ACUTE EFFECTS OF A ROBOTIC ANKLE EXOSUIT ON THE GAIT BIOMECHANICS, METABOLIC COST, AND MUSCLE ACTIVITY DURING WALKING IN PATIENTS UNILATERAL CEREBRAL PALSY

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Master's Thesis in Biomechanics

Biology of Physical Activity

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Fall 2021

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ABSTRACT

The ability to walk is important for mobility, community participation, and independence. However, for patients with Cerebral Palsy (CP), walking can be impaired due to these patients' neuromuscular and musculoskeletal limitations. The neural lesion that underlies CP leads to various motor impairments, such as muscle weakness, deficient motor control, and reduced joint range of motion, which can all inhibit patient's walking capacity. Current treatments for CP mostly focus on correcting or improving specific musculoskeletal deficiencies, but are commonly ineffective at improving patients' overall walking ability. New clinical technologies, such as exoskeletons and exosuits may enable enhanced gait therapy for patients with neuromotor dysfunction, such as those with CP. The early evidence using these devices in patients with motor impairments has been highly positive, showing improvements in biomechanics, muscle activity, and energy cost during robotically augmented walking. However, very little research has investigated the use of these devices in patients with CP. The purpose of this thesis was to investigate the acute effects of a robotic ankle exosuit on the gait biomechanics, muscle activity, and metabolic cost during walking in a small cohort of adolescents and young adults with unilateral CP.

Seven participants with unilateral CP (12-16 years old, GMFCS I) were recruited for this study. The protocol involved walking on a force-sensing treadmill while 3D motion capture, surface electromyography, and oxygen consumption were used to measure lower limb gait kinematics and kinetics, muscle activity, and metabolic cost. Three walking trials were performed: 1) normal walking without the exosuit, 2) walking with the exosuit while carrying the device's motor (onboard), and 3) walking with the exosuit with the motor offloaded from the body (offboard). The exosuit used in this study assists plantarflexion and dorsiflexion movements of the patient's affected ankle joint during walking via contractile cables at the front and rear of the foot. The results showed that the exosuit improved affected ankle mechanics (improved dorsiflexion at ground contact (*onboard: +9.98° [p=0.002], *offboard: +9.20° [p=0.004]) and increased peak plantarflexor moment at push-off (*onboard: +0.09 Nm/kg [p=0.037], offboard: +0.11 Nm/kg)) and amplified positive power generation at the knee in the unaffected leg (*onboard: +0.28 W/kg [p=0.041], *offboard: +0.19 W/kg [p=0.011]), as well as produced a trend towards generally reduced muscle activity across the lower limb muscles. These biomechanical and muscle activity changes likely contributed to the reduced metabolic cost observed while walking with the exosuit, especially in the offboard condition (onboard: -6.9%, offboard: -14.7%), however this reduction was not statistically significant. These results point to the potential of this exosuit, as well as similar robotic assistive technology, to augment walking mechanics, energetics, and muscle activity, and thus support future research with these devices to improve mobility in patients with CP.

Key words: Cerebral Palsy, Exosuit, walking, ankle, gait analysis, metabolic cost, robot

LIST OF ABREVIATIONS

CP	Cerebral Palsy
GRF	ground reaction force
COM	center of mass
PF	plantarflexion
DF	dorsiflexion
CPG	central pattern generator
WHO	World Health Organization
GMFCS	gross motor function classification system
ECM	extracellular matrix
TA	Tibialis Anterior
GM	Gastrocnemius Medialis
RF	Rectus Femoris
VL	Vastus Lateralis
BF	Biceps Femoris
EMG	electromyography
EEG	electroencephalography
CGA	clinical gait analysis
ICF	International Classification of Functioning, Disability, and Health
SEMLS	single-event multi-level surgery
BoNT-A	Botulinum Neurotoxin-A
SDR	selective dorsal rhizotomy
PT	physical therapy
NDT	neurodevelopmental therapy
ROM	range of motion
LTP	long-term potentiation
AFO	ankle-foot orthosis
VR	virtual reality
SD	standard deviation
CV	coefficient of variation
BW	body weight
IMU	inertial measurement unit
GC	ground contact
TO	toe off
CNS	central nervous system
RCT	randomized controlled trial

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1. INTRODUCTION

The ability of humans to walk is extraordinary. When everything works properly, the nervous system integrates a multitude of sensory information and generates carefully controlled motor commands that lead to stable and balanced gait (Nielsen 2003). This is a delicate process, however, and insult or injury to the neuromotor system can negatively impact the walking ability of those affected, making gait a strenuous and demanding task. Those with Cerebral Palsy (CP) – a movement disorder caused by damage or malformation of the developing brain – often present with abnormal walking patterns that are energetically inefficient and taxing on the muscles (Rose et al. 1990; Dallmeijer et al. 2011). The underlying nervous system dysfunction early in life impairs musculoskeletal development in those with CP, leading to weak muscles and suboptimal joint function (Graham et al. 2016). These physical limitations can prevent patients with CP from engaging in physical activity and exercise and can hinder community participation, which can both reduce quality of life. Current therapy practices and invasive interventions are only moderately effective in treating the neuromuscular deficiencies and musculoskeletal deformities present in CP (Novak et al. 2013).

The development of robotic assistive technology has begun blossoming in the past decade, and devices such as robotic gait trainers and exoskeletons are now being integrated into neurorehabilitation programs (Calabrò et al. 2016). These devices can be utilized to promote and train more normal and healthy movement patterns, improving patients' ability to walk and move on their own (Esquenazi et al. 2017). Further, untethered robotic assistive devices, such as exoskeletons, have the capacity to augment the movement capabilities of those more functionally limited patients at home and in the community, enabling them to participate in activities that would have been impossible without the device. Regaining the ability to walk is an invaluable achievement for severely impaired patients – a man with spinal cord injury said his first steps when walking in a mind-controlled exoskeleton felt like being the "first man on the moon" (Gallagher 2019). Wearable robots have such immense potential, as they can both transform and improve neurorehabilitation in the clinic as well as effectively nullify the motor impairments of those patients with more difficult to treat motor dysfunction.

Unlike in spinal cord injury and stroke (Federici et al. 2015), there has been limited research investigating the use of robotic assistive technology in patients with CP (Reyes et al. 2020). The aim of this thesis is to explore the effects of a unilateral soft exosuit (Figure 4D) on the gait biomechanics and metabolic cost of walking in a small cohort of children and adolescents with CP. This device was designed for motor rehabilitation following stroke (Awad et al. 2017), and this is the first investigation of its use in CP patients. The exosuit used here has the potential to be used in both therapeutic as well as everyday settings, so this thesis acts as a preliminary investigation into the effects of this device on walking mechanics and energy cost in children and adolescents with CP to begin to inform the optimal application of this device and similar devices moving forward.

The thesis will begin with a literature review, which aims to outline the key background research and present the foundational motivation for the experiment conducted herein. The study protocol and results will follow the literature review. A discussion of how the results from this thesis fit into the broader research fields of assistive technology and neuro-rehabilitation and the larger implications of the results from this study will conclude the thesis.

2. NORMAL GAIT BIOMECHANICS

Human bipedal walking is a fine-tuned movement pattern that has been developed and optimized throughout our evolutionary lineage. In fact, it is thought that the development of upright bipedal gait was an important step forward in human evolution, as walking on only two legs frees the upper limbs and hands for activities such as carrying, using tools, and generally manipulating the environment (Nielsen 2003). Bipedal gait sacrifices the stability and balance inherent to quadrupedal movement strategies, however, and takes more developmental time to learn and optimize as well as necessitates an integrated method of neural control (Gage et al. 2009). Remarkably, despite the intricate challenges that are posed by bipedal gait, the healthy human walking pattern is quite well optimized, requiring minimal energy expenditure and muscle activity to maintain forward progression (Sawicki et al. 2009). The complexity of healthy human walking in terms of both biomechanics and nervous system control make it very sensitive to pathological deviations in these systems, however. Neuromotor dysfunction and/or musculoskeletal deformity can have debilitating consequences on the walking pattern, leading to serious mobility challenges for these patients.

This section will focus on the healthy human walking pattern. A general biomechanical description of the movement pattern of normal gait will begin the section. The key biomechanical mechanisms underlying the energetic efficiency of human walking will then be examined. This brief overview of the healthy human gait pattern should help to set up the later examinations into pathological gait and how it deviates from the norm.

2.1 The Healthy Human Gait Pattern

The healthy human walking pattern can be generally modelled as an inverted pendulum, with the body's center of mass being vaulted up and over the standing leg before falling forward and ultimately being caught by the opposite leg as it touches the ground, restarting the pattern (Sawicki and Ferris 2008; Figure 1). There are five key prerequisites to the healthy gait pattern: (1) stability in the standing leg, (2) foot clearance when the leg swings, (3) appropriate pre-positioning of the foot before it contacts the ground, (4) sufficient step length, and (5) conservation of energy (Gage et al. 2009; Peterson and Walton 2016). Considering walking is a cyclical motion, it can be split into discrete cycles, termed gait cycles. The complete gait cycle begins when one of the feet strikes the ground and ends when this same foot again strikes the ground. The gait cycle consists of two main phases: stance phase (when the foot is on the ground) and swing phase (when the foot is off the ground). During typical walking, the stance phase makes up 60% of the gait cycle while the swing phase makes up the remaining 40%. Additionally, the opposite foot leaves the ground and touches down again at approximately 10% and 50% of the gait cycle, respectively. Thus, there are two periods where both legs are on the ground, termed double support, and they each make up about 10% of the full gait cycle. Single support, then, makes up about 40% of the gait cycle and corresponds to the swing phase of the opposing leg. (Gage et al. 2009.) The primary purpose of stance phase is to provide stability and redirect the body's center of mass in order to maintain the inverted pendulum walking pattern, while the primary purpose of swing phase is to advance the trailing limb while conserving metabolic energy (Peterson and Walton 2016).

Importantly, the muscles, and the forces they generate, are the main drivers of human movement. Muscle forces are directed via the rigid skeletal structures surrounding joints, which act as lever arms. Generally, a moment can be defined as a force acting upon a lever about an axis of rotation, and, if the line of force action and axis of rotation are perpendicular, then the mathematical value for the moment is given as the magnitude of the force multiplied by the length of the lever arm (Gage and Novacheck 2001). Thus, the forces produced by muscles create internal joint moments, which act to generate movement (Gage et al. 2009). Additionally, any movements that the body performs against the ground in resistance to gravity, such as standing or walking, generate ground reaction forces (GRF), which are equal in magnitude and opposite in direction to the force applied to the earth. Like muscle forces, the GRF acts on the skeletal levers of the body to produce external joint moments (Gage et al. 2009). Human locomotion is driven by a constant back-and-forth between these internal and external joint moments (Figure 1C).

The healthy walking pattern can be described by examining the progression of the GRF vector throughout the gait cycle (Figure 1A). Generally, the point of application of the GRF moves forward along the bottom of the foot throughout stance phase as the body's center of mass (COM) moves over the standing limb. At the start of the gait cycle, the foot strikes the ground with the heel and the GRF vector is directed behind the ankle and knee joint centers and approximately in-line with the hip joint center. During the initial loading response following ground contact, the stance limb absorbs the shock from the body's COM falling forward and down from its peak in the previous stance phase and acts to maintain the body's forward progression. The impact force on the limb during loading response is typically about 120% of body-weight. As stance phase continues, the point of origin of the GRF vector begins to shift forward, towards the front of the foot. Importantly, during the middle periods of single support, the GRF vector is guided in front of the knee joint and behind the hip joint, producing external extension moments at these joints. Near the end of stance phase, the heel begins to rise from the ground and the point of application of the GRF vector moves even farther forward on the foot. During this period, the limb must generate forward propulsive power to counteract the energy absorption and deceleration phases earlier in stance. Once the opposite leg touches down and the second double support period begins, the trailing limb begins to prepare for swing and the body-weight is shifted to the leading leg. During this period, the GRF vector is applied from the very front of the forefoot and begins to be directed well behind the knee joint center. This creates a strong external knee flexion moment, which, along with activity from the hip flexor muscles, drives the knee to flex rapidly. At the initiation of swing phase, the foot comes off from the ground, the GRF disappears, and, like a pendulum, the leg swings forward. At the end of swing phase, the limb must be properly pre-positioned for heel strike through activation of the ankle dorsiflexor muscles. Once the leading limb touches down again, the gait cycle begins anew. (Gage et al. 2009.)

The lower limb joints have varied roles within the normal walking pattern. Generally, the hip joint performs primarily positive mechanical work (produces forward propulsive energy), the knee joint performs mostly negative mechanical work (absorbs energy), and the ankle performs a combination of positive and negative mechanical work throughout the gait cycle (Farris and Sawicki 2012; Nuckols et al. 2020). The ankle is perhaps the most important joint during normal walking, as the actions of the muscles surrounding the joint are essential for manipulating the GRF vector during stance, producing forward propulsive power, enabling foot clearance during swing, and facilitating proper pre-positioning of the foot prior to ground contact. The movement pattern of the ankle and foot throughout the stance phase has been described as three rockers (Figure 1B) (Gage et al. 2009; Davids et al. 2007). The first rocker (heel rocker) involves the controlled descent of the full plantar aspect of the foot onto the floor following heel strike. The ankle dorsiflexor muscles work to slow the progression of the foot to flat and prevent a foot slap. As the weight is shifted onto the stance leg and the body's COM advances over the stationary foot, the second rocker (ankle rocker) begins. During the second rocker, the triceps surae muscles act to slow the forward progression of the tibia over the foot and direct the GRF in front of the knee and slightly behind the hip joint centers. These first two rockers are deceleration rockers, with the ankle joint performing negative mechanical work and absorbing energy. Contrastingly, the third rocker (forefoot rocker) acts as an acceleration rocker and involves the production of positive propulsive work to counteract the deceleration of the first two rockers and maintain the forward progression of the body's COM. The third rocker occurs at the end of stance phase, as the heel is lifted off the ground and the triceps surae muscle-tendon unit contracts to produce a burst of propulsive power to propel the limb up and forward. The force produced by the ankle plantarflexors during the third rocker accounts for approximately 50% of the propulsive force during normal walking (Gage 2004). Following the third rocker, the action of the ankle joint shifts to its role during swing phase, which involves appropriate activation of the dorsiflexor muscles to facilitate ground clearance and proper pre-positioning of the foot prior to the start of the next gait cycle. The actions of the ankle joint throughout stance and swing are critical for the maintenance of the healthy gait pattern. (Gage et al. 2009; Davids et al. 2007; Peterson and Walton 2016.)

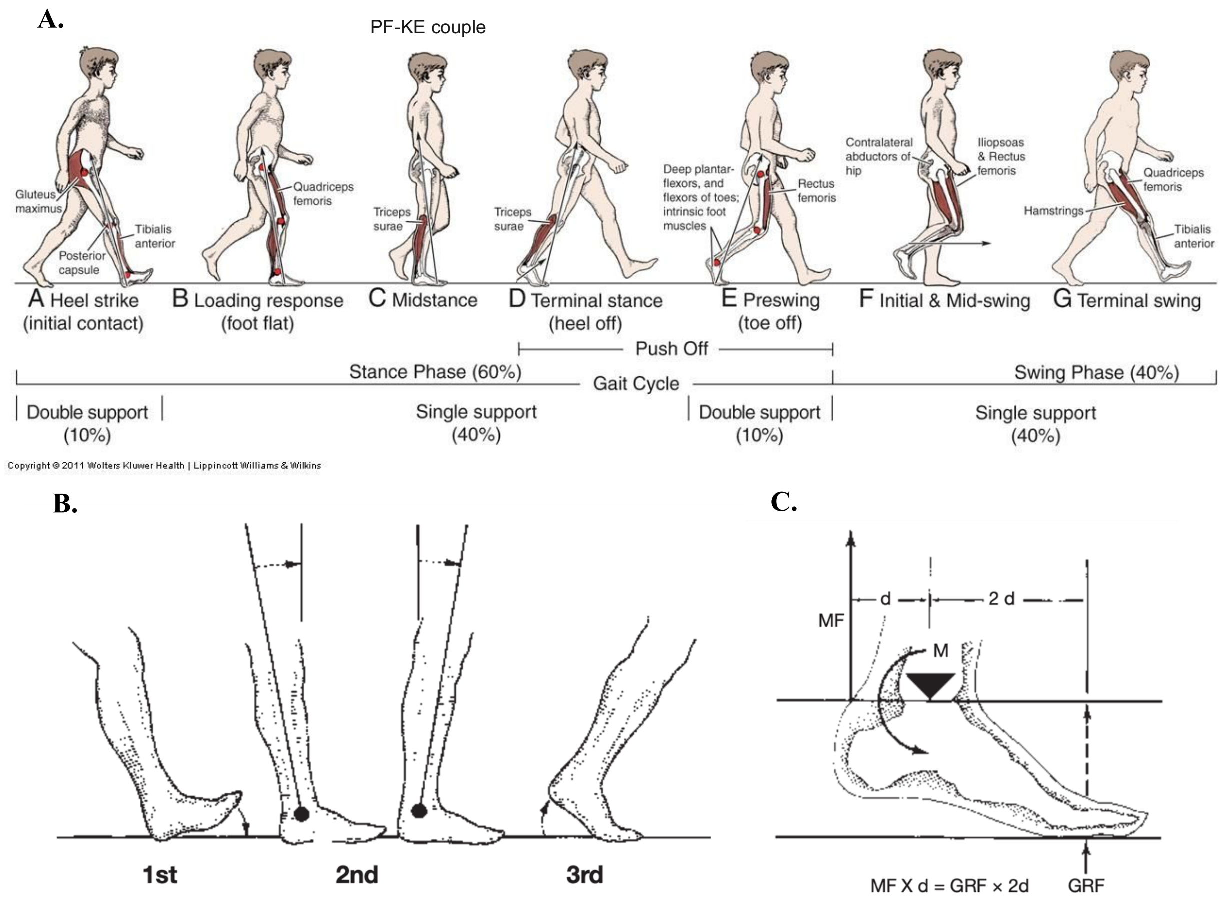

Figure 1: The Healthy Gait Pattern. A. Diagram displaying the full gait cycle with relevant gait phases. Particular attention should be paid to the trajectory of the GRF as the gait cycle progresses. Additionally, key muscle groups that are active at various phases of the gait cycle are highlighted. PF-KE: plantarflexion-knee extension. **B.** The three ankle rockers are displayed. The first rocker (heel rocker) involves the controlled descent of the foot to flat following heel strike; the second rocker (ankle rocker) involves the forward progression of the tibia over the foot and guidance of the GRF to produce external extension moments at the knee and hip; and the third rocker (forefoot rocker) involves the lift of the heel off the floor and the production of propulsive force from the ankle plantarflexors. **C.** The relationship between internal and external joint moments. Internal moments are produced by muscle forces (MF) while external moments are generated by the ground reaction force (GRF). In both cases, the forces act upon the bony levers of the body and the joint center acts as the fulcrum. The mechanical advantage is determined by the length of the moment arm, which is measured as the perpendicular distance from the force vector to the joint center (internal moment arm: d; external moment arm: 2d). Importantly, the internal and external moments must always be equal. In this case, then, considering the external moment arm is twice the length of the internal moment arm, the MF must be twice as great as the GRF in order to equalize the moments. Taken from Gage et al. 2009

The neural control of human walking is complex and involves a nuanced interplay between rhythmic motor commands generated by spinal networks, sensory input from proprioceptors and other sensory pathways throughout the body, and regulatory input from higher motor centers in the brain (Nielsen 2003). Research indicates that the control of rhythmic movement patterns, such as walking, is dictated by spinal networks termed central pattern generators (CPGs). These spinal CPGs generate rhythmic motor commands, and, in some animals, are capable of generating coordinated and functional walking patterns on their own (Grillner 1985). The evidence suggests CPGs likely play an important role in human walking, but their function is heavily dependent upon supraspinal control and regulation (Petersen et al. 2001). This may be related to the complexity of the human walking pattern, which necessitates more input from the brain and cannot be effectively controlled through spinal circuitry alone. Additionally, sensory feedback is vital for tuning and regulating the activity of the locomotor CPG. Sensory signals may directly act upon the motoneurons, contribute to corrective reflexes following a perturbation, and/or provide error signals that inform the brain of differences between the actual and intended movement, which can be used to update and improve the performance of future movements (Nielsen 2003). Essentially, the biomechanical complexity of the healthy human walking pattern necessitates a complex neuromotor control strategy.

2.2 Mechanisms of Energetic Efficiency

One of the essential principles of human locomotion is to minimize metabolic energy expenditure. Healthy humans innately self-select a walking pattern that is essentially energetically optimized and even small perturbations away from this pattern, such as increases in step length or changes in speed, lead to increases in energy cost (Saibene and Minetti 2003). Healthy human walking employs two major mechanisms to minimize energy expenditure: (1) provide limb stability and reduce muscle activity via manipulation of the GRF and use of gravitational potential energy; (2) optimize the necessary muscle activity through utilizing primarily eccentric muscle action, exploiting elastic energy storage in tendons, using biarticular muscles to transfer energy throughout the limb, and leveraging the stretch-shortening cycle to produce muscle force as effectively as possible.

Generally, there are three types of muscle action: (1) concentric action – the muscle shortens and performs positive mechanical work; (2) eccentric action – the muscle lengthens and performs negative mechanical work; (3) isometric action – the muscle is maintained at a static length and no mechanical work is performed. Eccentric lengthening is the most energetically efficient form of muscle action, with isometric action being slightly more energetically taxing, and concentric shortening consuming by far the most metabolic energy (Gage et al. 2009). Minimizing muscle activity is of course the best way to reduce metabolic cost, though. During the normal gait cycle, muscle activity during stance phase is reduced through manipulation of the line of action of the GRF to produce external joint moments, which can provide limb stability without direct muscle action. The plantarflexion-knee extension couple is one important part of the healthy gait cycle where this principle is applied. Basically, during the middle of stance phase, eccentric action of the triceps surae muscle group slows the forward progression of the tibia and directs the GRF vector in front of the knee joint. This generates an external knee extension moment, which stabilizes the joint against the thick posterior knee capsule without necessitating activity from the knee extensor musculature (Figure 1A). (Gage et al. 2009; Peterson and Walton 2016.) Similarly, later in stance as the body's COM moves over the stationary foot, the GRF vector is guided slightly behind the hip joint, producing an external hip extension moment. This again acts to stabilize the joint against the anterior ligamentous capsule, which enables the hip extensor muscles to deactivate (Gage et al. 2009). Thus, energy is conserved during stance phase through clever manipulation of the GRF to produce limb stability with minimal muscle activity. During swing phase, energy consumption is reduced by exploiting gravitational potential energy to swing the leg. Research indicates that humans self-select a comfortable walking speed and cadence to facilitate just enough limb flexion for ground clearance and to enable the leg to swing with only a minimal amount of extraneous muscle activity (Nielsen 2003; Griffin et al. 2003). When subjects are asked to walk at different speeds or are perturbed away from their comfortable walking pattern through changes to parameters such as step length or cadence, the metabolic cost of locomotion only ever increases (Saibene and Minetti 2003), which indicates healthy humans have an innate ability to self-optimize their own walking pattern.

The healthy gait pattern also aims to utilize the muscle action that is necessary during walking as effectively and efficiently as possible. Muscles primarily perform eccentric action during normal walking, as this is the most metabolically efficient (Gage et al. 2009). Eccentric action only acts to absorb energy on its own, though, and so is insufficient to produce the positive propulsive power necessary to maintain the inverted pendulum pattern of normal walking. Importantly, muscles are not the only structures within the body capable of generating propulsion. The action of the triceps surae muscle group during midstance, discussed above, not only acts to guide the GRF, but also functions to store elastic energy in the large and compliant Achilles tendon. This energy is then released during push-off to produce a burst of positive propulsive power. Evidence suggests the Soleus is particularly important in regulating the stiffness of the Achilles tendon during gait via essentially isometric muscle action during early and mid-stance (Cronin et al. 2013). In this way, the calf muscle-tendon unit acts like a clutch and spring during walking, with the efficient eccentric/isometric action of the triceps surae working to store energy in the elastic Achilles tendon spring that is subsequently released to generate the necessary propulsive power while using minimal metabolic energy. (Sawicki et al. 2009.) The efficiency of the work performed at the ankle joint is substantially better than would be expected if all of the positive work was performed through concentric muscle action, which suggests that this storage and release mechanism using the Achilles tendon accounts for a large proportion of the work performed at the ankle joint and plays a significant role in the energetic efficiency of the healthy gait pattern (Sawicki and Ferris 2008). Some concentric muscle action does certainly need to be performed during normal walking, however. Notably, though, even this activity can be augmented to produce force as effectively as possible through leveraging the stretch-shortening cycle. The stretch-shortening cycle indicates that the force-generating capacity of concentric muscle action is enhanced if the contraction is preceded by a stretch (Komi 2003, p. 184-200). During normal walking, most of the major muscle groups are stretched just prior to contracting, which augments the force produced by the muscle and likely permits a lower number of muscle fibers within the muscle to become active and consume energy compared to if the contraction was performed with no preceding stretch. Examples of this include the hamstrings being stretched at the end of swing phase via the inertia of the swing prior to their contraction at ground contact and the plantarflexors being stretched throughout midstance via the GRF before their contraction at the end of stance phase. (Gage et al. 2009.) Thus, the muscle activity during the healthy human walking pattern is optimized to produce all of the necessary force while consuming the minimal amount of metabolic energy.

Crucially, the mechanisms that underly the metabolic efficiency of healthy gait are dependent upon the intricate, coordinated actions of the neuromotor system. Muscles must be activated at the proper times and in just the right ways in order for all of these mechanisms to remain effective (Nielsen 2003). Further, human walking is not simply a stereotyped movement pattern, and gait, as well as the neuromotor activity that generates it, must be adaptable to changes in the environment or context in which it is performed (Ivanenko et al. 2009). The higher motor centers within the brain are essential in facilitating the energetic efficiency and adaptability of the human walking pattern. Lesions or damage to these higher motor centers, then, can have devastating effects on the walking ability of those affected.

3. CEREBRAL PALSY

An injury or lesion to the developing brain, which later manifests as motor impairments in the individual describes the condition termed Cerebral Palsy (CP). CP is the most common cause of childhood-onset lifelong disability (Graham et al. 2016). Not a disease entity in the traditional sense, CP describes a clinical classification that encompasses a multitude of heterogeneous motor impairments that share a similar cause; that cause being the damage incurred to the brain in the early years of development. The formal definition of Cerebral Palsy, outlined by an international panel of scientists, therapists, and clinicians, is as follows:

> "Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems." (Rosenbaum et al. 2006.)

CP excludes transient disorders, as well as progressive neurodegenerative diseases. However, the clinical symptoms of CP often change and evolve with time and age of the individual, as well as with therapy (Rosenbaum et al. 2006; Morgan and McGinley 2018). While CP is fundamentally a motor disorder with a neurological origin, the mobility and postural limitations in CP are often accompanied by additional impairments, such as cognitive or sensory deficits as well as epilepsy (Odding et al. 2006). This section will detail the various classification systems for CP as well as describe the skeletal muscle dysfunction that develops as a consequence of the initial brain lesion and how these abnormalities affect functional ability. The methodology and clinical importance of gait analysis in CP will be considered. An analysis of the deviant gait patterns that characterize CP will finish the section.

3.1 Epidemiology and Classification

The prevalence of CP is often reported as 2-3 cases per 1000 live births, with the most recent report from the Autism and Developmental Disabilities Monitoring (ADDM) network concluding a prevalence of 3.1 per 1000 live births in the USA (Christensen et al. 2014). Premature birth is the most-important risk factor for the development of CP. Damage or injury to the developing brain underlies 90% of CP cases, with only a small proportion of CP attributed to abnormal brain development (Morgan and McGinley 2018). The timing of the brain lesion in CP can occur in the prenatal (before birth), perinatal (during or around the time of birth), or postnatal (after birth and young infancy) periods. There is currently no consensus on the cut-off age for CP; however, it is assumed that the disturbance in the brain occurred before the affected task has developed (e.g., walking) (Rosenbaum et al. 2006). Common mechanisms that can underly the brain lesions in CP are periventricular leukomalacia (death of white matter tissue surrounding fluid-filled ventricles in the developing brain), birth asphyxia (suffocation during delivery that limits oxygen delivery to the brain), and postnatal infections or injury. Inflammation is suggested as a common final pathway that may underlie the permanent brain injury in CP (Morgan and McGinley 2018). The exact cause of the brain injury in CP is often unknown, however, with over 30% of CP cases having no discernable etiology. Importantly though, the timing of the brain lesion (prenatal, perinatal, or postnatal) can influence the musculoskeletal deformities presented in the patient as well as the associated co-morbidities (Wimalasundera and Stevenson 2016).

As CP is an umbrella term that describes a group of often heterogenous motor and functional impairments, further classification of each patient into distinct categories that better clarify their individual symptoms is important (Rosenbaum et al. 2006). Classification systems in CP group patients based on the type and topographical distribution of their motor abnormalities. The major types of CP are spastic, dyskinetic, and ataxic and each describe a unique dysfunction in movement and/or muscle tone. Spastic CP is by far the most common form, making up 85-90% of all CP cases (Wimalasundera and Stevenson 2016). Basically, spasticity describes a velocity-dependent overactivation of the stretch reflex in response to a passive muscle stretch (Lance 1980). This irregular spike in muscle activity contributes to the increased resistance to stretch (hyper-resistance) that characterizes muscles in CP. Section 3.2, which deals with skeletal muscle dysfunction in CP, will review spasticity and its contribution to hyper-resistance in more depth. However, for the purposes of classification, spasticity will simply describe the hyperreflexia that typifies the motor patterns of the dominant group of CP patients. Those with dyskinetic CP are characterized by involuntary uncontrolled movements. Dyskinetic CP is often further subdivided into additional categories of choreoathetotic (rapid, unorganized movements of proximal muscles and face in conjunction with slow writhing movements of the distal muscles) and dystonic (co-contraction of agonist and antagonist muscles) (Gulati and Sondhi 2018). Loss of orderly muscular coordination is the identifying motor impairment in the small proportion of those with ataxic CP (SCPE 2000). Many patients with CP may display a mixed type and present with a combination of the above motor impairments. However, it is recommended that cases be classified by their dominant tonal or movement abnormality (Rosenbaum et al. 2006).

Along with motor impairment type, CP is also classified by anatomical distribution. The small fraction of patients with dyskinetic and ataxic CP present with whole-body involvement with the upper extremities typically more affected than the lower limbs (Pakula et al. 2009). Thus, further division based on topographical distribution is unnecessary in these types. Those with spastic CP, however, show varying levels of impairment across different body regions, necessitating classification systems based on anatomical distribution of the motor impairment. The terms hemiplegia, diplegia, and tetraplegia or quadriplegia were previously used in the literature to describe the most-affected body regions. However, these terms rank only the extremities and fail to describe the involvement in the trunk and head regions. Further, the groups and the boundaries separating them are imprecisely defined, as different researchers and clinicians may use the same term while denoting different distributions (Rosenbaum et al. 2006; Paulson and Adams 2017). The terms unilateral or bilateral are now preferred to describe the topographical distribution of the motor impairment (SCPE 2000). Unilateral CP, in which one side of the body presents with substantially more pronounced impairments than the other, is the most common type (Reid et al. 2015). These classifications are more precise, although asymmetry in motor function within both classification groups may blur the dividing line between the two (Rosenbaum et al. 2006).

Classifying functional ability of each individual with CP using objective measures is also essential (WHO 2001). The gross motor function classification system (GMFCS) has been widely adopted to evaluate lower-limb function and has become the principal method to categorize motor disability level in CP (Palisano et al. 1997; Rosenbaum et al. 2008). Mobility is the primary focus of the GMFCS, which groups patients into one of five levels based on self-initiated movements, with emphasis on walking or wheeled mobility (Figure 2). Level 1 denotes minimal disability, whereas level 5 signifies total dependence on equipment or care givers for ambulation. The GMFCS level is independent of the motor-type classification or anatomical distribution of the patient (Wimalasundera and Stevenson 2016). Two versions of the GMFCS are available, one for younger children from ages 6-12 and another for older children of 12-18 years. While no version of the GMFCS has been created or validated for adults with CP, it is still commonly used to classify functional ability in older patients. Approximately 60% of children with CP are categorized in GMFCS levels I and II and thus present mild disabilities, retaining the ability to walk without aids (Morgan and McGinley 2018). Functional scales, such as the GMFCS, have enhanced study design and interpretation as well as encouraged mobility-related goal setting in the clinical setting (Damiano et al 2009).

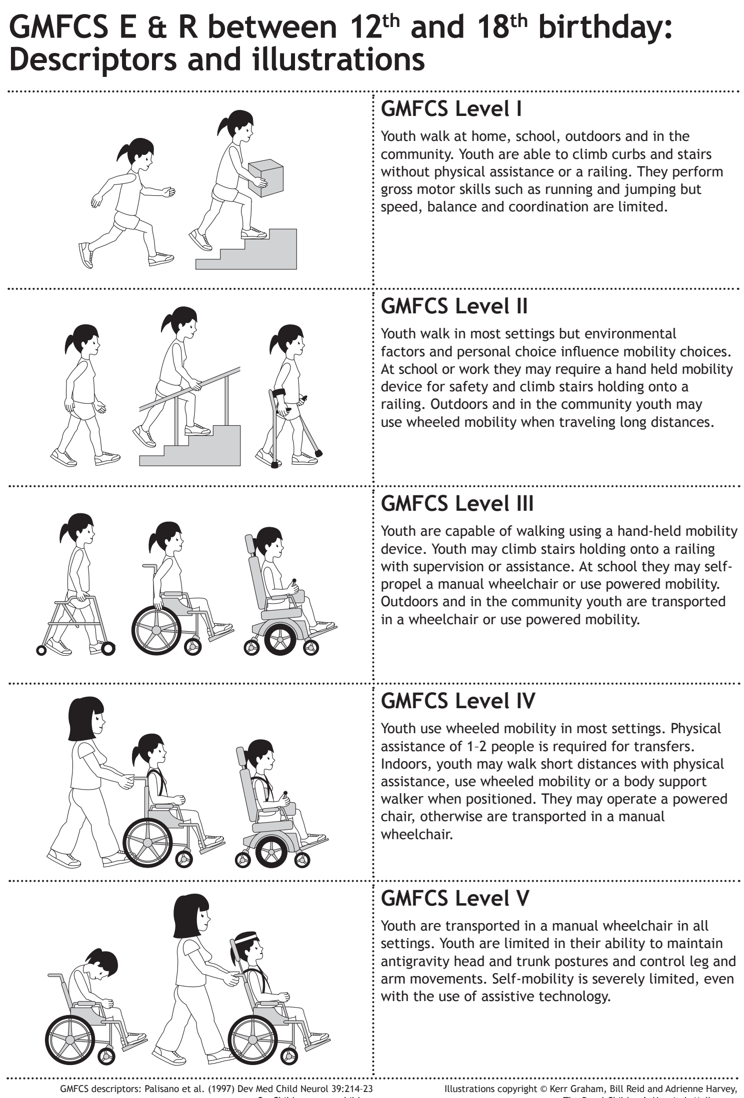

Figure 2: Illustrations of the five levels of the Gross Motor Function Classification System (GMFCS) along with their written descriptions. The GMFCS is used to classify the mobility deficiencies in children with Cerebral Palsy (CP). The GMFCS valid for ages 12-18 is shown. Source: www.Canchild.ca

3.2 Altered Skeletal Muscle Mechanics and Control

While the underlying cause of CP is neurological, the defining feature of disability in CP is musculoskeletal dysfunction and deformity. Skeletal muscle of those with CP shows stark abnormalities that limit its function and force-producing capabilities (Figure 3). Muscles are both shorter and smaller in CP and contain fibers of reduced diameter (Graham et al. 2016). The cross-sectional area, which is directly related to the force production of a muscle, is similarly reduced in CP. Due to their short length, the muscles in those with CP have a limited range over which to develop force and power, as well as a reduced shortening speed. (Barrett and Lichtwark 2010.) Additionally, muscle recruitment in CP is irregular, characterized by abnormal timing and reduced amplitude of neural signals to the muscles leading to impaired selective motor control (Morgan and McGinley 2018). Reduced neuromuscular inhibition may underlie the impaired motor control and coordination in CP, as well as the increases in co-contraction of agonist and antagonist muscle groups common in these patients (Graham et al. 2016). While healthy infants and young children generally show increased co-contraction to prioritize postural stability over mobility early in life, this diminishes as children mature and their movement patterns become more fluid. In CP, however, this increased co-contraction persists throughout childhood and into adulthood (Leonard et al. 1991). Similarly, muscle-length growth is driven by stretch in maturing children. While the bones grow during sleep, the muscles grow when children awake and move their bodies. In this way, muscles grow in tandem with the bone. The musculoskeletal dysfunctions discussed above as well as later in this section limit the ability of children with CP to move and play normally, however, leading to muscle growth deformities as the muscle is unable to keep up with the rate of growth of the bone (Gage and Novacheck 2001). These shortened and stiff muscles are termed contractures and greatly limit joint range of motion and functional ability in CP (Chan and Miller 2014). Further, just as muscle growth is influenced by the growing bones, so too do muscles, and the forces they exert, influence the shape of bones as they grow. Muscle contractures pulling on growing bone can lead to bony deformities such as hip subluxation, the torsion of long bones, and foot deformities, all of which are common in CP (Gage and Novacheck 2001). In all, children and adults with CP have considerable motor control deficits and show a significantly reduced ability to produce maximal force and rapid power (Wiley and Damiano 1998; Moreau et al. 2012).

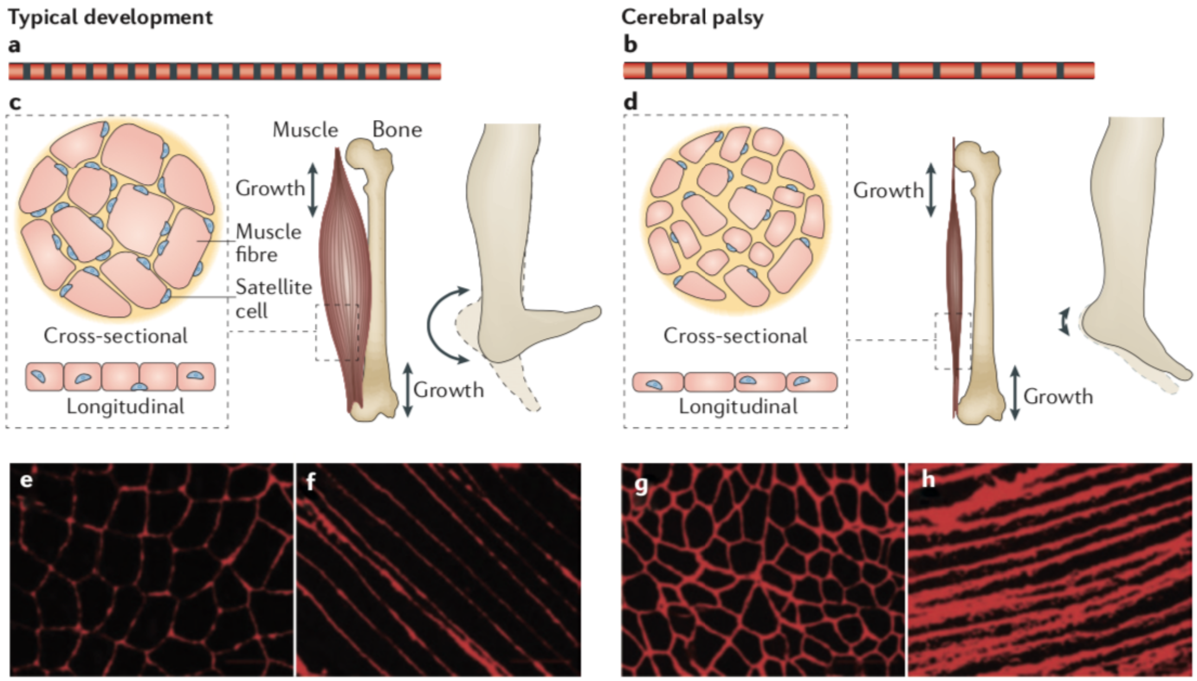

Figure 3: Morphological and Structural Alterations in Skeletal Muscle of Children with CP Compared to Typically Developing Children. **A**,**B**: Schematic illustration displaying the lengthened sarcomeres in CP (**B**) compared with the shorter sarcomeres observed in typically developing children (**A**).**C**, **D**: Graphics showing the morphological muscular deformities in CP and their effect on muskoloskeletal development. Typical development (**C**) compared to CP (**D**). Notice the diminished fiber CSA and reduced satellite cell number, as well as the reduced muscle size and muscle belly length that limits joint ROM and induces abnormal bone growth in CP compared to TD. **E–H**: Immunohistochemical staining of muscles for laminin, a molecular component of the extracellular matrix (ECM). **E** and **G** show cross-sections while **F** and **H** show longitudinal sections. The ECM content of the muscles of children with CP (**G**, **H**) is substantially amplified compared with typically developing children (**E**, **F**). Taken from Graham et al. 2016.

As briefly discussed in the previous section, the muscles of those with CP show a stark increase in resistance to passive stretch, termed hyper-resistance. Hyper-resistance in CP is multifaceted and consists of both neural and non-neural components (Van den Noort et al. 2017). Spasticity (the overactivation of the stretch reflex) and background muscle tone make up the neural component, whereas the abnormal mechanical properties of the muscle that influence its elasticity make up the non-neural component. Spasticity arises from abnormal spinal processing of signals from the stretch-sensitive muscle spindles within the muscle (Trompetto et al. 2014). As a result of the brain lesion during development, the inhibitory motor circuits in the spinal cord are deficient in spastic patients, leading to tonic overstimulation of the excitatory stretch reflex pathways (Nielsen et al. 2005). Thus, when a spastic muscle is stretched, it becomes active and contracts, adding to the resistance against the stretch. The amount of muscle activity is dependent on the velocity of the muscle stretch, with higher stretch velocities leading to greater muscle activation and subsequently more resistance (Pandyan et al. 2005). Patients with CP can also exhibit elevated background muscle activity, even in the absence of a stretching stimulus. This involuntary activity also contributes to hyper-resistance and seems to originate from unprompted synaptic input to the motor neuron pool driven by the damaged central nervous system in CP (Forman et al. 2019). It is important to consider, however, that the neural components of hyper-resistance, especially spasticity, have been hotly debated in the literature, and the techniques used to measure them are often not congruent with their underlying neurological mechanisms or key clinical features (Malhotra and Pandyan 2009). Further, the non-neural component of hyper-resistance seems to be more important in producing the amplified resistance to stretch and elevated muscle stiffness in CP than the neural components (Bar-On et al. 2015). The muscles of those with CP are intrinsically stiffer than normal. Hypertrophy of the extracellular matrix as well as an increased collagen content explain the increased passive muscle stiffness in CP and make up the non-neural component of hyper-resistance (Smith et al. 2011; Mathewson and Lieber 2015). Notably, while hyper-resistance certainly contributes to the functional limitations of those with CP and may influence the development of specific gait deviations (Bar-On et al. 2015), other motor impairments, such as muscle weakness, likely limit function and mobility to a greater degree (Ross and Engsberg 2007).

There are various tissue-level adaptations that underlie the functional deficits of skeletal muscle in CP. The most dramatic change in muscle structure occurs at the sarcomeric level, as is evident in those with contractures, whose muscles contain sarcomeres that are almost twice the normal length and much fewer in number (Smith et al. 2011; Mathewson et al. 2015). Paradoxically, the sarcomeres (the functional unit of muscle contraction) are highly lengthened while the muscle itself is shortened. These abnormally stretched sarcomeres generate lower active force and contribute to the muscle weakness in the CP population (Mathewson and Lieber 2015). During normal development, sarcomeres are added in series allowing the muscle fiber to grow in length while maintaining a close-to-constant sarcomere length. Children with CP, however, may have an impaired ability to add sarcomeres in series causing the lengthened sarcomeres even in shorter muscles (Graham et al. 2016). The geneexpression profiles of muscle in CP also differ from healthy muscle, characterized by increased expression of genes related to production of the extracellular matrix and altered expression of excitation-contraction coupling genes (Graham et al. 2016; Mathewson and Lieber 2015). Finally, the muscles of CP patients contain fewer than normal satellite cells – the stem cells within the muscle. Satellite cells are crucial for the growth and regeneration of skeletal muscle (Relaix and Zammit 2012). Thus, their reduced population is likely to contribute to the smaller muscle fiber size, inability to add sarcomeres in series, and even to the excess extracellular matrix in CP muscle (Graham et al. 2016).

These skeletal muscle dysfunctions at the tissue and whole-muscle level substantially limit functional performance in CP. Anaerobic endurance and peak muscle power are both subnormal in CP compared with typically developing children (Parker et al. 1992). Children with CP show more signs of muscle fatigue than their typically developing counterparts after brief walking periods as well (Eken et al. 2019). Importantly, the lower-limb muscle weakness in CP is correlated to reduced walking ability and gross motor function, with the strongest correlation existing with ankle plantar flexion strength (Eek and Beckung 2008). The ankle muscles are crucial in maintaining the inverted-pendulum motion of normal gait and in producing positive propulsive power at push-off (see section 2). In CP, however, the muscles surrounding the ankle often display some of the most severe impairments, which can greatly hinder gait and functional ability in these patients. Of the plantarflexors, the muscle fascicles in the gastrocnemius muscle are shorter and the Achilles tendon is lengthened in CP (Martín Lorenzo et al. 2018). Even in those high-functioning children without contracture, the plantarflexor muscles show increased passive muscle stiffness, as well as increased fascicle pennation angles compared with typically developing children (Kruse et al. 2017, 2018). In addition to the short and weak plantarflexor muscles, it has also been shown that the Achilles tendon moment arm length is reduced in CP (Kalkman 2018; Gallinger et al. 2020), which further compromises the ability to produce torque at the ankle during push-off. These mechanical changes reduce the functional ability of the plantarflexors in CP, as these muscles produce only a third of the positive lower limb work during gait compared to the usual two thirds (Olney et al. 1990). Further, the stiffness of the plantarflexors is linked to the severity of the motor impairment and corresponds to the development of deviant gait patterns (Boulard et al. 2019).

The ankle dorsiflexors also show deficiencies in CP, with research showing reduced muscle thickness, cross-sectional area, and fascicle length of the tibialis anterior (TA) muscle in the affected leg of those with unilateral CP compared to their less affected leg (Bandholm et al. 2009; Bland et al. 2011). Further, some research indicates that patients with unilateral CP show a sustained reduction throughout childhood in the common drive from the motor cortex to the spinal motoneuron pool controlling the TA muscle in their affected leg compared to their unaffected leg or to typically developing children (Petersen et al. 2013). The age-related increase in common drive to the ankle dorsiflexors during healthy development is essential for refining the control of the ankle muscles during gait (Petersen et al. 2010), and so the failure to increase common drive in those with CP suggests impaired development of ankle muscle motor control. The mechanical changes in TA architecture and deficits in TA neuromotor control are both related to aberrant gait kinematics, such as greater foot drop and reduced dorsiflexion (Bland et al. 2011; Petersen et al. 2013). The ankle muscles as a whole in CP show significantly reduced specific tension (torque/unit area) as well as reduced magnitude of muscle activity as measured by surface EMG (Elder et al. 2003). To conclude, the general skeletal muscle adaptations, as well as the specific dysfunction of the ankle muscles markedly affect mobility and function in CP patients (Ostensjø et al. 2004).

3.3 Gait in Cerebral Palsy

As previously mentioned, the majority of children with CP are ambulatory and can walk independently (Morgan and McGinley 2018). The lower-limb weakness and musculoskeletal deformities present in CP, however, lead to abnormal gait patterns that are markedly more energetically taxing than normal walking (Rose et al. 1990). Additionally, these deviant gait patterns place significant strain on certain muscle groups, forcing the muscles to work close to their maximal capacity (Dallmeijer et al. 2011). Thus, simply walking can be an exhausting activity for CP patients. Mobility challenges are likely strongly linked to the reduced levels of physical activity performed by children and adults with CP (Bjornson et al. 2007; Nieuwenhuijsen et al. 2011).

One of the essential pillars in the management and treatment of gait dysfunction in CP is clinical gait analysis (CGA). CGA describes the process of recording and analyzing the biomechanical metrics of a patient's gait in order to support clinical decision-making (Baker et al. 2016). Normally, optoelectronic tracking systems, which track movements using markers placed on the skin, are used to quantify gait kinematics. Kinematics refer to the movement of the various body segments and the accompanying joint angles. Complex 3-dimensional movements are commonly divided into their 2-dimensional components based on planes which divide the body. Flexion-extension movements occur within the sagittal plane, adduction-abduction within the frontal plane, and internal-external rotations within the transverse plane. In addition to optoelectronic systems, CGA often employs force plates imbedded into the ground to measure the GRF during walking. Using anthropometric and inertial body metrics, as well as the kinematic data, it is possible to calculate gait kinetics through inverse dynamics. Kinetics represent the forces applied by the body segments during gait and include the joint moments and joint powers. Electromyography (EMG) is also regularly used in CGA to quantify the magnitude and timing of muscular activity during gait. (Armand et al. 2016.)

The major aim of CGA in CP is to assess the severity, extent, and nature of the gait deviations to aid in successful prescription of treatment (Baker et al. 2016). Gait deviations can arise as a consequence of underlying neuromuscular or musculoskeletal problems, or as compensatory mechanisms to cope with the primary impairment. The crux of CGA, then, is to differentiate between the two in order to uncover the heart of the gait dysfunction (Sangeux and Stephane 2015). Compensatory deviations should resolve spontaneously once the primary impairment is dealt with (Davids and Bagley 2014). CGA has proven beneficial in refining surgical planning in CP, and pre-operative gait analysis is associated with improved post-operative outcomes in terms of gait and mobility (Lofterød et al. 2007; Filho et al. 2008). Additionally, CGA allows for the objective evaluation of gait changes after a treatment or intervention (Armand et al. 2016). The data that CGA provides helps to guide the planning of management strategies in CP, and its utility in influencing CP management is now widely recognized.

The high variability of clinical presentation in CP results in a range of pathological gait patterns. Classification systems to group gait patterns in CP have been developed to facilitate communication amongst clinicians and researchers and assist in the development of management strategies (Sangeux and Stephane 2015). Gait categories can quickly convey a general snapshot of an individual patient's gait impairments (Dobson et al. 2007). Generally, the walking patterns of those with unilateral CP are characterized by more pronounced distal impairment, whereas gait patterns in bilateral CP comprise more proximal involvement (Rodda and Graham 2001). The first gait classification system was proposed for unilateral spastic CP, and included four groups that were separated based on location and severity of impairment across the affected lower limb (Winters et al. 1987). Rodda and Graham (2001) built upon these groupings and added classifications that described the gait of those with bilateral CP – the gait pattern classifications for unilateral CP from Rodda and Graham (2001) are shown in Figure 4. Only unilateral CP gait patterns are described here because all of the participants in this thesis had unilateral CP, and so these classifications were most relevant.

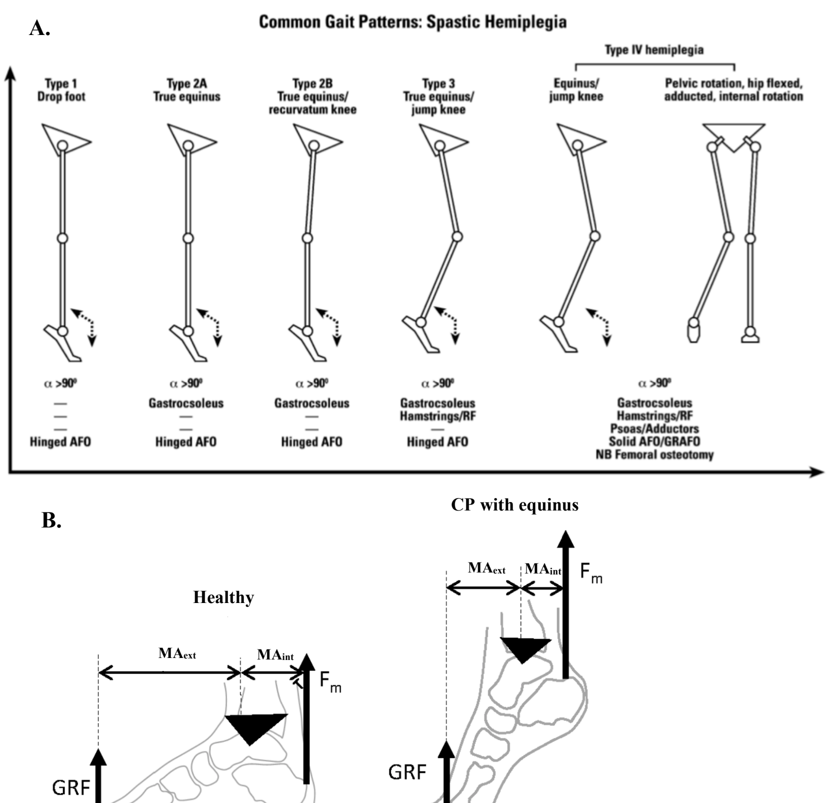

Figure 4: Deviant Gait Patterns in unilateral Cerebral Palsy. A. Gait pattern classifications from Rodda and Graham 2001 for unilateral CP (see their text for full descriptions of each gait pattern). Generally, gait patterns in unilateral CP are characterized by distal impairment with dysfunction of the more proximal joints becoming more apparent as the severity of the deviant gait pattern increases. **B.** Equinus gait as a method to shorten the external moment arm while walking. The healthy ankle is shown on the left while the ankle on the right displays a CP patient with a shortened internal moment arm (MA_{int}). Equinus gait, then, acts as a way to shorten the external moment arm (MA_{ext}) so as to reduce the magnitude of the external moment and release the high strength burden placed upon the triceps surae muscles. F_m: muscle force. Modified from (Kalkman 2018).

A deep dive into the clinical roots and biomechanical manifestations of all of the gait patterns that characterize unilateral CP is out of the scope of this review; however, a brief discussion of equinus gait (Type 2) is warranted as it is the most common gait dysfunction type in unilateral CP. Equinus gait involves excessive plantarflexion during stance as well as swing phase leading to a “toe walking” pattern. The cause of equinus is typically attributed to spasticity or contracture of the triceps surae muscle group (Rodda and Graham 2001). However, it is now suggested by some researchers that equinus gait is adopted as a compensatory mechanism to account for the reduced length of the Achilles tendon moment arm in CP (Kalkman 2018). The mechanical advantage describes the ratio of the internal to the external moment arm of a joint, and this ratio determines the internal muscle force necessary for overcoming an external resistance (Lee and Piazza 2009). The short Achilles tendon moment arm in CP reduces the mechanical advantage of the ankle joint, which places a high strength burden on the already weak plantar flexor muscles. Thus, it is theorized that CP patients walk in equinus in order to reduce the length of the external moment arm and equalize the mechanical advantage of the ankle during gait (Kalkman 2018; Figure 4B). Further, some evidence suggests the maturation of healthy feedforward motor control of the ankle muscles during gait is impaired in CP, which may be related to the development of equinus gait patterns (Lorentzen et al. 2019). Basically, children with CP do not show the age-related decline in dorsiflexor muscle activity while walking in equinus that is present in healthy individuals of various ages when they voluntarily walked on their toes. Healthy motor control is thought to be built upon a feedforward system, in which the sensory consequences from a movement are predicted before the movement is carried out and this prediction is compared to the real sensory feedback from the motor task (Krakauer et al. 2019). As the movement pattern is learned and optimized, the difference between the predicted and actual sensory feedback is reduced until eventually the predicted results of the movement become reliable enough that the real afferent feedback is no longer essential for the successful completion of the movement (Wolpert and Flanagan 2016). The age-related decline in co-contraction of the ankle muscles during “toe walking” in healthy individuals is likely related to the development of this sophisticated prediction-based motor control of gait. Co-contraction may be an age-dependent control strategy that prioritizes stability at a joint, but is reduced as sophisticated motor control programming is learned. Patients with CP, however, continue to display this elevated antagonist co-contraction during equinus gait potentially due to an inability to synthesize the motor and sensory signals necessary for the optimization of this feedforward motor control because of their underlying CNS lesion. (Lorentzen et al. 2019.)

It is important to recognize that gait deviations in CP lie on a continuum and these gait classifications are a simplification of the complex and unique walking patterns exhibited by any individual CP patient (Armand et al. 2016). Further, these classifications often only account for deviations in the sagittal plane, limiting their application in the planning of management and treatment. Finally, there is little evidence to support the links between classification groups and the principal impairments in CP, such as contractures or hyper-resistance, making the groupings arbitrary and less meaningful for clinicians. (Dobson et al. 2007.) Therefore, gait classifications are best used to streamline communication rather than facilitate clinical decision-making. To devise an individualized management plan that integrates all of the complexities of a patient's gait pattern, clinicians prefer to isolate biomechanical deviations at single joints and link these to the underlying impairments (Sangeux and Stephane 2015).

CGA and gait classifications are less applicable in dyskinetic and ataxic patients as these CP subtypes present variable movement patterns, making their gait challenging to assess and characterize (Baker et al. 2016). Spastic gait patterns, in contrast, are relatively consistent from stride-to-stride and from day-to-day. Long-term alterations in mobility can occur with age, however. Walking patterns in spastic CP typically degrade from "toe walking," which involves exaggerated plantarflexion, to patterns characterized by excessive hip and knee flexion, which eventually evolve into "crouch gait" (Rodda and Graham 2001). Increases in body weight (BW), accompanied by decreases in ankle strength and range of motion as children with CP mature, result in the development of less-functional gait patterns (Bell et al. 2002). Adults with deteriorated walking function also report greater frequency and intensity of pain in daily life, as well as reduced balance (Opheim et al. 2009; Benner et al. 2017). The development of crouch gait patterns is associated with higher levels of fatigue and lower quality of life in adults with CP as well (Lundh et al. 2018). Thus, treatment in CP is centered on enhancing functional mobility to improve participation and quality of life throughout the lifespan.

4. IMPROVING GAIT AND FUNCTION IN CEREBRAL PALSY

As there is currently no cure for CP, symptom management is crucial and helps to limit the negative effects of the motor impairments on CP patients' lives. CP treatment can be split into two main categories: invasive treatments and physical therapy. Invasive treatments, such as orthopedic surgery, attempt to remedy the mechanics of the joints whose function has been compromised by the abnormal musculoskeletal development in CP. Additionally, invasive pharmacological injections and even occasional neurosurgical procedures are used to treat excessive muscle tone and spasticity. Physical therapy is an essential part of CP management and aims to improve patients' functional abilities through exercise interventions or specific movement training. (Damiano 2006.) A great deal of therapeutic research and clinical practice in CP is focused specifically upon improving gait ability through gait training (Booth et al. 2018). This therapy strategy centers on theories of motor learning to augment the gait pattern of the patient towards a healthier and more functional pattern via targeted walking training.

CP management has evolved over the past 20 years with the inception of the International Classification of Functioning, Disability, and Health (ICF). The ICF is a framework that recognizes the multi-dimensionality of disability and splits the aspects that affect a person's level of function into five distinct components: body functions and structures, activities, participation, environmental factors, and personal factors (WHO 2001). The ICF emphasizes the function of the individual and has helped to shift the focus of CP management from treatment of specific impairments to a more holistic view that integrates all facets of a CP patient's health and environment, to form a treatment strategy that improves their independence, community participation, and overall quality of life (Novak et al. 2013; Franki et al. 2012; Damiano et al. 2009). There is currently no definitive standard of care for CP, however. Consequently, the type, timing, and sequencing of treatments, as well as their intensity and frequency, can vary dramatically (Damiano et al. 2009). This variability is compounded by the heterogeneous nature of CP, which makes finding the optimal treatment route for each individual patient a complex and unique puzzle.

This section will begin with a brief discussion on invasive treatments in CP, but will focus primarily on the non-invasive treatment of CP, with specific attention paid to gait training as a means to improve walking outcomes. A discussion on motor learning will preface the gait training subsection as a means to explore the therapeutic rationale underlying gait training in patients with motor disorders such as CP.

4.1 Invasive Treatments

Throughout childhood and into pre-adolescence, a majority of children with CP (especially those lower-functioning individuals) will undergo some form of orthopedic surgery to correct the musculoskeletal deformities that inhibit their mobility. Muscle contractures and bony deformities can lead to lever-arm dysfunction in CP, which inhibits the effective utilization of the forces exerted by the muscles for movement. These deformities can progressively worsen with growth and age, and, if left unchecked, can develop into more serious conditions, such as joint dislocations. The general principle guiding orthopedic surgery in CP, then, is to preserve or restore lever-arm function. (Armand et al. 2016; Gage and Novacheck 2001.)

Management of excessive muscle tone and spasticity via pharmacological agents and neurosurgical procedures is also a significant aspect of CP treatment. Injection of Botulinum Neurotoxin-A (BoNT-A), a neurotoxin that blocks the release of acetylcholine from the neuromuscular junction effectively preventing muscular contraction, is used to manage local spasticity. BoNT-A is injected into the spastic muscle helping to temporarily relieve extreme muscle tone with the aim of inhibiting the development of fixed contractures and enabling enhanced therapy during the period of reduced tone. (Damiano et al. 2009.) Critically, because injection of BoNT-A blocks muscle contraction, this intervention can lead to muscular atrophy, with contractile tissue being lost and replaced by fat and/or connective tissue (Multani et al. 2019b). The long-term consequences of denervation atrophy from BoNT-A are currently not well understood (Armand et al. 2016). Selective dorsal rhizotomy (SDR) is a neurosurgical procedure that divides sections of the dorsal sacral roots of the spinal cord, interrupting the overactive reflex pathways that cause spasticity in CP (Gulati and Sondhi 2018; Rumberg et al. 2016). It is used as a permanent global treatment for excessive muscle tone in the lower limbs (Armand et al. 2016). Importantly, the level of functional improvement after SDR is heavily dependent on patient selection (Damiano et al. 2009). Thus, it is crucial to proceed with the operation only in those patients for whom it is best suited.

4.2 Physical Therapy

Physical therapy (PT) plays an essential role in the management of the motor impairments in CP and almost all CP patients undergo PT at some point in their lives. The major objectives of PT are to reduce the physical impairments and facilitate the activity and participation needs of the patient, to help them in achieving their goals (Das and Ganesh 2019). PT can help to increase muscle strength and aerobic conditioning, as well as enhance lower-limb coordination for the promotion of self-sufficient ambulation (Damiano et al. 2009). PT interventions in CP may involve training to specifically enhance motor control and functioning, such as task-specific training, goal-directed functional training, and gait training, as well as strengthening interventions, stretching, and general physical exercise (Novak et al. 2013; Das and Ganesh 2019; Franki et al. 2012). Historically, PT for those with CP involved therapists passively moving patients' limbs through a particular movement pattern, with the idea of stimulating motor and sensory pathways to enable patients to better perform the trained movement (Klimont 2001). However, with the onset of the ICF and the integration of motor learning principles into CP therapy, PT for CP patients has transformed and now involves much more active participation on the side of the patient and task-specific training (Damiano et al. 2009). Additionally, PT for CP can involve general physical exercise intended to improve metabolic and cardiovascular health and increase muscle strength. Improving or maintaining physical capacity through exercise is essential throughout the lifespan in CP, because inactivity can worsen the motor impairments, making participation in physical activity even more challenging, leading to a vicious cycle of progressive disability (Damiano 2006). Recently, exercise and physical activity guidelines concerning CP specifically were published and advocated programs that comprise cardiorespiratory endurance training and muscle strengthening and encourage fragmentation of sedentary time (Verschuren et al. 2016). Because those with CP may be deconditioned due to their motor impairments and habitual inactivity, low-intensity, short training bouts spread throughout the day/week may be best to ease these individuals into the exercise program. (Verschuren et al. 2016). Endurance training, such as walking, running, and cycling, have shown positive improvements in aerobic capacity, anaerobic capacity, and muscle strength, as well as gross motor function and even quality of life in those with CP (Franki et al. 2012).

Strength training has been investigated fairly extensively as a means to strengthen the inherently weak muscles in those with CP. Initially, researchers believed that strength training would lead to increases in spasticity and muscle stiffness, and thus was contra-indicated in CP management programs (Damiano 2006). This view has now been strongly challenged, however, with multiple reviews reporting the positive effects of resistance training on strength outcomes, without the worsening of any motor impairments (Franki et al. 2012; Dodd et al. 2002; Park and Kim 2014). Interventions that focus initially on single-joint isolation exercises and progressively transition to compound multi-joint exercises are recommended (Verschuren et al. 2016). Presently, short-term programs, small sample sizes, and often inadequate study designs make it difficult to conclusively state the benefits of strength training in CP, though. For instance, the effects of strength training on gait and mobility are inconclusive, as some studies have reported gait benefits as a result of resistance training (Park and Kim 2014; Andersson et al. 2003), while others report increases in strength without improvements in gait or function (Damiano 2014; Ross et al. 2016). Some researchers have speculated that focusing on slow, compound exercises intended to increase maximal strength has hampered the positive effects of strength training on function in those with CP. They propose that exercises targeted at the specific muscles used in gait and focused on improving ballistic-power generation would translate more effectively to walking improvements (Williams et al. 2019; Graham et al. 2016).

The shortened and stiff muscles in those with CP can greatly limit joint range of motion (ROM) and mobility. Because of this, PT programs often include stretching interventions meant to lengthen the muscles and improve joint ROM. There are moderate levels of evidence to support the benefits of stretching for improving joint ROM and muscle stiffness in CP (Novak et al. 2013; Franki et al. 2012). Stretching is most effective when combined with other therapies that concurrently increase muscle strength and/or reduce spasticity (Damiano et al. 2009). The purpose of stretching in CP is not only to increase ROM about a joint, but also to build new contractile material via serial sarcomerogenesis to enable improved force production over the newly acquired ROM (Kalkman et al. 2020). In order for stretching to be effective, the muscle tissue must receive a sufficient lengthening stimulus. Importantly, though, the high stiffness of the muscles in CP increases the relative stiffness ratio of the muscle to the tendon. Because the more compliant tissue will always take up most of the stretching stimulus when the joint is rotated, the tendons may be bearing the majority of the stretch in those with CP, while the stiff muscle is left unchanged. (Kalkman 2018.) Further, as the muscles in those with CP have lengthened sarcomeres and reduced satellite cell populations, it is possible that the lengthening capacity of CP muscle fibers is reduced (Boulard et al. 2019; Graham et al. 2016). Thus, it is currently unclear if stretching actually has the ability to positively remodel the muscle in CP.

The chief purpose of PT, and all interventions in CP, really, is to improve the patient's functional abilities, making them more capable of participating in their communities and enhancing their quality of life (Castelli and Fazzi 2016; Graham et al. 2016). Most of the management strategies for CP, however, are targeted towards the body structures and functions or activities levels of the ICF, rather than on the participation level. Unfortunately, the positive effects of interventions on the body structures and functions level have not been shown to translate upstream to the activities or participation levels (Novak et al. 2013; Franki et al. 2012). Put simply, we do not know whether treatments for impaired body structure and/or function actually improve participation and quality of life outcomes in CP. Further, there has been much less investigation into therapy interventions in adults with CP compared with children, even though progressive loss of function can hinder participation and quality of life to an even greater degree in older patients (Jeglinsky et al. 2010). Thus, more research into optimal treatment strategies to improve participation and quality of life across the lifespan is certainly needed.

4.3 Motor Learning

The shift from impairment-focused rehabilitation, which was directed at improving general deficiencies, such as muscular weakness and poor range of motion, to therapy centered on functional elements of activity and participation, based on the ICF framework, has led to a greater emphasis on improving activities essential to everyday life, such as walking (WHO 2001). Gait training has emerged as a therapeutic method to specifically target and improve walking ability in those with neurological disorders, such as CP, via focused, repetitive walking practice. The foundational reasoning supporting gait training rests in motor learning neuroscience, which advocates for the use of repetitive, task-specific training to augment movement patterns (Kleim and Jones 2008). Thus, before discussing gait training in CP, it is important to outline the fundamental principles of motor learning.

Motor learning can be generally defined as changes in the performance of a movement, or learning of a new movement, triggered by experience or practice (Krakauer et al. 2019). Research into motor learning seeks to investigate the mechanisms that underlie this progression of motor skill. Neuroscience research over the past few decades has begun to reveal the adaptive capacity of the central nervous system (Winstein et al. 2014). The neural circuitry within the brain is continuously being remodeled and reorganized to encode new experiences and enable behavioral change (Kleim and Jones 2008). This neural plasticity is achieved by altering genetic, molecular, and cellular mechanisms that influence synaptic dynamics and neural network formation. The nervous system has the ability to adapt and transform itself throughout the lifespan, but neural plasticity is heightened during the early years of life and development (Ismail et al. 2017). This is important in regard to CP, as most patients begin therapy early during childhood, and thus should have a high capacity for neural change that could lead to functional improvements. Contrastingly, CP occurs as a result of a permanent brain lesion before or shortly after birth, so it is possible that the neural plasticity pathways themselves may be deficient in these patients, leading to inherently reduced capacity for adaptation (Ismail et al. 2017; Kitago et al. 2013). However, those with CP, as well as other neurological disorders, have absolutely shown the ability to improve the performance of motor skills, exhibiting their capacity for motor learning (Booth et al. 2018; Novak et al. 2013).

In order to learn a new motor skill or augment the performance of an established movement pattern, new neural circuits must be created, or existing neural networks must be adapted, and these changes must become ingrained into the neuromotor system (Kleim and Jones 2008). Motor adaptation research, which examines how humans adjust already well-practiced movements, such as reaching or walking, to changes in conditions or task-constraints, has helped to illuminate some of the neural mechanisms underlying motor learning. These investigations have revealed that the cerebellum is the motor system's dedicated neural center responsible for recalibrating our behaviors (Krakauer et al. 2019). The cerebellum acts to predict the consequences of efferent motor commands and integrate these predictions, as well as the actual motor outcomes, back into a forward model that iteratively modulates itself to improve the performance of future movements (Manto et al. 2012). Motor adaptation is driven by errors in this predictive model, as the sudden difference between the predicted and actual consequences of a movement, due to the new movement conditions or task-constraints, prompt the motor system to adjust the movement pattern in order to resynchronize the predictions with the real motor outcomes (Roemmich and Bastian 2018). Additional investigations using reinforcement learning paradigms, which use reward feedback to analyze how subjects modify movements to optimize performance and thus maximize reward, have revealed insights into the importance of motor variability for motor learning. Human movement is inherently variable, and evidence now suggests that, rather than being simply a consequence of motor system noise, motor variability may actually represent purposeful exploration of motor space (Dhawale et al. 2017; Krakauer et al. 2019). During reinforcement learning protocols, motor variability is elevated initially as the subject explores different movement strategies, then reduced gradually as the motor system homes in on action variants correlated with high reward (Dhawale et al. 2017; Kitago et al. 2013). By creating a mental association between a certain movement or movement strategy and a subsequent reward, reinforcement learning can ingrain movement patterns, and the neural circuits that underlie them, for long-term use (Roemmich and Bastian 2018).

Neuroscience research affirms that successful motor learning requires specificity of training. Thus, in order to promote the development of enhanced movement patterns, the therapy must be task-specific, meaning the trained behavior should emulate the goal task (i.e., gait) as much as possible (Winstein et al. 2014). Specific neural adaptations and their associated behavioral changes rely on specific kinds of experiences and behavioral training (Kleim and Jones 2008). For gait in particular, task-specific training and high volumes of practice are crucial for learning new favorable walking patterns (Krishnan et al. 2019). Notably, though, while physical activity and exercise are not specific enough to induce lasting plastic changes that improve the performance of a task, being active may help to promote a fertile environment that supports neural adaptations from more-focused rehabilitation (Fernandes et al. 2017).

Repetition and practice are also essential to imprint the skill into the neural circuitry, making the acquired behavior more automatic and resistant to decay (Kleim and Jones 2008). Long-term potentiation (LTP), in which the same sets of neurons are activated concomitantly and repetitively, may be the mechanism by which these behavioral networks are made permanent by inducing synaptogenesis (Grasselli and Hansel 2014). Importantly, a patient must perform enough repetitions of the desired task to “get over the hump” to maintain the skill and make further gains outside of therapy (Kleim and Jones 2008). Due to their motor impairments, patients with nervous system damage and consequent loss of some functional abilities tend to develop compensatory strategies in order to perform some fundamental activities of daily living, such as walking. Those with unilateral brain lesions, for example, rely heavily on their less-affected side for completing basic movements. This can lead to atrophy and further degradation of function on the affected side. (Kleim and Jones 2008.) Repetitive use of these maladaptive, compensatory strategies induces plasticity and neural adaptations that need to be overcome or undone with later therapy. Unfortunately, however, often motor rehabilitation places a strong emphasis on function post-therapy, rather than movement quality. This can mean compensatory movements are reinforced during therapy if they lead to better functional outcomes (i.e., faster gait speed), even though these movements may be maladaptive and degenerative for function in the long-term. (Winstein et al. 2014; Kitago et al. 2013.) In order to inhibit the development of these negative compensatory mechanisms, therapy must focus not only on functional outcomes but also on quality of movement, and should encourage the use of the impaired body regions. Constraint-induced movement therapy (training that encourages the use of the impaired limb through constraint of the less affected limb during task performance) and bimanual intensive therapy (training of bimanual tasks that involve equal use of both limbs) have both shown promise for upper-limb rehabilitation in unilateral CP (Reid et al. 2015; Novak et al. 2013).

Training intensity also strongly influences the extent of experience-dependent neural plasticity, and training must be sufficiently intense in order to induce neural adaptations and behavioral changes. Training during therapy should be performed at the challenge threshold at which the skill breaks down above the threshold and is overly easy below it (Winstein et al. 2014). The concept of use-it-or-lose-it is important for neurorehabilitation, as it indicates that disuse of certain brain regions and/or networks may lead to their further degradation via long-term depression (LTD) and thus loss of function. Notably, though, experiments in sensory deprivation have shown that, rather than a degradation of tissue, lack of use leads to reallocation of cortical territory. Thus, functional recovery may be supported, at least in part, through the shift of novel functions to residual brain regions post-lesion. (Kleim and Jones 2008.)

Finally, the training program must be built around the patient's goals and the patient must be actively engaged during therapy. Training skills that are related to self-management or that are associated with the patient's quality of life (i.e., gait) are more likely to be valued by the patient, leading to higher levels of intrinsic motivation during training and more willingness to practice the skill outside of the training environment (Winstein et al. 2014). Motivation and attention are both essential to promote the highest levels of beneficial plasticity from training (Kleim and Jones 2008). So, acquiring a new motor skill (or improving deficient movement patterns) requires repetitive and intense task-specific training that is engaging and motivates patients as they progress towards their goal.

4.4 Gait Training

Gait training, then, integrates these motor learning principles, and acts as a means to improve pathological gait through intense and repetitive task-specific walking practice (Booth et al. 2018). While practicing the task of walking sounds fairly simple, the methodologies and training protocols that fit under the gait training umbrella can vary quite dramatically. For instance, gait training can be performed overground or on a treadmill and can incorporate partial body-weight support, in order to reduce lower-limb loading and facilitate an upright posture during gait. For those more functional patients who maintain the ability to ambulate independently (GMFCS levels I-II), gait training may involve predominantly self-driven walking practice, during which gait is achieved actively through the volitional movements of the patients alone (Booth et al. 2018). Contrastingly, assisted gait training can be employed for those functionally limited patients who present with highly dysfunctional gait patterns and who may struggle to ambulate effectively on their own (GMFCS levels III-IV). For these patients, the therapist may physically guide the lower limbs through the gait cycle, providing manual assistance when necessary to enable successful walking training (Mattern-Baxter 2009). Additionally, some gait training interventions in CP have utilized slopes while walking (usually in the form of an inclined treadmill), while others have patients walk backwards during training. These alternative gait training methods are meant to specifically target aspects of the pathological gait pattern that are especially impaired (such as foot clearance during swing or positive power production at push-off) as well as to activate and strengthen weakened and impaired muscles that may not be strongly activated during level forward walking (Hösl et al. 2016; Kim et al. 2016). While gait training protocols may vary considerably, they all share the core aim of helping to build and reinforce motor pathways via walking practice for the development of a more functional gait pattern.

Functional gait training has shown improvements in gait speed as well as endurance and gross motor function over traditional therapy in one systematic review focused on children with CP (Booth et al. 2018). Multiple systematic reviews concentrating specifically on treadmill gait training with partial body-weight support in CP patients corroborate these findings, and point to improvements in mobility outcomes such as self-selected gait speed and gross motor function (Zwicker and Mayson 2010; Willoughby et al. 2009; Damiano and DeJong 2009). Treadmill gait training with an incline was shown to reduce ankle joint stiffness and improve dorsiflexion at ground contact in both children (Willerslev-Olsen et al. 2014) and adults (Lorentzen et al. 2017) with CP. Further, inclined treadmill gait training may enhance propulsive force generation during push-off as well as improve toe lift during swing through facilitating increased central drive to the ankle plantarflexor and dorsiflexor muscles (Lorentzen et al. 2020; Willerslev-Olsen et al. 2015). In this way, gait training may improve functional mobility by remedying the deficient motor control mechanisms that underlie much of the gait dysfunction in CP. Additionally, backwards gait training has also shown positive effects on balance, walking speed, and gross motor function – potentially even greater than those benefits incurred from forward gait training – in children with CP (Elnahhas et al. 2019). Finally, treadmill gait training, as well as functional overground gait training, have some of the highest levels of evidence for positive effects on gait across multiple large-scale systematic reviews that assessed a multitude of therapy interventions for CP (Novak et al. 2013; Franki et al. 2012; Das and Ganesh 2019). The variability in training protocols and addition of co-interventions within many of the gait training studies make it challenging to determine the optimal program or training dose for patients with CP, though. Further, it is unclear to what extent the gains in function incurred from gait training affect patients' participation and quality of life, as well as how long they are retained after training (Booth et al. 2018).

Although gait training has demonstrated positive effects on walking ability in those with CP, some methodological issues still limit its full therapeutic potential. For one, therapist-assisted gait training can place high physical strain upon the therapists, making it difficult for the patient to accumulate sufficient training intensity and volume due to therapist fatigue (Hesse 2008). The level of assistance and guidance trajectory provided by the therapist are also both inconsistent during training (Dobkin and Duncan 2012). Further, while gait training on a treadmill may allow for greater repetition of the stepping pattern and thus higher training volume than overground gait training, the walking pattern, and resultant training outcomes, may vary, depending upon the modality used (Celestino et al. 2014). Considering the specificity of training principle, gait improvements made on the treadmill may not translate as effectively to real-world walking performance as overground gait training (Roemmich and Bastian 2018). Unfortunately, overground gait training may be challenging for more functionally impaired patients, especially if they require some level of body-weight support during training. Further, when utilizing high levels of body-weight support during treadmill gait training, the activity of the relevant lower-limb muscles is reduced, which may lessen the training effect (Hesse 2008). As gait training is a fairly repetitive activity, patient engagement may also wane during therapy. This is especially true for pediatric rehabilitation, as children may lack the motivation to perform intense and repetitive walking therapy (Meyns et al. 2018). Considering patient engagement is essential for promoting beneficial neural plasticity and enabling the development of new motor pathways to augment motor skill performance, low levels of engagement or motivation during gait training may hamper the therapeutic effects (Kleim and Jones 2008; Winstein et al. 2014). Thus, to truly optimize gait training, the training modality should emulate free-living contexts, steady assistance should be provided to those patients who need it in a manner that mimics the healthy human walking pattern but does not physically fatigue the therapist, and patients should be actively engaged throughout training.

5. ASSISTIVE TECHNOLOGY

The neuromuscular deficiencies and musculoskeletal deformities that manifest in those with neuromotor disorders, such as CP, inhibit patients' functional abilities in everyday settings and make the delivery of sufficient therapeutic treatment challenging. Assistive technology acts as a means to combat these movement challenges and facilitate more natural and efficient movement patterns (Calabrò et al. 2016). For the purposes of this thesis, we can define two key aims of mobility-based assistive technology for neuromotor deficient patients:

> **Aim 1:** to enhance mobility and function at home and in the community and enable participation in activities that would be challenging if not impossible without the device
>
> **Aim 2:** to address the limitations of traditional therapeutic interventions, such as gait training, and improve neurorehabilitation in the clinical setting

Thus, assistive technology endeavors to augment patients' movement abilities both within the clinic as well as outside in the real world. Different assistive devices may match only one of these aims while others may seek to fulfill both.

Traditionally, assistive technology for CP has been comprised mostly of lower limb orthoses, which act to augment joint function by providing rigid or semi-rigid support to the joint and by directing the joint mechanics towards more normal patterns (Fish et al. 2001). Robotic assistive technology has now begun to be developed to address some of the limiting drawbacks of orthoses as well as to enhance mobility therapy for patients with neuromotor dysfunction. These devices apply robotic mechanical assistance to the joints of the user to improve general mobility and/or enable more optimal movement training (Calabrò et al. 2016).

This section will begin by focusing on the use of orthoses in CP and their benefits as well as crucial shortcomings. Robotic gait trainers, which supplement gait training therapy by providing assistance to the patient via an external robotic frame while they walk on the treadmill, will then be examined. Finally, the section will conclude with a discussion on exoskeletons and exosuits, which are external robotic devices that deliver assistance to the patients' movements without being tethered to the treadmill, and their current as well as potential future impact on the field of neurorehabilitation.

5.1 Orthotics

Orthoses are external devices similar to braces or splints, that are made of a rigid or semi-rigid material and are worn at a joint to prevent, limit, or enhance biological range of motion as well as manipulate the plane in which movements are performed (Fish et al. 2001). Commonly, orthoses are used to support and/or align the lower limb joints, prevent the development or worsening of musculoskeletal deformities, and improve gait (Davids et al. 2007). For those CP patients who exhibit deviant gait patterns at the ankle joint, such as foot drop or equinus, ankle foot orthoses (AFOs) can be used to correct the gait dysfunction (Wright and DiBello 2020). AFOs act to improve ankle-foot alignment by bracing the ankle in a neutral position as a means to prevent excessive plantarflexion during gait and potentially stretch shortened and contracted calf muscles (Figure 5A).

Lower limb orthoses, and specifically AFOs, have been shown to have positive effects on some gait parameters in CP. Research indicates AFOs are effective in their goal of reducing excessive plantarflexion and improving dorsiflexion kinematics during walking (Davids et al. 2007; Altschuck et al. 2019). Further, AFOs improve certain spatiotemporal gait metrics, such as gait speed and stride length in children with CP (Aboutorabi et al. 2017; Lintanf et al. 2018; Betancourt et al. 2019). Contrastingly, although one of the goals of orthoses is to make walking easier and more efficient for patients, the effects of AFOs on the metabolic cost of walking in CP is inconclusive with some studies indicating reduced energy cost while others report no change or even increases in energy expenditure with AFOs (Lintanf et al. 2018; Aboutorabi et al. 2017). Importantly, while orthoses have proven effective in blocking pathological movement patterns and enabling CP patients to walk in a more normal pattern, their rigid structure can act to inhibit normal joint mechanics during walking. Ankle propulsive power at the end of stance phase has been shown to be reduced with the use of AFOs in both healthy participants (Vistamehr et al. 2014) as well as in those with CP (Aboutorabi et al. 2017; Altschuck et al. 2019; Davids et al. 2007), meaning AFOs impede normal push-off during gait. AFOs also reduce gait adaptability, and thus uneven terrain and obstacles in the walking path can present a daunting hazard for the patient using an AFO (Van Swigchem et al. 2014). Further, AFOs reduce the activity of the plantarflexor and dorsiflexor muscles during gait (Lindskov et al. 2020; Romkes et al. 2006). Considering the ankle muscles are so crucial for generating and sustaining the healthy human gait pattern and that these muscle groups are so often severely weakened and impaired in those with CP, a reduction in their activity using AFOs is a troubling effect, as this may lead to muscle atrophy and overall reduced ankle function. Generally, because orthoses block or prevent pathological movement patterns and provide movement guidance and support through their rigid structure, this can lead to patients becoming dependent upon the devices for proper ambulation and can reduce their functional abilities when walking on their own (Aboutorabi et al. 2017). Thus, the limitations of orthotic interventions in CP call for assistive technology that aims instead to facilitate healthy movement patterns rather than block pathological movements.

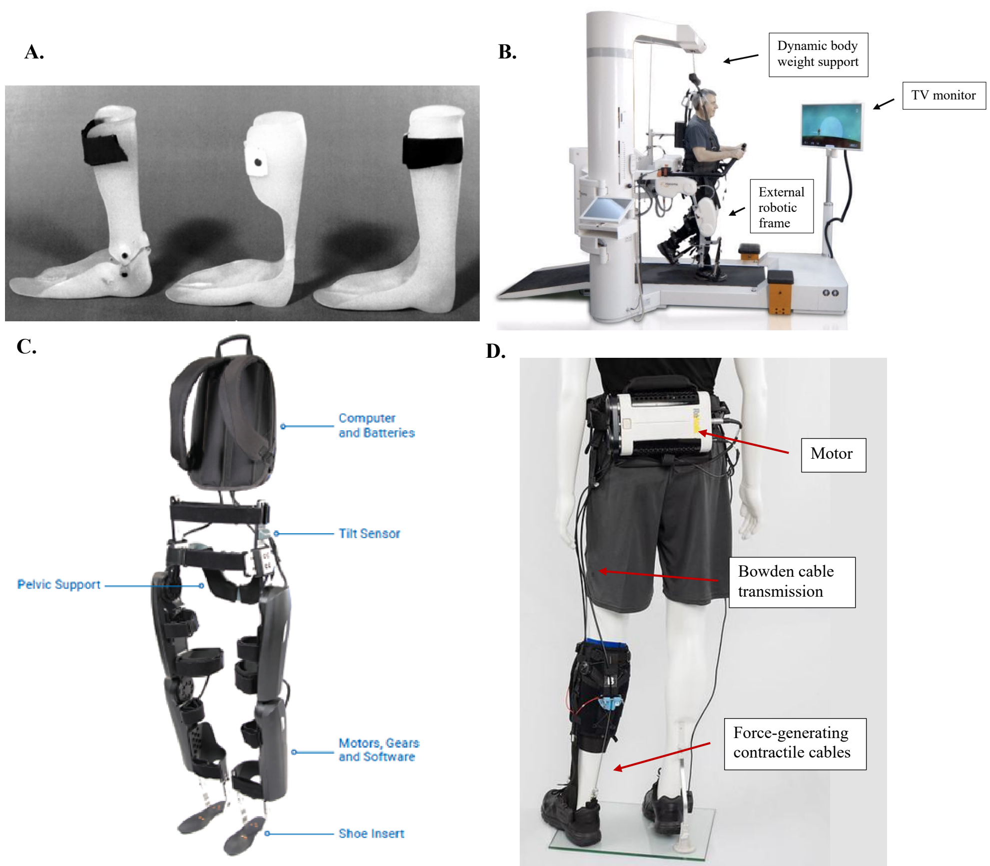

Figure 5: Assistive Technology for Patients with Neuromotor Dysfunction. A: Ankle foot orthoses (AFO) commonly employed for patients with CP to stabilize and support the distal joint during walking. **B:** Treadmill-based robotic gait trainer (Lokomat) that utilizes an external robotic frame to guide patients' limbs through a predetermined gait pattern. The amount of body weight support can be modified, and feedback can be given in real-time via the TV monitor. **C:** Exoskeleton device (ReWalk) that enables independent walking by providing mechanical assistance to the user through external robotic joints. Gait is initiated by lateral weight shifts, which are identified by the tilt sensors at the pelvis. **D:** Soft exosuit (ReStore exosuit) that assists in walking movements by providing mechanical power at the ankle joint via contracting Bowden cables powered by the motor worn at the waist.

5.2 Robotic Gait Trainers

As discussed earlier, traditional gait training with therapist assistance is limited by the inconsistent nature of the assistance and the high physical burden on the therapist, which can lead to patients receiving a suboptimal training stimulus for neuroplastic adaptations (Dobkin and Duncan 2012). Robotic gait trainers have been developed to combat the limitations of traditional therapist-assisted gait training. These devices utilize robotic mechanisms, such as motorized frames or programmable foot-plates, to assist the patient while they walk (Lefmann et al. 2017). Most commonly, robotic gait trainers are coupled to the treadmill and employ an external robotic frame that interfaces with the lower-limbs of the patient to provide mechanical power and guidance while they walk on the treadmill (Figure 5B). Other devices assist patients' gait using robotic foot plates, whose movements simulate the natural stance and swing phases of gait (Hesse et al. 2013). Robotic gait trainers reduce the physical effort of the therapists, allow for increased training intensity and volume, and improve the reproducibility of the walking kinematics during gait training (Calabrò et al. 2016). These devices can also more objectively quantify and track patients' progress and level of effort throughout therapy, to allow therapists to adjust the training intensity to consistently meet the patient's challenge threshold (Reyes et al. 2020). Kinematics and kinetics of gait can be reliably measured and tracked using some robotic gait trainers as well, giving potential insight into the progression and underlying mechanisms of recovery (Kitago and Krakauer 2013).

Gait training utilizing robotic gait trainers has only recently been adopted to treat CP, but it has shown potential in improving gait speed, endurance, and gross motor function (Carvalho et al. 2017). As a standalone intervention, however, robotic gait training has provided only limited functional gains in CP patients, leading researchers to suggest this training method should be embedded into a holistic therapy program to optimize its potential benefits (Ammann-Reiffer et al. 2020). Studies that have integrated treadmill-based robotic gait training as a supplement to traditional therapy programs have shown the addition of robotic therapy improves functional outcomes and can enhance conventional gait rehabilitation (Weinberger et al. 2019; Borggraefe et al. 2010; Sucuoglu 2020). The severity of impairments seems to impact the acquired functional gains, though, with more-functional patients (GMFCS levels I and II) incurring the greatest benefits from robotic gait training (Carvalho et al. 2017;

Borggraefe et al. 2010; Sucuoglu 2020). The ability of robotic gait training to alter the independent walking mechanics of those with CP is also uncertain, with some data displaying improved gait kinematics and balance following robotic gait training (Wallard et al. 2017), while other data present no changes in kinematic or temporospatial gait parameters with supplemental treadmill-based robotic therapy compared to conventional therapy alone (Drużbicki et al. 2013). Overall, the research using robotic gait trainers for CP therapy is currently inconsistent and inconclusive, and it is unclear if this technology provides sufficient therapeutic benefit to justify its great financial and time cost (Dobkin and Duncan 2012).

Importantly, while the assistance from robotic gait trainers may allow for higher training intensity and volume, it can also potentially reduce engagement, as patient effort can wain as they "ride the robot." Central drive from the motor cortices in the brain has been shown to be reduced when healthy participants walk passively using a treadmill-based robot compared to actively initiating the stepping movements (Wagner et al. 2012). Further, patients can begin to adapt to the given assistance while walking, which may again lead to a reduction in motor output to the muscles, possibly inhibiting function when they are forced to move without the assistance from the device (Wu et al. 2016). The addition of virtual reality (VR) and biofeedback can help to promote patient engagement during robot-assisted gait training (Lefmann et al. 2017). While still a relatively new protocol, rehabilitation that integrates VR has shown promising results for improving motor function in children with CP (Ravi et al. 2017; Chen et al. 2018). Treadmill training utilizing VR was effective in improving gait and balance in those with CP, beyond those gains incurred from treadmill gait training alone (Cho et al. 2016); and gamifying rehabilitation in combination with specialized robotic technology has shown potential to enhance patient engagement and improve gait function and quality of life in children with CP (Burdea et al. 2013; Bulea et al. 2017). Further, the incorporation of biofeedback during gait training can allow for therapists to modify treatment in real time to target specific deficiencies in an individual patient's movement patterns, tailoring the therapy to their unique impairments and their precise movement goals (Giggins et al. 2013). The addition of biofeedback to robot-assisted walking practice may improve the rate at which patients improve their gait mechanics in response to therapy (Fang and Lerner 2021).

Additionally, to contend with reduced motor activity during therapy, robotic gait trainers have the ability not only to provide assistance, but also to impose mechanical resistance during gait training. Targeted resistance delivered during the gait cycle requires patients to be actively engaged and can increase the voluntary activation of the lower-limb muscles, potentially enhancing motor neuron excitability, as well as selective motor control (Ekblom 2010). Currently, only a few studies have investigated the effects of robotic-resisted gait training in CP, but so far, the evidence is highly positive. Robotic resistance delivered during the early swing phase of gait was shown to improve gait speed and endurance as well as increase stride length in a small cohort of children with CP (Wu et al. 2017). A downward pelvic pull force, delivered by a robot, improved lower-limb extension and muscle activation patterns in children with CP who walked with a crouch gait pattern (Kang et al. 2017). Adaptive plantar flexion resistance during the stance phase of gait, applied via a wearable robot, enhanced plantar flexor muscle activity, and reduced co-contraction at the ankle in a cohort of spastic CP patients (Conner et al. 2020a). Thus, the use of therapy tools such as VR and biofeedback as well as robotic resistance may help to optimize gait training by boosting patient engagement and enabling therapy that is truly tailored to each individual patient.

Gait training using robotic gait trainers does have some significant limitations, however. Patients have little influence on the walking trajectory while using these devices, which may inhibit their ability to produce volitional gait without the assistance from the device (Calabrò et al. 2016). Further, treadmill-based robots generally constrain movements to the sagittal plane and fix the pelvis in the horizontal plane. This limits trunk rotations and can negatively affect walking dynamics as well as balance adjustments (Veneman et al. 2008). Muscle activation patterns are also altered while walking using these devices, with increased quadriceps and hamstring activity and reduced activity in the muscles surrounding the ankle, compared to unassisted treadmill walking (Hidler and Wall 2005). As the ankle muscles are so crucial for normal walking, a drop in their activity may again inhibit functional walking performance when patients walk without the device. A final critical limitation of robotic gait trainers is their stationary nature. Visuospatial flow, which describes the processing of visual and spatial information in the brain, is crucial for functional ambulation over variable terrain (Amboni et al. 2013). This is especially true of those with neurological disorders, who may have impaired proprioception and coordination, making visuospatial information all the more essential while walking (Deconink et al. 2006). Gait training performed on the treadmill or using robotic foot plates lacks variability in visuospatial flow, as patients walk while remaining stationary. This again limits the transferability of the training to real-world independent walking (Dobkin and Duncan 2012). Unfortunately, while robotic gait trainers seem to provide notable benefits above regular treadmill gait training with therapist assistance, these devices may fall into the same trap as AFOs, with patients becoming dependent upon the assistance that they provide, subsequently limiting their ability to walk unaided. So, technology that enables repetitive and intensive gait training in more ecologically valid environments, such as at home and in the community, may hold the key to improving the functional abilities of those with neurological movement disorders.

5.3 Exoskeletons and Exosuits

Exoskeletons are mechatronic devices made up of rigid segments and robotic joints that externally interface with the body segments and joints of the human user and assist the performance of movements (Figure 5C) (Bayon et al. 2016). Initially developed to enable independent upright locomotion for patients with spinal-cord injury, exoskeletons have now been tested, to varying degrees, across the neurological disease spectrum. Importantly, exoskeletons are not coupled to the treadmill, and thus can facilitate gait training and provide movement assistance to patients over a variety of different terrain and across diverse environments. The devices' control schemes generally rely upon detecting patients' subtle weight shifts and/or small movements of their trunk or lower limbs, which initiate the walking movements. The patient is not simply being taken through a predetermined walking pattern, but rather they have the ability, at least partially, to control the movement and assistance from the exoskeleton, which can improve coordination and balance for functional mobility gains (Calabrò et al. 2017). Exoskeletons can radically improve patient autonomy, well beyond those improvements incurred from AFOs or treadmill-based robotics, because of their adaptable and unrestricted nature (Federici et al. 2015). Robotic assistive devices can help to improve independence, social interaction, and socio-psychological development in those with motor disorders as well, and may even stimulate self-sufficiency by fostering an "I can do it" attitude in patients who previously struggled with activities of daily life (Damiano 2006). Early evidence suggests exoskeletons can lessen mobility impairments and enhance functional abilities in various neurological disease groups (Esquenazi et al. 2017; Federici et al. 2015). In those with spinal-cord injury, training with these devices has even shown the ability to induce changes in neural plasticity (Sczesny-Kaiser et al. 2015).

Surprisingly, there has been little investigation into the use of exoskeletons in CP, even though this population exhibits substantial mobility limitations and could greatly benefit from equipment that could improve function both in the rehabilitative setting as well as at home and in the community. So far, exoskeletons have shown promise in acutely improving gait dynamics and reducing the metabolic cost of walking, compared to walking without the device in children with CP (Lerner et al. 2018; Orekhov et al. 2020; Patane et al. 2017). In one study, an exoskeleton that provides bursts of knee extension assistance increased lower limb extension without reducing volitional muscle activity in a cohort of children with crouch gait from CP (Lerner et al. 2017). A lightweight exoskeleton that assists at the ankle was also shown to enhance ankle positive power production and knee extension during push-off, resulting in a more-efficient transfer of energy across the lower limb while walking (Lerner et al. 2019) and a consequent 19% reduction in the metabolic cost of locomotion (Lerner et al. 2018). In more functionally limited patients, a lower limb exoskeleton combined with a wheeled walker for support was shown to enhance gait stability by stabilizing pelvic kinematics (Aycardi et al. 2019). Thus, these initial studies show how exoskeletons can augment the mechanics and energetic efficiency of gait in patients with CP while they walk using the device, indicating their potential as assistive technology for use in everyday settings.

In harmony with these results, there have also been some positive preliminary investigations into the use of exoskeletons as rehabilitative devices in CP. In these studies, patients' independent walking ability is tested before and after a gait training intervention using the device. Gait training using established exoskeleton technology in patients with CP has shown improvements in self-selected walking speed, walking endurance, and gross motor function following the training period (Matsuda et al. 2018; Ueno et al. 2019; Kuroda et al. 2020). Similar results were seen in a study using a rigid exoskeleton that provides torque at the hip and knee for gait training, as the participants with CP displayed improved gross motor function and walking endurance as well as reduced metabolic cost of walking after the intervention (Kim et al. 2021). Custom-built exoskeletons that are more lightweight and personalized to the user have also demonstrated positive clinical results. A short training protocol of four sessions of exoskeleton-assisted overground gait training using a lightweight ankle exoskeleton improved independent walking speed and stride length, and shifted the muscle activity patterns of the ankle and knee extensor muscles to be less variable and closer to the activity patterns displayed during healthy gait in a small cohort of children with CP (Fang et al. 2020). Additionally, ten sessions of gait training using targeted resistance applied during push-off from this same ankle exoskeleton showed substantial benefits in ankle plantarflexion strength, metabolic cost of walking, and on the performance of functional tests following the training period (Conner et al. 2020b). Robotic gait training using a combined exoskeleton and wheeled walker device improved gait speed and endurance as well as lower limb muscle strength and gross motor function in a small cohort of CP patients (Bayón et al. 2018). One study even suggests that a single session of gait training using an exoskeleton may induce changes in walking mechanics, such as increases in gait speed and stride length as well as improvements in pathological gait mechanics in patients with CP (Mataki et al. 2020). Currently, however, the uncontrolled study designs and small sample sizes limit the generalizability and validity of these preliminary studies. Controlled clinical trials with larger samples and greater statistical power will be crucial to confirm the benefits of exoskeleton technology for patients with CP.

Important challenges remain for the integration of exoskeleton technology into real-world clinical care. Currently, most exoskeletons are bulky and expensive, and may pose potential safety risks to the patient, such as falling with the suit or system failure (Esquenazi et al. 2017). Further, the human-device interface of existing exoskeletons is often suboptimal, leading to some of the mechanical energy provided by the device being lost to the compression of soft tissue rather than movement assistance (Young and Ferris 2017). The anatomical restrictions, which limit who can use commercial exoskeleton devices, are also generally much too strict, and these devices must become more adaptable to be practical for different neurological disease patients with different body sizes and shapes (Federici et al. 2015). While exoskeletons require more volitional input from the patient than treadmill-based robotics, their intrusive design and unnatural control schemes mean walking with these devices is still a far cry from natural walking movements. Optimizing the control strategies and managing the level of assistance provided by the device is critical to assist the mobility of the user, while maintaining patient engagement and an appropriate level of effort (Grimmer et al. 2019). Some exoskeletons have experimented with intent-based controllers that utilize neural signals from the patient (i.e., EMG or EEG) to control the movement assistance from the device. Perfecting this control paradigm will enhance the man-machine interaction and likely improve motor learning outcomes (Herr 2009). Additionally, most robotic rehabilitative devices and exoskeletons are currently sized for adults, and it is unclear if these devices present too high of a weight penalty to be beneficial for pediatric populations (Reyes et al. 2020). The transfer of improved walking patterns acquired while wearing the device to outside environments (i.e., unassisted walking) also remains a key challenge. Finally, there is a dearth of studies investigating the effectiveness of exoskeletons in real-world environments (Federici et al. 2015). The potential of exoskeletons as both rehabilitative tools as well as everyday assistive devices is what makes this technology so exciting, so more study into the ecological validity of exoskeletons will be integral moving forward.

While rigid exoskeletons may enable independent upright ambulation and functional overground gait training in those highly impaired patients, more-functional patients may not require the level of support and assistance that these devices provide. Soft textile-based exosuits (Figure 5D) may be able to fill this niche for those less-impaired patients by providing mobility assistance to enable intense and repetitive gait training in diverse environments, while still requiring volitional activity to maintain a stable posture and initiate movements (Awad et al. 2017a). Unlike exoskeletons, exosuits lack a rigid frame and thus cannot support a user's full weight or move the limbs through the gait cycle without contribution from the patient. However, exosuits can assist movement performance by delivering mechanical power to the joints, using contractile cables. For the patient who presents with mobility impairments but retains the ability to ambulate independently, exosuits may be the ideal assistive device, due to their low mass, high level of comfort, and freedom of movement (Sawicki et al. 2020). Exosuits are also more adjustable and less expensive than exoskeletons, improving their translation into real-world clinical use (Federici et al. 2015). Thus, exosuits are more flexible than exoskeletons in both the literal and figurative sense.

The Harvard Biodesign Lab is the foremost group developing soft exosuits and researching their applicability in clinical populations. One of their devices, a unilateral soft exosuit designed to assist the paretic ankle of stroke patients (Figure 5D, ReWalk ReStore exosuit), was able to improve propulsion and ground clearance during gait, leading to a 10% reduction in the metabolic cost of walking in a sample of chronic stroke survivors (Awad et al. 2017a). Further, this device was able to improve walking ability overground and enabled patients to walk faster and farther in clinical tests (Awad et al. 2020a). Although the soft exosuit only provides mechanical power at the ankle, their data suggest the device has the capacity to fully augment the walking strategy by inducing more symmetrical COM power generation across the lower limbs (Bae et al. 2018). Further, they have found the exosuit can reduce patients' reliance on inefficient compensatory movements, such as hemiparetic hip hiking and circumduction (Awad et al. 2017b). After only five days of walking practice with the exosuit, post-stroke patients also displayed increases in both their exosuit-assisted and unassisted gait speed, suggesting this device has great promise as a rehabilitative robot as well (Awad et al. 2020b). Interestingly, the level of functional improvement induced by the exosuit was correlated with patients' initial walking speed, with those patients who walked the slowest incurring the greatest gains in function from the device (Awad et al. 2017a). Similar results were found in those studies that investigated the use of lightweight exoskeletons in CP patients (Lerner et al. 2019), suggesting that compact assistive technology, while unable to assist those with debilitating mobility deficiencies, is still beneficial (perhaps increasingly so) in patients with substantial deficits. While much more research investigating the effects of exoskeletons and exosuits in the clinical as well as everyday setting will be necessary to optimize the use of these technologies, so far, they have shown great promise for patients with neuromotor dysfunction, and their influence within the neurorehabilitation sphere is likely to only increase moving forward.

6. PURPOSE OF THE THESIS

The aim of this thesis was to investigate the effects of a soft exosuit that assists the affected ankle (Figure 5D) on the metabolic cost of walking, gait biomechanics, and muscle activity during walking in a small cohort of children and adolescents with unilateral CP. The exosuit device (ReWalk ReStore) was developed by the Harvard Biodesign lab for post-stroke patients to assist their mobility both in the community and rehabilitative setting. Research conducted using the device (or using preliminary prototypes with very similar design) in post-stroke patients has been very positive thus far, with results indicating the exosuit can reduce the metabolic cost of post-stroke gait (Awad et al. 2017a), improve the walking pattern and reduce adverse compensatory walking strategies (Bae et al. 2018; Awad et al. 2017b), and enhance patients' overground walking speed and endurance while wearing the device (Awad et al. 2020a). Only five sessions of exosuit-assisted walking practice also enabled post-stroke patients to walk faster on their own (Awad et al. 2020b). Thus, the results so far indicate the great potential of this exosuit as both a rehabilitative device as well as an assistive aid for use in everyday life for post-stroke patients.

This device has not been tested in any other neuromotor deficient patients, however. This will be its first investigation in patients with CP. Thus, this thesis is fairly exploratory in nature as it intends to describe the effects of the exosuit on the gait of CP patients without any preconceptions as to what those effects may be. This thesis focuses upon the acute effects of the exosuit on the metabolic cost of walking, gait mechanics (kinematics and kinetics), and muscle activity during walking in CP patients. It is tentatively hypothesized that the exosuit will reduce the metabolic cost of walking in our participants based on the previous studies with this device. Considering the exosuit was designed for adult post-stroke patients and our participants are children and adolescents with CP, it is very possible that the weight of the device as well as its potential imperfect fit onto smaller body sizes may just as well increase metabolic cost rather than reduce it, though, and so this hypothesis is a tentative one. No definitive hypotheses are given related to the effects of the device on gait mechanics or muscle activity during walking.

This thesis describes the acute effects of the exosuit while participants walk with the device compared to normal walking without the device. So, the results described herein (especially those related to metabolic cost and gait mechanics) will mostly be relevant to inform the use of the exosuit as an everyday assistive aid. Positive results in this regard would be reductions in metabolic cost and improvements in gait kinematics and kinetics, which together would indicate the device makes walking easier and more efficient, and reinstates a more normal gait pattern. Although this thesis does not explicitly evaluate the rehabilitative effect of the exosuit, the results from this thesis (especially those related to muscle activity) may still be relevant in understanding the potential of this device as a therapeutic tool. Positive results in this regard would involve increases in muscle activity (especially in those muscles that are most affected in CP) or changes in the muscle activity patterns to be closer to those exhibited during healthy gait while wearing the exosuit.

7. METHODS

7.1 Participants

Seven individuals with unilateral CP (12-16 years old) completed this cross-sectional study. Participants completed the study voluntarily and were free to withdraw from the study at any time. Participant characteristics are detailed in Table 1. This study aimed to determine whether a unilateral soft exosuit designed for adults could improve the walking mechanics and energetics of children and adolescents with CP. The age range of the participants reflects this aim. Additionally, only those with unilateral CP were chosen for this study, as the exosuit we employed assisted the ankle of only one limb at a time. The participants in this study all had high levels of motor function and could ambulate independently (all within GMFCS level I). Additionally, all participants had the necessary ankle range of motion to achieve a neutral ankle angle with no limiting contractures; however, some participants exhibited a drop-foot gait pattern or walked with slight equinus while walking normally.

This study was approved by the Helsinki University Hospital ethics committee (HUS/1074/2020). Participants were recruited from the rehabilitation unit of the New Children's Hospital in Helsinki. Inclusion criteria for this study included: diagnosis of unilateral spastic Cerebral Palsy, age of 8-20 years old, and the ability to ambulate independently and achieve a neutral ankle position. Patients were excluded if they underwent orthopedic surgery in the past 6 months, had any comorbidities or secondary impairments that could impact their safety throughout the protocol, or had any known cognitive or cooperative deficiencies that would limit their ability to understand and follow directions from investigators. Written informed consent from the parents of the participants and verbal assent from the participants themselves was obtained prior to the start of the measurement session.

7.2 Study Protocol

This study consisted of a single session with each participant, which comprised multiple walking trials. We aimed to compare the normal gait (i.e., without exosuit assistance or orthosis) to the exosuit-assisted gait. Additionally, investigating the effect of carrying the 4-kilogram exosuit motor on our young participants' walking pattern and energetic cost of walking was a secondary aim of the study. To address these aims, three main walking blocks were performed:

1. Normal gait
2. Exosuit-assisted gait with motor carried at participant's waist (Onboard)
3. Exosuit-assisted gait with weight of motor offloaded from participant (Offboard)

For those participants who utilized an orthosis, an additional walking block was performed with them wearing their prescribed orthosis; however, this data was not utilized for this thesis.

The measurement session began by taking the resting metabolic measurement from the subject as they sat quietly. Retroreflective markers were placed upon the bony landmarks of the patient and EMG electrodes with accompanying wireless transmitters were placed on the skin over the muscle of interest following the resting metabolic measurement (see following section for additional details). The subject then completed 3-4 overground walking trials at their comfortable self-selected walking speed. The average horizontal velocity of the posterior pelvis markers from these overground walking trials was used as an estimate for the participant's comfortable overground gait speed, and this speed was then used as the treadmill walking speed for the experimental walking blocks.

The experimental walking blocks consisted of the normal walking trial and the two exosuit walking trials (onboard and offboard), as described above. For the normal condition, subjects walked on the treadmill for 4 minutes, with the last 30 seconds being captured for the metabolic and motion capture data. The exosuit walking conditions began with 4 minutes of walking to warm up and adapt to the assistance from the device. The optimal level of dorsiflexion assistance (average: 44.3%) was determined during this adaptation period by adjusting the assistance level and inquiring as to what felt best for the subject, as well as by visually confirming the assistance was adequate to achieve a neutral ankle angle during swing phase. After the 4-minute warm-up, the exosuit walking trials commenced by beginning at the 0% plantarflexion assistance level (slack mode) and subsequently increasing the assistance level up to 100% plantarflexion assistance (assistive force equivalent to 25% of user's BW), in intervals of 20%. The dorsiflexion assistance level remained the same throughout the protocol. Subjects walked for 2-minutes at each plantarflexion assistance level and the final

30 seconds of the 2-minutes was captured for the metabolic and motion capture data. This process was equivalent for both onboard and offboard exosuit conditions.

Importantly, the location of the normal walking block was randomized in an attempt to minimize the effects of participant fatigue on the results. Thus, three subjects completed the normal walking block before walking with the exosuit, while four subjects first walked with the exosuit then finished with the normal walking block. However, the exosuit walking blocks were always back-to-back, as donning the exosuit and properly fitting the equipment to the subject was a time-consuming and challenging process, making it necessary to perform all walking with the exosuit together without removing the device.

7.3 Exosuit and Other Research Equipment

Three-dimensional gait analysis was the primary experimental method used in this study. An eighteen-camera motion capture system (Vicon Motion Systems, Oxford, UK) was used to capture participants' gait movements at 200 HZ. Retroreflective markers were placed on the anterior and posterior iliac crest, on the lateral aspects of the thigh, knee, and shank, on the lateral malleolus of the ankle, and on the heel and toes of the shoe in accordance with the plug-in gait lower body model (Vicon Motion Systems). Muscle activity data was captured at 1500-2000 HZ using a wireless EMG system (Noraxon, Scottsdate AZ, USA; Myon Aktos, Schwarzenberg, Switzerland). Bipolar electrodes were placed according to SENIAM guidelines (Hermens et al. 2000) to measure the activity of the Tibialis Anterior, Gastrocnemius Medialis, Soleus, Rectus Femoris, Vastus Lateralis, and Biceps Femoris of both the affected and unaffected limb. During the walking trials, participants walked on an instrumented tandem treadmill (AMTI, Watertown, MA, USA) that collected GRF data at 2000 HZ, which was used in the calculation of kinetic parameters. The metabolic cost of walking was assessed using a wearable metabolic system (Cosmed K5, Rome, Italy) that measured oxygen consumption (VO_2 ml/min) during the walking trials. The experimental setup is displayed in Figure 6.

Table 1: Participant Characteristics

Subject	Gender	Age	Height (cm)	Weight (kg)	GMFCS	Affected Leg	Orthosis	Treadmill walking speed (km/h)	DF assistance level (%)	On PF assistance level (%)	Off PF assistance level (%)
1	M	16	177	60	I	R	Yes	3.24	50	100	80
2	F	13	170	53	I	R	Yes	3.8	50	100	80
3	F	15	158	63.7	I	L	Yes	4	45	60	60
4	F	15	165	49	I	R	No	3.2	30	40	60
5	M	13	166	46.5	I	R	No	3.6	40	80	80
6	M	13	149	40	I	R	No	3.4	45	60	80
7	F	12	152	47	I	L	No	2.5	50	80	100
AVG (SD)	**NA**	**13.9 (1.5)**	**162 (10)**	**51.3 (8.2)**	**NA**	**NA**	**NA**	**3.39 (0.49)**	**44.3 (7.3)**	**74.3 (22.3)**	**77.1 (13.8)**

On = Onboard, Off = Offboard, DF = dorsiflexion, PF = plantarflexion

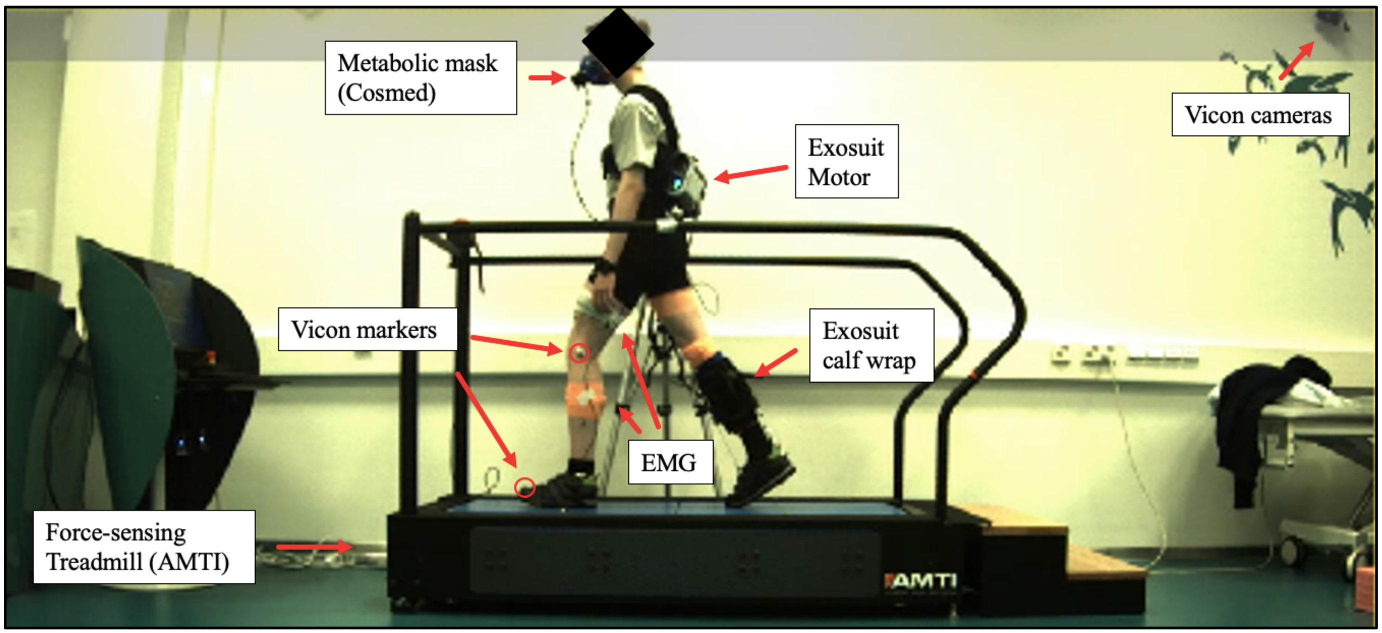

Figure 6: Experimental Setup. A participant walking on the force-sensing treadmill with the exosuit in the onboard condition is shown. The markers for 3D motion analysis, EMG transmitters for muscle activity analysis, and metabolic mask for oxygen consumption measurements are highlighted with the arrows. Further, the exosuit motor worn at the subject's waist and the exosuit calf wrap worn at the affected ankle joint are also shown. In the offboard condition, the exosuit motor was carried by one of the researchers standing to the side of the treadmill to offload the weight of the motor from the participant.

The exosuit device used in this study (ReWalk ReStore, Marlborough, MA, USA) assists the affected leg of the patient at the ankle via contraction and extension of Bowden cables fixed to connection points on special insoles worn within the shoe of the user. The shortening of the cable at the front of the foot assists with dorsiflexing the ankle during swing phase, while the shortening of the cable at the back of the foot assists with plantarflexion torque production during push-off. The maximal dorsiflexion assistance corresponds to the maximal cable travel distance (50mm), and so the level of dorsiflexion assistance was adjusted to enable users to reach a neutral ankle angle during swing phase. The maximal plantarflexion assistance corresponds to a peak assistive force at push-off equal to 25% of the user's bodyweight (BW). For this study we adjusted the level of plantarflexion assistance from 0% (slack mode) to 100% in intervals of 20%. The full exosuit system consists of a calf wrap and accompanying liner (worn underneath the calf wrap to prevent unwanted movement of the wrap with shortening of the cables), waist strap, batteries, inertial measurement units (IMUs) worn on the shoes to track progress of the gait cycle and provide plantarflexion and dorsiflexion assistance at the proper time, the Bowden cables, and the motor (Figure 5D).

7.4 Data Analysis

Although subjects walked using six different plantarflexion assistance levels (0%, 20%, 40%, 60%, 80%, and 100%) during the exosuit walking blocks, for this thesis project, only the walking trials at the assistance level that gave the greatest reduction in metabolic cost of walking were analyzed. An investigation into the effects of the varied assistance levels on gait biomechanics and metabolic cost of walking is planned for the future; however, this thesis is focused upon the potential of the exosuit device to augment the metabolic efficiency of the subjects' gait and examine the biomechanical alterations that accompanied these metabolic changes. For this reason, a deeper biomechanical examination was only performed on those exosuit walking trials that improved the metabolic cost of transport to the greatest degree. Thus, in this thesis, there were three walking conditions for each subject: normal walking, the best exosuit onboard, and the best exosuit offboard. The optimal plantarflexion assistance level could, and often did, vary between subjects and between the onboard and offboard conditions within subjects (onboard average assistance: 74.3%; offboard average assistance: 77.1%).

The metabolic cost of walking was calculated by averaging the VO_2 (ml/min) from the 30 seconds of captured data for each walking trial then subtracting the resting VO_2 (ml/min). This net oxygen consumption during walking was then normalized to the subject's BW (kg) and their treadmill walking speed (m/min) to give the metabolic cost of walking (ml/kg/m). For the onboard trial, the subject's true BW was used for this normalization (did not include the weight of the exosuit motor). The exosuit walking trials at the assistance level that gave the lowest value for the metabolic cost of walking were taken for further biomechanical analysis.

Joint kinematics and kinetics were calculated using the plug-in gait model (Vicon Nexus software). Joint moments calculated using inverse dynamics are reported as internal moments, and a positive direction represents the moment production by the extensor muscle groups at the hip, knee, and ankle. A minimum of 10 representative strides with clean foot contact over the treadmill force plates were taken from each walking trial and used for the calculations. Gait kinematics and kinetics were averaged and normalized to the gait cycle using Vicon Polygon software. For the exosuit onboard walking trial, the additional weight of the exosuit motor was accounted for by multiplying the kinetic data from this trial by the following correction factor: $subjects\ BW/[subjects\ BW\ +\ 4kg\ exosuit\ motor]$. The exosuit-generated moment applied to the affected ankle joint during push-off was calculated by multiplying the length of the external exosuit lever arm (38 mm) to the assistive plantarflexion force provided by the contraction of the Bowden cable at the back of the foot. The external exosuit lever arm was derived using two retroreflective markers placed on the posterior cable of the exosuit and calculating the distance from the linear vector created by these two markers (acting as the surrogate force vector) to the ankle joint center. The magnitude of assistive plantarflexion force was calculated considering that 100% plantarflexion assistance was equivalent to an assistive force of 25% of the user's BW, and then calculating the applied assistive force based on the actual assistance levels for each subject's exosuit walking trials. Subtracting the exosuit-generated moment from the total ankle moment gave the biological contribution to the ankle plantarflexion moment during the exosuit walking trials.

The motion capture marker trajectories were filtered with a 6 HZ low-pass Butterworth filter. GRF data was filtered with a low-pass Butterworth filter at 10-15 HZ. EMG data was bandpass filtered between 20-500 HZ, then a 31-sample sliding RMS window was applied and the resulting data was normalized to the gait cycle using a custom python script. The mean value across the full gait cycle was taken from this EMG data for each muscle to quantify the average magnitude of muscle activity during each of our walking conditions. This mean value was normalized to the maximal muscle activity measured during the normal walking trial for each respective muscle.

Unfortunately, the EMG recording from one of our participants (subject 6) cut out early in the measurement session, and so the muscle activity data from this subject was lost. Thus, the EMG results reflect the data of only 6 subjects. Further, we encountered some difficulties with cable movement artifact in our EMG data, and not all of this artifact contamination could be filtered out of the data, as much of the artifact signal lay within the frequency range of the muscle activity signal. Thus, separating the contributions from real muscle activity and cable movement artifact to the total signal was challenging in our data. The data from some subjects was excluded from individual muscles for this reason, as their data seemed unreasonable compared to the rest of the subjects' data, likely due to high levels of cable movement artifact contamination. In detail, the data from subject 3 and subject 4 was omitted from the totaled Soleus activity of the affected leg; the data from subject 4 was omitted from the totaled Gastrocnemius Medialis activity of the unaffected leg; the data from subject 2 was omitted from the totaled Soleus activity of the unaffected leg; and the data from subject 7 was omitted from the totaled Biceps Femoris activity of the unaffected leg. Therefore, because of these limitations, the EMG data presented in this study should be considered with some caution.

In this study, the spatiotemporal, kinematic, kinetic, and muscle activity data were analyzed and averaged independently for the two legs. This was done considering our subjects all had unilateral CP and the exosuit device only assisted the affected limb, so differential effects between the affected and unaffected leg on the variables of interest were expected.

7.5 Statistical Analysis

The Shapiro-Wilk test was used to check if the data were normally distributed. One-way repeated measures ANOVA was used to compare the metabolic, biomechanical, and EMG variables between the three conditions (normal, onboard, and offboard). The significance level was set at $p \leq 0.05$ and a Bonferroni correction was applied to account for multiple comparisons for all statistical tests. Mauchly's test of sphericity was used to test for homogeneity of variances between conditions. If the assumption of sphericity was violated, the Greenhouse-Geisser significance value was reported. For those variables that were found to be non-normally distributed, Friedman's one-way ANOVA with Wilcoxon signed ranks post-hoc test was used to test for differences between walking conditions. Statistical analysis was performed using SPSS software.

8. RESULTS

8.1 The Metabolic Cost of Walking

Our oxygen consumption data revealed a reduction in the metabolic cost of walking for both exosuit walking conditions (Figure 7). The subjects showed a 6.9% and 14.7% reduction in the metabolic cost of walking in the onboard and offboard conditions, respectively, compared to their normal walking (normal: 0.179±0.062 ml/kg/m; onboard: 0.167±0.049 ml/kg/m; offboard: 0.153±0.057 ml/kg/m). The subjects had the most energetically efficient gait when walking with the exosuit assistance while not having to carry the device's motor (offboard condition), as was expected. However, it is notable that the metabolic cost of walking was still reduced compared to normal in the onboard condition, when the energetic benefit of the exosuit assistance had to compete with the energetic burden of carrying the 4kg exosuit motor.

The reductions in the metabolic cost of walking with the exosuit were not statistically significant, however (ANOVA $p=0.22$). The coefficient of variation (CV), which gives the extent of variability in relation to the mean as a percentage, was high for our metabolic data for all three of our walking conditions (normal CV: 35%; onboard CV: 29%; offboard CV: 37%). This suggests high variability in the metabolic cost of walking between the subjects in our small sample, which likely limited the statistical analysis. Further, the effects of the exosuit on metabolic cost were variable from subject to subject, with changes in the onboard condition ranging from a 42% reduction to a 34% increase in metabolic cost and changes in the offboard condition ranging from a 53% reduction to a 6% increase in metabolic cost compared to the normal walking condition.

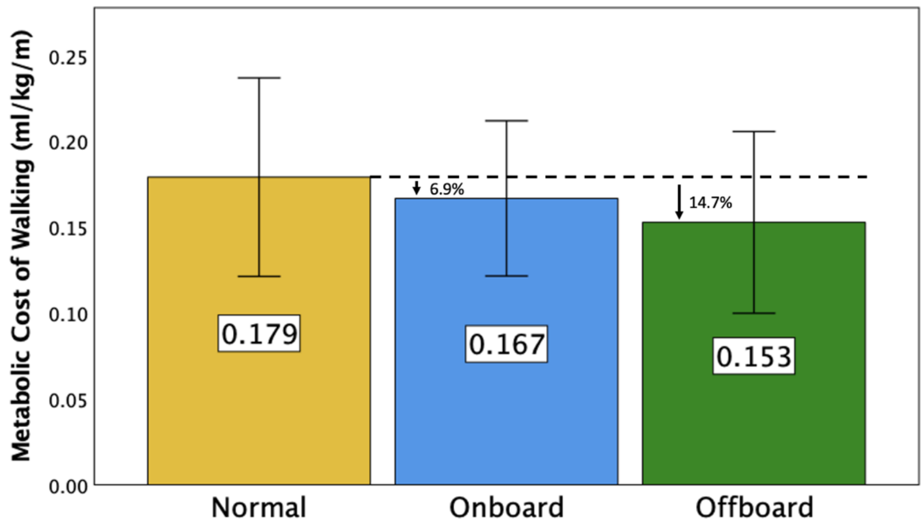

Figure 7: Changes in the Metabolic Cost of Walking using the Exosuit. *The average metabolic cost of walking (ml/kg/m) are shown for the normal, onboard, and offboard conditions. Mean values are shown within the boxes. Error bars represent 95% confidence intervals.*

8.2 Spatiotemporal Variables

The spatiotemporal variables for the three walking conditions are presented at the top of Table 2. There was a slight increase in step length in the onboard condition for the affected leg (+0.020m) as well as for both exosuit walking conditions in the unaffected leg (onboard: +0.033m, offboard: +0.013m). Stance time also increased in both exosuit walking conditions for both the affected and unaffected leg compared to normal walking (affected onboard: +0.033s, affected offboard: +0.018s; unaffected onboard: +0.036s, unaffected offboard: +0.040s). Stride time similarly increased in both the affected and unaffected leg with the exosuit (affected onboard: +0.05s, affected offboard: +0.04s; unaffected offboard: +0.05s, unaffected offboard: +0.03s), while cadence was reduced with the exosuit for both legs (affected onboard: –3.9 steps/min, affected offboard: –3.1 steps/min; unaffected onboard: –4.1 steps/min, unaffected offboard: –3.2 steps/min). None of these exosuit-induced changes in spatiotemporal variables reached statistical significance, though.

Table 2: Key Biomechanical Variables. Results are presented as mean ± standard deviation.

		Affected leg			Unaffected leg		
		Normal	Onboard	Offboard	Normal	Onboard	Offboard
Spatiotemporal Variables	Step Length (m)	0.531±0.06	0.551±0.06	0.531±0.08	0.589±0.07	0.622±0.07	0.602±0.05
	Stance Time (s)	0.756±0.13	0.789±0.13	0.774±0.12	0.799±0.14	0.835±0.12	0.839±0.13
	Stride Time (s)	1.22±0.22	1.27±0.19	1.26±0.19	1.22±0.22	1.27±0.20	1.25±0.19
	Cadence (steps/min)	100.6±15.8	96.7±13.9	97.5±14.1	100.8±15.7	96.7±14.1	97.6±14.0
Ankle Mechanics	Dorsiflexion during Swing (degrees)	-0.06±5.3	6.32±5.8*	5.44±6.1	7.78±4.9	7.89±4.7	8.20±5.0
	Dorsiflexion at GC (degrees)	-6.95±6.6	3.03±6.7*	2.25±6.3*	5.21±5.1	5.48±5.0	5.63±5.3
	Peak Total Ankle Moment (Nm/kg)	1.08±0.14	1.17±0.09*	1.19±0.09	1.37±0.26	1.33±0.24	1.38±0.27
	Maximum Ankle Power (W/kg)	1.19±0.46	1.13±0.39	1.08±0.40	2.38±0.99	2.14±0.90	2.28±1.0
	Minimum Ankle Power (W/kg)	-0.85±0.35	-0.73±0.27	-0.81±0.30	-0.80±0.22	-0.91±0.37	-0.90±0.43
Knee Mechanics	Knee Flexion during Stance (degrees)	19.5±5.8	22.2±7.7	22.0±8.3	19.0±4.4	22.8±6.7	22.4±5.6*
	Knee Flexion during Swing (degrees)	57.8±6.9	53.8±7.1	54.1±6.5	58.6±6.2	60.3±3.5	60.5±3.8
	Knee Extension during Stance (degrees)	6.55±5.51	6.28±5.25	7.30±6.16	2.67±2.46	4.61±4.50	3.95±4.78
	Peak Knee Extensor Moment (Nm/kg)	0.30±0.11	0.42±0.22	0.37±0.26	0.43±0.11	0.58±0.13	0.57±0.12
	Maximum Knee Power (W/kg)	0.25±0.19	0.40±0.32	0.34±0.27	0.30±0.17	0.58±0.27*	0.49±0.16*
Hip and Pelvis Angles	Upward Pelvic Obliquity (degrees)	2.58±2.37	3.46±0.80	3.55±0.45	4.13±3.37	3.60±1.98	4.12±2.67
	Downward Pelvic Obliquity (degrees)	-4.22±3.37	-3.67±2.01	-4.17±2.66	-2.61±2.37	-3.47±0.90	-3.55±0.47
	Hip Flexion at GC (degrees)	33.5±7.0	36.0±8.6	35.1±8.5	37.6±6.9	39.5±7.7	38.9±10.3
	Hip Extension at TO (degrees)	-3.26±6.6	-5.35±6.7	-4.26±7.9	-5.91±4.6	-7.27±4.6	-6.65±6.0
	Hip ROM during Stance (degrees)	36.7±5.0	41.3±6.1	39.4±5.2	43.5±6.2	46.8±5.6	45.5±7.3
	Hip Adduction during Stance (degrees)	-5.93±4.70	-5.96±4.08	-6.45±4.16	-1.91±4.52	-2.83±2.87	-3.83±2.60
	Hip Abduction during Swing (degrees)	2.78±5.20	4.09±3.68	4.01±3.49	8.12±5.08	8.38±4.08	8.31±4.94
GRF Variables	1st Peak vGRF (%BW)	106.5±5.4	108.1±7.8	110.1±8.8	107.6±7.3	111.2±10.2	115.1±8.8*
	2nd peak vGRF (%BW)	101.9±2.2	104.6±1.0*	105.2±2.9	107.9±5.5	109.1±5.1	111.2±5.0
	Peak Anterior GRF (%BW)	11.3±2.8	11.8±2.8	12.1±3.3	15.0±3.1	15.3±2.9	15.6±2.8
Muscle Activity (Presented relative to maximal activity from normal trial as %)	Mean Tibialis Anterior activity (%)	36.3±19.3	28.3±14.9	25.4±17.5*	33.2±13.9	33.1±13.7	31.6±13.7
	Mean Gastrocnemius Medialis activity (%)	28.6±15.9	22.7±15.2	24.8±19.3	25.1±7.9†	27.4±9.5†	26.1±11.1†
	Mean Soleus activity (%)	26.9±11.0†	31.1±8.2†	29.0±4.9†	28.2±6.6†	31.6±10.6†	31.0±9.0†
	Mean Rectus Femoris activity (%)	30.4±9.6	29.2±9.4	25.9±9.0	31.1±9.1	30.7±8.8	26.7±10.5
	Mean Vastus Lateralis activity (%)	28.1±8.7	26.9±9.9	25.1±10.7	31.6±11.8	34.6±15.1	32.0±14.4
	Mean Biceps Femoris activity (%)	41.4±15.1	39.6±13.8	34.4±11.8	24.0±4.5†	24.4±6.8†	24.7±8.1†

GC = ground contact, TO = toe off, ROM = range of motion, GRF = ground reaction force, BW = body weight. * represents a significant difference from normal condition ($p<0.05$). † indicates the data from one or more subjects had to be excluded (see text for additional details)

8.3 Ankle Joint Mechanics

The affected ankle joint showed some of the most substantial biomechanical changes in response to the exosuit, as was expected, considering the device assisted at the affected ankle (Figure 8, Table 2). In terms of joint angles, the exosuit improved ankle dorsiflexion both during swing (*onboard: +6.38° [significant increase: p=0.030], offboard: +5.50°) as well as at ground contact (*onboard: +9.98° [significant increase: p=0.002], *offboard: +9.20° [significant increase: p=0.004]). Thus, the Bowden cable at the front of the foot reduced the foot drop in our participants and enabled them to reach a degree of dorsiflexion much closer to their unaffected leg (dorsiflexion at ground contact in the affected leg was 80% and 72% closer to the unaffected leg in the onboard and offboard conditions, respectively, compared to during normal walking without the exosuit).

The exosuit, and its Bowden cable assisting at the rear of the foot, also influenced the ankle joint kinetics of the affected leg. The exosuit delivered an average of 0.069±0.021 Nm/kg and 0.072±0.013 Nm/kg of assistive plantarflexion torque at the affected ankle in the onboard and offboard conditions, respectively. This assistive torque resulted in an increase in the peak total ankle moment in both exosuit walking conditions (*onboard: +0.09 Nm/kg [significant increase: p=0.037], offboard: +0.11 Nm/kg). However, the biological ankle plantarflexor moment (calculated by subtracting the exosuit-generated moment from the total ankle moment) was only minimally increased in the exosuit walking conditions compared to normal walking (onboard: +0.017 Nm/kg, offboard: +0.038 Nm/kg), and these changes were not statistically significant (Figure 8B). Unexpectedly, while the exosuit increased the peak total ankle moment in the affected leg, it simultaneously reduced the peak positive ankle power at push-off (onboard: −0.062 W/kg, offboard: −0.112 W/kg). These reductions in ankle power were not significant, however.

Walking with the exosuit produced no significant changes in the ankle mechanics of the unaffected leg. Further, no substantial changes were observed in biomechanical gait variables in either the frontal or transverse plane at the ankle joint while walking with the exosuit, and so no variables or curves from these planes are reported.

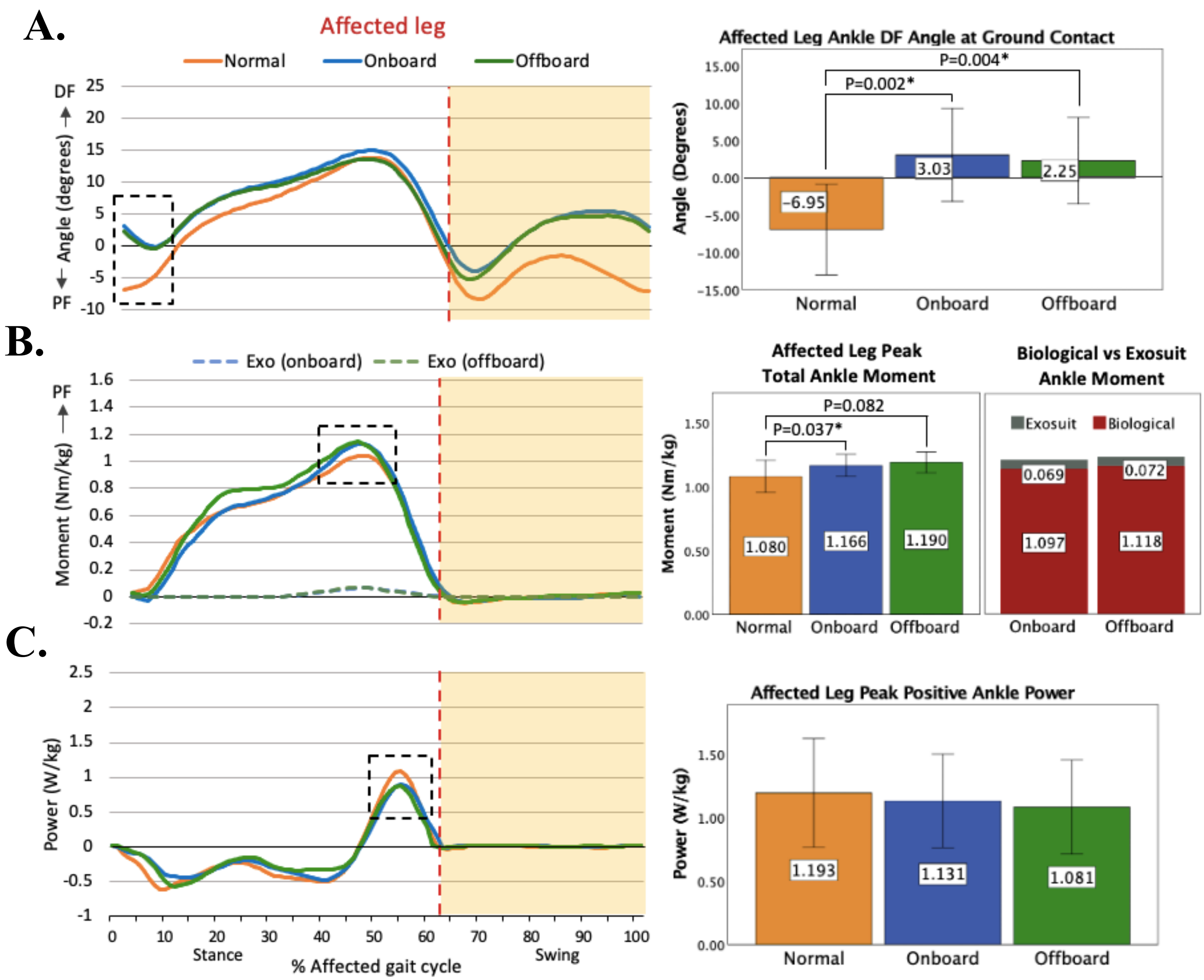

Figure 8: Affected Ankle Mechanics with the Exosuit. Ankle joint angles (A.), moments (B.), and powers (C.) for the sagittal plane are displayed for the affected leg in the three walking conditions (normal, onboard, and offboard). Additionally, for the moment graph (B.), the exosuit generated moment curves in the onboard and offboard condition are displayed. The ankle mechanics in the unaffected leg were unchanged with the exosuit, so no curves are shown. The curves are normalized to the average gait cycle and the vertical red dotted line indicates toe off, with stance phase coming before this line and swing phase after the line (shaded region). The dotted boxes within the graphs highlight regions of interest where the exosuit induced a change in the joint mechanics compared to the normal walking condition. These highlighted boxes are further explored with the bar graphs, which display the mean values of the key variables and any important statistical differences that were found between the two exosuit conditions and normal walking. Further, the contributions from the biological moment and exosuit-generated moment to the total peak ankle plantarflexor moment are shown in the far-right bar chart in B. The error bars in the bar charts represent the 95% confidence intervals. Statistical differences are given with the brackets, with significant differences (p<0.05) denoted with an *.

8.4 Knee Joint Mechanics

Unlike at the ankle, the exosuit induced changes in knee joint mechanics in both the affected (Figure 9) as well as the unaffected (Figure 10) leg. There was an increase in peak knee flexion during stance with the exosuit in both legs (affected onboard: +2.7°, affected offboard: +2.5°; unaffected onboard: +3.8°, *unaffected offboard: +3.4° [significant increase: p=0.031]). Further, the maximal knee flexion angle during swing was reduced with the exosuit, but only in the affected leg (onboard: -4.0°, offboard: -3.7°).

In terms of joint kinetics, we observed increases across both limbs in the peak knee extensor moment (affected onboard: +0.12 Nm/kg, affected offboard: +0.07 Nm/kg; unaffected onboard: +0.15 Nm/kg, unaffected offboard: +0.14 Nm/kg) as well as peak positive knee power (affected onboard: +0.15 W/kg, affected offboard: +0.09 W/kg; *unaffected onboard: +0.28 W/kg [significant increase: p=0.041], *unaffected offboard: +0.19 W/kg [significant increase: p=0.011]). Similar to the ankle joint, there were no changes in frontal or transverse plane knee mechanics during exosuit-assisted gait compared to normal walking; hence, no variables or curves from these planes are reported for the knee joint.

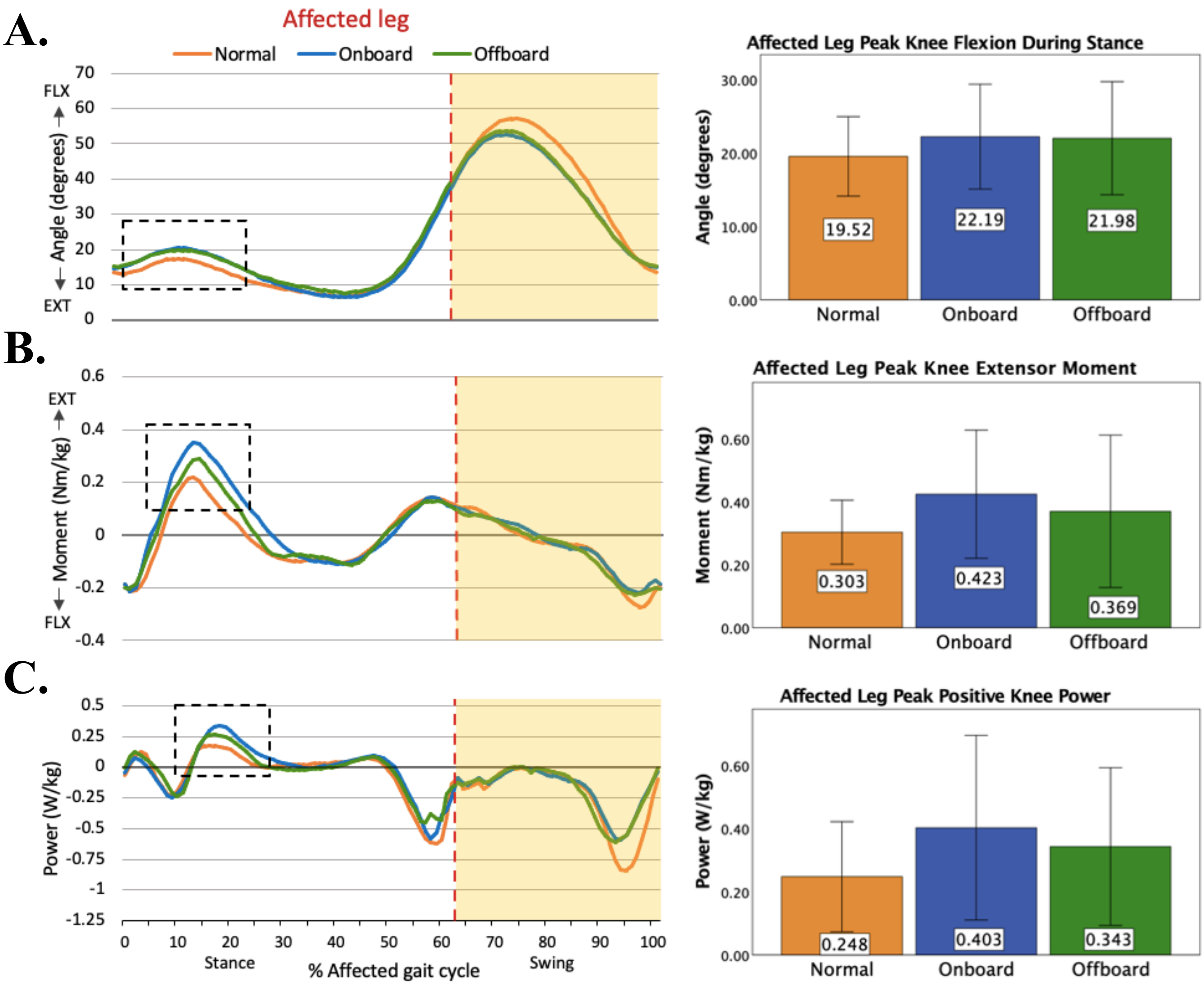

Figure 9: Affected Knee Mechanics with the Exosuit. Knee joint angles (A.), moments (B.), and powers (C.) are displayed for the affected leg in the three walking conditions. The curves are normalized to the average gait cycle and the vertical red dashed line represents toe off, with the shaded region indicating swing phase. Areas where the exosuit induced a change in the joint mechanics compared to the normal walking condition are highlighted with the dotted boxes and further explored in the bar graphs. The bar graphs display the mean values of the key variables within the boxes and the error bars represent the 95% confidence intervals. Statistical differences between the the exosuit walking conditions (onboard and offboard) and normal walking are given with the brackets, with an * representing statistically significant differences ($p<0.05$).

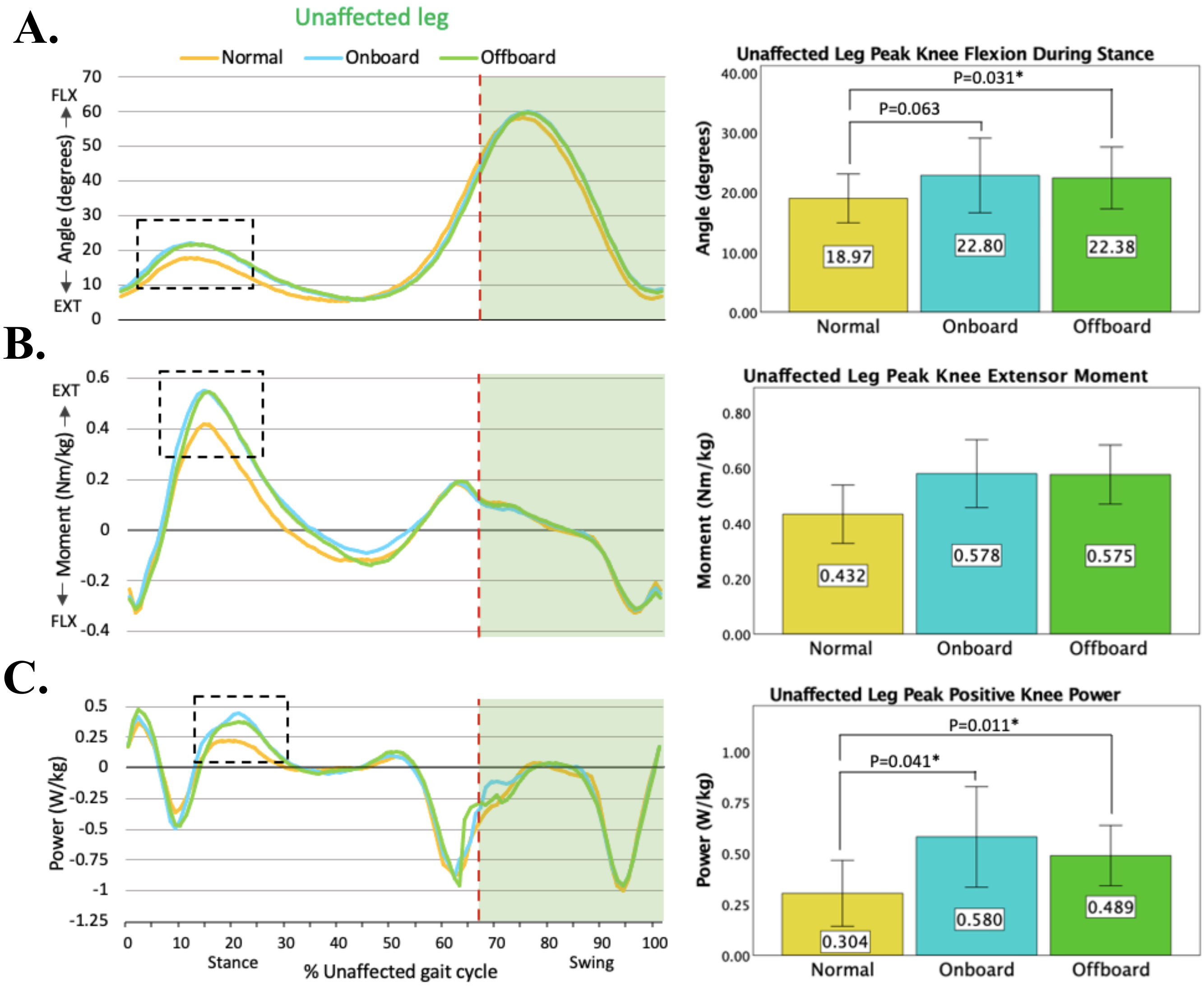

Figure 10: Unaffected Knee Mechanics with the Exosuit. Knee joint angles (A.), moments (B.), and powers (C.) are displayed for the unaffected leg in the three walking conditions. The curves are normalized to the average gait cycle and the vertical red dashed line represents toe off. The dotted boxes represent areas where the exosuit induced a change in the joint mechanics compared to the normal walking condition and are further explored in the bar graphs. The bar graphs display the mean values of the key parameters within the boxes and the error bars represent the 95% confidence intervals. Statistical differences between the the exosuit walking conditions and normal walking are given with the brackets, with an * representing statistically significant differences (p<0.05).

8.5 Hip and Pelvis Joint Mechanics

Walking with the exosuit induced some changes in hip and pelvis joint angles compared to the normal walking condition in both the sagittal and frontal planes (Figures 11 & 12, Table 2). In the sagittal plane, we observed a slight increase for both legs in the degree of hip flexion at ground contact (affected onboard: +2.5°, affected offboard: +1.6°; unaffected onboard: +1.9°, unaffected offboard: +1.3°) as well as in the degree of hip extension (more negative angle) at toe off (affected onboard: −2.1°, affected offboard: −1.0°; unaffected onboard: −1.4°, unaffected offboard: −0.7°) during exosuit-assisted walking compared to normal walking. These changes led to a greater hip range of motion during stance (calculated as the maximal hip extension angle at toe off subtracted from the hip flexion angle at ground contact) with the exosuit across both legs (affected onboard: +4.6°, affected offboard: +2.7°; unaffected onboard: +3.3°, unaffected offboard: +2.0°).

For the frontal plane hip and pelvis kinematic parameters, we observed differing effects of the exosuit on the affected (Figure 11) compared to the unaffected (Figure 12) leg. In terms of pelvic obliquity (the up and down movement of each side of the pelvis during gait), there was an increase (more negative angle) in the peak downward pelvic obliquity during stance in the unaffected leg (onboard: −0.86°, offboard: −0.94°), while there was an increase in the peak upward pelvic obliquity during swing in the affected leg (onboard: +0.88°, offboard: +0.97°) with the exosuit. Similar adaptations to the exosuit were observed in the hip adduction/abduction angles, with the exosuit increasing hip adduction (more negative angle) during stance in the unaffected leg (onboard: −0.92°, offboard: −1.92°), while simultaneously increasing hip abduction during swing in the affected leg (onboard: +1.31°, offboard: +1.23°). These changes to the hip and pelvis kinematics of the affected leg trended towards improved limb symmetry using the exosuit (peak upward pelvic obliquity was 33.7% and 23.7% more symmetrical while peak hip abduction during swing was 14.6% and 14.0% more symmetrical in the onboard and offboard conditions, respectively). None of the changes in hip or pelvis kinematics with the exosuit reached statistical significance, though.

There were no substantial changes in hip joint kinetics (moments and powers) with the exosuit in either the affected or unaffected leg, so these data are not reported.

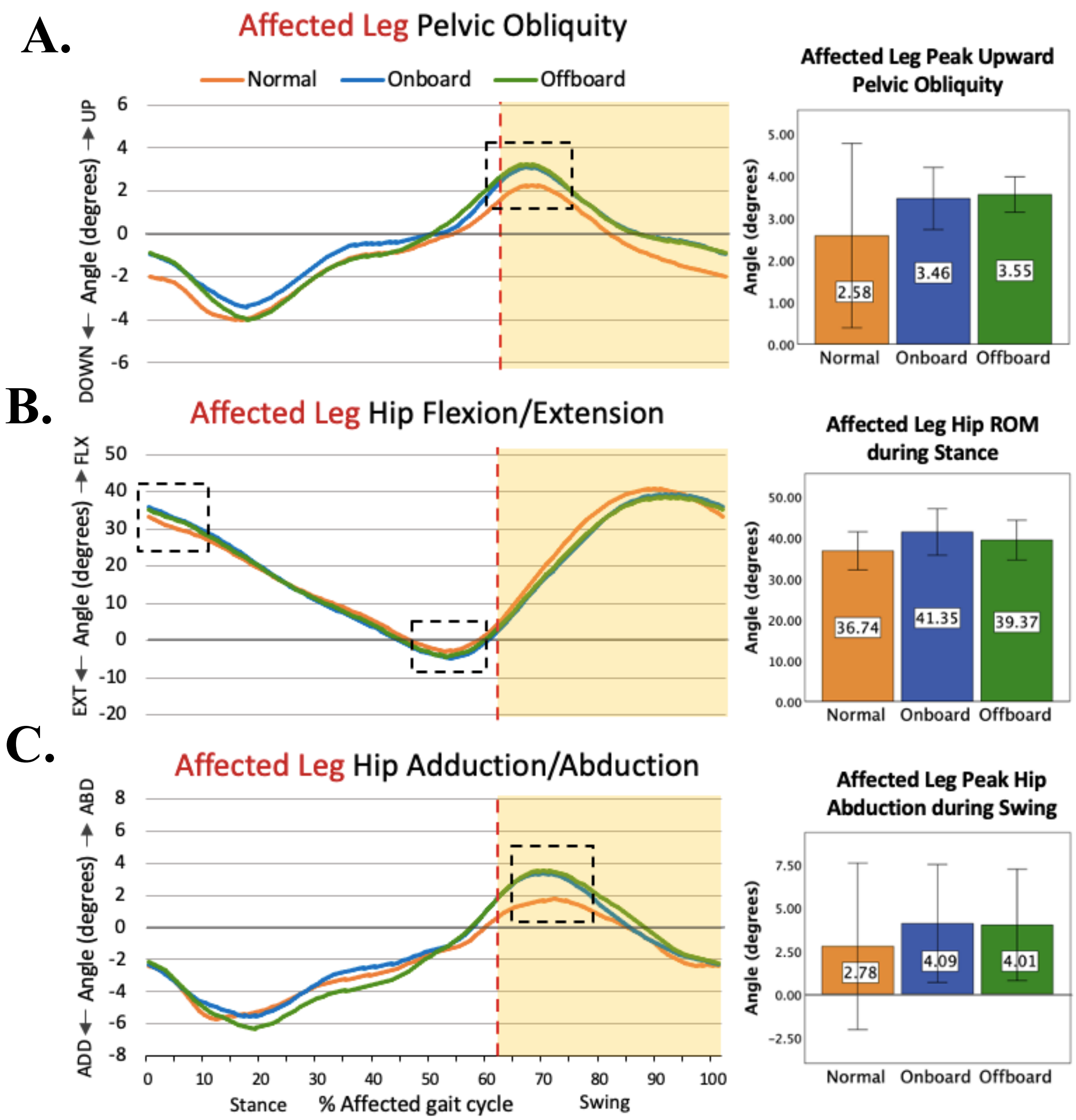

Figure 11: Affected Side Hip and Pelvis Angles with the Exosuit. Pelvic obliquity (A.), hip flexion/extension (B.), and hip adduction/abduction (C.) are displayed for the three walking conditions on the affected limb. The angle curves are normalized to the average gait cycle with the red vertical dashed line indicating the toe off event. Regions where the exosuit induced a change in the joint kinematics are emphasized using the dotted boxes and further highlighted in the bar charts. For the middle row bar charts, hip range of motion during stance was calculated as the maximum hip extension angle at push-off subtracted from the hip flexion angle at ground contact. Pelvic obliquity and hip adduction/abduction both concern joint kinematics in the frontal plane, with pelvic obliquity signifying the upward and downward tilting of either side of the pelvis and hip adduction/abduction representing the movement of the leg toward (adduction) or away from (abduction) the midline of the body. The mean value of the variable of interest is shown in the boxes within the bar charts, and the error bars represent the 95% confidence intervals.

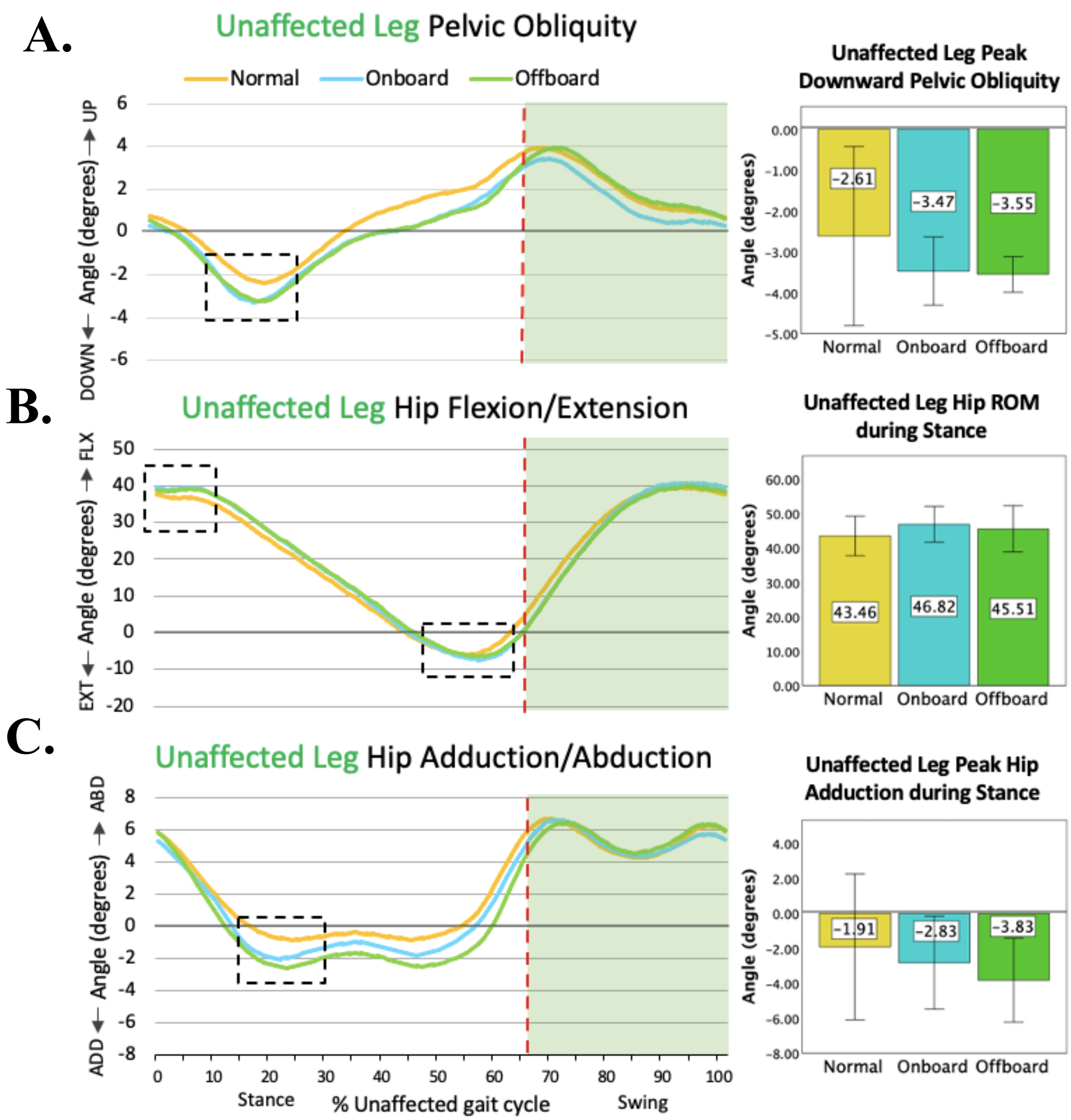

Figure 12: Unaffected Side Hip and Pelvis Angles with the Exosuit. The pelvic obliquity (A.), hip flexion/extension (B.), and hip adduction/abduction (C.) are displayed for the unaffected limb for the three conditions. The kinematic curves are normalized to the average gait cycle and the red vertical dashed line indicates toe off. The dotted boxes highlight regions where the exosuit induced a change in the joint angles compared to the normal condition. These parameters are further explored in the bar charts. The hip ROM during stance (B.) was calculated as the maximum hip extension angle at push-off subtracted from the hip flexion angle at ground contact. Pelvic obliquity and hip adduction/abduction are both frontal plane movements, with pelvic obliquity signifying the upward and downward tilting of either side of the pelvis and hip adduction/abduction representing the movement of the leg toward (adduction) or away from (abduction) the midline of the body during walking. The mean value of the variable of interest is shown in the boxes within the bar charts, and the error bars represent the 95% confidence intervals.

8.6 Ground Reaction Force Variables

The vertical ground reaction force showed some changes with the exosuit compared to normal walking in both the affected and unaffected legs of our participants (Figure 13, Table 2). The first peak of the normalized vertical ground reaction force, corresponding to loading response during gait, was increased with the exosuit in both limbs (affected onboard: +1.6% BW, affected offboard: +3.6% BW; unaffected onboard: +3.6% BW, *unaffected offboard: +7.5% BW [significant increase: p=0.036]). The second peak of the vertical ground reaction force, corresponding to the vertical force produced at push-off, similarly increased in both legs with the exosuit (*affected onboard: +2.7% BW [significant increase: p=0.018], affected offboard: +3.3% BW; unaffected onboard: +1.2%, unaffected offboard: +3.3% BW). The increase in this second peak of the vertical ground reaction force was somewhat more pronounced in the affected leg, likely corresponding to the addition of the assistive force from the exosuit, which increased the force generation from this limb. Contrastingly, however, the changes in the peak anterior component of the horizontal ground reaction force were minor with the exosuit in both legs (affected onboard: +0.5% BW, affected offboard: +0.8% BW; unaffected onboard: +0.3% BW, unaffected offboard: +0.6% BW). Thus, the assistive plantarflexion force from the exosuit slightly increased the magnitude of vertical force produced by the affected leg at push-off, but did not significantly increase the anterior propulsive force generation from this leg.

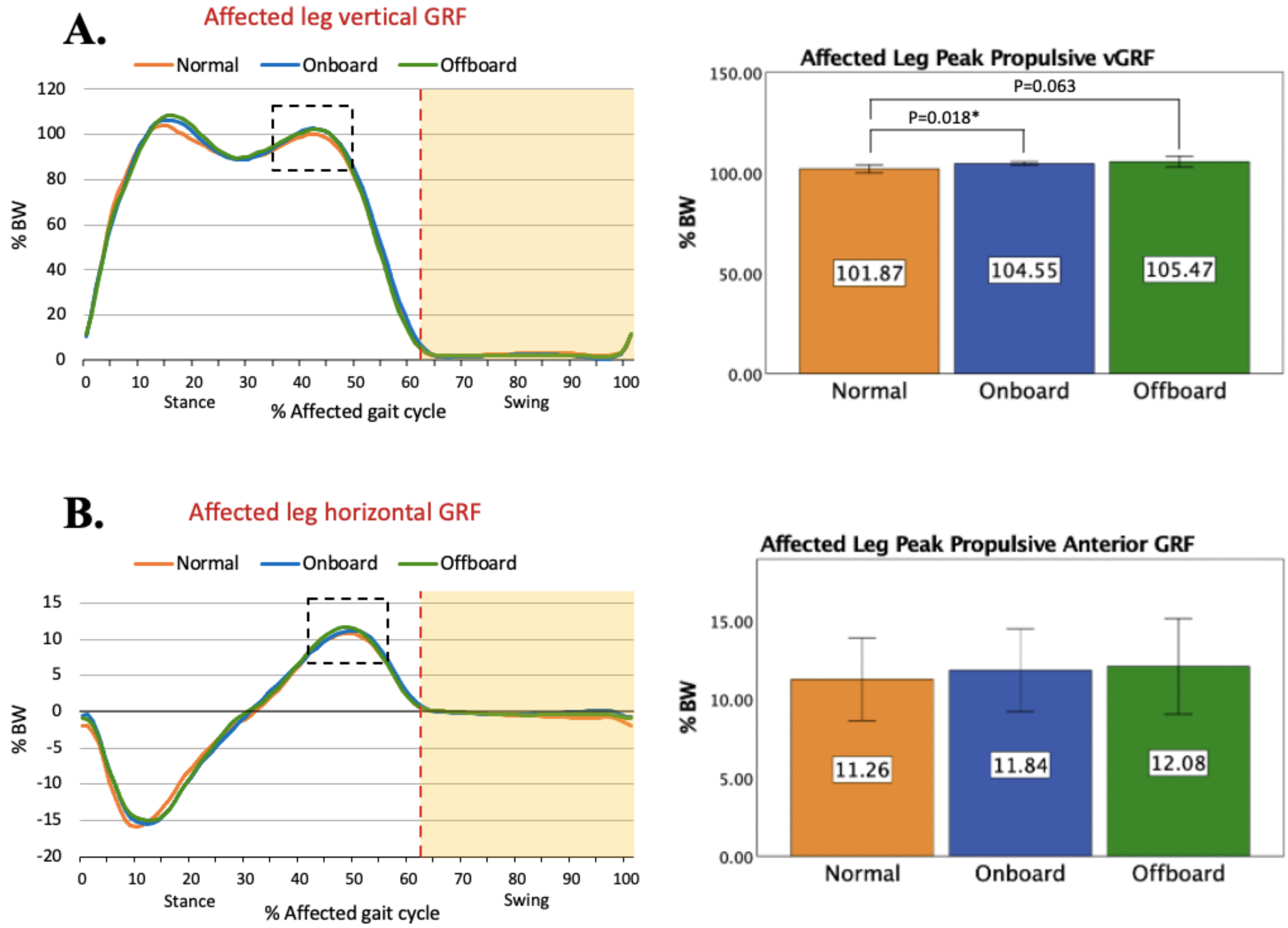

Figure 13: Exosuit-Induced Changes in GRF. The vertical (A.) and horizontal (B.) GRF curves for the affected leg are given. The red vertical line denotes the toe off event. The bar chart in A. represents the second propulsive peak of the vertical GRF, while the bar chart in B. represents the peak propulsive anterior GRF. The mean values for the variables are given in the boxes and the error bars represent the 95% confidence intervals. The GRF data shown has been normalized to participants' body weight, and is thus given as a percentage of body weight (BW). Statistical differences are displayed by the brackets, with an * denoting a significant difference (p<0.05).

8.7 Muscle Activity

The mean muscle activity across the full gait cycle relative to the maximal activity during normal walking expressed as a percent for those muscles examined in this study are presented at the bottom of Table 2 and in Figure 14. For the most part, the exosuit produced no major changes in muscle activity in the unaffected leg. There was a slight increase in Soleus activity in the unaffected leg with the exosuit (onboard: +3.4%, offboard: +2.8%), but this change was not significant ($p=0.322$). In the affected leg, we saw a reduction in Tibialis Anterior activity while walking with the exosuit (onboard: −8.0%, *offboard: −10.9% [significant reduction: $p=0.028$]). The other muscles of the affected leg showed more inconsistent changes, with slight reductions in Gastrocnemius Medialis (onboard: −5.9%, offboard: −3.8%), Rectus Femoris (onboard: −1.2%, offboard: −4.5%), Vastus Lateralis (onboard: −1.2%, offboard: −3.0%), and Biceps Femoris (onboard: −1.8%, offboard: −7.0%) activity as well as a slight increase in Soleus (onboard: +4.2%, offboard: +2.1%) activity with the exosuit compared to normal walking. Generally, there was a trend towards reduced muscle activity using the exosuit compared to walking without the device, especially in the offboard condition, though (Figure 14). However, none of the changes in activity of the muscles other than the Tibialis Anterior in the affected leg reached statistical significance.

It is important to note that the variability in the muscle activity data was quite high, with the CV often exceeding 50% for many of the muscles we assessed. The range of variability in the data, expressed as the maximum and minimum CV, was 31.0% to 77.6% in the affected leg, and 18.7% to 50.7% in the unaffected leg. This high variability in the muscle activity data likely limited the statistical analysis.

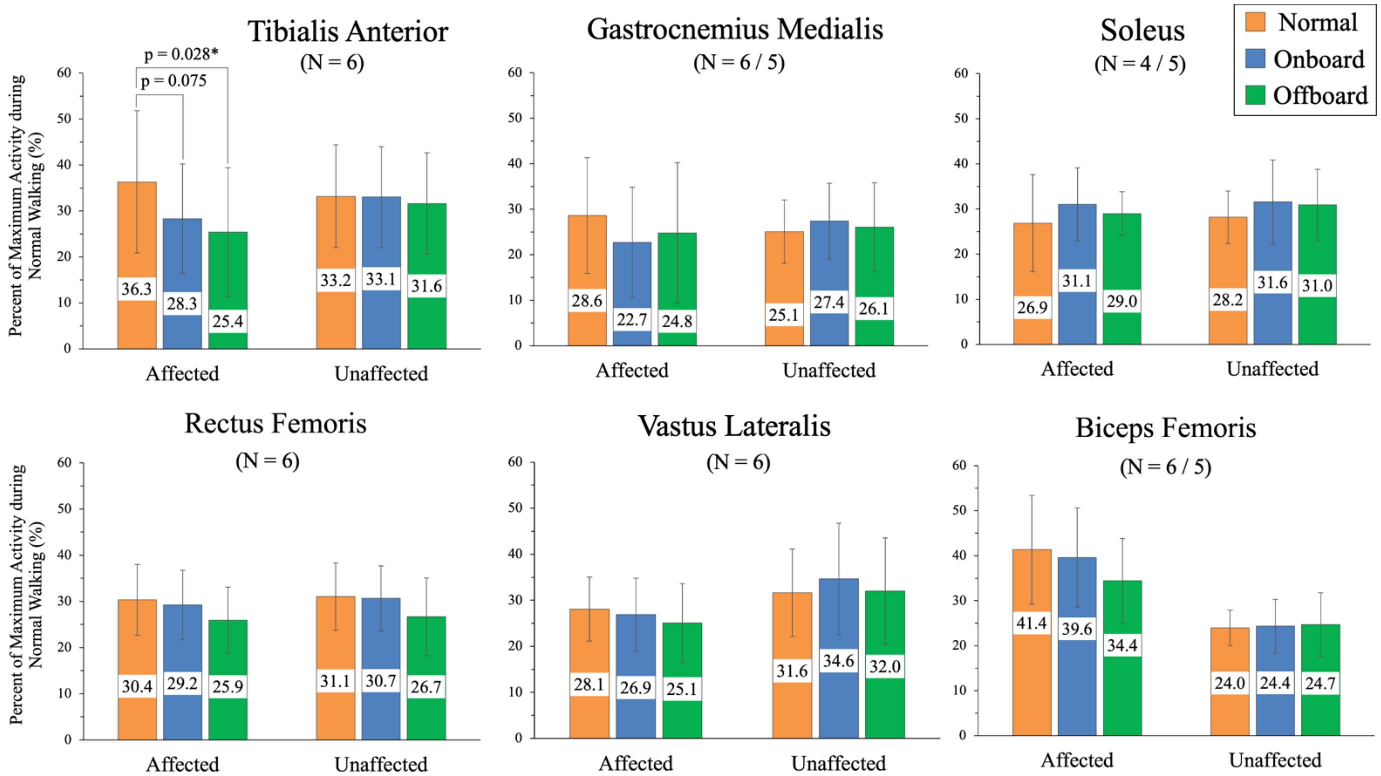

Figure 14: Lower Limb Muscle Activity with the Exosuit. The muscle activity for the Tibialis Anterior, Gastrocnemius Medialis, Soleus, Rectus Femoris, Vastus Lateralis, and Biceps Femoris muscles are displayed for the affected and unaffected leg for the three measured walking conditions (normal, onboard, and offboard). The values of the bars represent the mean muscle activity over the full gait cycle normalized to the maximal activity measured during the normal walking trial for each respective muscle. The above charts display muscle activity data from only 6 subjects, as the EMG data from subject 6 was lost. Additionally, some additional subjects' data was excluded from some muscles (see text for details). The numbers under the muscle names denote the number of subjects that are represented for that muscle, with the first number signifying the affected leg and the second number signifying the unaffected leg (if all six subjects were taken for the affected and unaffected leg data, then only a single number is displayed). The error bars signify the 95% confidence intervals. Statistical differences are shown via brackets, with an * denoting a significant difference ($p<0.05$). The absence of brackets signifies no significant differences were present for that muscle between conditions.

9. DISCUSSION

The main purpose of this thesis was to investigate the effects of a soft unilateral exosuit (ReWalk ReStore) on the walking mechanics and energetics in a small cohort of children with CP. The results reveal the exosuit reduced the metabolic cost, augmented lower limb joint mechanics, and altered the muscle activity patterns during walking amongst our participants. In terms of energetics, the metabolic cost of walking was reduced by 6.9% when participants walked while carrying the exosuit motor (onboard condition), and was reduced by 14.7% when participants walked with the motor offloaded (offboard condition), compared to walking without the device (normal walking). However, these changes were not significant. Additionally, the exosuit, and the assistance it provided at the affected ankle augmented the walking mechanics at the ankle, knee, and hip. Walking with the exosuit induced greater ankle dorsiflexion during swing as well as at ground contact and increased the peak ankle plantarflexor moment in the affected leg, amplified the peak knee extensor moment and peak positive knee power during midstance in both legs, and altered hip and pelvis kinematics across both limbs compared to normal walking. Further, the overall level of muscle activity in the affected leg during walking was altered with the exosuit, as the device facilitated reduced activity in the tibialis anterior as well as produced a trend towards reduced activity in the Gastrocnemius Medialis, Rectus Femoris, Vastus Lateralis, and Biceps Femoris muscles. This reduction in muscle activity was especially prevalent in the offboard condition. Taken together, these results support the continued investigation of this exosuit device for enhancing and treating pathological gait and should help to inform the future use of this exosuit moving forward. The results of this thesis, in combination with relevant literature, also raise important questions about the true effects of robotic assistive technology and how these devices might best be used to improve the functional abilities of those with motor deficits.

To explore these questions, this discussion section will be primarily structured around the two key aims of robotic assistive technology (see section 5). To reiterate, these aims are as follows:

> **Aim 1:** to enhance mobility in community settings and enable participation in activities that would be challenging if not impossible without the device (i.e., the device goes home with the patient and is used as an assistive aid to boost patient function when needed)

Aim 2: to improve neurorehabilitation via robotic gait training using the devices in the clinical setting (i.e., the device stays in the lab/clinic and is used as a therapy tool to improve patients' independent walking ability)

Importantly, different outcome measures and experimental results are associated with these two different aims. Reducing the metabolic cost and/or enabling increased overground walking speed would be positive results in regard to Aim 1, as these would suggest that walking with the device makes walking easier, faster, and more efficient. Contrastingly, improving joint mechanics during gait and altering muscle activity to healthier patterns would be positive outcomes in regard to Aim 2, as these results would indicate the device has the capacity to train a more normal walking pattern and augment muscle activity. In this final section of the thesis, I will examine how the results from our study fit into this paradigm. Additionally, the relation of the results from this thesis to relevant literature in the field of assistive technology and neurorehabilitation will be discussed within the context of these two key aims. Theories regarding the potential for future research using exoskeleton and exosuit devices for patients with neuromotor dysfunction will also be examined. Finally, the section will conclude with a discussion on the limitations of the thesis.

9.1 ***Aim 1*** *– The Results of the Thesis and Relevant Research*

We observed a reduced metabolic cost while walking with the exosuit compared to normal walking in both the onboard and offboard conditions. Although these reductions did not reach statistical significance in the present study due to variable metabolic effects in our small cohort, it is possible that the addition of a few more participants could help to drive the energetics results towards statistical significance. The observed trends in metabolic cost while using the exosuit suggest the device can help to make walking easier and more efficient for patients with CP, though, and thus are positive results in regard to Aim 1 of robotic assistive technology. The 6.9% metabolic reduction observed in the onboard condition is especially relevant, as the onboard condition involves the patient carrying the entire autonomous device, and thus, should be representative of how the device would be used in everyday settings. Of course, future research investigating the metabolic effects of the full device in overground walking conditions will be integral to better understand how the device may perform in more variable and authentic environments.

Our results are generally in line with those from other recent studies using exosuits and exoskeletons to assist the ankle joint in patients with neuromotor deficits. Of particular importance are those studies that also use the ReWalk ReStore Exosuit, as this is the same device used in the present thesis. Multiple studies have been done examining the effects of the ReStore device on the gait of post-stroke patients (Awad et al. 2017a; Bae et al. 2018; Awad et al. 2020a; Awad et al. 2020b). In one particularly relevant study using a preliminary prototype of the ReStore, the researchers observed a 10% reduction in the metabolic cost of walking with the exosuit device powered compared to walking with the device unpowered in their cohort of nine chronic stroke patients (Awad et al. 2017a). The participants walked on a treadmill with the motor offloaded from the body in this study, however. In a subsequent study using a more finalized prototype of the exosuit during overground walking, the stroke patients were able to walk both faster and farther in clinical tests when the device was providing active assistance; however, the powered exosuit did not reduce the metabolic cost of walking when the patients had to walk while carrying the exosuit motor overground (Awad et al. 2020a). Taken together, these results indicate the ReStore exosuit can facilitate improved walking capacity in post-stroke patients, but is only able to significantly improve the metabolic cost of walking in these patients when the heavy 4 kg motor is offloaded from the body.

Other relevant research has been conducted using a bilateral ankle exoskeleton device (Biomotum Spark) that was designed for children with CP (Lerner et al. 2019; Lerner et al. 2018; Orekhov et al. 2020). This device assists plantarflexion and dorsiflexion bilaterally at the ankle joint using contractile cables, a dynamic hinge joint, and a force-sensing footplate (similar mechanism to the ReStore exosuit used in the present thesis). Experiments using the Biomotum Spark exoskeleton have also examined the energetic changes induced by the device during walking, and the results have shown a 19% reduction in the metabolic cost of walking on the treadmill using the exoskeleton compared to walking without the device (Lerner et al. 2018). Further, the Spark reduced the metabolic cost of overground walking by 8.5% in these same CP patients (Orekhov et al. 2020). Importantly, the device was custom-fitted to the patients in these studies and the reductions in metabolic cost that were observed were incurred with participants walking while carrying the device's 1.1-kilogram motor. Thus, these data suggest that, for CP patients, custom-fitting the device and reducing the mass of the motor as much as possible may be key for enabling more energetically efficient gait even while patients carry the full system. It may be that the weight of the exosuit motor used in this thesis (4 kg) was slightly too heavy for our cohort of children and adolescents with CP to elicit a significant reduction in the metabolic cost during the onboard walking condition. Future research investigating overground walking using the full exosuit system in CP patients will be crucial to better understand the energetic effects of wearing the device in community settings.

The assistance level of the device is also an important aspect to consider when the goal is to make walking easier and more efficient for the patients. In this study, we progressively increased the plantarflexion assistance level from the exosuit throughout the protocol and chose the assistance level that gave the greatest reductions in metabolic cost to further analyze biomechanically. The energetically optimal assistance level differed between our participants and between the onboard and offboard walking conditions (Table 1). While some of our participants incurred the greatest metabolic benefits from the device at the highest assistance level (i.e., 100%, corresponding to a peak force of 25% BW), some others benefitted most from the device at lower assistance magnitudes (60-80%) and their metabolic cost of walking only increased at these higher assistive levels. Interestingly, these data contrast with a study that investigated the metabolically optimal assistance level for a soft exosuit that bilaterally assisted the ankle plantarflexors and hip flexors in a cohort of healthy subjects (Quinlivan et al. 2017). In their data, the highest assistance level (corresponding to a peak assistive force of 75% of BW) gave the greatest metabolic reductions, and the healthy participants only further reduced their walking energy expenditure as the assistance level increased (Quinlivan et al. 2017). The disparity between our data and these results may indicate that healthy participants can adapt to high assistance magnitudes from robotic devices and still leverage the applied forces for metabolic gain; however, patients with neuromotor impairment, such as our patients with CP, may be unable to adapt to and/or fully exploit higher magnitude assistance and these high forces may become perturbing to the patients' gait cycle, leading to increases in energy cost at these high assistance levels. Currently, most study protocols that investigate the effects of robotic assistive technology on walking in clinical patients have utilized a single fixed assistance level (Awad et al. 2017a; Lerner et al. 2019), though, so cannot address how metabolic cost may change with varying assistance. Thus, more research is needed to better understand the relationship between assistance level and metabolic cost during walking in patients with motor impairments and to investigate the optimal assistance level for incurring the greatest metabolic gains in various clinical populations.

*9.2 **Aim 2** – The Results of the Thesis and Relevant Research*

Instead of focusing on making walking easier and more efficient in everyday settings, Aim 2 of robotic assistive technology is focused upon using these devices as rehabilitative tools to enhance mobility therapy in the clinic. Thus, the key outcomes associated with Aim 2 differ from Aim 1 and are centered upon the device inducing a healthier biomechanical walking pattern and augmenting muscle activity. Although facilitating a more energetically efficient gait may enable longer bouts of walking training (Awad et al. 2017a), reducing the metabolic cost of walking is not a key focus of Aim 2. In fact, inducing a slightly more metabolically taxing gait using the device may actually be preferred, as training with this device should then stimulate greater cardiometabolic adaptations in the patient.

Our results from this thesis showed conflicting results in regard to Aim 2, with the exosuit inducing improvements to joint mechanics during walking, but also producing a trend towards reduced overall muscle activity. Regarding the gait biomechanics, the most pronounced changes with the device included increased ankle dorsiflexion during swing and at initial contact in the affected leg, as well as increased peak knee extensor moment and power during midstance in both legs. These changes to knee and ankle mechanics induced by the exosuit were both towards more normal walking patterns (see Fukuchi et al. 2018 for reference), and so suggest the exosuit could act to train more normal walking biomechanics. Notably, though, while the peak affected ankle plantarflexor moment was increased with the exosuit, the biological contribution to the peak moment was almost unchanged. This indicates that the force delivered by the exosuit to augment ankle plantarflexion does increase the overall ankle moment, but may not assist in training the affected ankle to produce greater force on its own.

In post-stroke patients, similar results have been observed in regard to changes in joint mechanics in response to the ReStore exosuit. These data have shown improved ankle dorsiflexion during swing phase, increased propulsive force generation from the paretic limb, and more symmetrical COM power generation across legs using the powered exosuit compared to unpowered (Awad et al. 2017a; Bae et al. 2018). Interestingly, although the

ReStore only directly assists the paretic ankle, the researchers observed changes in whole lower limb joint mechanics in both the paretic and non-paretic leg (Bae et al. 2018). Our data displayed similar results, with the exosuit inducing changes not only to affected ankle mechanics, but also to knee and hip joint mechanics in both the affected as well as the unaffected leg in our cohort of CP patients. In a separate study, the ReStore exosuit was shown to reduce hip hiking and circumduction in stroke patients, indicating that the device can lessen the reliance on inefficient compensatory walking mechanisms post-stroke (Awad et al. 2017b). Similar biomechanical results have been observed using the Biomotum Spark exoskeleton in CP patients. Compared to normal walking, walking with the exoskeleton produced greater stance phase lower limb extension, increased positive power generation at the ankle, and reduced positive hip power in a cohort of five CP patients (Lerner et al. 2019). Taken together, these results imply robotic ankle assistance can fully augment the overall walking strategy of patients with neuromotor dysfunction and thus may be able to guide patients towards a healthier gait pattern.

The results in regard to muscle activity changes resulting from robotic ankle assistance, however, are less positive for the potential therapeutic aims of these devices. In our study, the exosuit caused reduced activity in the affected Tibialis Anterior (TA) muscle as well as produced a trend towards reduced activity in the Gastrocnemius Medialis (GM), Rectus Femoris (RF), Vastus Lateralis (VL), and Biceps Femoris (BF), especially in the offboard walking condition. These changes in muscle activity likely contributed to the reductions in metabolic cost observed with the exosuit, but also may point to suboptimal therapeutic potential using the device. Reduced muscle activity during gait training with the exosuit could lead to a poor training stimulus and overall diminished function when the patient has to walk without the device (Wu et al. 2016). Taken together with our biomechanical results, these data suggest our patients were able to leverage the assistive forces delivered from the exosuit to augment their walking pattern while simultaneously reducing the active output from their muscles. For instance, the assistance provided at the front of the foot from the exosuit improved ankle dorsiflexion but, in so doing, enabled the patients to reduce their dorsiflexor muscle activity as they began to rely on the device for foot clearance. Similar results have been observed in patients with CP in response to bilateral ankle assistance from the Biomotum Spark exoskeleton. These results display reductions in plantarflexor muscle activity during treadmill as well as overground walking in response to active plantarflexion assistance from the exoskeleton device (Lerner et al. 2019; Orekhov et al. 2020). Again, these results indicate that robotic plantarflexion assistance may allow patients to reduce their active muscle output by relying on the device to supply propulsion. The effects of the ReStore exosuit on muscle activity in post-stroke patients has only been minimally investigated, but in a small study on eight hemiparetic stroke patients, the data showed no significant changes in dorsiflexor or plantarflexor muscle activity when walking with the exosuit overground compared to walking with the device unpowered (Sloot et al. 2018). While maintaining muscle activity levels during exosuit-assisted walking would be a more positive result compared to reduced muscle activity, it would still likely not be sufficient to induce the lasting neuroplastic changes that would be essential to transforming patients' walking abilities. If these devices are to act as effective therapeutic tools, they must promote active engagement from the patient as well as facilitate changes to motor output that are in-line with the target gait pattern.

From our results, though, we did observe a trend towards increased activity in the soleus muscle while walking with the exosuit, especially in the onboard condition (Figure 14). Considering the ankle plantarflexors are often one of the most impaired muscles in patients with unilateral CP, an increase in soleus activity during exosuit-assisted walking would be a positive therapeutic result. Further, this increased activity in the soleus muscle may suggest that robotic ankle assistance may not always facilitate reduced muscular activity, but may instead act as a catalyst for increased motor output in certain situations. Some studies back up this idea and show that robotic assistance can also have beneficial effects on motor output in clinical patients. These papers show that robotic gait assistance can elicit a more symmetrical motor program and induce muscle activity patterns that more closely correlate to healthy patterns during walking (Coenen et al. 2012; Aurich Schuler et al. 2013). Importantly, though, the EMG data presented in this thesis has many limitations (see section 9.7) and thus, it is challenging to interpret the muscle activity of our patients with high levels of confidence. Future investigations which more closely examine the muscle activity changes induced by robotic ankle assistance and their relation to muscle activity patterns exhibited during healthy walking will be crucial going forward.

Interestingly, wearable robotic devices have the capacity not only to provide assistance, but also targeted resistance during walking, which may have more positive therapeutic effects on muscle activity compared to robotic assistance. The Biomotum Spark exoskeleton has the capacity to provide adaptive plantarflexion resistance during the push-off phase, with the aim of stimulating greater volitional motor output from the plantarflexors and inducing targeted strength gains (Conner et al. 2020a). Results using this targeted resistance mode have shown increases in plantarflexor activity in combination with reductions in dorsiflexor activity leading to overall reduced levels of co-contraction at the ankle joint during walking in response to the exoskeleton-applied resistance in CP patients (Conner et al. 2020a). Thus, as long as the patients are functional enough to cope, robotic resistance may actually be a better option for facilitating improved motor output during robotic gait therapy than robotic assistance. Future studies will be crucial to better understand the most optimal robotic therapy strategy for each individual patient.

While no controlled clinical trials using lightweight ankle devices to augment gait training in patients with neuromotor dysfunction have been performed to my knowledge, pilot studies using the ReWalk ReStore exosuit and the Biomotum Spark exoskeleton have been performed in post-stroke and CP patients, respectively, to examine the therapeutic potential of training over multiple sessions with these devices. In a preliminary study using the ReStore exosuit, 36 post-stroke patients underwent five sessions of exosuit-assisted walking training. Following the training, the patients could walk faster both with the exosuit as well as on their own, suggesting patients improved their proficiency in using the device and increased their independent walking capacity (Awad et al. 2020b). In a similar pilot study using the Biomotum Spark, six subjects with CP underwent 4 sessions of overground gait training while the exoskeleton applied bilateral assistance to the ankle. The results displayed increased walking speed and stride length during both exoskeleton-assisted walking and when walking without the device following the training sessions (Fang et al. 2020). Interestingly, the exoskeleton walking training also improved stride-to-stride repeatability of soleus and vastus lateralis muscle activity, which suggests the assistance provided by the exoskeleton may act as a proprioceptive cue during robotic gait training to guide the motor output to the muscles to be less variable (Fang et al. 2020). Pilot investigations into the therapeutic effects of gait training using targeted resistance using the Biomotum Spark exoskeleton have also been performed. These studies show that, following ten training sessions of exoskeleton-resisted gait therapy, a cohort of six CP patients displayed increased ankle plantarflexor strength, faster walking speed, augmented muscle coordination, reduced metabolic cost of unassisted walking, and improved performance in functional tests (Conner et al. 2020b; Conner et al. 2021). Thus, so far, the preliminary results have been highly positive in regard to the therapeutic potential of robotic gait training using lightweight exoskeletons and exosuits in patients with neuromotor dysfunction, but controlled clinical trials with greater sample sizes comparing therapy using these devices to traditional rehabilitation will be crucial to confirm these positive preliminary findings.

9.3 Theories for Observed Metabolic Cost Reductions

It is important to understand not only how the results from this thesis fit in with similar research, but also to theorize how, biomechanically, the exosuit may have elicited the gait changes that it did in our sample of patients with CP. As stated, the exosuit reduced the metabolic cost of walking by 6.9% and 14.7% in the onboard and offboard conditions, respectively, compared to normal walking. But it remains unclear how these energy cost reductions were achieved. This section will outline some potential theories as to how the exosuit may have facilitated the metabolic changes that we observed. It is important to repeat, however, that the metabolic changes in this thesis were trends and not statistically significant.

The “metabolic cost of generating muscle force hypothesis” proposes that the metabolic rate during human movement is largely determined by the active muscle volume required to generate force against the ground and the rate that this volume generates force (Griffin et al. 2003). This theory also suggests the energetic cost of swinging the legs during human locomotion is negligible and that the majority of metabolic energy is consumed during the stance phase, when the muscles produce force against the ground to support the body weight and generate propulsion. It is possible that our exosuit reduced the metabolic cost of walking in our participants by shrinking the active muscle volume required during walking and by reducing the rate at which this volume needed to generate force. Considering that biomechanical changes in response to robotic assistance often do not effectively explain metabolic cost reductions using these devices, some researchers in the field have suggested that exoskeletons and exosuits make human walking more efficient by reducing the active muscle volume (Beck et al. 2019). The trend towards reduced muscle activity in many of the large lower limb muscles that we observed is in line with this hypothesis, and suggests that the assistance from our exosuit may have reduced the volume of active muscle required for walking. Further, while not statistically significant, we observed trends towards increased stance time and reduced affected ankle power with the exosuit compared to normal walking (Table 2). It has been suggested that stance time and metabolic cost are inversely related, and that increasing the time the foot spends on the ground reduces metabolic cost by allowing for reduced rate of force development and more efficient muscle activity (Kram and Taylor 1990). Thus, the increased stance time and reduced ankle power we observed may suggest the assistance from the exosuit enabled the muscles, especially the plantarflexors, to produce force against the ground at a slower rate using more economical muscle action, which would be more metabolically efficient. Importantly, the ankle plantarflexors have been shown to account for over half of the active muscle volume during normal walking (Griffin et al. 2003), so facilitating a more energetically efficient work rate for the ankle musculature may be a major mechanism by which our exosuit reduced metabolic cost. Thus, our results indicate that robotic assistance applied at the ankle by a soft exosuit may reduce the energy cost of walking through reducing the volume of muscle that is active as well as enabling this volume to generate force at a slower rate; however, future examinations using measures that can more effectively quantify combined muscle mechanics and activity parameters in real-time, such as ultrasound and/or high-density EMG, during exosuit-assisted walking will be necessary to confirm this theory.

One of the main mechanisms underlying the energetic efficiency of healthy gait involves the storage and release of elastic energy in the Achilles tendon (Sawicki et al 2009). Eccentric action of the plantarflexors throughout stance phase works to store energy in the compliant Achilles tendon, which is subsequently released at push-off to generate a significant proportion of the propulsive force necessary to continue the inverted pendulum gait pattern (Sawicki and Ferris 2008). This process is so efficient, because it produces force through a combination of near isometric muscle action and passive tendon mechanics, which both require little to no metabolic energy (see section 2.2 for more details). However, to successfully execute this storage and release mechanism requires high levels of central motor control and spinal reflex function to activate the plantarflexors at the appropriate timing and magnitude (Ishikawa and Komi 2008). For CP patients, deficits in motor control and muscle weakness are commonly most pronounced distally (at the ankle), and thus generating this delicate pattern of muscle activity may be challenging, if not impossible (Wiley and Damiano 1998). The inability to effectively utilize this energy storage and release mechanism at the ankle may impose greater propulsive force requirements onto less efficient joints, such as the hip, and require the use of more concentric muscle action during walking (Sawicki et al. 2009). Thus, the metabolically expensive nature of pathological gait may be partly caused by patients' inability to employ the movement strategies that underlie the efficiency of healthy gait due to their impairments.

However, assistive technologies, such as our exosuit, may be able to facilitate this energetically efficient storage and release mechanism at the ankle through the assistance that they provide. Interestingly, it has been shown that the assistance provided by an ankle exosuit (ReWalk ReStore) can act to augment joint mechanics, using energy storage and release mechanisms that are similar to healthy ankle joint function. In the study, the researchers observed that much of the mechanical power delivered by the exosuit was being absorbed into the interface materials of the device, rather than directly assisting the ankle joint. Rather than being dissipated, however, this energy was then returned viscoelastically during exosuit offloading to assist with ankle plantarflexion during push-off. (Yandell et al. 2017). Passive ankle exoskeletons commonly utilize this same mechanism, and employ a spring, in parallel with the plantarflexor muscles, to store and subsequently release energy to assist with propulsion (Collins et al. 2015). Thus, it may be possible that exoskeletons and exosuits could improve locomotion economy in patients with pathological gait by facilitating this energy storage and release mechanism at the ankle joint. However, there have been no studies investigating whether this storage and release mechanism is occurring using either powered or passive devices in clinical populations with gait deficits. Further, it is unknown whether training with robotic assistive devices that employ this energy storage and release strategy would improve patients' capacity to perform this walking strategy on their own, or if patients with neuromotor dysfunction are even capable of efficiently storing and releasing energy during walking with their limiting impairments. Thus, future research would be required to understand whether and how exoskeletons or exosuits may be able to assist patients to perform more efficient walking mechanisms, such as this storage and release of energy at the ankle joint.

Interestingly, in our study, we also observed changes in knee joint biomechanics in response to the exosuit that may have contributed to the more efficient gait pattern with the device. Although the exosuit only provided mechanical assistance at the affected ankle joint, our patients displayed increased knee flexion during stance, peak knee extensor moment, and peak positive knee power across both legs during exosuit-assisted walking, compared to normal walking (Figures 9 & 10). While these changes to knee dynamics should point to increases in knee muscle activity, in contrast, we observed a trend towards reduced activity in both the knee extensor and flexor muscles measured in this study during the exosuit walking trials (Figure 14). These results indicate that our patients were able to leverage the assistance from the exosuit at the ankle joint to augment knee joint mechanics and produce a more dynamic gait pattern without increasing their volitional muscle activity. Interestingly, these changes in knee joint dynamics have not been observed in those studies using the ReStore exosuit in post-stroke patients or the studies using the Biomotum Spark exoskeleton in CP patients (Bae et al. 2018; Lerner et al. 2019). In their experiments, there were no major changes in knee joint kinetics in response to robotic ankle assistance in their samples of post-stroke or CP patients. Thus, the changes we observed to knee dynamics in response to the ankle exosuit may be novel findings, and future investigations should examine the mechanisms by which ankle assistance can augment the biomechanics at more proximal joints, such as the knee.

9.4 Stimulating Gait Adaptation Using Robotic Assistive Technology

If exoskeletons and exosuits are to function as effective therapeutic tools and improve patients' independent mobility, as laid out in Aim 2, they must be capable of inducing lasting gait adaptation. Motor adaptation, as discussed in section 4.3, involves adjusting movement patterns in response to changes in conditions or imposed task-constraints (Roemmich and Bastian 2018). Thus, gait adaptation can be defined as changes to the gait pattern induced by alterations to the conditions in which walking is performed. During robotic gait training, the mechanical forces delivered by the device act to transform the walking conditions, with the aim of triggering adaptive responses towards a more functional gait pattern for the patient

(Severini et al. 2020). Understanding how gait adaptation occurs and how to best facilitate it, then, are both essential to inform robotic gait therapy.

Research investigating how people modify their walking strategy in response to robotic perturbation has helped to illuminate some of the driving forces behind gait adaptation. It has been shown that gait stability is the primary mediator of locomotor adaptation, and adaptations to preserve gait stability in response to a destabilizing perturbation will be implemented even at the cost of metabolic efficiency or gait symmetry (Severini et al. 2020). Basically, the locomotor system will always act to maintain gait stability and prevent a fall. Metabolic cost becomes an essential driving force for gait adaptations in conditions where gait stability is secured. Importantly, the healthy human gait pattern is shaped by the drive for energetic efficiency, and each individual's self-selected gait is learned and optimized throughout development to be the most efficient movement pattern for them (Saibene and Minetti 2003). Thus, the walking pattern is well ingrained into the motor circuitry and is generally resistant to change. However, research indicates that, in healthy humans, the gait pattern can be adapted in response to changes in the energetic landscape in which walking is performed (Selinger et al. 2015). These changes can be induced by robotic perturbations to change the energetic optimum of certain gait parameters away from the individual's self-selected patterns (i.e., alter the energetically optimal cadence or step length for instance). This research has shown that healthy people can adapt their gait pattern in response to the new energetic landscape and find the new most efficient walking pattern, but are only able to do so when prompted to change their self-selected pattern and explore the new motor conditions (Selinger et al. 2015). These results indicate that, without exploration of the new motor conditions, the motor system may stubbornly retain the self-selected gait pattern even when it is no longer energetically optimal; but also suggest that locomotor adaptation is possible when subjects are pushed to explore the new motor space and their motor system is given a chance to recognize that the self-selected pattern is no longer optimal and identify the new best movement pattern for the given conditions. Finally, gait symmetry is another factor that can influence walking adaptations, but changes to gait symmetry generally only occur when they are necessary to preserve stability or minimize metabolic cost (Severini et al. 2020). Overall, then, the research indicates that, while ingrained and resilient, human gait is adaptable to new conditions so long as the subject fully explores the new motor space. Further, the way the gait is adapted depends upon the way in which the movement conditions are changed, with perturbations to gait stability being corrected at all costs, changes to the energetic environment inducing adaptations when linked with motor exploration, and gait symmetry being modified when needed.

In order for gait adaptation to occur, the training or therapy must stimulate adaptation in the underlying neural networks that control walking. As mentioned in section 2.1, the neural control of human walking involves a complex interplay between pattern-generating spinal circuits (CPGs), sensory feedback, and supraspinal regulatory control (Nielsen et al. 2003). Thus, adapting these networks, and the interactions between them in a beneficial manner is a complex and challenging task. Importantly, there are two main neural mechanisms through which motor adaptation can occur. Feedback adaptation is a reactive, reflex-driven process to modify movement patterns quickly in response to sudden changes in movement conditions (Severini et al. 2020). In the context of walking, feedback adaptation can take the form of rapid reflexes to prevent a fall and maintain gait stability following a balance perturbation. Due to the small latency between perturbation and reaction, it is thought that feedback adaptation is mediated primarily by spinal reflex circuits (Morton and Bastian 2006). However, just as feedback adaptation is fast-acting, it is also short-lived, as the adaptive response is simply a reaction to the changing conditions or perturbation and is thus not stored or ingrained into the motor circuitry (Severini et al 2020). Contrastingly, feedforward adaptation is mediated by changes to the predictive model that underlies human movement patterns (Roemmich and Bastian 2018). This predictive model was discussed in section 4.3, but to review: prior to the performance of a movement, the central nervous system (CNS) creates a prediction for the consequences of the motor action based upon prior experience, and subsequently compares the prediction to the actual sensory outcomes of the movement. The amount of error between the predicted consequences and the real outcomes is fed back into the model in order to update it and improve the performance of future movements. The Cerebellum is the primary brain region that integrates these predictions and outcomes. (Krakauer et al. 2019; Manto et al. 2012.) Feedforward adaptation occurs, then, when there is a large mismatch in the motor predictions and actual motor outcomes, due to changes in movement conditions or imposed task-constraints. This sudden mismatch triggers the motor system to adjust the movement pattern and update the feedforward model in order to resynchronize the predictions with the real motor outcomes. (Roemmich and Bastian 2018.)

Feedforward adaptation is a gradual process, though, as modifying the predictive model within the CNS and applying it to the new conditions takes time (Severini et al. 2020). Consequently, feedforward adaptations are also lasting and, once the movement conditions are returned to normal, the adapted movement pattern usually persists for at least a short time (Krakauer et al. 2019). The lasting impressions of feedforward adaptation are termed after-effects. Crucially, motor adaptation, including gait adaptation, relies upon these two neural mechanisms in a context-dependent manner. For instance, if the changes to the movement conditions severely perturb gait stability, the adaptive response will be based primarily upon feedback adaptation, as the motor system must react quickly to the new conditions and change the movement pattern promptly to prevent a fall. Conversely, if the new movement condition rather disturbs a less vital gait variable, such as energetic cost or walking symmetry, but does not disturb stability, then the subsequent motor adaptation will rely primarily on feedforward mechanisms, as the adaptation process does not need to be immediate, and the motor system can take its time to learn the new motor space and modify its predictive model to suit the new conditions. (Severini et al. 2020.) Thus, all of this indicates that the motor networks that control walking can undergo different kinds of adaptive responses, and, crucially, the kind of adaptation that is elicited and whether it is lasting strongly depends upon the method that is employed to instigate it.

So, how does this research on gait adaptation relate to the results of this thesis, and how can it be applied to robotic gait therapy as a whole? While this thesis was focused on the acute effects of the exosuit device and no outcomes related to gait adaptation were explicitly measured, we did observe some significant changes to various biomechanical parameters, as well as a reduction in energetic cost while participants walked with the device providing assistance. These results suggest that the robotic forces from the exosuit prompted some acute biomechanical gait adaptations in our subjects. However, it is unclear what kind of motor adaptation may have been elicited, as well as whether these adaptations would be lasting once the patient returns to walking without the device. Future research will be necessary to better characterize and understand the gait adaptations that occur in response to robotic ankle assistance in patients with CP.

Overall, though, the research on gait adaptation can also help to inform robotic gait therapy more generally. Perhaps most importantly, robotic gait therapy should aim to elicit feedforward gait adaptation, as these changes would then be more lasting and ingrained into the motor circuitry (Kitago and Krakauer 2013). In order to improve patients' independent walking ability in the long term, training with the device must be able to induce neuroplastic changes to the predictive model that patients use to control their gait. It is also essential that the device does not perturb gait stability, as this would not only trigger more reactive feedback adaptation, but of course could also lead to dangerous trips and falls. When patients are first using the exosuit or exoskeleton, they should also be encouraged to explore different movement strategies using the device, to prompt their motor system to find the best way to move synergistically with the robotic forces (Selinger et al. 2015). Importantly, if walking with the device is able to elicit feedforward adaptation, then this should produce after-effects, meaning the patients should continue to walk with their new adapted pattern even when the device is removed, at least for a short time. During this after-effects period, reinforcement learning (briefly discussed in section 4.3) could be leveraged to better ingrain the learned adaptations and make them more lasting. Reinforcement learning involves using reward feedback to guide motor learning (Roemmich and Bastian 2018). In the case of robotic gait therapy, once the patients are displaying after-effects following gait training with the device, reward could then be given if the patient continues to execute the learned movement pattern on their own (Dhawale et al. 2017). In this way, this reinforcement learning period should create a mental association between the new adapted gait pattern and the subsequent reward, helping to ingrain the movement pattern, and the new neural connections that underlie it, for long-term use (Roemmich and Bastian 2018). Future research should aim to integrate these insights from motor adaptation research to inform robotic gait training protocols.

9.5 Implications for Patients with Cerebral Palsy

It is important to consider that, for patients with CP, the cerebral lesion occurred before the onset of walking, and thus CP patients develop their specific gait pattern under the neuromotor restrictions imposed by their brain injury (Rosenbaum et al. 2006). This is in contrast to some other neuromotor impaired groups, such as post-stroke patients or those with spinal cord injury, who most often suffer the neural lesion later in adulthood, after healthy movement patterns have already been well established. Gait training for these patients, then, aims to stimulate the damaged nervous system to re-learn the lost movement (such as walking). Contrastingly, patients with CP have no experience with truly "healthy" walking and thus have no motor memory to pull from during gait training. For patients with CP, gait training must teach them the healthy walking pattern from scratch, and this concept has some important implications that may guide future research and therapy methods for this patient group.

Research suggests that patients with CP have adapted fundamentally different mechanisms of neural control to operate their walking pattern (Piitulainen et al. 2021; Bekius et al. 2020; Short et al. 2020). For instance, studies using muscle synergy analysis have indicated that patients with CP recruit fewer muscle synergies during walking compared to those with typical development, which suggests CP patients utilize a simplified motor control strategy during gait (Bekius et al. 2020; Steele et al. 2015). Additionally, electroencephalography (EEG) studies have reported that CP patients display altered cortical activity patterns during walking compared to healthy patterns, with these studies showing that brain activity is elevated during walking in those with CP (Short et al. 2020; George et al. 2021). These results are corroborated by research using dual task walking paradigms in patients with CP, that have reported a higher cost to gait stability while walking and concurrently performing a cognitive task, as compared to those with typical development (Piitulainen et al. 2021). Together, these findings suggest that more attention and cortical resources may be required for walking in CP, perhaps as a means to compensate for patients' impaired musculoskeletal function and deficient motor control; however, these theories are still speculative, and the underlying mechanisms that explain these differences in gait-related motor output in CP are currently not well understood.

Beyond the irregular patterns of motor control during walking, it is also currently unclear how and why each individual CP patient adopts the specific gait pattern that they do. As discussed in section 2.2, the minimization of energy expenditure is a crucial driving force that has likely shaped the biomechanical characteristics of the healthy gait pattern (Gage et al. 2009). However, pathological gait may be mediated by fundamentally different mechanisms compared to healthy walking. For instance, recent data suggest that minimizing metabolic cost may not be as essential for patients with unilateral CP and that instead, these patients may adopt their asymmetric walking pattern as a means to equalize the muscular efforts between their affected and unaffected leg (Kulmala et al. unpublished). Further, not only are the mechanisms that explain each patient's particular walking pattern still unclear, but the changes to the neural architecture that might instigate a transformation towards more "normal" walking patterns in patients with neuromotor damage are also not well understood. For instance, some research in spinal cord injured patients suggests that, even after gait therapy, once a normal kinematic walking pattern has been regained, patients still display a highly altered pattern of muscle activity, as compared to the general healthy muscle activation pattern during walking (Grasso et al. 2004). This indicates that functional improvement following a neural lesion may not depend upon a return to "healthier" muscle activation patterns, but instead, that constraints placed onto the neuroplastic capabilities of patients following neural injury may force the damaged nervous system to adopt different patterns of muscle activity that are distinct from the healthy pattern to control their walking movements (Ivanenko et al. 2009). Importantly, though, these divergent muscle activity patterns can still accomplish the desired healthy gait pattern. Thus, these data indicate that pathological gait may be shaped by fundamentally different mechanisms compared to healthy walking and that gait therapy for those with neuromotor impairment should focus on training a more functional movement pattern, but should allow the patient to achieve this improved movement pattern through whatever neuroplastic means they have available to them.

Taken together, this research has important implications for CP therapy, as, these data allude to the idea that aiming for "normal" gait may not actually be the best target for patients with CP. Considering that CP patients establish their walking patterns post-lesion and these patterns are strongly shaped by the neuromotor and subsequent musculoskeletal constraints imposed by the lesion, it may be that the specific gait pattern adopted by each CP patient works as a best-fit biomechanical solution for his or her specific spectrum of impairments. Essentially, the gait pattern of each CP patient likely represents an attempt by the CP motor system to optimize functional ability given the individual's neuromotor and musculoskeletal deficiencies, and it may be that pushing this patient towards more "normal" walking will only destabilize this delicate optimization process and may actually reduce their function in the long term. This concept is corroborated by data from a large-scale clinical study in 147 patients with CP that showed an inverse relationship between changes to gait speed and changes in gait deviation index (a summary measure of the kinematic similarity between a patient's gait and the healthy walking pattern), following three common treatment approaches in CP (BoNT-A injection, SDR, and SEMLS) (Shuman et al. 2019). While not the primary focus of the study, the inverse trend from this large data set indicated that the evaluated treatments increased the gait deviation index score (i.e., made the walking pattern of the patients more "normal"), however, at the same time these treatments reduced the patients' gait speed (Shuman et al. 2019). Thus, these data point back to the idea that changes towards movement "normality" may not necessarily equate to improvements in functional ability in those with CP.

Overall, these data point to the importance of individualizing the therapy strategy for patients with CP and, beyond that, indicate that a "function-focused" therapy strategy, that attempts to harness each patient's residual functional abilities and strengthen their weaknesses to boost the efficacy of their self-selected movement pattern, may be a more effective treatment approach for some patients, compared to attempting to push them towards "normal movement." In the context of this thesis, robotic assistive (and potentially resistive) technology, such as exoskeletons and exosuits, present an exciting means through which this personalized and function-focused therapy might be delivered, as these devices have the potential to be adaptable and tailored to each patient. Beyond therapy, these devices could also boost patients' functional abilities in everyday settings. Thus, devices such as exoskeletons and exosuits may play an essential role in shaping the future of CP rehabilitation and even enhancing patients' everyday life. However, much still remains unknown regarding the clinical use of these devices, and significantly more research will be necessary before this technology can be fully integrated into standard neurorehabilitation practice.

9.6 Possibilities for Future Research

One vital area for future research involves optimizing the engineering and design of robotic assistive devices, to enable them to deliver the best possible therapy, while still being affordable and practical to use in clinical practice. The control strategy is one crucial aspect that influences the utility of the device, as the exoskeleton or exosuit must have the capacity to deliver mechanical forces that are tailored to each individual user's unique movement pattern, while remaining feasible for use in a clinic or even during everyday life. Some research has investigated the use of human-in-the-loop control paradigms, which involve integrating physiological measurements taken from the user (often metabolic cost) and use an algorithm to deliver robotic forces that attempt to optimize these user-derived measurements in real-time (e.g., find a robotic assistance profile that leads to the greatest reduction in metabolic cost for that particular user) (Ding et al. 2018; Poggensee and Collins 2021). While this human-in-the-loop control is highly individualized, it is also complex and time-consuming, and may be too challenging to implement in a clinical context. Further research has investigated the use of an offline assistance optimization program to control an exosuit device, using pre-recorded walking kinematics of the patient to form a best-guess assistance profile based on their movement pattern (Siviy et al. 2020). While more feasible to employ in a clinical setting than human-in-the-loop control, it is unclear whether this control method is able to accurately predict the optimal assistive profile for each individual patient. Intent-based controllers that utilize real-time muscle or brain activity measurements from the user to control the robotic forces from the device may be the best methods to truly sync user intent with device function; however, decoding these noisy physiological signals into clear control signals for the robot is a complex task, even for healthy gait, and only becomes more challenging in patients with neuromotor deficiencies (Contreras-Vidal et al. 2018; McCain et al. 2019). Future research into the most feasible control scheme for clinical populations will be essential moving forward.

Optimizing the magnitude of the robotic forces that are delivered to a joint or joints by an exoskeleton or exosuit is also complex, with research displaying varying results regarding how assistance magnitude relates to changes in walking mechanics and metabolic cost (Quinlivan et al. 2017; McCain et al. 2019; Sawicki and Ferris 2008; Poggensee and Collins 2021). The power requirements of these devices should also be further explored. Unpowered exoskeletons have been shown to be capable of altering gait mechanics and reducing energy cost in healthy subjects, even without adding any net energy to the user's movements (Collins et al. 2015; Nuckols and Sawicki 2020); however, the adaptability of these passive exoskeletons is unclear. A pseudo-passive device that utilizes the passive approach of storing and subsequently releasing energy to the user, while retaining a small motor that could inject small amounts of positive power into the movement where necessary, may be optimal, as this device could be small and lightweight, while remaining adaptable (Sawicki et al. 2020). However, to my knowledge, no such device has been tested in either healthy or clinical populations. Overall, though, in order to determine the optimal control paradigm or assistance profile or passive-powered balance, it will be essential to compare different device designs to one another. This comparative research, which alters various aspects of the design of the device to test the benefits or drawbacks of each feature in isolation, is sorely lacking as of now.

In terms of the true rehabilitative potential of exoskeletons and exosuits, much is still unknown. While preliminary pilot studies in patients with CP, as well as post-stroke patients, have shown highly positive effects on mobility and function following short training interventions using lightweight robotic ankle devices (Conner et al. 2021; Awad et al. 2020b), these studies have very small sample sizes, short intervention periods, and do not use any control group to compare the effects of their robotic gait training intervention to conventional therapy. Very few true randomized controlled trials (RCT) have been conducted comparing robotic gait training using exoskeletons or exosuits to conventional therapy in patients with neuromotor deficiency, and there have been none conducted thus far in patients with CP. Thus, performing these RCTs will be crucial to elucidate whether robotic gait training using these devices is actually more beneficial than conventional therapy, especially in patients with CP.

Further, to inform the design of these RCTs, it will be important to investigate whether and to what extent exoskeletons and exosuits are able to elicit motor adaptation in neuromotor impaired patients. In healthy participants, research has shown that walking with powered robotic ankle assistance acutely alters the motor control strategy that participants use to walk (Steele et al. 2017; Jacobs et al. 2018). These studies indicate that walking with robotic ankle assistance can change the activity patterns of individual muscles, with the changes being most pronounced in the timings of the muscle firings, rather than the level of activity, and these motor control adaptations are consolidated over multiple sessions using the device. There is a scarcity of research investigating this topic in clinical populations, but a pilot investigation in children with CP has shown that applying robotic plantarflexor resistance during walking induces changes in ankle muscle activity towards more normal patterns, with simultaneous reductions in co-contraction (Conner et al. 2020a). However, it is still unclear how the damaged neuromotor system in CP adapts its muscle coordination strategy in response to robotic forces, and how these acute motor control adaptations progress with time as patients become more proficient at walking synergistically with the device. Investigations into the acute effects of exoskeletons and exosuits on muscle coordination in CP patients and other neuromotor deficient populations could help to illuminate the adaptive capacity of these patients' motor systems and may provide important data for distinguishing between responders and non-responders to robotic gait training.

Additionally, there is a paucity of research investigating the translation of exoskeletons and exosuits into real-world environments. Some investigations have examined walking on slopes of varying incline while using exoskeletons and exosuits and have shown reductions in energy cost of both uphill and downhill walking (Sawicki and Ferris 2009; Galle et al. 2015; Chen et al. 2020). However, these studies are performed in the lab using treadmills with healthy subjects. In order to truly test the adaptability of these devices to real-world terrain and determine their capacity to enhance real everyday mobility, studies must be performed with patients using these devices in real-world settings. Wearable metabolic systems and even marker-less motion capture could enable the assessment of energy cost and gait kinematics using exoskeletons and exosuits in various outdoor environments, which would greatly inform the true potential of these devices to one day leave the lab and assist patients during everyday life.

Finally, very little research has examined the qualitative experience of using exoskeletons and exosuits in clinical practice. The data from the few studies that have investigated the subjective experience of using exoskeletons in patients with spinal cord injury and stroke show that these devices have the potential to meaningfully boost patients' sense of autonomy and self-efficacy, but patients can struggle with unrealistic expectations associated with this new technology and with effectively learning to use these complex devices (Manns et al. 2019; Thomassen et al. 2019; Kinett-Hopkins et al. 2020). Further, therapists and clinicians express concerns regarding patient selection for robotic gait therapy and the high resource and time demand of using these devices in daily clinical practice (Ehrlich-Jones et al. 2021; Mortenson et al. 2020; Read et al. 2020). These data indicate that patients and therapists alike consider exoskeletons and exosuits as promising clinical technology; however, many challenges remain that limit the integration of these devices into regular clinical practice. The true utility of these devices will be measured by their effectiveness in routine rehabilitation, not by measurements obtained in the lab, and thus, more focus must be given to device practicality and the subjective patient and caregiver experience of using the device in real clinical settings. Moreover, no qualitative studies on patient experience using exoskeletons or exosuits have been conducted in patients with CP. In order to facilitate patient engagement during training with the device and enhance adherence to using the device in everyday life, it will be important to understand how CP patients actually perceive using and training with these devices.

9.7 Limitations of the Thesis

The results of this study showed a robotic ankle exosuit improved walking mechanics at the ankle, augmented knee joint dynamics, and produced a trend towards reduced metabolic cost of walking in seven patients with unilateral CP. However, it is important to discuss the limitations of this experiment and these data. Perhaps the most pertinent limitation was our small sample size, which limits the generalizability of our findings. Further, our sample was fairly homogenous, which likely aided in our ability to detect the fairly small biomechanical changes induced by the exosuit; however, this homogeneity means these results really only speak to the effects of this exosuit in patients similar to our sample (12-16 years old with high functional abilities). Future research should include a larger and more varied sample of patients, in order to be more generalizable and better describe the effect of these devices across a broader spectrum of CP patients.

An additional limitation was the single-session nature of this study. For many of our participants, the measurement session for this study was their first time using the exosuit device, and thus the patients likely did not have enough time to become fully accustomed and comfortable walking with the exosuit. Some research has shown that it may take over 100 minutes of accumulated walking time with novel robotic assistance to fully adapt to the augmented walking conditions in healthy participants (Poggensee and Collins 2021), and this adaptation time may be even greater in clinical populations. Our participants only walked with the exosuit for approximately 30-40 minutes in total, and so likely did not achieve full adaptation to the device. Further, because our participants were novel users to the exosuit, there could have been a learning effect over the course of the measurements that influenced our results. This may help to explain why we tended to observe the lowest oxygen consumption values near the highest assistance levels in our ramp up protocol and may have influenced the slight differential biomechanical effects of the offboard versus the onboard condition, since the offboard condition was always performed following the onboard condition. We also did not standardize the amount of time that each participant spent walking with the exosuit, and so each of our participants may have adapted to the exosuit to different extents over the course of our protocol, and it is impossible to isolate the effects of adaptation to the device in our final results. This single-session design was chosen to minimize the burden on the patients for participating in the study; however, due to this protocol, our data may have been influenced by progressive motor adaptation in the participants, and this should be better taken into account in future research.

Similarly, the effects of fatigue may have had some confounding effects on our data. Our protocol involved continuous walking on the treadmill with the exosuit while wearing the motor (onboard) for up to 20 minutes, as the assistance from the device was progressively increased. Then, following a short break, another walking bout of up to 20 minutes was completed using the exosuit with the motor offloaded (offboard). This volume of continuous walking was tiring for some of our subjects, and thus fatigue may have impacted our data, especially near the end of the exosuit walking trials. These long walking trials were chosen to enable participants to reach and maintain steady-state walking for the metabolic captures; however, providing more short breaks within each walking trial could have helped to reduce participant fatigue and its potential confounding effects.

Finally, this thesis is limited by some inexperience with the research methods and analysis techniques. Much of the equipment used for this research (e.g., the force-sensing treadmill, wireless EMG sensors, and exosuit device) were brand new for this project, and so the data presented here may be slightly limited by the inexperience of the research team in using this equipment. In particular, cross-plate contacts while walking on the treadmill and a high degree of cable movement artifact contamination in the EMG data were some of the most prominent technical issues that we faced. Fortunately, the cross-plate contact problem was resolved during data processing; however, issues with cable movement artifact persisted in the EMG data even after filtering, and thus the EMG results presented here are highly limited. Further, as a master's student who is still a novice in using many of these measurement and data analysis techniques, these results may contain a greater degree of human-error than would be the case for a more experienced researcher. However, even considering these limitations I have a high degree of confidence in the results presented in this thesis.

10. CONCLUSION

This thesis aimed to investigate the acute biomechanical and metabolic changes induced from walking using a unilateral robotic ankle exosuit (ReWalk ReStore) in a small cohort of adolescents with unilateral CP. Our results revealed that walking with the exosuit providing assistance improved ankle joint mechanics in the patients' affected leg and augmented knee joint dynamics across both legs as well as produced trends towards reductions in metabolic cost and lower limb muscle activity. These results display the capacity of unilateral robotic ankle assistance delivered by a powered exosuit to augment the walking strategy in patients with CP and thus may point to the potential of these devices to train a healthier walking pattern in CP patients. Further, the observed trends in metabolic cost suggest robotic exosuits have promise in improving the efficiency of gait in CP, alluding to the potential of these devices to enhance everyday mobility in these patients. While this thesis and similar pilot studies with comparable devices present promising preliminary results, more research is necessary before exoskeleton and exosuit technology can be confidently integrated into regular clinical practice. Specifically, studies comparing the effects of robotic gait training with these devices to conventional therapy strategies as well as research into the implementation of these devices in the real-world will be integral moving forward. Clinical exoskeletons and exosuits present an exciting area of study as, when optimized, they may help patients all across the functional spectrum to live their lives without limitations, and I, for one, am excited to be a part of helping to shape this future and empowering those with disabilities to realize their once-impossible goals.

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