RESISTIVE ROBOTIC GAIT TRAINING TO RESTORE NEUROMUSCULAR FUNCTION IN CEREBRAL PALSY

by

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ABSTRACT

Individuals with cerebral palsy (CP) have deficits in strength and neuromuscular coordination, which contribute to a slow and inefficient gait pattern that makes walking difficult for an overwhelming majority of this population. Previous interventions seeking to address these aspects of gait dysfunction in CP have been unsuccessful to date in addressing both muscle weakness and motor control. In an effort to address this gap in clinical care, we developed and validated an adaptive control scheme in conjunction with an untethered ankle exoskeleton device to provide ankle plantar flexion resistance during walking that was responsive to user input. We found that compared to baseline, walking with adaptive plantar flexion resistance resulted in a $45 \pm 35\%$ increase in stance-phase plantar flexor activity ($p = 0.02$) and a $46 \pm 25\%$ reduction in stance-phase co-contraction at the ankle ($p = 0.02$) for children and young adults with CP.

This modality was then applied in a pilot clinical trial in CP, whereby six pediatric participants completed ten, 20-minute training sessions with adaptive plantar flexion resistance over four weeks. We observed significant improvements in measures of strength ($17 \pm 8\%$ increase in ankle plantar flexion strength, $p = 0.02$), preferred walking speed on a treadmill ($39 \pm 25\%$ increase, $p = 0.04$), energetic efficiency ($33 \pm 9\%$ reduction in metabolic cost of transport, $p = 0.03$), and measures of mobility ($11 \pm 9\%$ improvement in timed up and go performance, $p = 0.04$; $13 \pm 9\%$ increase in six minute walk test distance, $p = 0.04$). These improvements in gross measures of performance were likely a result of observed improvements in neuromuscular control and mechanical efficiency, with training resulting in a $29 \pm 11\%$ decrease in co-contraction at the ankle ($p = 0.02$), a $33 \pm 13\%$ more typical soleus
muscle activation profile (p = 0.01), a 7 ± 3% increase in neural control complexity (p < 0.01; measured via muscle synergy analysis), and a 58 ± 34% more mechanically efficient gait pattern (p < 0.05). Overall, this novel resistive robotic gait training paradigm demonstrated significant promise in improving strength and neuromuscular control at the ankle for improved mobility in children with CP.

To further enhance the efficacy of this intervention, we developed an electrodeless audiovisual biofeedback system that utilized force sensitive resistors to display real-time plantar pressure to a user while walking. In validating this system against a soleus electromyography (EMG) biofeedback system in eight individuals with CP, which was considered the gold standard, we found comparable increases in mean soleus muscle activation relative to baseline (43 – 58%, p < 0.05), as well as mean (68 – 70%, p < 0.05) and peak (71 – 82%, p < 0.05) medial gastrocnemius activation, with strong relationships between the two systems for these outcome variables (R = 0.89 – 0.94). When this system was applied to our adaptive plantar flexion resistance scheme, it rapidly increased mean (36%, p < 0.05) and peak (46%, p < 0.05) soleus activation relative to resistance alone. The integration of this plantar pressure biofeedback system may help to improve active engagement with our resistive ankle exoskeleton scheme, reducing the necessity of constant verbal coaching or long acclimation periods.

Finally, we aimed to better understand the underlying neuromuscular response to walking with our resistive ankle exoskeleton, as well as answer fundamental questions about reflex modulation in CP. We tested the effect of changes in motor task complexity, requiring varying levels of ankle stability, on soleus H-reflex excitability in this population. We found that individuals with CP displayed the typical decrease in
soleus H-reflex excitability with increased standing task complexity (-26 ± 27%, p = 0.04). We also observed significant inverse relationships between soleus H-reflex amplitude and co-contraction at the ankle during both complex standing (R = -0.58, p < 0.01) and walking (R = -0.52, p < 0.01) tasks, suggesting the presence of reciprocal inhibition, which was previously thought to be absent in CP.
Chapter 1

INTRODUCTION

1.1 Background

The most common physical disability in childhood is cerebral palsy (CP) [1]. CP is a movement disorder caused by an insult to the developing brain, resulting in detrimental primary and secondary effects [2]. Physical activity and functional independence are essential stimuli for healthy development and the transition from adolescence to young adulthood [3]. Children with cerebral palsy (CP) are significantly less physically active than their typically developing peers [4], contributing to a weaker musculoskeletal system that is prone to low-energy fractures and further inactivity [5]. The lower physical activity levels seen in children with CP is likely explained, in large part, by their metabolic cost of walking [6], which is 2 – 3 times higher than typically developing children [7]. High levels of co-contraction between agonist and antagonist muscles have been shown to be a significant contributor to this elevated metabolic cost [8]. A vicious cycle can ensue (Fig. 1), whereby decreased activity leads to declines in mobility, which leads to further deficits in coordination and strength. As a result, while a child with CP may be able to ambulate independently, they can lose mobility transitioning into adulthood and eventually become wheelchair-bound [9]. Ultimately, declines in mobility for individuals with CP leads to decreased survival [10].

Gait dysfunction in CP is characterized by both deficits in strength and coordination of movement [11]. Several interventions have attempted to ameliorate gait dysfunction in individuals with CP, such as strength training to address the muscle activation component. While increases in strength and aspects of gait, such as stride
length, were significantly improved, there has been inconclusive evidence on the effectiveness of strength training for improving mobility in individuals with CP [12–15]. A potential explanation for the lack of efficacy of strength training for improving walking function is the idea of task-specificity for motor learning [16]. In order for a task to truly be improved, such as walking, that specific task must be practiced within its functional context [17].

Figure 1.1. Contribution of gait dysfunction to decreased survival for individuals with cerebral palsy.

One task-specific modality that has been tested in children with CP for addressing walking dysfunction is gait training. One particular focus has been on partial body weight support treadmill training (PBWSTT) [18,19], but a downside of PBWSTT is that it can lead to an inactive user, whereby the support provided on the
treadmill does not necessitate active user engagement and instead leads to passive movements [20,21]. Assistive robotic gait training (RGT) has also gained popularity recently, whereby a robotic system assists limb movements of a user during walking and will sometimes also incorporate partial body weight support [22]. However, the negative effects of passive user engagement observed with PBWSTT likely also exist with assistive RGT. In fact, in a recently conducted meta-analysis of the effects of assistive RGT on mobility (i.e., six-minute walk test performance, self-selected walking speed, and gross motor function) in children with CP, it was found that assistive RGT was not more effective than the standard of care, such as physical therapy or traditional treadmill gait training (Conner et al, In Review; see Appendix A, Fig. A.1). These findings are supported by the observation that resistive RGT, in which limb movements are resisted instead of assisted, was more effective than assistive RGT in a randomized controlled trial with children with CP [23].

Interventions focused only on strength, such as resistance training to address muscle weakness [13–15,24,25], lack the task-specificity for true motor learning [17]. Interventions only focused on coordination do not address the important building blocks of movement, such as muscle strength, which is strongly correlated to walking ability [26]. Ideally, an intervention could address both of these aspects and promote active user engagement, which is paramount to motor learning [27].

1.2 Purpose

The overarching purpose of this work was to develop a clinically viable intervention to improve walking function for individuals with CP, enabling a more physically active and independent lifestyle. Utilizing the current literature on gait dysfunction in CP, principles of motor learning, the weaknesses of previously tested
Interventions for this population, and technology recently developed in our lab, we hypothesized that a resistive robotic gait training intervention that specifically targeted strength and coordination at the ankle during walking could have significant benefits on mobility for individuals with CP. After initial development and testing of this intervention, we aimed to improve our understanding of the neural mechanisms behind expected improvements in mobility after training, as well as increase the overall effectiveness by addressing any limitations that arose during our pilot clinical trial. Ultimately, this work was designed to lay the foundation necessary to test this intervention in a randomized controlled trial to determine its true efficacy against the standard of care, and assist with its translation to the clinical world.

1.3 Preface

The chapters that follow represent the work that has been done to date to develop, test, and understand this novel robotic gait training intervention. Chapter 2 describes the initial development and validation of adaptive plantar flexion resistance to increase neuromuscular engagement of the ankle plantar flexors in children with CP [28]. After validating the ability of this modality to increase neuromuscular engagement while walking in this population, we explored the potential training effects on strength, walking efficiency, and clinical measures of mobility, which are detailed in Chapter 3 [29]. In discovering the significant benefits of this intervention on strength, efficiency, and mobility, we also aimed to understand how training with adaptive plantar flexion resistance impacted neuromuscular control, leading to the analysis outlined in Chapter [30]. To address a potential weakness of this intervention, which was the necessity of verbal coaching and a multi-visit acclimation period for effective volitional engagement with the exoskeleton device, we validated and tested
an audiovisual biofeedback system that could be integrated with training or used as a standalone intervention, the results of which can be found in Chapter 5 [Conner et al, In Review]. The finding that training with adaptive plantar flexion resistance led to improved neuromuscular control at the ankle motivated Chapter 6, where we explored a potential underlying mechanism of resistive robotic gait training by analyzing reflex modulation in children with CP [Conner et al, In Preparation].

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Chapter 2

Adaptive Ankle Resistance from a Wearable Robotic Device to Improve Muscle Recruitment in Cerebral Palsy

2.1 Introduction

The ankle plantar flexors are a key component of efficient gait, accounting for approximately 50% of propulsive forces during walking [31]. In addition to propulsion, the plantar flexors extend the knee joint during midstance for improved posture, and play an indispensable role in the exchange between the potential and kinetic energy of the center of mass, contributing to an inverted pendulum movement [32]. Reduced function of the ankle plantar flexor muscles is likely a significant contributor to the gait dysfunction in a majority of children with spastic cerebral palsy (CP), a neuromuscular disorder arising from injury to the brain before cerebral development is complete [33]. Children with spastic CP have significantly weaker isometric strength of the lower extremities than their typically developing peers [34], and muscle weakness in children with CP is significantly correlated to walking ability and gross motor function, with the strongest correlation existing with plantar flexion strength [26]. This is in agreement with muscle weakness being more pronounced distally in children with CP [35]. Additionally, strength to weight ratio in children with CP is predictive of independent ambulatory ability [36]. This relationship is supported by the findings of a feasibility study on powered plantar flexion assistance using an ankle exoskeleton for children with CP, which resulted in improved gait kinematics and reduced the energy cost of walking[37], which is typically 2 to 3 times higher in this population [7].

Several interventions are typically implemented to ameliorate gait dysfunction in children with CP. Some children receive orthopedic surgery to addresses lever arm
dysfunction caused by the secondary bone deformities due to abnormal loading forces [24]. However, these procedures do not address muscle weakness, which is an equally important component in the moments produced at joints for movement. Physical therapy (PT) is central to the maintenance of function in CP, but there is limited evidence on the effectiveness of various PT interventions for improving mobility in this population. Strength training, specifically, was found to have moderate evidence of no effect on walking speed or stride length, and inconclusive evidence regarding improvements in gross motor function [14,15]. In a randomly controlled trial of 51 children with CP, 12 weeks of progressive strength training did not lead to improved mobility [25]. There is an apparent disconnect between the contribution of plantar flexion weakness to gait dysfunction and the effectiveness of strength training for improving gait in CP.

One possible explanation for this may be the specificity of training principle of motor learning that is applied in therapeutic interventions, which suggests that to improve a motor task, that specific task needs to be practiced within a functional context [17]. Previous studies [12,13,25] looking at the effect of strength training on walking ability in children with CP have been limited by resistance exercises that strengthen the lower limbs through an isolated movement. While this serves to increase strength, it does not train the motor control that would allow an individual to effectively utilize this strength during gait. Research suggests that improving neuromuscular function requires repetitive volitional engagement during functional tasks [16].

There have also been studies investigating the use of task-specific gait training. In particular, focus has been on partial body weight supported treadmill training via
devices such as the Lokomat, with observed improvements in gross motor function, walking speed, and endurance [38–42]. One potential weakness of this task-specific training is the relative unloading of body weight, which serves as an important afferent signal for modifying the amplitude of muscle activation [43–45]; prolonged unloading over time may result in muscle atrophy and declines in neuromotor performance of the plantar flexors [46]. In addition, the majority of robot-assisted treadmill training for individuals with CP have used a tethered system (e.g., Lokomat [47]), which does not offer the possibility for training overground or in more ecologically valid contexts, such as at home. Another promising modality for task-specific training in individuals with CP is the use of biofeedback, where features such as gamification and virtual reality provide cues for improved walking. Studies on biofeedback training have been generally positive [48–50], yet more research is needed to determine if biofeedback alone is sufficient for transferring motor learning to real world performance [51].

There is a growing understanding that to improve walking ability, individuals with CP require both increased strength and improved selective neuromuscular control. Coupled with our knowledge on the important role of the ankle plantar flexor muscles during walking, this suggests that effective gait rehabilitation interventions should be designed to provide ankle plantar flexor resistance that is perfectly timed during walking to elicit the desired neuromuscular firing pattern that reinforces appropriate function, leading to improved strength, coordination, and gait. This is supported by the finding that increasing engagement of the soleus muscle while walking can lead to improved gait kinematics [52]. Additionally, to promote neuroplasticity and motor learning, active neuromuscular engagement has been shown to be superior to passive engagement for improved performance and cortical
reorganization [27]. This motivates the need for controlling a functional resistance intervention so that it is responsive to user input to maximize active engagement. We theorize that adaptive plantar flexor resistance provided during the propulsive phase of walking could lead to both increased strength and improved neuromuscular control following a suitable training intervention. However, we are not aware of any studies that have demonstrated a joint-level wearable intervention capable of eliciting improved neuromuscular engagement of a limb with neurological-deficiency during a functional locomotor task.

The first goal of this study was to develop and validate a control scheme for a wearable exoskeleton capable of providing adaptive resistance proportional to the biological ankle moment during walking for individuals with spastic CP. The second goal of this study was to test the feasibility of walking with plantar flexor resistance for individuals with spastic CP, and assess the neuromuscular response to resisted walking for preliminary clinical validation of this functional training concept. We hypothesized that walking with resistance would increase more-affected-limb, stance-phase plantar flexor muscle activity. In addition, we hypothesized that with our proportional resistance control scheme, the increase in stance-phase plantar flexor activity would not be matched by an increase in stance-phase dorsiflexor activity, leading to overall reduced ankle co-contraction. To test these hypotheses, we recruited eight total individuals with spastic CP to walk with our adaptive ankle resistance platform.
2.2 Methods

2.2.1 Exoskeleton Platform for Wearable Resistance

We used a previously developed untethered ankle exoskeleton suitable for use with individuals with CP as the platform for providing wearable plantar flexor resistance [53]. Briefly, this lightweight ankle exoskeleton, with customizable foot inserts and calf cuffs for individualized fit (Figure 2.1), provides bilateral ankle torque using high-performance DC motors (EC-4pole, Maxon) powered by an onboard battery (910 mAh E-flite 6S) to actuate a pulley aligned with each ankle joint in the sagittal plane via a Bowden cable transmission. Torque sensors (TRT-500, Transducer Techniques) at the ankle joint provide feedback for the motor torque controller. The exoskeleton’s control module contains a custom printed circuit board, wireless communication, a microcontroller, motor drivers, and signal processors. The exoskeleton is controlled wirelessly via a custom MATLAB graphical user interface (GUI). The microcontroller implements a finite state machine and resistance control algorithm, and streams experimental data to the GUI.
Figure 2.1. Theoretical concept of the adaptive functional resistance intervention: 1) Embedded sensors are used to estimate the biological ankle moment in real-time; 2) Plantar flexor resistance is provided proportional to each individual user’s estimated ankle moment in real-time; as a result, resistance is controlled to be responsive to user input; 3) Adaptive resistance requires the user to increase their volitional engagement of the plantar flexors and acts as a mechanical cue for the neuromuscular system to recruit additional motor units to improve “push off” during late stance.

We developed a purpose-built exoskeleton resistance controller based on two primary design criteria. The first criterion was task-specificity: the controller must facilitate increased neuromuscular firing of the plantar flexor muscles during the portion of the gait cycle when they function to propel the body forward (i.e. push-off). The second criterion was user engagement: the controller should be responsive and provide a mechanical cue in response to changing user input (i.e. as someone pushes harder, more resistance is provided). To meet these goals, we implemented a proportional joint-moment control scheme designed to provide adaptive resistance for a user to actively engage with during the stance phase of walking (Figure 2.1) [53]. Embedded foot sensors (FlexiForce A201, Tekscan) placed under the ball of the foot were used to estimate the biological ankle moment in real-time. Plantar flexor
resistance from the exoskeleton during walking was provided by multiplying a nominal torque setpoint (e.g. 0.15 Nm/kg) by the relative estimated ankle joint moment established from the embedded foot sensors and a calibration trial. The relative estimated ankle joint moment was calculated by normalizing the instantaneous estimated ankle moment during training by the peak estimated ankle moment measured during a calibration trial. Therefore, if the real-time estimated ankle moment reached the estimated peak from the calibration trial, the relative estimated ankle joint moment would be equal to 1, and 0.15 Nm/kg of resistance torque would be applied. If the relative estimated ankle joint moment was not equal to 1, the resistance torque would be scaled accordingly. The torque setpoint was modified to prescribe an appropriate level of resistance for each user across visits.

2.2.2 Participants

Eight individuals diagnosed with spastic CP were recruited for this study to validate the control scheme and clinically assess the neuromuscular response of walking with the functional resistance intervention. This study was approved by the Northern Arizona University Institutional Review Board (#986744), and informed written consent was received from adult participants, or from a parent or legal guardian for minor participants. An additional consent was obtained for publication of any identifying videos or images. Controller validation (Goal 1), requiring access to an instrumented treadmill and motion capture system, was completed at the Northern Arizona University Human Performance Laboratory (Flagstaff, AZ). The feasibility and neuromuscular response protocol (Goal 2), requiring electromyography measurement and increased access to potential participants, was completed at the Northern Arizona University – Phoenix Biomedical Campus (Phoenix, AZ).
Inclusion criteria for participation in this study included the ability to walk continuously for at least six minutes with or without support, age 9 to 21 years, Gross Motor Function Classification System (GMFCS) Levels I – II, and the ability to follow simple directions. Exclusion criteria included orthopedic surgery within the past six months or any conditions that would prevent safe participation.

We recruited eight individuals with CP for participation in this study (Table 2.1): ages 9 – 17 years old, seven males and one female, and GMFCS I (n = 4) and II (n = 4). The first two participants (Subjects V1 & V2) completed a one visit protocol for the validation of the adaptive resistance control scheme. The other six participants (Subjects 1 – 6) completed a 4-5 visit protocol for the neuromuscular validation of the resistance intervention (Figure 2.2).

2.2.3 Experimental Evaluation

2.2.3.1 Goal 1: Validation of the adaptive resistance control scheme

Participants were first evaluated by a licensed physical therapist for physical characteristics, GMFCS level, and gait type (Table 2.1). To validate that the ankle resistance torque was provided proportional to the instantaneous biological ankle moment, we measured the correlation between estimated biological ankle moment and time-synced exoskeleton torque. For this controller validation, two participants (Subjects V1 – V2) walked with resistance (torque magnitude set to 0.15 Nm/kg) at a self-selected speed on a split-belt in-ground instrumented treadmill (Bertec; 960 Hz). Participants were outfitted with reflective markers on the lower extremity, pelvis, and trunk. Three-dimensional marker trajectories were recorded using a motion capture system (Vicon, 10 cameras; 120 Hz; Figure 2.2A) (for marker set description [37]).
Participants began the trial with a 60 – 120 second calibration period while walking at their self-selected speed on the treadmill. Next, the torque setpoint of 0.15 Nm/kg of resistance was applied, and exoskeleton torque, estimated biological ankle moment, three-dimensional marker trajectories, and ground reaction forces were recorded over ten consecutive gait cycle. Using the recorded marker trajectories, a previously reported OpenSim full-body musculoskeletal gait model [54] was scaled to the anthropometrics of each participant. The model had 18 primary body segments and 21 degrees of freedom; a ball-and-socket joint at the third lumbar vertebra, 3 translations and 3 rotations at the pelvis, a ball-and-socket joint at each hip, tibiofemoral joints with coupled translation and rotation, and revolute ankle and subtalar joints. Joint kinematics and kinetics were calculated in OpenSim via inverse kinematics and inverse dynamics, respectively [55]. Kinematic and kinetic data were filtered using a 4th order zero-lag Butterworth filter at 6 Hz and 12 Hz, respectively.

2.2.3.2 Goal 2: Feasibility of plantar flexor resistance and assessment of neuromuscular response

Participants were evaluated by a licensed physical therapist on their first visit for physical characteristics, GMFCS level, gait type, and plantar flexor strength (Table 2.1), and outfitted with a custom ankle exoskeleton. Plantar flexor strength was tested using a hand-held dynamometer placed under the pad of the foot with the participant lying supine. Participants were instructed to push as hard as possible for three seconds, and the average of three trials was recorded. Participants then spent four to five “acclimation” visits walking at a self-selected speed on a treadmill with exoskeleton ankle resistance, as we anticipated a learning effect with this new training modality. The magnitude of resistance was initially set at 0.075 Nm/kg and increased over
subsequent visits based on user performance (i.e. reaching the prescribed torque setpoint), rate of perceived exertion, and self-identified soreness before and after a visit. Soreness was self-identified at the end of each visit on the following scale: none, mild, moderate, severe, and very severe. Participants walked for 20 minutes with resistance on each acclimation visit. Seated rest breaks were provided based on participant preference. While walking with resistance, participants were advised to focus on their more-affected side, or limb with greatest impairment, as determined by asking the subject and/or parent or guardian, and confirmed by the physical therapist. Additionally, to distinguish the more-affected limb from the less-affected (or unaffected) limb, maximum voluntary contractions (MVC) of the plantar flexors of each limb was tested (Table 2.1). Differences in ankle torque generated between limbs aligned with the self-reported more-affected/less-affected limbs for all subjects but Subject 3, who was non-verbal (his parent believed that he did not understand the MVC directions and as a result, limb dominance was based on self-report & therapist assessment).

Frequent verbal instruction was given to the participants while walking with resistance: variations of “push against the resistance”. Output from the control assembly provided the research team with real-time feedback on engagement with the exoskeleton (i.e. how well participants were pushing against the resistance during stance phase), and the level of resistance was decreased or increased according to performance and rate of perceived exertion. Subject 3 was unable to receive or acknowledge the instruction to push against resistance because of verbal communication deficits. In an attempt to address this shortcoming, we provided this participant with our real-time feedback of his plantar flexor engagement.
Assessment of more-affected limb neuromuscular response to resisted plantar flexion was completed following the visit when the research team assessed appropriate acclimation and engagement with the device, as indicated by reaching the prescribed resistance setpoint on ≥ 50% of gait cycles and subjective feedback from participants that they could feel the resistance when walking. Participants’ lower extremities were bilaterally outfitted with surface electromyography (EMG) sensors (Noraxon, Scottsdale, AZ; 1500 Hz) on the soleus (SOL) and tibialis anterior (TA). To clinically assess the intervention, we isolated the effects of adaptive resistance by having participants walk with the exoskeleton on the treadmill at a self-selected speed under two conditions in the following order: 1) No Resistance: wearing the exoskeleton while it maintained zero torque at the ankle joint – motors actively compensated for system dynamics and friction so the joint rotated freely, and 2) Resistance: wearing the exoskeleton as it provided plantar flexor resistance via the proportional control scheme (Figure 2.1). Walking speed was not changed between conditions. Consistent with the acclimation visits, participants walked for a total of 20 minutes with two to three breaks depending on participant preference, and the last five minute block was used for data collection (i.e. the first 15 minutes served as warm-up and practice). EMG activity was recorded for 30 seconds during each condition within this last five minute block. Embedded foot sensors detected gait events.

2.2.4 Data Processing and Statistical Analysis

All data were analyzed in MATLAB (v2019a, The MathWorks, Inc., Natick, MA). The distribution of all variables was found to be normal using a Kolmogrov-Smirnov test with small-sample Lilliefors correction [56]. Significance level for this feasibility study was set at α = 0.05 without correction for multiple comparisons.
2.2.4.1 Goal 1: Validation of the adaptive resistance control scheme

To validate the adaptive resistance control scheme, we quantified the Pearson’s product moment correlation coefficient ($R$) over ten gait cycles between the biological ankle moment (normalized by peak moment within a trial) and exoskeleton torque (normalized by the prescribed level of resistance). With coefficients of $0.7 – 0.9$ indicating a high correlation [57], our goal was to fall within this range, which would indicate that the controller was responding directly to user input and ankle demand. We also quantified the root mean square error (RMSE) between the normalized peak biological ankle moment and normalized peak exoskeleton resistance over the ten gait cycles.
Figure 2.2. Experimental setup for controller and neuromuscular validation: (A) Participant outfitted with the device and reflective markers on an instrumented treadmill for collection of 3D kinematics and kinetics while walking with resistance for validation of the control scheme (subjects V1 & V2). (B) Participant outfitted with a custom ankle exoskeleton and bilateral soleus and tibialis anterior surface EMG sensors for assessment of the neuromuscular response to walking with resistance (subjects 1 – 6). (C) Ankle exoskeleton components worn by all participants.

2.2.4.2 Goal 2: Feasibility of plantar flexor resistance and assessment of neuromuscular response

EMG signals were de-meaned, band pass filtered (4th order butterworth, 15 - 380 Hz band-pass cutoff), rectified, and low-pass filtered (4th order butterworth, 7 Hz low-pass cutoff), and then down-sampled to align with the gait events recorded by the force sensitive resistors. Muscle activity over the 30 second trial was then segmented by gait events. We computed the average EMG amplitude of each muscle during
stance phase. Average amplitudes were then normalized to the average peak amplitude from the No Resistance trials. Additionally, co-contraction during push-off phase was calculated as the normalized ratio of TA activity (antagonist) to SOL activity (agonist) for each stance phase cycle. Outcomes were grouped by more-affected and less-affected limb. To assess the relationship between level of resistance and magnitude of neuromuscular response to resistance in the more-affected limb, we quantified the Pearson’s product moment correlation coefficient ($R$) between prescribed level of resistance and percent change in average muscle activation levels and co-contraction between No Resistance and Resistance conditions [57]. Paired t-tests were used to compare average muscle activation levels and co-contraction between No Resistance and Resistance conditions for both more-affected and less-affected limbs. Cohen’s d ($d$) was used to calculate effect size, where 0.2 was considered a small effect, 0.5 a medium effect, and 0.8 a large effect [58]. Significance level for this feasibility study was set at $\alpha = 0.05$ without correction for multiple comparisons.

2.3 Results

2.3.1 Goal 1: Validation of the adaptive resistance control scheme (Subjects V1 – V2)

There was a very high correlation between the normalized biological ankle moment and rectified normalized exoskeleton torque ($R = 0.92 \pm 0.04$) for both Subjects V1 and V2 (see Figure 2.3). In addition, the RMSE between peak biological ankle moment and peak exoskeleton resistance torque over ten gait cycles was $6.3 \pm 0.4\%$. 
Table 2.1. Participant characteristics and walking protocol information

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Height (cm)</th>
<th>Body mass (kg)</th>
<th>GMFCS level*</th>
<th>Gait typeb</th>
<th>Gait speed (m/s)</th>
<th>Resistance level (Nm/kg)</th>
<th>MVC (Kg-f)</th>
<th>R</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>M</td>
<td>9</td>
<td>137.0</td>
<td>30.7</td>
<td>I</td>
<td>Mild crouch and apparent equinus</td>
<td>0.75</td>
<td>0.15</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V2</td>
<td>M</td>
<td>13</td>
<td>151.0</td>
<td>44.0</td>
<td>I</td>
<td>Crouch</td>
<td>1.00</td>
<td>0.15</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>17</td>
<td>173.5</td>
<td>54.4</td>
<td>II</td>
<td>Crouch</td>
<td>0.58</td>
<td>0.13</td>
<td>14 28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>14</td>
<td>143.0</td>
<td>42.0</td>
<td>II</td>
<td>Crouch</td>
<td>0.45</td>
<td>0.15</td>
<td>9 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>16</td>
<td>157.0</td>
<td>42.5</td>
<td>II</td>
<td>Winters type II (late-stance hyperextension) Crouch</td>
<td>0.40</td>
<td>0.16</td>
<td>27 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>15</td>
<td>160.5</td>
<td>59.0</td>
<td>I</td>
<td>Crouch</td>
<td>0.67</td>
<td>0.17</td>
<td>21 29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>16</td>
<td>160.5</td>
<td>68.5</td>
<td>I</td>
<td>Poor eccentric control of pre-tibial group* Crouch</td>
<td>0.72</td>
<td>0.15</td>
<td>32 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>12</td>
<td>131.5</td>
<td>30.2</td>
<td>II</td>
<td>Crouch</td>
<td>0.49</td>
<td>0.20</td>
<td>13 16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*GMFCS: Gross Motor Function Classification System

bGait type: as identified by a licensed physical therapist, with 'crouch’ gait defined by those parameters set by Gage et al[31] and ‘Winters type II’ defined by those parameters set by Winters et al[59]. Note: all subjects were characterized by a weakened push-off on their affected side.

*Poor eccentric control of pre-tibial group: Subject 5’s gait type did not fit a specific criteria as defined by Gage or Winters, but instead was characterized by poor control of the ankle on heel strike and push-off.

cMVC: maximum voluntary contraction of the ankle plantar flexors, average of three trials for each side.

2.3.2 Goal 2: Feasibility of plantar flexor resistance and assessment of neuromuscular response (Subjects 1 – 6)

All participants (Subjects 1 – 6) tolerated increased level of resistance beyond the initial setpoint of 0.075 Nm/kg. Following acclimation, the average tolerated resistance was 0.16 ± 0.02 Nm/kg, which ranged from 0.13 – 0.20 Nm/kg (Table 2.1). Self-identified soreness levels ranged from none – moderate throughout the visits.
Figure 2.3. Validation of adaptive ankle resistance control: A) recorded ankle moments and resistance torque values from Subjects V1 and V2, with very high correlation ($R = 0.92 \pm 0.04$) between biological ankle moment (blue) and magnitude of torque resistance by the exoskeleton (red). The resistance torque curve was rectified (i.e. plotted in the same direction as the biological moment) to assist with visualizing proportionality; B) Normalized biological ankle moment plotted against normalized exoskeleton resistance torque for Subjects V1 (closed circles) and V2 (open circles) over ten consecutive gait cycles.

In the more-affected limb, there was a moderate correlation between prescribed level of resistance and increase in SOL activity ($R = 0.69$), and high correlations between prescribed level of resistance and decrease in TA activity and co-contraction ($R = -0.84$ and $-0.73$, respectively).
Figure 2.4. Neuromuscular response: more-affected limb average stance phase soleus (A) and tibialis anterior (B) muscle activity, and co-contraction level (C) for No Resistance and Resistance conditions for Subjects 1 – 6 while walking at a self-selected speed on the treadmill. Muscle activity was normalized to the peak stance phase activity of the No Resistance condition and averaged over the 30 second walking trial. Co-contraction was calculated as the ratio of averaged, normalized tibialis anterior to soleus muscle activity for each stance phase of gait. *$p < 0.05$

We observed changes in more-affected limb muscle activity and co-contraction (Figure 2.4A-C). For the more-affected limb, SOL activity increased $45 \pm 35\%$ ($p = 0.02$, $d = 1.33$), TA activity decreased $26 \pm 24\%$ ($p < 0.05$, $d = -1.07$), and co-contraction level decreased $46 \pm 25\%$ ($p = 0.02$, $d = -1.42$). A representative SOL
activity curve (Subject 1) can be seen in Figure 2.5. Individual EMG plots of more-affected limb stance-phase SOL and TA activity are reported in supplementary material (see Appendix A, Fig. A.2). No significant difference was seen in the less-affected limb SOL ($p = 0.24, d = 0.55$) or TA ($p = 0.38, d = 0.39$) activity, or less-affected limb co-contraction level ($p = 0.55, d = 0.26$).

![Figure 2.5](image)

Figure 2.5. Representative neuromuscular response during resisted gait: Subject 1 displayed increased (25%) average soleus activity from No Resistance to Resistance condition during stance phase.

### 2.4 Discussion

We successfully completed our first goal of validating that the adaptive resistance controller applied resistance proportional to the biological ankle moment during walking. For the two participants who completed the validation protocol of this
study, there was a very high correlation between biological ankle moment and the magnitude of exoskeleton resistance \( R = 0.92 \pm 0.04 \), Figure 2.3) and low RMSE between peak biological ankle moment and peak resistance torque \( (6.3 \pm 0.4\%) \). This result agrees with our previous study on proportional control for ankle plantar flexor assistance [53].

With regards to Goal 2, the findings from this study indicate that gait training with plantar flexor resistance delivered via an untethered exoskeleton is feasible for individuals with spastic CP, GMFCS levels I and II. All individuals tolerated walking with resistance, and were able to maintain their baseline self-selected walking speed when resistance was applied. For the six participants who underwent the neuromuscular response protocol, a similar level of resistance \((0.16 \pm 0.02 \text{ Nm/kg})\) was attained after four to five sessions of 20-minute resisted walking trials. Previous studies have found that children with CP have peak biological ankle moments of around 1 Nm/kg while walking [37,60], meaning the average tolerated resistance after acclimation represented approximately 16% of the biological plantar flexor ankle moment. Participants’ perceived soreness level after each training session ranged from none – moderate. Importantly, no subjects selected severe or extremely severe after training. Four to five acclimation visits seemed to be appropriate for the anticipated “learning” that is required with this modality, as it allowed all six participants to reach a resistance level and degree of engagement that resulted in moderate soreness. While it is plausible that further acclimation visits would result in an even greater neuromuscular response, this must be balanced with the expected training effect of this intervention.
The results of this study support our hypothesis that proportional ankle resistance during gait in individuals with CP would increase plantar flexor muscle activity. Specifically, soleus activity significantly increased only for the more-affected limb. On the less-affected side, soleus activity increased for three of the six subjects. This may be explained by the direction to focus on the more-affected side. Additional research is needed to assess how the user’s focus on an individual limb affects their neuromuscular response to the intervention. An important consideration from these results is the level of resistance and magnitude of response. As an initial, feasibility study, level of soreness was closely monitored and resistance levels were increased conservatively. It is reasonable to assume that participants could train at a higher level of resistance than prescribed in this study, and this would likely be associated with an even greater neuromuscular response. This assumption is supported by the finding that there was a moderate correlation between prescribed level of resistance and increase in soleus activity ($R = 0.69$), and high correlations between prescribed level of resistance and decrease in tibialis anterior activity and co-contraction ($R = -0.84$ and -0.73, respectively). These moderate to high correlations between resistance level and neuromuscular response also support the unique effect of adaptive resistance compared to verbal coaching alone.

Similar to the findings here, a previous study [52] found that a downward pelvic pull was also able to improve activation of the soleus, as well as coordination of the gastrocnemius muscle in children with CP. This improvement in neuromuscular activation led to an improved walking pattern, as the gastrocnemius could more effectively extend the knee during mid-stance and propel the center of mass forward at toe off. With the finding that our exoskeleton resistance protocol can also increase
plantar flexor activity during stance phase, training with our adaptive ankle resistance device may lead to improved walking kinematics similar to what was observed from the downward pelvic pull system. It is important to note, however, that our study did not look directly at gastrocnemius activation profiles as this study did[52], so this potential effect on kinematics should be interpreted with caution. In addition, we had the novel finding of decreased antagonist activity, as the previous study did not measure the response of the tibialis anterior.

A pleasantly surprising outcome of this study was the finding that stance-phase TA activity of the more-affected limb was significantly decreased during walking with resistance. Combined with the significant increase in SOL activity of the more-affected limb, this resulted in a substantial decrease in co-contraction during stance phase. While we anticipated that SOL activity would increase relative to TA activity resulting in a decrease in co-contraction, we did not anticipate that there would be a significant decrease in TA activity. On the less-affected side, changes in TA activity and co-contraction level was less consistent across subjects. Our significant finding of decreased co-contraction of the more-affected limb may be the most compelling feature of this proposed intervention. Children with spastic CP can present with increased co-contraction between the ankle plantar flexors and dorsiflexors [61], which likely plays a role in the higher metabolic cost of walking seen for this population [8]. The mechanism behind this reduction in co-contraction, characterized by both an increase in agonist activity and decrease in antagonist activity, is not immediately clear. One possible explanation is that resisted plantarflexion while walking results in increased or improved reciprocal inhibition [62]. With contraction of the soleus muscle and subsequent plantarflexion, there is stretch of the tibialis
anterior. Stretch of muscle spindles within the tibialis anterior will lead to excitation of motoneurons and antagonist contraction. With typical, voluntary movements, however, the excitation of the stretched antagonist muscle is blocked by reciprocal inhibition via Ia inhibitory interneurons. It has also been shown that there is supraspinal involvement within reciprocal inhibition, with antagonist muscles decreasing activation right before an agonist muscle contracts. Reciprocal inhibition is impaired in CP, and this impairment is a common explanation for the co-contraction seen in this population. It is possible, given decreased TA activity despite increased SOL activity, that our protocol had an effect on reciprocal inhibition.

The key principle of adaptive ankle resistance with a wearable robotic platform compared to previous gait training interventions for individuals with CP is the ability to address both task-specificity and active engagement. One potential benefit of adaptive ankle resistance compared to other task-specific training protocols is the resulting increase in neuromuscular engagement while walking, which can help to drive motor learning. The ability to monitor a user’s instantaneous biological ankle moment in conjunction with the resistance torque applied via the wearable platform offers a unique opportunity to quantify and provide feedback of the user’s engagement in real-time while walking.

The successful validation of this wearable functional resistance exoskeleton system provides a unique opportunity to design future training interventions that match closely with the ASAP (Accelerated Skill Acquisition Program) framework[17]. The ASAP framework has eight principles for an evidence-based intervention for learning or relearning of motor skills to optimally affect neural plasticity: 1) Challenging and meaningful practice: With a controllable level of
resistance, we are able to prescribe an appropriate level of difficulty; 2) Addresses important changeable impairments: plantar flexion weakness is a clear contributor to gait dysfunction in CP; 3) Overload and specificity: individuals are able to walk with resistance for repetitive muscle activation, and this practice occurs during the functional task of walking with no artificial breakdown of the movement; 4) Preserves natural task: we are able to provide resistance during walking; 5) Avoids artificial task breakdown: despite the focus on plantar flexion, participants still incorporate the whole task of walking; 6) Ensures active engagement: walking with resistance necessitates active engagement with the exoskeleton; 7) Balances immediate and future needs: the untethered aspect of the device allows for the potential of training in more ecologically valid contexts, such as at school or the playground; 8) Task-specific self-confidence: the ability to “level up” on resistance can serve as a motivator or confidence boost for users. [17]

We are confident in the experimental design and results of this study, but there are notable limitations. First, as a pilot study focused on the potential to improve neuromuscular activation of the more-affected limb, we asked participants to only focus on one side while walking and did not assess gait kinematics or kinetics for Goal 2. It is possible that the same results could have been achieved without this direction, in addition to similar improvements on the less-affected side. It will also be critical for future investigations to assess the effects of this intervention on gait kinematics and kinetics. Second, it is possible that participants could increase plantar flexor activity simply with the instruction to “push” during the propulsion phase. However, this does not seem likely, as our data showed moderate to high positive correlations between neuromuscular response and resistance level, indicating the need for a resistive,
afferent signal to recruit additional motor units. Additionally, resistance is necessary for modifying training intensity, which is an important factor in stimulating muscular adaptations [63] and promoting neuroplasticity [64]. Third, future research should investigate the effects of plantar flexor resistance on gastrocnemius activity, which was not feasible in this study due to the location of the exoskeleton calf cuff. Finally, we had a limited sample size and our participants were all GMFCS I – II, meaning the proposed training has only been validated for ambulatory individuals with spastic CP. While this does not allow us to generalize our results to all individuals with CP, the findings of this pilot and feasibility study serve as an important first step for the development of this potentially transformative intervention. It is also important to note that this study serves as an initial investigation into the feasibility and neuromuscular response of wearable adaptive resistance. Any effects of this intervention, and changes in the neuromuscular response once training has finished, are a topic for future studies.

In conclusion, this study has shown the validity and feasibility of a novel training system and protocol for increasing plantar flexor activity within the functional context of walking for individuals with spastic CP. Proportional resistance of plantar flexion during the propulsive phase of gait leads to increased agonist muscle activity and decreased antagonist muscle activity of the more-affected limb in individuals with spastic CP, with the combined effect of reducing co-contraction. Future studies should explore the use of this wearable adaptive resistance platform in a longitudinal training intervention to improve neuromuscular function and gait in individuals with CP.
Chapter 3

Wearable Adaptive Resistance Training Improves Ankle Strength, Walking Efficiency and Mobility in Cerebral Palsy: A Pilot Clinical Trial

3.1 Introduction

Affecting 17 million people globally [65], cerebral palsy (CP) is a movement disorder caused by injury to the developing brain, characterized by deficits in strength [34] and neuromuscular coordination [65]. These deficits lead to inefficient movement patterns that elevate the energy cost of walking by 2 – 3 times that of unimpaired individuals [7] and reduce walking speed by 10 – 40% [66]. Physical activity, an essential stimulus for healthy development, is dramatically lower for children with CP [4] and is negatively associated with the higher energy cost of movement [6]. While surgical and pharmacological interventions successfully contribute to the management of the most severe presentations of CP [2], lifelong walking disability remains for nearly all individuals affected by CP. Addressing the fundamental neuromuscular deficits preventing efficient movement, therefore, is an essential task in the care of individuals with CP.

Treatment strategies for improving the gait of individuals with CP typically consist of a combination of orthopedic surgery, physical therapy, and assistive devices [24]. Orthopedic surgery, while effective in improving lever arm dysfunction by the modification of muscle and tendon origin and insertion points, is not able to directly address the muscle weakness [34] and neuromuscular coordination deficits [65] seen in CP. In addition, physical therapy has limited evidence for improving mobility, with interventions such as strength training lacking the task specificity necessary for improving walking function [15]. Recently, treadmill training with partial body-weight support has gained traction as a potential task-specific intervention for improving
mobility in CP [67]. However, a potential weakness of this training modality is the relative unloading, which could lead to muscle inactivation [44] and atrophy [46] over time. Additionally, the equipment required for this type of training is expensive and tethered [47], leading to limited access for patients.

There is a vital need for an effective and widely-available intervention capable of increasing the dose of task-specific gait therapy for children with CP. To meet this need, a wearable robotic device was recently developed to address deficits in muscle recruitment and reinforce neuromuscular control patterns that may produce lasting improvements in locomotor function [28]. Utilizing onboard sensors and a closed-loop control strategy that responds immediately to user input, this novel training modality provides perfectly synchronized resistance to re-train ankle plantar flexor muscle function during the stance phase of walking. This device, unlike passive gait training interventions, provides an opportunity to monitor user engagement in real-time, allowing for the immediate performance feedback necessary for increasing task skill [17].

The goal of this foundational clinical trial was to determine the efficacy of the first intervention using wearable adaptive resistance for improving gait in children with spastic CP. We hypothesized that this neuromuscular gait re-training intervention would strengthen the plantar flexors, increase preferred gait speed, and reduce the energy cost of walking. We also hypothesized that these improvements would translate to better performance on clinically validated tests of walking function.
3.2 Methods

3.2.1 Participants

Participants diagnosed with spastic hemi- or diplegic CP were recruited from physical therapy clinics in the local area. Inclusion criteria included Gross Motor Function Classification System (GMFCS) levels I – II, ability to walk with or without a walker for at least six minutes, age between 10 – 21 years, and the ability to follow simple directions. Exclusion criteria included orthopedic surgery within the past six months or any conditions that would prevent safe participation. This study was approved by Northern Arizona University’s Institutional Review Board (#986744) and registered at ClinicalTrials.gov (NCT04119063). Informed written consent was provided by a parent or legal guardian for each participant after the nature and possible consequences of the study was explained; participants provided verbal assent. Additionally, informed consent to publish identifying information was obtained from all the participants and their parents or legal guardian.

Table 3.1. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Gender</th>
<th>Age (y:m)</th>
<th>GMFCSa</th>
<th>Distribution</th>
<th>Gait typeb</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>M</td>
<td>16:11</td>
<td>II</td>
<td>Diplegic</td>
<td>Crouch</td>
</tr>
<tr>
<td>S2</td>
<td>M</td>
<td>13:11</td>
<td>II</td>
<td>Hemiplegic</td>
<td>Crouch</td>
</tr>
<tr>
<td>S3</td>
<td>M</td>
<td>15:11</td>
<td>II</td>
<td>Diplegic</td>
<td>Winters type II</td>
</tr>
<tr>
<td>S4</td>
<td>M</td>
<td>14:10</td>
<td>I</td>
<td>Hemiplegic</td>
<td>Crouch</td>
</tr>
<tr>
<td>S5</td>
<td>F</td>
<td>16:5</td>
<td>I</td>
<td>Hemiplegic</td>
<td>Stiff knee</td>
</tr>
<tr>
<td>S6</td>
<td>M</td>
<td>11:8</td>
<td>II</td>
<td>Diplegic</td>
<td>Crouch</td>
</tr>
</tbody>
</table>

aGMFCS: Gross Motor Function Classification System

bGait type: ‘Crouch’ gait defined by those parameters set by Gage et al [31] and ‘Winters type’ defined by those parameters set by Winters et al [59].
3.2.2 Wearable adaptive resistance device

Each participant was outfitted with a battery-powered, custom fit, lower limb ankle exoskeleton device (Fig. 3.1). The robotic device consisted of an actuation & control assembly worn at the waist, and ankle assemblies worn bilaterally on the legs (Fig. 3.1B). Motors remotely actuated the carbon fiber ankle assemblies via Bowden cables to generate ankle torque in the sagittal plane. Using custom force sensors placed under the forefoot, the ankle moment was estimated and a proportional level of resistance to plantar flexion was applied bilaterally in real-time during each stance phase. Exoskeleton resistance torque was measured bilaterally at the ankle assembly level using a torque sensor that was aligned with the ankle joint at the lateral malleolus. Users started with a calibration procedure that calculated the average peak ankle moment while walking. A resistance level could then be set (i.e., 0.1 Nm/kg), whereby this magnitude of resistance would be applied proportional to the instantaneous, estimated ankle moment. In other words, when peak ankle moment was reached (typically occurring in late stance), 0.1 Nm/kg would be applied. If only 50% of peak ankle moment was estimated (i.e., early stance), only 0.05 Nm/kg would be applied. If 0% of peak ankle moment was estimated (i.e., swing phase), 0 Nm/kg would be applied. This proportional application of resistance to plantar flexion occurred instantaneously and throughout the entire gait cycle for both ankles.

The typical user response to overcome the resistance was to increase activation of the ankle plantar flexors and decrease activation of the ankle dorsiflexors (reduce co-contraction) (Fig. 3.1) [28]. The closed-loop control scheme was designed to maximize neuromuscular engagement by being immediately responsive (i.e., adaptive) to user input. The device was controlled via a custom MATLAB graphical user
interface (v2019b, Natick, MA, USA), and weighed 1.75 kg. Additional details on the exoskeleton design and adaptive ankle resistance control scheme can be found in [28].

Figure 3.1. A wearable adaptive resistance device for neuromuscular gait re-training: a) Using the real-time estimation of biological ankle moment via embedded foot sensors, a proportional level of resistance to plantar flexion is applied that serves as an afferent signal for increasing motor unit recruitment of the plantar flexors, resulting in increased push-off for forward progression; b) Components of the wearable adaptive resistance device worn by all participants while training. The wireless robotic device included a waist-mounted control and actuation assembly, and carbon fiber ankle assemblies that were customized for each participant.
3.2.3 Assessments

Participants completed twelve total visits: a pre-assessment (first visit), ten training sessions, and a post-assessment (last visit). On the first visit, participants were evaluated by a licensed physical therapist to determine baseline physical characteristics, GMFCS level, and walking pattern. The following outcome measures were then evaluated on the first and last visit: plantar flexor strength, preferred treadmill walking speed, metabolic cost of transport, timed up and go (TUG) time, and six-minute walk test (6MWT) distance.

Plantar flexor strength was evaluated using a maximum voluntary contraction (MVC). Lying supine, participants were instructed to push as hard as possible for 3 seconds into a hand-held dynamometer, and an average of three trials was recorded. Values were then averaged between limbs and normalized to body mass. Using the physical therapist’s assessment, MVC measures, and input from parents/guardian, a more-affected and less-affected side were determined for training purposes.

To assess the metabolic cost of transport, a metabolic mask was worn for collecting oxygen and carbon dioxide levels (TrueOne 2400, Parvo Medics, Salt Lake City, UT, USA). First, these expired gases were recorded during quiet sitting and standing. Next, participants walked on a treadmill at a self-selected speed while being spotted by a laboratory technician. Preferred walking speed was identified by asking participants to choose a speed that they would normally walk at while at school or home. The treadmill speed was then increased and decreased to confirm preferred walking speed. Participants walked for approximately six minutes, or until oxygen consumption plateaued, indicating a stabilized metabolic cost of walking.

Two reliable, clinical measures for children with CP, the TUG [68] and 6MWT [69], were used to measure the effect of training on mobility. For both measures, we
followed standard testing procedures [68,69]. S4 presented behavioral issues and was not able to complete the 6MWT without periods of running on his final assessment, which was out of compliance with instructions to only walk.

3.2.4 Training

Participants completed ten training sessions over four weeks. The first session began with resistance set at 0.025 – 0.075 Nm/kg while walking at a preferred treadmill walking speed (Fig. 3.1). When necessary, instruction was given to participants while they walked to “push against the resistance”, where the focus was on their more-affected side. Using real-time feedback of the estimated biological ankle moment and exoskeleton ankle torque, the research team was able to assess how well participants were reaching the prescribed level of resistance. Training included 20 minutes of walking per visit, separated by one to two rest breaks depending on participant preference. At the end of each session, participants were asked to rank their level of soreness on the following scale: None, Mild, Moderate, Severe, and Very Severe. Resistance was increased by 0.5 – 1 Nm per session if participants both 1) reached their prescribed level of resistance > 50% of the training session, and 2) had a perceived level of soreness between None and Moderate. All six subjects completed ten training sessions.

3.2.5 Data processing & statistical analysis

For analysis of metabolic data, we identified areas of “steady state” for both standing and walking using Kendall’s tau-b approach [70], which is able to categorize time series data as rising, falling, or stable. The null hypothesis of this analysis was that a data point falls within a steady state window, and rejection of the null
hypothesis indicated non-steady data. This technique for determining which data points can be considered steady state for a condition was found to contribute to a five-fold reduction in variability of measured oxygen costs while walking for individuals with CP [70]. Brockway’s standard equation was used to determine metabolic cost for each steady-state region [71]. Net metabolic cost (W) was calculated by subtracting the metabolic cost of quiet standing from the metabolic cost of walking. To normalize to body size and differences in walking speed, metabolic cost was then divided by body mass (kg) and walking speed (m/s) for a final measure of body-mass-normalized metabolic energy required to walk a unit distance (i.e., metabolic cost of transport, J/kg-m).

We assessed all outcome measure data for normality and the presence of outliers. Normality was tested using the Kolmogorov-Smirnov test with small sample Lilliefors correction [56]. Outliers were defined as any data point 1.5 times the interquartile range below the first quartile or above the third quartile. Data falling within this outlier definition were removed for statistical comparison and calculation of means, and not included in figures unless explicitly noted. We assessed our a priori hypotheses using two-tailed paired t-tests, and accounted for multiple comparisons using a Holm-Bonferroni correction. Significance level was set at \( \alpha < 0.05 \). Cohen’s d (d) was used to calculate effect size, where 0.2 was considered a small effect, 0.5 a medium effect, and 0.8 a large effect [72].

3.3 Results

Six participants (five males, one female) with mild-to-moderate gait impairment from CP (all independent ambulators) completed pre- and post-assessments and ten training visits (Table 3.1).
Figure 3.2. Training progression, strength and speed outcomes: a) Training progression with indication of the resistance level (Nm/kg) for each of the ten training visits (v2 – v11) and the resulting soreness level from each session: None (green), Mild (yellow), Moderate (light orange), Severe (dark orange), and Very Severe (red); b) Maximum voluntary contraction values for the plantar flexors, presented as the average between both limbs and normalized to body mass; c) Preferred walking speed (m/s) on the treadmill.

All data assessed in the statistical comparisons were normally distributed. S3’s pre-assessment metabolic cost of transport, an unrealistic 16.9 J/kg-m, met the definition of an outlier and was subsequently removed from any statistical analyses.
There was a significant increase in average plantar flexion strength by 17 ± 8% after training (p = 0.02, d = 1.90; Fig. 3.2b, Table 3.2). Preferred walking speed on the treadmill increased by 39 ± 25% after training (p = 0.04, d = 1.63; Fig. 3.2c, Table 3.2). Level of resistance reached by visit ten ranged from 0.14 – 0.27 Nm/kg. The average soreness level for all participants and visits was Moderate; the range of soreness levels spanned None – Severe, with no participants reaching a Very Severe level (Fig. 3.2a).

### Table 3.2. Strength and mobility outcomes

<table>
<thead>
<tr>
<th></th>
<th>Plantar flexor strength (N/kg)*a</th>
<th>Preferred treadmill walking speed (m/s)*</th>
<th>Timed up and go (s)*</th>
<th>Six-minute walk test (m)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>S1</td>
<td>3.79</td>
<td>4.73</td>
<td>0.58</td>
<td>0.89</td>
</tr>
<tr>
<td>S2</td>
<td>2.57</td>
<td>2.74</td>
<td>0.45</td>
<td>0.63</td>
</tr>
<tr>
<td>S3</td>
<td>4.73</td>
<td>5.59</td>
<td>0.40</td>
<td>0.63</td>
</tr>
<tr>
<td>S4</td>
<td>4.16</td>
<td>4.46</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>S5</td>
<td>3.65</td>
<td>4.52</td>
<td>0.72</td>
<td>0.85</td>
</tr>
<tr>
<td>S6</td>
<td>4.71</td>
<td>5.75</td>
<td>0.49</td>
<td>0.80</td>
</tr>
<tr>
<td>Median</td>
<td>3.97</td>
<td>4.62</td>
<td>0.53</td>
<td>0.73</td>
</tr>
</tbody>
</table>

*a*Indicates the maximum voluntary contraction value for the plantar flexors, presented as the average between limbs and normalized to body mass.

Note: S4 was not able to follow the instructions to “walk only” and thus, could not complete the six-minute walk test.

*p < 0.05

Metabolic cost of transport, evaluated at a participant’s within-visit preferred walking speed on the treadmill, decreased from pre- to post-assessments by 33 ± 9% (p = 0.03, d = -2.31; Fig. 3.3a,3.3d). TUG times decreased by 11 ± 9% (p = 0.04, d = -1.16; Fig. 3.3b, Table 3.2) and 6MWT distances increased by 13 ± 9% (p = 0.04, d = 1.61; Fig. 3.3c, Table 3.2).
Figure 3.3. Walking efficiency and clinical mobility outcomes. Pre- (red) and post-assessment (blue) a) group-level metabolic cost of transport, representing the metabolic cost per unit distance of walking while participants walked on a treadmill at their within-visit preferred speed, b) timed up and go (TUG) times, averaged over 3 trials, c) six-minute walk test (6MWT) distance, and d) individual, steady-state metabolic data. *Indicates outlier, excluded from statistical analysis.
3.4 Discussion

Wearable adaptive ankle resistance was designed to provide precise, perfectly synchronized resistance within the functional task of walking. The novel closed-loop control scheme that responded in real-time to user input acted as a neuromuscular cue to elicit improved function of the ankle plantar-flexors. Adaptive ankle resistance training of ten, 20-minute sessions over four weeks was safe and effective for children and adolescents with CP (See Appendix C, Videos C.1 and C.2).

We found that participants’ soreness levels ranged from None – Severe. Importantly, “Severe” soreness was only noted three times, representing <5% of questionnaire responses across the study, and no participants indicated a “Very Severe” level. Soreness level did not appear to negatively affect training efficacy with all participants safely completing the entire 20-minute duration of all 10 of their training sessions. In fact, the protocol was designed to elicit moderate soreness after each session, increasing resistance, if necessary. The training progression for participants depended on both soreness level and the ability to match the targeted level of resistance for more than 50% of the training session. Active engagement is a critical aspect of neuromuscular re-training [27]. Therefore, our ability to assess engagement with resistance was an essential aspect of this training modality. Using real-time displays of exoskeleton resistance and estimated biological ankle moment, we were able to track “performance” by analyzing how well a participant’s biological ankle moment matched the prescribed level of resistance. This helped to prevent passivity while training, as we could adjust resistance or further instruct participants based on their ability to engage with resistance. We observed that participants were more likely to be sore with a higher percentage of gait cycles reaching the prescribed resistance level, supporting our criteria for increasing the level of resistance.
Our finding of increased average plantar flexion strength may be a positive indicator of the tissue-level changes that are possible with this wearable resistance training modality. Plantar flexion strength is significantly associated with walking ability for individuals with CP [26], who are weaker than their typically developing peers [34]. Strength is a necessary building block for function, and the increases in strength with training likely contributed to the improved walking efficiency and performance we observed.

Metabolic cost of walking, an important, inversely-related indicator of physical activity levels in children with CP [6], significantly improved after the intervention. We observed a significant reduction with a very large effect size in metabolic cost of transport (-33%, p = 0.03, d = -2.31) when compared to the metabolic cost of transport during the pre-assessment (Fig. 3.3a,3.3d). This reduced metabolic cost of transport occurred at participants’ final preferred speed, which was 39% faster than their pre-assessment speed (p = 0.04, d = 1.63). These results suggest that following the intervention, participants could walk 39% faster while using 33% less energy per unit distance, on average.

To confirm that changes in metabolic cost of transport could translate to improved performance on tests of speed and endurance, we included the TUG and 6MWT as part of the pre- and post-assessment; outcomes from both improved. Time on the TUG test, representing performance in agility and speed, decreased 11%. The TUG requires participants to walk as quickly as possible, and involves a sit to stand and stand to sit movement that requires careful control and good functional strength beyond the task of walking [73]. The observed 13% improvement in 6MWT, a test of endurance, may be attributed to the improved walking efficiency following ankle
resistance training. This is a particularly promising finding given the significant association between 6MWT performance and physical activity levels in children with CP [74].

Compared to treadmill training alone, our wearable resistance intervention elicited similar or greater improvements in a fraction of the training time. Provost and colleagues studied the effect of intensive body weight-supported treadmill training for six individuals with CP, GMFCS level I, ages 6-14 [75]. The intervention consisted of 30 minutes, twice daily training with 0-30% weight support over 12 total sessions. Effects of body weight-supported treadmill training on walking efficiency, assessed using the Energy Expenditure Index (EEI), an indirect measure of energy expenditure based on heart rate, improved for all six children (d = -1.24, calculated from the individual participant data provided), yet 6MWT distance did not improve. Despite the shorter training period in our study (200 minutes versus 720 minutes), we still observed clinically-meaningful reductions in metabolic cost of transport (-33%) with an effect size of -2.31, and did observe improvements in 6MWT distance (13%). In a study by Aviram and colleagues [76], 43 individuals with spastic CP, GMFCS levels II – III, ages 14 – 21 years underwent 30 bi-weekly, 40-minute treadmill training sessions under the supervision of a physical therapist with progressive increases in treadmill speed. After training, individuals had a 10.1% decrease in TUG time (-1.21 ± 0.40 s) and a 12.1% increase in 6MWT distance (29.1 ± 6.9 m). Individual subject data were not provided preventing comparison of effect size, nor was energy expenditure assessed. Notably, the total accumulated training time was approximately 1200 minutes, six times the duration of our intervention.
3.4.1 Study limitations

There are limitations of this study worth noting. First, this study lacked a control group. Therefore, we rigorously compared our findings to relevant intervention studies comprised of only treadmill walking. We found that our adaptive resistance intervention resulted in similar or greater improvements following a dramatically shorter intervention duration. The next step, after these promising findings, is a randomized controlled trial (RCT) that will include a dose-matched control group.

Second, this study had a small sample size. Despite this limitation, we observed mainly large and very large effect sizes for our outcome measures. Participants in this study were also limited to an age of at least 10 years old and GMFCS levels I – II. It is important to consider these participant characteristics because it is possible that training effects would look different for younger individuals with CP, when neuroplasticity may be higher [77], and for individuals with lower functional levels, such as GMFCS level III, where there may be more room for improvement in strength [26] and gait efficiency [78]. As a pilot study, this inclusion criteria allowed us to be confident in the feasibility of this training intervention, and our findings now provide justification for broadening the inclusion criteria for future explorations of this training modality.

Third, verbal instruction was provided during each functional ankle resistance training session. Therefore, the impact of verbal instruction on our outcomes is unknown. Real-time biofeedback has shown promise in gait training for children with CP [48], and will be studied as an automated approach for providing feedback during our future implementations of adaptive resistance training. Finally, to better understand the mechanisms of improved walking efficiency with wearable adaptive
resistance training, future work should evaluate changes in neuromuscular control of the lower limbs.

3.4.2 Conclusions

Wearable adaptive resistance training was found to be a feasible and effective modality for improving locomotor performance in individuals with CP who had lifelong, deeply engrained walking patterns. A short, four-week intervention was able to significantly improve ankle strength, walking efficiency and performance on clinical tests of speed and endurance. We expect that this intervention may be suitable for other patient populations affected by neuromuscular impairment because it aligns with the guiding principles of neuroplasticity – task-specificity and top-down active engagement [17]. This relatively low-cost, battery-powered, and wearable intervention was designed for translation to both clinical practice and personal use at home, and as an untethered device, training can take place under a variety of contexts, including overground walking [79]. The inherent accessibility of this wearable intervention provides individuals with the opportunity to significantly increase the frequency of targeted neuromuscular rehabilitation.
Chapter 4

Pilot evaluation of changes in motor control after wearable robotic resistance training in children with cerebral palsy

4.1 Introduction

The ankle plantar flexor muscles play a key role in mechanical energy recovery while walking, extending the knee joint, preventing excessive ankle dorsiflexion during midstance, modulating center of mass vertical displacement, and providing the single-largest contribution to forward propulsion across all lower-extremity muscle groups [31,32]. This allows the motion of the body’s center of mass to follow an arced, inverted pendular pattern that provides an effective exchange in potential and kinetic energy [80]. Activation of the ankle plantar flexor muscles is reduced, less modulated, and often accompanied by co-activation of the antagonist dorsiflexor muscles in a majority of individuals with spastic cerebral palsy (CP) [81], a movement disorder arising from injury to the brain during infancy [65]. These muscle activation characteristics likely contribute directly or indirectly to reduced energy exchange [82], elevated metabolic cost of transport [8], and lower levels of physical activity [4] in CP.

Impaired neuromuscular control in children with CP may be explained in part by deficits in cortical organization [83]. It has been shown that the variance in muscle activity accounted for by one muscle synergy is associated with the level of motor control complexity [84]. Children with CP have greater variance accounted for by one muscle synergy while walking compared to typically developing peers, leading to the conclusion that these children use a simplified control strategy [85]. This measure of motor control in children with CP plays a significant role in explaining treatment outcomes for this population [86].
Current standard of care for children with CP has not been successful at improving neuromuscular control [87]. Surgical procedures, while a critical component in the management of musculoskeletal health for individuals with CP [2], may have limited influence on neuromuscular control of movement [88]. Lower-limb orthoses, which serve to mitigate misalignment and contractures [65], are not specifically designed to train motor control. Physical therapy has shown limited evidence of improving motor function and walking ability [14,15]. Gait training with partial body-weight support may lead to muscle atrophy over time [46] and negatively impact muscle activation timing [44]. Functional electrical stimulation is a bottom-up approach that has failed to produce lasting changes in neuromuscular control or gain traction as an effective tool for treating CP [89]. There is an apparent gap in our ability to effectively address deficits in the neuromuscular control of walking for individuals with CP.

We recently developed an untethered, ankle exoskeleton device that provides resistance proportional to the estimated, real-time biological ankle moment to foster increased volitional engagement of the ankle plantar flexor muscles while individuals with CP walk with the device [28]. It was observed that four weeks of training with this novel paradigm led to significant and rapid improvements in ankle strength and mobility-related outcomes for individuals with CP [29]. Changes in neuromuscular control and gait mechanics after training with this new therapeutic tool have not yet been explored.

The primary goal of this study was to explore potential underlying neuromuscular and biomechanical mechanisms behind observed improvements in mobility after training with adaptive ankle resistance, and evaluate the user experience
of this task-specific gait re-training intervention. We hypothesized that repeated neuromuscular gait re-training with adaptive ankle resistance that responds directly to user input would improve the ankle plantar flexor muscle activation profile and decrease co-contraction across the ankle joint during device-free walking. We also hypothesized that these changes would reflect improved motor control complexity, as indicated by muscle synergy analysis. We further hypothesized that the combination of improved plantar flexor activation, reduced co-contraction, and more complex muscle coordination would lead to a more mechanically efficient gait pattern.

4.2 Methods

4.2.1 Participants

This study was approved by the Northern Arizona University Institutional Review Board (#986744). The protocol was completed at the Northern Arizona University – Phoenix Biomedical Campus (Phoenix, AZ) and registered at ClinicalTrials.gov (NCT04119063). Informed written consent was provided by a parent or legal guardian for each participant.

We recruited six individuals diagnosed with hemiplegic or diplegic CP based on the following inclusion criteria: Gross Motor Function Classification System (GMFCS) levels I – II, the ability to walk with or without a walker for at least six minutes, age between 10 – 21 years, and the ability to follow directions. Individuals were excluded from the study if they had orthopedic surgery within the past six months, botulinum toxin injections to the lower limbs within the past four months, or any conditions that would prevent safe participation. Data from five participants are reported in this study due to a motion capture recording equipment failure for one
participant and the resulting absence of experimental biomechanics data needed for this analysis (Table 4.1).

Table 4.1. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Gender</th>
<th>Age (y:m)</th>
<th>Height (cm)</th>
<th>Body mass (kg)</th>
<th>GMFCS level</th>
<th>Hemi- or diplegic</th>
<th>More-affected side</th>
<th>Gait type</th>
</tr>
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<td>173.5</td>
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<td>Di</td>
<td>Right</td>
<td>Crouch</td>
</tr>
<tr>
<td>P2</td>
<td>M</td>
<td>13:11</td>
<td>143.0</td>
<td>42.0</td>
<td>II</td>
<td>Hemi</td>
<td>Right</td>
<td>Crouch</td>
</tr>
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<td>59.0</td>
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<td>Hemi</td>
<td>Right</td>
<td>Crouch</td>
</tr>
<tr>
<td>P4</td>
<td>F</td>
<td>16:5</td>
<td>160.5</td>
<td>68.5</td>
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<td>Left</td>
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<tr>
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<td>131.5</td>
<td>30.2</td>
<td>II</td>
<td>Di</td>
<td>Right</td>
<td>Crouch</td>
</tr>
</tbody>
</table>

aGMFCS: Gross Motor Function Classification System.
bGait type: ‘Crouch’ gait defined by those parameters set by Gage et al [31].

4.2.2 Wearable Resistance Platform

Our exoskeleton ankle resistance therapy (exo-therapy) utilized a custom battery-powered ankle exoskeleton that provided resistance to plantar flexion (Fig. 4.1a). The device had an actuation and control assembly that was worn at the waist, and ankle assemblies worn bilaterally. Both hemiplegic and diplegic participants wore a bilateral exoskeleton for consistency. Detection of gait events and real-time estimates of ankle moment from the embedded force sensors allowed the device to provide proportional resistance to ankle plantar flexion [28]. An onboard microcontroller with Bluetooth allowed for remote control via a custom MATLAB
graphical user interface and visualization of the estimated ankle movement and exoskeleton torque, allowing us to assess user performance in real-time; participants were blinded to this real-time visualization of their performance.

Figure 4.1. Wearable adaptive resistance training. a) Pictures of the exoskeleton used to deliver adaptive ankle resistance b) Schematic depiction of the proposed mechanisms underlying the neuromuscular response to wearable adaptive resistance training, including increased neural complexity (as indicated by an increase in the number of muscle synergies recruited for walking), improved inhibition of antagonist muscles about the ankle, and enhanced muscle activation timing of the plantar flexor muscles for more typical activation timing (experimental data from P1).

4.2.3 Pre- and Post-Assessment

A separate pre-assessment visit was completed within 48 hours before a participant’s first training session, and a separate post-assessment visit was completed
within 48 hours after a participant’s last training session (Fig 4.2). During the pre-assessment, participants were evaluated by a licensed physical therapist to determine physical characteristics, GMFCS level and each participant’s more- and less-affected lower-limbs. For both the pre- and post-assessments, wireless surface electromyography (EMG) sensors (Noraxon; 1000 Hz) were placed on the soleus (SOL), tibialis anterior (TA), vastus lateralis (VL), and semitendinosus (ST) according to SENIAM recommendations for consistency between visits [90]. Participants were outfitted with 38 reflective markers for measuring 3D kinematics of the legs, pelvis, and trunk using eight motion capture cameras (Vicon; 100 Hz). Participants walked on a treadmill at a self-selected speed while being monitored by a laboratory technician. Preferred walking speed was identified by asking participants to choose a speed that they would normally walk at school or home. The treadmill speed was then increased and decreased to confirm preferred walking speed.

Oxygen and carbon dioxide levels were assessed using a metabolic measurement system (TrueOne 2400, Parvo Medics). Metabolic measurements were taken while participants stood for two minutes, followed by six minutes of walking at their preferred treadmill speed, or until oxygen consumption levels stabilized. Once a steady state of oxygen consumption was reached, kinematic and EMG data were recorded for 30 seconds of walking. During the post-assessment, if the participant’s preferred speed differed from his or her preferred speed during the pre-assessment, all measurements were taken at the pre-assessment preferred speed so that pre- and post-assessment speeds were matched. For metabolic cost measurements at a participants’ final preferred speed, see [29].
During the post-assessment visit, a usability questionnaire was completed with study participants to determine 1) if they would like to train with the device again, 2) if the level of difficulty was sufficient, and 3) if they had any additional comments about their experience. Parents or guardians were then asked to comment on their experience with the training intervention. A summary of questionnaire results are reported in Appendix D.1.

Figure 4.2. Study visit allocation. Participants completed 12 total visits: a pre-assessment, ten training visits, and a post-assessment.

4.2.4 Exoskeleton Ankle Resistance Therapy (Exo-therapy)

Training consisted of ten 20-minute treadmill walking sessions, separated by 48 – 72 hours (Fig 4.2), with ankle resistance at each participant’s preferred speed. One to two rest periods were provided during each session, depending on participant preference. The nominal resistance setpoint was initialized between 0.025 – 0.075 Nm/kg, which represents the maximal amount of resistance that would be applied during a gait cycle (i.e., the amount of resistance applied when the peak biological ankle moment was reached, typically at push-off). Participants were instructed to focus on engaging their ankle plantar-flexor muscles, with an emphasis on their more-
affected limb. Verbal coaching was provided as needed. Following the completion of each session, participants were asked to rank their level of soreness on the following scale: none, mild, moderate, severe, and extremely severe. If participants had both 1) a perceived level of soreness between none and moderate, and 2) reached their prescribed level of resistance for more than 50% of the training session, then the prescribed resistance level was increased by 0.5 – 1 Nm for the next training session. An interval of 0.5 – 1 Nm was used based on pilot testing of sufficient magnitudes to induce a noticeable change in difficulty level.

4.2.5 Data Processing & Statistical Analysis

An OpenSim musculoskeletal model was scaled to the anthropometrics of each participant [55]. Joint angles across 10 continuous gait cycles were calculated in OpenSim via inverse kinematics (pre- and post-musculoskeletal gait model videos can be found in Appendix C, Video C.3). Participant EMG signals were bandpass filtered (4th order Butterworth, 20 - 400 Hz band-pass cutoff), rectified, and low-pass filtered (4th order Butterworth, 10 Hz low-pass cutoff), and then time normalized from 0 – 100% of the gait cycle [91]. The EMG curves were then averaged over the same 10 gait cycles and normalized to the maximal activity recorded during walking within a visit for each respective muscle [52]. For consistency across participants with diplegia and hemiplegia, all EMG measures were assessed for the more-affected limb only.

Co-contraction between the soleus and tibialis anterior was calculated using a co-contraction index (CCI) [92], which captures the temporal and magnitude components of an EMG signal [93], as in Equation 1:
\[
CCI = \sum_{i=1}^{101} \frac{\text{LEMG}(i)}{\text{MEMG}(i)} \left( \text{LEMG}(i) + \text{MEMG}(i) \right)
\]

Eq. 1

where \(i\) represents the individual time points of the time-normalized gait cycle (0 – 100\%, or 101 total data points), \(\text{LEMG}\) represents the normalized magnitude of the less active muscle at time point \(i\), and \(\text{MEMG}\) represents the normalized magnitude of the more active muscle at time point \(i\).

We assessed the relationship between the soleus EMG profile for our participants and the typical (control) soleus EMG profile from unimpaired individuals by calculating the Pearson product moment correlation coefficient \((R)\) [57]. The typical soleus EMG curve were from unimpaired individuals walking at a non-dimensional speed of 0.25 [94], which was very close to the non-dimensional speed of our participants (0.21); non-dimensional walking speed was calculated by dividing walking speed by the square root of gravity multiplied by leg length [95].

The variance in muscle activity accounted for by one muscle synergy \((\text{VAF}_1)\) was calculated using non-negative matrix factorization (NNMF) [96] [85], as in Equation 2:

\[
\text{VAF}_1 = 1 - \frac{\|\text{EMG} - W^*C\|}{\|\text{EMG}\|^2}
\]

Eq. 2

where \(\text{EMG}\) represents a matrix containing the normalized and averaged EMG data recorded for each muscle; \(W\) represents the relative activation level in a synergy and is a 4 x 1 matrix, with a separate row for each muscle; and \(C\) represents the activation level of a synergy over the gait cycle.
The mechanical efficiency of each individual’s pre- and post-training gait patterns was calculated using energy recovery analysis (Fig. 4.4) [82]. Center of mass mechanical energy recovery is significantly lower in children with CP [82], which may contribute to the higher metabolic cost of walking in this population [7]. This measure was quantified as the exchange between kinetic and potential energy of the center of mass (COM) movement (Eq. 5) by considering the external work ($W_{ext}$, Eq. 3) on the COM and the work done by the COM ($W_{ne}$, Eq. 3) [82].

$$W_{ext} = \sum_{i=1}^{101}(|\Delta PE + \Delta KE|)$$  \hspace{1cm} \text{Eq. 3}

$$W_{ne} = \sum_{i=1}^{101}(|\Delta PE| + |\Delta KE|)$$  \hspace{1cm} \text{Eq. 4}

$$ER = 100 \cdot \frac{(W_{ne} - W_{ext})}{W_{ne}}$$  \hspace{1cm} \text{Eq. 5}

where $i$ represents the individual time points of the time-normalized gait cycle (0 – 100%, or 101 total data points), $\Delta PE$ represents the change in potential energy of the COM between $i$ and $i + 1$, and $\Delta KE$ represents the change in kinetic energy of the COM between $i$ and $i + 1$.

Metabolic cost of transport was calculated using participants’ expired gas data (TrueOne 2400, Parvo Medics, Salt Lake City, UT, USA). First, steady state regions for both quiet standing and walking data were determined by Kendall’s tau-b approach [70], which has been shown to contribute to a five-fold reduction in variability of measured oxygen costs while walking for individuals with CP [70]. Metabolic cost of each region was calculated using Brockway’s standard equation [71], and a net metabolic cost (W) was determined by subtracting the metabolic cost of quiet standing from the metabolic cost of walking. Net metabolic cost was then divided by body mass.
(kg) and walking speed (m/s) for a final measure of body-mass-normalized metabolic energy required to walk a unit distance (i.e., metabolic cost of transport, J/kg-m).

Primary outcome measures included CCI, relationship of experimental soleus EMG profile to a typical profile, energy recovery, and metabolic cost of transport. Secondary outcome measure included VAF$_1$. All outcome variables were assessed at matched speeds (i.e., pre vs. post-training, both at the initial preferred speed).

We assessed all outcome measure data for normality and the presence of outliers. Normality was tested using the Kolmogorov-Smirnov test with small sample Lilliefors correction [56]. Outliers were defined as any data point below the first quartile or above the third quartile of the 1.5 interquartile range [97]. No data met the definition as an outlier. We evaluated our outcome measures using two-tailed paired t-tests. Multiple comparisons were corrected for with a Holm-Bonferroni correction for our primary outcome variables. Significance level was set at $\alpha = 0.05$. Cohen’s $d$ (d) was used to calculate effect size, where 0.2 was considered a small effect, 0.5 a medium effect, and 0.8 a large effect [72].

4.2.6 Supplementary Analysis

To provide better context for any changes in motor control complexity after exo-therapy, we retrospectively matched our participants by age and GMFCS level to patients with motor control complexity data who underwent two of the most common procedures for children with CP – single event multi-level surgery (SEMLS) and selective dorsal rhizotomy (SDR). See Appendix D.2 for further details on this analysis.
4.3 Results

All participants were able to continue walking at or above their initial walking speed through progressive increases in plantar flexor resistance and indicated an interest in training with the device again. The average level of resistance increased by 0.015 ± 0.012 Nm/kg across the training sessions; a majority of the participants indicated the levels of resistance were “just right”, with two participants indicating that it “could have been harder”.

Figure 4.3. Neuromuscular outcome measures. Individual (color-coded circles) and group mean (bars) pre- and post-exo-therapy neuromuscular variables, including a) co-contraction index (CCI) between the soleus and tibialis anterior; b) the relationship of the experimental soleus activation profile to a typical activation profile at a non-dimensional speed of 0.25; c) variance in muscle activity of the soleus, tibialis anterior, vastus lateralis, and semitendinosus that could be explained by one muscle synergy (VAF₁). ‘Typical’ values were calculated using a publicly available dataset [30] of individuals walking at a non-dimensional speed of 0.25.

4.3.1 Neuromuscular control

Following exo-therapy, more-affected limb co-contraction between the soleus and tibialis anterior decreased by 29 ± 11% (p = 0.02, d = -2.27; Fig. 4.3a) and the relationship (R) between experimental and the typical soleus curve increased by 33 ±
13% (p = 0.01, d = 2.93; Fig. 4.3b; see Appendix A, Fig. A.3 for individual participant EMG curves) during walking at the same speed. The variance in muscle activity of the soleus, tibialis anterior, vastus lateralis, and semitendinosus explained by one muscle synergy decreased by 7 ± 3% (p = 0.006, d = -2.32; Fig. 4.3c). When compared to age- and GMFCS-matched control data (Appendix B, Table B.1), exo-therapy resulted in greater reduction in $VAF_1$ than both SEMLS (p = 0.0004) and SDR procedures (p = 0.0003) (Appendix A, Fig. A.4).

4.3.2 Gait Efficiency

Whole-body center of mass potential-kinetic energy exchange recovery increased by 58 ± 34% (p = 0.04, d = 1.57; Fig. 4.4; see Appendix A, Fig. A.5 for individual energy curves) when walking at the same preferred speed, with a pre-assessment average of 30% and a post-assessment average of 47% (typically developing average is 66%). Metabolic cost of transport decreased by 29 ± 15% (p = 0.02, d = -1.60; Fig. 4.5, see Appendix A, Fig. A.6 for individual metabolic curves) when walking at the same speed.
Figure 4.4. Center of mass mechanical efficiency. a) Group average pre-exo-therapy (red), group average post-exo-therapy (blue), and typical unimpaired (gray) potential energy (PE, solid lines) and kinetic energy (KE, dashed lines) curves. Pie charts indicate the group average center of mass (COM) energy exchange recovery percentage; For efficient energy exchange and increased recovery, potential and kinetic energies should be 180º out of phase with equal and opposite amplitudes. The typical, unimpaired curve was adopted from Bennett et al [82].

Figure 4.5. Metabolic cost. Individual (color-coded circles) and group mean (bars) pre- and post-exo-therapy metabolic cost of transport, representing the body-mass-normalized metabolic energy required to walk a unit distance. Both pre- and post-measures were collected at the pre-exo-therapy preferred walking speed on the treadmill.
4.4 Discussion

Our results support the hypotheses that there would be improvements in neuromuscular control after this exo-therapy training protocol (Fig. 4.3), translating to improvements in mechanical and metabolic efficiency (Figs. 4.4,4.5). In children with CP, ankle power is significantly reduced [33], potentially due to ineffective muscle activation profiles and co-contraction. In our prior validation study of the resistance controller, we observed a significant decrease in ankle co-contraction when individuals walked with resistance [28]. The present study found that there was a carry-over of this desirable reduction in co-contraction to walking without the device following exo-therapy. We theorize that reductions in co-contraction may be due to improvement in reciprocal inhibition (Fig. 4.3a), which is impaired in children with CP [62]. We also observed a significant increase in the similarity of our participants’ more-affected limb soleus muscle activity profiles compared to the activation pattern from unimpaired individuals (Fig. 4.3b), reflecting improved activation timing.

We found a modest, but significant reduction in the variance in muscle activity that can be explained by one muscle synergy (VAF$_1$) following exo-therapy (Fig. 4.3c), which suggests the potential for improved motor control complexity. Smaller VAF$_1$ in children with CP has been shown to be a strong predictor of positive treatment outcomes, independent of the treatment [86].

Exo-therapy was designed to capitalize on the core principles of motor learning, including task-specificity, repetition, and active engagement [17]. Our wearable system allowed participants to train within the task-specific, functional context of walking, and achieve repetitive, high-volume practice. Applying resistance to plantar flexion necessitated active user engagement to maintain speed on the treadmill. Additionally, the adaptive nature of the proportional joint-moment control
scheme made it so that resistance was immediately responsive to user input, creating an experience that fostered active engagement while still being feasible for various levels of motor function (i.e., GMFCS levels I and II). This was supported by the positive user experience when training with the device.

Afferent signals from load receptors play a critical role in muscle activation timing while walking [43], and the phase-specific resistance of this intervention may have served as a supraphysiologic signal for the plantar flexors to fire at the appropriate time. Motor control theory also dictates that the modular recruitment of muscles (i.e., muscle synergies) become more specific with greater biomechanical constraints [98]. With resistance as a new biomechanical constraint, there may have been a demand for greater precision in motor control by the participants, necessitating increased neural complexity as indicated by the significant changes in VAF₁. These features of exo-therapy may have worked together to facilitate rapid motor learning for improved neuromuscular control. Exo-therapy may have potential to facilitate the treatment of walking disability across the broad spectrum of neurological disorders.

This study had several limitations. First, we did not include a direct control group to isolate the effects of exo-therapy independent of structured treadmill walking, which should be considered when interpreting our findings. However, the 20 minutes of training completed during each visit was likely not a significant departure from typical walking volume. To the best of our knowledge, no prior studies of treadmill-only training in CP have reported similar findings to those reported here. Second, as a feasibility and preliminary assessment study, we had a limited sample size. Despite the limited sample, there were very large effect sizes, and the number of participants closely matches those of other device-centered neurorehabilitation studies [50,52].
Third, the device’s calf cuff prevented recording of gastrocnemius activity, and given its unique role during walking [99], the response of this muscle to training should be explored in future studies. Finally, proper engagement with the exoskeleton device required some verbal cues. However, the use of verbal cues is consistent with other studies that have investigated robotic gait training paradigms for children with CP [67,100,101], and seems to be a necessary feature for teaching individuals effective engagement with a novel device.

### 4.4.1 Conclusion

The findings from this study indicate the potential for treadmill training with exo-therapy to positively affect neuromuscular function of the ankle musculature in children with CP. We observed improved soleus activation timing and coordination, improved energy transfer, reduced co-contraction, and increased complexity of neuromuscular control. This novel training modality could supplement the current standard of care for individuals with CP, offering increased access to targeted neuromuscular rehabilitation.
Chapter 5

Under Pressure: Design and Clinical Validation of Electrodeless Plantar Flexor Biofeedback for Neuromuscular Gait Training

5.1 Introduction

Effective recruitment of the ankle plantar flexor muscles is necessary to modulate the forward and vertical progression of the center of mass for an efficient exchange of potential and kinetic energy during bipedal walking [32,80]. Individuals with cerebral palsy (CP) [81], stroke [102], and the elderly [103], often lack the neuromuscular control to effectively utilize their plantar flexors during walking. For individuals with CP, the most prevalent pediatric-onset movement disorder, there is broad clinical agreement that plantar flexor dysfunction often contributes to gait impairment [104], creating a barrier to an active lifestyle and predisposing this population to a host of secondary effects associated with inactivity [105], including an eventual loss of independent ambulation [9]. For this reason, interventions designed to improve neuromuscular control of the ankle plantar flexors could have a significant impact on long-term mobility for individuals with CP, or any other patient populations that experience reduced motor control at the ankle.

Several audiovisual biofeedback systems have been developed for individuals with CP with the goal of modulating upper or lower limb control [106,107]. To date, most audiovisual biofeedback studies aimed at increasing lower-limb muscle control during have utilized an electromyography (EMG)-based system, whereby a user’s muscle activity is displayed to them in real-time [48,49,108]. While EMG-based audiovisual biofeedback provides direct feedback of the intervention’s target (i.e., increased muscle activity), there are significant limitations to the EMG biofeedback modality that prevents widespread adoption in clinical or home settings, including
motion artifact noise during walking; skin-electrode interface reliability challenges, like hair and sweating; the necessity and complexity of proper anatomical placement of the sensors, particularly when placing sensors on small limbs; and the cost of an EMG system. This may explain why, despite a demonstrated benefit of plantar flexor EMG-based biofeedback for improving ankle function and gait symmetry in CP nearly three decades ago, this gait training tool has failed widespread adoption in clinical practice. Practical biofeedback modalities capable of increasing plantar flexor recruitment during gait training would likely have widespread appeal.

We theorize that a potential alternative to a plantar flexor EMG-based biofeedback system could be an underfoot plantar pressure-based system that would measure and provide feedback on the change in forefoot pressure generated from plantar flexor muscle recruitment. Pressure sensors are inexpensive and could be quickly and easily accommodated by most footwear [109]. If effective, plantar pressure-based biofeedback may expand access to neuromuscular gait training by offering a practical solution for in-clinic and at-home use. Before a plantar pressure-based system like this could be clinically translated, however, it should be validated by comparing changes in muscle activity with those observed from an EMG-based system during walking.

The primary aim of this study was to clinically validate the use of a plantar pressure-based audiovisual biofeedback system to increase ankle plantar flexor engagement during walking by comparing changes in muscle activation levels to an EMG-based audiovisual biofeedback system in CP. We hypothesized that both biofeedback modalities would result in a significant increase in plantar flexor activity while walking, with no difference and strong relationships between the two systems,
validating the use of the plantar pressure-based system as an alternative to an EMG-based system. In addition, we sought to determine if combining plantar pressure-based biofeedback system with a robotic ankle exoskeleton used for functional ankle resistance gait training in cerebral palsy [28] could increase engagement with the device. Therefore, our secondary aim was to compare changes in plantar flexor activity between walking with plantar flexor resistance alone and when combined with plantar pressure biofeedback in CP. We hypothesized that the addition of plantar pressure biofeedback would increase activation of the plantar flexors when walking with ankle exoskeleton resistance, supporting the use of this biofeedback modality to increase engagement during functional gait training.

Figure 5.1. Experimental protocol, beginning with A) Audiovisual biofeedback (only) in the form of a live bar graph that displayed either soleus muscle activity (measured by an EMG sensor) or plantar pressure (measured by an FSR) in a random order that was blinded to the participant, followed by B) Ankle exoskeleton resistance with and without audiovisual plantar-pressure based biofeedback.
5.2 Materials and Methods

We developed a simple plantar pressure-based biofeedback system comprised of a force sensitive resistor (FSR) placed under the ball of the fore-foot that responded to plantar flexor muscle activity indirectly through push-off with the ground (Fig. 5.2). We compared our system to EMG-based biofeedback, which we considered the “gold standard”, given that it provides direct feedback of the metric that a user is attempting to modulate (i.e., muscle activation), and has been tested in previous studies [49,110].

5.2.1 Plantar pressure biofeedback system

Plantar pressure was measured using an FSR (FlexiForce A502, Tekscan) secured to a carbon fiber foot plate and aligned with the pad of the foot. The FSR was wired to a custom printed circuit board with microcontroller and Bluetooth transceiver. A 5-second calibration procedure was completed at the beginning of each walking trial. The instantaneous plantar pressure data were then normalized by the average peak stance phase pressure during the calibration period and transmitted at 100 Hz to a laptop running a real-time MATLAB graphical user interface (GUI) in the form of a moving bar graph. A “target” horizontal line was also included on the bar graph, which was initially set to 10% above the average peak plantar pressure from the calibration period. The target was then automatically adjusted based on each user’s performance. Specifically, if a user reached their target greater than 75% of steps within a minute, the line was increased by 10%. If a user reached their target less than 50% of steps within a minute, the line was decreased by 10%. If a user reached their target between 50 – 75% of steps within a minute, the line was held constant. If a participant reached the target line, the bar graph changed from red to green, and a
“ding” sound was emitted from the laptop speakers. Once the bar dropped back below the target line, the bars changed back to red (Fig. 5.1).

For consistency across the testing conditions presented in this study, and to eliminate the added mass as a confounding factor, the plantar pressure biofeedback system was housed within the ankle exoskeleton gait training device (Fig. 5.2A; see section II.C. below). Feedback was delivered to each participant’s more impaired limb. To demonstrate the broader applicability of our approach, we also created a stand-alone system with a smartphone application and the necessary components condensed into a portable casing that can be attached to a user’s footwear (Fig. 5.2B).

Figure 5.2. A) Untethered ankle exoskeleton consisting of a motor and control assembly, cable transmission, and bilateral ankle assemblies; B) Standalone plantar pressure biofeedback system using a force sensitive resistor (FSR).
5.2.2 **EMG biofeedback system**

used a commercially available system for EMG-based biofeedback (Desktop DTS, Noraxon), which displayed real-time soleus muscle activity after filtering with a 1000 ms root mean square envelope. The filtered muscle activity was presented in an identical display as the plantar pressure-based system; the same auditory feedback was also provided. To match the plantar pressure-based system, a “target” horizontal line was also set at 10% above a user’s baseline peak soleus activity, with the same performance-based adjustments to this target as the plantar pressure system (Fig. 5.1). Feedback was provided on each participant’s more impaired limb.

5.2.3 **Ankle exoskeleton gait training device**

For testing the application of the plantar pressure-based biofeedback system, participants were outfitted with a custom lower limb ankle exoskeleton (Fig. 5.2). The device, the details of which can be found in [28,53], consisted of a motor and control assembly worn at the waist that actuated pulleys aligned with the ankle joint using a Bowden cable assembly to provide resistance to plantar flexion proportional to each user’s estimated, real-time biological ankle moment. During the ankle exoskeleton resistance conditions, participants walked with 0.15 Nm/kg of plantar flexor resistance delivered to their more impaired limb (same side as biofeedback delivery).

5.2.4 **Participants**

This protocol was approved by the Northern Arizona University Institutional Review Board (#986744) and completed at the Northern Arizona University – Phoenix Biomedical Campus (Phoenix, AZ). The protocol utilized participants recruited for a clinical trial, which was prospectively registered at ClinicalTrials.gov (NCT04119063). Prior to starting the study, informed written consent was provided by
each participant if 18 years or older, or the parent/legal guardian in the case of minors (minors also provided verbal assent).

Participant inclusion criteria was as follows: confirmed diagnosis of CP (hemi- or diplegic distributions), Gross Motor Function Classification System (GMFCS) level I – III, the ability to walk on a treadmill with support for at least ten minutes, and 10 – 21 years of age. Exclusion criteria included orthopedic surgery within the past six months, botulinum toxin injections to the triceps surae muscles within the past six months, and any other conditions that would preclude safe participation. Six participants were recruited (Table 5.1).

Table 5.1. Participant characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (y)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>GMFCS&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>12</td>
<td>1.40</td>
<td>39.5</td>
<td>I</td>
</tr>
</tbody>
</table>

<sup>a</sup>GMFCS: Gross Motor Function Classification System

### 5.2.5 Protocol

To begin, height, weight, and lower limb anthropometrics were measured for each participant. Next, participants were outfitted with reflective markers on their lower limbs in accordance with Vicon’s lower body Plug-In Gait model (Vicon, 100 Hz; Denver, CO, USA), and wireless surface EMG sensors (Noraxon, 1000 Hz;
Scottsdale, AZ, USA) were placed on the more affected limb’s soleus, medial gastrocnemius, and tibialis anterior muscles according to SENIAM recommendations.

Participants walked under the following five conditions at a self-selected speed on the treadmill for two minutes and 30 seconds while lower body kinematics and muscle activity were measured: 1) baseline (i.e., no audiovisual biofeedback or resistance), 2) unilateral plantar pressure-based audiovisual biofeedback, 3) unilateral EMG-based audiovisual biofeedback, 4) ankle exoskeleton resistance with no audiovisual biofeedback, and 5) unilateral plantar pressure-based audiovisual biofeedback with ankle exoskeleton resistance. All participants started with the baseline condition, followed by the plantar pressure and EMG biofeedback only conditions in random order, and ending with the ankle exoskeleton resistance alone and combined with plantar pressure biofeedback conditions (Fig. 5.1). For consistency across conditions, users wore the ankle exoskeleton during each condition. For the baseline condition, plantar pressure biofeedback only, and EMG biofeedback only conditions, the footplates were detached from the ankle pulleys to eliminate any residual torque application. P1, a younger participant, was re-tested on a separate day for the biofeedback only conditions because he did not initially understand the goal of meeting his target level on each step as opposed to sporadically achieving the target.

5.2.6 Data analysis

Twenty gait cycles of each condition were analyzed. Three-dimensional marker data was used to calculate ankle and knee joint angles for both biofeedback conditions versus baseline using Vicon’s Plug-In Gait Model and inverse kinematics. Angle data was low-pass filtered (4th order Butterworth, 6 Hz low-pass cutoff) and an average curve for both ankle angle and knee angle was generated. For individual plots
of joint angles during baseline walking and the two biofeedback conditions, please see Appendix A, Fig A.7.

EMG data was bandpass filtered (4th order Butterworth, 20 - 400 Hz band-pass cutoff), rectified, and low-pass filtered (4th order Butterworth, 10 Hz low-pass cutoff), and then time normalized to a gait cycle (heel strike to heel strike). The 20 recorded gait cycles were averaged together for a single activation curve for each muscle, and normalized to peak baseline activation of that respective muscle.

Peak stance phase ankle plantar flexion and knee extension angles were calculated for each condition. We chose to assess lower limb kinematics to determine if either system resulted in compensatory strategies that would negatively impact gait. In addition, mean and peak propulsive phase (51 – 100% of stance phase [99]) soleus and medial gastrocnemius activation was calculated for the baseline and audiovisual biofeedback only conditions. Only mean and peak propulsive phase soleus activation was calculated for the resistance and resistance plus plantar pressure biofeedback conditions, as movement of the calf cuff when the exoskeleton was active interrupted the EMG signal from the medial gastrocnemius. Finally, stance-phase co-contraction at the ankle between the soleus and tibialis anterior was calculated for the baseline and audiovisual biofeedback only conditions using a co-contraction index (CCI) [93]:

$$CCI = \sum_{i=1}^{101} \frac{LEMG(i)}{MEMG(i)} \left(LEMG(i) + MEMG(i)\right)$$  

Eq. 1

where $i$ represents the individual time points of stance phase (0 – 100%, or 101 total data points), $LEMG$ represents the normalized magnitude of the less active muscle at time point $i$, and $MEMG$ represents the normalized magnitude of the more
active muscle at time point $i$. CCI values for the audiovisual biofeedback conditions were then normalized to baseline values.

5.2.7 Statistical analysis

We validated plantar pressure-based biofeedback through three main statistical comparisons: (1) by assessing the change in muscle activity relative to baseline; (2) by comparing the change in muscle activity relative EMG biofeedback; and (3) similar to other validation studies [111,112], by assessing the relationship to EMG-based biofeedback.

The primary outcome measures for our $a$-priori hypotheses included peak propulsive phase soleus and medial gastrocnemius muscle activity. Secondary outcome measures included ankle CCI, and peak ankle plantar flexion and knee extension angle. To assess our primary objective of validating plantar pressure vs EMG biofeedback, we performed one-way repeated measures Analysis of Variance (RM ANOVA) to determine the effect of biofeedback condition on these outcome measures. If a significant effect of walking condition was found, we ran two-tailed pairwise comparisons with Holm-Bonferroni correction for multiple comparisons. In addition, we assessed the relationship between the plantar pressure-based and EMG-based primary outcome measures by calculating a Pearson product-moment correlation coefficient ($R$), where 0.3 was considered a weak relationship, 0.5 a moderate relationship, and 0.7 a strong relationship [57].

To assess our secondary objective related to evaluating the application of the plantar pressure-based biofeedback system while used in conjunction with ankle exoskeleton resistance, we performed one-way RM ANOVA to compare mean and peak soleus activation between baseline walking, ankle exoskeleton resistance alone,
and ankle exoskeleton resistance with plantar pressure-based biofeedback. Significant main effects were followed up with two-tailed pairwise comparisons with Holm-Bonferroni correction for multiple comparisons. P8’s medial gastrocnemius data was not available for the primary objective due to a dropped signal from the EMG sensors. Significance level was set at $p < 0.05$.

### 5.3 Results

All participants successfully completed the protocol, walking with both biofeedback systems, and with ankle exoskeleton resistance with and without plantar pressure biofeedback.

#### 5.3.1 Plantar pressure vs. EMG biofeedback

There was a significant effect of walking condition on mean soleus activity ($p < 0.01$; Fig. 5.3A). Pairwise comparisons indicated a significant increase in mean soleus activity for both the plantar pressure-based ($43 \pm 33\%$, $p = 0.02$) and EMG-based systems ($58 \pm 42\%$, $p = 0.02$) relative to mean baseline soleus activity, with no difference between the two systems ($p = 0.09$). There was no significant effect of walking condition on peak soleus activity ($p = 0.08$; Fig. 5.3B). Strong relationships were observed between the two systems for both mean ($R = 0.89$) and peak ($R = 0.92$) soleus activation.
A significant effect of walking condition was observed for both mean (p < 0.01; Fig. 5.4A) and peak (p < 0.01; Fig. 5.4B) medial gastrocnemius activity. Pairwise comparisons indicated a significant increase in mean medial gastrocnemius activation for both the plantar pressure-based (68 ± 50%; p = 0.03) and EMG-based (77 ± 44%; p = 0.01) systems relative to baseline, with no difference between systems (p = 0.33). Additionally, both systems had a significant increase in peak medial gastrocnemius activation relative to baseline (plantar pressure-based: 82 ± 51%, p = 0.02; EMG-based: 71 ± 35%, p < 0.01), but no difference was observed between systems (p = 0.36). There were strong relationships between the two systems for both mean ($R = 0.94$) and peak ($R = 0.90$) medial gastrocnemius activation.
A significant effect of walking condition on ankle CCI was found (p < 0.01; Fig. 5.5); pairwise comparisons indicated a significant increase for the EMG-based system relative to baseline walking (52 ± 41%, p = 0.03), but no difference between the plantar pressure-based system and baseline walking (p = 0.07) or between the two systems (p = 0.07).

Finally, a significant effect of walking condition was observed for both peak knee extension and peak ankle plantar flexion angle (p < 0.05), but pairwise comparisons were all non-significant.
Figure 5.5. Average co-contraction index (CCI) between the soleus and tibialis anterior during the stance phase of gait for the two audiovisual biofeedback systems alone; Error bars represent standard error of the mean, brackets indicate pairwise comparisons between plantar pressure-based and EMG-based systems, and upward arrows represent significant pairwise comparisons between baseline walking and the respective audiovisual biofeedback system; *p < 0.05.

5.3.2 Ankle exoskeleton resistance with vs. without plantar pressure biofeedback

There was a significant effect of walking condition on mean soleus activity (p < 0.01; Fig. 5.6A). Pairwise comparisons indicated a significant increase for the combined ankle exoskeleton resistance and plantar pressure biofeedback condition relative to baseline (47 ± 39%, p = 0.04) and resistance alone (36 ± 36%, p = 0.04) conditions; no difference was found between baseline and resistance alone (p = 0.31). Similarly, a significant effect of walking condition was found for peak soleus activity (p = 0.01; Fig. 5.6B), with significantly higher peak activity for the combined system versus resistance alone (46 ± 39%, p = 0.03), but no difference was observed between the combined system and baseline (p = 0.08), or resistance alone versus baseline (p = 0.34).
Figure 5.6. A) Mean and B) peak propulsive phase soleus activation relative to baseline activity for ankle exoskeleton resistance with and without biofeedback, and C) representative soleus activation curves across the three walking conditions: baseline (blue), exoskeleton resistance alone (green), and exoskeleton resistance with plantar pressure biofeedback (purple); Error bars represent standard error of the mean, brackets indicate pairwise comparisons between resistance alone and combined with plantar pressure biofeedback, upward arrows represent pairwise comparisons between baseline walking and the combined condition; *p < 0.05.

5.4 Discussion

We achieved our primary goal of validating a plantar pressure biofeedback system for increasing ankle plantar flexor muscle activity relative to EMG biofeedback, and demonstrated several expected and one surprising benefit of our novel system compared to the “gold-standard.” The findings from this study partially supported our hypothesis that both plantar pressure-based and EMG-based audiovisual biofeedback systems would increase ankle plantar flexor muscle activity while walking, with significant increases in mean soleus muscle activity and mean and peak medial gastrocnemius activity relative to baseline for both systems, and trends toward increases in peak soleus activity. Importantly, there was no difference in activation
between the two biofeedback modalities, and strong relationships for all primary outcome variables between the two systems. Our finding of consistent gait kinematics across both biofeedback conditions indicated that participants did not adopt any compensatory movement strategies in response to feedback that could negatively affect their gait. Additionally, our findings supported the hypothesis that the addition of the plantar pressure-based system would significantly increase engagement of the plantar flexors when walking with ankle exoskeleton resistance. We observed significant increases in propulsive phase mean and peak soleus and medial gastrocnemius activation when combining ankle exoskeleton resistance with plantar pressure biofeedback vs. baseline and resistance alone.

While an ankle plantar flexor EMG-based audiovisual biofeedback system provides direct feedback of a muscle’s activation level, a plantar pressure-based system provides indirect feedback of a muscle’s activation level, focusing instead on the functional output of the muscle (i.e., plantar flexor force). With the EMG-based system, a user could raise the bar past their target level by contracting their soleus muscle without necessarily increasing plantar flexor force if the antagonist dorsiflexor muscle (i.e., tibialis anterior) was contracting at the same time. Our finding of increased co-contraction at the ankle with the EMG-based system relative to baseline indicates that this strategy was indeed adopted by our study participants. With the plantar pressure-based system, on the other hand, increasing co-contraction at the ankle would counter the desired output of increase plantar flexor force, likely explaining why we did not observe increases with this system relative to baseline. With the goal of using this type of system to train improved neuromuscular control at the ankle for enhanced walking ability, this finding supports the use of a plantar
pressure-based system for a more functional outcome. This is corroborated by the observation reported in the literature that external focus of attention (i.e., increased force against an FSR) is superior to internal focus of attention (i.e., increased activation of the soleus) for functional motor learning [113].

To our knowledge, this is only the second study to evaluate the ability of an audiovisual biofeedback system to influence ankle plantar flexor muscle activity while walking in CP. The previous study focused on the spatiotemporal and kinematic outcomes, and did not report the neuromuscular response (i.e., relative triceps surae activation) while walking with feedback [49]. The findings from the present study, therefore, are particularly enlightening, indicating that providing feedback in this manner to children and young adults with CP results in significantly increased neuromuscular recruitment while walking after only a few minutes of acclimation.

We observed statistically significant increases in mean and peak propulsive phase medial gastrocnemius activation with both biofeedback systems. The medial gastrocnemius serves a unique role relative to the soleus during walking, contributing more to forward propulsion [99]. It has been observed that individuals with CP have deficits in neuromuscular control of the medial gastrocnemii during the push-off phase of gait, leading to reduce ankle power and a slow and inefficient gait pattern [114]. Our finding of increased recruitment of this essential plantar flexor muscle, specifically during the propulsive phase of gait, supports the potential of this audiovisual biofeedback system to positively impact walking performance in this population.

We previously developed ankle exoskeleton resistance to improve neuromuscular control and gross mobility in children with CP [28]. It was recently
observed that multi-week training with the device used in this study resulted in significant improvement in ankle plantar flexor strength, coordination at the ankle while walking, walking efficiency, and performance on clinical tests of mobility [29,30]. While these findings demonstrated the potential of this novel robotic gait training system for individuals with neuromuscular impairments, effective engagement with the device required regular verbal cues and coaching, which was consistent with other robotic gait training interventions for pediatric populations [67,100,101]. The findings from the present study are particularly encouraging, therefore, as we found that the application of the plantar pressure biofeedback system resulted in rapid and significant increases in neuromuscular engagement with the device without the need for constant verbal cues or a long acclimation period.

This study was motivated by the desire to test a more clinically accessible form of audiovisual biofeedback to improve neuromuscular control at the ankle while walking. From our anecdotal observations on the amount of time required to set up both systems, it became clear that a plantar pressure-based system was a less resource- and time-intensive process. For example, one can consider the complexity of placing the sensor for the two systems: for the plantar pressure-based system, it simply requires placing the sensor on the medial forefoot of the shoe insole. For the EMG-based system, one must utilize anatomical landmarks to locate an appropriate measurement spot of a muscle belly, which can be challenging for young children with low muscle volume; carefully prepare the skin interface by shaving hair and swabbing with alcohol; and carefully securing the sensor components to the skin to mitigate disturbances in the signal from movement artifacts. In addition, there are notable differences in the cost required for both systems, with materials required for a plantar
pressure-based system coming in at a fraction of the price of the materials required for an EMG-based systems. These practical differences, in conjunction with the findings from this study that a plantar pressure-based system is able to produce comparable or even more-favorable neuromuscular control at the ankle, support the future investigation of plantar pressure-based systems in clinical settings.

There are notable limitations of this study. First, we tested a relatively small sample of individuals with CP, which is an inherently heterogenous condition. Still, we observed relatively consistent increases in muscle activity across our participants with both audiovisual biofeedback systems. In addition, the primary aim of this study was to validate the plantar pressure-based system against an EMG-based system for a clinical population, and not necessarily to demonstrate any kind of training effect that may require greater statistical power. Second, this clinical validation was limited to individuals with CP. The primary outcome of improved plantar flexor recruitment, however, could be valuable to several patient populations with deficits in neuromuscular control at the ankle. Third, due to the interference of calf cuff from the exoskeleton device, we were not able to measure medial gastrocnemius activity during the resistance conditions. Finally, we only tested the audiovisual biofeedback systems with a single gait training device that focused on resisting limb movement, while several training devices exist that aim to assist limb movements. Future work should explore the use of a plantar pressure-based audiovisual biofeedback system with assistive robotic gait training.

5.4.1 Conclusion

We demonstrated that a simple plantar pressure-based biofeedback system is capable of increasing functional recruitment of the ankle plantar flexor muscles in
children and young adults with CP. We observed comparable or even more-favorable neuromuscular control at the ankle when using this system relative to direct EMG biofeedback. Application of this plantar pressure-based biofeedback system to an ankle exoskeleton device used for functional resistance gait training led to enhanced neuromuscular recruitment. Future studies and clinical interventions should evaluate if functional training with this simple, low-cost system can result in lasting improvements in walking ability in CP and other patient populations.
Chapter 6

Evidence of reciprocal inhibition in cerebral palsy with soleus H-reflex modulation to changes in standing and walking task complexity

6.1 Background

Locomotion in humans involves a dynamic interplay between spinal reflexes and supraspinal modulation of those reflexes based on sensorimotor input to align with a specific task [45]. An example of this spinal reflex modulation that has been heavily studied in both healthy adults [115–119] and those with neurological injury [120–123] is the Hoffman (H-) reflex. The H-reflex is a measure representing a monosynaptic reflex [124], whereby electrical stimulation of a peripheral nerve leads to propagation of an action potential along sensory Ia afferent axons, which typically fire in response to a stretched muscle. This signal synapses on alpha motoneurons, which are located on the ventral horn of the spinal cord for lower limb muscles, and leads to production of action potentials that travel down efferent fibers to the neuromuscular junction of the respective muscle to create a twitch [125]. With locomotion, the soleus H-reflex is often studied by eliciting a twitch via stimulation of the posterior tibial nerve, and the amplitude of this twitch can be measured by surface electromyography (EMG) and compared between conditions to make inferences on modulation [126].

It is well known that the soleus H-reflex is highly modulated during dynamic tasks and is strongly dependent on background motor activity [116]. For example, during gait, this reflex will increase progressively with increasing soleus muscle activity during stance phase, but will be almost completely absent during swing phase in healthy adults, when the antagonist dorsiflexors are strongly activated and where extension of the ankle would lead to high levels of co-contraction that could impede clearance of the foot [115,127,128]. It has also been observed that reflex
excitability, measured as H-reflex gain or the change in H-reflex amplitude relative to change in background motor activity [126,129,130], will decrease in response to more complex standing [131,132] and walking [133] tasks that require greater stability at the ankle. It is hypothesized that in addition to reciprocal inhibition on antagonist muscles, this involves a central control mechanism to preserve the finite motor pool for the task at hand. The general consensus is that these supraspinal mechanisms for controlling reflex excitability mainly involve presynaptic inhibition of the Ia afferents that would synapse on the respective muscle [133].

Given the importance of soleus reflex modulation during various motor tasks and the significant involvement of supraspinal control, it would be beneficial to understand how neuromuscular disorders affecting the brain, such as cerebral palsy (CP), the most prevalent pediatric-onset movement disorder caused by injury to the developing brain [65], may influence this modulation and subsequently impact motor control. Few studies [62,120], however, have explored soleus H-reflex modulation in individuals with CP across motor tasks. Specifically, it is not known how individuals with CP modulate their soleus H-reflex excitability in response to increased task complexity or changes in stability. This is of particular interest because there is wide clinical acceptance that deficits in neuromuscular control at the ankle significantly contribute to the slow and inefficient gait patterns for this population, and this may be linked to deficits in reciprocal inhibition that would typically control reflex modulation, as suggested by Leonard and colleagues [62]. In addition, recent studies exploring the effect of resistive robotic gait training protocols designed to increase neuromuscular engagement at the ankle in CP have demonstrated benefits on neuromuscular control [30,52], as well as decreased levels of co-contraction at the
ankle [28], but it is unclear if and/or how these interventions are influencing reflex modulation for this population. This may be linked to the effect of task complexity and instability on reflex modulation given the increased neuromuscular demands of walking with resisted limb movements. Overall, a better understanding of how individuals with CP modulate spinal excitability with a given motor task can be leveraged by future interventions seeking to enhance neuromuscular control for improved function in this population.

The purpose of this study was to test the effect of standing task complexity on soleus H-reflex modulation in children and young adults with CP. We hypothesized that children and young adults with CP would display the same decrease in soleus H-reflex excitability with increased task complexity as healthy individuals. In addition to standing task complexity, we sought to explore the effect of walking with a resistive ankle exoskeleton device that provided adaptive plantar flexion resistance on soleus H-reflex modulation in CP. We hypothesized that the increased complexity of walking with resisted limb movements would also result in a decrease in soleus H-reflex amplitude. Finally, to test for the presence of reciprocal inhibition with each task, we assessed the relationship between reflex size and level of co-contraction. Given previous observations of deficits in reciprocal inhibition with this population [62], we hypothesized that this relationship would be non-significant.

6.2 Methods

This study was approved by the Northern Arizona University Institutional Review Board (#986744), and utilized participants recruited for a clinical trial, which was prospectively registered at ClinicalTrials.gov (NCT04119063). The protocol was completed at the Northern Arizona University – Phoenix Biomedical Campus.
(Phoenix, AZ), and informed written consent was provided by a parent or legal guardian for each participant.

6.2.1 Participants

Individuals between the ages of ten to 18 years with a confirmed diagnosis of CP, Gross Motor Function Classification System (GMFCS) levels I – III, the ability to stand on one leg with support, and the capacity to walk for at least ten minutes on a treadmill with support were recruited for this study. Given the scheduling demands of a pediatric participant, and the inherent discomfort of electric reflex testing, recruited participants had the option of completing one or both of the following protocols, which were held on separate days: 1) a standing task complexity protocol, and 2) a resistive ankle exoskeleton protocol (i.e., walking task complexity).

Nine total participants (seven males and two females) were recruited across both protocols. Seven participants completed the standing task complexity protocol, six participants completed the resistive ankle exoskeleton protocol, and four participants completed both. See Table 6.1 for participant characteristics and the protocol(s) completed by each respective participant.
Table 6.1. Participant characteristics and respective protocols completed

<table>
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<tr>
<th></th>
<th>Age (y)</th>
<th>Gender</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>GMFCS</th>
<th>CP type</th>
<th>Protocol(s)</th>
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<tbody>
<tr>
<td>P1</td>
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<td>Standing</td>
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<td>M</td>
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<td>Standing task</td>
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<td>Complex</td>
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<tr>
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<td>M</td>
<td>176</td>
<td>62.1</td>
<td>2</td>
<td>SD</td>
<td>Both</td>
</tr>
<tr>
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<td>M</td>
<td>165</td>
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<td>SD</td>
<td>Resistive ankle</td>
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<tr>
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<td>1</td>
<td>SH</td>
<td>Exoskeleton</td>
</tr>
</tbody>
</table>

*aGMFCS: Gross Motor Function Classification System
bCP type: spastic hemiplegic (SH); spastic diplegic (SD)

6.2.2 H-reflex setup

Wireless surface electromyography (EMG) sensors were placed on the non-dominant leg of each participant for measuring reflex responses and muscle activity (BIOPAC Systems, Goleta, CA, USA; 2000 Hz). Bipolar electrodes (Ag-AgCl) were placed on the soleus and tibialis anterior muscles according to SENIAM recommendations [90].

To evoke a soleus H-reflex, stimulating electrodes (Ag-AgCl) were placed in the popliteal fossa of the participant’s non-dominant leg for stimulation of the posterior tibial nerve, with the cathode electrode just superior to the popliteal fossa and the anode electrode just inferior to the popliteal fossa [126]. Stimulations were 1 ms, square-wave pulses ranging from 0.1 – 50 mA. Standing, H-reflex amplitudes were evoked at a low level of stimulation, and the position of the stimulating electrodes were adjusted to find an ideal stimulating location, as indicated by a large
H-reflex amplitude without the presence of an M-wave. This setup was completed prior to H-reflex testing for both protocols.

Figure 6.1. A) Standing task complexity protocol, where 15 soleus H-reflexes with consistent M-wave amplitudes were elicited under two conditions: standing on two legs with eyes open (i.e., baseline condition), and standing on the non-dominant leg with eyes closed (i.e., complex condition); B) Resistance ankle exoskeleton protocol, which consisted of five acclimation visits to plantar flexion resistance with soleus EMG audiovisual biofeedback, followed by a sixth testing visit. Twelve soleus H-reflexes with consistent M-wave amplitudes were elicited at mid-stance during baseline walking and resisted walking, with ~30 minutes of resistance acclimation prior to testing the resisted condition. Note: no audiovisual biofeedback was used during the resisted condition H-reflex testing.

6.2.3 Standing task complexity protocol (participants P1 – P6)

Soleus H-reflex responses were recorded for participants under two conditions: 1) stable, 2-legged stance with eyes open (i.e., baseline condition), and 2) unstable, 1-legged stance on the non-dominant leg with eyes closed (i.e., complex condition [131]) (Fig. 6.1A). Given the variation in functional level associated with CP, and the possibility that not all participants could stand on one leg unsupported, each
participant was given the option to support themselves during the complex condition by placing one hand on a stabilizing surface that was approximately waist height. If the participant chose to use support for the complex condition, they were instructed to also use support for the baseline condition.

Starting with the baseline condition and a stimulation level of 0.1 mA, stimulation level was increased until a small M-wave was present. The size of this M-wave was held constant (within ± 10%) across conditions to ensure a consistent, effective stimulus strength. For each condition, 15 reflexes were evoked, and background EMG (bEMG) activity of the soleus and tibialis anterior was measured 50 ms before each respective stimulation.

6.2.4 Resistive ankle exoskeleton protocol (participants P4 – P9)

Participants were outfitted with a custom, untethered lower limb robotic device, the details of which can be found in [28,134] (Fig. 6.2). Briefly, this device consisted of an actuation & control assembly worn at the waist, and ankle assemblies worn bilaterally on the legs. Motors remotely actuated the carbon fiber ankle assemblies via Bowden cables to generate ankle torque in the sagittal plane. Using custom force sensors placed under the forefoot, the ankle moment could be estimated and a proportional level of resistance to plantar flexion could be applied in real-time during each stance phase. The proportional application of resistance to plantar flexion occurred instantaneously and throughout the entire gait cycle. This closed-loop control scheme was designed to maximize neuromuscular engagement by being immediately responsive (i.e., adaptive) to user input [53]. The device was controlled via a custom MATLAB graphical user interface (v2019b, Natick, MA, USA), and weighed approximately 1.75 kg.
Two conditions were tested for this protocol: 1) a baseline condition, whereby users walked at a self-selected speed on the treadmill while wearing the device with footplates detached from the ankle pulley (i.e., un-resisted), and 2) a resisted condition, whereby users walked at a matched speed to the baseline condition on the treadmill while receiving 0.15 Nm/kg of adaptive plantar flexion resistance. Participants wore the device during both conditions to account for the device’s weight being a potential confounder.

Prior to the H-reflex testing, participants completed five “acclimation” visits across two weeks, where they walked with adaptive plantar flexion resistance for at least 20 minutes on each day, totaling approximately 120 minutes over the five visits. During the acclimation visits, resistance level was progressively increased from 0.1 – 0.2 Nm/kg, while treadmill speed was held constant. For the acclimation visits only, participants also had audiovisual biofeedback displaying their real-time soleus muscle activation levels in the form of a smoothed signal and a target activation level for each
Biofeedback was displayed for the more-affected limb only, and the target activation level would adjust in real-time based on a user’s performance. Biofeedback was not used during H-reflex testing to avoid the confounding effect of a dual-task on reflex modulation [135]. On the sixth acclimation visit, users began with H-reflex testing of the baseline condition, followed by approximately 30 minutes of resistance acclimation, and ending with H-reflex testing of the resisted condition (Fig. 6.1B).

For both conditions, stimulations were delivered during midstance on the non-dominant side, identified by force sensors embedded in the footplates of the device. Starting with the baseline condition, stimulation level was increased until a small M-wave was present. H-reflexes were then evoked and recorded if the associated M-wave amplitudes were within ± 10% of this initial M-wave to ensure a consistent, effective stimulus strength. Twelve reflexes that met this criteria were recorded for each condition, in addition to bEMG activity of the soleus and tibialis anterior 50 ms prior to each stimulation.

6.2.5 Data and statistical analysis

H-reflex amplitudes were measured as the peak-to-peak magnitude of the raw, non-rectified EMG signal where the H-reflex occurred (typically 40 – 50 ms post-stimulation) [126]. Background EMG signals were band-passed filtered (4th order Butterworth, 20 – 400 Hz) and rectified, and the mean activity 50 ms before stimulation was calculated. To account for the effect of background motor activity on reflex size [125], and the potential changes in motor activity between tested conditions, H-reflex amplitudes were normalized by dividing by their respective bEMG mean activity (adjusted H-reflex). In addition, co-contraction at the ankle was calculated as the overlap in muscle activity between the soleus and tibialis anterior.
Specifically, activation levels of each muscle were normalized to the mean activity of that muscle during the baseline condition of each protocol. Next, the mean overlap in the normalized activation curves of the soleus and tibialis anterior was calculated 50 ms prior to each stimulation [136].

Within each participant and condition, measured data was assessed for the presence of outliers. Outliers were defined as any data point 1.5 times the interquartile range below the first quartile or above the third quartile [97]. Data falling within this outlier definition were removed for statistical comparison and calculation of means, and were not included in figures unless otherwise noted. Following this outlier analysis, normality was tested using a Kolmogorov-Smirnov test with small sample Lilliefors correction [56]. For normally distributed data, we compared outcome measures between conditions (within each protocol) using two-tailed paired t-tests, and for non-normally distributed data, we compared outcomes using a Wilcoxon signed-rank test. Significance level was set at $\alpha < 0.05$. In addition, we calculated the effect size between conditions using Cohen’s $d$ ($d$), where 0.2 was considered a small effect, 0.5 a medium effect, and 0.8 or above a large effect [72].

Finally, we assessed the relationship between modulation of H-reflex amplitudes and ankle co-contraction levels as an indicator of reciprocal inhibition [137]. Specifically, we ran a Pearson correlation between adjusted H-reflex amplitude and ankle co-contraction levels for the complex conditions (i.e., one-legged, eyes closed standing or resisted walking) using individual data points from each participant, normalized to within-subject baseline median values. To prevent outliers from significantly influencing the relationship between these two variables, we removed
any ratios between these two variables that were 1.5 times the interquartile range below the first quartile or above the third quartile [97].

6.3 Results

Change in adjusted H-reflex amplitude during the resistive ankle exoskeleton protocol was not normally distributed, while all other data was normally distributed. Results for each respective protocol are presented below.

Figure 6.3. Standing task complexity results: Group (black) and individual (gray) A) normalized H-reflex amplitudes and B) ankle co-contraction levels during one-legged, eyes closed standing (complex) relative to two-legged, eyes open standing (baseline); Bars represent standard error of the mean. *p < 0.05, d = Cohen’s d effect size.
6.3.1 Standing task complexity protocol (participants P1 – P6)

There was a significant decrease in adjusted H-reflex amplitude from the baseline to complex standing condition (-26 ± 27%, p = 0.04, d = -0.97). Six of seven participants had a decrease in their adjusted H-reflex from baseline, with P4 having the only increase during the complex condition (Fig. 6.3A). We observed a significant increase in co-contraction levels at the ankle from the baseline to complex condition (85 ± 63%, p = 0.01, d = 1.27). All participants but P4 displayed a decrease in adjusted H-reflex amplitude and an increase in co-contraction with the complex condition (Fig. 6.3B).

Figure 6.4. Relationship between adjusted H-reflex amplitude and ankle co-contraction level during the standing complex condition, normalized to baseline median values. **p < 0.01.

There was a significant inverse relationship between adjusted H-reflex amplitude and co-contraction level during the complex condition, normalized to baseline median values (R = -0.58, p < 0.01; Fig. 6.4).
6.3.2 Resistive ankle exoskeleton protocol (participants P4 – P9)

No significant differences were found between the baseline and complex conditions for adjusted H-reflex amplitude (p = 0.57, $d = 0.25$; Fig. 6.5A) or ankle co-contraction level (p = 0.81, $d = 0.11$; Fig. 6.5B). Two of the six participants (P4 and P5) who displayed an increase in adjusted H-reflex amplitude also displayed a decrease in ankle co-contraction, while three of the six participants (P6 – P8) who displayed a decrease in adjusted H-reflex amplitude also displayed an increase in ankle co-contraction. P9 displayed decreases in both adjusted H-reflex amplitude and ankle co-contraction.

![Figure 6.5. Resistive ankle exoskeleton results: Group (black) and individual (gray) A) adjusted H-reflex amplitudes and B) ankle co-contraction levels during resisted walking relative to baseline walking; Bars represent standard error of the mean. $d =$ Cohen’s d effect size.](image)
Finally, there was a significant inverse relationship between adjusted H-reflex amplitude and co-contraction level during the resisted walking condition, normalized to baseline median values ($R = -0.52$, $p < 0.01$; Fig. 6.6).

![Figure 6.6](image)

Figure 6.6. Relationship between adjusted H-reflex amplitude and ankle co-contraction level during the resisted walking (i.e., complex) condition, normalized to baseline median values. **p < 0.01.

### 6.4 Discussion

The purpose of this study was to explore the effect of changes in standing and walking task complexity on soleus H-reflex modulation in children and young adults with CP. Our original hypothesis of decreased soleus H-reflex excitability with increased task complexity was supported by our findings. Specifically, we observed a significant decrease in soleus H-reflex amplitudes relative to background motor activity with increased standing task complexity, accompanied by a significant increase in co-contraction at the ankle. Additionally, we found no significant group changes in soleus H-reflex amplitudes during walking with a resistive ankle.
exoskeleton device. These findings are likely related to differences in compensation across participants to walking with ankle plantar flexion resistance, as demonstrated by variable changes in co-contraction at the ankle by participants with this condition. This is supported by significant inverse relationships observed between in adjusted soleus H-reflex amplitude and ankle co-contraction level for the complex conditions (R = -0.52 to -0.58, p < 0.01 for both).

Six of the seven participants who completed the standing task complexity protocol had a reduction in their soleus H-reflex excitability with increased task complexity. The single participant (P4) that did not display decreased H-reflex amplitudes was also the only participant to have a reduction in co-contraction at the ankle with the complex condition. Functionally, co-contraction at the ankle serves to stabilize the joint in novel, unstable, or otherwise challenging environments [138], so it was anticipated that participants would have increased levels of co-contraction when moving to one-legged standing with eyes closed, where increased ankle stability would assist with postural control. The fact that P4 did not display this decrease may indicate that this condition was actually equally as stable as two-legged, eyes open stance. The reason behind this is not entirely clear, but it could be that this participant used too much support during one-legged stance, thereby reducing the instability/complexity of this condition and negating the pathways that would typically reduce reflex amplitude.

The apparent variability in reflex modulation with ankle plantar flexion resistance may be due to differences in compensation when walking with this device. Three of six participants had a decrease in co-contraction at the ankle, which is consistent with previous findings of children with CP walking with this device [28].
The reason for decreased co-contraction is not clear, but may be due plantar flexion resistance creating more stability at the ankle during stance phase and offloading the dorsiflexors, or a necessary adaptation to increase effective plantar flexor force to overcome the resistance, and most likely a combination of both. Increased co-contraction with resistance may have been a sign that individuals were not fully acclimated to the device, resulting in a more conservative and guarded stepping strategy. Similar to the standing task complexity protocol, however, we observed decreased soleus H-reflex amplitudes for all individuals who increased ankle co-contraction levels and vice versa, except for P9. In analyzing P9’s response, we can consider the functional relevance of the soleus reflex during the stance phase of gait, which has been proposed to be mainly for assistance with plantar flexion force production [139]. While other participants who had decreased co-contraction at the ankle also had an increase in reflex amplitude, which may have assisted in overcoming the increased resistance to plantar flexion, it is possible that P9 did not need an increase in his soleus H-reflex amplitude, as would be expected, because his level of force production was sufficient, which is plausible given his high gross motor function level (GMFCS level I). With that being said, one would still expect this participant’s soleus H-reflex to go down with increasing levels of ankle co-contraction due to reciprocal inhibition.

Reductions in H-reflex amplitudes relative to background motor activity in response to challenging or unstable conditions has been observed in several contexts for healthy individuals. For example, as noted previously, healthy individuals respond to increased standing task complexity by reducing their soleus H-reflex gain, which is a measure of spinal excitability [131]. In addition, it was found that compared to
typical treadmill walking, difficult beam walking with a matched level of soleus muscle activity had lower soleus H-reflex excitability [133]. In each of these studies, a higher level of antagonist muscle activity was inferred, or directly measured as increased co-contraction at the ankle joint, and inversely related to changes in soleus H-reflex amplitude or gain, which was similarly observed in the present study. The exact mechanism behind this inverse relationship is not entirely clear, but has been proposed to involve reciprocal inhibition by the agonist muscle on Ia afferents to the antagonist muscle, with variable, task-dependent input from supraspinal centers via presynaptic inhibition of the Ia afferents [140]. It has been proposed that supraspinal, task-dependent input is particularly important during unstable conditions when a large reflex could detrimentally impact motor performance [133].

It was previously found that children with CP have deficits in reciprocal inhibition, indicated by increased soleus H-reflexes with the onset of tibialis anterior activation (i.e., increased ankle co-contraction) as opposed to decreased reflex amplitudes [62]. Evidence to support otherwise was found in this study, where across both protocols, those individuals who displayed an increase in co-contraction at the ankle had an accompanying decrease in soleus H-reflex amplitude relative to background motor activity. We also found a significant inverse relationship between adjusted soleus H-reflex amplitude and co-contraction at the ankle during both standing and walking complex tasks, which matches the response of healthy adults [141]. While this relationship points to reciprocal inhibition as a potential mechanism for decreased reflex size, it is likely that supraspinal presynaptic inhibition also played a role. Overall, it would appear that our findings support the notion that children and young adults with CP do exhibit reciprocal inhibition during both standing and
walking tasks. There are two methodological differences between the previous study and our study that may explain these contradictory findings. First, the previous study [62] did not normalize H-reflex amplitudes to background motor activity, which is necessary given the relationship between these two variables and the possibility of changes in motor activity between conditions [125]. Second, the previous study [62] appeared to keep M-waves consistent within a trial type, but not across trials, which could have led to variable effective stimulus strengths between conditions [126].

The findings from this study have significant implications for the field of neurorehabilitation. First, contrary to previous findings, it would appear that individuals with CP still demonstrate reciprocal inhibition of the soleus reflex with activation of the dorsiflexors. Deficits in reciprocal inhibition were hypothesized to be a major contributing factor to the high levels of co-contraction and spasticity observed in this population [62], but this may not be the case. Recent evidence has suggested that spasticity observed in this population is at least partially due to differences in muscle morphology [142], and likely also involves multifactorial deficits in neuromuscular coordination unrelated to reciprocal inhibition [143,144]. Second, these findings indicate the presence of spinal reflex modulation when walking with ankle plantar flexion resistance, which could have significant benefits for patient populations who have demonstrated deficits in this area, such as those with spinal cord injury [122].

There are notable limitations of the present study that should be considered. First, we tested a relatively low sample size of an inherently heterogenous patient population. Still, we observed large effect sizes during our standing task complexity protocol, and gathered important evidence for the presence of reciprocal inhibition in
individuals with CP that was previously unknown. Second, we only analyzed soleus H-reflex amplitudes during mid-stance of the gait cycle, and it is possible that there were differences in phase dependent modulation between baseline and resisted walking. Limiting our analysis to one part of the gait cycle was deliberate in order to reduce the number of stimulations necessary for this pediatric population, and it has been previously found that individuals with CP already demonstrate the phase dependent modulation seen in their typically developing peers [120]. Finally, we did not assess the training effect of adaptive plantar flexion resistance on reflex modulation, as was done previously with assistive robotic gait training [145], or the effect of adding audiovisual biofeedback to this modality, which should be explored in future investigations.

6.4.1 Conclusions

Children and young adults with CP retain the ability to decrease their soleus H-reflex in response to increasing levels of antagonist activation, both during complex standing tasks and walking with a resistive robotic exoskeleton device. This is likely due in part to reciprocal inhibition, which was previously thought to be absent in this population, as well as a function of presynaptic inhibition from supraspinal centers. Future work should expand on the present findings by assessing the training effects of resistive robotic gait training on reflex modulation, and the impact of audiovisual biofeedback.
Chapter 7

CONCLUSION

The overarching goal of this work was to develop and test an intervention that would holistically address the neuromuscular deficits associated with CP that contribute to gait dysfunction. Utilizing principles of motor learning and the neuromuscular control of gait, we developed and tested a novel, resistive robotic gait training paradigm that was incorporated within an untethered, wearable ankle exoskeleton device for easy translation to the clinic or at-home setting. Specifically, we found that gait training with adaptive plantar flexion resistance resulted in significant benefits in strength, neuromuscular control, and clinical measures of mobility for children with cerebral palsy. We also further improved the overall effectiveness and accessibility of this modality by integrating an audiovisual biofeedback system, and used this technology to answer fundamental questions about neuromuscular control in CP. This work provides the evidence and framework for the design of a randomized controlled trial to test the effectiveness of this intervention against the standard of care, such as physical therapy or traditional gait training. Ultimately, we hope that this work contributes to a technology that is beneficial for individuals with a variety of movement disorders, providing accessible, targeted neurorehabilitation that will restore neuromuscular function and enable a physical active and independent lifestyle.
APPENDICES
Appendix A
SUPPLEMENTARY FIGURES

A. Six minute walk test

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RCT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smamia 2011</td>
<td>68.8</td>
<td>12.14</td>
<td>9</td>
<td>67.4</td>
<td>14</td>
<td>9</td>
<td>22.2% 0.72 [-0.25, 1.68] 2011</td>
</tr>
<tr>
<td>Peri 2017</td>
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<td>110.2</td>
<td>12</td>
<td>35.3</td>
<td>182.6</td>
<td>10</td>
<td>29.0% 0.11 [-0.73, 0.95] 2017</td>
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<td>Wu 2017</td>
<td>42.2</td>
<td>73.7</td>
<td>11</td>
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<td>212.9</td>
<td>10</td>
<td>27.6% 0.28 [-0.58, 1.14] 2017</td>
</tr>
<tr>
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<td>188.9</td>
<td>8</td>
<td>13.5</td>
<td>178.3</td>
<td>8</td>
<td>21.3% 0.86 [-0.92, 2.64] 2020</td>
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<tr>
<td>Total (95% CI)</td>
<td>40</td>
<td>37</td>
<td>100.0%</td>
<td>0.28 [-0.17, 0.73]</td>
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<td></td>
<td></td>
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</tbody>
</table>

Test for overall effect: Z = 1.22 (P = 0.22)

Heterogeneity: Tau² = 0.00; Chi² = 1.13, df = 3 (P = 0.77); I² = 0%

Favors RCT Favors Control

B. Free walking speed

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RCT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
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<td>Druzbicki 2013</td>
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<td>26</td>
<td>0.04</td>
<td>0.14</td>
<td>9</td>
<td>24.3% -0.14 [-0.90, 0.62] 2013</td>
</tr>
<tr>
<td>Wu 2017</td>
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<td>0.02</td>
<td>11</td>
<td>0.04</td>
<td>0.29</td>
<td>10</td>
<td>18.9% 0.23 [-0.63, 1.09] 2017</td>
</tr>
<tr>
<td>Wallard 2018</td>
<td>0.12</td>
<td>0.17</td>
<td>14</td>
<td>0.02</td>
<td>0.2</td>
<td>16</td>
<td>26.2% 0.52 [-0.21, 1.25] 2018</td>
</tr>
<tr>
<td>Ammann-Reiffer 2020</td>
<td>0.06</td>
<td>0.1</td>
<td>8</td>
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<td>0.54</td>
<td>8</td>
<td>14.6% -0.05 [-1.03, 0.93] 2020</td>
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<tr>
<td>Total (95% CI)</td>
<td>68</td>
<td>52</td>
<td>100.0%</td>
<td>0.20 [-0.18, 0.57]</td>
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</table>

Test for overall effect: Z = 1.64 (P = 0.10)

Heterogeneity: Tau² = 0.00; Chi² = 4 (P = 0.76); I² = 0%

Favors RCT Favors Control

C. GMFM-D

<table>
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<tr>
<th>Study or Subgroup</th>
<th>RCT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
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<tr>
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<td>20</td>
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<td>0.05 [-0.29, 0.39]</td>
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Test for overall effect: Z = 0.29 (P = 0.77)

Heterogeneity: Tau² = 0.00; Chi² = 4 (P = 0.76); I² = 0%

Favors RCT Favors Control

D. GMFM-E

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<tr>
<th>Study or Subgroup</th>
<th>RCT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
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<td>26.8</td>
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<td>14</td>
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<td>Wu 2017</td>
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<td>19.4</td>
<td>11</td>
<td>1.4</td>
<td>21.5</td>
<td>10</td>
<td>15.9% -0.01 [-0.87, 0.85] 2017</td>
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<td>29.5</td>
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<td>12.1% 0.03 [-0.95, 1.01] 2020</td>
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<td>Klobucka 2020</td>
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<td>20</td>
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<td>33.8% 0.31 [-0.26, 0.92] 2020</td>
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<td>100.0%</td>
<td>0.23 [-0.11, 0.57]</td>
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</table>

Test for overall effect: Z = 1.32 (P = 0.19)

Favors RCT Favors Control

Figure A.1. Assistive robotic gait training meta-analysis results: Comparison of changes in A) six minute walk test performance, B) self-selected walking speed, and Gross Motor Function Measures (GMFM) D (standing) and E (walking, running and jumping) after assistive robotic gait training versus standard of care (i.e., physical therapy or standard gait training); Smamia 2011 [100], Druzbicki 2013 [67], Wu 2017 [146], Peri 2017 [147], Wallard 2017 [148], Wallard 2018 [101], Klobucka 2020 [149], Ammann-Reiffer 2020 [150].
Figure A.2. Stance-phase muscle activity: Individual EMG plots of average soleus and tibialis anterior stance-phase, normalized muscle activity taken over 30 seconds of walking with No Resistance (green line) and walking with Resistance (blue line). Shading indicates ± 1 standard deviation. Note: S3 was a nonverbal participant and as a result, did not receive the same instructions for engaging with resistance as the other subjects.
Figure A.3. Individual soleus activation curves. Average, normalized soleus activation curves pre (red) and post (blue) training, both at the same preferred walking speed, compared to a typical soleus activation profile (gray, dashed). Vertical lines indicate pre (solid red), post (solid blue), and typical (dashed gray) toe-offs, and “R” indicates the Pearson product moment correlation coefficient between the experimental and typical activation profiles. Experimental curves were normalized to peak activation levels and averaged over ten gait cycles.
Figure A.4. Retrospective comparison of change in VAF1. $\Delta\text{VAF1}$ for three interventions: exoskeleton ankle resistance therapy (Exo-therapy, circles), single event multi-level orthopedic surgery (SEMLS, squares), and select dorsal rhizotomy (SDR, triangles). Both SEMLS and SDR have three, age- and GMFCS-matched controls for each study participant with the same corresponding color. Increases in VAF1 (i.e., positive change) represent a decrease in neural complexity, while decreases in VAF1 (i.e., negative change) represent an increase in neural complexity.
Figure A.5. Individual energy recovery curves. Pre and post potential energy (solid lines) and kinetic energy (dashed lines) curves at the same preferred walking speed, plotted as variations about their respective means, and individual pre and post energy recovery percentages.

Figure A.6. Individual metabolic cost curves. Pre- (red) and post-exo-therapy (blue) metabolic cost of transport steady state regions for each participant, representing the body-mass-normalized metabolic energy required to walk a unit distance. Values to the right of each curve indicate the average of each steady state region.
Figure A.7. Ankle (top row) and knee (bottom row) joint angles across Baseline (blue), EMG-based biofeedback (yellow), and plantar pressure-based biofeedback (orange) conditions. Shading indicate ± 1 standard deviation, and negative joint angles indicate extension.
## Appendix B

### SUPPLEMENTARY TABLES

Table B.1. Individual matched-control participant characteristics

<table>
<thead>
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<th>Participant</th>
<th>Matched control</th>
<th>Control gender</th>
<th>Control age (y:m)</th>
<th>Control GMFCS level&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup>GMFCS: Gross Motor Function Classification System.<br>
<sup>b</sup>Intervention type: Single event multi-level orthopedic surgery (SEMLS), selective dorsal rhizotomy (SDR).
Appendix C

SUPPLEMENTARY VIDEOS

C.1 Subject 2 training progression with wearable adaptive resistance.

C.2 Subject 6 training progression with wearable adaptive resistance.

C.3 Pre- and post-intervention scaled musculoskeletal models in OpenSim at preferred walking speed.
Appendix D

SUPPLEMENTARY ANALYSES

D.1 Usability Questionnaire Results

All participants indicated an interest in training with the device again. Participant responses to the usability questionnaire included “my favorite part was wearing the exoskeleton”, “it felt like something I could do”, and “I liked that the levels kept going up so there was more of a challenge”. Parent/guardian responses included “we can tell that he is walking better” and “his physical therapist noticed a difference in how he was walking”.

D.2 Retrospective analysis of changes in motor control complexity

D.2.1 Methods

We retrospectively matched our participants by age and GMFCS level to patients who underwent SEMLS or SDR at Gillette Children’s Specialty Healthcare (St. Paul, MN, USA) from 2005 – 2018. The three most-similar age- and GMFCS-matched controls were assigned to each study participant for both SELMS and SDR (i.e., total of six matched controls/participant; Supplementary Table 1). Two-tailed, independent t-tests were run to assess differences in the change in VAF1 between exo-therapy vs. SEMLS and SDR. Significance level was set at $\alpha = 0.05$. 
D.2.2 Results

When compared to age- and GMFCS-matched control data (Supplementary Table 1), exo-therapy resulted in greater reduction in VAF1 than both SEMLS (p = 0.0004) and SDR procedures (p = 0.0003) (Supplementary Fig. 2).

D.2.3 Discussion

A rehabilitative tool that is able to lower VAF1, therefore, could improve treatment outcomes from SEMLS or SDR for children with CP [151]. Importantly, we found that the increased neural complexity with exo-therapy was significantly greater than the changes seen with SEMLS or SDR (Supplementary Fig. 2). This finding supports the use of exo-therapy to complement rehabilitation before or after these common procedures, whereby doing so could induce neuromuscular changes not previously possible with surgery alone.
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