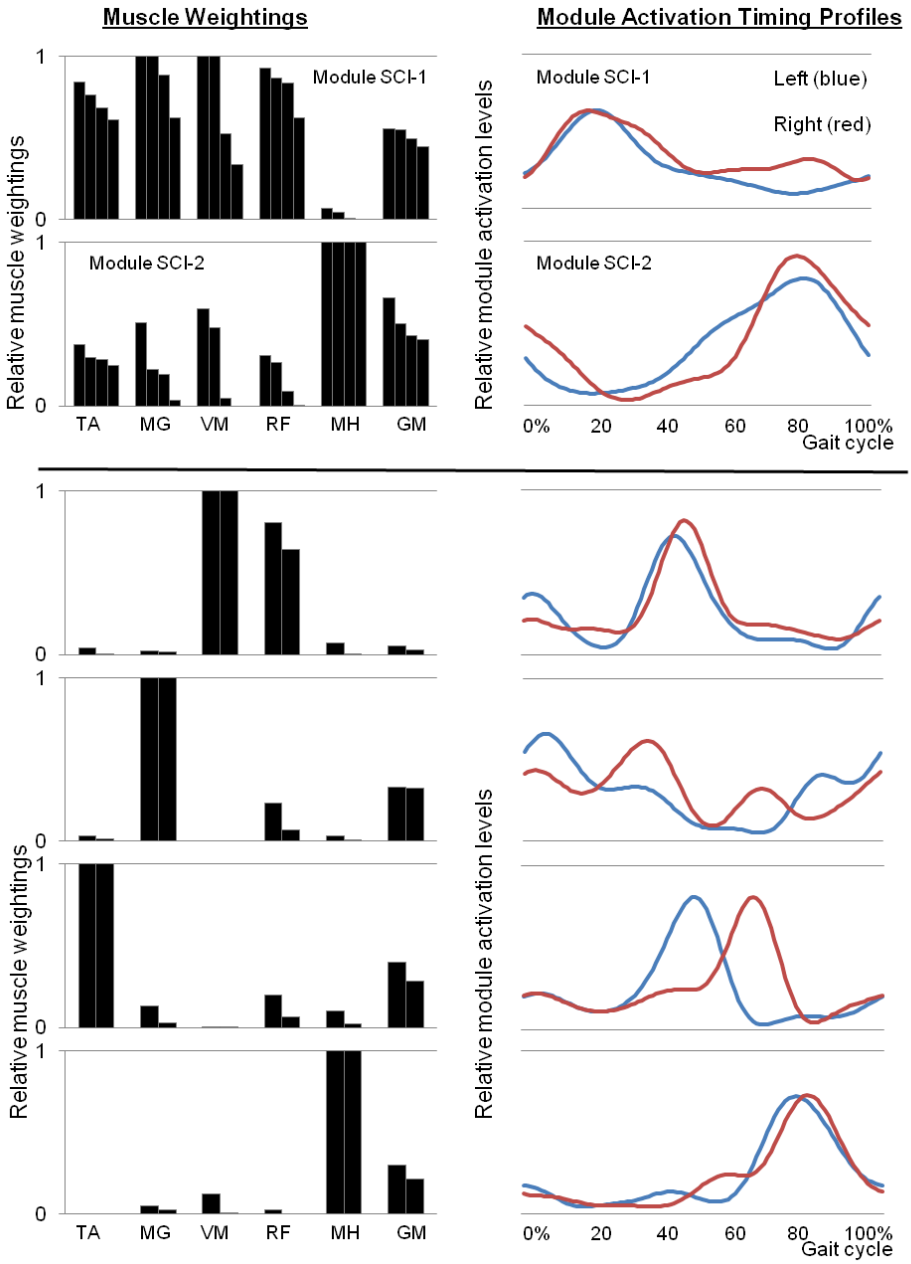

Figure 3-4. Muscle module weightings and timing profiles identified during treadmill (TM) stepping in children with incomplete spinal cord injury (ISCI). Top panel displays muscle module weights for both lower extremities (LEs) in two children with ISCI. Activation timing profiles represent the relative activation of the two modules for the right (red) and left (blue) legs across the gait cycle (0-100%). The bottom panel displays the muscle module weights for both LEs of a child with ISCI who used 4 modules during TM stepping. Activation timing profiles for both LEs of this child are displayed. Muscle weights for the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM) muscles are represented.

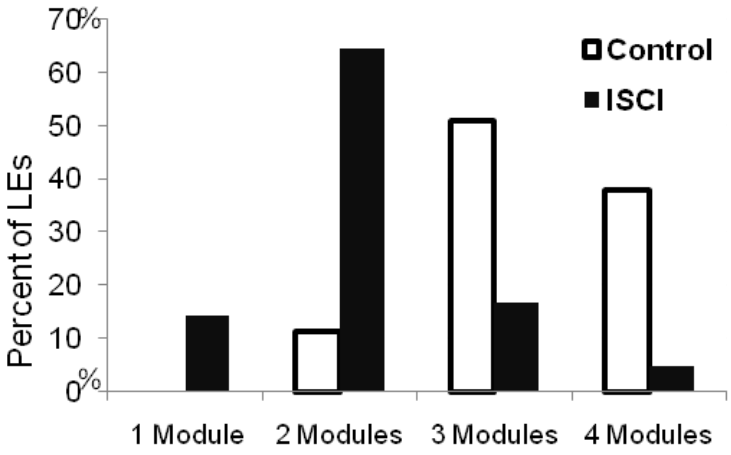

Figure 3-5. Percent of lower extremities (LEs) in each group that required 1 to 4 modules to explain ≥90% of the variance in the EMGs across all locomotor tasks for controls (white) and children with incomplete spinal cord injury (ISCI) (black).

CHAPTER 4
LOWER EXTREMITY MUSCLE ACTIVATION DURING VOLUNTARY MOVEMENTS, STEPPING, AND OTHER LOCOMOTOR TASKS IN CHILDREN WITH SEVERE INCOMPLETE SPINAL CORD INJURY

4.1. Background

Neuromuscular control of reciprocal stepping and walking is controlled by oscillating spinal networks (Calancie et al. 1994; Dobkin et al. 1995; Grillner 1979), descending supraspinal input (Drew et al. 2002; MacKay-Lyons 2002; Norton and Gorassini 2006), and task-specific sensory input (Dietz et al. 2002; Grillner and Rossignol 1978; Rossignol 2006). Spinal cord injury (SCI) disrupts descending input to spinal networks at and below the lesion level. Residual descending activation of muscles below the lesion is clinically assessed using tests of volitional isolated joint movements and muscle strength (Marino et al. 2003). Outcomes from these tests are used to predict walking recovery in individuals with SCI (Burns et al. 1997; Crozier et al. 1992; Mulcahey et al. 2007; Waters et al. 1994; Zorner et al. 2010)

Following SCI, however, motor pool activity below the lesion level is highly dependent on sensory input. Sensory inputs such as lower extremity (LE) weight bearing (Edgerton et al. 1992; Harkema et al. 1997), rate of reciprocal limb loading (Barbeau and Rossignol 1987; Beres-Jones and Harkema 2004), and LE kinematics during stepping (Andersson et al. 1978; Dietz et al. 2002) can significantly contribute to the regulation of motor pool activation and influence muscle coordination during stepping and walking. Based on this, Maegele and colleagues (2002) compared the mean amplitudes of electromyograms (EMGs) recorded from LE muscles during attempted voluntary single-joint movements, multi-joint movements approximating stepping performed in supine and weight-bearing stepping in adults with complete and

incomplete SCI (ISCI). Within this group, which included individuals who could walk with assistance or the use of devices, the greatest amplitude of EMGs recorded from the LEs occurred during weight-bearing stepping. Attempted single-joint movements were associated with mass co-activation of agonist and antagonist muscle groups. Reciprocal activation was more apparent during weight-bearing stepping and muscles that were not active during attempted volitional movements often became active during stepping (Maegele et al. 2002).

The findings from Maegele et al. (2002) suggest that clinical tests of voluntary isolated joint movement and strength do not reflect the potential to activate motor pools during upright, weight-bearing stepping. Further, in adults with SCI, the afferent input associated with upright, rhythmic, weight-bearing steps can induce rhythmic activation of muscles below the lesion level to a greater extent than attempted volitional movements which are presumed to be under descending cortical control. These findings are further supported by the outcomes from studies examining the effect of locomotor interventions in adults with ISCI (Behrman and Harkema 2000; Dietz et al. 1995; Wernig and Muller 1992; Wernig et al. 1995). Studies assessing the effect of locomotor training (LT), a rehabilitation intervention that enhances LE sensory input associated with stepping to promote walking function, indicate that individuals with little to no volitional, isolated joint movements or strength in LE muscles are responsive to LT and demonstrate improvements in walking function and recovery. Moreover, gains in walking function may occur without parallel increases in strength or isolated joint movement (Behrman and Harkema 2000; Dietz et al. 1995; Wernig and Muller 1992; Wernig et al. 1995).

A small percentage (≤ 10%) of the population of individuals with SCI is represented by children younger than 15 years (National Spinal Cord Injury Association Resource Center 1995). Because of their immature and developing musculoskeletal systems, the inability to weight-bear in upright and ambulate results in severe, secondary impairments such as scoliosis (Bergstrom et al. 1999; Dearolf et al. 1990) and hip dislocation (McCarthy et al. 2004). Experimental studies using neonate animals, however, suggest that the immature and developing spinal cord has great potential for repair and reorganization after injury (Bregman and Goldberger 1982; Bregman and Goldberger 1983; Kunkel-Bagden et al. 1992), as well as response to locomotor-specific training (Howland et al. 1995). We recently reported on a child with severe, chronic ISCI with little to no volitional isolated joint movements in his LEs who recovered reciprocal leg movements and independent ambulation with a rolling walker (Behrman et al. 2008). Not only was this child's recovery not predicted from clinical tests of joint movement and strength, but following 76 sessions of LT, walking recovery occurred independent of significant changes in voluntary isolated joint movement or strength (Behrman et al. 2008).

This case report (Behrman et al. 2008) and ongoing work in our laboratory suggests that similar to adults, children with ISCI also may be responsive to an ensemble of locomotor-specific input to generate a motor output. Furthermore, muscle activation during attempted isolated joint movements may not necessarily be predictive of, or associated with the ability to activate LE muscles below the lesion during locomotor tasks. Comparisons of LE muscle activation (EMG recordings) in response to locomotor-specific afferent input and muscle activation during attempted isolated joint

movements in children with ISCI have not been previously conducted, but may be important for the development of clinical assessments to determine walking potential and response to activity-based therapeutic interventions (Behrman and Harkema 2007).

The purpose of this study was to compare LE muscle activation during volitional, isolated joint movements with LE muscle activation during rhythmic locomotor tasks (treadmill stepping, overground walking, pedaling, and supine LE flexion/extension) in children with chronic ISCI. The guiding hypothesis was that children with ISCI would demonstrate greater muscle activation during locomotor tasks as evidenced by greater amplitude of EMG signals recorded in LE muscles when compared to muscle activation during volitional, isolated joint movements. Additionally, based on sensory modulation of spinal networks, LE muscle activation was expected to be greatest during locomotor tasks requiring LE weight-bearing.

4.2. Methods

Participants: Five children with ISCI, American Spinal Injury Association Impairment Scale (AIS) C, for >1 year, ages 3-12 years (Table 4-1), participated. All children were medically healthy and free from musculoskeletal impairment. Inclusion criteria for the children with ISCI included clinical signs of upper motor neuron injury such as ankle clonus or positive Babinski reflex to rule out lower motor neuron injuries. Medical approval for participation was obtained for all children. Parents provided informed consent for each child's participation and children of an appropriate age assented (all except subject SCI-7 who was <4 years old) to participate in this University of Florida Institutional Review Board approved study.

General procedures: In order to characterize volitional LE movement and SCI severity, the children were evaluated according to the American Spinal Injury

Association (ASIA) International Standards for Neurological Classification of Spinal Cord Injury (American Spinal Injury Association 2006). The severity of their injuries were classified based on the ASIA impairment scale (AIS) and volitional LE movements were assessed using the lower extremity motor score (LEMS) (American Spinal Injury Association 2006) (Table 4-1). Lower extremity EMGs were recorded from 6 muscles in the right leg during 3 isolated joint movements and a variety of rhythmic, reciprocal locomotor tasks. Isolated joint movements included hip flexion, knee extension, and ankle dorsiflexion. Locomotor tasks included treadmill (TM) stepping, overground (OG) walking, pedaling, and supine LE flexion/extension (details in the following sections). All tests and movement assessments were video recorded to allow for review and verification of the correct procedures.

Isolated joint movements: Tests of voluntary isolated joint movements were performed while the child was in a supine position. From this standardized position, which is used to test motor function following SCI (Marino et al. 2003), the examiner could easily communicate and demonstrate the movements to each child. The children were provided with several demonstrations of each movement and movements were practiced by moving the child's limbs to show the child the desired movement. Each child also performed similar upper extremity movements to confirm understanding of the instructions. For instance, elbow extension was practiced and demonstrated to confirm that each child understood the desired movement for knee extension. The verbal instructions and demonstrations guided the children to perform the movements, or attempt to perform the LE movements through full range and to move the limb in a smooth, controlled manner. The children were encouraged to give their best effort.

Locomotor tasks: The children with ISCI required assistance to perform most tasks. Physical assistance was provided in a manner to promote rhythmic leg movements and appropriate limb kinematics associated with normal or typical performance of each locomotor task. Two to three trials of each task were performed. The trials were each 30 to 60 seconds in duration for treadmill stepping, pedaling, and supine flexion/extension (Table 4-1).

Treadmill stepping: Children with ISCI wore a body weight support harness (Robertson Harnesses, Henderson, NV) which was attached to a fixed overhead support to unweight approximately 40% of their body weight and to prevent falls while walking on a 2.5 foot wide, standard TM surface. Body weight support and manual assistance during TM stepping were provided in accordance with locomotor training principles (Behrman and Harkema 2000). For instance, children were assisted to maintain an upright posture, step with appropriate LE kinematics, and were encouraged to swing their arms reciprocally.

Overground walking: Ambulatory children (n=2) walked independently across a 15-foot walkway using reverse rolling walkers (Table 4-1).

Pedaling: The children were assisted as needed, to perform pedaling at a consistent rhythmic pace on a stationary bicycle or adapted tricycle. Children were secured at their waist and chest for safety and foot straps were used to prevent their feet from slipping off the pedals.

Supine LE flexion/extension: Rhythmic, reciprocal LE flexion and extension movements of the hip and knee, mimicking cycling or stepping movements were

performed in a supine position. Children were assisted to perform consistent, rhythmic, full-range movements for several repetitions.

Data acquisition: To obtain overground gait speed, identify cycles of locomotor activity, and to discern discrete trials of isolated joint movements, the children were instrumented with reflective markers using the modified Helen Hayes marker set (Kadaba et al. 1989). Kinematic data were acquired with an eight-camera passive motion analysis system (Vicon Motion Systems, Los Angelos, CA). Electromyograms were recorded using Ag-AgCL surface electrodes placed bilaterally on LE muscles: tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM). Electrodes were placed longitudinally over the muscle belly with an inter-electrode distance of 2.0 cm. Inter-electrode distance was decreased for smaller children to minimize cross-talk (Winter et. al. 1994) and electrodes and leads were secured with tape and medical wrap to prevent mechanical artifact. EMG data were acquired using a synchronized, telemetry system (Konigsberg Instruments, Pasadena, CA) and sampled at ≥2000 Hz using Vicon software and saved to disk for off-line analysis.

Data analysis: Data were analyzed using custom MatLab programs (The Mathworks, Natick, MA). Overground gait speed was calculated based on the trajectory of a reflective marker affixed to a bony landmark on the child's trunk, e.g. C-7 spinous process. (Overground gait speed = $\Delta d / \Delta t$, where d=distance and t=time based on the trajectory of the marker ball.) Cycles of locomotor activity were determined by visual inspection of the trajectory of the reflective markers affixed to the child's LEs. To make comparisons across tasks, locomotor cycles were consistently defined as initial contact

of the right LE to the next consecutive contact of the right LE during TM stepping or OG walking. In a similar manner, cycles of pedaling and supine flexion/extension were defined by each revolution of the LE, starting with the initiation of extension motion of the LE to the next subsequent onset of limb extension. Thus, cycles of locomotor activity were defined by active limb extension, such as pushing downward during pedaling or weight bearing (stance) during walking, and limb flexion, such as during the swing phase of gait. Trials of volitional joint movements were determined based on the child's movement or apparent movement attempts in response to verbal instruction and were verified by visual inspection of the raw EMG recordings and review of video.

To reduce signal noise and movement artifact, EMG data were high-pass filtered at 30 Hz with a zero lag fourth-order Butterworth filter, demeaned, rectified, and low pass filtered with a zero lag fourth-order 25 Hz, Butterworth filter. Locomotor EMG data were re-sampled at each 1% of the activity cycle and divided into two bins or regions based on the flexion or extension phase of locomotor activity. Given the variability in motor control across the sample population, an a priori threshold to discern periods of EMG activity (versus periods of inactivity) was not set. Instead, for each trial of activity, performed by each child, periods of EMG activity and inactivity were determined according to a k-means clustering algorithm (Den Otter et al. 2006). The k-means cluster algorithm partitions EMG data with similar means. The number of clusters was set to 5 and the EMG data partitioned into the cluster with the lowest cluster value was determined to correspond to period of muscle inactivity. Mean EMG amplitude was therefore determined based on the mean of data partitioned into the remaining 4 clusters. For each subject, the mean EMG amplitude was calculated for each of the two

data bins from the locomotor trials (flexion and extension or stance and swing phases) and for each trial of isolated joint movement (one data bin).

Statistical analysis: A one-way analysis of variance (ANOVA) (Friedman's test) was used to assess for significant differences in the distribution of mean EMG amplitudes recorded in each muscle across all isolated joint movements and locomotor tasks except OG walking (n=2) (Table 4-2). Follow-up pair-wise comparisons were conducted using Wilcoxon signed-rank tests. To compare mean EMG amplitudes during voluntary isolated joint movement to mean EMG amplitudes recorded during locomotor tasks, specific pair-wise tests were conducted (Table 4-3). Tests were selected to compare the mean amplitude of a given muscle during a typical voluntary isolated joint movement test (i.e. VM activation during knee extension) to activation of that same muscle during locomotor tasks that incorporate very little weight bearing (pedaling) or no weight bearing (supine flexion/extension). Tests also were conducted to compare EMG amplitudes during voluntary isolated joint tasks to locomotor tasks with relatively high LE weight-bearing (TM stepping). To further determine if the mean amplitudes of EMGs were higher during weight-bearing locomotor tasks, we compared the mean amplitudes of EMGs recorded during TM walking (a task with relatively high LE weight-bearing) to the mean amplitudes recorded during pedaling (a seated task with relatively little LE weight-bearing) (Table 4-3). Because data from OG walking were acquired from only 2 children, these data were not included in the statistical analyses. For all tests, the significance level was $P<0.05$. We did not correct for multiple pair-wise comparisons and the unadjusted P values are reported (Rothman 1990; Saville 1990) (Table 4-3).

4.3. Results

Five children with chronic ISCI (males, 9+/- 3 years old), classified as AIS 'C', participated. The cause of each child's injury is reported in Table 4-1 and was different for each child. Four of the children had a SCI for more than two years and two children incurred SCIs as infants (< 1 year old). Scores on the LEMS were <5/50 and 3 children could not perform volitional single-joint isolated movements and scored 0/50 on the LEMS (Table 4-1).

Two of the 5 children had previously participated in a LT program. Following LT, both achieved the ability to walk independently with a reverse rolling walker (Behrman et al. 2008). One of these two children, subject SCI-5, whose spinal cord was injured as an infant, had not developed walking prior to LT at approximately an age of 5.5 years (Table 4-1).

All children were cooperative and actively participated in the locomotor tasks and the tests of LE isolated joint movement (Table 4-1). All children followed instructions and demonstrated the ability to perform isolated joint movements of the upper extremity.

Mean EMG amplitudes were higher during locomotor tasks compared to mean EMGs recorded during volitional isolated joint movements: The distribution of mean amplitudes of EMG signals recorded from each of 6 LE muscles in the children with ISCI was significantly different ($P<0.05$) across the voluntary isolated joint movements and rhythmic, reciprocal locomotor tasks (Table 4-2). Follow-up pair-wise comparisons of the mean amplitudes of the EMG signals recorded during voluntary isolated joint movements and mean amplitudes recorded during supine flexion/extension indicated that three of the six LE muscles had significantly higher EMG amplitudes during this locomotor task ($P<0.05$) (Table 4-3). Specifically, the mean

amplitudes of recordings from the VM, RF, and MG muscles were higher during supine flexion/extension when compared to the mean amplitudes during voluntary isolated joint movements ($P<0.05$). Pair-wise comparisons of the mean amplitude of EMGs recorded during pedaling and voluntary isolated joint movements indicated that mean amplitudes of the EMGs recorded from the RF muscle were greater during pedaling than the mean amplitude recorded during attempted isolated knee extension ($P<0.05$). Pair-wise comparisons of the mean amplitudes of EMGs recorded during TM stepping and voluntary isolated joint movements indicated that all muscle recordings, except those from the TA muscle were higher during TM stepping (Tables 4-2, 4-3, 4-4; Figures 4-1, 4-2). There were no instances where the statistical outcomes indicated that the mean EMG amplitudes were higher during the voluntary isolated joint movements.

Mean EMG amplitudes were highest during weight-bearing locomotor tasks: As stated in the previous section, for each muscle, except the TA, the mean amplitudes of the recorded EMG signals were higher during TM stepping than the signals recorded during voluntary isolated joint movements. In addition, all muscles except the TA muscle, exhibited mean EMG amplitudes that were higher during TM stepping than the amplitudes recorded during pedaling ($P<0.05$) (Table 4-3).

To more closely inspect the statistical results in this small sample of children and to provide a description of the data, we reviewed outcomes for each of the 6 muscle recordings for each child across all movements and locomotor tasks, including OG walking (n=2). For each LE muscle recording from each child (6 muscles x 5 children), we identified which movement or task resulted in the highest mean amplitude of the EMG signal. In 22 of 30 instances (6 muscles x 5 children), the mean amplitudes of

activation were highest either during TM stepping or during OG walking. In 5 instances, the mean EMG amplitudes were highest during the extension phase of the supine flexion/extension task, and on one occasion, the EMG amplitude was highest during the flexion phase of pedaling. Two children exhibited the greatest amplitudes of muscle activation during attempted isolated hip joint flexion. Subject SCI-5 demonstrated the greatest mean amplitude of activation of the TA muscle during this isolated joint task and subject SCI-6 exhibited the greatest mean amplitude of MG activation during attempted hip flexion as well (Figure 4-3).

Observational analysis of LE kinematics during attempted isolated joint movements: A secondary observational analysis of limb movements from video recordings of each child attempting to perform isolated joint movements was conducted. Specifically, from our video review we first determined if the child was able to produce an observable movement. Second, if LE movement occurred, we determined if the movement was an isolated joint movement or a multi-joint movement, such that more than one LE joint moved. We observed a total of 14 movement attempts (4 children attempted 3 isolated joint movements and one child attempted two isolated joint movements). In 8 of the 14 observations, no limb movements occurred. In the remaining 6 observations, multi-joint movements, rather than single-joint movements occurred. Thus, overall, the children were unable to produce isolated, single-joint movements. Multi-joint responses occurred during attempted hip flexion in 2 children, during attempted knee extension in 3 children, and one child exhibited a multi-joint response during attempted ankle DF. During attempts to perform isolated hip flexion, ankle DF simultaneously also occurred. Knee extension movements were

accompanied by hip extension movements, and in two of the three instances, ankle plantar flexion also was observed. During attempted isolated ankle DF, simultaneous hip flexion also occurred.

The inability to perform an isolated joint movement was particularly evident when subject SCI-5 was instructed to flex his right hip. To perform this movement, the child first flexed his contra-lateral LE (i.e. hip and knee flexion of the left LE), then forcefully extended the limb, which then enabled him to flex his right hip. This right hip flexion was accompanied by full knee flexion and ankle DF. This child, who ambulates independently with a rolling walking, exhibited the highest amplitude of TA EMG activation during an attempted isolated movement of hip joint flexion that resulted in a multi-joint movement of the hip, knee, and ankle. Furthermore, when attempting to perform isolated ankle DF, he was unable to produce any visible movement.

4.4. Discussion

The data indicate that LE muscle activation in children with chronic ISCI during rhythmic reciprocal locomotor tasks is greater than muscle activation during attempted isolated LE joint movements. Mean amplitudes of LE EMGs were greatest during weight-bearing locomotor tasks, which included TM stepping and OG walking. When children with ISCI attempted to perform LE single-joint movements, not only were the amplitudes of the EMGs significantly less than during TM stepping, but the children often were unable to move the desired joint or only could perform multi-joint movements. This was evident in all children including two children who ambulated independently using reverse rolling walkers. These findings indicate that the level of muscle activation during voluntary isolated joint movements in children with ISCI does

not necessarily reflect the potential to activate LE muscles during upright, weight-bearing locomotor tasks.

Task-specific sensory inputs may enhance LE muscle activation: Greater amplitudes of EMGs recorded from LE muscles during TM stepping and OG walking compared to the amplitudes of EMGs recorded during voluntary isolated joint movements may be explained by the ensemble of sensory input associated with walking. Evidence from animal models of SCI and studies of humans with clinically complete SCIs indicate that the afferent input associated with stepping modulates LE muscle activation (Andersson et al. 1978; Barbeau and Rossignol 1987; Beres-Jones and Harkema 2004; Dietz et al. 2002; Edgerton et al. 1992; Harkema et al. 1997; Lovely et al. 1986; 1990). In particular, the amount of loading or weight bearing on the LEs is positively associated with the amplitude of EMGs recorded from the LE muscles of uninjured adults and from adults with complete SCI, as well as adults with ISCI (Harkema et al.1997). Furthermore, rhythmic loading and unloading of the LEs as well as the velocity of hip joint extension is associated with increased LE muscle activation (Beres-Jones and Harkema 2004). While all five children with ISCI performed rhythmic leg movements during all of the locomotor tasks, TM stepping and OG walking required the greatest amount of LE loading and also incorporated hip joint extension. During pedaling, the children were seated and could not achieve hip extension due to the seated position on the bicycle or adapted tricycle. Supine LE flexion/extension was performed without LE weight-bearing and hip joint extension could not be achieved due to supine positioning on the mat.

The effect of this sensory input on LE muscle activation may be explained by studies of spinally transected cats that indicate that neuronal circuits in the lumbo-sacral spinal cord are responsive to this ensemble of task-specific sensory input (Andersson et al. 1978; Barbeau and Rossignol 1987; Edgerton et al. 1992; Lovely et al. 1986). Thus, following SCI in the cervical or thoracic spinal cord, these neural circuits are not directly damaged and may interact with afferent input from the LEs. While the presence of spinal cord neuronal networks in humans has not been confirmed, evidence suggests similar control mechanisms may exist and remain present after human SCI (Bussel et al. 1996; Calancie et al. 1994; Dimitrijevic et al. 1998; Nadeau et al. 2009). The children we studied had injuries above the lumbo-sacral spinal cord and therefore, if present, these neuronal networks were not directly injured and may have been responsive to the sensory input associated with TM stepping and OG walking. These children, however, had incomplete injuries and the increased amplitude of EMGs recorded during TM stepping also may be associated with enhanced supraspinal control or interactions between spinal and supraspinal mechanisms.

These findings in children with ISCI are consistent with Maegele et al. (2002) who reported increased amplitude of LE EMGs in adults with complete and incomplete SCI during treadmill stepping. Interestingly, also consistent with Maegele et al. (2002), we did not find a significant difference in the amplitude of TA activation during TM stepping when compared to EMGs recorded during attempted isolated movements. Ankle DF movement and TA activation may be controlled to a greater extent (compared to other LE muscles) by descending corticospinal activation (Capaday et al. 1999). Therefore task-specific sensory input that is spinally mediated may have less of an effect on the

amplitude of TA activation. This may be one explanation for why EMGs recorded from the TA muscle during TM stepping were not significantly greater than during attempted volitional movements.

Children with ISCI are unable to produce voluntary isolated LE joint movements: During each child's attempts to perform voluntary isolated LE joint movements, not only was the amplitude of EMGs significantly lower than EMGs recorded during weight-bearing locomotor tasks, but in all instances, the child was either unable to move the limb or multi-joint movements, rather than single-joint movements occurred. The inability to activate muscles of a single LE joint and the use of multi-joint movement patterns have been described in adults with ISCI and may be due to more generalized motor control, rather than control of discrete joint movements (Maegele et al. 2002; Wernig et al. 1992). The inability to control isolated LE joint movements is likely due to impaired descending input at and below the spinal cord lesion (McKay et al. 2005) and further points to the critical role that sensory input may have in modulating LE muscle activation after ISCI (Edgerton et al. 2004).

Methodological considerations: While these findings in children with ISCI are highly consistent with previous investigations of muscle activation in adults with SCI (Maegele et al. 2002; Wernig and Muller 1992), this study was conducted in a small sample of 5 children. This sample of 5 children, however, was diverse in terms of the etiology of SCI, the age of injury, duration of injury, rehabilitation experience and also functional outcomes following injury. For instance, it is notable that two children incurred injury to their spinal cords as infants and before the development of walking and that two of the five children could ambulate independently with a reverse rolling

walking. Yet, each child had a LEMS < 5/50 (range 0-4/50), was unable to produce isolated single joint movements of the LE, and exhibited higher amplitudes of EMGs recorded during weight-bearing locomotor tasks. Therefore, despite our limited sample size, the results of this study may be more robust given the diversity that was evident in the children we studied.

The outcomes of this investigation may be further strengthened by kinematic measures of LE joint movement, quantitative measurement of the amount of LE weight-bearing during the locomotor tasks, and a more extensive examination of voluntary isolated joint movements. While the secondary qualitative video analysis of LE movements was consistent with prior investigations, better understanding of movement control and intra-limb coordination could be gained by quantitative measurements of LE joint movements. Additionally, measurements of LE weight-bearing during the locomotor tasks would be useful for determining the association between LE weight-bearing and mean amplitudes of LE EMGs recorded in children with ISCI. Furthermore, a more extensive battery of tests to examine voluntary isolated joint movements would provide more specific results regarding the capacity of children with ISCI to activate LE muscles such as the MG, MH and GM muscles.

Another potential consideration is the use of tests to assess LE joint movement and strength in young children that may have difficulty following instructions or putting forth maximal effort during the tests (Mulcahey et al. 2007). We provided verbal instructions and multiple demonstrations to each child and also verified their understanding by testing movements that were unimpaired. Each child demonstrated understanding by performing these movements. Additionally, several attempts and

trials of movement were recorded and verified by visual inspection of the EMG recordings and simultaneous video recordings.

Clinical Application: Following pediatric-onset SCI, tests of isolated joint movement and strength in the muscles below the lesion level are used to characterize the severity of injury and predict functional outcomes, including the potential to develop or regain walking function (Mulcahey et al. 2007; Vogel et al. 2007). Our data suggests, however, that the amplitude of LE muscle activation during tests of voluntary isolated joint movements does not necessarily reflect the potential to generate muscle activation during locomotor tasks, especially during tasks that incorporate LE weight bearing and sensory inputs associated with walking. Consistent with the findings from Maegele et al. (2002), our data indicate that the amplitude of LE muscle activation is greater during TM stepping than during attempts to perform voluntary single-joint movements.

Not only were our findings consistent across all children, but our sample was diverse and included non-ambulatory children, as well as those who could ambulate independently. Moreover, two children in our study had not developed normal, unimpaired locomotion prior to injury. Thus, the data suggest, that regardless of ambulatory status, daily practice of locomotor tasks, or even the development of walking prior to injury onset, in children with chronic, ISCI, the amplitude of muscle activation is greater during weight-bearing locomotor tasks. Furthermore, despite these diverse factors associated with each child's injury, all scores on the LEMS were <5/50, two children were ambulatory, and all children demonstrated higher amplitudes of EMG signals recorded during TM stepping compared to EMGs recorded during attempted isolated joint movements.

These findings therefore indicate that tests of LE muscle activation in children with ISCI should include assessments of muscle activation during weight-bearing locomotor tasks. Weight-bearing locomotor tasks, such as TM stepping, provide an ensemble of task-specific sensory inputs that may modulate or enhance the activation of LE muscles below a spinal cord lesion in children with ISCI. Furthermore, given the higher amplitudes of EMGs recorded from LE muscles during TM stepping and OG walking, our data suggest that interventions designed to promote LE muscle activation and walking function after injury should incorporate weight-bearing locomotor tasks.

Locomotor training is a rehabilitation intervention that enhances task-specific sensory input during intense, repetitive TM stepping to improve walking function in adults with ISCI (Behrman and Harkema 2000; Wernig and Muller 1992; Wernig et al. 1995). Our report on a child with severe, chronic ISCI with little to no volitional isolated joint movements in his LEs, who recovered the ability to walk OG using a reverse rolling walking following 76 sessions of LT (Behrman et al. 2008) suggests that volitional isolated joint movements may not be a prerequisite for regaining walking function. Moreover, this prior report (Behrman et al. 2008) along with the findings from this current study and prior investigations in adults with ISCI (Maegele et al. 2002; Wernig and Muller 1992) point to the potential benefits of providing task-specific sensory input associated with weight bearing locomotion to enhance the activation of LE muscles below the level of the spinal cord lesion in children with ISCI.

4.5. Tables and Figures

Table 4-1. Subject demographics and participation for each child with incomplete spinal cord injury (ISCI).

Subject	Age (yrs)	Injury level	Etiology	Age of injury (yrs)	LEMS	OG gait speed (m/s)	TM speed (m/s)	Pedal	Supine flex/ext	Hip flexion	Knee ext	Ankle DF
SCI-1	9	C7	GSW	3.5	4/50	0.57	0.56	X	X	X	X	X
SCI-4	12	T4-T8	Tumor Rsx	8.5	0/50*	----	0.58	X	X	X	X	----
SCI-5	7	C4-7	Unknown*	6 mo	4/50	0.36	0.83	X	X	X	X	X
SCI-6	12	T10	MVA	10.5	0/50*	----	0.64	X	X	X	X	X
SCI-7	3	C1-T6	Tr. Myelitis	5 mo	0/50*	----	0.89	X	X	X	X	X
Avg.	9					0.47	0.70					
SD	3					0.15	0.15					

Notes: All subjects were male. Ages are reported in years (yrs) or months (mo). The Lower Extremity Motor Score (LEMS) is based on isolated joint strength in five bilateral muscles. Asterisks (*) indicate an inability to perform isolated joint movements in the standardized position (American Spinal Injury Association 2006). Overground (OG) and treadmill (TM) gait speeds are reported. An 'X' indicates the child performed the movement or task (Pedaling (Pedal), supine lower extremity flexion/extension (Supine flex/ext), hip flexion, knee extension (knee ext), ankle dorsiflexion (ankle DF)). Dashed lines (--) indicate that the movement or locomotor task was not performed or EMGs were not usable. Average (Avg.) and standard deviations (SD) are reported. Etiologies of the spinal cord injuries are reported as gunshot wound (GSW), unknown* and suspected cause of transverse myelitis or trauma secondary to motor vehicle accident (MVA), surgical re-section secondary to tumor (Tumor Rsx) and transverse myelitis (Tr. Myelitis)

Table 4-2. Friedman's one-way analysis of variance (ANOVA) test results to compare the distributions of mean amplitudes of electromyogram signals recorded during voluntary isolated joint movements and locomotor tasks.

Muscle	Number of subjects (n) included in each analysis	Friedman's test (ANOVA) statistic and degrees of freedom	Significance (P value)
TA	4	$\chi^2(8)=15.933$	0.043
MG	4	$\chi^2(8)=17.200$	0.028
VM	4	$\chi^2(8)=23.533$	0.003
RF	4	$\chi^2(8)=23.200$	0.003
MH	4	$\chi^2(8)=23.267$	0.003
GM	4	$\chi^2(8)=27.133$	0.001
TA	5	$\chi^2(7)=08.333$	0.304
MG	5	$\chi^2(7)=14.733$	0.040
VM	5	$\chi^2(7)=21.467$	0.003
RF	5	$\chi^2(7)=21.000$	0.004
MH	5	$\chi^2(7)=21.467$	0.003
GM	5	$\chi^2(7)=23.133$	0.002

Notes: The distribution of mean amplitudes recorded from each of the following muscles was compared: tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH) and gluteus medius (GM).
Isolated joint movements included ankle dorsiflexion (DF), hip flexion (flex), knee extension (ext). The locomotor tasks included supine flexion/extension, pedaling and treadmill stepping (TM step). Mean amplitudes were calculated for each phase of the locomotor task (extension (ext), flexion (flex), stance (st) and swing (sw)). A one-way analysis of variance (ANOVA) was conducted for all tasks and n=4 due to unusable data for one subject during ankle DF. Therefore data from this subject was not included in this model. To include data from this subject, a second ANOVA was performed, n=5 and the task of ankle DF was omitted from the test. For pair wise comparisons n=5 unless noted otherwise.

Table 4-3. Statistical test results from pair wise comparisons of mean electromyogram amplitudes recorded during voluntary isolated joint movements and locomotor tasks.

Muscle	Voluntary isolated joint movement and/or task(s) that were compared	Significance (P value)
TA	Ankle DF & supine flex (n=4)	0.068
TA	Ankle DF & pedal flex (n=4)	0.068
TA	Ankle DF & TM step-sw (n=4)	0.068
MG	Knee ext & supine ext	0.043
MG	Knee ext & pedal ext	0.080
MG	Knee ext & TM step-st	0.043
VM	Knee ext & supine ext	0.043
VM	Knee ext & pedal ext	0.500
VM	Knee ext & TM step-st	0.043
RF	Hip flex & supine flex	0.043
RF	Hip flex & pedal flex	0.225
RF	Hip flex & TM step-sw	0.043
RF	Knee ext &supine ext	0.043
RF	Knee ext & pedal ext	0.043
RF	Knee ext & TM step-st	0.043
MH	Hip flex & supine flex	0.893
MH	Hip flex & pedal flex	0.686
MH	Hip flex & TM step-sw	0.043
GM	Knee ext &supine ext	0.080
GM	Knee ext & pedal ext	0.686
GM	Knee ext & TM step-st	0.043
TA	TM step-sw & pedal flex	0.138
MG	TM step-st & pedal ext	0.043
VM	TM step-st & pedal ext	0.043
RF	TM step-st & pedal ext	0.043
MH	TM step-st & pedal ext	0.043
MH	TM step-sw & pedal flex	0.043
GM	TM step-st & pedal ext	0.043

Notes: Electromyograms were recorded from the following muscles: tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH) and gluteus medius (GM). Isolated joint movements included ankle dorsiflexion (DF), hip flexion (flex), knee extension (ext). The locomotor tasks included supine flexion/extension, pedaling and treadmill stepping (TM step). Mean amplitudes were calculated for each phase of the locomotor task (extension (ext), flexion (flex), stance (st) and swing (sw)). For the pair wise comparisons n=5 unless noted otherwise.

Table 4-4. Mean amplitudes of electromyogram signals (micro volts (μV))recorded from the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH) and gluteus medius (GM) muscles during voluntary isolated joint movements and locomotor tasks.

	Hip flex	Knee ext	Ankle DF	Supine ext	Supine flex	Pedal ext	Pedal flex	TM step-st	TM step-sw	OG walk-st	OG walk-sw
TA	10.1	4.3	3.7	9.8	10.0	7.8	7.2	13.8	18.1	23.8	22.5
SD	9.8	3.2	1.2	6.5	6.7	5.3	5.2	10.7	19.6	1.8	4.8
MG	7.6	5.1	3.2	15.9	11.4	11.1	10.7	18.1	16.3	37.4	25.2
SD	6.7	4.5	1.8	13.1	10.0	7.6	8.0	8.5	9.7	0.2	3.6
VM	6.2	11.9	3.2	33.0	12.1	11.7	10.0	27.3	16.5	56.1	55.4
SD	4.2	14.1	1.7	33.6	13.5	15.0	12.1	26.9	14.8	7.6	27.6
RF	5.8	5.9	3.6	18.1	10.6	9.2	8.1	18.8	12.0	33.1	30.2
SD	3.2	5.6	2.7	11.8	5.6	7.0	5.6	12.1	6.9	7.8	22.0
MH	14.4	12.2	5.6	22.6	16.7	14.5	9.9	23.9	39.3	42.3	43.8
SD	10.4	13.5	4.0	19.6	12.0	10.1	4.2	12.9	23.1	2.8	1.4
GM	4.4	3.7	2.7	8.9	6.1	4.4	4.5	13.7	11.8	29.1	21.0
SD	1.6	1.7	0.7	8.8	4.3	3.6	4.0	13.6	9.4	1.2	3.6

Notes: Standard deviations (SD) are indicated. Isolated joint movements included hip flexion (flex), knee extension (ext), ankle dorsiflexion (DF). Locomotor tasks included supine flexion/extension, pedaling, treadmill stepping (TM step) and overground walking (OG walk). Mean EMG amplitudes were calculated for each phase of the locomotor task (extension (ext), flexion (flex), stance (st) and swing (sw)).

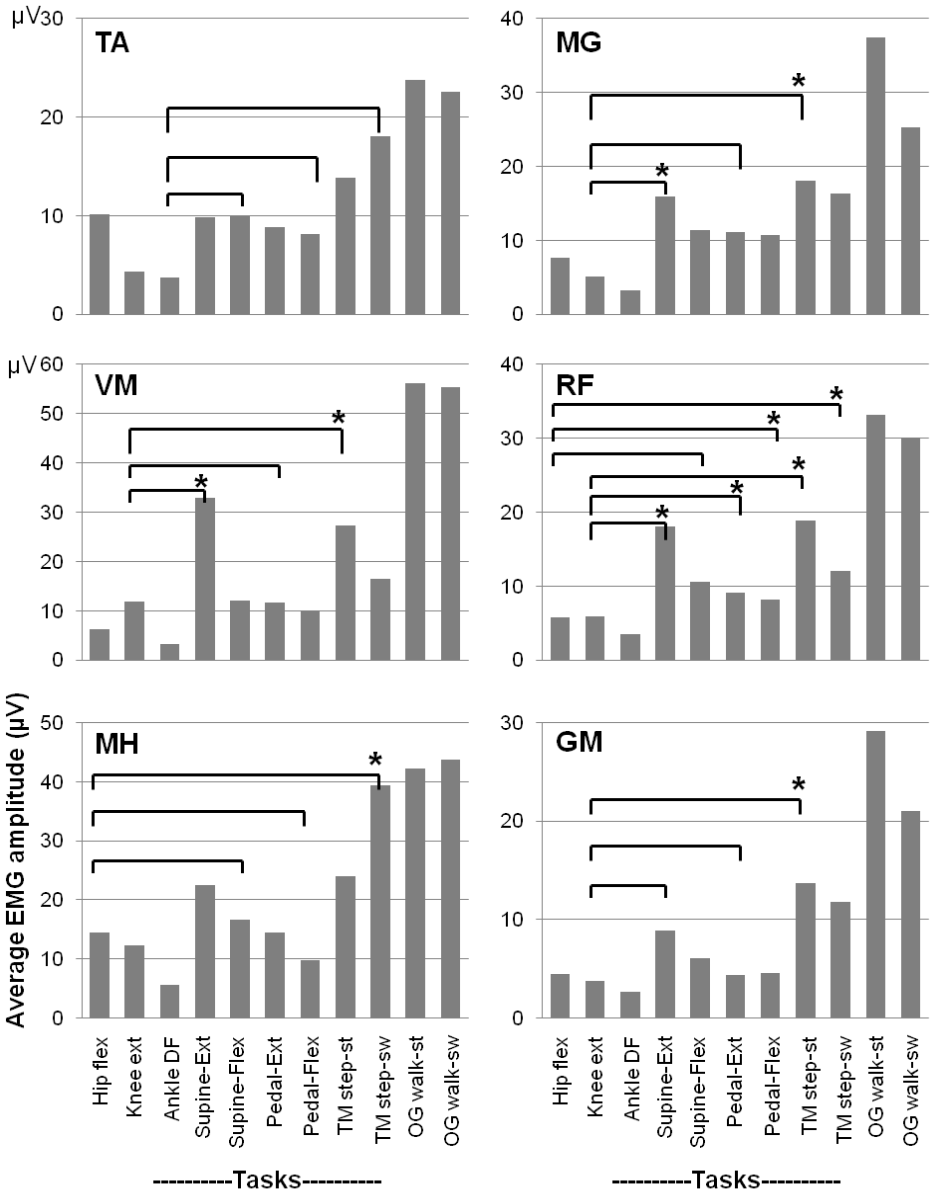

Figure 4-1. Mean amplitude of electromyogram signals (micro volts, μV) recorded from lower extremity muscles during voluntary isolated joint movements and locomotor tasks. EMGs were recorded from the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH) and gluteus medius (GM) muscles during hip flexion (flex), knee extension (ext), ankle dorsiflexion (DF), supine flexion/extension, pedaling (pedal), treadmill stepping (TM step) and overground walking (OG walk). Mean EMG amplitudes were calculated for each phase of the locomotor task (extension (Ext), flexion (Flex), stance (st), swing (sw)). Bars indicate comparisons of mean EMG amplitudes during isolated joint movements and locomotor tasks. Asterisks (*) indicate a significant pair wise comparison ($P<0.05$).

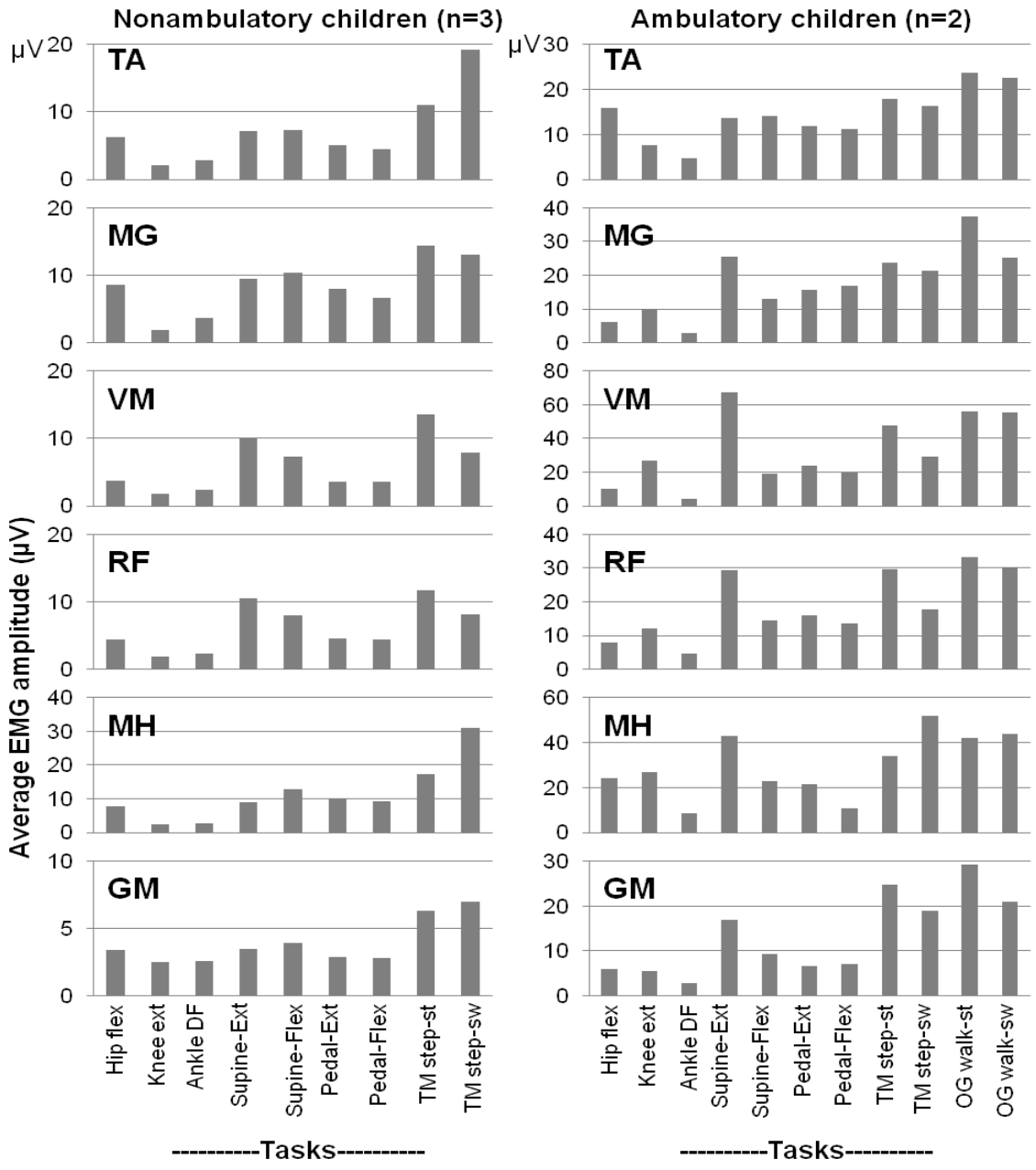

Figure 4-2. Mean amplitude of electromyogram (EMG) signals (micro volts, μV) recorded from the lower extremity muscles of non-ambulatory children (n=3) and ambulatory children (n=2) during voluntary isolated joint movements and locomotor tasks. EMGs were recorded from the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH) and gluteus medius (GM) muscles during hip flexion (flex), knee extension (ext), ankle dorsiflexion (DF), supine flexion/extension, pedaling (pedal), treadmill stepping (TM step) and overground walking (OG walk). Mean EMG amplitudes were calculated for each phase of the locomotor task (extension (Ext), flexion (Flex), stance (st), swing (sw)).

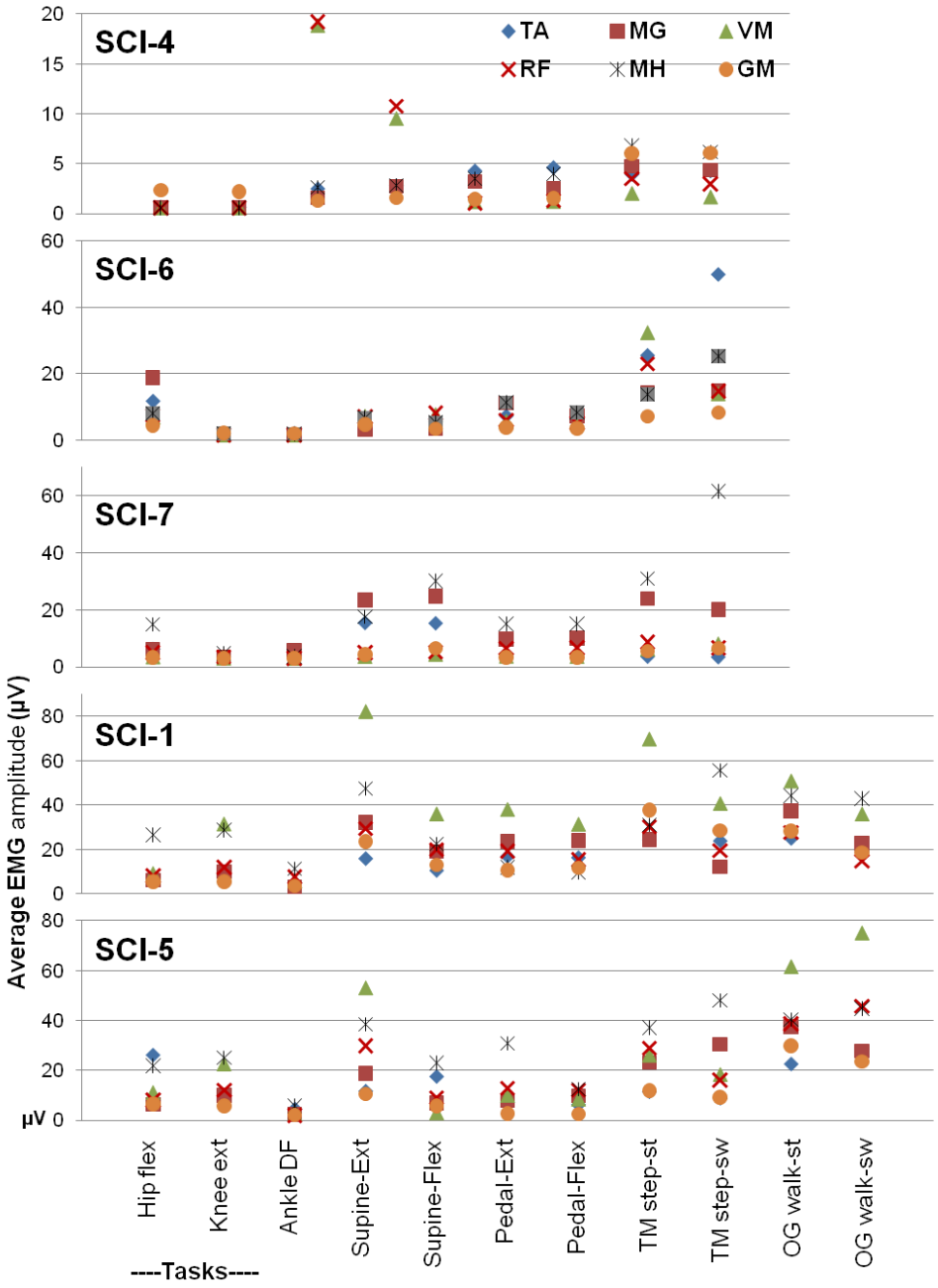

Figure 4-3. Mean amplitude of electromyogram (EMG) signals (micro volts, μV) recorded from each child with incomplete spinal cord injury during voluntary isolated joint movements and locomotor tasks. EMGs were recorded from the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH) and gluteus medius (GM) muscles during hip flexion (flex), knee extension (ext), ankle dorsiflexion (DF), supine flexion/extension, pedaling (pedal), treadmill stepping (TM step) and overground walking (OG walk). Mean EMG amplitudes were calculated for each phase of the locomotor task (extension (Ext), flexion (Flex), stance (st), swing (sw)).

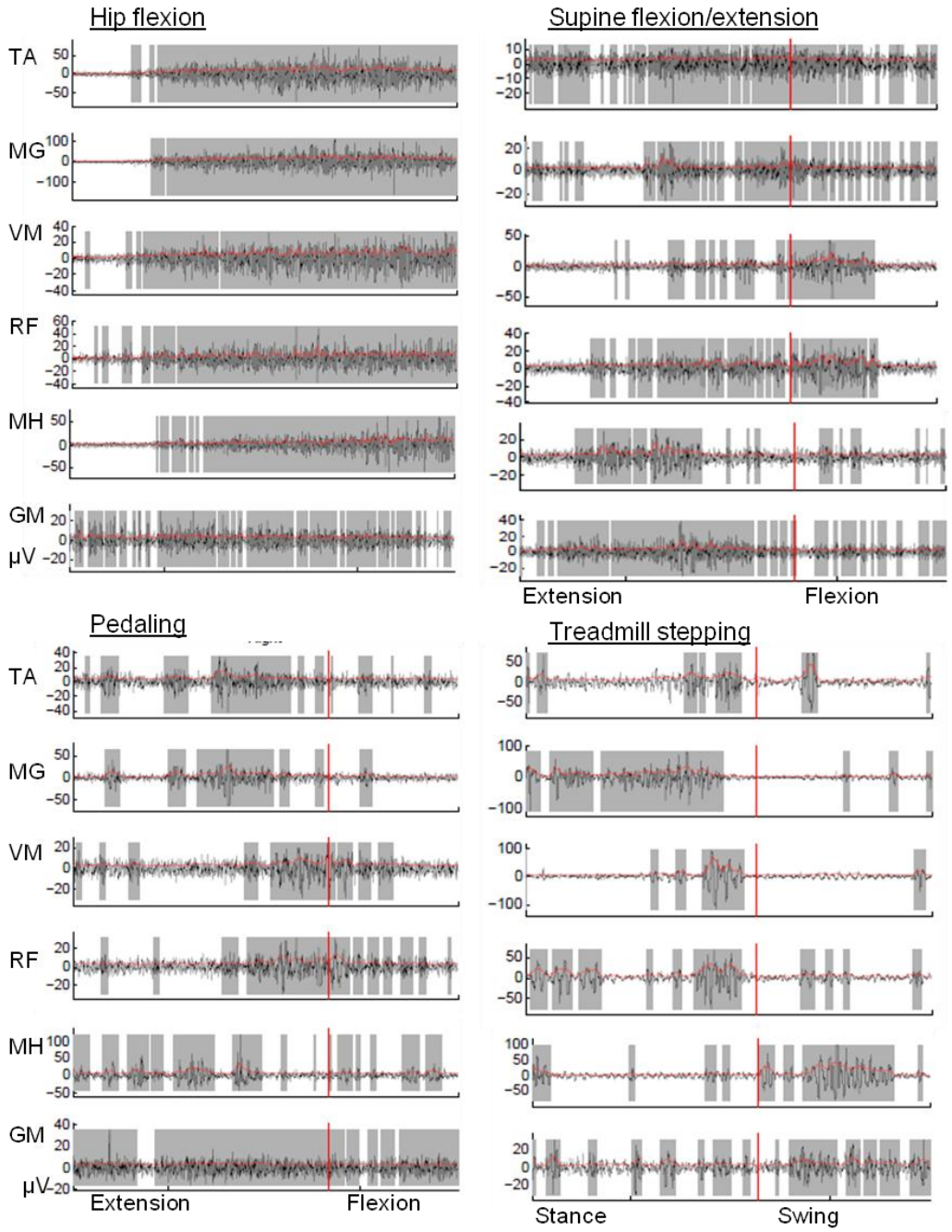

Figure 4-4. Electromyogram (EMG) signals recorded from the right lower extremity of subject SCI-6, a non-ambulatory child, during hip flexion and one cycle of activity for supine flexion/extension, pedaling, and treadmill stepping. Black EMG tracing is the raw signal. Red EMG tracing is the processed signal. Shaded gray regions indicate periods of activation identified by the k-means cluster algorithm. Vertical red lines differentiate the phases of each locomotor task. EMGs were recorded from the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM) muscles.

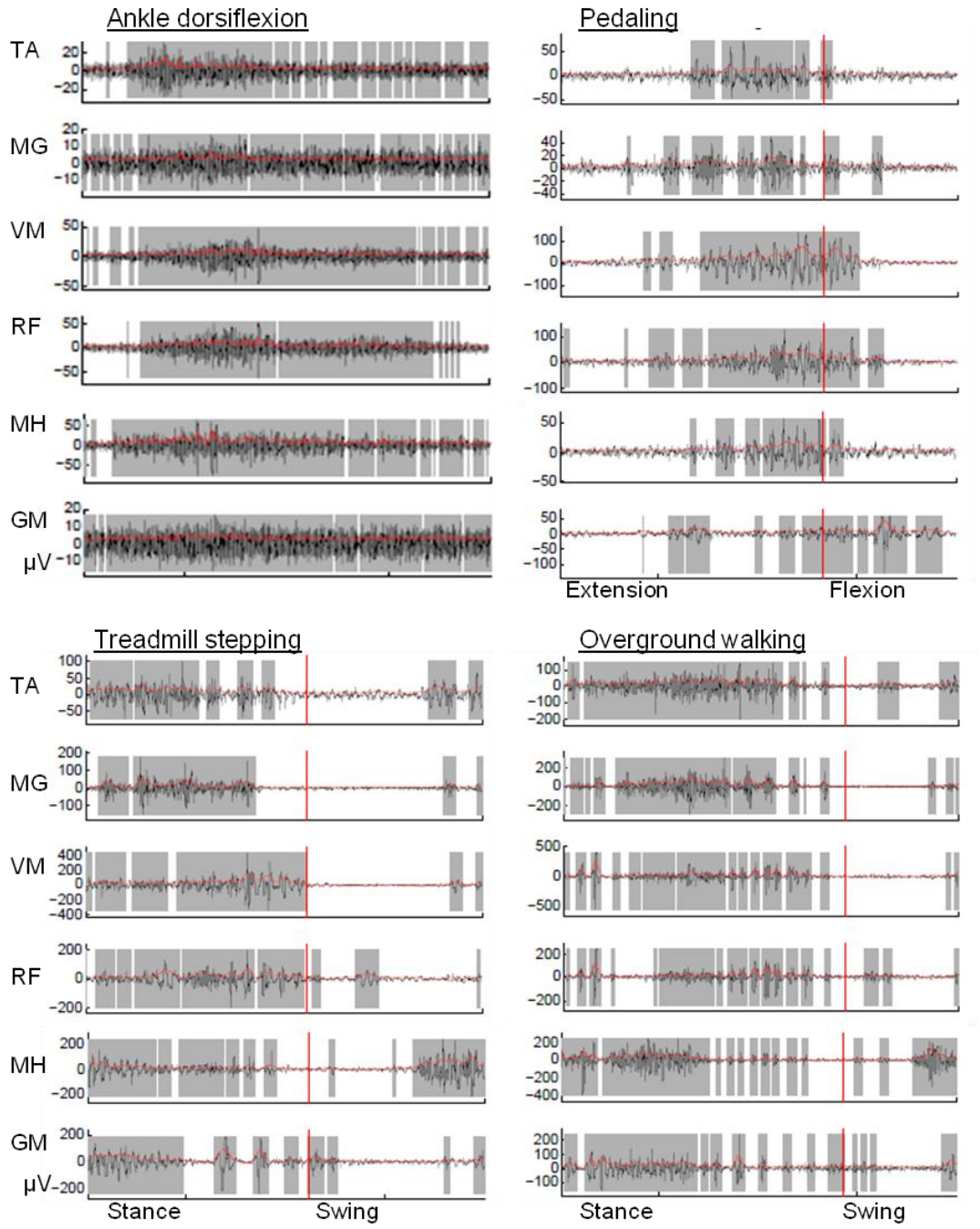

Figure 4-5. Electromyogram (EMG) signals recorded from the right lower extremity of subject SCI-1 during ankle dorsiflexion and one cycle of activity for pedaling, treadmill stepping and overground walking. Black EMG tracing is the raw signal. Red EMG tracing is the processed signal. Shaded gray regions indicate periods of activation identified by the k-means cluster algorithm. Vertical red lines differentiate the phases of each locomotor task. EMGs were recorded from the tibialis anterior (TA), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), and gluteus medius (GM) muscles.

CHAPTER 5
MECHANISMS OF RESPONSE TO LOCOMOTOR TRAINING IN ADULTS WITH MOTOR INCOMPLETE SPINAL CORD INJURY

5.1. Background

More than half of all individuals with spinal cord injuries have an incomplete injury (National Spinal Cord Injury Statistical Center 2006) and are likely to regain some degree of walking function (Burns et al. 1997). However, spinal cord injury (SCI) alters neuromuscular control of walking resulting in severe impairments of gait speed, limb kinematics, and upright balance control (Barbeau et al. 2002). Regaining walking function is a primary goal for individuals with SCI (Ditunno et al. 2008) and is a focus of rehabilitation following injury. Locomotor training (LT) is a rehabilitation intervention that promotes walking recovery and is founded on animal and translational human studies of walking control. LT focuses on recovery of walking and the reinstatement of pre-injury movement patterns rather than reliance on compensatory braces and devices (Behrman and Harkema 2007; Levin et al. 2008). LT enhances afferent input to neural networks below the level of the lesion to promote appropriate neuromuscular activation during repetitive, task-specific practice (Behrman and Harkema 2007; Dietz et al. 2002; Harkema et al. 1997; Maegele et al. 2002). Following LT, individuals with incomplete SCI (ISCI) demonstrate improved spatiotemporal features of gait (Field-Fote et al. 2005), more normal lower extremity joint kinematics (Field-Fote and Tepavac 2002; Grasso et al. 2004; Ivanenko et al. 2003), require less assistance (Behrman and Harkema 2000; Wernig et al. 1995), and walk at faster speeds (Behrman and Harkema 2000; Dobkin et al. 2006; Field-Fote and Roach 2011; Wernig et al. 1992; Wirz et al. 2005).

While LT is a promising intervention for individuals with ISCI, the neuromuscular mechanisms underlying walking recovery and response to LT are not well understood (Barbeau et al. 1999; Gorassini et al. 2009; Grasso et al. 2004). Studies examining patterns of muscle activation during walking and following LT in individuals with ISCI suggest changes in muscle coordination may be associated with improved walking function after LT (Dietz 1994, 1998). Decreased co-activation of antagonist muscles may underlie gait improvements post LT (Dietz 1994, 1995) and individual muscles may demonstrate more appropriate timing (Gorassini et al. 2009). However, prior work also suggests that individuals with ISCI may develop 'motor equivalence' or individual motor solutions to control the limb during stepping (Grasso et al. 2004; Ivanenko et al. 2003). Furthermore, reports indicate that muscle coordination post LT does not revert to patterns used by uninjured persons walking at similar speeds (Gorassini et al. 2009; Grasso et al. 2004; Ivanenko et al. 2003).

Studies of synchronous muscle activation have provided insights into how the nervous system controls complex tasks, such as walking (Bizzi et al. 2008; Ivanenko et al. 2004; Tresch et al. 1999). Neuromuscular activation during healthy human locomotion is organized in a low-dimensional, modular-control framework such that functional muscle synergies are activated in association with biomechanical task demands across the gait cycle (Clark et al. 2010; Ivanenko et al. 2004, 2005). Studies applying decomposition techniques to multiple recordings of surface electromyography (EMG) demonstrate consistent timing of 4 to 5 patterns of muscle activity in association with specific events across the gait cycle during walking in healthy adults (Clark et al. 2010; Ivanenko et al. 2004; 2005). Furthermore, recent evidence supports that the

patterns of muscle co-activation are stable and reproducible in individuals without gait impairment and at variable gait speeds (Clark et al. 2010). Computer simulations further support that muscle composition and timing of module activation results in appropriate biomechanical output, associated with coordinated walking (Neptune et al. 2009).

Investigations of neuromuscular control in individuals post-stroke have provided evidence that the modular control mechanisms used during walking are indicative of the complexity of locomotor output in the paretic limb and also reflect the severity of gait impairment (Bowden et al. 2010; Clark et al. 2010). The number of modules produced by the nervous system to control the paretic limb of individuals post-stroke during walking is reduced compared to uninjured adults (Bowden et al. 2010; Clark et al. 2010). Furthermore, Clark and colleagues (2010) reported that a decreased number of modules are associated with reduced locomotor output complexity based on the finding that modules are co-activated rather than discretely activated in the paretic limb. Additionally, in the paretic limb of individuals post-stroke, modular control is associated with clinical measures of walking performance (Bowden et al. 2010) as well as biomechanical control during walking (Clark et al. 2010). Specifically, altered modular control has been associated with reduced overground gait speed, greater step length asymmetry, and greater propulsive asymmetry. Moreover, following 36 sessions of LT, gait recovery was associated with restoration of modular control mechanisms (Clark et al. 2009). An increased number of modules in the paretic limb was associated with greater gains in gait speed as well as improved biomechanical control (Clark et al. 2009).

Current approaches to elucidate the neuromuscular mechanisms underlying walking recovery and response to LT in individuals with SCI have not provided clear or consistent outcomes (Dietz 1994, 1998; Gorassini et al. 2009; Grasso et al. 2004; Ivanenko et al. 2003). Studies of walking control in healthy individuals (Clark et al. 2010; Ivanenko et al. 2004; Neptune et al. 2009) and individuals post stroke (Bowden et al. 2010; Clark et al. 2010) suggest that examination of modular control mechanisms, in association with task biomechanics and muscle coordination, may provide insight into control mechanisms underlying gait recovery after ISCI and mechanisms of response to interventions, such as LT. Understanding motor control solutions post ISCI may promote advancement of training paradigms that target mechanisms associated with walking recovery as well as lead to more specific measures of walking recovery. Therefore, the purpose of this study was to examine modular control mechanisms, as well as specific changes in muscle coordination and biomechanical control during walking in ambulatory individuals with ISCI prior to and following a locomotor training intervention.

This study was based on two primary hypotheses. First, compared to individuals without injury (controls) walking at a similar speed, individuals with ISCI would demonstrate a) altered modular control as evidenced by a reduced number of modules required to explain muscle activity during walking, b) altered muscle coordination as determined by the duration of muscle activation within specific regions of the gait cycle, and c) altered stepping biomechanics as evidenced by decrements in foot trajectory range and the minimal and maximal leg angles achieved during stepping. Second, following LT, individuals with ISCI would display a) increases in gait speed, as well as

changes in b) the number of modules produced by the nervous system to control walking c) changes in muscle coordination and d) altered stepping biomechanics.

5.2. Methods

Participants: Ten adults with chronic (≥ 6 months) ISCI (Table 5-1) were enrolled. Individuals with ISCI were selected from a cohort of individuals with ISCI who were participating in a larger clinical study. These individuals were selected from this parent study because they could perform at least 3 steps without an assistive device or physical assistance during treadmill (TM) walking. After inspection of the data, two subjects' data were not included in the final analyses due to inconsistencies in the data or incomplete data sets. Therefore, data from a group of 8 adults with chronic ISCI were included in the final analyses (6 males, 44.9 ±14.8 years) (Table 5-1). The control group included 13 subjects who represented a sub-set of the control subjects previously reported on by Clark et al. (2010). This sub-set was selected because they each completed walking trails at 0.30 m/s and were <70 years old (3 males, 57.7 ± 4.7 years). The data from all 13 control subjects are included in all subsequently described analyses, except for the analysis of modular control, where data from 10 control subjects were included. Three subjects were omitted due to missing or partial data sets.

Individuals with ISCI had an upper motor neuron lesion non-congenital in origin, received medical approval to participate, were healthy, and were free from musculoskeletal impairments. Control subjects were healthy adults, free from musculoskeletal or neurological impairments and ambulated full time without a device or assistance. All procedures were conducted at the Malcom G. Randall Veteran Affairs (VA) Medical Center, Brain Rehabilitation Research Center in Gainesville, Florida.

Participants provided informed consent to participate in this VA and University of Florida Institutional Review Board approved study.

Locomotor Training: Individuals with ISCI completed 45 sessions of locomotor training (LT). LT sessions were conducted 3-5 days per week and included 30 minutes of stepping on a treadmill with partial body weight support (BWS). Physical assistance to optimize stepping kinematics was provided either manually by a licensed physical therapist and skilled trainers, or using a robotic device (Lokomat, Hocoma Inc., Rockland, Massachusetts) (Table 5-1). In each LT environment (manually or robot-assisted), training principles were optimized relative to stepping speed, kinematics, maximal lower extremity (LE) loading and the incorporation of reciprocal arm-swing (Behrman and Harkema 2000, 2007). To complete 30 minutes of stepping practice, stepping bouts were alternated with standing bouts based on the subject or trainer's fatigue. The length of each bout varied according to the subject's needs. On average, LT was conducted at speeds between 0.70 m/s and 1.0 m/s and BWS varied between 14% and 35% of each individual's body weight. Based on each subject's progress, he or she was progressed in their training by stepping with decreased BWS, faster speeds, or with less physical assistance. Skills practiced in the treadmill environment were not specifically practiced over ground during the training session. Subjects were, however, encouraged to practice in their home and community.

Experimental set-up and procedures: Standard assessments were conducted to characterize the individuals with ISCI, the severity of their lesion, and their overground walking function. Individuals with ISCI were assessed according to the American Spinal Injury Association (ASIA) International Standards for Neurological and Functional

Classification of Spinal Cord Injury (American Spinal Injury Association 2006). The Lower Extremity Motor Score (LEMS) was determined based on strength in 5 key LE muscles (American Spinal Injury Association 2006). Self-selected, overground gait speed was computed as the individual walked with their typical assistive device across an instrumented walkway (GAITRite, CIR Systems, Inc, Havertown PA) (Table 5-1).

Subjects were instrumented with retroreflective markers according to a modified Helen Hayes marker set (Kadaba et al. 1989) with additional marker clusters attached to rigid plates located on each thigh, lower leg. Subjects completed three 30-second walking trials at a self-selected speed on an instrumented split-belt treadmill (Tecmachine, Andrezieux Boutheon, France). Control subjects walked at 0.3 meters/second (m/s) to provide speed-matched comparisons. To assess walking recovery (relative to movement strategies used by neurally intact individuals that did not rely on external compensations) individuals with ISCI wore a safety harness attached to an overhead cable and walked without braces, devices, or physical assist.

Bilateral ground reaction forces (GRFs) were recorded at 2000 Hz and kinematic data were recorded at 100 Hz using a 12-camera motion analysis system (Vicon Motion Systems, Los Angelos, CA). Surface electromyograms (EMGs) were recorded at 2000 Hz (Konigsberg Instruments, Pasadena, CA) using Ag-AgCl surface electrodes from eight bilateral LE muscles: tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH), and gluteus medius (GM).

Data Analysis: Kinetic and kinematic data were processed using Visual 3D (C-Motion, Inc., Germantown MD). Raw kinematic and kinetic data were low pass filtered

using a fourth-order zero-lag Butterworth filter with cutoff frequencies of 6 and 20 Hz, respectively. Kinetic data were normalized by each subject's body weight and used to determine the step cycle for each LE. EMG signals were high-pass filtered using a fourth-order zero-lag Butterworth filter at 40 Hz. Signals were demeaned, rectified, and low-pass filtered at 20 Hz or smoothed using a 4 Hz filter (for subsequent analysis using non-negative matrix factorization). All data were time-normalized to 100% of each leg's gait cycle. EMG data from each LE were further divided according to 6 regions of the gait cycle 1) first double- support, 2) first 50% of ipsilateral single-leg stance, 3) second 50% of ipsilateral single leg stance, 4) second double-support, 5) first 50% of ipsilateral swing, and 6) second 50% of ipsilateral swing (Bowden et al. 2010). Custom Matlab programs (Mathworks, Inc., Natick, MA) were used to calculate outcome measures.

Non-negative matrix factorization: EMG data for each muscle were normalized to its peak value for each trial. For each subject and each LE, the original EMG data (EMG_o) from each walking trial were combined into an m x t matrix where m is the number of muscles (8 muscles) and t is the time (t=number of cycles of activity x101 (i.e. 0-100% of the activity cycle)). A non-negative matrix factorization (NNMF) algorithm (Lee and Seung 1999; Ting and Macpherson 2005) was applied to the original m x t matrix. After the number of modules (n) was specified, the NNMF algorithm reconstructed EMG_o by iteratively populating two matrices. For all trials, n was specified to reconstruct the EMG data (EMG_r) using 1 to 5 modules.

Matrix 1 X Matrix 2= EMG_r
Matrix 1= m x n (relative weighting of each muscle within each module)
Matrix 2= n x t (activation of the module across the cycle of locomotor activity)

The NNMF algorithm permits muscles to belong to more than one module, with the weighted contribution of a muscle within a module held constant across the cycle of activity. The reconstructed data, EMG_r, was compared to the original EMG data, EMG_o, by calculating the sum of the squared errors, $(EMG_o-EMG_r)^2$. The NNMF algorithm iteratively reconstructs the data (EMG_r) until the sum of the squared errors is minimized.

Determining the number of modules to reconstruct the original EMG data: For comparison, the NNMF algorithm reconstructed the EMG data using 1 to 5 modules. To determine how well the reconstructed model (EMG_r) adequately explained the variability in the original EMG (EMG_o), the variance accounted for (VAF) was calculated.

$$VAF=1- (EMG_o - EMG_r)^2 / EMG_o^2$$

The overall VAF was calculated for each subject and LE, as well as for each of the 8 muscles and for each region of the gait cycle. Calculation of the VAF across these portions of the data allowed for verification that the data were adequately reconstructed across all muscles and regions of the original data.

Determination of Number of Modules Required: To determine the minimum number of modules required to adequately reconstruct the EMG data, the reconstructed models and VAF values for 1 to 5 modules were reviewed. The fewest number of modules such that the overall VAF was ≥90% and each individual muscle VAF and region of the gait cycle with a VAF≥90% was identified. Thus, 15 criteria were reviewed for each subject, leg, and trial of locomotor activity (Clark et al. 2010). In some instances, the overall VAF was ≥90% but the VAF values for all muscles and regions of the data were <90%. In these cases, if the addition of another module to the

reconstructed model did not increase the VAF for that muscle or region more than 3%, the reconstructed model was accepted (Ting and MacPherson 2005). These criteria indicate that the addition of a module did not make a significant contribution to the reconstructed model. Across all criteria, standards were established to ensure adequate agreement between the reconstructed EMG and the original EMG recordings.

Muscle Coordination: To examine muscle coordination, the relative timing of activation of each muscle within each of the 6 gait regions was determined. To identify periods of relative EMG activation, EMG data were partitioned into periods of activity and inactivity using a k-means clustering algorithm (Den Otter et al. 2006). The k-means cluster algorithm partitions EMG data with similar means. The number of clusters was set a priori to five. EMG data partitioned to the cluster with the lowest value was determined to correspond to periods of inactivity. For each region of the gait cycle, the percent of time that each muscle was active was computed.

Biomechanical Outcomes: Leg angle was calculated based on the angle between a line from the pelvis center of mass (COM) and the foot COM and vertical (Peterson et al. 2010). Foot trajectory range was calculated based on the change in angle of the foot (relative to a global reference frame) from toe off during late stance to initial foot contact during early stance (i.e. maximal downward orientation to maximal upward orientation).

Statistical Analysis: Group differences between controls (13 individuals, n=26 LEs or 10 individuals, n=20 LEs for the modular control analysis) and individuals with ISCI (8 individuals, n=16 LEs) (Hypothesis 1) in the number of modules required to account for EMG activation, individual muscle timing in each of 6 gait regions, and gait

biomechanics were assessed using the Wilcoxon rank-sum test. The significance level for between-group differences was set to $P<0.05$. To examine the effect of LT on gait speed and mechanisms of walking control (Hypothesis 2), within group comparisons (individuals with ISCI pre vs. post-LT) of modular control, individual muscle timing, and gait biomechanics were conducted using the Wilcoxon signed-rank test. The significance level for these within-group comparisons was set to $P<0.05$. Comparisons of pre and post-LT outcome measures were compared for each subject's LE (i.e. subject SCI-01, right LE muscle timing for the TA in gait region 1 pre-LT versus muscle timing in the same muscle/gait region post-LT) using the Wilcoxon signed-rank test. The significance level for individual comparisons was set to $P<0.005$. The association between changes in TM gait speed and changes in gait biomechanics was assessed using Spearman's correlation. In all cases, we did not correct for multiple comparisons and the unadjusted P values are reported (Rothman 1990; Saville 1990).

5.3. Results

Subject demographics and gait speed pre and post-LT: Across the group of eight adults with chronic ISCI, all had injuries classified according to the ASIA Impairment Scale (AIS) as 'D', and outcomes on the LEMS ≥ 40/50, indicating sufficient strength to move their limb against gravity and take resistance when tested during standard manual muscle tests (American Spinal Cord Injury Association 2006) (Table 5-1). Individuals with ISCI walked overground using their typical gait device at speeds of 0.18 m/s to 0.80 m/s and one individual was unable to walk overground (Table 5-1). During TM walking assessments, individuals with ISCI walked without braces, devices, or assistance at an average speed of 0.27 m/s (range 0.15 to 0.50 m/s, SD= 0.10 m/s). Following LT, gait speed increased an average of 0.26 m/s (range -0.05 to 0.65 m/s,

SD=0.23 m/s) and post-LT gait speed averaged 0.54 m/s (range 0.15 to 0.95 m/s, SD=0.30 m/s, P=0.017) (Table 5-2).

The following sections will provide results for group comparisons of individuals with ISCI pre-LT and controls, followed by within-group comparisons of individuals with ISCI pre and post-LT, individual comparisons, and in some cases, results for individual data. Data for each of the primary outcomes are presented: modular organization, muscle coordination and gait biomechanics.

Modular organization in controls and adults with ISCI pre-LT: For 10 control subjects (n=20 LEs), 4 modules was most often required to explain LE muscle activation (3.75 +/- 0.64 modules, mode=4) recorded in 8 muscles during treadmill walking at 0.30m/s (Table 5-2). Across all control LEs, five modules were required 10% of the time, four modules were required 55% of the time, and three modules were required 35% of the time.

The composition of each of the control modules (C-1, C-2, C-3, C-4) in the 4-module set, which represented a sub-set of previously described data, was consistent with our prior report (Figure 5-3) (Clark et al. 2010). Briefly, Module C-1 consisted of co-activation in VM, RF, and to a slightly lesser extent GM. This module was active primarily in early to mid stance. Module C-2 primarily consisted of SO and MG activation and was active during mid to late stance. Module C-3 consisted of TA and RF activation and was distinctly active during early to mid swing. Module C-4 mainly consisted of LH and MH activation and was active during late swing and early stance (Figure 5-3) (Clark et al. 2010).

The number of modules required to account for LE muscle activation during walking across the eight subjects with ISCI (n=16 LEs) did not differ from control subjects (P=0.847) (Tables 5-2, 5-3). Across 16 LEs, four modules were most often needed to explain muscle activity during walking (3.8 +/- 0.75 modules, mode=4) (Table 5-2). Four modules were required 44% of the time, three modules 37% of the time, and 5 modules 19% of the time. Each module in the 4-module group (SCI-1a, SCI-2a, SCI-3a, SCI-4a) had a relatively similar composition and timing as identified in the control modules (Figure 5-4). However, inspection of the weighted contribution of each muscle and timing curves suggests greater variability in the muscle composition and timing of each module identified in the individuals with ISCI. Module SCI-1a primarily consisted of VM, RF, and GM activation, and was active during early to mid stance which is consistent with the biomechanical requirement of weight acceptance at this time in the gait cycle (Clark et al. 2010; Neptune et al. 2009). Module SCI-2a consisted of MG and SO activation during mid to late stance, consistent with the biomechanical subtask of propulsion (Clark et al. 2010; Neptune et al. 2009). Module SCI-3a was dominated by TA activation and to a lesser extent, RF and MH activation. Module SCI-3a typically displayed peak activation during early to mid swing during which time ground clearance is needed for successful stepping (Neptune et al. 2009). Module SCI-4a consisted of MH and LH as well as GM activation during late swing into early stance which is consistent with timing for limb deceleration in preparation and associated with initial contact of the limb (Figure 5-4) (Neptune 2009).

Three modules were required to account for muscle activation in seven of the 16 LEs. Each module in this set of 3 modules displayed greater co-activation across

multiple muscles and less distinct activation timing (Figure 5-5). Module SCI-1b demonstrated features similar to modules SCI-1a and SCI-2a. This module (SCI-1b) consisted of activation of the VM and GM, as well as SO, MG, and RF and was active throughout stance. Module SCI-2b in the 3-module set exhibited muscle composition and timing characteristics similar to module SCI-2a. This module (SCI-2b) consisted primarily of TA and RF activation as well as contributions from MH and GM, and was active during early to mid swing. Module SCI-3b demonstrated features similar to module SCI-2a and SCI-4a in that it consisted of muscle activation from MG as well as MH and LH and timing varied during stance and swing.

Modular organization in adults with ISCI post-LT: Following LT, the overall number of modules needed to explain muscle activation during walking did not change (P=1.000) (Tables 5-2, 5-4). Four modules were most often needed to account for muscle LE muscle activation (3.81 +/- 0.54 modules, mode=4) (Table 5-2). While the average number of modules required to account for muscle activation in each LE did not change post-LT, nearly half of all LEs exhibited a change in the number of modules needed (Table 5-2, Figure 5-6). Four LEs exhibited an increase in the number of modules, while four legs decreased in the number of modules required. Across the 9 LEs that did not initially require 4 modules pre-LT, six LEs required 4 modules following LT and three did not change. Thus, following LT, 69% of the LEs required 4 modules (Figure 5-6). The set of 4 modules (SCI-1c, SCI-2c, SCI-3c, SCI-4c) identified post-LT was relatively consistent in composition and timing with the set of 4 modules identified during walking pre-LT and in controls (Figure 5-4) (Clark et al. 2010).

Muscle coordination in controls and adults with ISCI pre-LT: Group comparisons of muscle timing (the percentage of time each muscle was active in each of 6 gait regions) in control subjects (13 control subjects; n=26 LEs) and subjects with ISCI (8 subjects with ISCI, n=16 LEs) revealed significant differences ($P<0.05$) in the timing of activation in 26 of 48 comparisons (8 muscles x 6 gait regions) (Table 5-3). Of these 26 differences, 21 were due to increased duration of muscle activity in individuals with ISCI. The highest proportions of group differences were present in gait regions 4 (late stance) and 6 (second half of swing). Sixteen of the 26 differences in muscle activation timing occurred in gait regions 4, 5, and 6 and in nearly instances, individuals with ISCI exhibited prolonged duration of muscle activation. In contrast, decreased duration of muscle activation was identified in the SO muscle during gait regions 2 through 4 (mid through late stance) and in GM in gait regions 2 and 3 (mid stance) (Table 5-3).

Muscle coordination in individuals with ISCI post-LT: Within-group comparisons of muscle timing pre and post-LT identified a significant change (reduction) in muscle timing post-LT in the GM muscle in gait region 3, during mid to late swing ($P=0.015$). Post-LT changes in SO duration (increased) in mid to late stance (region 3) and GM timing (decreased) in region 4 (late stance) approached significance ($P=0.070$ and $P=0.079$, respectively) (Table 5-4; Figure 5-7). A high level of variability in the timing of muscle activation was evident in the EMG recordings from individuals with ISCI pre and post-LT (Figure 5-7).

While few within group differences in muscle timing were identified, pre-post comparisons of each of the 16 LEs across 8 muscles within 6 gait regions identified

changes in muscle timing (P<0.005) post-LT in 25% of the comparisons (193/768; 16 LEs x 8 muscles x 6 gait regions=768) (Figure 5-1). A relatively high proportion of these changes (39 of 193 changes, 20%) occurred in gait region 4 during late stance. Of these 39 changes in late stance, 24 represented decreased duration of muscle activation post-LT. In contrast, the 36 changes in muscle timing in gait regions were largely due to increased duration of muscle activation (Figure 5-1).

Each significant change in muscle activation (P<0.005) was evaluated to determine if the change was due to muscle timing becoming more or less similar to the timing exhibited by control subjects. Of the 193 significant changes in muscle timing, 72 (37%) were due to post-LT muscle timing becoming more similar to controls (for that specific LE/muscle/gait region) (Figure 5-2). Significant changes in muscle timing towards control values were most apparent during late stance (region 4) and early swing (region 5). More than half of these changes were due to decreased duration of muscle activation post-LT.

For each LE of each subject with ISCI, the total number of significant changes in muscle timing was determined (Table 5-2; Figure 5-9). Five subjects demonstrated six or more significant changes (P<0.005) in muscle timing. Of the three subjects that did not exhibit changes in muscle timing, one subject decreased slightly in their post-LT TM gait speed (SCI15) and another increased only 0.10 m/s in their post-LT gait speed (SCI08) (Table 5-2; Figure 5-10). SCI07 also did not exhibit changes in muscle timing post-LT; however, he made the largest gain in TM gait speed post-LT and visual inspection of his LE EMGs recorded pre and post-LT indicated muscle timing similar to controls (Figure 5-11).

Gait biomechanics in controls and adults with ISCI pre-LT: Individuals with ISCI exhibited altered gait biomechanics relative to controls walking at a similar speed as evidenced by decreased maximal leg angle (P=0.000) and decreased foot trajectory range (P=0.000). The minimal leg angle, which is achieved when the LE is in an extended position during late stance did not differ between the two groups (P=0.400) (Tables 5-2, 5-3; Figure 5-8).

Gait biomechanics in individuals with ISCI post-LT: Following LT, within group comparisons of subjects with ISCI revealed significant changes in all biomechanical outcomes (P<0.05) (Tables 5-2, 5-4; Figure 5-8). Minimal leg angle decreased (more negative angle as the leg is posterior to the pelvis) (P=0.002) and maximal leg angle increased (P=0.006). Foot trajectory range also increased (P=0.002), indicating greater excursion of the foot angle (relative to the global reference frame) from terminal stance to initial contact. For each biomechanical outcome measure, the total change for both LEs in each ISCI subject was correlated with changes in TM gait speed post-LT. Maximal leg angle changes and changes in foot trajectory range positively correlated with changes in TM gait speed (r=0.738, P=0.037; r=0.833, P=0.010 respectively).

For each biomechanical outcome measure, individual comparisons of each LE pre and post-LT were assessed. Although five subjects exhibited significant changes (P<0.005) in biomechanical control across the three outcome measures, post-LT changes in biomechanical control were not detected in three individuals with ISCI. These three individuals also did not exhibit significant changes in muscle timing (Table 5-2).

5.4. Discussion

The results suggest that the modular organization of muscle coordination during unassisted TM walking without devices is preserved in adults with chronic ISCI (AIS 'D') (American Spinal Injury Association 2006). The majority of the LEs in the group of injured adults (pre-LT) exhibited modularity similar to controls walking at comparable speeds. While this fundamental low-dimensional organization of coordinated muscle activity was preserved, the timing of individual muscles across the gait cycle was altered, largely due to prolonged activation in each gait region, relative to controls. Furthermore, individuals with ISCI walked with impaired gait biomechanics as evidenced by reduced maximal leg angles and foot trajectory ranges during stepping.

Following 45-sessions of LT, a greater number of LEs required four modules to explain walking muscle activation, suggesting modular control was altered post-LT and more similar to controls. A large number of individual muscle changes (across the 16 LEs) were evident post-LT and are likely associated with the changes in modular control. More than one third (37%) of the significant muscle timing changes post-LT represented muscle timing more similar to controls, which was largely due to decreased duration of muscle activation. Concomitant with individual changes in muscle timing were changes in minimal and maximal leg angles and foot trajectory range. Changes reflected more normal gait biomechanics in the group of individuals with ISCI post-LT. Furthermore, improved gait biomechanics were associated with gains in unassisted TM gait speed following LT.

This study examined walking function and underlying control mechanisms relative to walking performance prior to injury, i.e. without the use of braces and assistive devices. The experiments were directed at examination of recovered walking

rather than walking control relative to external compensations such as braces and devices. The results suggest that fundamental patterns of muscle activation may be preserved in ambulatory individuals with chronic ISCI and that the overall contribution of LE muscles and timing of each motor module is similar to uninjured controls. The intense stepping practice provided by LT may alter modular control as well the timing of individual muscle activation across the gait cycle, and also lead to improvements in step biomechanics. While overall modularity may be preserved post SCI, the variability of muscle timing pre and post-LT suggests that individuals with ISCI may adopt individual motor solutions and prioritize limb position to achieve functional stepping. The use of an individual motor solution may reflect the unique impact of an individual's injury, their past and recent motor experiences, including rehabilitation and daily step practice, as well as the plasticity within their neuromuscular system. These findings also indicate that improved LE biomechanical control is associated with post-LT gait improvements, as evidenced by increased gait speed without reliance on devices or braces.

Modular organization of walking in adults with ISCI pre-LT: The data suggest that similar to controls, three or four independently timed motor modules may account for LE muscle activation during walking in adults with chronic ISCI. In the 4-module set, for both groups, the weighted contribution of muscle activation was similar. The modules detected in both groups displayed activation timing that corresponded appropriately to the biomechanical requirements of walking (i.e. weight acceptance, propulsion, ground clearance, limb deceleration) (Neptune et al. 2009). The pattern of muscle co-activation and timing of the modules identified in the individuals with ISCI is consistent with previous studies of modular control in healthy adults (Clark et al. 2010),

individuals post-stroke (Bowden et al. 2009; Clark et al. 2010; Davis and Vaughan 1993), as well as studies of modular control using computer simulations (Neptune et al. 2009).

Ivanenko et al. (2003) previously examined the modular organization of muscle activation during walking in healthy adults and adults with SCI. A set of five temporal patterns of muscle activation were identified. Although these patterns exhibited consistent timing across the gait cycle and corresponded to stepping biomechanics, the muscle contributions to each factor or module varied across individuals with SCI and between the groups (Ivanenko et al. 2003). Several methodological differences exist between this prior study of individuals with SCI and our investigation, such as the severity and chronicity of the subjects' injuries, differing computational approaches and criteria for selecting the number of factors (modules), as well as a large disparity in the number of EMG recordings (i.e. Ivanenko et al. recorded from more than 20 muscles across the upper and lower limbs and trunk) (Ivanenko et al. 2003).

A portion of the LEs in both groups required three modules to explain walking muscle activation. The three-module sets in both groups exhibited greater muscle co-activation and less distinct activation timing. Clark et al. (2010) reported that individuals post-stroke co-activate modules, resulting in two or three modules being sufficient to account for walking muscle activation, especially when gait impairments are severe. Thus, four fundamental modules were identified in the adults post-stroke, but the modules were not individually activated (Clark et al. 2010). Gizzi et al. (2011) recently challenged the notion that motor modules post stroke are similar to healthy controls. Their study of post-stroke modular control suggests that healthy motor modules do not

sufficiently account for muscle activation during ambulation, but that modularity is indeed preserved post-stroke (Gizzi et al. 2011). Our report, taken together with these studies of modular control in individuals with neurologic injury, suggests that modular organization of muscle coordination persists after central nervous system damage. This is consistent with studies of amphibian limb control indicating that functional limb movements are controlled by the flexible combination of functional muscle groupings or synergies (Cheung et al. 2005; d'Avella et al. 2003; Giszter et al. 1993; Tresch et al. 1999) and these control mechanisms are present in the absence of supraspinal (Tresch et al. 1999) and afferent input (Giszter et al. 1993). Although fundamental patterns of limb control remain when descending and afferent input is removed, vertebrate experiments also indicate that the modulation of neuromuscular modules is distributed across the neural axis. Neurologic injury, therefore, alters the activation of these functional muscle groups (Cheung et al. 2005; Hart and Giszter 2004). Following human ISCI, not only is descending supraspinal input altered, but ascending input from the level of the lesion and below the injured spinal segments is also changed. Furthermore, since motor output and walking performance is impaired, afferent input from abnormal movement strategies further disrupts afferent input.

Modular control of locomotion post LT: Although the overall number of modules required to explain muscle activation during walking did not change (P=1.000) following LT and remained consistent at four modules, nearly half of LEs exhibited a change in the number of modules required. Six of the nine LEs that did not initially require four modules were altered post-LT and were explained by four modules following training. This finding suggests that LT altered the modular coordination of

muscle activation. Furthermore, these changes may reflect more normal or appropriate neuromuscular control indicating that LT stabilized or normalized the modular organization of walking control.

Changes in modular control post-LT may be attributed to neuromuscular adaptations or activity-dependent plasticity associated with the intensive, repetitive stepping practice provided by LT (Behrman and Harkema 2007; Edgerton et al. 2004; Edgerton et al. 2007; Hodgson et al. 1994; Wolpaw and Tennissen 2001). Translated from animal models of SCI and walking recovery (Barbeau and Rossignol 1987; de Leon et al. 1998; Lovely et al. 1986; Hodgson et al. 1994), LT emphasizes repetitive stepping and speeds approximating normal gait speed (0.80-1.2 m/s) (Craik and Dutterer 1995) with upright trunk posture, appropriate limb kinematics, and LE limb loading (Behrman and Harkema 2007; Beres-Jones and Harkema 2004; Dietz et al. 2002; Edgerton et al. 1992; Harkema et al. 1997). This ensemble of sensory inputs improves patterns of muscle activation during stepping (Edgerton et al. 2004; Maegele et al. 2002) and enhances activity-dependent plasticity (Edgerton et al. 2004). Therefore, repetitive task-specific practice using stepping strategies in a manner similar to uninjured adults may lead to changes in the muscle activation, reflecting more normal neuromuscular control (Dietz et al. 2002).

Neural changes associated with LT may have occurred via numerous mechanisms, such as strengthening residual or intact pathways (Barbeau and Rossignol 1987; de Leon et al. 1998) which may be associated with increased corticospinal tract activation (Norton and Gorassini 2006; Thomas and Gorassini 2005) as well as activation of spinal circuitry (Barriere et al. 2008). Furthermore, changes in

neuromuscular control may be mediated by mechanisms associated with interlimb coordination, which also is emphasized during LT (Tester et al. 2010; Zehr et al. 2007).

Muscle coordination and gait biomechanics in adults with ISCI pre-LT: Although modular control mechanisms exhibited by the two groups was similar, timing of individual muscles across six gait regions as well as LE biomechanics were altered in the individuals with ISCI. Across the large number of differences in muscle timing between the two groups, most differences were due to prolonged muscle activation in each gait region. This is consistent with prior studies of muscle timing relative to controls (Dietz et al. 1995; Gorassini et al. 2009). Gorassini et al (2009) investigated the burst duration of four LE muscles and identified prolonged activation of thigh and calf muscles across the step cycle. Prolonged muscle activation in individuals with ISCI is likely associated with the spastic gait pattern often exhibited by individuals with ISCI (Scivoletto et al. 2008). Altered muscle timing and gait biomechanics also may reflect different movement strategies used by the individuals with ISCI. For instance, each subject with ISCI relied on an assistive device to walk over ground. To examine walking relative to normal walking abilities, however, individuals were required to TM walk without devices or assistance. Without the use of external compensations individuals with ISCI may have adopted motor compensations to achieve functional stepping without their typical assistive.

Muscle coordination in adults with ISCI post-LT: Pre and post-LT individuals with ISCI exhibited varied muscle coordination or timing across the gait cycle (Figure 5-7). This is consistent with prior studies (Gorassini et al. 2009; Ivanenko et al. 2003) and may be explained by the group's varied injury characteristics, such as duration of injury,

injury level, and ambulation and rehabilitation experience. Given these diverse injury characteristics and experiences, as well as varied muscle timing pre-LT, it was not unexpected that individuals with ISCI demonstrated individualized changes in muscle timing in response to LT (Dietz 2011). Although LT afforded consistent, repetitive stepping practice, this was accomplished with an altered or 'new' nervous system post-injury (Edgerton et al. 2007)

Within-group changes in muscle timing post-LT were evident only for the duration of GM activation in mid stance which was reduced post-LT (P=0.015) (Table 5-4; Figure 5-7). This change in muscle timing reflects more normal activation, as the gluteals are primarily active in early stance for body support (Neptune et al. 2004). What is most meaningful is that five of eight individuals demonstrated numerous individualized changes in muscle timing following LT. These five individuals also exhibited improved gait recovery and gait biomechanics. Overall, 37% of these individualized changes were in the direction of muscle timing similar to controls and were primarily associated with decreased duration of muscle activation. Gorassini et al. (2009) also identified varied responses in muscle timing following a treadmill walking intervention. This study identified decreased duration of quadriceps activation and increased duration of the hamstrings, TA and SO in the group that responded to the intervention. Changes in the duration of muscle activation, however, were quantified across the entire step cycle, rather than for specific regions within the gait cycle. Furthermore, the walking intervention differed from ours in that step practice on the treadmill was conducted at a slow pace (0.20-0.60 m/s), which is well-below normal walking speeds (Gorassini et al. 2009).

While more than one third of the changes in muscle timing were more similar to controls, overall responses appeared to be individualized. This is consistent with previous studies that indicated muscle timing does not revert to normal and individuals with ISCI may develop altered muscle coordination to achieve functional stepping (Ivanenko et al. 2003). Another explanation for altered muscle timing is that the stepping movement strategies post-LT remained altered. While gait deviations were diminished, as evidenced by more normal gait biomechanics, gait deviations may have persisted and altered muscle timing post-LT.

Gait biomechanics in adults with ISCI pre-LT: Prior to LT, individuals with ISCI used stepping strategies that were characterized by reduced maximal leg angles and decreased foot trajectory ranges compared to controls. Reduced maximal leg angle reflects an impaired ability to bring the leg or foot sufficiently anterior to the pelvic COM during terminal swing, in preparation for initial contact. Reduced maximal leg angle may be associated with impaired spatiotemporal gait characteristics and altered step kinematics such as reduced step length or increased knee flexion at initial contact.

Reduced foot trajectory range relative to controls walking at similar speeds may be due to decreased foot angle at terminal stance and/or at initial contact. At terminal stance, foot angle may be reduced if propulsion of the body COM during mid to late stance is decreased which is associated with insufficient activation of the ankle plantar flexors as well as early or increased activation of RF during late stance or pre swing (Neptune et al. 2004; Turns et al. 2007). Indeed, compared to controls, individuals with ISCI exhibited decreased duration SO activation during mid to late stance and increased duration of the RF during late stance (gait region 4) (Table 5-3; Figure 5-7).

Increased RF activation may be associated with premature unloading of the stance limb, which interferes with propulsion generation during late stance (Turns et al. 2007). Thus, the altered muscle timing exhibited by the individuals with ISCI may underlie these alterations in gait biomechanics. At initial contact, decreased foot angle is associated with decreased ankle dorsiflexion or ground clearance during swing and is a common gait impairment in individuals with ISCI (Barthelemy et al. 2010).

Gait biomechanics in adults with ISCI post-LT: Post-LT, minimal and maximal leg angles and foot trajectory range improved to be more similar to controls. Increased maximal leg angle may be related to several factors such as increased step length associated with increased gait speed and increased knee joint extension at initial contact, compared to pre-LT. A decrease in the minimal leg angle, indicating that the foot COM was more posterior to the pelvis COM at terminal stance may be associated with improved postural alignment including upright trunk posture and greater hip and knee extension at terminal stance. Furthermore, because gait speed post-LT increased, forward propulsion of the body COM likely increased (Neptune et al. 2003). Forward propulsion is associated with increased gait speed and walking function in individuals with ISCI (Gregory et al. 2007) as well as individuals post stroke (Bowden et al. 2006; Balasubramanian et al. 2007). Moreover, a recent study identified leg extension angle (i.e. minimal leg angle) to be a predictor of leg propulsion in controls and adults post stroke (Peterson et al. 2010).

An increase in the foot trajectory range post-LT suggests individuals increased their downward foot angle (plantarflexion) at terminal stance and/or increased their positive foot angle at initial contact (dorsiflexion). Across this range of movement that

occurs during swing, numerous biomechanical and neuromuscular adjustments may have contributed to increased foot trajectory ranges. Control of the foot during this period in the gait cycle is critical for foot clearance and to advance the leg forward. Furthermore, the position of the foot during swing has been proposed as a control feature of walking such that individuals with ISCI may control foot kinematics using varied motor strategies in order to achieve functional walking (Ivanenko et al. 2003). Our finding of increased foot trajectory range in association with increased gait speed is consistent with studies that identified this as an important control mechanism (Grasso et al. 2004; Ivanenko et al. 2003).

Methodological considerations: This study examined 8 ambulatory adults with chronic ISCI. Interestingly, although this study examined a group of individuals with injuries classified as AIS 'D' and all had scores on the LEMS >40/50 (range 40 to 45/50, SD=2.6), individuals demonstrated highly diverse initial walking abilities (pre-LT) and varied responses to LT. Although the heterogeneity in walking ability that was observed is not unique to this study of individuals with ISCI (Behrman et al. 2011), increased variability in the data may have affected the ability to detect between and within group differences. Moreover, this study specifically examined walking control relative to pre-injury movement strategies. This required that individuals walk without external compensations such as assistive devices that would have likely stabilized or constrained movement variability. Furthermore, stepping without external support from devices and braces may have decreased the number of consecutive steps that the subjects were able to take during each stepping trial. Therefore, the data set may be influenced by data representing fewer steps and greater movement variability.

The methodology used in this study for assessing modular control is consistent with previous studies, including the parameters to determine the number of modules required to account for muscle activation (Clark et al. 2010; Ting and Macpherson 2005). Therefore, the determination of the number of modules and comparisons to previous studies of modular control is appropriate. Modular control exhibited by individuals with ISCI was similar to uninjured control subjects, as evidenced by similar muscle contributions and activation timing. Future studies, however, may build upon our findings and examine whether the selection and relative level of muscle activation that was identified in each control module is sufficient to account for muscle activation recorded in the LE muscles of individuals with ISCI (Gizzi et al. 2001; Torres-Oviedo et al. 2006).

Finally, although several mechanisms of walking control were examined and the outcomes are consistent with prior studies of walking function in adults with neurologic injury, there are likely numerous mechanisms underlying walking control and response to LT. For instance, individual muscle timing was examined, but the amplitude of muscle activation was not evaluated. This was likely altered in individuals with ISCI and may have been affected by LT (Dietz and Harkema 2004). Furthermore, this study focused select biomechanical outcomes that have functional relevance in individuals with neurologic injury (Ivanenko et al. 2003; Peterson et al. 2010).

Clinical application: Impairment-level tests of voluntary muscle strength and the LEMS have traditionally been associated with walking function following ISCI (Burns et al. 1997; Crozier et al. 1992; Scivoletto et al. 2008). Based on this, one would expect that scores of >40/50 on the LEMS would be associated with nearly complete recovery

of walking function. The homogeneous sample of adults with ISCI (8/8 subjects with injuries classified as AIS 'D') did not, however, demonstrate homogeneity in their initial walking speed (Table 5-2) or in the underlying mechanisms associated with walking control. In order to better discriminate walking function and control, a task-specific approach to examine locomotor control and the effect of LT on walking recovery was used. This task-specific approach uniquely minimized or eliminated external compensations during the examination of walking and thus removed this influence on underlying control mechanisms and performance of walking after ISCI (Melis et al. 1999; Visintin and Barbeau 1994). This novel approach provided the opportunity to examine walking in a manner that more closely approximates 'pre-injury' walking strategies. Furthermore, while responses to LT overall demonstrated a significant increase (P=0.017) in gait speed and, on average, gait speed increased 0.26+/-0.23m/s, individual responses to LT varied (-0.05 to 0.65 m/s). This finding, along with our examination of the neuromuscular and biomechanical control variables, therefore, broadens our understanding of the complex factors contributing to walking recovery after ISCI.

Emerging evidence suggests that examinations of task-specific motor control relative to normal or pre-injury movement strategies better discriminate levels of functional ability after ISCI and therefore may provide more specific data or knowledge of factors associated with recovered function or response to therapeutic interventions (Behrman et al. 2011). While new approaches for examining functional recovery are being developed (Behrman et al. 2011), we remain limited in our standardized assessments of walking function that do not discriminate or account for *how* an

individual walks (Jackson et al. 2008; Steeves et al. 2007) and the impact of altered gait strategies (e.g. use of a walker) on the capacity of the nervous system to control walking (Harkema 2001; Visintin and Barbeau 1994). Although rehabilitation of walking now emphasizes principles based on the neuromuscular control of walking and the necessity of task-specific training, clinical assessments of motor control and function continue to emphasize impairment-level tests or measures of walking that do not differentiate how an individual walks or their walking function relative to strategies used prior to injury (recovery) (Jackson et al. 2008; Scivoletto et al. 2008).

Summary: Our task-specific examination of walking provides evidence of fundamental patterns of neuromuscular activation suggesting that a modular organization of muscle coordination persists in ambulatory adults with chronic ISCI. While these basic patterns of muscle co-activation may serve as an underlying control mechanism and were responsive to LT, individuals with ISCI exhibited altered muscle coordination relative to controls prior to and following LT. Ambulatory adults with ISCI therefore may develop individualized motor solutions to achieve functional stepping and appropriate limb biomechanics. This investigation provides evidence of this in that muscle timing varied while LE biomechanics improved in association with gains in walking speed post-LT. These findings of varied walking control and response to LT in a group of adults, all with similar injury classifications and LE muscle strength, point to the necessity to apply more discriminatory, task-specific assessments that examine function recovery.

5.5. Tables and Figures

Table 5-1. Participant demographic information at the time of enrollment.

Subject Gender	Age (years)	Injury level	AIS	Injury duration (months)	LEMS (max=50)	OG gait speed (m/s)	Assistive device	LT
SCI-01M	45	C5-6	D	10.0	43.0	0.41	RW	R
SCI-05M	55	C4	D	45.5	45.0	0.38	cane	R
SCI-07F	48	C5	D	25.5	46.0	0.80	cane	M
SCI-08M	26	T3-4	D	11.0	40.0	0.21	RW	R
SCI-11M	66	C7	D	78.0	49.0	0.68	cane	M
SCI-13F	47	C4	D	6.5	43.0	0.18	RW	R
SCI-15M	21	C6	D	7.0	45.0	*	RW	M
SCI-19F	51	C4-5	D	7.5	45.0	0.75	cane	R
Avg	45			24.0	44.5	0.49		
SD	15			26.0	2.6	0.26		

Notes: The American Spinal Injury Association Impairment Scale (AIS), lower extremity motor score (LEMS), overground (OG) gait speed, assistive device use such as a rolling walker (RW) or single point cane (cane), locomotor training (LT) intervention using robotic (R) or manual (M) assistance, as well as the average (Avg) and standard deviation (SD)values are indicated. The asterisk (*) indicates that the subject could not walk overground to complete the assessment

Table 5-2. Summary of data for the subjects with incomplete spinal cord injury and average control data.

Subject	Pre TM m/s	Post TM m/s	TM chge m/s	Pre mod	Post mod	Pre foot traj	Post foot traj	Pre angle min	Post angle min	Pre angle max	Post angle max	Num mscl chgs
SCI-01	0.30	0.63	0.33	4/4	4/3	21.4/29.7	35.4*/40.4*	-13.9/-10.9	-21.3*/-20.0*	7.7/9.0	16.3*/16.7*	6/18
SCI-05	0.25	0.40	0.15	3/3	3/3	16.2/15.3	26.6*/25.8*	-5.4/-9.3	-15.1*/-18.4*	7.9/4.8	6.7/4.4***	9/11
SCI-07	0.30	0.95	0.65	5/4	4/4	56.9/36.8	92.8/59.7	-17.8/-17.2	-28.0/-27.8	13.3/10.6	17.1/16.7	0/0
SCI-08	0.15	0.25	0.10	3/3	4/4	13.8/12.5	00.0/33.0	-14.8/-10.6	-18.1/-13.9	2.2/5.1	4.5/5.3	0/0
SCI-11	0.50	0.90	0.40	4/4	3/4	51.2/43.6	65.6*/59.6*	-20.7/-20.2	-22.3*/-22.5*	7.2/7.8	12.6*/13.2*	17/22
SCI-13	0.24	0.30	0.06	3/3	4/4	14.0/19.2	22.1*/27.6*	-9.19/-5.6	-15.4*/-11.8*	-0.2/2.5	1.9/3.8	22/38
SCI-15	0.20	0.15	-0.05	5/5	4/5	0.2/37.6	30.1/29.4	-20.1/-22.7	-21.4/-18.8	7.0/6.9	5.6/5.6	0/0
SCI-19	0.25	0.70	0.45	4/4	4/4	54.2/27.0	76.3*/46.1	-18.2/-20.7	-21.3*/-23.2**	6.0/2.8	14.3*/14.8*	26/24
Avg.	0.27	0.54	0.26	3.81	3.81	28.09	41.90	-14.83	-19.96	6.29	9.97	
SD	0.10	0.30	0.23	0.75	0.54	16.96	23.45	5.68	4.54	3.39	5.63	
Control Avg.						49.96		-16.87		11.18		
Control SD						13.87		3.39		2.17		

Notes: Individual pre and post-locomotor training (LT) treadmill (TM) gait speeds are indicated as well as the change in TM gait speed (TM chge). Average data for each individual is present for pre and post-LT (post) for the number of modules required (mod), foot trajectory range (foot traj), minimal leg angle (angle min), maximal leg angle (angle max) and the total number of significant changes in each subject's lower extremity (Num muscle chgs). Data are indicated for each subject's right and left leg (left/right). Astersks indicate the following: *P<0.005, **P=0.007, ***P<0.005, decrease in post-LT value

Table 5-3. Group comparisons of muscle activation timing, the number of modules required (Modules), minimal (Min) leg angle, maximal (Max) leg angle, and foot trajectory (traj) range are indicated for individuals with incomplete spinal cord injury (ISCI) and controls (C).

Gait region:	Region 1	Region 2	Region 3	Region 4	Region 5	Region 6
TA	P=0.062	P=0.092	P=0.907	P=0.000 (ISCI>C)	P=0.000 (ISCI>C)	P=0.979
MG	P=0.001 ISCI>C	P=0.604	P=0.147	P=0.008 (ISCI>C)	P=0.484	P=0.000 (ISCI>C)
SO	P=0.062	P=0.006 (ISCI<C)	P=0.023 (ISCI<C)	P=0.046 (ISCI<C)	P=0.143	P=0.003 (ISCI>C)
VM	P=0.856	P=0.001 (ISCI>C)	P=0.000 (ISCI>C)	P=0.233	P=0.716	P=0.338
RF	P=0.108	P=0.604	P=0.087	P=0.000 (ISCI>C)	P=0.001 (ISCI>C)	P=0.013 (ISCI>C)
LH	P=1.000	P=0.009 (ISCI>C)	P=0.016 (ISCI>C)	P=007 (ISCI>C)	P=0.468	P=0.021 (ISCI>C)
MH	P=0.244	P=0.979	P=0.484	P=0.001 (ISCI>C)	P=0.014 (ISCI>C)	P=0.005 (ISCI>C)
GM	P=0.032 (ISCI>C)	P=0.007 (ISCI<C)	P=0.000 (ISCI<C)	P=0.623	P=0.002 (ISCI>C)	P=0.001 (ISCI>C)

Modules	P=0.847
Min leg angle	P=0.400
Max leg angle	P=0.000 (ISCI<C)
Foot traj range	P=0.000 (ISCI<C)

Notes: Muscle timing for the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM) are indicated for each of the six gait regions. Unadjusted P values are reported and for each significant comparison (P<0.05) whether the outcome variable was greater in individuals with ISCI (ISCI>C) or less than (ISCI<C) the control group is indicated.

	Region 1	Region 2	Region 3	Region 4	Region 5	Region 6	Number of legs with altered timing
TA	2 TOT 2 INCR 0 DECR	2 TOT 2 INCR 0 DECR	1 TOT 1 INCR 0 DECR	4 TOT 2 INCR 2 DECR	3 TOT 0 INCR 3 DECR	6 TOT 2 INCR 4 DECR	18 TOT 9 INCR 9 DECR
MG	4 4 0	4 3 1	3 3 0	3 1 2	2 1 1	5 2 3	21 14 7
SO	4 2 2	3 1 2	2 2 0	2 1 1	5 4 1	4 3 1	20 13 7
VM	5 4 1	5 3 2	5 3 2	7 3 4	3 3 0	3 3 0	28 19 9
RF	7 4 3	3 1 2	5 3 2	6 4 2	3 0 3	3 2 1	27 14 13
LH	5 4 1	4 2 2	5 1 4	5 2 3	4 2 2	4 2 2	27 13 14
MH	6 4 2	4 2 2	4 2 2	6 1 5	5 2 3	3 1 2	28 12 16
GM	3 2 1	5 1 4	4 1 3	6 1 5	3 2 1	3 3 0	24 10 14
Number of legs with altered timing in each gait region	36 TOT 26 INCR 10 DECR	30 TOT 15 INCR 15 DECR	29 TOT 16 INCR 13 DECR	39 TOT 15 INCR 24 DECR	28 TOT 14 INCR 14 DECR	31 TOT 18 INCR 13 DECR	193 TOT

Figure 5-1. Proportion of lower extremities (LEs) (n=16 LEs) with significant changes (P<0.005) in post-locomotor training muscle timing within each of the 6 gait regions for individuals with incomplete spinal cord injury. Timing changes are indicated for the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). The total (TOT) number of changes for each muscle and gait region is indicated in black. The numbers below the total indicate the number of legs exhibiting an increase (INCR) in the duration of activation (red) or a decrease (DECR) (blue). The muscle and gait regions with five or more significant changes are shaded based on whether the majority of the changes represent increases (red) or decreases (blue) in timing. The final column and row indicate the total number of LEs with altered muscle timing in each of the 8 muscles and the 6 gait regions.

	Region 1	Region 2	Region 3	Region 4	Region 5	Region 6	Number of legs with altered timing
TA	1/2 1 INCR 0 DECR	2/2 2 INCR 0 DECR	0/1	2/4 0 INCR 2 DECR	1/3 0 INCR 1 DECR	2/6 0 INCR 2 DECR	8/18 (44.4%)
MG	0/4	2/4 1 1	2/3 2 0	1/3 0 1	2/2 1 1	3/5 0 3	10/21 (47.6%)
SO	3/4 1 2	1/3 1 0	1/2 1 0	2/2 1 1	1/5 0 1	0/4	8/20 (40.0%)
VM	0/5	1/5 0 1	2/5 1 1	3/7 1 2	2/3 2 0	1/2 1 0	9/28 (32.1)
RF	1/7 0 1	1/3 0 1	3/5 2 1	2/6 0 2	2/3 0 2	0/3	9/27 (33.3%)
LH	0/5	1/4 0 1	1/5 0 1	1/5 0 1	3/4 1 2	2/4 1 1	8/27 (29.6%)
MH	0/6	1/4 1 0	1/4 1 0	5/6 0 5	3/5 0 3	2/3 0 2	12/28 (42.9%)
GM	1/3 1 0	1/5 1 0	1/4 1 0	4/6 0 4	1/3 0 1	0/3	8/24 (33.3%)
Number of legs with altered timing in each gait region	6/36 (16.7%)	10/30 (33.3%)	11/29 (37.9%)	20/39 (51.3%)	15/28 (53.6%)	10/31 (32.3%)	72/193 (37.3%) Changes more like controls

Figure 5-2. Proportion of the significant changes (P<0.005) in muscle timing (pre versus post-locomotor training (LT) as indicated in Figure 5-1) that resulted in post-LT muscle timing more similar to controls. Timing changes are indicated for the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). The numerator indicates the number of changes that represent timing more similar to controls, out of the total number of significant changes (denominator) in that muscle and gait region. Numbers in red indicate changes in timing more similar to controls due to an increase (INCR) in the duration, whereas blue numbers indicate greater similarity to controls due to decreased (DECR) duration. The final column and row indicate the total proportion of LEs that exhibited muscle timing more similar to controls post-LT.

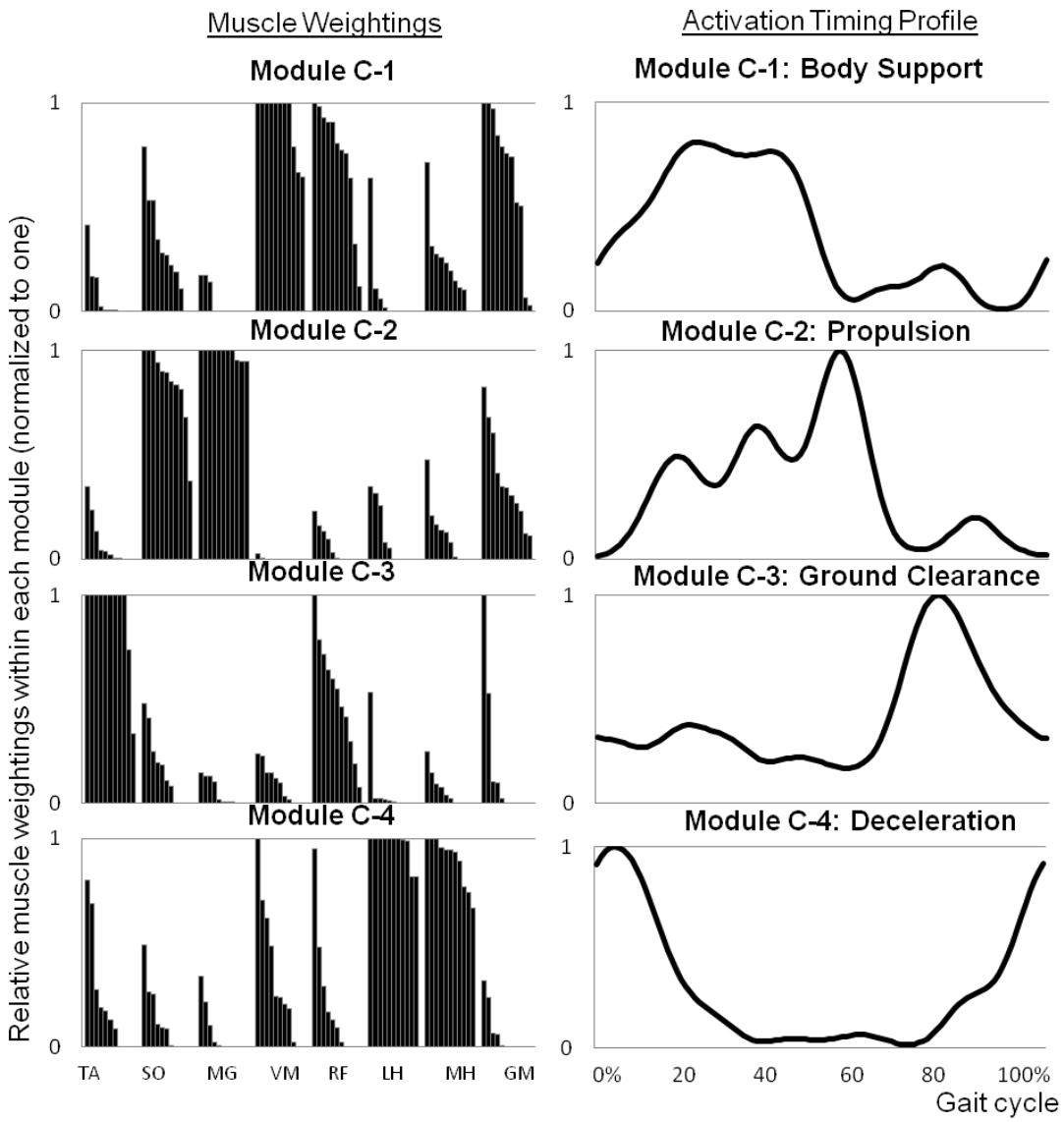

Figure 5-3. Module muscle weights and activation timing curves (C-1, C-2, C-3, C-4) for control subjects walking at 0.30 m/s. Module muscle weights for each control leg (n=20) are represented in the bar graphs for tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). The relative strength of representation of each muscle within a module is indicated. Muscle weights are normalized to the muscle with the greatest representation, which is set to one. Activation timing curves indicate the relative module activation across the gait cycle (0 to 100%).

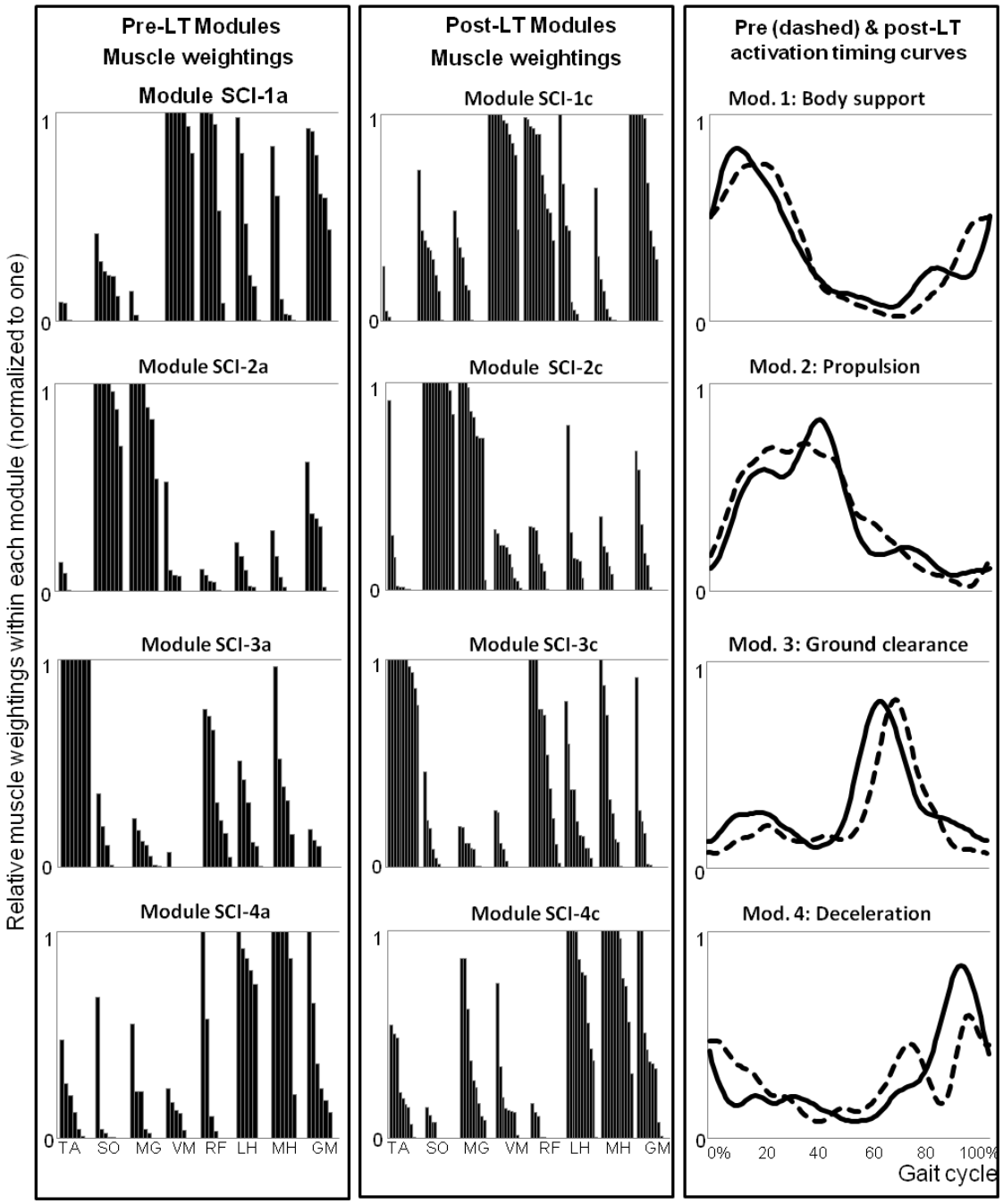

Figure 5-4. Module muscle weights and activation timing curves for individuals with incomplete spinal cord injury pre and post-locomotor training. Module muscle weights for each leg (n=16) are represented in the bar graphs for tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). The relative strength of representation of each muscle within a module is indicated. Muscle weights are normalized to the muscle with the greatest representation, which is set to one. Timing curves indicate the relative module activation across the gait cycle (0 to 100%).

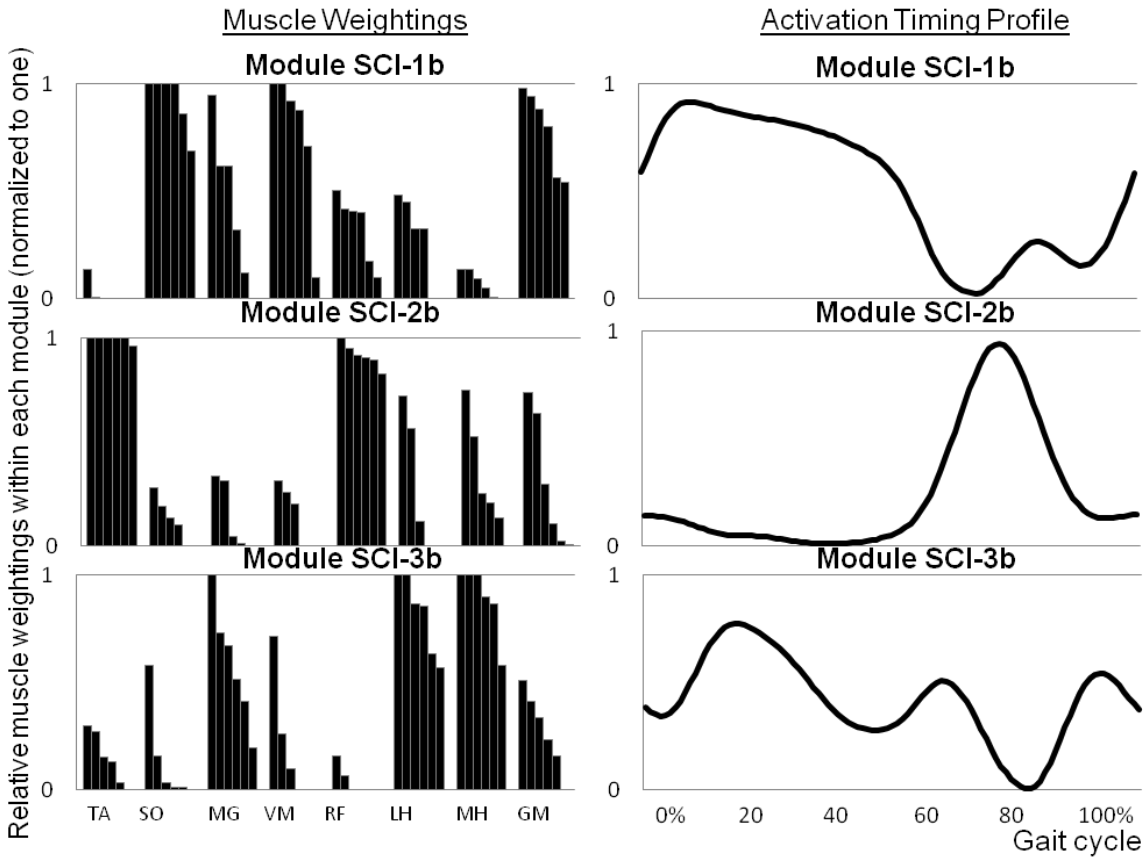

Figure 5-5. Module muscle weights and activation timing curves for individuals with incomplete spinal cord injury pre-locomotor training for lower extremities that required three modules to account for muscle activation. Module muscle weights for each leg (n=6) are represented in the bar graphs for tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). The relative strength of representation of each muscle within a module is indicated. Muscle weights are normalized to the muscle with the greatest representation, which is set to one. Activation timing curves indicate the relative module activation across the gait cycle (0 to 100%).

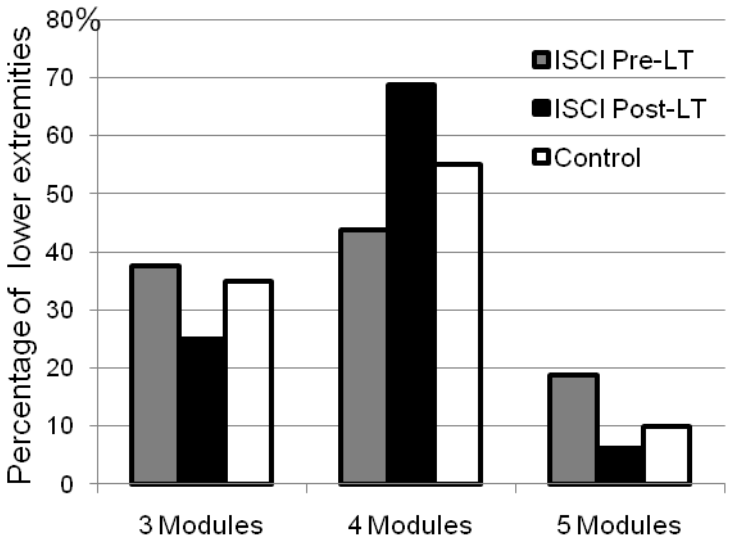

Figure 5-6. Percentage of lower extremities in each group that required three, four, or five modules to account for muscle activation during walking in subjects with incomplete spinal cord injury pre and post-locomotor training, and for controls walking at 0.30 m/s.

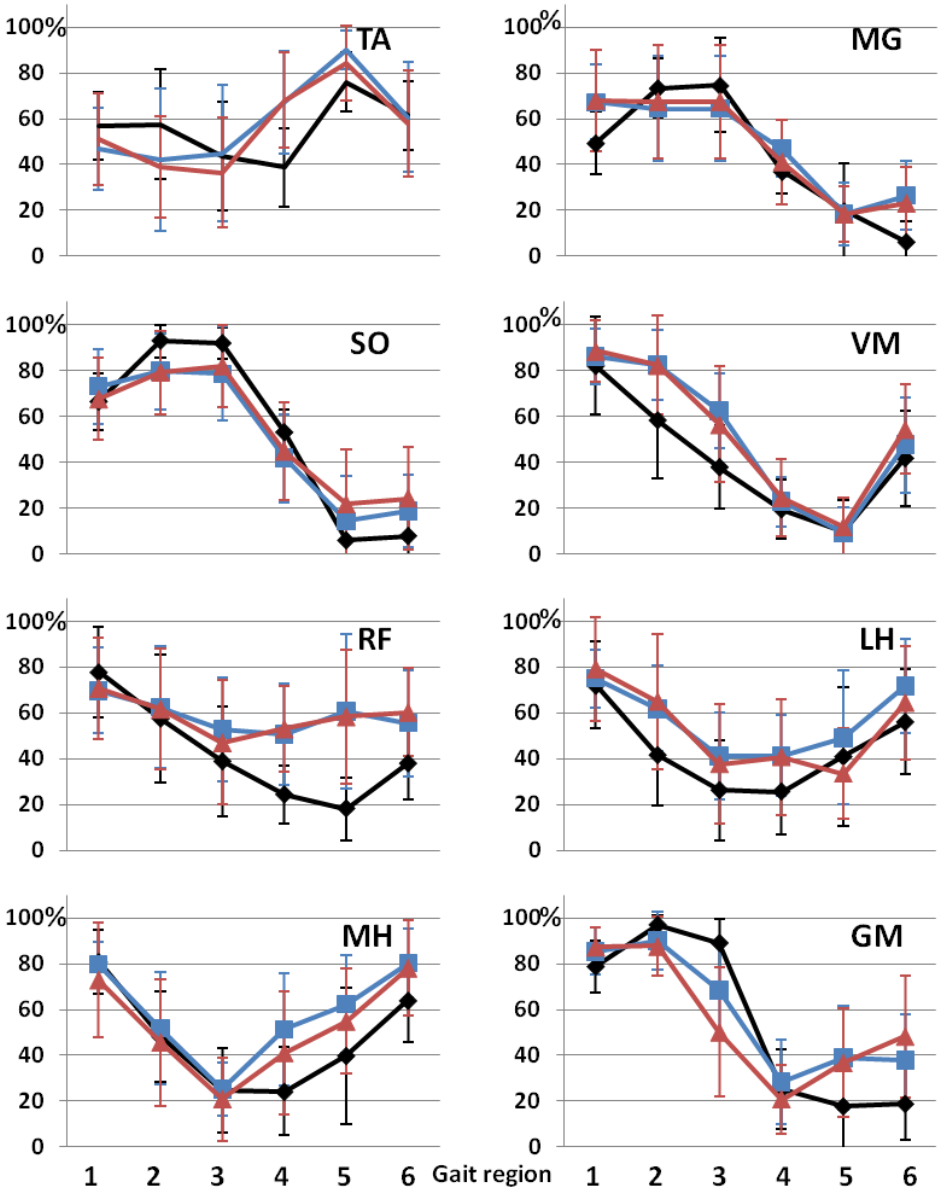

Figure 5-7. Percent of time each muscle was active in each of six gait regions for controls (black) and individuals with incomplete spinal cord injury pre (red) and post-locomotor training (blue). The percent of activation is indicated for tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM). Bars represent standard deviations.

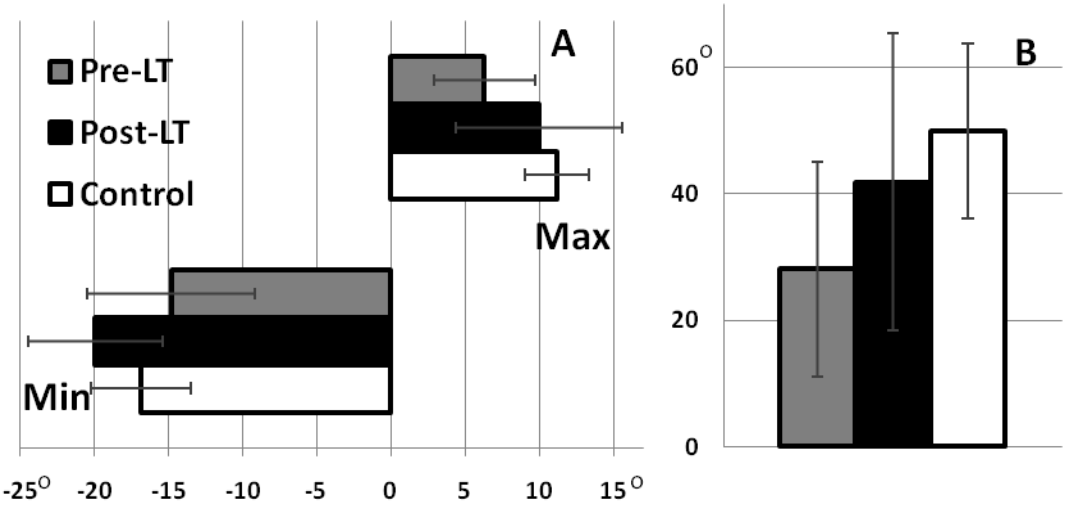

Figure 5-8. Average minimal (Min) and maximal (Max) leg angles (degrees) (A) and foot trajectory ranges (degrees) (B) for controls and subjects with incomplete spinal cord injury (ISCI) pre and post-locomotor training. Bars represent standard deviations.

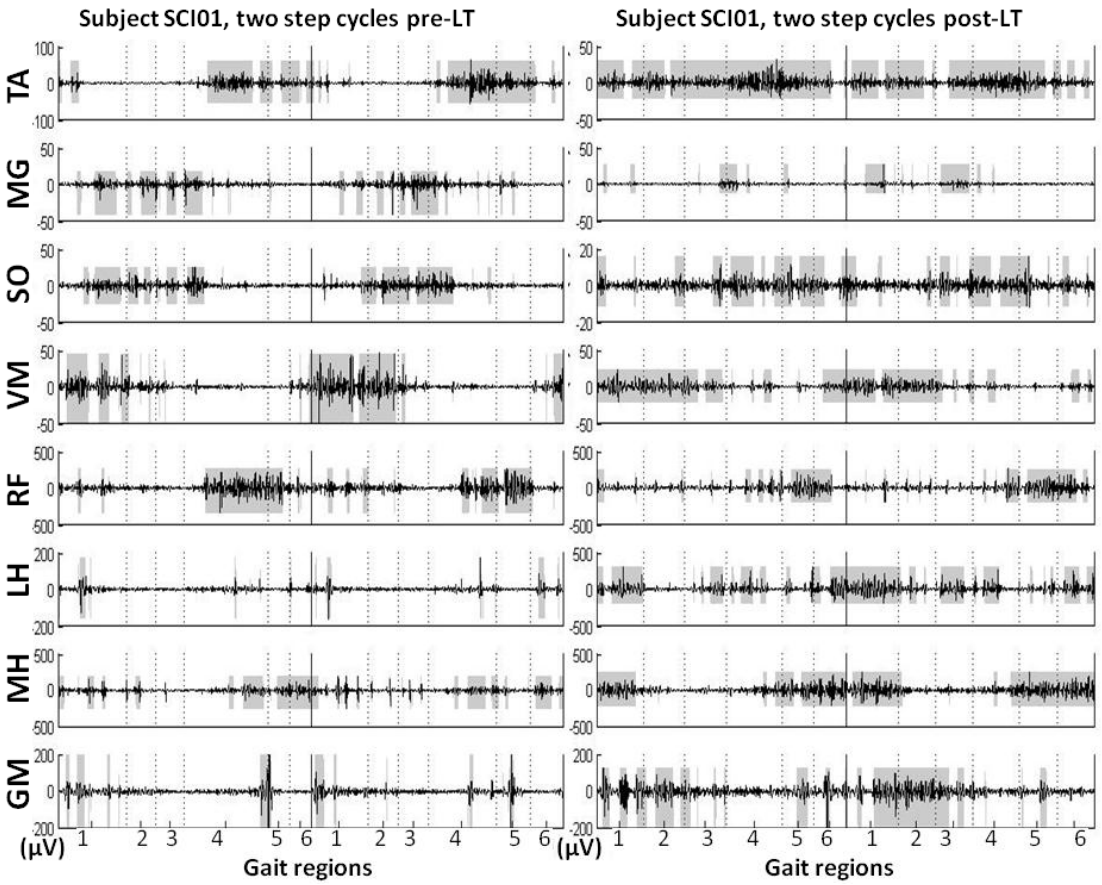

Figure 5-9. Processed EMGs from two representative step cycles for the right lower extremity from subject SCI-01 pre and post-locomotor training. Vertical dashed lines separate the six gait regions and the solid vertical line separates the two step cycles. Grey shading indicates periods of activation identified by the k-means cluster algorithm. EMG recordings for the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM) are represented. Subject SCI-01 exhibited 18 changes in muscle timing ($P<0.005$) across the eight muscles and six gait regions, such as increased duration of TA in regions one, two, and three ($P=0.001$ for all three regions), decreased duration of SO in regions one and two ($P=0.003$ for both) and increased duration of LH in region one ($P=0.001$).

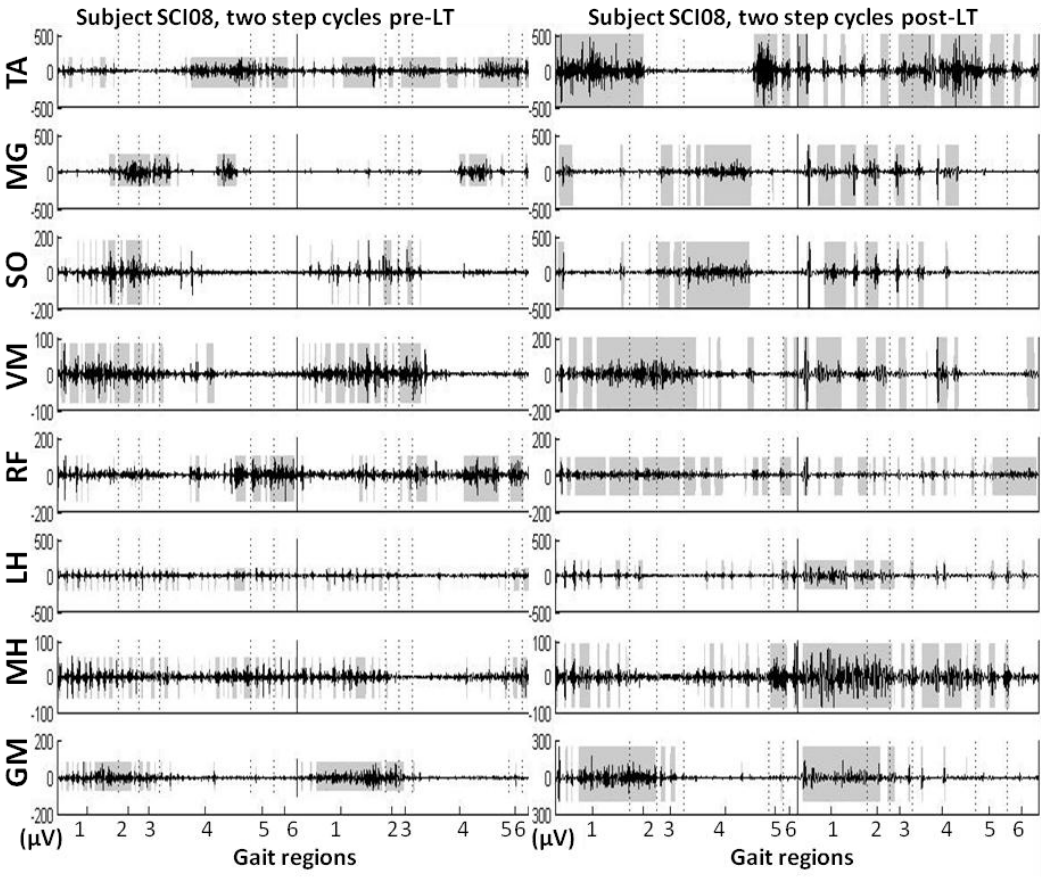

Figure 5-10. Processed EMGs from two representative step cycles for the left lower extremity from subject SCI-08 pre and post-locomotor training (LT). Vertical dashed lines separate the six gait regions and the solid vertical line separates the two step cycles. Grey shading indicates periods of activation identified by the k-means cluster algorithm. EMG recordings for the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM) are represented. Subject SCI-08 did not exhibit changes in muscle timing post-LT.

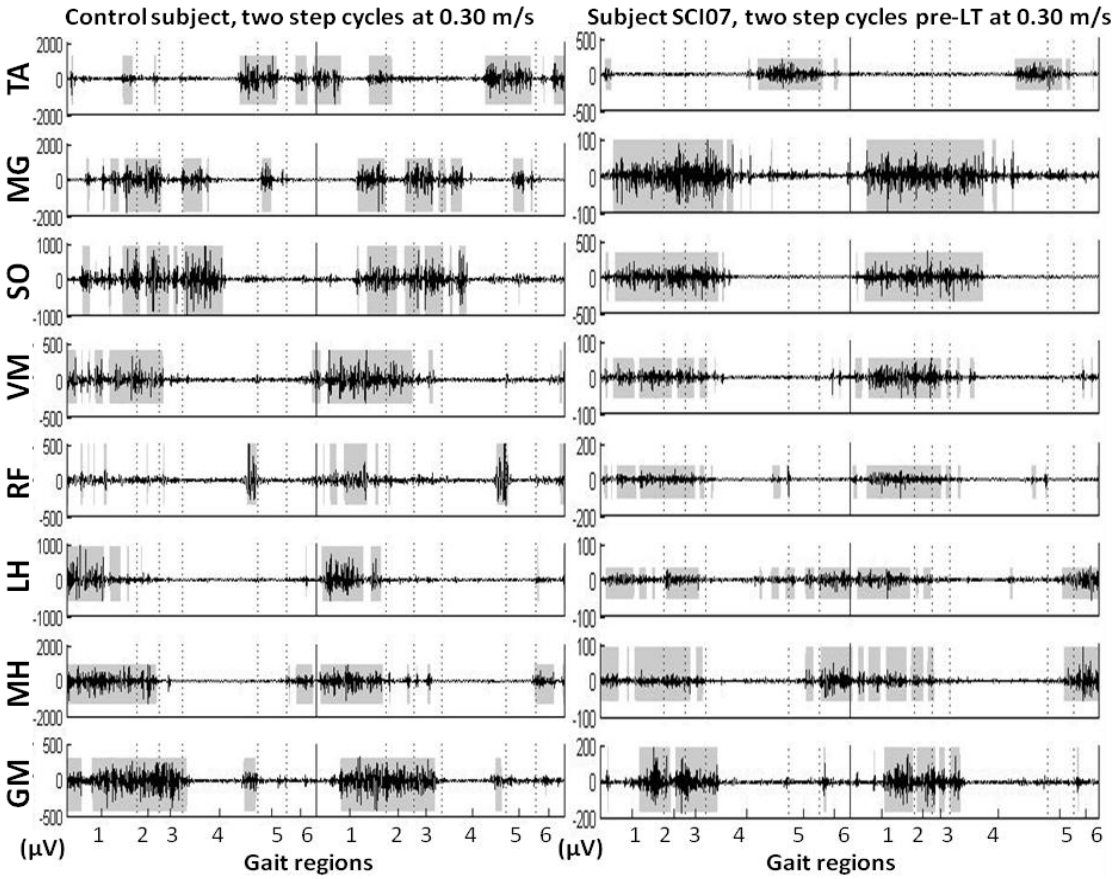

Figure 5-11. Processed EMGs from two representative step cycles from a control subject and from the left lower extremity of subject SCI-07, pre-locomotor training (LT). Vertical dashed lines separate the six gait regions and the solid vertical line separates the two step cycles. Grey shading indicates periods of activation identified by the k-means cluster algorithm. EMG recordings for the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SO), vastus medialis (VM), rectus femoris (RF), lateral hamstrings (LH), medial hamstrings (MH) and gluteus medius (GM) are represented. Subject SCI-07 did not exhibit changes in muscle timing post-LT.

CONCLUSION

Evidence of activity-dependent plasticity and oscillating spinal networks that are responsive to task-specific sensory input lead to the development of locomotor training (LT), a rehabilitation intervention that promotes walking recovery after incomplete spinal cord injury (ISCI). While this activity-based therapy improves walking function in adults with ISCI and is emerging as a beneficial approach for children with ISCI, it remains unclear how walking is controlled following human ISCI. Furthermore, clinical assessments of neuromuscular function following ISCI are incongruent with current principles of locomotor control. Moreover, the underlying mechanisms associated with improved walking function post-ISCI and walking recovery relative to pre-injury movement strategies have not been elucidated. Therefore, despite advancements in our knowledge of locomotor control, we remain limited in our understanding of walking function in humans with ISCI. Thus, this was the basis for these investigations of walking and locomotor control in adults and children with ISCI.

The first investigation of children with chronic ISCI examined neuromuscular control of walking and other rhythmic, reciprocal locomotor tasks such as pedaling, crawling, and stair climbing. Computational algorithms applied to multiple electromyogram (EMG) recordings from lower extremity (LE) muscles were used to identify a set of fundamental muscle activation patterns used to control walking and other locomotor tasks. Although a limited set of muscle activation patterns were identified in children without injury as well as children with ISCI, reduced neuromuscular complexity, evident by a reduced number of patterns, was identified in the children post-ISCI. In both groups of children, the patterns of muscle activation used to control

treadmill walking explained >86 percent of the EMG variance in the other locomotor tasks, indicating that similar neuromuscular control mechanisms are used across tasks.

Shared neuromuscular control mechanisms used across varied locomotor tasks suggests that current training paradigms that activate spinal neural networks for the control of walking may have benefits that extend to a variety of other rhythmic, locomotor tasks. Preliminary evidence of this emerged in our case reports of a child with severe chronic ISCI who recovered reciprocal stepping enabling independent ambulation with a rolling walker following LT (Behrman et al. 2008). This child's walking recovery was associated with recovery of other rhythmic locomotor tasks such as pedaling, crawling, and stair climbing (Fox et al. 2010). The findings from this investigation of children with ISCI and evidence from these case reports suggest that activity-based therapies such as LT may enhance the control of varied locomotor tasks.

A second investigation of children with ISCI compared the amplitude of LE muscle activation during voluntary isolated joint movements to the amplitude of LE muscle activation during rhythmic reciprocal locomotor tasks. Because clinical assessments of LE muscle activation rely on tests of voluntary isolated joint movements, we sought to determine if muscle activation during these tests reflects the potential to activate LE muscles during rhythmic locomotor tasks. Similar to prior studies of LE muscle activation in adults with ISCI (Maegele et al. 2002), this investigation of children with ISCI revealed that the mean amplitudes of signals recorded from LE EMGs was higher during rhythmic locomotor tasks. Furthermore, amplitudes were greatest during treadmill stepping and overground walking, suggesting that the task-specific sensory input, such as LE weight bearing and kinematics,

modulate the amplitude of LE muscle activation. These findings indicate that muscle activation during clinical tests of voluntary isolated joint movement does not necessarily reflect the capacity to activate muscles during rhythmic, reciprocal locomotor tasks. Clinical assessments of LE muscle activation in individuals with ISCI should therefore incorporate tests of muscle activation during weight-bearing, locomotor tasks such as treadmill stepping.

In a third experiment, neuromuscular and biomechanical control of walking in adults with ISCI prior to and following 45 sessions of manual or robot-assisted LT was examined. Although individuals in this group of 8 adults each had an injury categorized by the American Spinal Injury Association (ASIA) Impairment Scale (AIS) as 'D' and a lower extremity motor scores (LEMS) of >40/50 (American Spinal Injury Association 2006), initial overground walking speed and the use of assistive devices varied (0.18 m/s using a rolling walker to 0.80 m/s using a cane, and one individual could not complete the overground walking assessment). Compared to controls, pre-LT muscle timing and LE biomechanics were altered during treadmill walking at an average speed of 0.27 +/- 0.10 m/s. A fundamental set of muscle activation patterns was identified in the controls and the group of individuals with ISCI. Similar to the outcomes from prior studies of neuromuscular activation during walking (Clark et al. 2010), this investigation identified patterns of muscle activation that appeared to coincide with biomechanical functions during walking. Following 45-sessions of LT, walking recovery was evident by increased gait speed during treadmill walking without the use of assistance, devices, or braces (speed increased 0.26 +/- 0.23 m/s). Although improvements in LE biomechanical control were associated with increases in gait speed, changes in muscle

timing post-LT appeared to be individualized. Following LT, the fundamental patterns of muscle activation identified in the individuals with ISCI appeared to stabilize and exhibited characteristics more similar to controls.

Although this investigation examined a group of adults with similar injury classifications and LE muscle strength scores, varied levels of walking ability and underlying control mechanisms pre-LT were evident. Furthermore, responses to LT were heterogeneous in terms of the gains in gait speed exhibited and the underlying control mechanisms associated with walking function post-LT. Overall, this investigation provides evidence of fundamental patterns of muscle activation used to control walking in ambulatory adults with chronic ISCI. Following LT, individualized motor solutions were used to achieve functional stepping and appropriate limb biomechanics. These results not only provide evidence of how walking is controlled post-ISCI and the underlying mechanisms associated with walking recovery, but the findings also reflect the need to develop more task-specific measures of walking function and recovery post-ISCI.

In summary, these investigations of children and adults with ISCI provide evidence of underlying neuromuscular control mechanisms and the role of task-specific sensory input used to control walking and other rhythmic locomotor tasks. This evidence will provide a foundation for the development of task-specific assessments of motor function and locomotor control in adults and children with ISCI. Furthermore, these findings will contribute to the development of activity-based interventions that aim to activate the neuromuscular system and promote locomotor recovery following ISCI.

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BIOGRAPHICAL SKETCH

Emily Jane Fox was born in Miami, Florida in 1970. Her parents, David and Francine Gomberg moved to Miami from Ohio, where they met at Case Western Reserve University. Francine is a nurse and healthcare administrator and David is a hydrologist and fisherman. Emily has a younger brother, Sam, who is an environmental lawyer and expert on energy policy and the use of clean and alternative energies. Emily grew up in Cape Coral, Florida and entered the University of Florida as an undergraduate in 1988.

After earning her Bachelor of Science in Physical Therapy from Florida A & M University, Emily worked as a clinician at Brooks Rehabilitation in Jacksonville, FL. Ms. Fox returned to the University of Florida in 1997 to pursue a Master of Health Science in Motor Control. Through her master's studies, Emily worked with Dr. Andrea Behrman PhD, PT, Floyd Thompson PhD and Mark Trimble PhD, PT and was introduced to the study of mechanisms underlying walking control and the effects of spinal cord injury on walking function, as well as innovative rehabilitation approaches to improve walking after neurologic injury. After earning her Master of Health Science in 2000, Emily became Board Certified in Neurologic Physical Therapy.

As a faculty member at the University of St. Augustine for Health Sciences (2000-2007) Emily enjoyed teaching courses in neurologic physical therapy and mentoring students. During this time, the profession of Physical Therapy transitioned to an entry-level Doctor of Physical Therapy (DPT) degree. Emily therefore returned to school to advance her clinical skills and achieved a DPT degree in 2006.

In 2007, Emily returned again to the University of Florida to study with Dr. Behrman and entered the Rehabilitation Science Doctoral degree program. Under the

guidance of her Supervisory Committee, Emily studied mechanisms underlying the control and recovery of walking and other locomotor tasks in adults and children with spinal cord injury. As a doctoral student and physical therapist, Emily served as the coordinator and physical therapist for the Kids STEP Study. This experience introduced Emily to pediatric physical therapy and issues unique to children with neurologic injuries. Emily was mentored in pediatric physical therapy by Shelley Trimble, PT.

Emily received her PhD from the University of Florida in 2011. She will continue her academic training and study of motor control as a post-doctoral fellow and will pursue an academic research faculty position. Emily's career aspirations include advancing rehabilitation of walking for children with neurologic disorders.

Emily is married to Jeff Fox, a dedicated husband and father. Together, they have two sons, Jacob and Ben. Emily and Jeff, along with their families, are dedicated to teaching their children the value of education, the importance of protecting and preserving the environment, and how to be thoughtful, responsible, contributing members of their local and global communities.