The Interaction Between Over-Ground Exoskeleton Gait Training and Muscle Spasticity

by

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

Master of Science in Kinesiology

in the Graduate Academic Unit of Kinesiology

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This thesis is submitted to the
Faculty of Kinesiology

THE UNIVERSITY OF NEW BRUNSWICK

April 2021

ABSTRACT

The objectives of this thesis were to establish normative biomechanical and physiological patterns of the lower limb during exoskeleton gait in able-body (AB) users; and to determine if the AB data could aid the interpretation of spinal cord injury (SCI) exoskeleton users, with an investigative consideration to spasticity. Five able-body and two SCI participants were recruited and underwent a series of exoskeleton walking trials using the Ekso GaitTrainer™. Kinematics and EMG at the knee joint were collected using the BioTone™ kit. For analysis, data was cycled using % gait cycle and analyzed using statistical parameter mapping and qualitative case study analyses. Results demonstrated that exoskeleton gait does not resemble normal gait. The AB data assisted in the interpretation of SCI participant data and suspected spastic activity; as well as developing a benefit-risk framework to individually assess the safety of patient users on a case-to-case basis.

Keywords: Spinal cord injury, exoskeleton, gait training, spasticity, exoskeleton gait

DEDICATION

To my parents Amy and Duane, to my brother Dylan, and my late grandmother Peggy, thank you for believing in me; your continuous support and encouragement; I am so grateful and owe every success to you.

ACKNOWLEDGEMENTS

I would like to thank many individuals that have supporting me throughout this process. First and foremost, I would like to thank my supervisor Dr. Chris McGibbon for taking me on as a student and providing this amazing opportunity; your patience and understanding was greatly appreciated. In addition, I would like to thank Andrew Sexton and Benjamin Tremblay for their assistance, I deeply appreciate it. I would like to extend a big thank you to Shane McCullum and the helpful staff and patient-volunteers at the Stan Cassidy Centre for Rehabilitation, truly could not have done this without you.

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List of Symbols, Nomenclature or Abbreviations

OEGT: Over-ground Exoskeleton Gait Training

SCI: Spinal Cord Injury

MAP: Muscle Activity Pattern

AB: Able-Body

CNS: Central Nervous System

EMG: Electromyography

ISNCSCI: International Standards for Neurological Classification of Spinal Cord Injury

ASIA: American Spinal Injury Association

AIS: ASIA Impairment Scale

ROM: Range of Motion

MAS: Modified Ashworth Scale

WPT: Wartenberg Pendulum Test

F1Amp: First Flexion Amplitude

E1Amp: First Extension Amplitude

Plat: Plateau Angle

RI: Relaxation Index

ERI: Extension Relaxation Index

IC: Initial Contact

GT: Gait Training

FDA: United States Food and Drug Administration

SCCR: Stan Cassidy Centre for Rehabilitation

SOP: Standard Operating Procedure

PI: Principal Investigator

SL: Step Length

SH: Step Height

ST: Swing Time

SPM: Statistical Parameter Mapping

1D: One-Dimensional

SD: Standard Deviation

0D: Zero-Dimensional

CC: Correlation Coefficient

Chapter 1: Introduction

Powered robotic devices, such as the Ekso GaitTrainer™ (Ekso GT™), were introduced into rehabilitation clinics more than a decade ago (Ferris et al., 2009) as a method of delivering over-ground gait training for people with neurological injury or disease. Although there are numerous benefits to regaining upright ambulation; such as improved bladder and bowel control, cardiovascular fitness and preservation of bone density (Baunsgaard et al., 2018; Jacobs & Nash, 2004); over-ground exoskeleton gait training (OEGT) aims specifically to reestablish gait function in persons with brain or spinal cord injury (SCI) (Sale, Franceschini, Waldner, & Hesse, 2012). However, it remains unclear if OEGT provides benefits that translate into improved independent gait function (Backus et al. 2019).

Much of the research to date has focused on safety and utility of exoskeletons in the rehabilitation setting, and the mobility and physiological health while using an exoskeleton (Fisahn et al., 2016; He et al., 2017; Miller, Zimmermann, & Herbert, 2016; Sale et al., 2012). There is limited knowledge of the effect of OEGT on locomotor function and recovery in neurologically compromised populations (Ramanujam et al., 2018; Sylos-Labini et al., 2014; Talaty, Esquenazi, & Briceno, 2013). Contributing to the issue is a lack of understanding of the biomechanical interactions between exoskeleton and user which can reveal how the body responds to exoskeleton walking (De Luca et al., 2019; Ramanujam et al., 2018; Stylos-Labini et al., 2014; Swank, Wang-Price, Gao, & Almutairi, 2019). It is largely unknown how to interpret the neuro-biomechanical responses during OEGT of users with SCI. Specifically, the ability to determine if muscle

activity patterns (MAPS) during OEGT are functional (motor) responses or pathological (spasticity) responses is not possible. Consequently, there are two distinct knowledge gaps that this thesis will address.

Knowledge Gap 1 – Lack of normative kinematic and electromyography data

To develop improved OEGT therapies to facilitate return of neuromuscular function, investigations of the locomotor response of healthy individuals, in addition to those with neurological trauma, are required (Ivanenko et al., 2013). Studies that have assessed able-body (AB) subjects with an over-ground exoskeleton (De Luca et al., 2019; Ramanujam et al., 2018; Stylos-Labini et al., 2014; Swank et al., 2019) suggest that lower-extremity MAPs do not mimic those during normal gait. While enlightening, these studies were limited in terms of establishing comprehensive normative data. As these studies only used individual exoskeleton step parameter settings, providing a narrow window for data comparison. As such, there is a gap in knowledge of what lower-extremity MAPs ought to look like during OEGT with a "healthy" central nervous system (CNS). Without this knowledge, the ability to interpret MAPs during OEGT in people with neurological injury may be greatly hindered. Collecting data under a variety of step parameter settings would establish a more comprehensive understanding of the lower-extremity MAPs during exoskeleton gait.

Objective 1

The first objective of this thesis was to establish normative biomechanical (knee flexion angle) and physiological (knee muscle electromyography (EMG)) patterns of AB users walking with the Ekso GT™ in "FirstStep" mode, where the therapist (operator) is

initiating the steps for the patient (user) – the first stage of OEGT. Here we specifically explored the effects for multiple combinations of step parameter inputs (step height, step length, and swing time) to the Ekso GT™ in a 3-way repeated measures design, to determine which parameters were most influential on the resulting kinematic and EMG patterns.

Knowledge Gap 2 – Lack of understanding of the influence of spasticity on OEGT

People with SCI experience a variety of muscle impairments that further complicate the ability to interpret MAPs during OEGT. While there are obvious deficits related to paralysis (ie. reduced neural drive) (Chen et al., 2016; Miller, Zimmermann, & Herbert, 2016; Lajeunesse et al., 2016), many people with SCI also have upper motor neuron syndrome of which spasticity is one component that disrupt the muscle's natural reflex (ie. hyper-activity during passive stretch). This makes it difficult to understand if muscle activity during OEGT represents a return of neural drive or a pathological response to muscle stretch. This hyper-sensitivity to muscle stretch, called "spasticity" (Lance, 1980), affects the majority of persons with SCI (Hsieh et al., 2008). Currently there are no studies that have focused on the influence of spasticity on MAPs during OEGT in people with SCI, in part because there is currently no normative data for interpreting MAPs during OEGT (ie. Knowledge Gap 1).

A major factor contributing to the paucity of published data on the impact of muscle spasticity on OEGT is a general concern that spasticity could interfere with the exoskeleton's ability to produce feasible walking patterns (Ekelem, & Goldfarb, 2018) or perhaps cause strain injury to muscle by forcing muscle lengthening under a spastic

contraction (Carpentier, Kiekens, & Peers, 2013). However, the literature is generally unclear on this topic because people with high spasticity tend to be excluded from OEGT research (Louie, Eng, & Lam, 2015). In contrast, some studies with stationary exoskeleton systems have shown reduced spasticity after exoskeleton training (Mirbagheri, Kindig, Niu, Varoqui & Conaway, 2013; Mirbagheri, Ness, Patel, Quiney, & Rymer, 2011; Swinnen et al., 2010).

Taking into consideration that half of persons with SCI who experience spasticity are affected by severe spasticity (Hsieh et al., 2008), there could be speculations on whether current SCI-exoskeleton research is fully reflective of the patient population. Spasticity not only restricts exoskeleton prescription to a portion of the patient population, but the exclusion parameters for spasticity are also inconsistent across exoskeleton gait studies (Louie, Eng, & Lam, 2015). A review of the literature reveals a clear gap in our understanding of how spasticity affects, or is affected by, OEGT. While a number of researchers suggest that spasticity could interfere with the exoskeleton's ability to produce feasible walking patterns (Ekelem, & Goldfarb, 2018), upon further investigation of the primary sources (Aach et al., 2013; Esquenazi et al., 2012; Kolakowsky-Hayner, 2013) cited by this study, there is little to no objective evidence to support or not support a recommendation of OEGT to users with spasticity.

Objective 2

The second objective was to determine if the AB data can aid the interpretation of SCI participant data during exoskeleton walking. Specifically, we answer the question of how this information might be used to evaluate the benefits and risks of OEGT. Using a

case study design, this objective focused on determining if the EMG responses during Ekso GT™ walking in persons with SCI can be interpreted from matched comparison with the set of normative AB patterns derived in Objective 1. Elements of a framework are then described for future study that can classify Ekso GT™ performance in terms of its benefits (return of motor drive) and risks (inducing spastic contractions).

Impacts of the Research

This research could potentially improve the delivery of OEGT for people with SCI and represents a first step towards interpreting muscle activity during exoskeleton use that separates desired motor responses from undesired pathological responses. A better understanding of this interaction could lead to the development of objective, evidence-based recommendations for the prescription of OEGT for those who experience problematic spasticity. Addressing this issue could potentially enable clinical trials of OEGT to be more inclusive of people with spasticity. Specifically, we propose the fundamental elements of a new framework for evaluating the neuromuscular benefits and risks of OEGT that could be useful as both a screening tool and an outcome measure for longitudinal assessment of neurophysiological responses to OEGT. The framework could make over-ground robotic exoskeletons applicable to a larger portion of users and better promote its advancement in the neurorehabilitation.

Chapter 2: Literature Review

Robotic exoskeletons were originally designed for military application and have been adopted for use by clinical populations that experience a variety of muscle impairments. To provide a base understanding of how exoskeletons affect human locomotion it is important to investigate the response of healthy and patient populations to the afferent inputs from exoskeletons (Ivanenko et al., 2013). Understanding how exoskeletons affect human locomotion could promote the identification of interactions between the exoskeleton and the user with muscle spasticity, while also providing therapists with the information needed to develop safe and effective patient specific OEGT programs. To justify the need for this research we first describe the field and the specific gaps that motivated this research.

2.1 Population

Many neurologically compromised clinical populations experience impaired walking and could benefit from OEGT; including multiple sclerosis, traumatic brain injury, cerebral palsy, SCI, and stroke (Calabro et al., 2016). These neurologically compromised populations can have two types of upper motor neuron syndrome: brain and spinal cord, each having a different pattern of spasticity. Brain types tend to experience spasticity in the flexors of the upper limbs and extensors of the lower limbs, whereas spinal types tend to be in the extensors of the upper limb and the flexors and extensors of the lower limbs. The spasticity that many people with these conditions have is considered to be problematic, which according to conventional practice is an exclusion for receiving OEGT. Therefore, current published OEGT research may not be reflective of the broader

SCI patient population. Research suggests concerns for spasticity interfering with the exoskeleton's ability to produce feasible walking patterns, adding potential for muscle strain injury (Ekelem, & Goldfarb, 2018). For the purposes of this paper, individuals with SCI will be the focus population.

2.1.1 Spinal Cord Injury

The World Health Organization and International Spinal Cord Society (2013) reported that between 250,000 and 500,000 SCIs occur worldwide every year. In the United States, approximately 200,000 people were living with SCIs in 2013, while Canada reported 85,000 from a survey conducted in 2010 (National SCI Statistical Center, 2013; Noonan, Fingas, Farry, et al., 2012). For both countries, the highest incidence of traumatic SCI was reported to be individuals under age 30, with a higher rate in males over females (National SCI Statistical Center, 2013; Noonan, Fingas, Farry, et al., 2012). Injuries were reported to occur in several different ways; including falls, violent sports, and traffic accidents, with traffic accidents being responsible for 40% to 60% of incidences (Singh et al., 2014). Injuries to the spinal cord are often life-altering events, requiring extensive rehabilitation and adjustment by both the individual and supporting family and friends. The sequelae of a SCI not only affect the individual's physical well-being, but social and psychological as well; leading to a reduction in quality of life.

Injuries to the spinal cord can disrupt motor, sensory and autonomic systems, classified by the severity of losses (complete or incomplete) and the neurologic level of injury. A complete lesion occurs when the spinal cord is severely injured, resulting in no

motor and sensory function in the most distal sacral segments (American Spinal Injury Association, 2021). An injury is determined to be incomplete when some motor and/or sensory function remains below the level of injury (American Spinal Injury Association, 2021). An injury level in the cervical spinal cord results in tetraplegia (affects all four limbs) whereas an injury level in the thoracic or lumbosacral spinal cord result in paraplegia. It was suggested by Dobkin et al. (2007) that the most visible disability of individuals who experience SCIs was the inability to walk and produce a reciprocal gait pattern at a velocity suitable for community ambulation.

The International Spinal Cord Society and the American Spinal Injury Association together developed and endorsed the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). This standard is used throughout the world to classify spinal cord injury by neurologic level and severity of injury. The neurologic level of injury is determined by physical examination and is the most rostral level with intact motor and sensory function (see Appendix A). The American Spinal Injury Association (ASIA) scale to classify impairment severity is called the ASIA Impairment Scale (AIS). The severity of the injury is graded by a letter designation between "A" and "E," with "A" being most severe, and "E" being motor and sensory functions are "normal" (American Spinal Injury Association, 2021).

Experiencing an SCI can result in loss or alteration of motor and sensory function in the upper limbs, trunk, or lower limbs, as well as autonomic dysfunction depending on the level of injury (Lajeunesse et al., 2016). Impairments that result from an SCI can leave patients at an increased risk of respiratory problems, impaired bladder and/or bowel function, and pressure ulcers; as well as other potential conditions including osteoporosis,

cardiovascular disease, and diabetes (Chen et al., 2016; Miller, Zimmermann, & Herbert, 2016). Other secondary complications can affect joints and the surrounding musculature including muscle atrophy, contractures, and muscular spasticity (Chen et al., 2016; Miller et al., 2016). The recovery of physical function after an SCI continues to be limited because of degenerative processes affecting the function of the neural and circulatory systems, including apoptosis and demyelination (Miller et al., 2016). The symptoms of these secondary conditions result in persons with SCI experiencing a variety of discomforts: with many reporting lower quality of life because of them (Stampacchia et al., 2016).

2.2 Spasticity

In 1980, Lance first described spasticity as "a motor disorder, characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron syndrome" (Lance, 1980). Spasticity is a form of hypertonia; what separates it from the other types of hypertonia is the velocity-dependent increases in stretch-reflexes and exaggerated tendon reflexes (Noth, 1991).

2.2.1 The Role of Stretch Reflex in Spasticity

Every reflex response in the body follows the same sensory cycle known as the reflex arc. The reflex arc consists of three main steps: incoming afferent information, central processing of the information, and an efferent output resulting in the reflex to occur. A muscle reflex is described by Latash (1998) as “a muscle contraction induced by an external stimulus that cannot be changed by "purely thinking"” (p. 64), describing a

muscle reflex as an involuntary response. For most muscles (excluding facial muscles), central processing occurs within units of the spinal cord. The incoming, afferent, signals enter for processing through the dorsal horns of the spinal cord. Once the afferent signal is processed, the efferent, or outgoing information exits through the anterior horns of the spinal cord.

A muscle reflex involves many components of muscle physiology; muscle spindles are embedded amongst muscle fibers and are responsible for sensing changes in length and velocity (Latash, 1998). Muscle spindles provide afferent information to the central processing unit, from the afferent fiber group Iα (Iα-afferent). Group Iα is a collection of specialized sensory receptors that provide information about both velocity and length. The α-motoneurons are neurons that innervate a muscle and receive information from the central processing unit indicating if the muscle should contract or not. In a simple monosynaptic reflex, the synapse of the Iα-afferent fibers from the muscle spindle, would be in direct communication with the synapse of the α-motoneuron (Latash, 1998). This communication would result in a signal from the muscle spindle to excite the α-motoneuron resulting in a muscle contraction.

The response of muscle contraction is not always the goal of a muscle reflex. For a muscle to lengthen and stretch without disruption, a disynaptic reflex is performed involving communication at the second synapse (Latash, 1998). The second synapse originates from the Iα-interneuron which receives excitatory signals from the Iα-afferent fibers and produce inhibitory signals to the α-motoneuron (Latash, 1998). This inhibition enables the muscle to be stretched without the result of a contraction. The inhibition of

the α-motorneuron can happen two ways: postsynaptic and presynaptic (Latash, 1998). Postsynaptic inhibition occurs at the postsynaptic membrane, inhibiting the signal before exciting the connecting neuron. Presynaptic inhibition occurs before the message is sent across the synapse at the presynaptic membrane. Iα-interneurons provide presynaptic inhibition to α-motoneurons, stopping a muscle contraction (Latash, 1998). This concept is considered to be involved in reciprocal inhibition. Which is the process of muscles on one side of a joint relaxing to satisfy the muscle contracting on the other side (Mukherjee & Chakravarty, 2010).

Although the underlying causes for the loss of volitional muscle control and the origins of spastic behaviors are not entirely understood, suggestions of possible mechanisms and pathophysiology have been discussed (Mirbagheri et al., 2011; Mukherjee & Chakravarty, 2010; Trompetto et al., 2014). For purposes of this paper, three mechanisms of spinal cord inhibition will be discussed. These mechanisms involve descending signals from within the spinal cord that affects the stretch reflex.

The first mechanism involves presynaptic inhibition of Iα-afferent terminals, as discussed above. This inhibition occurs at an axon-to-axon synapse within the spinal cord, and upon activation reduces the amount of mediator released from the Iα-afferent terminals to the α-motoneuron. Mukherjee and Chakravarty (2010) suggested that if a reduction in the normal presynaptic levels occurs, there will be an increase in response from the α-motoneurons that may result in spasticity. It is important to note that a reduction in presynaptic inhibition was present in persons with SCI and multiple sclerosis

but not for hemiplegic stroke patients (Mukherjee & Chakravarty, 2010); suggesting that a reduction in presynaptic inhibition affects some persons with spasticity but not all.

The second mechanism relates postsynaptic inhibition at the membrane of α-motoneurons and includes the disynaptic reciprocal Iα inhibition (Trompetto et al., 2014). In persons with spasticity, co-activation of agonist and antagonist muscles is common, which is a failure of reciprocal inhibition. Mukherjee and Chakravarty (2010) suggest that since Iα inhibitory interneurons are stimulated by descending motor fibers, damage to this could cause a reduction in reciprocal inhibition.

All of these mechanisms of spinal cord inhibition are found to be decreased in persons with spasticity. For further explanation on the mechanisms and pathophysiology of spasticity refer to "Spasticity Mechanisms – for the clinician" by Mukherjee and Chakravarty (2010), and “Pathophysiology of spasticity: implications of neurorehabilitation” by Trompetto and colleagues (2014).

Examining the stretch reflex in persons with spasticity involves thresholds, where the muscle is stretched to the point of inducing muscle activity. The moment the muscle contracts and displays action in response to an external stimulus is considered the threshold. Levin and Feldman (1994) conducted a study on the upper limbs of persons with hemiparetic spasticity to examine the static and dynamic stretch reflex thresholds. Levin and Feldman (1994) determined that persons with spasticity experience a decrease in both static and dynamic stretch thresholds. Additionally, Levin and Feldman (1994) suggested that these thresholds were dependent on velocity. It was noticed that persons with spasticity were unable to increase the stretch reflex threshold even during slow velocities of stretching.

Levin and Feldman (1994) concluded that the regulation of the stretch reflex, which plays a vital role in motor control, may be impaired in persons with spasticity. A later study by Levin, Selles, Verheul, and Meijer (2000) examined the coordination of agonist and antagonist muscles in persons with stroke, focusing on dynamic movements. Levin et al. (2000) moved the upper limb through seven angular velocities (in flexion and extension), each faster than the prior. They were able to determine that for persons with spasticity the dynamic stretch reflex thresholds were a decreasing function of velocity and fell inside the normal physiological range of the joint, as shown in Figure 1. Movements that occurred outside the dynamic threshold range resulted in the co-activation of the flexors and extensors (Levin et al., 2000).

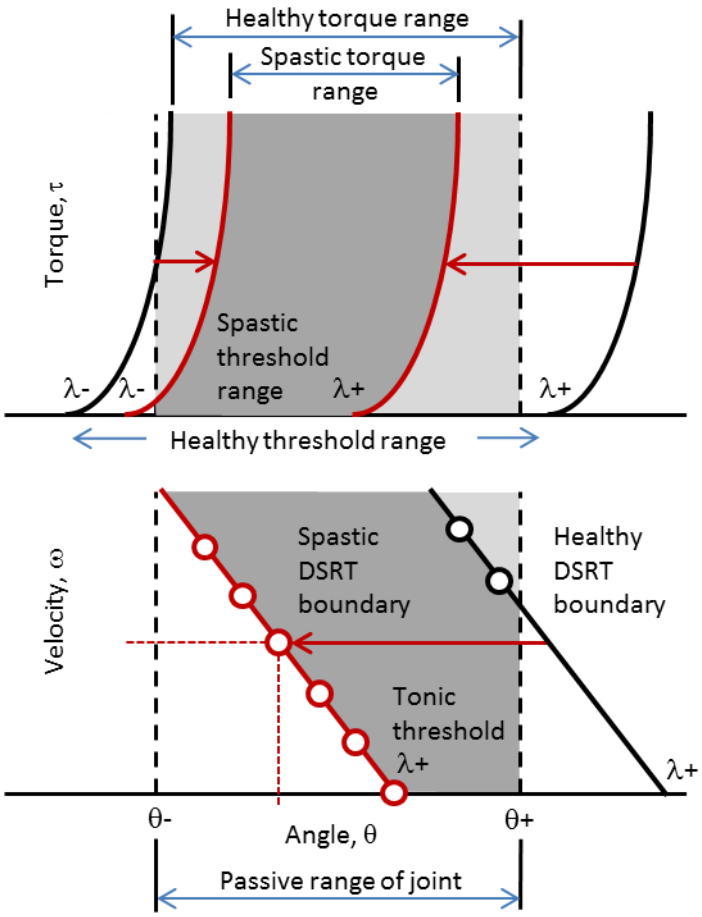


Figure 1. Pathology of the dynamic stretch reflex threshold in people with spasticity (adapted from Levin et al (2000).

These findings suggest the failure of reciprocal inhibition mechanism, as mentioned above by Mukherjee and Chakravarty (2010). Although the exact causes for spasticity remain unclear, such studies have shed some light on the phenomena of spasticity.

2.2.2 Clinical Impacts of Spasticity

Spasticity is a secondary condition that is common among people with injury of the brain or spinal cord. Although muscle contractions of spasticity may contribute to the maintenance of muscle tone, muscle mass, and blood circulation; it can also be a

significant contributor to secondary complications such as: contractures, weakness, and pain (Hsieh et al., 2008; Malhotra et al., 2008). It has been suggested that spasticity affects about 65% - 98% of SCI survivors, with half experiencing severe spasticity and a quarter reporting spasticity as a significant problem (Adams & Hicks, 2005; Hsieh et al., 2008). Spasticity can hinder voluntary movement and therefore can have unfavorable impacts on the person's ability to achieve functional goals and perform activities essential for daily living (Malhotra et al., 2008).

The effects of spasticity on daily living are suggested to cause shorter life span; as well as having physical, social, and emotional costs on the individual (Mirbagheri et al., 2011). Physically, spasticity can interfere with various body functions such as ambulation, lower and upper limb control, as well as bowel and bladder function (Hsieh et al., 2008). Socially, the limited range of motion (ROM), pain, and muscle weakness can reduce participation at the workplace and in daily activities (Hsieh et al., 2008). Emotionally, spasticity can have a detrimental effect. With the physical and social burdens of spasticity, both having negative consequences on the individual's quality of life, it is no surprise that the emotional state is affected. The effects of spasticity can negatively contribute to emotions, experiencing embarrassment, frustration, and depression, as well as reducing the quality of life for patients (Bhimani, McAlpine, & Henly, 2012).

2.2.3 Evaluation of Spasticity

Spasticity is highly variable and unique to each individual, with occurrence and intensity can fluctuate from day to day or even hour to hour. Ideal measurements of

spasticity, in terms of muscle response to an externally imposed force, are threshold angles and patterns of muscle activation (Malhotra, Pandyan, Day, Jones, & Hermens, 2009). Levin (2005) has stated a valid measure of spasticity is one that is based on conceptual framework that describes the physiological properties controlling posture and movement, along with the possible impairments that result in the motor disorder. Platz, Eickhof, Nuyens, and Vuadens (2005) suggested there are a variety of scales used to assess the psychometric properties of spasticity: (A) scales that assess tone (resistance to passive movement), (B) scales that assess ROM and posture at rest, and (C) scales for other clinical phenomena associated with spasticity, such as tendon reflexes and spasms. To further understand and evaluate spasticity, Hsieh et al. (2008) suggested that the patient perspective was the best way to measure the balance of controlling spasticity versus total suppression of it. Another exploratory article, on the patients' perspectives of spasticity, recommended that understanding personalized patient perspective can aid in customizing intervention methods to optimize patient rehabilitation outcomes (Bhimani, McAlpine, & Henly, 2012).

Modified Ashworth Scale

The Modified Ashworth Scale (MAS) is a spasticity assessment measure used to quantify the severity of spasticity by using a stretch reflex test qualitatively. The technique involves an assessor, usually a trained clinician, that moves a limb passively through the joint's ROM over a count of one second. The assessor then grades the resistance encountered by using a set of rules that quantify the reflex activity elicited from the passive movement (Pandyan, Price, Rodgers, Barnes, & Johnson, 2001). The scoring scale for MAS is in Table 1. The MAS assesses muscle overactivity and muscle

activity globally around the selected joint and does not rate spasticity selectively (Yelnik, Albert, Bonan, & Laffont, 1999). Levin (2005) suggested that although the MAS does a satisfactory job in determining the resistance felt to the displacement of the passive limb, it is unable to quantify the velocity sensitivity of the resistance. This is the differentiating feature of spasticity from other tone disorders.

The velocity-dependent nature of spasticity can cause variability in MAS scores because of fluctuations in the speed of stretch performed by the assessor (Levin, 2005). This variability has led to the MAS having intra- and inter-rater reliability issues. Intra-rater reliability problems may be attributed to the assessor's inability to produce the same external force for every passive movement being implemented. Whereas interrater reliability issues stem from the individual interpretation of MAS performance. Each assessor has a personal interpretation of resistance for scoring spasticity using the MAS. Ansari et al. (2009) suggested another contributor to intra- and inter-rater reliability issues was the mass of the limb segments being tested; with examiners reporting greater difficulties in determining the reflex mediated resistance in heavier limbs, such as the lower limbs compared to upper limbs. Even given the intra- and inter-rater reliability conflicts, MAS is still the "gold standard" and the most commonly used clinical measure of spasticity (Levin, 2005; Pandyan et al., 2001).

Table 1. The Modified Ashworth Scale used by clinical practitioners for scoring spasticity through passive movement.

Grade	Modified Ashworth Scale (Bohannon & Smith, 1987)
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the ROM when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Wartenberg Pendulum Test

The Wartenberg Pendulum Test (WPT) is another method of measuring and evaluating spasticity: only the WPT is used to assess spasticity quantitatively. The WPT provokes the stretch reflex during a passive oscillation movement of the lower limb (Bajd & Vodovnik, 1984) controlled by gravity, thus eliminating variability due to tester-induced motions and better characterizing response of the knee extensors that bring the leg to rest (He, Norling & Wang, 1997). This method measures the passive component of hypertonicity (i.e., plateau angle), as well as the active component from inappropriate stretch-reflex contraction (relaxation index). The person is instructed to relax and allow gravity to induce the limb's descent into oscillations (He et al.,1997).

The WPT differs from the MAS by using objective measurement to assess the mobility and range of a joint. The person begins seated with legs hanging freely off the

edge of a chair or bench. The assessor raises one of the lower limbs, so that the knee joint is extended to a horizontal position, instructs the patient to relax and releases the limb allowing it to swing freely, like a pendulum, until coming to rest. Jamshidi and Smith (1996) suggested that a rest period of 30 seconds should be used between repetitions, to allow the recovery of the reflex pathways. The objective measures recorded during the gravity-induced fall of the lower limb, uses EMG and goniometers or video motion analysis to measure muscle activity the angular velocity ratio of knee joint (angle vs time) (Hsieh et al., 2008; Jamshidi & Smith, 1996).

The objective measures of the WPT allow for quantitative analysis of selected text metrics which quantify specific intervals of the WPT. Figure 2 represents a basic example output of a WPT. The first flexion amplitude (F1amp) reflects the initial drop of the lower limb and the angle of the first oscillation. The first extension amplitude (E1amp) reflects the knee extension of the first oscillation. The oscillations continue until the lower limb stops at its naturally, relaxed, flexed position, representing the plateau angle (Plat). These test metrics are used to calculate two additional test metrics; the dividend of F1amp by the Plat results in the relaxation index (RI), while E1amp divided by Plat produces the extension relaxation index (ERI).

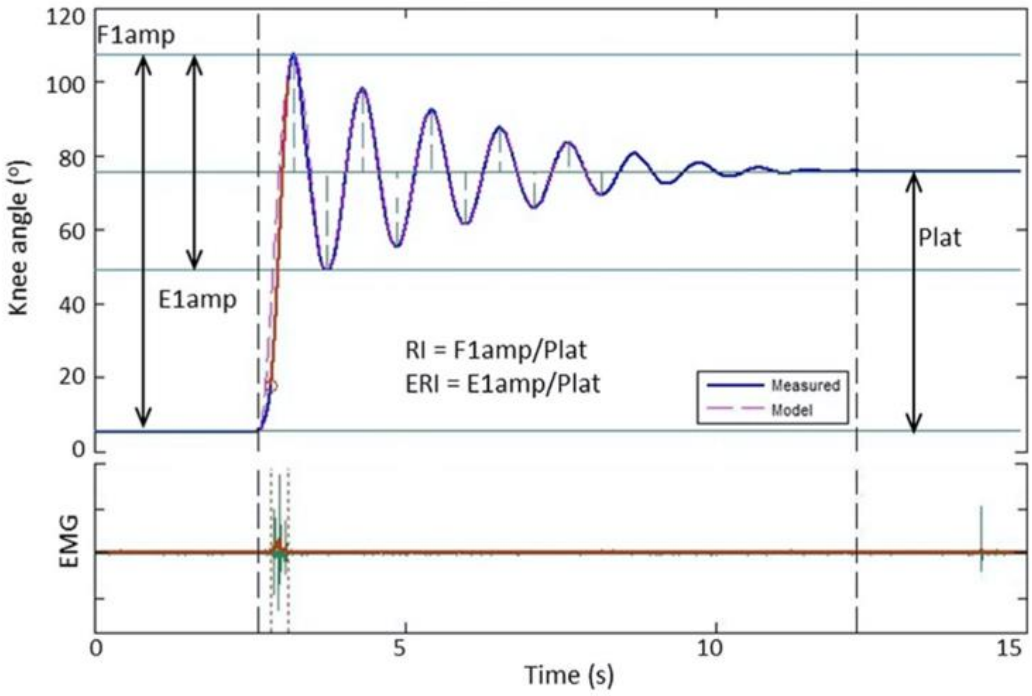


Figure 2. Pendulum test metrics include the plateau angle (Plat), first flexion amplitude (F1amp), and first extension amplitude (E1amp) which are used to compute the relaxation index (RI) and the extension relaxation index (ERI) (Whelan et al., 2018).

A study by Whelan et al. (2018) examined knee extensor spasticity on people with upper motor neuron syndrome using the WPT and analyzed which test metric best reflects spasticity as measured by the MAS. The test metrics are demonstrated on the knee angle time curve of Figure 2. The initial and second swing of the WPT were deemed important for detecting extensor spasticity. Three notable test metrics were considered good predictors of clinical spasticity: F1amp, the maximum angular velocity, that stretches the knee extensors; Plat, resting flexion angle, the extensors ending length; and RI, which accounts for changes in muscle length and structure as a result of spasticity. These three selected test metrics will be the points of analysis to determine any change in spasticity.

2.3 Gait

Human gait has been a source of scientific inquiry for more than a century (Braune & Fischer, 2012). Gait is defined as a dynamically balanced process that includes statically unbalanced phases throughout the cycle (Barbareschi, Richards, Thornton, Carlson, & Holloway, 2015) and is regarded as a semi-automated human function that requires minimal cognitive awareness but a large amount of neurological control (Takakusaki, 2013). Understanding how neurological injury affects the biomechanics of walking, however, is a sub-field of gait analysis that is several decades old (Perry & Davids, 1992; Sutherland, 1978). Motor and sensory impairment from neurological injury can therefore have consequential impacts on walking ability, which is often quantified from gait analysis using spatio-temporal measures as well as kinematic profiles of the lower-extremity joints (Winter, 2009) during the gait cycle.

A gait cycle is the time interval between successive instances of initial contact (IC) for the same foot and is comprised of two phases ("stance phase" and "swing phase") that each leg completes in a temporally overlapping fashion to achieve efficient locomotion. The stance phase is approximately 60% of the gait cycle and occurs when the foot is in contact with the ground and is defined by into two events: IC and toe-off. The swing phase is approximately 40% of the gait cycle and occurs when the foot is off the ground and moving forward into the next step. This is also broken into three parts: initial, mid, and terminal swing. The gait cycle is summarized in Figure 3.

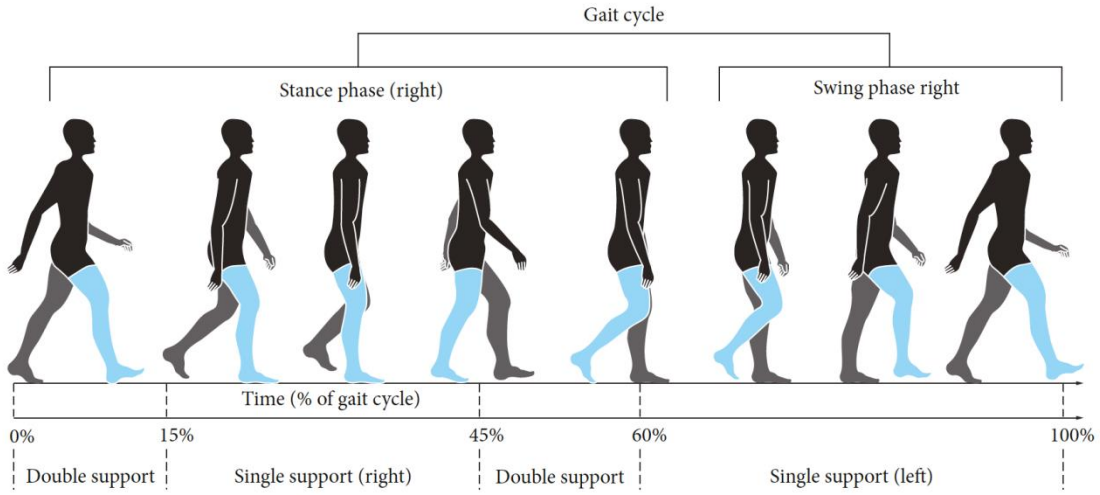


Figure 3. A full gait cycle broken into stance and swing phases

(https://creativecommons.org/licenses/by/4.0/).

2.3.1 Knee Gait Kinematics and Electromyography

Performing the complex task of human gait requires a combination of autonomous and automatic mechanisms for control. Takakusaki (2013) suggested there are five neurological levels of muscle control responsible for the "normal" movement. These five levels include the reflex arc from the muscle spindle, the spinal cord multi-segmental interaction, the vestibular system within the brain, the midbrain/subthalamus area, and the cerebrum. The reflex arc is considered to be a form of hyperreflexia; a slow or quick stretch that can be responsible for spasticity and rigidity in the presence of CNS injury. However, the communication between the spinal cord and multiple body segments is also a form of hyperreflexia, is responsible for flexion/extension of the hip and knee of gait. The vestibular system and the midbrain/subthalamus control the reflexes required for postural control and the body's position in space. The vestibular system aids in keeping the trunk upright, while the midbrain/subthalamus initiates the signal to step or stand.

Electromyography of thigh muscles and kinematics of the knee joint during gait are the primary interest in this thesis. During gait, the knee joint transitions through flexion and extension movements to complete a gait cycle. Figure 4 demonstrates a typical knee flexion/extension waveform of gait. In a typical gait cycle, the knee has four peak knee angles of interest for analysis (Winter, 2009). The first flexion occurs at approximately 10% of the gait cycle (K1), which indicates the load acceptance of stance before extending into full single-limb support. The midstance minima begins at about 40% of the gait cycle (K2), entering into swing phase. The third peak knee flexion occurs during swing at approximately 75% of the gait cycle (K3). Following peak knee flexion, the knee extends over the remaining 20% of the gait cycle where the end of swing minima occurs around 95% gait cycle (K4). End of swing minima happens before the slight flexion of the knee at the IC which restarts the gait cycle.

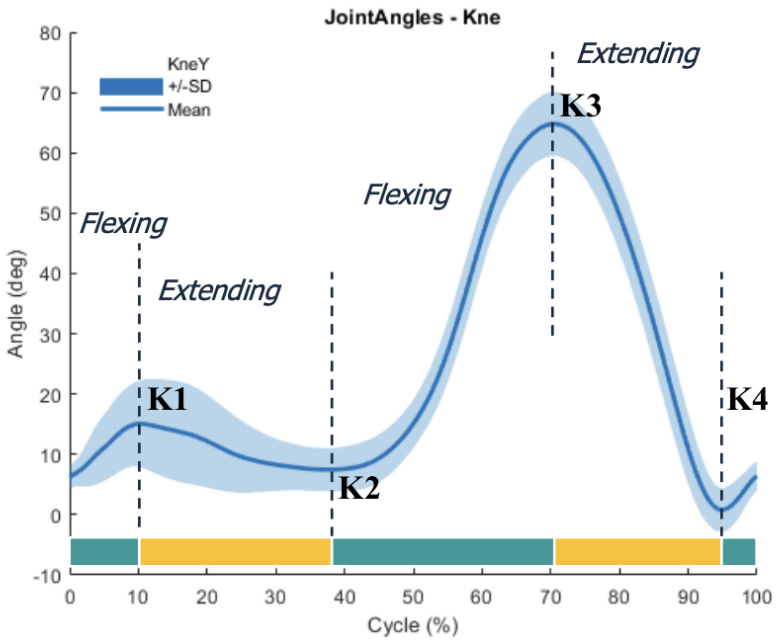


Figure 4. Knee joint kinematics for an entire gait cycle of normal gait. The y-axis is knee angle in degrees and the x-axis is %GC.

The knee follows a repetitive cycle to provide the movement of gait. Gait requires the interaction of multiple body systems to produce such a naturally complex, metabolically efficient movement. These body systems include the sensory, neuromotor, and musculoskeletal systems (Morais et al., 2010). Focusing only on the lower limbs, a variety of muscle groups work in synergy to generate gait. The contribution of the flexors and extensors of the knee, the quadriceps and hamstrings, respectively, during gait is describe by Strazza et al. (2017). The quadriceps, particularly the rectus femoris and the vastus lateralis, are the primary impact absorbers during the weight acceptance portion of the stance phase. The knee extensors provide eccentric contraction during the stance phase to control knee flexion and can contribute to limb progression during the swing

phase. The hamstrings, in particular the biceps femoris, mainly provide a protective mechanism for the knee, preventing hyperflexion at the terminal swing phase.

Throughout a gait cycle, the activation of flexor and extensor muscles of the knee can vary from stride to stride (Strazza et al., 2017). Although firing patterns may differ between muscles, there are moments of co-contraction that occur throughout a gait cycle. Strazza et al. (2017) suggest the main activity of the vastus lateralis and the biceps femoris during the gait cycle were detected at the same relative percentage as rectus femoris. The main periods of activation and co-contraction for these muscle groups occurred during the late swing phase and early stance phase. These co-contractions protect the stability of the knee joint during the terminal swing to stance transition. For further description of the activation and co-activation patterns of the knee joint during gait, please refer to "Surface-EMG analysis for the quantification of thigh muscle dynamic co-contractions during normal gait" by Strazza et al. 2017.

2.3.2 Gait Rehabilitation

The impaired mobility experienced by people with SCI can reduce independence, quality of life, and life expectancy. Rehabilitation is to restore health through training and therapy and is needed to help these individuals recover and regain mobility (Chen et al., 2016). In neurologic conditions such as SCI, loss of walking ability is associated with a reduced quality of life (Sale et al., 2012). An effective rehabilitation plan is a personalized one and provides intensive, task-specific, and multisensory stimulation input; it was stated that adaptation of the central nervous system is highly influenced by sensory input, experience, and learning (Sale et al., 2012). This adaptation within the

central nervous system and motor system stems from the concept of neural plasticity. Poli et al. (2013) define neural plasticity as the functional adaptations and recovery mechanisms that are a result of changes in neuronal organization.

Rehabilitation interventions are strategically designed by teams of qualified clinicians, involving a variety of different methods and equipment. Gait rehabilitation programs, such as gait training (GT), are directed toward improvements in gait function and performance. GT focuses on improving walking ability and is a common therapy implemented in the rehabilitation plan of SCI. The primary focus of GT is the recovery of lost motor patterns and therefore, the reactivation of muscle groups.

2.3.3 Evolution of Gait Training

Physiotherapy is implemented to strengthen and restore functionality to muscle groups and the skeleton: ultimately improving coordination of movement (Sale et al., 2012). GT is a type of therapy that has developed in different methodologies over time. These different methods include but are not limited to manually assisted over-ground training, manually assisted treadmill training, both with and without body weight support, and finally treadmill and robotic OEGT. The original, and still most popular method of GT is manually assisted over-ground training. This included a patient being manually supported, usually by a therapist, between a set of parallel handrails. One or two additional therapists would be on the ground, next to the patient's lower limbs, ready to assist in movement. From there, the patient would hold the handrails, and with support from the therapist behind them, the other therapist would manually pick up each lower limb separately, moving the limb through the ROM that resembles the swing phase, and

returning the foot to the ground. The manual method often includes a body weight support tether which eliminates some of the strain for a therapist supporting the weight of the patient and allowed for patient's body weight to be gradually introduced during gait.

Treadmills were introduced to increase the number of steps a patient could take in a straight line without having to reposition to continue. The use of treadmills in GT may involve a body weight support harness and a large amount of therapist involvement. Treadmill GT with body weight support involved the patients being suspended over a treadmill while manual assistance was provided to stimulate walking movements (Mirbagheri et al., 2011). The manual method of GT does have its drawbacks, as the therapist will experience physical constraint and ergonomically unfavorable positions, resulting in fatigue (Chen et al., 2013). Therapist fatigue will lead to shorter therapy sessions, a loss of intensity, and a negative impact on gait pattern replication (Chen et al., 2013). Advancements in GT happened when robotics were introduced to the process.

Robotic assisted gait training has been more recently introduced, in part to address the challenges of traditional GT, such as involvement of multiple therapists and training (Alcobendas-Maestro et al., 2012; Chen et al., 2013; Poli et al., 2013; Swinnen et al., 2010). Some exoskeletons are designed in combination with a treadmill, while others involve the patient walking over-ground. These suits allow patients to experience longer, more intense, reproducible gait patterns during therapy sessions (Grosu et al., 2015). It is clear that, over time, GT has evolved and advanced to benefit both the patients and therapists involved.

2.4 Exoskeletons

Advances in robotics have led to the development of powered exoskeletons. Exoskeletons are considered to be wearable robots that are designed around the shape and function of the human body (Sale et al., 2012). Exoskeletons establish a quasi-symbiotic relationship between the robot and the human, exhibiting physical interaction with the human user (Grosu et al., 2015; Pons, 2010). These interactions suggest that exoskeleton work in cooperation with the physiological and biomechanical systems of the human body (Ferris, 2009).

Exoskeleton technology ranges from single joint to multi-segment apparatuses, depending on the purposes and complexity of the design. Types of rehabilitation exoskeletons are designed based on the part of the human body being supported. These robots are classified as upper limb, lower limb, full-body, or specific joint support exoskeletons (Chen et al., 2016). Powered exoskeletons are designated as class II medical devices by the FDA (Miller et al., 2016). The FDA describes class II medical devices as "devices for which general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device". Exoskeletons use power actuators at the human joints to simulate moving the limb through its ROM. A lower limb exoskeleton tends to have actuators at the hip and/or knee joints to assist facilitation of standing, walking, climbing stairs, and performing activities of daily living for those with mobility impairments. The knee actuator, for example, stabilizes the knee during the stance phase and assists the knee through its ROM during the swing phase of gait (Pons, 2010). The main clinical application for lower limb exoskeletons resides in GT of patients with neurological disorders. These lower limb exoskeletons can be divided into two categories

non-mobile robots and over-ground rehabilitation robots (Chen et al., 2013). Both types of lower limb exoskeletons use a source of body weight support. Still, the big difference is non-mobile lower limb exoskeletons tend to be in combination with a treadmill, whereas over-ground suits allow for greater mobility and environmental interaction (Lajeunesse et al., 2016).

2.4.1 Exoskeleton Gait Training

Wearable exoskeleton technology is being researched as a tool of rehabilitation therapy to improve the quality of life for individuals affected by gait impairments and neurological impairments (De Rossi et al., 2011). Schiele and van der Helm (2006) determined that therapy is more effective if the movement input is cyclic, reproducible, rhythmical, and physiological. Exoskeletons are implemented under therapist supervision and provide intensive, task-orientated, consistently precise movements, that can improve the muscle strength and movement coordination in people with neurological disorders (Wirz et al., 2005). As previously mentioned, lower limb exoskeletons relieve the physical involvement and impacts on the therapists during GT sessions.

Alleviating the workload of the therapist, betters the use of the therapist's expertise and time by transitioning focus towards the target of functional rehabilitation (Poli et al., 2013). This change in focus promotes more meaningful tasks such as interacting with patients, assessing outcomes of therapy sessions, and intervening in sessions if necessary (Chen et al., 2013). Many of these lower limb exoskeletons have gait variability, offering adjustable control to the robotic forces produced, and different levels of assistance. For therapists to optimize the patient's training quality and motor recovery, unique

rehabilitation programs are designed around the patient's condition and abilities, using a combination of non-robotic and robotic treatment methods (Chen et al., 2013; Poli et al., 2013). Unfortunately, techniques for determining an individual's training parameters, such as walking speed, have not yet been established for GT (Sale et al., 2012).

Despite the lack of research in training parameters/protocol, Wirz et al. (2005) reported significant changes in functional limitations after treadmill exoskeleton use, including increased over-ground gait speed, improved gait endurance, and a decrease in time taken to complete a Time Up and Go test. Also reported, were increases in general walking ability, lower limb motor strength, and postural stability (Wirz et al., 2005).

Further studies on spasticity and exoskeleton GT have demonstrated in a reduction of muscle spasticity, with Miller et al. (2016) claiming that in five studies, 38% of patients reported a decrease in spasticity after exoskeleton GT. This decrease of spasticity may be explained by the physiological and automatic properties of gait being stimulated in persons who are unable to walk without an assistive device (Stampacchia et al., 2016).

To date, there has been little attention on researching knee joint kinematics during exoskeleton gait. Table 2 is a summary of research studies on the knee flexion angle of AB and SCI populations during OEGT. These articles suggest that researchers are curious about the effects of OEGT on the knee joint. Considering the success of exoskeleton GT, without a method to determine individual protocols, Wirz et al. (2005) suggested that developing specific treatment algorithms and understanding knee activation pathologies would aid clinicians in deciding which physical interventions and parameters would be best to maximize recovery and function of patients.

Table 2. A collection of recent research studies on knee flexion angle and OEGT of AB and SCI participants.

Article	Exoskeleton	Participants	Knee Kinematics	Flexor EMG	Extensor EMG
Neuromechanical adaptations during a robotic powered exoskeleton assisted ... (Ramanujam et al., 2018)	Ekso GT™	4 SCI 4 AB	Yes	Yes	Yes
EMG patterns during assisted walking in ... (Sylos-Labini et al., 2014)	MINDWAL-KER	4 SCI 6 AB	Yes	Yes	Yes
Walking With a Robotic Exoskeleton Does Not Mimic Natural Gait: A ... (Swank et al., 2019)	Ekso GT™	15 AB	Yes	Yes	Yes
Differentiating Ability in Users of the ReWalkTM ... (Talaty et al., 2013)	Rewalk®	12 SCI	Yes	No	No
Exoskeleton for Gait Rehabilitation: Effects of Assistance, Mechanical Structure, and Walking Aids on ... (De Luca et al., 2019)	Ekso GT™	8 AB	No	Yes	Yes

2.5 Gap Statement Revisited

Exoskeletons listed in Table 2 were designed as a tool for GT of individuals with neurological disorders. However, a greater understanding of the physical interactions between exoskeleton and user is needed for developing treatment strategies and protocols to maximize functional recovery and reduce the possibility of injury. For example, Stampacchia et al. (2016) have reported that it is not known if new robotic exoskeletons are well accepted by persons with SCI, particularly those who experience severe spasticity. Stampacchia et al. (2016) also stated that no one rehabilitation protocol for over-ground GT using powered exoskeletons has been proposed to be most effective.

The progress in the field of rehabilitative robotics requires investigation of the kinematic compatibility and quality of the physical interaction, to develop treatment algorithms and protocols that help clinicians decide on appropriate physical intervention measures (Chen et al., 2016; Wirz et al., 2005). Investigating the locomotor response to the exoskeleton movement of healthy subjects and those with neurological injury, is vital for developing improved rehabilitation approaches and mechanisms for locomotor function (Ivanenko et al., 2013).

The current research study aimed to provide insight into the physical interactions between exoskeleton and human locomotor patterns to assist therapists in designing personalized OEGT protocols. More specifically, the development of a normative database using observation of AB locomotor patterns during OEGT will aid in the interpretation of muscle activity patterns (MAPs) in neurologic populations such as those with SCI. Salient to interpreting MAPs during exoskeleton use is the ability to identify and discriminate spastic contractions from eccentric contractions that normally occur

during various phases of gait when a muscle is lengthening. We propose an approach for accomplishing this in the clinic by using simple wearable sensors. As such, this study is a first step toward developing a framework for OEGT prescription that takes into account muscle spasticity.

Chapter 3: Methods

The objective of this study was to examine the physical interactions of the knee joint and exoskeleton during gait training. Two separate studies, AB and SCI, were conducted to achieve this objective. Both studies included a series of exoskeleton gait trials and WPTs. The AB participants' gait trials were performed under four different conditions of a predetermined combination of exoskeleton step parameters, as well as gait trials not wearing the exoskeleton. Step parameter settings for the SCI participants were determined from their previous gait training sessions (required for their eligibility). The WPTs were conducted pre- and post-gait trails for the SCI participants to help determine any change in spasticity. The primary outcome measures of the study were knee joint angle, along with knee extensor and flexor EMG.

3.1 Human Subjects

Both the AB study and SCI study are on file with the Research Ethics Board at the University of New Brunswick, REB #2017-049 and #2019-053 respectively. The SCI study required additional ethics approval from the Horizon Health Network Research Ethics Board and is on file under 2019-2719.

3.2 Recruitment

Both studies took place at the Stan Cassidy Center for Rehabilitation (SCCR), in Fredericton, New Brunswick. Recruitment procedures for the AB and SCI studies were as follows.

3.2.1 Able-Body Participants

Healthy, adult participants with no diagnosed muscle or joint conditions (arthritis, injury, etc.) were recruited by word of mouth. Interested individuals were contacted via email, which included a summary of the research and the inclusion criteria for potential participants. The inclusion criteria were determined from the Ekso GT™ user criteria in the Clinical Training Manual provided by the manufacturer. This included age range (18-65 years), a height range (152.4-193.04 cm), and a maximum weight of 99.79kg. Potential participants replied with verbal confirmation of participation and a date and time were scheduled for visit 1. The beginning of visit 1 included a further explanation of the study and obtaining informed consent.

3.2.2 Spinal Cord Injury Participants

SCI participants were recruited by SCCR staff. The Standard Operating Procedure (SOP) used by the SCCR was followed for obtaining informed consent from the participants. The SOP ensures that sufficient and legal informed consent is properly obtained and documented for each participant of the clinical study. The SOP began with the therapist approaching the participant and considering them suitable to use the Ekso GT™. Participants selected for the SCI study had at least 1500 steps of previous GT sessions in the Ekso GT™ with the trained therapists on site. Previous experience ensured the participant had been cleared for safe use of the Ekso GT™ and that all required Ekso GT™ measurements were collected and fit confirmed before data collection. For full Ekso GT™ inclusion and exclusion criteria see Appendix B.

Once a therapist identified a potential participant, the person was approached and informed of the study in detail and asked for voluntary participation. Upon a verbal confirmation from the participant, the therapist contacted the principal investigator (PI) via email to arrange a time for a testing session. Prior to beginning of this test session, a further explanation of the study was provided by the PI, and signed informed consent was obtained.

3.3 Materials

3.3.1 Ekso GT™

The Ekso GT™, Figure 5, is a commercial (FDA and Health Canada approved) exoskeleton "that enables individuals to stand up and walk over ground with full weight bearing, reciprocal gait in a clinical setting". The Ekso GT™ is a lower limb exoskeleton geared towards SCI and stroke patients. Specifically, the Ekso GT™ is FDA and Health Canada approved for individuals with spinal cord injuries at levels T3 to C7 (AIS D), and stroke patients with hemiplegia. The exoskeleton enables individuals with lower limb weakness or paralysis to stand and walk over a level surface, with the additional aid of a walker, crutches, or a cane for maintaining balance. The Ekso GT™ has powered motors at the knees and hips that are initiated by either patient actions or by the therapist's actions. A patient must use the Ekso GT™ under the direction of a therapist who has undergone the Ekso GT™ certification training administered by the Ekso Bionics™ Clinical Training Team.

The Ekso GT™ is designed to be easily adjusted to fit different individuals and allows for a variety of parameters to be adjusted for personalized therapy protocols of

the patients. For purposes of this study only these parameters were adjusted:

- step length
- step height
- swing time

Figure 5. The Ekso Gait Trainer (GT)™ developed by Ekso Bionics™.

3.3.2 The BioTone Kit

The BioTone kit was developed for capturing flexion and extension kinematics, as well as muscle EMG of a particular joint. The BioTone kit consists of a fibre optic goniometer, 2-channel EMG, and an accelerometer system for quantifying joint kinematics and muscle activity during active or passive movements (Figure 6; McGibbon, Sexton, Jones & O'Connell, 2013). Goniometers are used to measure the

angle between two body segments, by tracking the physical signal produced from angular change (Tao, Liu, Zheng, & Feng, 2012). The BioTone kit also has a 2-channel EMG system that uses DuoTrode Ag-AgCl electrodes. EMG was used to collect electrical signals of muscle activity during muscle contraction. The accelerometer was used to detect foot strikes. The sensors were connected to an analog interface (BioSI™). That manages the sampling and transmits data to a laptop computer for storage, processing, and real-time display of sensor data.

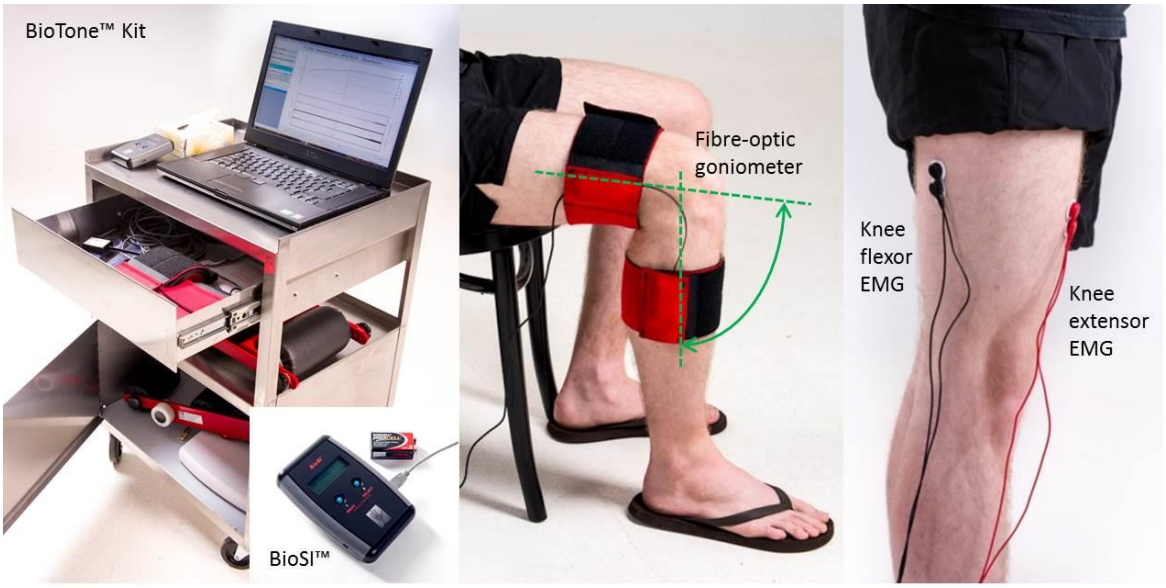


Figure 6. BioTone Kit goniometer setup.

3.4 Procedure

Procedures for both studies were similar, with differences only due to populations. Participants were asked to meet at the SCCR located on the grounds of the Dr. Everett Chalmers Regional Hospital. Participants were brought to the activity gym, where the PI explained the study in detail and presented the participant with a clipboard

containing the study information and consent form. Participants were reminded their consent was voluntary, and there was freedom to withdraw from the study at any time without explanation.

For both studies, the PI collected demographic information, including: sex, age, height, and weight from the participants. The participants were asked to sit in a wheelchair with a reclining back function where the PI applied and set up the BioTone kit. The EMG sensors and goniometer were placed on one leg, with two electrodes placed on the hamstrings and quadriceps. The AB population had electrodes on the bicep femoris and vastus lateralis, while the SCI participants were on the bicep femoris and the rectus femoris. A reference (ground) electrode placed on the back of the neck for AB and pisiform bone of the wrist of SCI. The skin area was prepped using a razor to remove any hair and the area cleaned with an alcohol wipe to ensure proper contact of the sensors. The EMG cables were run under the participant's clothing; this was to prevent the cables from catching on the Ekso GT™ or any other surroundings. The PI then set up the goniometer on the medial side of the knee joint. An upper cuff was strapped around the thigh, with a lower cuff around the upper portion of the shank. The goniometer was placed in the pocket of each cuff, with the cable fed through their clothing as the EMG cables were. All cables were connected to the BioSi™ and directly connected to a laptop, by USB, to collect data.

The first test conducted was the Wartenberg Pendulum Test (WPT) in a reclining wheelchair. Participants were reclined back until the thigh was a parallel with the floor, allowing the lower leg to hang off the edge freely. The PI then talked the participant through every movement, beginning with straightening the limb out, slowly, until it was

in line with the upper portion of the leg. At this point, the PI zeroed the goniometer on the software to ensure accurate data collection. The PI then explained to the participant that a hand was going to be placed under the shank, just above the ankle, to support the leg. The PI explained the hand would be removed, and that the participant should let gravity take its course, allowing the leg to drop and swing until it stops, as illustrated in Figure 7. The PI then informed the participant to close their eyes and relax. A quiet EMG signal confirmed relaxation. The PI then removed the hand, allowing the leg to swing freely until coming to a stop. This process was repeated three times, with 30-second breaks between each trial. Once the three WPTs were complete, the participant was transferred over to the Ekso GT™.

Figure 7. Instrumented pendulum test.

The next portion of the testing session consisted of walking trials wearing the Ekso GT™. Before beginning data collection of Ekso GT™ gait trials, the goniometer had to be removed from the lower cuff and the lower cuff removed from the participant. The upper cuff remained on the thigh of the participant. The participant was secured in

the Ekso GT™, which was situated in an armless chair. The goniometer was kept in the pocket of the upper cuff and securely taped to the lower leg strap of the Ekso GT™ (Figure 8). Before standing the participant from the chair, the Ekso GT™ was checked for proper fit by moving each leg through its ROM. The Ekso GT™ gait trials commenced once the placement of the goniometer had been confirmed, and the participant had been stood up to zero the goniometer once again.

The procedure for the Ekso GT™ gait trials was dependent upon population and is described in sections 3.5.1 and 3.5.2. When the data collection of the gait trails was finished, the BioSI™ system was stopped, and the participant was returned to the armless chair and sat down. The goniometer was removed from the lower leg strap of the Ekso GT™ and the pocket of the upper leg cuff around the thigh. The PI helped the participant in doffing the Ekso GT™ and getting up from the chair.

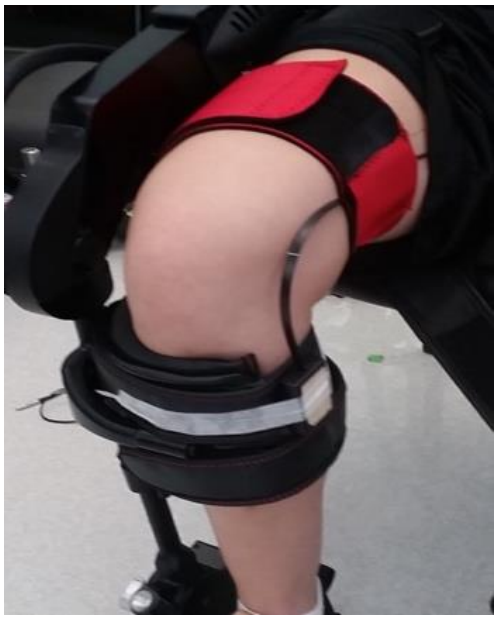


Figure 8. The fibre optic goniometer taped to the lower leg strap of the Ekso GT™.

When the testing session was complete, the goniometer and EMG wires were disconnected from the BioSI™. The goniometer was removed from the leg cuffs, and the wire pulled from under the clothing. Leg cuffs were unstrapped and removed from the leg, and the EMG wires disconnected from the sensors and removed from under the participant's clothing. The EMG sensors were removed, and the area cleaned with a wipe to remove any left-over gel. The patient was thanked for participating in the study.

3.4.1 Able-Body Study

The AB study participants were asked to attend two visits. The first visit lasted from 60 to 90 minutes; during which, demographics were collected, and informed consent was signed. The main purpose of the first visit was for the naïve AB participants to be fitted and gain some experience using the Ekso GT™. The fit of each participant was determined according to the Ekso Bionics™ fitting instructions. The fitting process involved the PI taking a variety of anthropometric measurements (lower, upper leg length, and hip-width) using a measuring caliper provided by Ekso Bionics™. Using the conversion chart supplied by Ekso Bionics™, a participant's Ekso GT™ fit profile was determined.

The Ekso GT™ was set to the participant's fit profile, and the participant was asked to sit on the chair with the Ekso GT™ while the PI secured the fit. The PI then provided instructions on what to expect when standing up and walking in the Ekso GT™. Participants were instructed to be as passive as possible, allowing the exoskeleton to guide the movement. The participants were stood up and walked in the Ekso GT™ until they communicated feeling comfortable and familiar with the movements of the

exoskeleton. Then the participant was sat back down and the Ekso GT™ doffed, completing the first visit.

The second visit was set for the next day and lasted between 120-150 minutes. The second visit was when data collection occurred. Participants were set up with the goniometer and EMG sensors on the right leg and three WPTs were conducted. Following the WPTs, the accelerometer was taped to the back of the heel. Participants performed three straight gait tests at a normal pace for approximately 20 steps. The participants then donned the Ekso GT™, where the accelerometer was moved to the heel of the Ekso GT™'s footplate (see Figure 9) and prepared for gait trails.

Figure 9. The accelerometer taped to the heal of the footplate to Ekso GT™.

Ekso GT™ gait trails consisted of four different conditions (see Table 3) with each condition performed in three different step lengths (SL) (12", 15", and 18") with three repetitions of each, for a total of 36 trials (3 SLs x 3 trials x 4 conditions). Data was collected over trials of 20 steps and separated by a short break. Each condition consisted

of different gait setting parameter combinations for step height (SH) and swing time (ST). The order of the conditions, as well as the SL order of the conditions, were randomized for each participant. When all trials were completed, the participant doffed the exoskeleton, and the testing session was finished.

Table 3. Displays the different step height and swing time settings across all four conditions.

Condition	Step Height	Swing Time
1 (Expected Max Velocity)	Max	Min
2	Max	Max
3	Min	Min
4 (Expected Minimum Velocity)	Min	Max

Note: all conditions will be performed in three different step heights. Max step height was 7.62cm, whereas minimum was less than 2.54cm. Max swing time was 2.5 second, and minimum was 0.8 seconds.

3.4.2 Spinal Cord Injury Study

The SCI participants attended one testing session that lasted between 60-90 minutes. The participant's therapist provided the PI with demographic information from the participants chart, as well as date and classification of injury (ISNCSCI), and AIS score. The participant was assisted in laying on a therapy plinth, where the therapist evaluated the participant's MAS score of the knee extensors. The goniometer and EMG sensors were attached to the most spastic leg (highest MAS) by the therapist, and the PI conducted the three WPTs.

Participants were then assisted over to the Ekso GT™ and secured in the exoskeleton as previously described. Data was collected over a series of three walking tests of 20 steps using the participant's step settings that were selected by the therapist from their prior Ekso GT™ training. A two-minute break separated gait trials. Upon completion of the gait trials, the participant was returned to the armless chair to doff the Ekso GT™. Participants were assisted back to the reclining wheelchair, where the PI conducted three post-WPTs. When post-WPTs were complete, the participant had the BioTone kit removed, the testing session was finished, and the participant was thanked for their time.

3.5 Research Questions

The research questions of this study were chosen for exploratory purposes and were not hypothesis driven. These questions were selected to provide further insight into the interaction between exoskeleton and user during gait. By measuring knee flexion angle and flexor and extensor EMG, of AB and SCI participants, biological signal data was compiled to explore over the gait cycle.

3.5.1 Research Question 1

What do able-bodied gait patterns look like when walking with the exoskeleton?

1a. How does exoskeleton gait effect the magnitude of biological signals such as knee flexion angle and electromyography across the gait cycle?

1b. How do different combinations of exoskeleton gait step parameters affect knee flexion angle and electromyography?

1c. How does exoskeleton gait affect the timing of these biological signals during a complete gait cycle?

3.5.2 Research Question 2

What is the interaction between exoskeleton gait and spasticity?

2a. Can able-bodied knee flexion angle and electromyography during exoskeleton gait help interpret how exoskeletons interact with spinal cord injury patients during exoskeleton gait training?

2b. Is spasticity occurring during exoskeleton gait?

2c. Can a short session of over-ground exoskeleton gait training reduce spasticity?

3.6 Data Analysis

The data was transmitted to a nearby laptop by the BioSI™ interface during data collection. The raw data were exported into Matlab for processing. Figure 10 illustrates a step-by-step flowchart of the processing required for the data to go from data to output data. The knee angle data from the goniometer was used to analyze knee flexion angles during gait trials. Muscle activity during gait trials was determined from the EMG signals of the flexors and extensors of the knee. The processed cycled gait data was used to conduct the statistical analyzes for both the AB and SCI study.

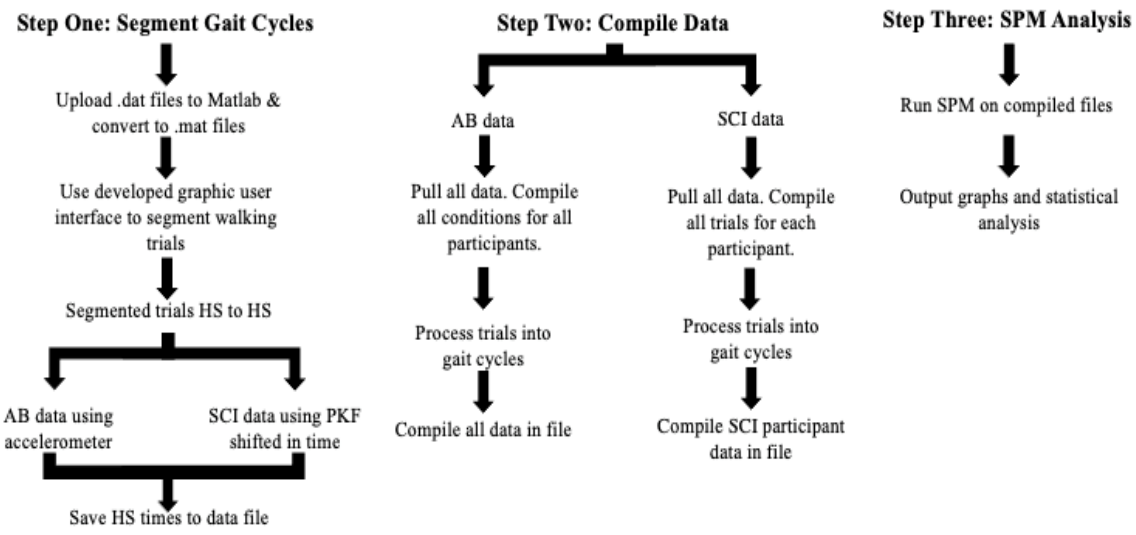


Figure 10. A flowchart displaying the three steps required for processing and data formatting.

3.6.1 Case Study Analysis

The SCI participant data was further analyzed using a variety of Case Study analysis techniques, as determined by the Encyclopedia of Case Study Research (Mills, Durepos & Wiebe, 2010). Each SCI participant was treated as an embedded single-case study; a combination of three different methodologies of case study analyses was used to examine the SCI participant data. Descriptive techniques such as graphs and tables aided in the observational reflection of embedded patterns within the EMG and knee flexion angle data. Pattern matching analysis added further inquiry by comparing the observed patterns in the AB data to the data of the SCI participants. Additional pattern matching analysis of the WPT data was used to establish if a short session of OEGT can reduce spasticity. Explanation building was the primary methodology for determining the interaction between OEGT and muscle spasticity, as well as to decide if OEGT is a successful method of GT for persons with SCI. A combination of data analysis and

statistical analysis techniques were used to discern the final analysis of both the AB data and SCI participant case studies.

3.7 Statistical Analysis

Statistical analysis was completed with custom written Matlab (MathWorks, Natick, MA) code and publicly available statistical parameter mapping (SPM) toolbox (Pataky, 2016). A combination of quantitative and qualitative analysis methodologies was used to analyze the AB and SCI participant data. A series of 3-way repeated measure ANOVAs were conducted in congruence with case study analysis techniques to establish and develop evidence for explanation building.

3.7.1 Statistical Parameter Mapping

Over the years, methods used in functional data analysis have evolved to consider the time-dependent structure of continuous biomechanical data. SPM was initially utilized to compare patterns of 3D and 4D functional neuroimaging, such as brain positron emissions tomography scan. Only within the last ten years has SPM been applied to one-dimensional (1D) biomechanical curves such as knee flexion angle (Pataky, 2016). SPM uses Gaussian smoothing and random field theories to adjust statistical thresholds to control for the family-wise error rate and allow calculated p-values of time clusters (Herbert-Losier et al., 2015). An alpha value is used to calculate the critical height threshold F-statistic (F*). The F* is used to determine the significant difference in the magnitude of signals. A significant difference in signal magnitude is suggested to occur when the observed test statistic field crosses the F*. See Figure 11 for an observational example of an SPM output. For a more in-depth explanation and a copy of the SPM

Matlab toolbox used for this study, please refer to "rft1d: Smooth One-Dimensional Random Field Upcrossing Probabilities in Python" by Pataky, (2016).

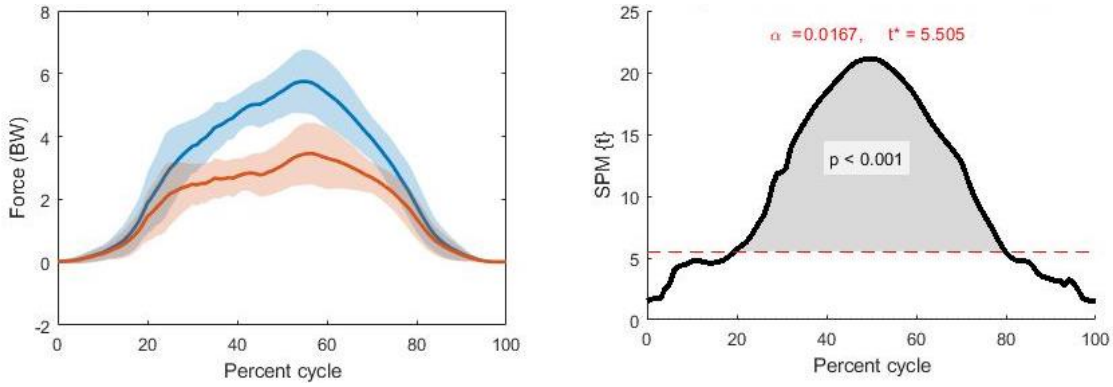


Figure 11. Displays an example of SPM analysis.

3.7.2 Able-Body Study Analysis

***Research Question 1a*:** How does exoskeleton gait affect the magnitude of biological signals such as knee flexion angle and EMG?

This research question was answered using SPM to compared knee flexion angle curves and EMG signals of Ekso GT™ to those of normal gait. Regions of the gait cycle were deemed significantly different when the computed F-statistic exceeded the critical F* value. Regions that are significantly different will highlight regions for discussion and explanation building on the effects of exoskeleton gait on the biological response of the user.

***Research Question 1b*:** How do different combinations of exoskeleton gait step parameters affect knee flexion angle and electromyography?

This research question was answered using three, 3-way (2x2x3) repeated-measures ANOVAs conducted using SPM (function “anova3rm”). The independent variables in the model were SH (min, max), ST (min, max), and SL (min, med, max). The

dependent variables were normalized time series (%GC) for knee flexion angle and flexor and extensor EMG. Each test was assigned an alpha of 0.05. The 3-way ANOVA determined what effect each independent variable had on the dependent variables, as well as any interaction effects between independent variables. Table 4 displays multiple comparisons within each independent variable for any one dependent variable.

Table 4. The multiple comparisons within each independent variable for any one dependent variable of research question 1a.

Step Height Effect	2x(2x3)		
	SL=min	*SL=med*	*SL=max*
ST=min	C1min vs C3min	C1med vs C3med	C1max vs C3max
ST=max	C2min vs C4min	C2med vs C4med	C2max vs C4max

Swing Time Effect	2x(2x3)		
	SL=min	*SL=med*	*SL=max*
SH=min	C3min vs C4min	C3med vs C4med	C3max vs C4max
SH=max	C1min vs C2min	C1med vs C2med	C1max vs C2max

Step Length Effect	3x(2x2)	
	ST=min	*ST=max*
ST=min	C3min vs C3med vs C3max	C4min vs C4med vs C4max
ST=max	C1min vs C1med vs C1max	C2min vs C2med vs C2max

Research Question 1c: How does exoskeleton gait affect the signal timing during a complete gait cycle?

This research question was answered by conducting three separate 3-way repeated-measures ANOVAs, where the independent variables were the same as in research question 1a. However, for this test, the dependent variables were discrete parameters: cycle time (s), absolute peak knee flexion time (s), and normalized peak knee flexion time (%GC). For consistency, the 3-way ANOVA test were also conducted using SPM, which allows for zero-dimensional (0D) data (data of a discrete point in time). As before, each dependent variable was assigned an alpha of 0.05.

3.7.3 Spinal Cord Injury Study Analysis

For the SCI case studies, only two statistical analyses were required for the supplemental research questions. In addition, non-statistical case study analysis methodologies were used, as previously explained in 3.6 Data Analysis.

***Research Question 2a*:** Can able-bodied knee flexion angle and electromyography during exoskeleton gait help interpret how exoskeletons interact with spinal cord injury patients during exoskeleton gait training?

This research question was answered by comparing the AB Ekso GT™ gait knee flexion angle curves and EMG signals to the SCI. A cross-correlation and root mean square error tests were conducted to gain a perspective of AB data compared to SCI data. Using these two tests helped determine which of the four AB Ekso GT™ conditions was closest to the SCI data. A cross correlation co-efficient closest to one and the smallest root mean squared error resulted in the closest similarity. For further analysis a series of

plots were generated superposing all AB conditions and the SCI knee flexion angle and EMG (flexion and extension).

***Research Question 2b*:** Is spasticity occurring during exoskeleton gait?

This research question was answered by comparing the SCI participant data to the AB exoskeleton gait data; specifically, comparing persons with SCI EMG activity to AB EMG activity during flexion and extension movement of the knee to determine whether spasticity is occurring during OEGT. This case analysis is the first step toward the development of a benefit/risk framework for therapists to follow to determine a patient's expected risks and potential benefits from OEGT.

Research Question 2c: Can a short session of over-ground exoskeleton gait training reduce spasticity?

This research question was answered analyzing the test metrics of the WPT. First flexion amplitude (F1Amp), relaxation index (RI), and plateau angle (Plat) were recommended as the as the best classifiers for extensor spasticity. A reduction of spasticity was determined by comparing the pre WPT F1Amp, RI, and Plat to the post WPT. A short session of OEGT reduced spasticity if the F1Amp, RI, and Plat values increased in magnitude post GT.

Chapter 4: Results

4.1 Participants

4.1.1 Able-Body Study

Participants met all inclusion criteria and were selected on a first response basis. A total of six AB participants recruited three males and three females. Participants were all university students with an average age of 24 ± 1.79 years, height of 172.17 ± 11.92 cm, and weight of 72 ± 12.96 kg.

Five out of six participants were used for data analysis only. Participant 1 was a pilot participant and presented difficulties getting rectus femoris EMG which required a switch in protocol from rectus femoris to vastus lateralis EMG. Therefore, data from participant 1 was excluded in the results analyses.

4.2 Signal Magnitude Analysis

Research Question 1a

Biological signal data (knee flexion angle and EMG) of the four Ekso GT™ conditions were analyzed against the normal gait data of five AB participants using SPM. The SPM plots for normal gait and the four Ekso GT™ gait conditions are in Figure 12.

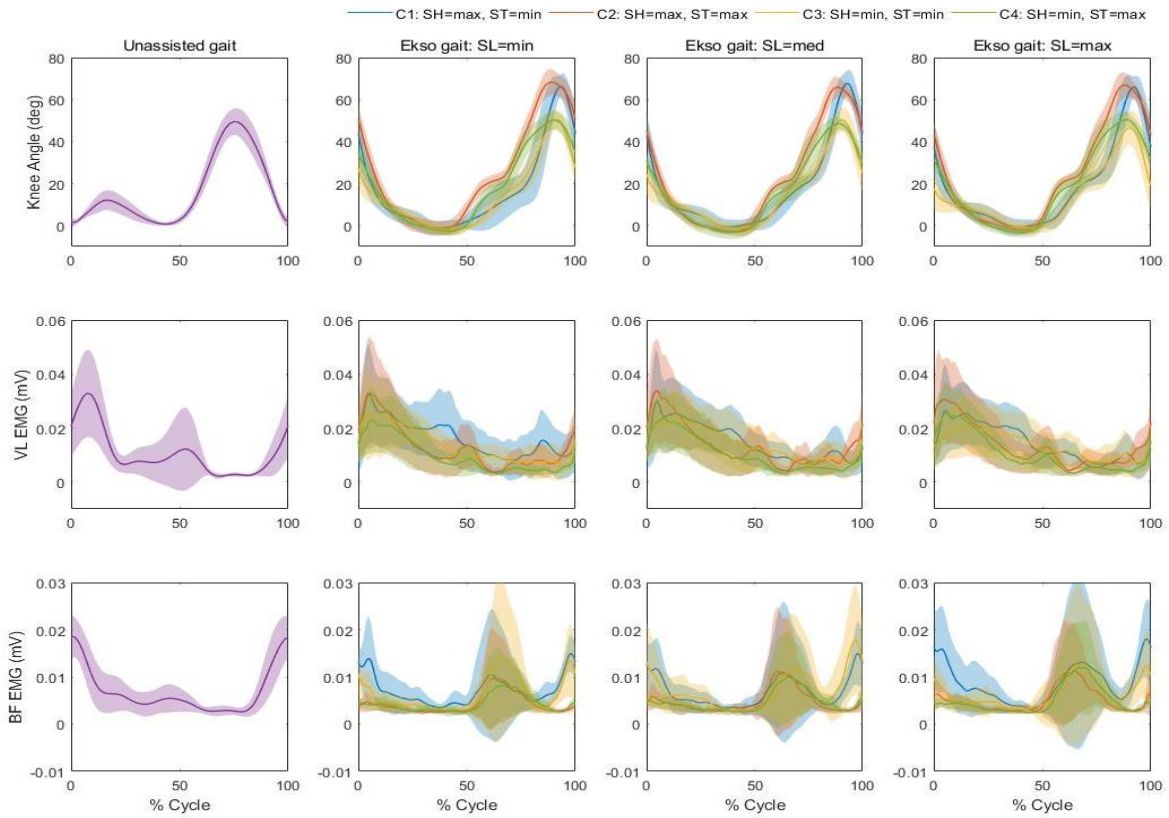


Figure 12. Biological signal data (knee flexion angle and flexor and extensor EMG) for normal gait and the three SLs for the Ekso GT™. The x-axis represents %GC and the y-axis represents knee angle (degs) for the top plot and EMG (mV) for the bottom two plot rows. For Ekso GT™ gait all four conditions are plotted. The blue data is Condition 1, red is Condition 2, yellow is Condition 3, and green is Condition 4.

The SPM results for Condition 1 can be seen in Figure 13. F-statistic plots for knee flexion angle, extensor EMG, and flexor EMG display the calculated critical heights (F*), 80.721, 106.766, and 106.766 respectively. Significant difference in Ekso GT™ gait knee flexion angle compared to normal gait were found from approximately 75%-80% and 90%-100% gait cycle ($p<0.001$), suggesting that there are differences between knee flexion angle during swing phase. No significant differences were detected between

EMG waveforms. For individual participant results of normal gait and Condition 1 please refer to Appendix C and Appendix D, respectively.

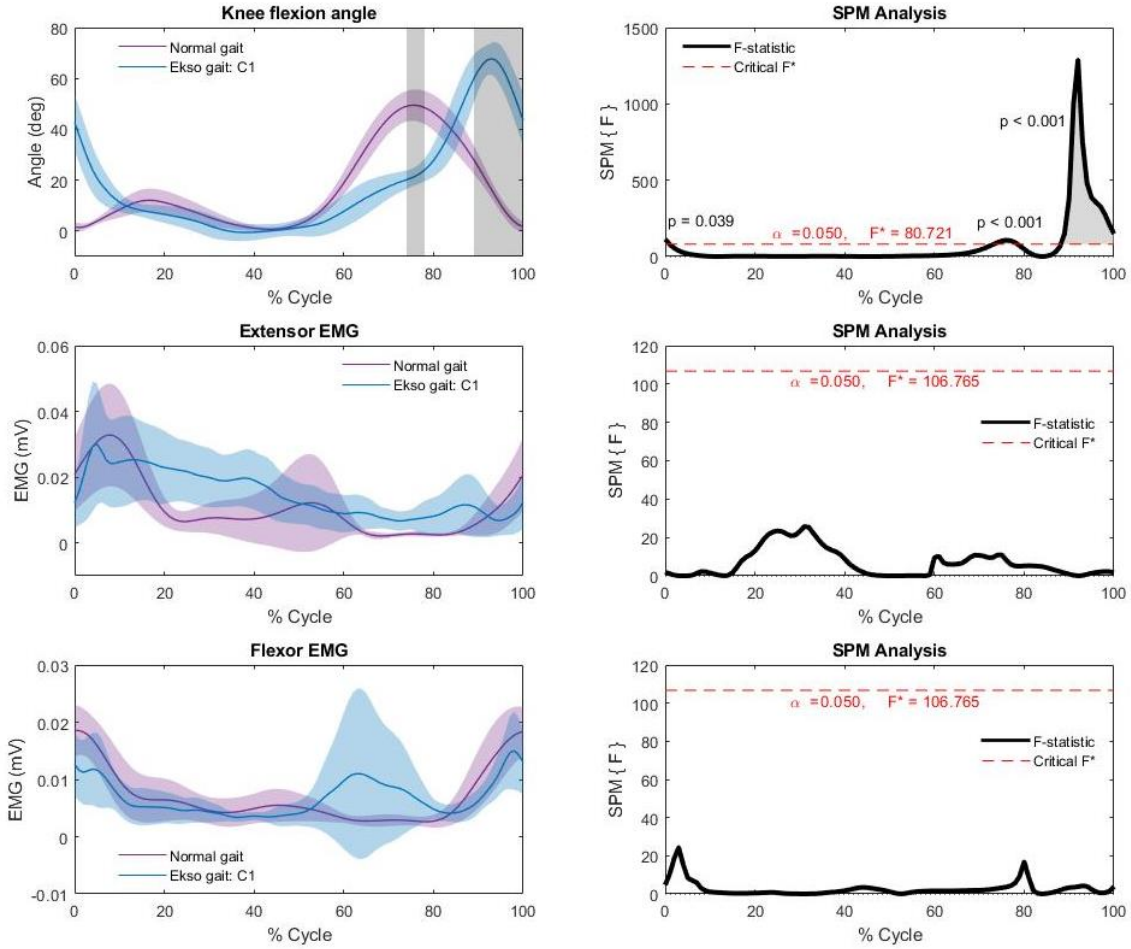


Figure 13. SPM results for Condition 1 compared to normal gait. Plots on the left are the superimposing signals with the x-axis representing %GC and the y-axis representing knee angle (degs) for the top plot and EMG (mV) for the bottom two plot rows. Normal gait results are in purple while Condition 1 results are in blue. The plots on the right are the SPM result plots signals with the x-axis representing %GC and the y-axis representing F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

The SPM results for Condition 2 can be seen in Figure 14. F-statistic plots for knee flexion angle, Extensor EMG, and Flexor EMG display the calculated F* values

79.019, 106.765, and 106.765 respectively. A significant difference in knee flexion angle compared to normal gait were found from approximately 0%-5% ($p=0.039$) and 80%-100% gait cycle ($p<0.001$), suggesting in difference in knee angle at IC and swing phase. Difference in Flexor EMG was significant just after 0% gait cycle until approximately 5% gait cycle, suggesting that Ekso GT™ gait has lower EMG at IC than normal gait. No significant differences were found for Extensor EMG magnitude. For individual participant results of Condition 2 please refer to Appendix E.

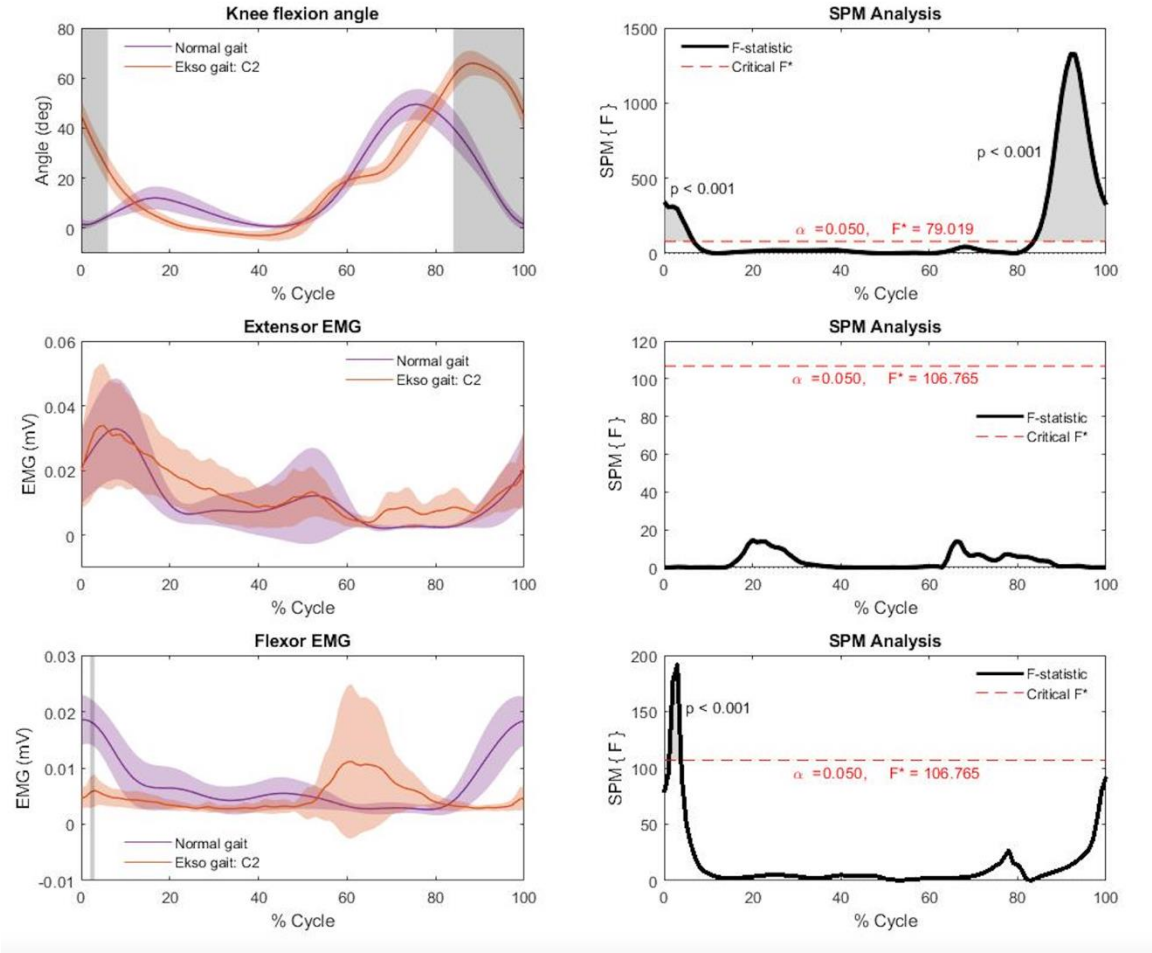


Figure 14. SPM results for Condition 2 compared to normal gait. Plots on the left are the superimposing signals with the x-axis representing %GC and the y-axis representing knee angle (degs) for the top plot and EMG (mV) for the bottom two plot rows. Normal gait results are in purple while Condition 2 results are in red. The plots on the right are the SPM result plots signals with the x-axis representing %GC and the y-axis representing F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

The SPM results for Condition 3 can be seen in Figure 15. F-statistic plots for knee flexion angle, extensor EMG, and flexor EMG display the calculated F* values 77.266, 106.765, and 104.322 respectively. Significant difference in knee flexion angle compared to normal gait were found from approximately 70%- 80% and 85%- 95% gait

cycle ($p<0.001$), suggesting that there are differences between knee flexion angle during swing phase. No significant differences were found for flexor or extensor EMG magnitudes. For individual participant results of Condition 3 please refer to Appendix F.

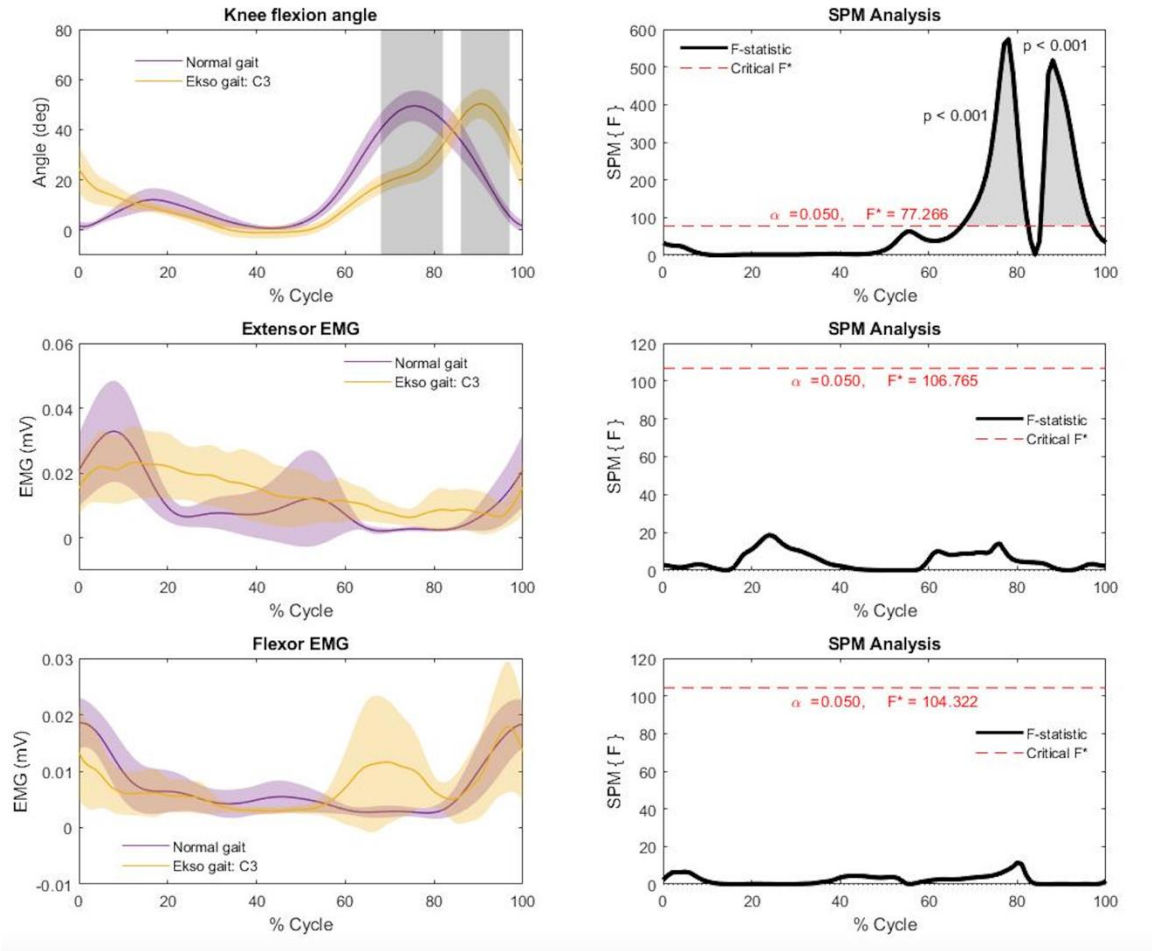


Figure 15. SPM results for Condition 3 compared to normal gait. Plots on the left are the superimposing signals with the x-axis representing %GC and the y-axis representing knee angle (degs) for the top plot and EMG (mV) for the bottom two plot rows. Normal gait results are in purple while Condition 2 results are in yellow. The plots on the right are the SPM result plots signals with the x-axis representing %GC and the y-axis representing F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

The SPM results for Condition 4 can be seen in Figure 16. F-statistic plots for knee flexion angle, extensor EMG, and flexor EMG display the calculated F* values 65.807, 106.765, and 106.765 respectively. Significant difference in knee flexion angle compared to normal gait were found from approximately 0%- 10% and 85%- 100% gait cycle ($p<0.001$), suggesting in difference in knee angle during early weight acceptance and swing phase. No Significant differences were found for flexor or extensor EMG magnitudes. For individual participant results of Condition 4 please refer to Appendix G.

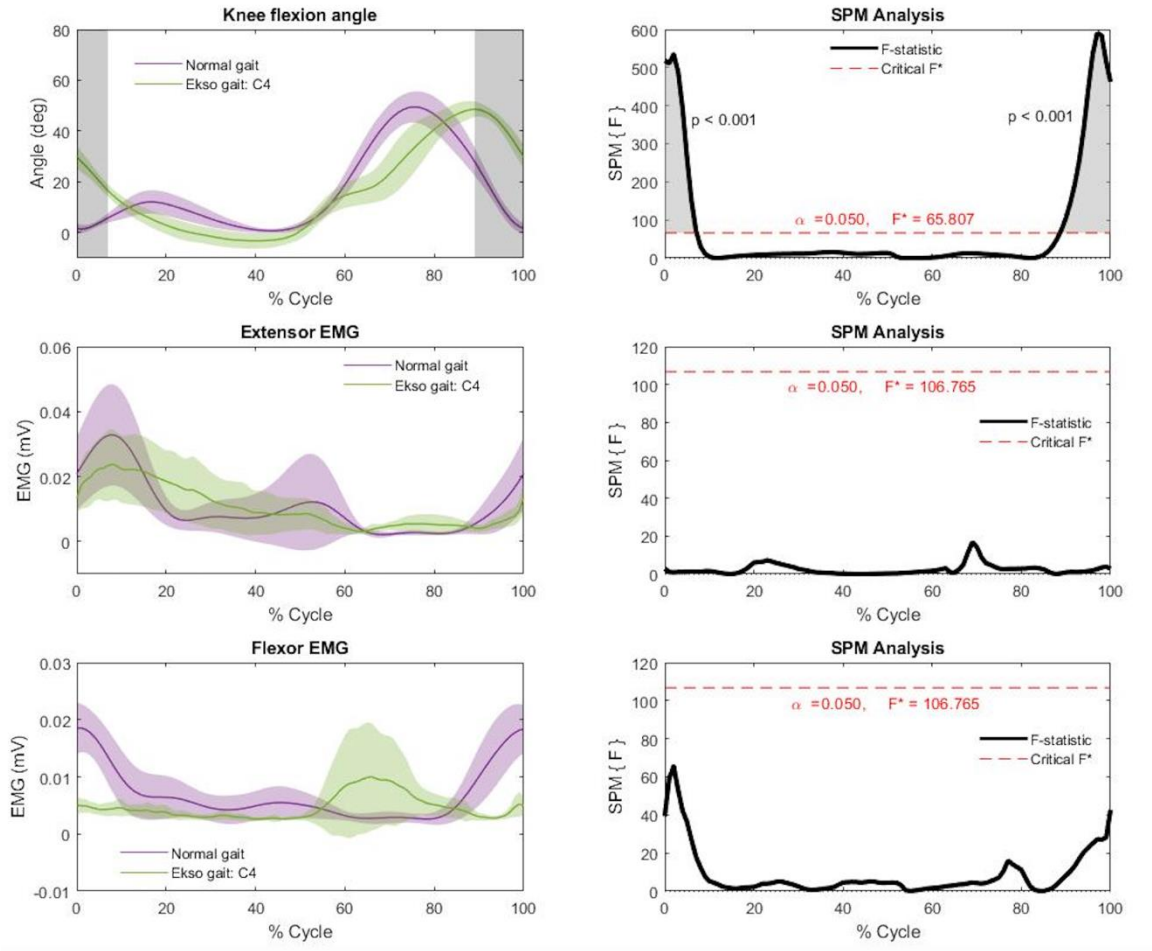


Figure 16. SPM results for Condition 4 compared to normal gait. Plots on the left are the superimposing signals with the x-axis representing %GC and the y-axis representing knee angle (degs) for the top plot and EMG (mV) for the bottom two plot rows. Normal gait results are in purple while Condition 2 results are in green. The plots on the right are the SPM result plots signals with the x-axis representing %GC and the y-axis representing F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

Research Question 1b

Biological signal data (knee flexion angle and EMG) of the four Ekso GT™ conditions were analyzed against one another to determine how different combinations of exoskeleton gait step parameters affect knee flexion angle and electromyography. The

SPM results of the three-way ANOVA examining the effects of SH, ST, and SL on knee flexion angle or knee flexion angle are shown in Figure 17. Results determined a significant main effect from SH on knee flexion angle from 0%-5% ($p=0.007$) and 85%-100% gait cycle ($p<0.001$), suggesting that SH had an effect for results at IC and during swing phase. A significant effect on knee flexion angle was also found for SL from 0%-5% ($p=0.002$) and 90%-100% ($p=0.003$) gait cycle, suggesting that SL also had an effect for results at IC and during swing phase. There was no significant main effect of ST on knee flexion angle. No significant interaction effects were found.

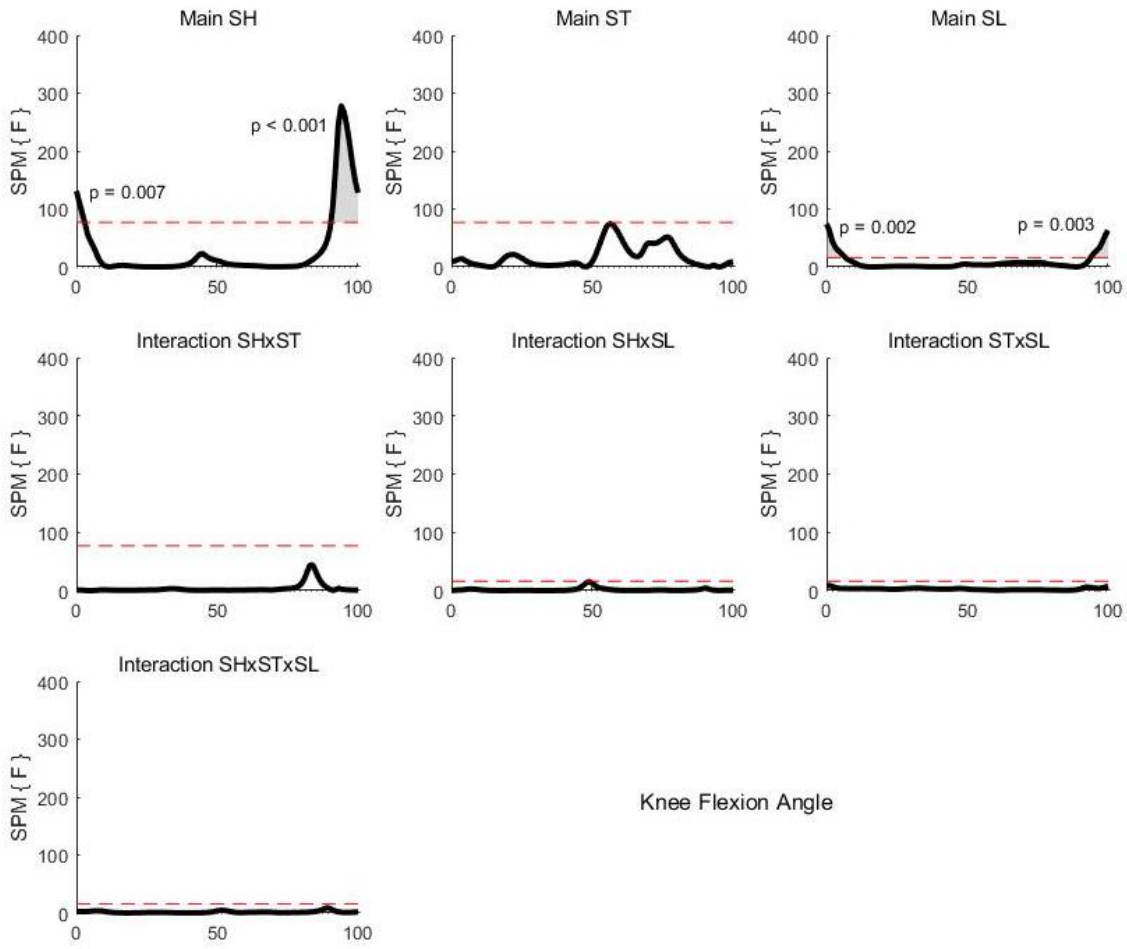


Figure 17. SPM results of the three-way repeated measures ANOVA examining the effects of SH, ST, and SL on knee flexion angle. The x-axis represents %GC and the y-axis represents F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

The SPM results of the three-way ANOVA examining the effects of SH, ST, and SL on knee flexor EMG are shown in Figure 18. Results determined no significant main effects from any variable (SH, ST, or SL). In alignment with this result, there were also no significant interaction effects of variables on knee flexor EMG. The combined results suggest that knee flexor EMG was not affected by exoskeleton gait setting parameters.

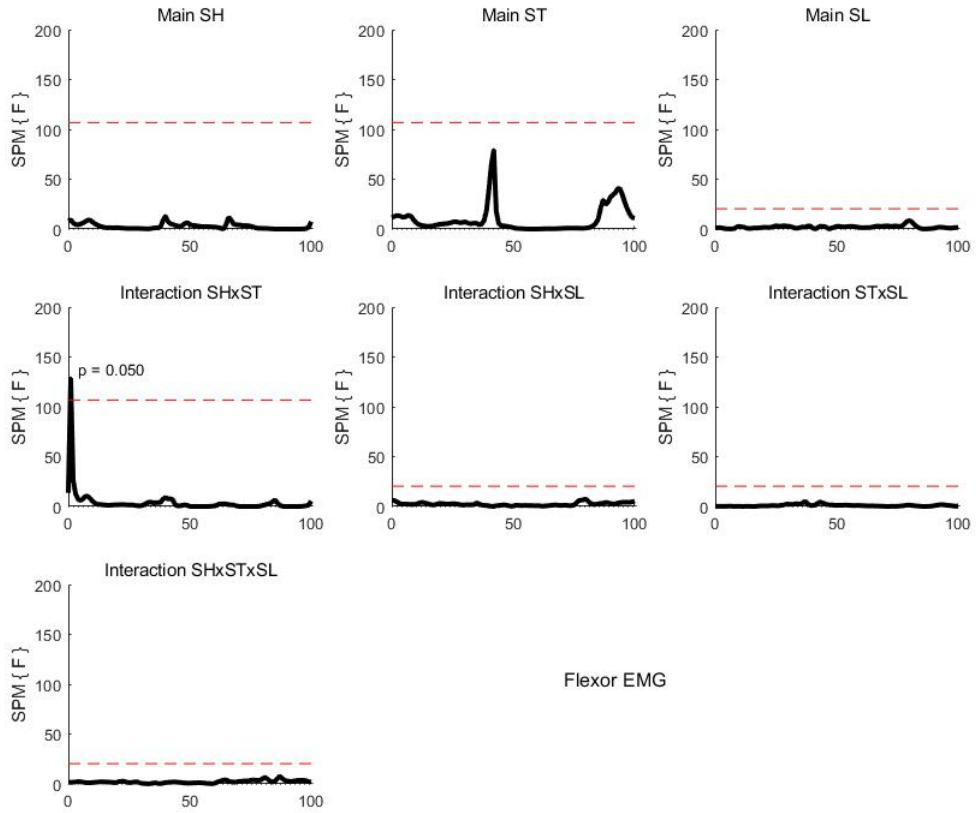


Figure 18. SPM results of the three-way repeated measures ANOVA examining the effects of SH, ST, and SL on knee flexor EMG. The x-axis represents %GC and the y-axis represents F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

The SPM results of the three-way ANOVA examining the effects of SH, ST, and SL on knee flexion angle or knee extension, or extensor EMG are shown in Figure 19. Results determined a significant main effect from ST on extensor EMG from 25%-30% ($p<0.001$), suggesting that ST had an effect of extensor activity during stance phase. No significant main effect was found for SH or SL. There were also no significant interaction effects of the independent variables on extensor EMG.

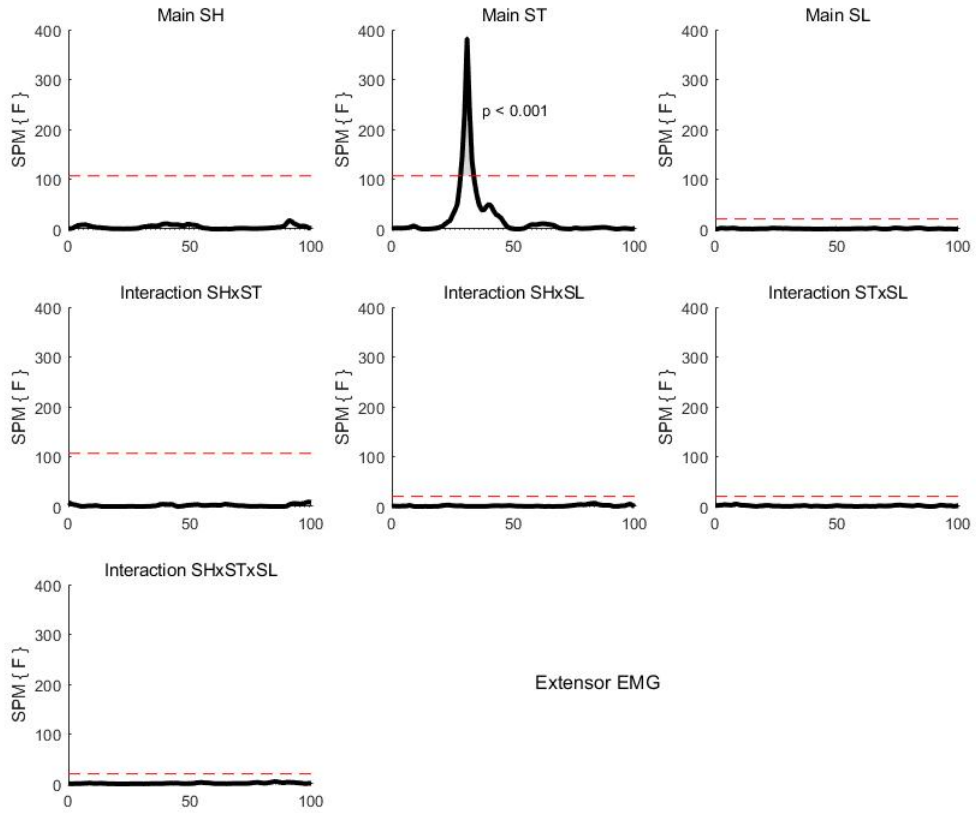


Figure 19. SPM results of the three-way repeated measures ANOVA examining the effects of SH, ST, and SL on knee extensor EMG. The x-axis represents %GC and the y-axis represents F-statistics. Red dotted lines mark the F* value and results over this line are considered significant.

4.3 Signal Timing Analysis

Research Question 1b

Three separate biomechanical gait characteristics were selected to examine how exoskeleton gait effects the signal timing (knee flexion angle and EMG) during a complete gait cycle. Means and standard deviation (SD) for cycle times (s), absolute peak knee flexion times (s) and normalized peak knee flexion times (%GC) were calculated for

the three SLs of each Ekso GT™ condition and normal gait. The means and SDs for gait cycle times are displayed in Figure 20.

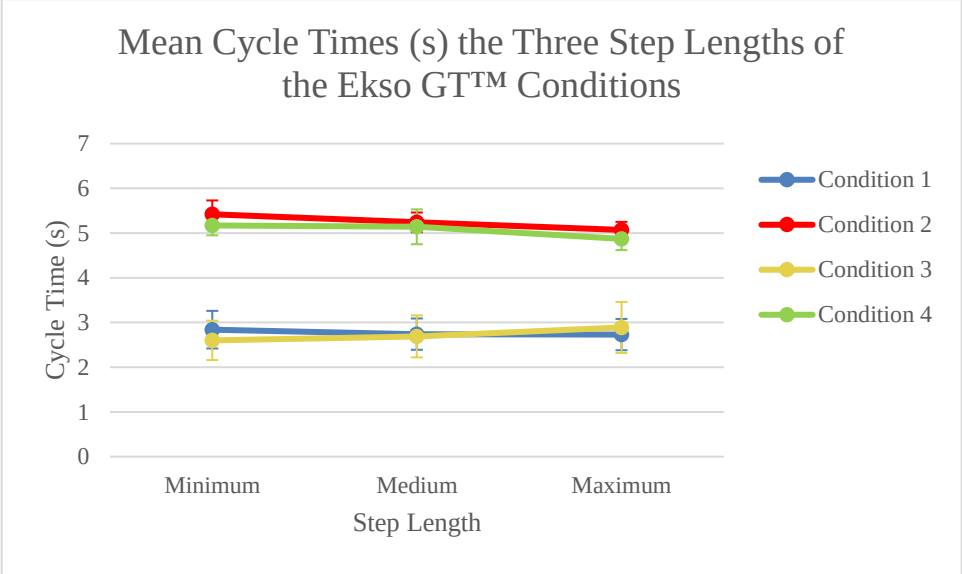


Figure 20. Means and SD for cycle times (s) for the three SLs of each Ekso GT™ conditions. The error bars represent standard deviation.

A three-way ANOVA was conducted to test for significant effects or interactions of SH, ST, and SL on gait cycle time. Results for cycle time ANOVA are in Table 5. Significant main effect results was found for ST ($F(1,4) = 164.598$, $p<0.001$), suggesting ST had a significant effect on gait cycle time. A significant interaction effect was found for ST and SL ($F(2,8) = 12.462$, $p=0.004$), suggesting the interaction of exoskeleton gait parameters ST and SL effect gait cycle times.

Table 5. The three-way repeated measures ANOVA results examining the effects of SH, ST, and SL on gait cycle time.

Effects	F-statistic	Degrees of Freedom	P-value
Step Height (SH)	2.331	1, 4	0.202
Swing Time (ST)	**164.598**	**1, 4**	**0.001**
Step Length (SL)	2.420	2, 8	0.151
SH x ST	1.110	1, 4	0.035
SH x SL	6.185	2, 8	0.024
ST x SL	**12.462**	**2, 8**	**0.004**
SH x ST x SL	3.012	2, 8	0.106

Another three-way ANOVA was conducted on the mean absolute peak knee flexion times for the three SLs of each Ekso GT™ condition and normal gait. Absolute peak knee flexion time means and SDs are reported in Figure 21.

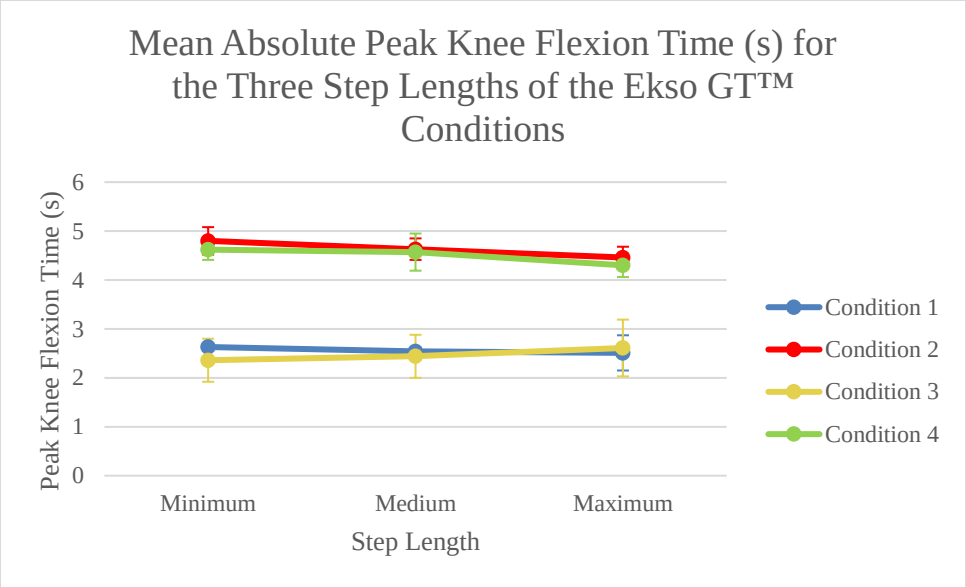


Figure 21. Means and SD for absolute peak knee flexion time (s) for the three SLs of each Ekso GT™ conditions. The error bars represent standard deviation.

The three-way ANOVA conducted to test for significant effects or interactions of SH, ST, and SL on absolute peak knee flexion times are displayed in Table 6. The ANOVA results for absolute peak knee flexion time reveal a significant main effect for ST ($F(1,4) = 131.315$, $p<0.001$), suggesting ST had a significant effect on absolute peak knee flexion time. A significant interaction effect was found for ST and SL ($F(2,8) = 8.646$, $p=0.0100$), suggesting the interaction of exoskeleton gait parameters ST and SL also effect absolute peak knee flexion times.

Table 6. The three-way repeated measures ANOVA results examining the effects of SH, ST, and SL on absolute peak knee flexion times (s).

Effects	F-statistic	Degrees of Freedom	P-value
Step Height (SH)	2.229	1, 4	0.210
Swing Time (ST)	**131.315**	**1, 4**	**0.001**
Step Length (SL)	4.428	2, 8	0.051
SH x ST	0.153	1, 4	0.716
SH x SL	4.077	2, 8	0.061
ST x SL	**8.646**	**2, 8**	**0.010**
SH x ST x SL	3.292	2, 8	0.091

A final three-way ANOVA was conducted on the mean normalized peak knee flexion times for the three SLs of each Ekso GT™ condition and normal gait. Normalized peak knee flexion time means and SDs are reported in Figure 22.

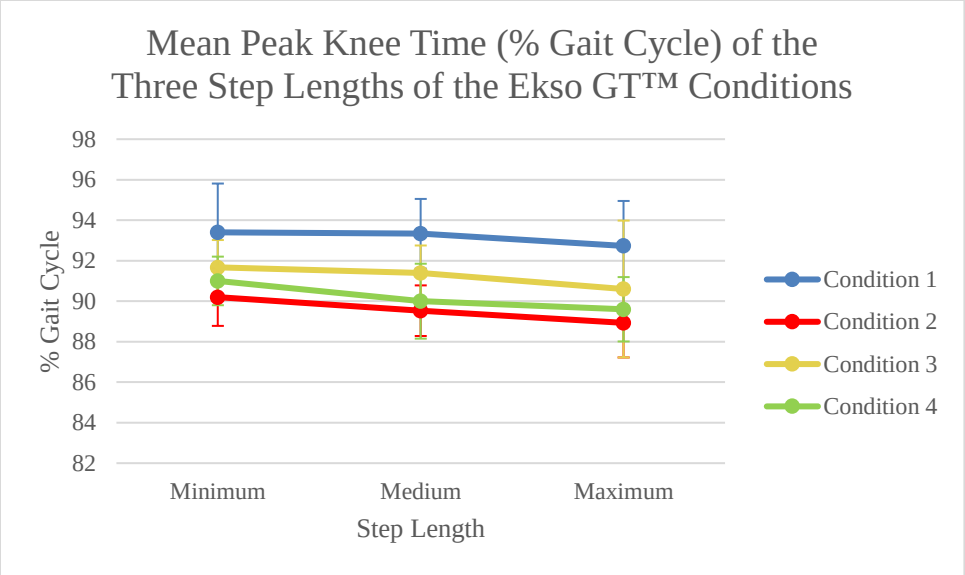


Figure 22. Means and SD for Peak knee time (%GC) for the three SLs of each Ekso GT™ conditions. The error bars represent standard deviation.

A three-way ANOVA was conducted to test for significant effects or interactions of SH, ST, and SL on normalized peak knee flexion times (%GC). Results for normalized peak knee flexion times ANOVA are in Table 7. Significant main effect results were found for ST ($F(1,4) = 18.015$, $p=0.0132$) and SL ($F(2,8) = 15.807$, $p=0.002$), suggesting that ST and SL each had a significant effect on normalized peak knee flexion times. A significant interaction effect was found for SH and ST ($F(1,4) = 14.338$, $p=0.0193$), suggesting the interaction of exoskeleton gait parameters SH and ST effect normalized peak knee flexion times of a full gait cycle.

Table 7. The three-way repeated measures ANOVA results examining the effects of SH, ST, and SL on normalized peak knee flexion times (%GC).

Effects	F-statistic	Degrees of Freedom	P-value
Step Height (SH)	4.250	1, 4	0.108
Swing Time (ST)	**18.015**	**1, 4**	**0.013**
Step Length (SL)	**15.807**	**2, 8**	**0.002**
SH x ST	**14.338**	**1, 4**	**0.019**
SH x SL	0.117	2, 8	0.891
ST x SL	0.433	2, 8	0.663
SH x ST x SL	0.035	2, 8	0.965

4.4 Case Study Analyses

Two case studies were conducted on SCI participants. These analyses were compared with the AB participant data in attempts to determine if AB data could aid in the interpretation of SCI data. Each SCI participant displayed unique patterns and responses to the Ekso GT™ and are reported using observational, explanation building, as well as statistical approaches.

4.4.1 Case SCI01

The participant was a 56-year-old male weighing 84kg, standing 183cm and an inpatient at the SCCR. He was 23 months post injury and was classified as a C4 AIS C SCI. Oral antispasticity medication was prescribed of baclofen 20mg four times a day. The PT measured extensor MAS of both knees at beginning of data collection, scoring

SCI01 1 for the left knee extensors and a 0 for the left knee extensors. Therefore, the BioTone kit was placed on SCI01's left leg. The Ekso GT™ Patient Form provided additional measures including MAS scores for the knee flexors, as well as lower limb muscle strength (manual muscle test, MMT) and ROM. These data are presented in Table 8. Previous gait training sessions with the Ekso GT™ allowed the PT to tailor a combination of exoskeleton gait parameter settings best suited for the patient. These Ekso GT™ gait settings can also be seen in Table 8.

Table 8. Lower limb Ekso GT™ Patient Form results and Ekso GT™ gait parameter settings for SCI01.

Knee Muscle	**ROM**		**Strength**		**MAS**	
Knee Flexors	R	L	R	L	R	L
	138	134	1+	2+	2	1+
**Knee Extensors*	0	0	N/A	N/A	0	1

Gait Parameter	**Setting**
Step Height (cm)	0.254
Swing Time (s)	1.3
Step Length (cm)	30.48

**Indicates knee extensor MAS were collected at the beginning of data collection.*

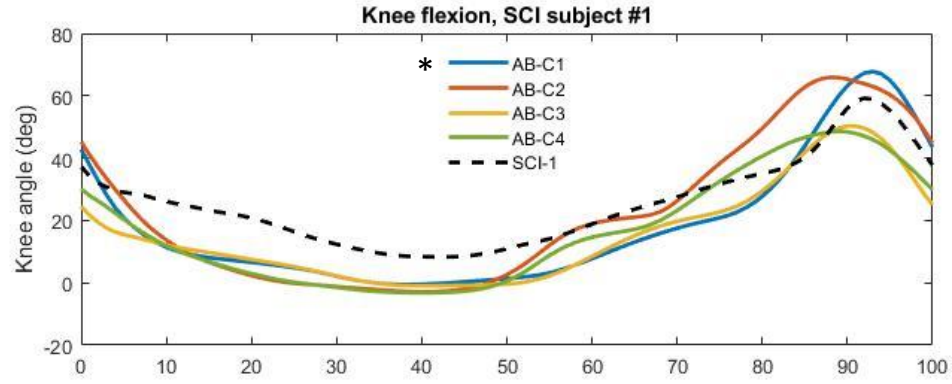
To review raw data from SCI01's please refer to Appendix H. Plots generated from all of SCI01's data include knee flexion angle and flexor and extensor EMG data of all gait cycles for every Ekso GT™ gait trial.

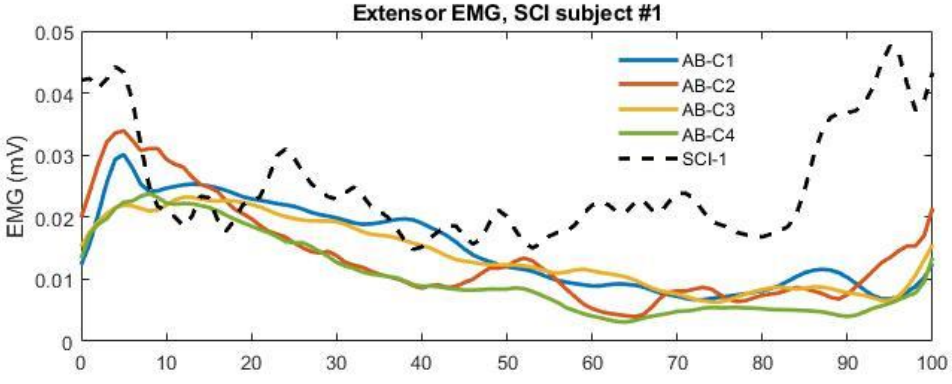
Research Question 2a

Data from SCI01 was superimposed on the same plot as the data from AB Ekso GT™ conditions, to display the differences in knee EMG and kinematics (

Figure 23).

Figure 23 clearly illustrates the difference in EMG signal magnitudes. Knee flexion angle for SCI01 begins with the same flexed IC and continues to produce a similar gait cycle profile as the AB population. Extensor EMG appears to be similar to AB participants until 50% gait cycle when swing phase begins. An increase in extensor EMG occurs entering pre-swing and initial swing phase, with a dramatic increase as the knee enters peak knee flexion. Flexor EMG remained active across the entire gait cycle with an increase happening at 10-50% of the gait cycle, suggesting SCI01 was experiencing more flexor activity during the extension into stance phase than the AB population did.


Knee flexion, SCI subject #1
Knee angle (deg)
*
AB-C1
AB-C2
AB-C3
AB-C4
SCI-1


Extensor EMG, SCI subject #1
EMG (mV)
AB-C1
AB-C2
AB-C3
AB-C4
SCI-1

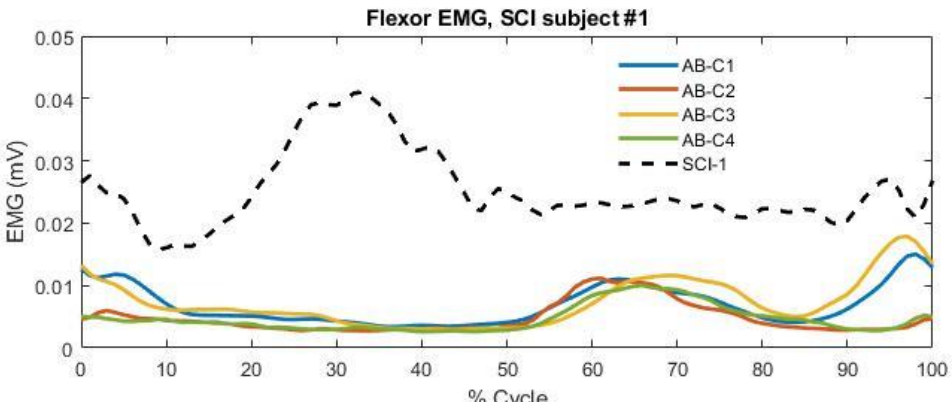

Flexor EMG, SCI subject #1
EMG (mV)
AB-C1
AB-C2
AB-C3
AB-C4
SCI-1
% Cycle

Figure 23. SCI01 data superimposed on the data from AB Ekso GT™ conditions. The x-axis represents %GC and the y-axis represents knee angle (degs) for the top plot and EMG (mV) for the bottom two plots. SCI01 data is reflected by the dotted line, and the AB conditions represented by the designated colors.

Cross-correlation and RMSE tests determined if AB biological signaling during exoskeleton gait can help interpret signal outputs of persons with SCI. The cross-correlation and RMSE results are reported in Table 9 . Correlation coefficients (CC) reflect that SCI01 knee flexion angle have strong positive correlations with all AB Ekso GT™ conditions (CC>0.90). Flexor and extensor EMG showed moderate positive correlations (CC>0.80) to AB data. For all cross correlations the lag was zero frames. RMSE values are close for all AB conditions. High CC values and low RMSE for all conditions suggest that AB data can be used to help interpret SCI data. Observational of Figure 23 shows that SCI01 best matched AB Condition 1 (blue line). This observational analysis was confirmed in Table 9 reporting Condition 1 having the highest CC and one of the lowest RMSE values.

Table 9. Results of cross-correlation and RMSE for AB Ekso GT™ conditions and SCI01.

	Knee Flexion (degs)		**Extensor EMG (mV)**		**Flexor EMG (mV)**	
AB Condition	*XCorr*	*RMSE*	*XCorr*	*RMSE*	*XCorr*	*RMSE*
*Condition 1**	0.936*	10.2*	0.865	0.0148	0.852	0.0200
Condition 2	0.935	11.5	0.879	0.0147	0.832	0.0218

Condition 3	0.953	10.5	0.876	0.0152	0.831	0.0197
Condition 4	0.934	10.7	0.832	0.0176	0.851	0.0218

**Indicates condition with highest XCorr and lowest RMSE values.*

Research Question 2b

Normal muscle function and EMG activity was required to determine if AB participant data during exoskeleton gait can help detect possible spastic activity. Analyzing the knee flexion curve indicates positive slopes as flexion and negative slopes as extension. When a joint extends, typically the extensor muscle contracts (concentric contraction), the flexor muscle relaxes and lengthens. The vice versa occurs for a joint flexion. Spastic activity could therefore be any increase in EMG activity while the muscle is lengthening or stretching that is not a normal or expected eccentric contraction.

The knee flexion angle profiles of AB participants and SCI01 were strongly correlated, such that the AB EMG activity can be used as a reference of normal knee muscle activity in the Ekso GT™. Therefore, increases in eccentric EMG activity outside the AB eccentric activation pattern were considered probable spasticity. Examining knee angle of SCI01 in

Figure 23 revealed a best match result with AB Condition 1. Figure 24 compares the relative mean of SCI01 to the sample mean and SD of AB Condition 1. Figure 24 shows an increase in extensor EMG entering pre-swing and initial swing phase. As the knee

enters peak knee flexion a dramatic increase in eccentric extensor overactivity is observed. Extensor EMG activity during flexion of the knee suggests the extensor is active when it should be relaxed and lengthening. Therefore, spastic activity of the extensor is suspected for SCI01 during swing phase of exoskeleton gait. This division of normal and spastic EMG activity is represented by the shaded rectangle beneath the EMG graph in Figure 24. The shaded rectangle indicates the regions of appropriate EMG activity and suspected spasticity.

Observation analysis of SCI01's flexor EMG in

Figure 23 revealed an increase of flexor EMG during stance phase. The Ekso GT™ gait lands with a flexed knee at IC which then requires the knee to extend as full stance phase is entered. Flexor EMG activity during extension of the knee suggest overactive, eccentric activity of the bicep femoris. Therefore, spasticity of the bicep femoris is also suspected for SCI01 during the stance phase of exoskeleton gait. Again, the shaded rectangle beneath the EMG graph indicates regions absent of EMG activity and those with appropriate EMG activity. SCI01 demonstrates an interesting flexor EMG pattern, with almost continuous activity being present. The knee flexors of SCI01 were active for both the eccentric and concentric regions of gait. Figure 24 illustrates this continuous

EMG activity for the extensor during swing phase and for the entire gait cycle for the flexors.

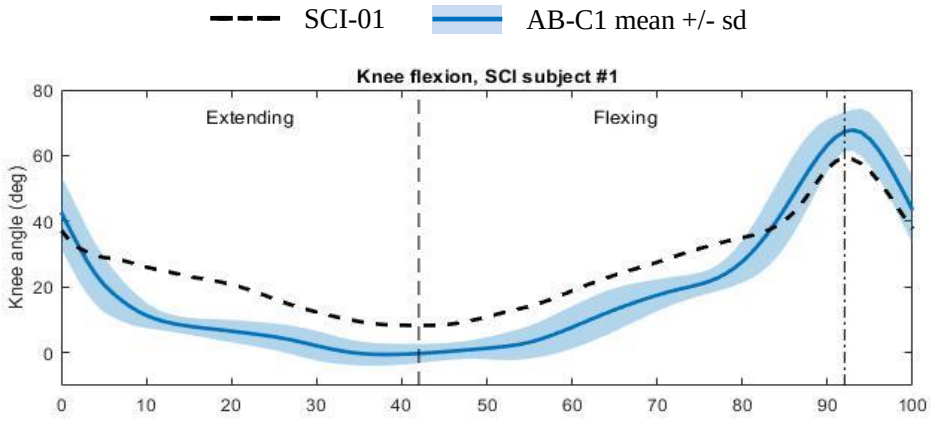


Figure 24. SCI01 data superimposed on the data from AB Ekso GT™ Condition 1. The x-axis represents %GC and the y-axis represents knee angle (degs) for the top plot and EMG (mV) for the bottom two plots. SCI01 data is reflected by the dotted line, and the AB conditions represented by the blue line. SD is represented by the shaded blue area. Overactive eccentric and concentric activity are indicated by the colors correlated to the figure's table of contents.

Research Question 2c

The test metrics of pre and post WPTs for SCI01 are reported in Table 10. A closer examination of RI, f1Amp, and Plat values reveal no reduction of extensor spasticity from a short session of exoskeleton GT for SCI01. SCI01 post WPT had a 0.02 increase in RI from pre WPT (1.05-1.03=0.02), a 5.1 degree decrease in f1Amp (61.9-67.0=-5.10) and a Plat.

Table 10. Results of AB participant mock WPT and SCI01's WPT metrics for pre and post timepoints. Within-subject means and SDs are shown for SCI01 and AB means and SDs reflect the group. Bolded columns represent the test metrics recommended to classify extensor spasticity. Standard deviation is represented in brackets.

	WPT	Plat	f1Amp	e1Amp	RI	ERI	Ncyc
AB		**50.6 (10.8)**	**84.0 (10.7)**	58.9 (8.3)	**1.69 (0.23)**	1.20 (0.28)	8.1 (3.4)
SCI01	*Pre*	**65.0 (0.9)**	**67.0 (10.9)**	24.9 (9.8)	**1.03 (0.21)**	0.38 (0.15)	6.7 (3.8)
	Post	**59.1 (1.2)**	**61.9 (16.2)**	25.0 (14.4)	**1.05 (0.28)**	0.42 (0.25)	4.7 (1.2)

4.4.2 Case SCI02

The participant was a 50-year-old female weighing 67kg, standing 152cm and an inpatient at the SCCR. SCI02's injury was classed as a T10 AIS D SCI. Data for the study was collected eight months post injury. The participant received botulinum toxin type A intramuscularly in right quadriceps 2 weeks prior to data collection. At data collection, the participant had a MAS score of 1+ for the right knee extensors and 0 for the left knee extensors. The Ekso GT™ Patient Form data and gait parameter settings for SCI02 can be seen in Table 11.

Table 11 Lower limb Ekso GT™ Patient Form results and Ekso GT™ gait parameter settings for SCI02.

Knee Muscle	ROM		Strength		MAS	
Knee Flexors	R	L	R	L	R	L
	137	130	1+	2+	1+	1
**Knee Extensors*	0	0	N/A	N/A	1+	0

Gait Parameter	Setting
Step Height (cm)	0.254
Swing Time (s)	1.5
Step Length (cm)	30.48

**Indicates knee extensor MAS were collected at the beginning of data collection.*

To review raw trial data for SCI02 please refer to Appendix I. Plots generated from all of SCI02's data display knee flexion angle and flexor and extensor EMG data of all gait cycles for every Ekso GT™ gait trial.

Research Question 2a

Data for SCI02 was superimposed on the same plot as the data from AB Ekso GT™ conditions, to display the differences in knee EMG and kinematics (Figure 2525). Knee flexion angle for SCI02 begins with the same flexed IC and continues to produce a similar gait cycle profile as the AB population. Flexor and extensor EMG of SCI02 were very quiet for the entire gait cycle suggesting that minimal muscle activity was occurring during exoskeleton gait.

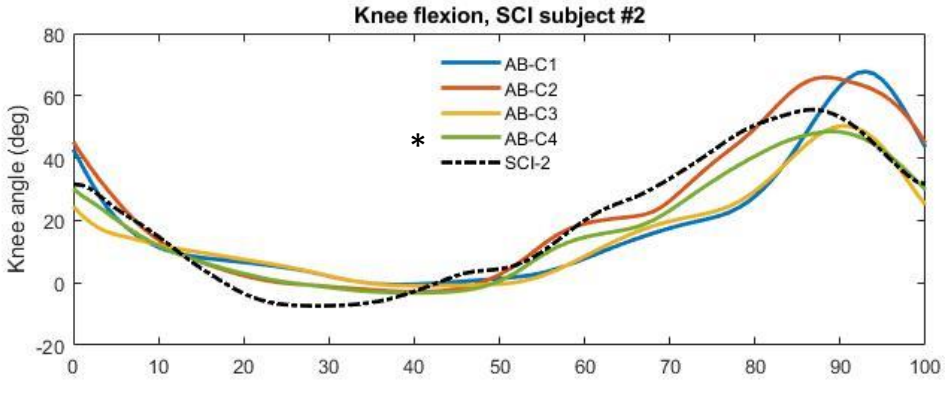


Figure 25. SCI02 data superimposed on the data from AB Ekso GT™ conditions. The x-axis represents %GC and the y-axis represents knee angle (degs) for the top plot and EMG (mV) for the bottom two plots. SCI02 data is reflected by the dotted line, and the AB conditions represented by the designated colors.

The results of the cross-correlation and RMSE for SCI02 are reported in Table 12 and reflect similar results to SCI01. Knee flexion angle has a strong positive correlation with all AB Ekso GT™ conditions (CC>0.90), while the extensor EMG showed moderate positive correlations (CC>0.80). Again, for all cross correlations the lag was zero frames (not shown). Cross-correlation and RMSE results for SCI02 are reported in

Table 12. RMSE values are low and close across all AB conditions. High CC values and low RMSE for knee flexion angle of all conditions suggest that AB data can be used to help interpret SCI data. Observational analysis of Figure 25 shows that SCI02 best matched AB Condition 4 (green line). This observational analysis was confirmed in Table 12 reporting Condition 4 having the highest CC and the lowest RMSE values.

Table 12. Results of cross-correlation and RMSE for AB Ekso GT™ conditions and SCI02.

	Knee Flexion (degs)		**Extensor EMG (mV)**		**Flexor EMG (mV)**	
AB Condition	*XCorr*	*RMSE*	*XCorr*	*RMSE*	*XCorr*	*RMSE*
Condition 1	0.907	12.1	0.876	0.0098	0.921	0.0036
Condition 2	0.979	7.2	0.828	0.0099	0.896	0.0048
Condition 3	0.953	10.3	0.893	0.0083	0.884	0.0042
*Condition 4**	0.988*	6.0*	0.815	0.0072	0.908	0.0048

**Indicates condition with highest XCorr and lowest RMSE values.*

Research Question 2b

The knee angle from Figure 25 helped decide that Condition 4 was the best-matched condition for SCI02. The comparison of the relative mean of SCI02 and the sample mean, and SD of AB Condition 4 are presented in Figure 26. Figure 26 provided a closer look at the eccentric or concentric EMG activity and was used to determine if spasticity occurred during exoskeleton gait. Overactive eccentric activity, outside of the normal AB, was observed for SCI02's flexor EMG. The burst of eccentric flexor activity suggests SCI02 may have had spastic activity of the knee flexors during the early-mid stance phase of exoskeleton gait. Interestingly, SCI02 had a continuous contraction EMG

pattern similar to that of SCI01 at the knee flexors, albeit at a much lower intensity. Figure 26 demonstrates the continuous contraction by illustrating the knee flexor EMG activity for both the eccentric and concentric contraction phases of the gait cycle.

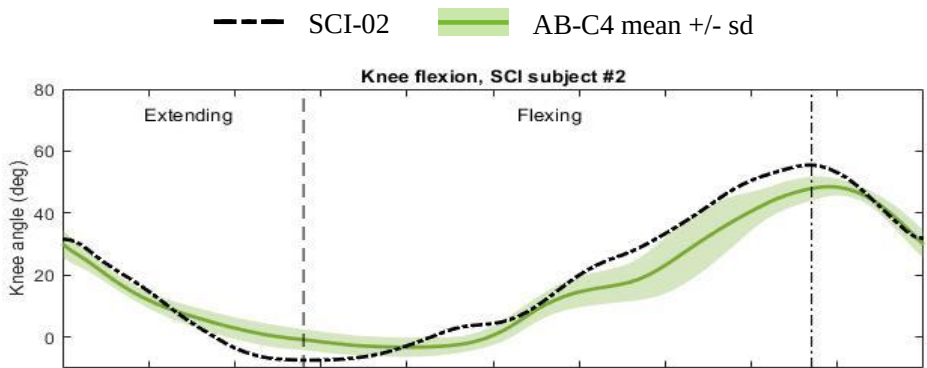


Figure 26. SCI02 data superimposed on the data from AB Ekso GT™ Condition 4. The x-axis represents %GC and the y-axis represents knee angle (degs) for the top plot and EMG (mV) for the bottom two plots. SCI01 data is reflected by the dotted line, and the AB conditions represented by the green line. SD is represented by the shaded green area. Overactive eccentric and concentric contractions, as well as underactive concentric activity are indicated by the colors correlated to the figure's table of contents.

Research Question 2c

The test metrics of pre and post WPTs for SCI02 are reported in Table 13. A closer examination of RI, f1Amp, and Plat values revealed a reduction of extensor

spasticity from a short session of OEGT for SCI02. SCI02 post WPT had a 0.09 increase in RI from pre WPT (0.86-0.77= 0.09), an 18.3 degree increase in f1Amp (40.0-21.7=18.30), and a 19.4 degree increase in Plat (46.0-26.6= 19.4). These increased values suggest that SCI02 was able to reach a greater knee flexion angle before entering the next oscillation of the knee joint, indicating a potential reduction of spasticity after a short session of exoskeleton gait therapy.

Table 13. Results of AB participant mock WPT and SCI02's WPT metrics for pre- and post-time points. Within-subject means and SDs are shown for SCI01 and AB means and SDs reflect the group. Bolded columns represent the test metrics recommended to classify extensor spasticity. Standard deviation is represented in brackets.

	WPT	Plat	f1Amp	e1Amp	RI	ERI	Ncyc
AB		**50.6 (10.8)**	**84.0 (10.7)**	58.9 (8.3)	**1.69 (0.23)**	1.20 (0.28)	8.1 (3.4)
SCI02	*Pre*	**26.6 (7.7)**	**21.7 (10.9)**	8.8 (5.2)	**0.77 (0.23)**	0.31 (0.13)	20.7 (24.0)
	Post	**46.0 (4.3)**	**40.0 (9.1)**	17.9 (4.9)	**0.86 (0.13)**	0.38 (0.08)	6.7 (1.2)

4.4.3. Benefit-Risk Framework Model

Results of the case studies developed the basis for the benefit-risk framework. Figure 27 shows the sample line of questioning a therapist may follow when analyzing a patient's biological signal data. This line of questioning is the basis of the benefit-risk framework and is a tool to help identify the people who may benefit from a neuroplastic change of the motor pattern for gait function. The framework presents with final recommendations for the safety of the patient receiving OEGT.

Spasticity was suspected when overactive eccentric EMG was detected outside of the AB functional pattern, for example, knee extensor muscle activity during knee flexion

and knee flexor activity during knee extension. Therapists may follow the question flow design to arrive at a recommendation for users. Furthermore, biomedical engineers who design exoskeletons for rehabilitation of brain and spinal cord injuries may also utilize such a tool in terms of designing controllers that detect in real-time when spastic contractions are being induced and implementing on-the-fly adjustment of the robot's motors (and relevant parameters) to avoid strain injury of spastic muscle.

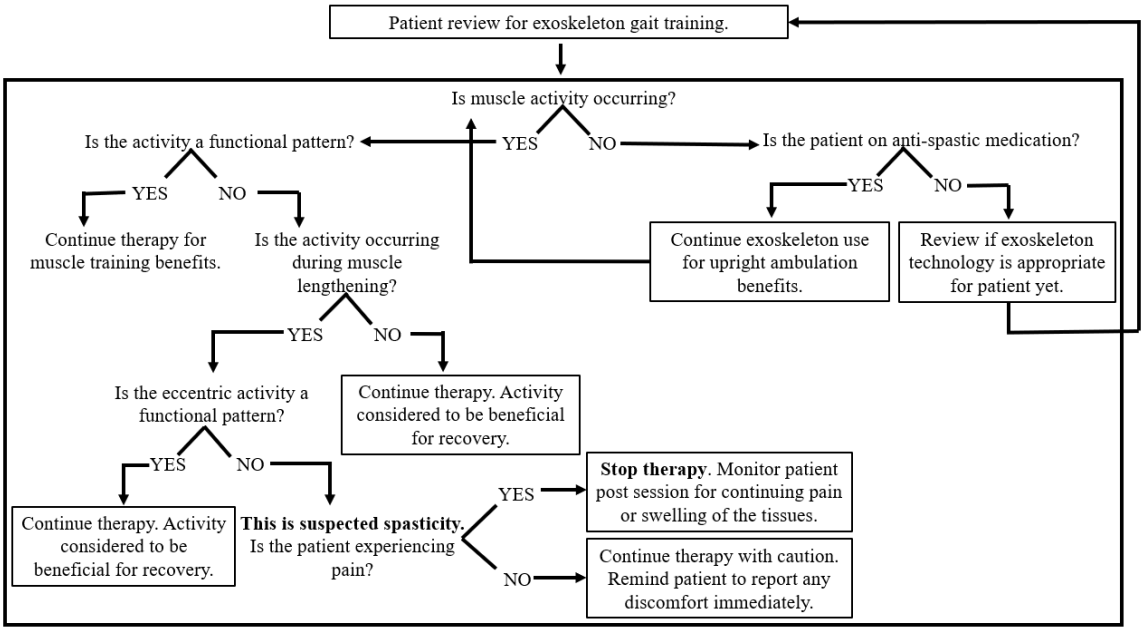


Figure 27. A question flow chart for analysis of patient biological signal data. A tool to identify the people who may benefit from a neuroplastic change of the motor pattern for gait function, in the presented benefit risk ratio framework.

Chapter 5: Discussion

5.1 Summary of Major Findings

The objectives of this study were to establish normative biomechanical (knee flexion angle) and physiological (knee muscle EMG) patterns of able-bodied users walking with the Ekso GT™ in "FirstStep" mode; and to determine if the AB data can aid the interpretation of SCI participant data during OEGT, with emphasis on differentiating spastic muscle activity from desired muscle activity. The latter objective proposed a framework for evaluating the influence of spasticity on muscle activity patterns during OEGT. The proposed framework may be useful for: 1) more precise screening for spasticity as an exclusion criterion for OEGT, 2) assisting therapists in terms of selecting appropriate stepping parameters, 3) providing researchers who study spasticity a way to monitor spasticity longitudinally during OEGT, and 4) providing biomedical engineers who design exoskeletons a way to integrate spasticity management into robotic controllers.

5.1.1 Able-body OEGT: What does it tell us?

Overall, AB participant data suggests that Ekso GT™ gait is not the same as normal gait. Both biomechanical (knee flexion angle) and physiological (EMG) waveforms deviate from patterns of normal gait, confirming the findings of others (Ramanujam et al., 2018; Swank et al., 2019; Sylos-Labini et al., 2014; Talaty et al., 2013). Most notable is that the Ekso GT™ consistently established foot contact prior to fully extending the knee, in both AB and SCI participants, such that peak knee flexion occurs later in the IC-IC gait cycle. The reason for this behavior is likely to ensure

stability of the Ekso GT™ during stepping and explains in part why walking speed is so limited in these devices.

Indeed, our AB participants walked two to three times slower when wearing the Ekso GT™. In addition to a longer cycle time the Ekso GT™ resulted a phase lag in peak knee flexion time (~ 90% gait cycle) compared to normal gait (76.5% gait cycle). The gait cycle phase lag observed, confirmed with comparing the timing of peak knee flexion, was highly consistent across step parameters; again suggesting, the knee trajectory produced by the Ekso GT™ is a design feature meant to increase stability.

The AB data were also used to explore the effects of the different Ekso GT™ step parameter settings (step height (SH), step length (SL), and swing time (ST)) on the function and activity at the knee joint. Results showed that only SH and ST had a significant effect on knee flexion angle and EMG while SL had very little effect. Increasing SH increased the peak knee flexion angle while decreasing ST shifted the peak knee angle closer to IC. Corresponding EMG activity confirms this with AB Conditions 1 and 3 displaying great bursts of EMG nearing the end of PKF and entering stance phase. This suggests therapists should primarily focus on SH and ST settings because SL does not significantly affect knee flexion angle or EMG during OEGT.

5.1.2 SCI user data: What can it tell us?

The results of two SCI participants compared to the Ekso GT™ normative patterns suggests that the data of AB users can be useful when interpreting SCI data during Ekso GT™ gait training. However, regardless of patient muscular input, the Ekso GT™ managed to maintain its knee trajectory profile with little variability; this is

probably because the Ekso GT™ uses impedance control to enforce the desired trajectory of the knee (Chen et al., 2013). A burst of EMG that occurred when the muscle was lengthening, and that was outside the normative profile, was concluded to be spastic activity. When applied as a logical test using knee flexion angle and EMG signals during OEGT, it was demonstrated that inappropriate (spastic) muscle activity could be differentiated from desired (motor) responses of muscle.

As shown in Figure 23 and Figure 25, the two SCI participants produced very different muscle activity profiles for Ekso GT™ gait. SCI01 displayed EMG activity of both the knee flexors and extensors that had regions of desired activity and regions of overactive spastic activity (Figure 23), suggesting there may be both neural benefits and potential risks for this participant when partaking in OEGT. On the other hand, SCI02 display minimal overall EMG activity (Figure 25), suggesting little spasticity interference while using the Ekso GT™. Further investigation of knee flexion angle revealed an AB condition closest to each SCI participant (see Figure 24 and Figure 26). The comparison of the AB condition closest to the SCI participant explored eccentric and concentric activation patterns of the flexor and extensors of the knee. These cases are discussed in detail below, however, we can conclude the safety and benefit of exoskeleton use should be evaluated on a case-by-case basis and requires a thorough evaluation of the patient. Using a benefit-risk framework would help therapists assess a patient's potential for exoskeleton use as a gait training tool.

5.2 Interpretation

Previous exoskeleton research focused primarily on user safety and feasibility for target populations (Fisahn et al., 2016; He et al., 2017; Miller, Zimmermann, & Herbert, 2016; Sale et al., 2012). Further research examined improvements of gait outcome measures (Baunsgaard et al., 2018; Morawietz & Moffat, 2013). Comparisons between normal and exoskeleton gait has led to studies publishing knee kinematics of AB and SCI populations during exoskeleton use (Ramanujam et al., 2018; Swank et al., 2019; Sylos-Labini et al., 2014; Talaty et al., 2013). The majority of published data was collected using one set of exoskeleton gait setting parameters per participant. The present study stands apart from current literature in this regard. The presented research was approached with a conscious awareness of spasticity and intention to examine, and develop explanation, for the interaction of spasticity and exoskeleton gait.

5.2.1 Signal Magnitude

The investigation of healthy individuals and those with neurological trauma is required to understand the afferent input an exoskeleton has on locomotor response (Ivanenko et al., 2013). Results of AB participants using the Ekso GT™, support previous research that stated, “walking with an exoskeleton does not mimic natural gait” Swank et al. 2019. An observational analysis, comparing biological signals of normal gait to Ekso GT™ gait, revealed differences in the gait cycle. The occurrence of a flexed knee at the moment of IC was found to be common among exoskeleton users (Ramanujam et al., 2018; Swank et al., 2019; Sylos-Labini et al., 2014; Talaty et al., 2013). A study by Talaty et al. (2013), using the Rewalk™, demonstrates the effect swing speed has on knee

angle during gait. The results determined the slower the swing speed the more flexion in the knee joint at IC. Talaty et al. (2013) results provide explanation why condition 3 (max ST, min SH) had the least amount of knee flexion at IC. Upon further examination of the kinematic knee curve during Ekso GT™ gait first flexion (K1), beginning at ~10% gait cycle, does not exist. Again, this seems to be a common theme across exoskeleton gait studies (Ramanujam et al., 2018; Swank et al., 2019; Sylos-Labini et al., 2014; Talaty et al., 2013). Discovery of a flexed IC and lack of load acceptance, during single stance support, shows that the exoskeletons are landing with a flexed knee and extending as weight is transferred into swing phase instead of landing extended and cushioning the weight transfer into swing phase. As the Ekso GT™ extends into weight transfer this is matched with extensor activity of AB participants as an active response to starting the knee extension into swing.

The results of swing phase during Ekso GT™ gait begins near the same point of the gait cycle as normal gait. This finding was observationally similar across studies of AB exoskeleton users that displayed normal and exoskeleton knee flexion angle (Ramanujam et al., 2018; Swank et al., 2019). The initiation of swing phase coincides with a burst of flexor activity in AB participants. This is suggested to be an instinctive response in attempts to lift the foot for toe clearance during swing. Similar results are shown in other AB Ekso GT™ users (Ramanujam et al., 2018). Following the initiation of swing phase Ekso GT™ gait implements a delayed peak knee flexion. The shift of peak knee flexion in the gait cycle was seen in results of AB and SCI users alike (Ramanujam et al., 2018; Swank et al., 2019; Sylos-Labini et al., 2014; Talaty et al., 2013). The result of a shift in peak knee flexion helps to wrap back to the beginning and

explain the flexed IC that starts of the exoskeletons gait cycle. Late peak knee flexion could result in the exoskeleton having to extend too much in a short time frame, producing a flexed knee at IC. Ramanujam et al. (2018) reported exoskeleton gait increasing the percent of stance phase and decreasing the percent of ST; this coincides with findings of a shifted peak knee flexion in the exoskeleton gait cycle.

5.2.2 Signal Timing

Work by Ramanujam et al. (2018), reports on exoskeletons slowing gait speed of AB users. Although gait speed analysis is beneficial in many cases, it was not chosen for the signal analysis of this study. Currently, using the signal timing data selected for this study to analyze Ekso GT™ gait has not been previously used to examine kinematic data. Analysis of signal timing data was conducted using two independent variables: time and %GC. The results of gait cycle and peak knee time were significantly affected by ST and SL, as conditions with slower STs resulted in a longer gait cycle and peak knee time (Figure 20 and Figure 21). Analysis conducted in %GC revealed a shift greater than 10% in peak knee flexion (Figure 22). The result of this shift aided in the comprehension of kinematic knee data of Ekso GT™ gait.

5.2.3 Exoskeleton Gait Parameters Settings

Reporting exoskeleton gait parameter settings programmed for an individual, with reference to knee flexion angle and EMG data, can provide researchers and therapists with a better understanding of the influence of exoskeleton use on gait recovery patterns. On reviewing the collection of research studies on knee flexion angle and OEGT of AB and SCI participants (Table 2), only one of the articles report the exoskeleton settings

used for every participant (Ramanujam et al., 2018). The current study presented results of different combinations of gait parameter settings. Analysis showed that SL and SH had a significant effect on knee flexion angle at the beginning and end five percent of the gait cycle (Figure 17). This suggests that SL and SH influence terminal swing and IC. Conditions with lower SH resulted in lower IC and PKF magnitudes compared to conditions with higher SH (Figure 15 and Figure 16).

A study by Talaty et al. (2013), compared three groups using the Rewalk™ in different swing phase speeds (slow, medium, and fast). Results demonstrated that faster swing phases produce a more flexed knee at IC. The results of ST using the Ekso GT™ effects all variables measured for signal timing. Naturally, increasing ST would increase cycle time and allow more time to perform the flexion extension motion of the knee (Figure 20). Interestingly enough, ST had a significant main effect extensor EMG during stance phase in AB users (Figure 19). This effect was suggested to occur as a result of the AB user instinctively activating the knee extensors to extend from the flexed IC of the Ekso GT™. The effects of how different gait parameter setting combinations influence neuromuscular response of exoskeleton users requires further research. Future research in this area could aid therapists in understanding the impact of the chosen settings for their patients.

5.2.4 Case SCI01

The case of SCI01 presented a knee flexion angle pattern that was similar to the AB participants. However, the most revealing differences were in their EMG patterns

which showed muscle activity at moments when muscles should be relaxed and stretching (

Figure 24). These patterns, particularly in the knee extensors, were noticeable in persons with SCI with spasticity in the study by Ramanujam et al. (2018); two SCI participants with spasticity of the knee extensors (MAS>1) had a burst of extensor activity around the time of peak knee flexion, when the knee extensors should be relaxed and stretching. These related findings provide further evidence to the possibility of potential spastic activity during Ekso GT™ gait training. To determine if the observed spasticity during OEGT is ultimately harmful or helpful requires future investigation in a larger, longitudinal study.

An additional observation was the EMG activity of the extensors and flexors of the knee appeared to have continual activation, transitioning from eccentric into concentric contraction (Figure 24). This observation stimulates further interest into muscle spasticity during gait. A recommended future study would examine non-exoskeleton gait in people with SCI to see if this abnormal pattern is due to CNS injury or an adaptation (or possible a maladaptation) to compensate for impairment, irrespective of the OEGT.

5.2.5 Case SCI02

SCI02 had a very similar knee flexion angle pattern to that of AB participants but exhibited a very small amount of muscular input during Ekso GT™ gait (Figure 25). The knee flexion angle closely followed the pattern of AB Condition 4 (Figure 26). Observation of Figure 26 shows more EMG activity and the similar occurrence of

concentric and eccentric contraction throughout the gait cycle, just like SCI01. Although EMG activity was lower intensity than SCI01, SCI02 experienced overactive eccentric flexor EMG that persisted into the concentric phase.

It may be important that this participant was treated with botulinum toxin, to the knee extensor, which acts local to the muscle injected, whereas spasticity management for SCI01 was via baclofen which acts globally. The implication is that type of antispastic medication may play a role in how muscles to respond to OEGT. There is a lack of reporting in the OEGT research literature of use, type, and dose of antispasticity medications, making it difficult to corroborate these findings. Nevertheless, it cannot be dismissed that the type of antispasticity medication could hinder the neuromuscular adaption goal of GT. Therefore, it is suggested that future studies include participant antispasticity medication and dose if applicable.

5.2.6 Exoskeleton Gait and Spasticity

Clinically, measuring spasticity faces barriers in real time analysis; biological signal data analysis enables assessment of spasticity in real time. Both participants presented spasticity during the pre WPT. Participants performed better post WPT, but improvements were small and not considered to be significant. These small improvements to active spasticity (changes in relaxation index) suggest that a short session of Ekso GT™ gait training may not significantly reduce spasticity, but it may induce change to the passive resistance to stretch (larger plateau angle post OEGT see Table 10 and Table 13). Deciding whether exoskeleton GT is considered a successful GT method involves looking at the big picture and weighing the benefits and risks (for

example: standing and walking measures; quality of life measures; and independence measures).

5.3 Benefit-Risk Framework

This study provided two very different SCI cases and demonstrated the importance of including biological outcome measures as a part of their comprehensive assessment and evaluation. Data analysis resulted in different stories for Ekso GT™ gait training for the two SCI participants; these stories were derived from the biological outcome data and participant's clinical status, demonstrating the relative benefit of OEGT on muscle activation patterns need to be considered.

The benefit of OEGT would be represented by SCI muscle activation patterns that are temporally aligned with AB muscle activation pattern, suggesting that the Ekso GT™ training is eliciting neuromuscular responses that are desirable for locomotion. On the contrary, risks would be muscle activation patterns that are not temporally aligned with AB muscle patterns; such abnormal activations during muscle lengthening are most likely spasticity as a result of dysfunctional peripheral control, whereas activations occurring incorrectly during muscle shortening would implicate irregular central control (Figure 27).

Benefit-risk analysis of SCI01 and SCI02 provided an example of how this framework could be implemented clinically. SCI01 exhibited both normal and abnormal activations. Occurrence of both activation patterns could leave therapists to consider "how do the benefits compare to the risks?". Therapists may ask questions such as "is there so much spasticity and/or abnormal muscle activity that continuing to use the

training device would be risky?" or "are there more beneficial muscle activations compared to risky ones?" and if so, "would continuing the training prompt improvements in community walking?". Longitudinal studies with clinical monitoring of muscle spasticity and spasticity treatments are needed to answer these questions.

SCI02 provided a different benefit-risk scenario. SCI02 exhibited little abnormal activations during gait, suggesting very few risks. SCI02 also exhibited muscle activity, although minimal, still provides evidence for potential neuroplastic benefit and no spastic interference to Ekso GT™ function. As such, this patient may also experience the secondary benefits from upright walking (cardiovascular, bone density, bladder/bowel function, etc.). The proposed framework for benefit-risk assessment could be a tool for therapists when developing personalized OEGT protocols for patients and for better discrimination of persons with SCI eligible to participate in OEGTs.

5.4 Limitations

This study was limited by two primary factors: small sample size and study duration. The study initially aimed to recruit six SCI participants; after over a year of the study being open only two SCI were recruited. A recent meta-analysis reveals that majority of SCI research studies are published with small populations (Zimmermann et al 2019), with a study by Piira et al. 2019 admitting it took 10yrs to recruit 24 patients. No accelerometer was used on SCI participants that resulted in the SCI data being cycled using the AB data. The knee extension EMG was chosen to return to rectus femoris, for purposes of the WPT results. Knee extensor EMG of AB and SCI were collected from two different muscle, vastus lateralis and rectus femoris, respectively. These two muscles

are reported to have similar co-activation patterns during gait (Strazza et al., 2017). The rectus femoris can sometimes act as a hip flexor early during the transition into swing phase while the vastus lateralis does not; typically, this results in the rectus femoris having three moments of muscle activation during gait and with the vastus lateralis co-contracting at only two of the moments (Strazza et al., 2017).

Although there is strong evidence from our study, and studies of others, that the observed knee trajectory during exoskeleton walking differs from a normal trajectory by design; it cannot be excluded that slow walking and/or walking with a walker explain the observed gait patterns. Future study of AB subjects should include an unassisted "walker gait" trial in the AB and, if possible, for SCI participants as well. Although this data would have been beneficial to investigate, reports confirm that an assistive walker can decrease lower limb joint range of motion, as well as gait speed, cadence and step length (Martins et al., 2014). A review of the different walking aids with exoskeletons reported no significant differences between the knee flexion angle of walking aids (De Luca et al., 2019). These supporting documents suggest the comparisons of normal gait to exoskeleton gait with a walker presented in this study should be considered meaningful data when exploring the interaction of exoskeletons on human gait.

5.5 Final Comments and Conclusions

The study has provided original research in the field of biomechanics, exoskeleton technology, as well as therapist implementation, patient safety and usability. This study was unique in its dual study design and attention to spasticity. The multiple gait setting parameter design of the AB data confirmed previous research reporting that exoskeleton

gait does not resemble normal gait. The database compiled from the multiple gait parameter setting design helped to establish a solid base for the comparison to SCI case study data. Usefulness of a normative exoskeleton gait database, as presented, suggests that future studies in the area of exoskeleton gait analysis should consider developing normative data bases with healthy subjects of all ages; not relying on the traditional "normal gait" patterns (e.g. Winter, 2009) for comparative purposes.

The combination of biological signal data from two populations contributes further insight to the biological response of lower limbs to exoskeleton gait. Deeper exploration into the EMG muscle activity patterns revealed concerns for suspected spastic activity, in the biological signals of one SCI patient, during exoskeleton gait. On the other hand, the second SCI patient had biological signals that were notably reduced potentially due to a recent treatment of botulinum toxin.

These observations support the importance of biological signal data as a tool in the therapist's toolbox when using exoskeleton devices on patients. Biological signal data can aid the therapist when evaluating the benefits and risks of using an exoskeleton for gait therapy. Having access to biological signal data as a therapist would promote educated selection of exoskeleton gait parameter settings. This knowledge would also help understand the patient's benefit/risk ratio when using exoskeleton technology as a therapeutic tool and when using it in conjunction with anti-spasticity medications. Supporting therapists and patients with biological signal data will provide opportunity for real time feedback and opportunity to address progress and potential for plasticity of neuromuscular innervation.

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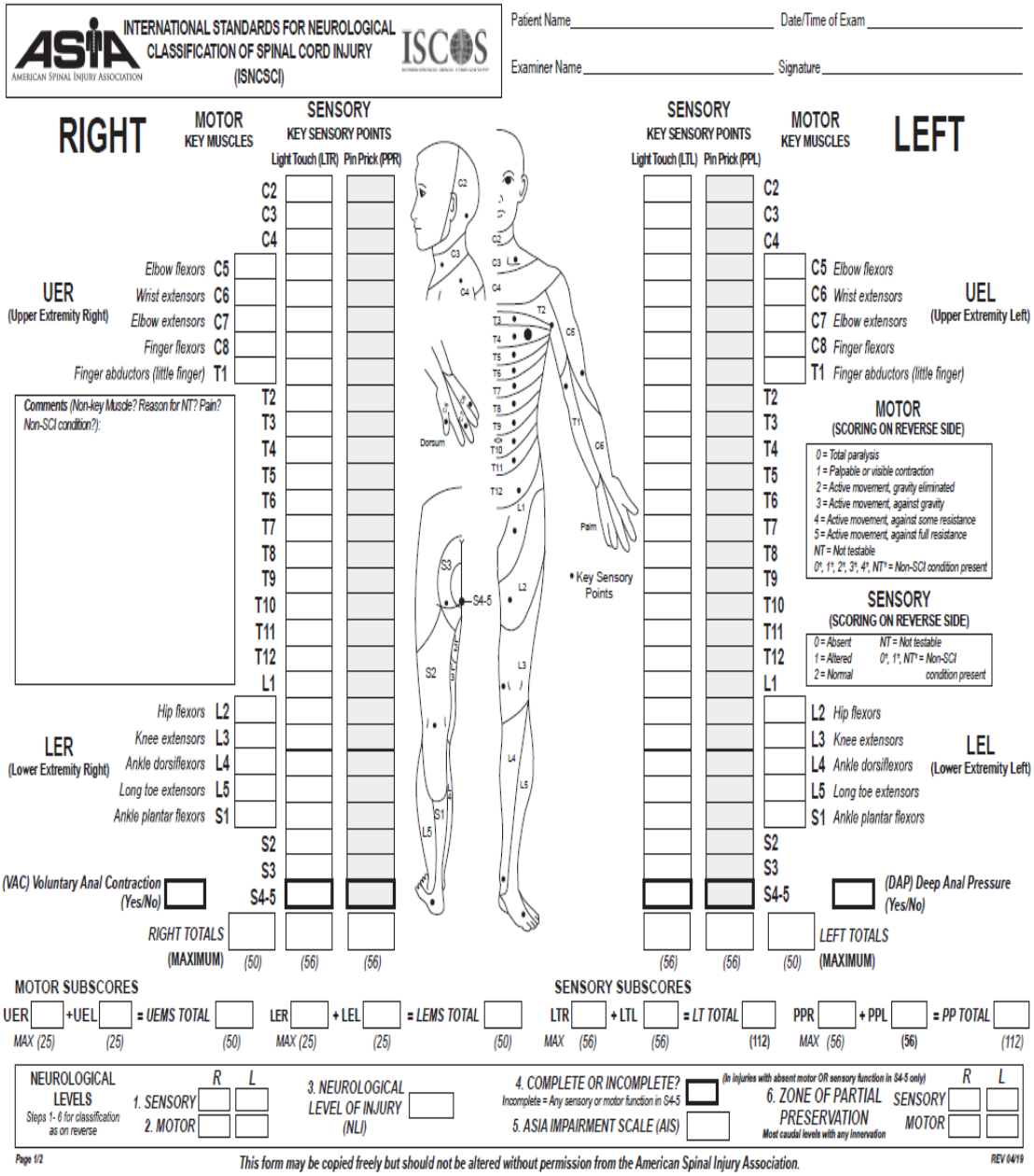
Appendix A

International Standards for Neurological Classification of Spinal Cord Injury Worksheet



Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present [a]

Sensory Grading

0 = Absent **1** = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal **NT** = Not testable

0*, 1*, NT* = Non-SCI condition present [a]

[a] Note: Abnormal motor and sensory scores should be tagged with a "*" to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

INTERNATIONAL SPINAL CORD SOCIETY

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No**, then injury is **Complete**.*
*Otherwise, injury is **Incomplete**.*

5. Determine ASIA Impairment Scale (AIS) Grade.

Is injury Complete? If YES, AIS=A

NO ↓

Is injury Motor Complete? If YES, AIS=B

NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO ↓ **AIS=C** **YES** ↓ **AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Ekso Gait Trainer Exclusion Criteria

Exclusions:

- □ History of severe neurological injuries other than (spinal cord injury or stroke)
- □ Severe concurrent medical diseases: infections, circulatory, heart or lung, pressure sores
- □ Standing hip width of 18" (45.72cm) or more
- □ Must have leg discrepancy less than half an inch (1.27cm) and lower leg discrepancy less than ¾ of an inch (1.91cm)
- □ Severe spasticity (Modified Ashworth 4)
- □ Unstable spine or unhealed limbs or pelvic fractures
- □ Heterotopic ossification
- □ Significant contractures
- □ Psychiatric or cognitive situations that may interfere with proper operation of device
- □ Cognitive impairments resulting in inability to follow directions
- □ Pregnant women
- □ Colostomy
- □ Poor skin integrity in areas in contact with the device
- □ Decreased standing tolerance due to orthostatic hypotension
- □ Range of motion restrictions that would prevent a participant from achieving a normal reciprocal gait pattern, or would restrict a patient from completing normal sit-to-stand or stand-to-sit transitions
- □ Unresolved deep vein thrombosis
- □ Uncontrolled Autonomic Dysreflexia
- □ Lower limb prosthesis

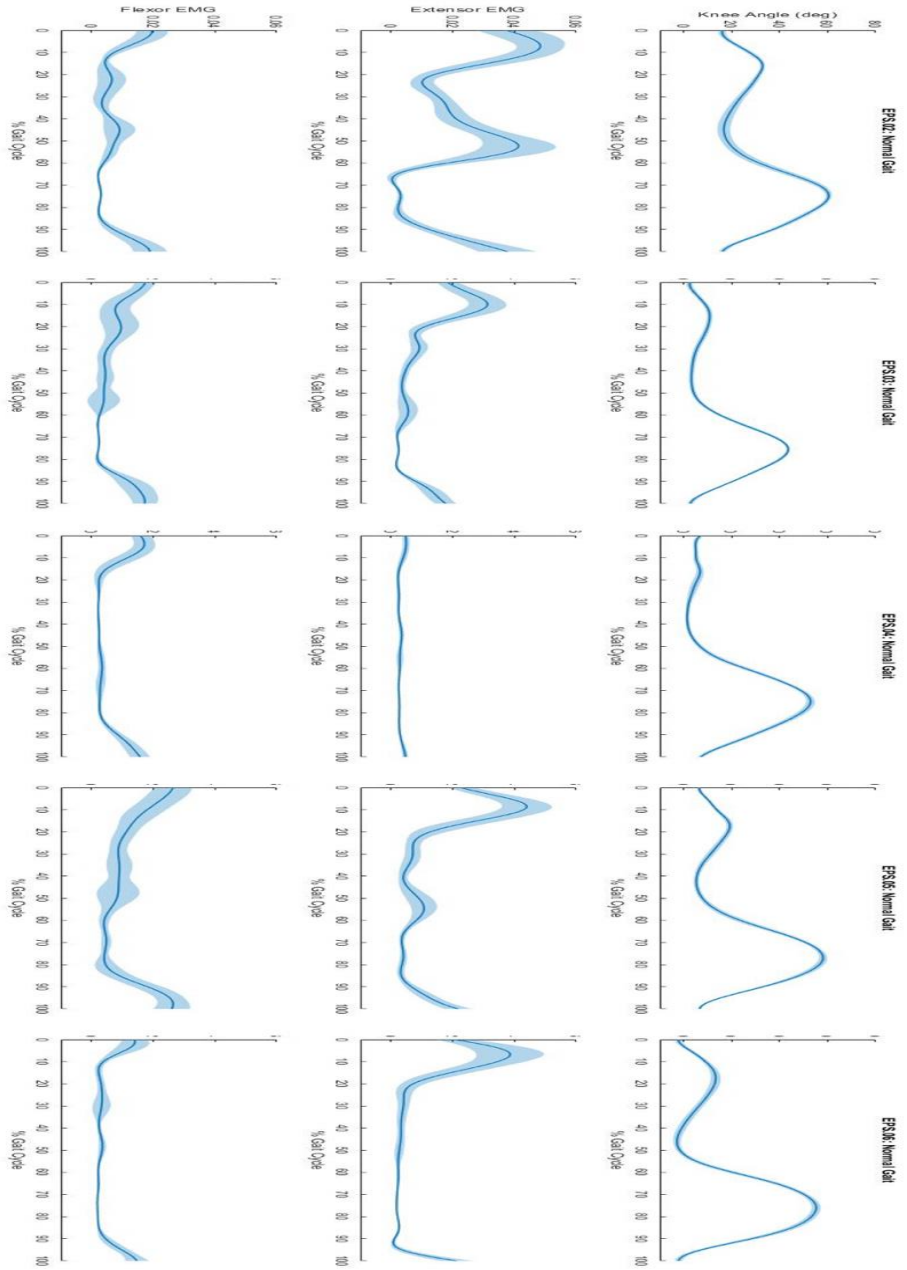
Research Study Inclusion Criteria

Inclusions:

- □ Previous spinal cord injury or stroke
- □ Height 5'-6'4
- □ Weighing 220lbs or less
- □ Age range 19-65
- □ 0-3 Modified Ashworth Score
- □ Completed 1500 steps in the Ekso GT™ exoskeleton

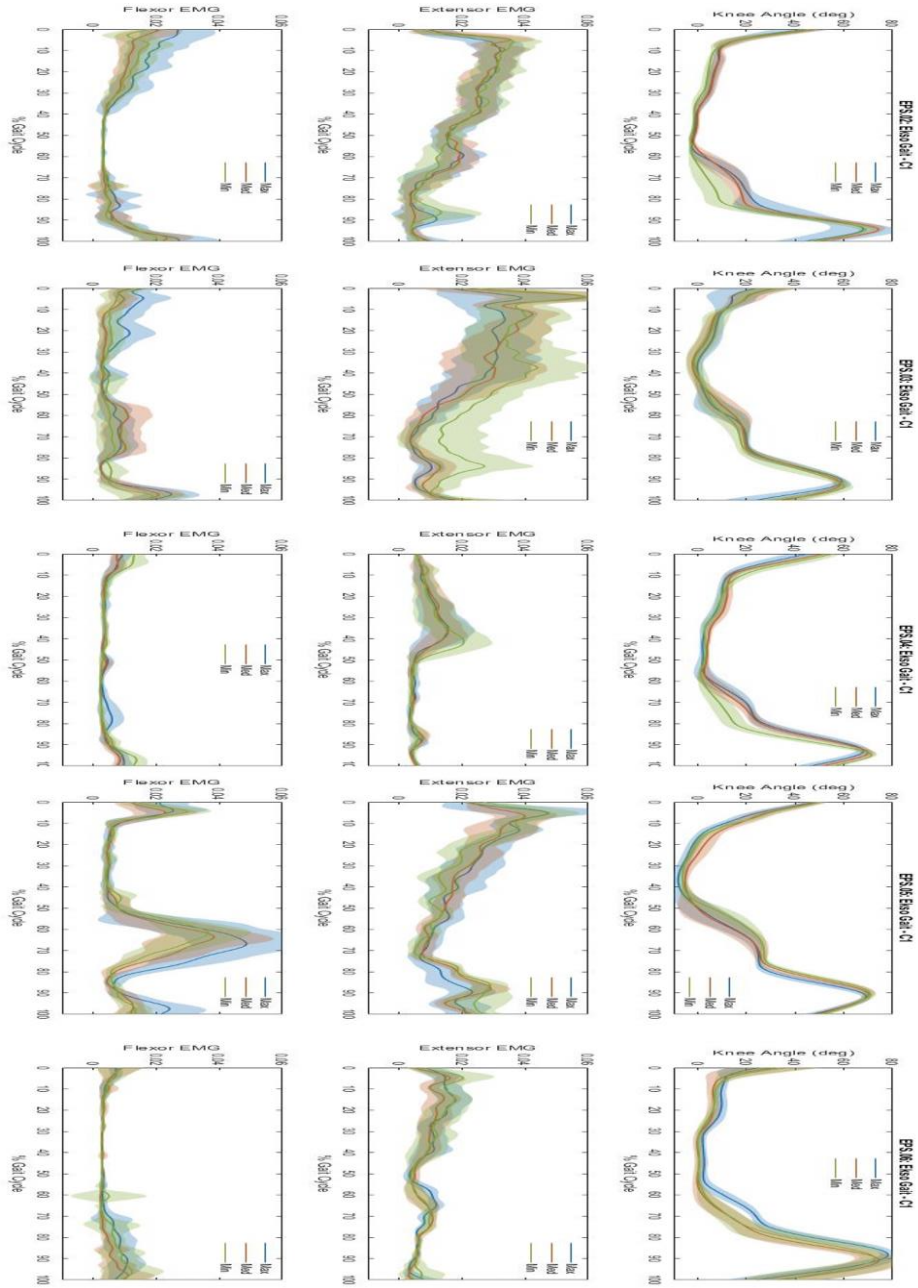
Appendix C

Individual able-body participants' normal gait data



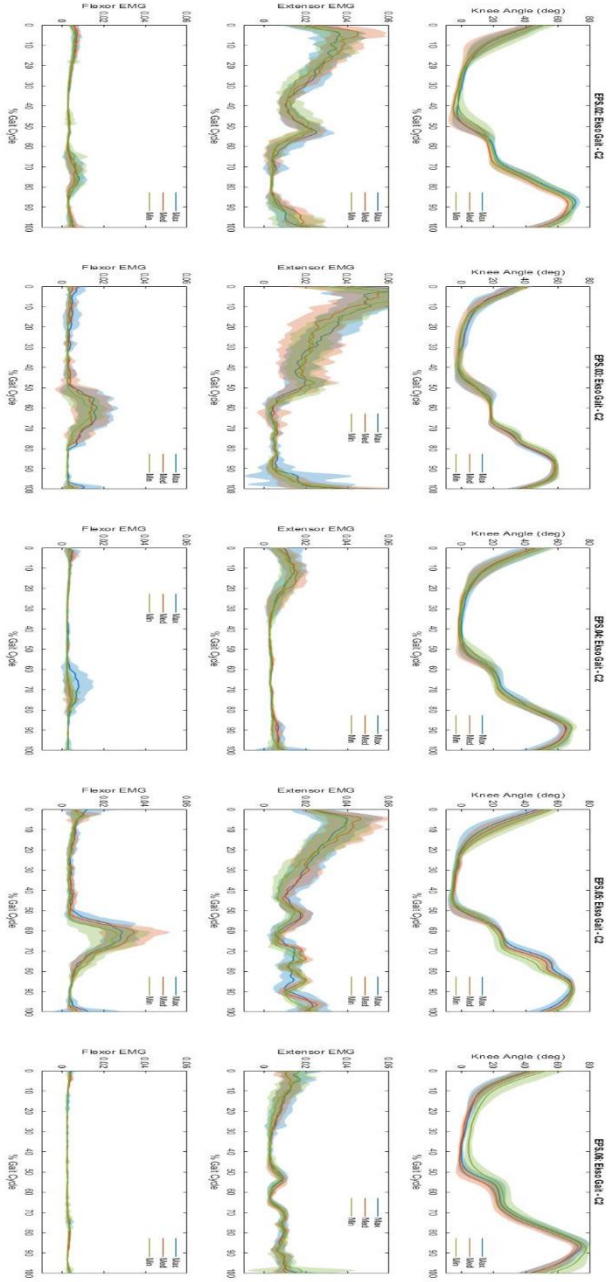
Appendix D

Individual able-body participants' Condition 1 exoskeleton gait data



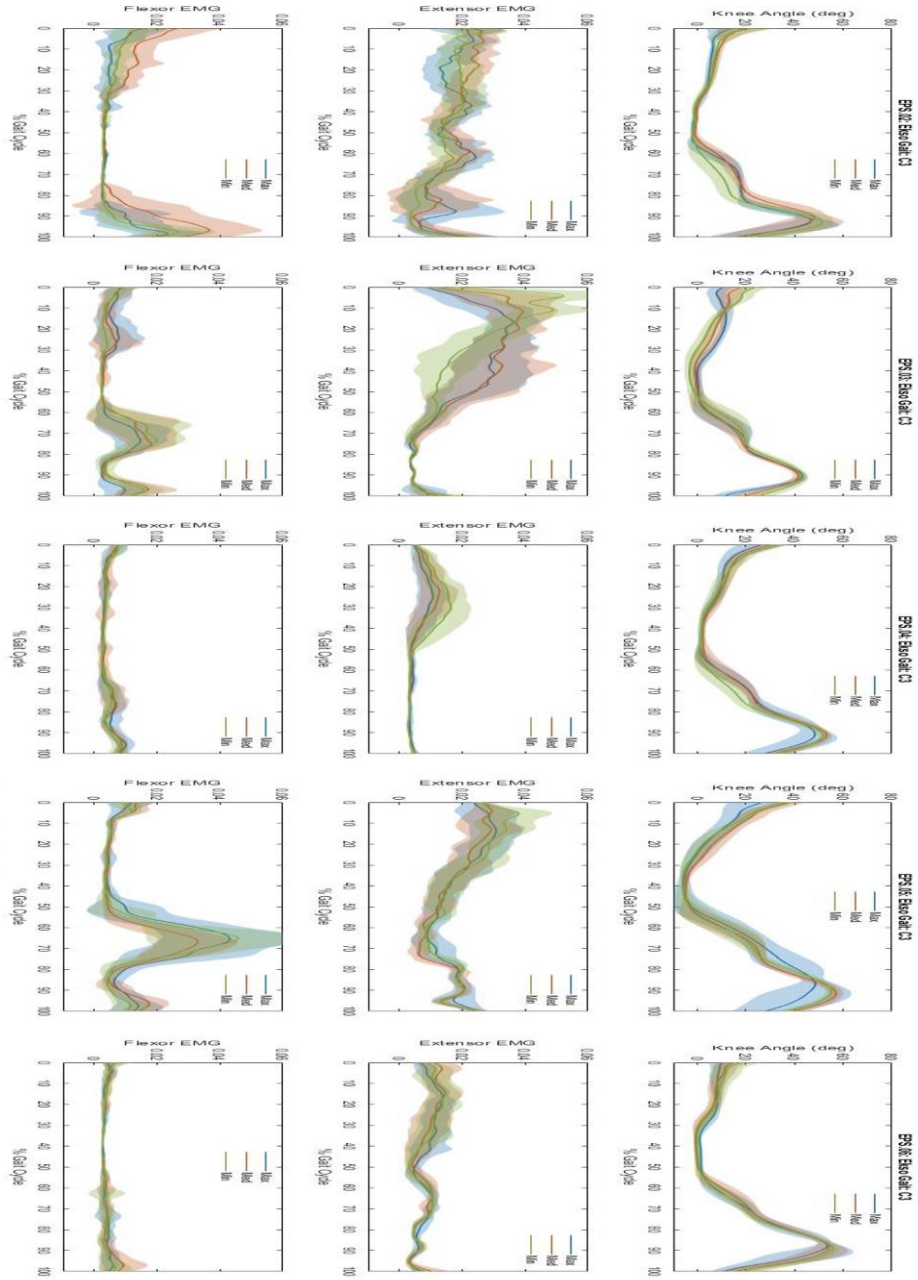
Appendix E

Individual able-body participants' Condition 2 exoskeleton gait data



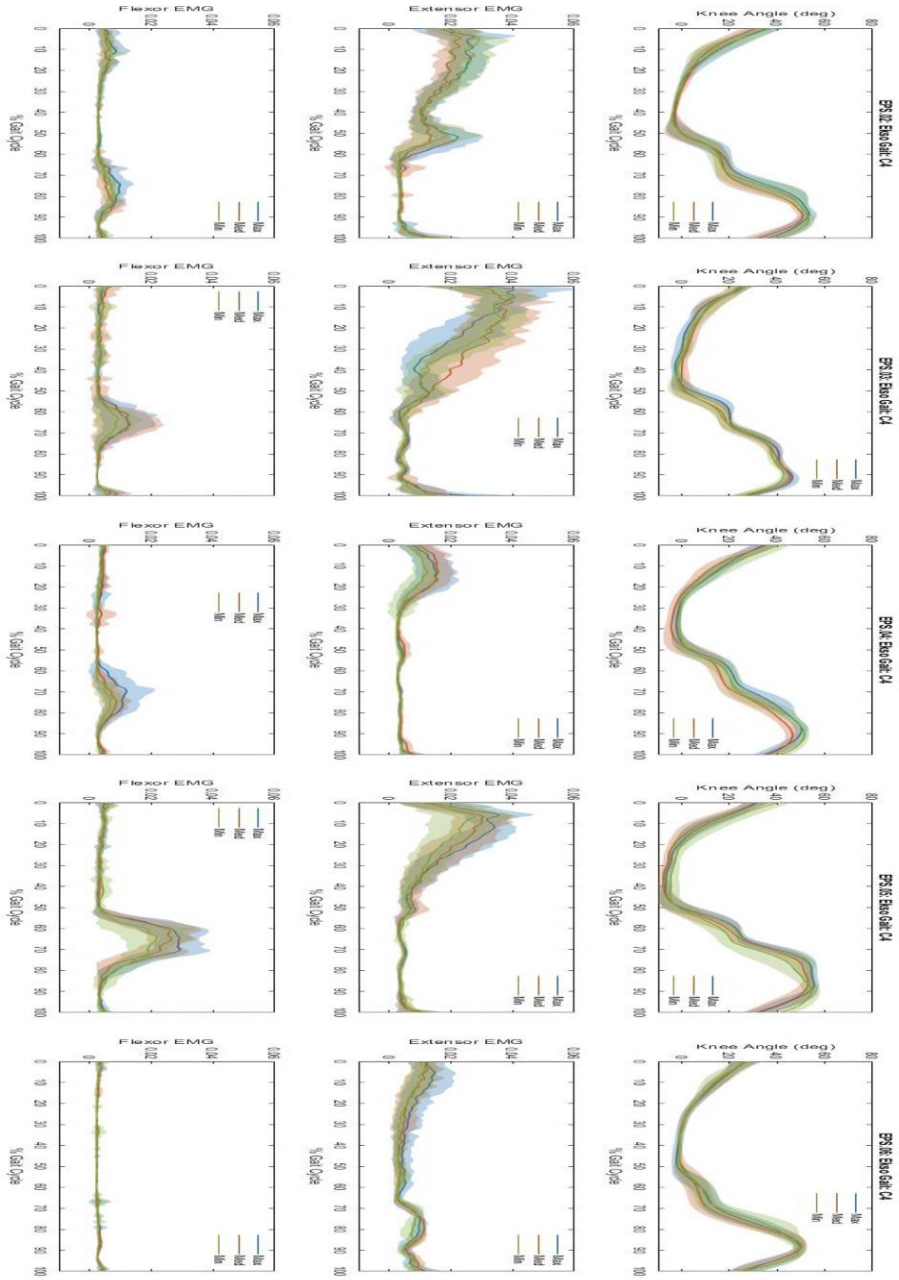
Appendix F

Individual able-body participants' Condition 3 exoskeleton gait data



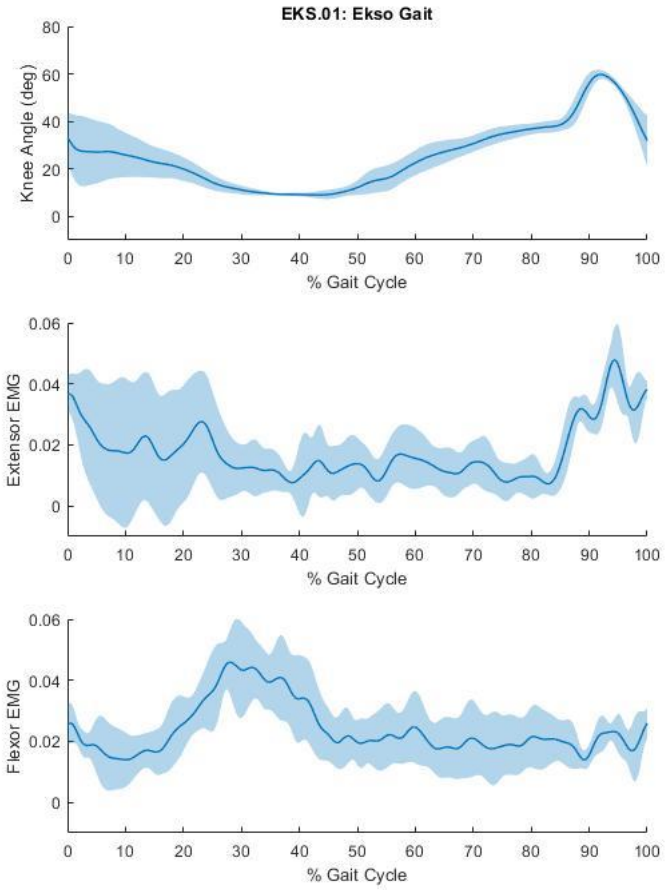
Appendix G

Individual able-body participants' Condition 4 exoskeleton gait data



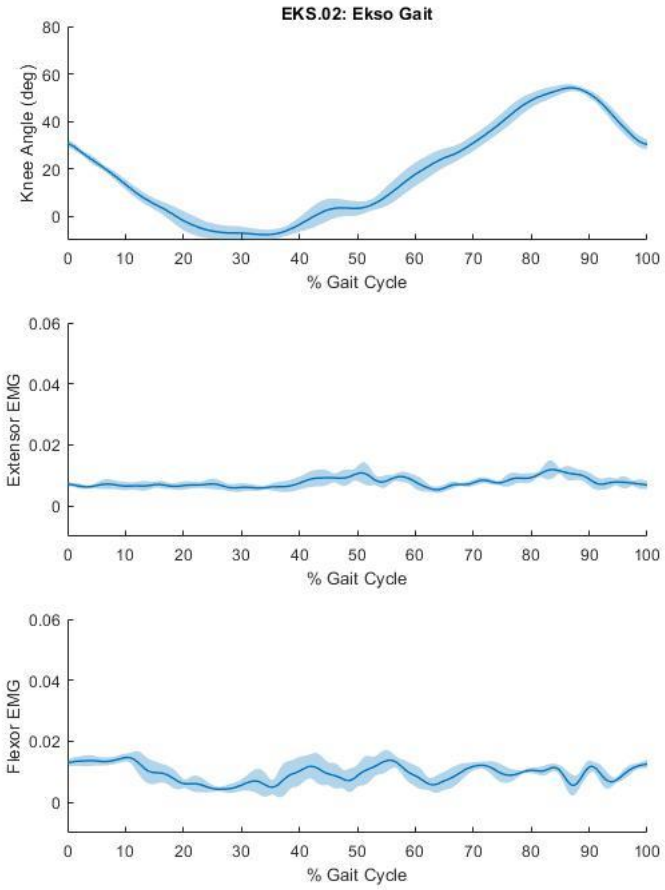
Appendix H

SCI01 exoskeleton gait data



Appendix I

SCI02 exoskeleton gait data



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2. Brain Repair Centre's AMAP Annual Meeting 2019, Nova Scotia, Canada – Speaker Presentation: "*The Interaction Between Over-Ground Exoskeleton Gait and Muscle Spasticity*".
3. Brain Repair Centre's AMAP Annual Meeting 2020, Nova Scotia, Canada – Speaker Presentation: "*The Interaction Between Overground Robotic Gait Training and Lower Limb Spasticity in People with Spinal Cord Injury*".