INTERRELATIONSHIPS AMONG BRAIN, MUSCLE AND PHYSICAL ACTIVITY IN CHILDREN WITH CEREBRAL PALSY

by

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(Under the Direction of Christopher Modlesky)

ABSTRACT

The purpose of this dissertation is to examine the relationships among the brain, muscle and physical activity in children with CP. The aim of the first study was to determine the relationship(s) between physical activity, muscle co-contraction and muscle strength in children with CP. The main finding was that muscle co-contraction did not relate to functional strength in children with CP. However, muscle co-contraction during the more difficult stages of a progressive lateral step-up test was inversely related to physical activity in children with CP. The aim of the second study was to assess the relationships between muscle strength, muscle co-contraction and brain activity in the prefrontal cortex in children with CP. The main finding was that muscle weakness was associated with altered prefrontal cortex hemodynamic activation patterns in children with CP. Additionally, muscle co-contraction did not significantly relate to functional strength in children with CP.

In conclusion, children with CP experience increased levels of muscle co-contraction associated, to a greater degree, by increased muscle weakness rather than pathological increases in antagonistic muscle activity. The ability to properly modulate

muscle co-contraction could potentially influence physical activity participation in children with CP. Furthermore, the inability to modulate muscle co-contraction in children with CP was related to altered patterns of brain hemodynamic activation compared to typically developing children.

INDEX WORDS: Cerebral palsy, physical activity, muscle co-contraction, muscle strength, functional near-infrared spectroscopy, prefrontal cortex

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DEDICATION

This dissertation is dedicated to all children with cerebral palsy. Your perseverance will always be an inspiration. Being challenged in life is inevitable, how we react is a personal choice.

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CHAPTER 1

INTRODUCTION

Cerebral palsy (CP) is a heterogeneous condition with multiple causes, clinical types, neuropathology patterns and developmental pathologies [1]. Cerebral palsy is the most common childhood disability [2, 3] with an estimated 17 million people affected worldwide, as of 2018 [4]. It has been suggested that CP would be better named "*the cerebral palsies*" given that within the clinical spectrum there are many causes and many types and degrees of disability [1]. Nevertheless, clinical symptoms are permanent and non-progressive, and any changes are mainly associated with disorder of posture and movement control [5, 6]. Depending on the severity and location of lesion, CP may result in significant limitations on a person's ability to carry out daily activities [7]. Based on the location of injury to the brain and subsequent motor types, CP has been classified into spastic, dyskinetic (dystonia, chorea and athetosis), ataxic and mixed pattern [2]. Depending on the limbs involved, CP can be further classified into quadriplegia- involving all four limbs, diplegia- involving two limbs but primarily, the lower extremities and hemiplegia- a unilateral disturbance [1]. Spastic CP is the most common form of CP, occurring in about 80% of the cases [2] and can be characterized by abnormal coordination patterns, co-activation of antagonist muscles and abnormal postural control [8]. Spasticity can be defined as a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome

[9]. Clinical symptoms often manifest through the musculoskeletal system. Children with CP commonly have reduced physical activity levels [10-12], increased levels of muscle weakness [13, 14] and higher levels of muscle co-contraction [13, 15-17] compared to typically developing peers. The underlying cause of these symptoms is thought to be a result of an elevated level of spasticity [4, 18].

With a reduced level of physical activity, children with CP are at higher risk for developing secondary cardiometabolic disease including hypertension, visceral adipose tissue, and obesity [11, 19-21]. Furthermore, it is also well known that physical activity can positively influence brain plasticity and function in children [22] and across the lifespan [23-25]. Another common symptom that children with CP experience as a result of injury to the brain is muscle weakness [14, 17]. Muscle weakness is defined as the inability to produce an anticipated level of force [26]. Children with CP commonly undergo physical therapy as a mean to reduce muscle weakness. However, optimal physical therapy programs are yet to be determined [27].

Therefore, in order to evaluate the effectiveness of therapeutic interventions, clinical assessments are often adopted. Measures of interest can include physical activity and functional strength, which can be evaluated using activity monitors [12] and validated functional strength assessments, such as the lateral step-up test (LSUT) [28, 29]. The LSUT requires contributions from muscles acting at the three primary joints of the lower extremities (i.e., the hip, knee, and ankle). Furthermore, evidence suggests that lateral stepping produces greater activation of involved muscles as well as greater power production at the knee and ankle compared to other forms of stepping [30, 31]. As a result, the LSUT has been proposed as an effective movement for lower body

strengthening as part of a resistance training program for children with CP [32]. Previous studies using the LSUT to assess functional strength mostly include a single step height. However, the LSUT can easily be expanded to include multiple step heights and thus, examine a response to increasing levels of task demands.

One potential mechanism thought to contribute to the muscle weakness experienced in children with CP is excessive co-activation of antagonist muscles [13, 17, 33], also referred to as muscle co-contraction [34]. Co-contraction suggests an increase in antagonist muscle activation, such that there is an increase in simultaneous activation of agonist and antagonist muscle groups during movement [13, 35]. Co-contraction is a naturally occurring motor control strategy which results from a required increase in joint stability or movement accuracy [13, 18, 36]. However, co-contraction in clinical populations, including children with CP, can reach a point where the simultaneous contraction of agonist and antagonist muscles becomes excessive and no longer aids, but rather impairs performance [13, 15]. In which case, the undesired increase in co-contraction can be referred to as pathological co-contraction [18]. Research studies which have assessed co-contraction in elderly populations have suggested that pathological co-contraction may be positively related to age and risk of falling [37-39]. Muscle electromyography (EMG) values in those post-stroke demonstrated an increase of antagonistic activity (i.e. co-contraction) during gait [40, 41]. Lamontagne et al.[41] suggested that co-contraction in those post-stroke can lead to increased energy cost of locomotion but that pathological co-contraction can also be attributed to adaptive behavior, where the non-paretic limbs' increase in co-contraction serves as support to the paretic limb. In studies assessing co-contraction in children with CP, results suggest that

children with CP experience a higher level of co-contraction compared to typically developing children [42-44]. However, most studies have focused on isometric testing, passive movement, and gait. In order to assess the level of contribution that pathological co-contraction may have on muscle weakness in children with CP, pathological co-contraction may be best evaluated during controlled movements. Furthermore, understanding how physical activity and muscle co-contraction are related in children with CP should be further evaluated. Targeting the effects that co-contraction may have on functional ability in children with CP could provide valuable information into how therapeutic interventions are designed.

There is strong evidence that muscle weakness in children with CP is composed of both neural and musculoskeletal components [45]. However, the relationship between the two is less understood. Previous studies have shown that higher levels of aerobic fitness have been associated with both larger prefrontal cortex volumes in older adults [25] and increased neural processing efficiency in children [46]. Additionally, physical activity has shown to be a valid predictor of physical fitness, which includes muscle strength [47]. Therefore, the interrelationships between physical activity, neurological, and muscular components should be explored in children with CP, who could benefit from both improved central, and peripheral adaptations. To our knowledge, no studies have assessed relationship between brain and muscle activity in children with CP during a lower limb functional strength assessment. However, the neural substrates of muscle co-contraction have been studied using functional magnetic resonance imaging (fMRI). Results demonstrated that a distributed cerebellar-parietal-frontal network is present in the regulation of muscle co-contraction [48]. Whether elevated cerebellar-parietal-frontal

network activity is present in children with CP remains unclear. Therefore, the exploration of prefrontal networks is warranted. Unfortunately, limitations inherent to the use of fMRI, such as such as restricted mobility and susceptibility to movement artifacts [49-51] make it difficult to apply in children with CP.

Recently, functional near-infrared spectroscopy (fNIRS) has become a powerful neuroimaging tool that yields results similar to those of fMRI [49], but without the previously mentioned limitations. Functional near-infrared spectroscopy captures hemodynamic changes in the cortical tissue in response to external stimuli or movement [52], a process known as neurovascular coupling [53, 54]. When using fNIRS, a better temporal resolution (12.5 Hz, typically) compared to fMRI (0.3-0.6 Hz) is obtained, allowing the identification and isolation of signal effectives of respiration (~0.2-0.3 Hz) and cardiac pulsations (~1 Hz) [55]. These factors make fNIRS a viable option for motor control studies of freely-moving individuals in natural environments [56].

The prefrontal cortex (PFC) is active during physical activity levels and has shown to differ in the way it is activated in clinical populations during movement. Results from previous studies have revealed an increase in PFC activation during gait and postural control tasks in older adults, individuals with Parkinson's disease, and individuals post-stroke [57-59]. Increased activation of the PFC may be a marker of pathological co-contraction. The use of fNIRS to study disorders associated with childhood-onset brain injury, such as CP, has only recently begun to gain momentum [60, 61]. As a result, few studies have assessed brain activity during movement in children with CP using fNIRS. The paucity of studies may be related to inherent limitations presented by wired fNIRS instruments, such as reduced comfort and wiring constraints

which, over the past decade, have been overcome by the development of wireless fNIRS systems [56]. To our knowledge, studies that have used fNIRS to assess brain activity, including the PFC, in children with CP have focused mainly on upper extremity motor tasks [62-64], while those assessing brain activity during lower extremity motor tasks in children with CP have focused on regions other than the PFC [60, 65, 66]. Therefore, understanding the relationship between lower extremity function and PFC activation is essential and clinically relevant. Findings could provide insight on the mechanisms underlying muscle adaptations related to centrally mediated neuroplasticity and brain function in children with CP.

In summary, children with CP have shown to be less physically active than their typically developing peers [67]. As interventions aim to improve functional deficits in children with CP, it remains important to understand the underlying mechanisms. In particular, the mechanisms that may influence or be influenced by reduced physical activity in children with CP and the secondary effects that this may have on brain function, pathological musculature, and functional strength.

Therefore, the purposes of this dissertation will be 1) to evaluate the effects of muscle co-contraction on lower limb functional strength and its relationship to physical activity participation in children with CP and 2) to assess the relationship between prefrontal hemodynamic activity and muscle co-contraction in children with CP during a lower limb functional strength assessment. Findings from this dissertation could potentially help clinicians and researchers better understand the underlying effects of sedentary behavior and secondary implications related to brain health, pathological muscular function, functional strength and intertwined relationships that may exist in children with CP

CHAPTER 2

LITERATURE REVIEW

2.1 Cerebral palsy (CP)

Cerebral palsy (CP) is the most common physical disability of childhood, occurring in one out of 323 children in the United States [5]. Understood to be an umbrella term, CP has always been known as a disorder of movement and posture resulting from a non-progressive injury to the developing brain [2]. Aside from movement disorders, CP also encompasses abnormalities in balance and sensory abilities [6]. Intertwined, abnormalities often lead to limitations in an individual's ability to carry out daily and functional activities [68]. Due to the broad range of abnormalities, acute classifications of CP were developed to appreciate CP as more than just a movement disorder. Using motor type and distribution as primary factors for classification, studies have been able to report more meaningful, clinically relevant outcomes [2].

Based on motor distribution, CP has been classified into one of four categories: monoplegia, diplegia, hemiplegia and quadriplegia with the latter three being the most common types of diagnoses. Monoplegia describes CP affecting a single limb, but is rarely diagnosed [69]. Diplegia impacts both sides of the body with a higher prevalence reported in the lower limbs compared to the upper limbs [2]. Hemiplegia describes impact to one side of the body with an increased level of impairment typically observed in the upper limbs compared to the lower limbs [4]. Finally, quadriplegia is used to

describe impact to both sides of the body with an equal distribution of impact between lower and upper limbs [4].

In order of frequency, CP has been further classified based on motor types, which includes four categories: spastic, dyskinetic, hypotonic and ataxic CP [69] with spastic CP affecting approximately 80% of children with CP [5]. Trauma to the motor cortex typically results in spasticity; a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome [9]. Common clinical manifestations of spasticity include muscle stiffness and rigidity during movement [69].

Additionally, motor function can also be referenced to classify functional ability in individuals with CP. The most commonly used measure of gross motor function is the Gross Motor Classification System [70]

2.1.1 Classification of gross motor function in children with CP

It is well understood that children with CP exhibit reduced functional ability compared to typically developing children [4] . Although the range of developmental difficulties is wide spread, a hallmark of these conditions remains a disorder in the development of gross motor function [28]. Gross motor function in children with CP is typically assessed using the gross motor classification system (GMFCS). Using a five-point scale, higher numbers are indicative of increased motor function deficit [29]. The GMFCS is also age-dependent, so the need for reclassification as individuals grow is important [71].

A child is classified as GMFCS I if they are able to walk indoors and outdoors with no limitations. Furthermore, they are able to climb stairs without the use of railings, run and jump with or without some limitations. A child classified in GMFCS II indicates being able to walk, but with limitations. This may imply the use of a hand-held mobility device before the age of four, use of railings on stairs, and/or the inability to run or jump. A child classified in GMFCS III can typically walk with assistance of a mobility device indoors, but may need to resource to a wheelchair, or similar device, for ambulation in community settings requiring a longer distance. A classification of GMFCS III may also indicate that assistance is needed to transition between floors, sitting and standing, and while using stairways. GMFCS IV indicates that the child requires the use of a wheelchair, or similar wheeled device, in most settings. Self-supported sitting is common but self-mobility is limited. Finally, a classification of GMFCS V implies that the child manifests severe limitations related to ambulation. Complete assistance with transfers is usually required [30].

2.2 Spasticity

There is much debate regarding the proper definition of spasticity and whether proposed definitions truly capture spasticity as an entity rather than a general motor disorder [72]. However, the most popular definition is that published by Lance [9] which states that spasticity is “a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome.” This definition emphasizes that spasticity is only one of the many features of

an upper motor neuron (UMN) syndrome including clasp-knife phenomenon, increased tendon reflexes, clonus, and flexor and extensor spasms [73, 74]. The lack of agreement between researchers is heavily influenced by the heterogeneity of spasticity [75] although, clinically, it is clear that spasticity is strongly associated with limited functional ability. Rather than focusing on a proper definition, the literature suggests that focus should be placed on further understanding the pathophysiology of spasticity. Doing so would allow for proper isolation from other positive features of UMN syndrome and could lead to more adequate measurements of spasticity in clinical settings [25].

2.2.1 Pathophysiology of spasticity

Spasticity is a complex phenomenon which does not result from a single mechanism but rather from changes along interdependent neural pathways [76] which can differ based on the etiology, location, and timing of an upper motor neuron (UMN) lesion, as is CP [72]. Although much of the information available regarding the pathophysiology of spasticity derives from animal models and adult pathologies, [72] the inter-relating mechanisms behind spasticity can be broadly categorized into spinal and supraspinal mechanisms regulating spasticity [74]. In humans, the three important pathways housing these mechanisms are the corticospinal, reticulospinal, and the vestibulospinal tracts [72, 74]. Although some influence from excitatory pathways may be inter-related in a patient with spasticity, hypotheses suggest that spasticity may develop more as a result of disruptions to inhibitory spinal pathways. Although the literature identifies multiple inhibitory mechanisms which could be involved in the development of spasticity, dysinaptic reciprocal inhibition is thought to be the primary pathway involved in the

pathophysiology of spasticity [74]. During voluntary contractions, activity of antagonist muscles is typically inhibited parallel to the primary activation of the agonist muscle. This regulatory behavior, known as dysinaptic reciprocal inhibition, is modulated through descending spinal pathways of either the corticospinal, rubrospinal or vesitbulospinal tracts and their respective interneurons [77]. However, after a lesion to the brain, these pathways can become damaged resulting in reciprocal inhibition failure. The inability to properly regulate this inhibitory behavior results in co-contraction of antagonist and agonist muscle groups in spastic patients [74].

In early research, it was thought that presynaptic inhibition also played a major role in the development of spasticity [78]. Similar to dysinaptic reciprocal inhibition, presynaptic inhibition is an inhibitory pathway which suppresses α-motor neuron excitability of antagonist muscle groups during voluntary movement [79, 80]. However, inhibition is modulated through GABA-ergic axo-axonic synapses on motor neuron terminals. Upon activation, a reduction in the amount of neurotransmitter released by Ia terminals on the motor neuron is observed [81]. This suppression of unimportant Ia afferent information results in normal tone in healthy populations [74, 79]. Brain lesions therefore, could result in damage to regulatory behavior causing an increased response from α-motor neurons by Ia input, ensuring spasticity in patients with an UMN lesion. Early techniques used to evaluate presynaptic inhibition supported this theory and suggested that spasticity involved reduced presynaptic inhibition of Ia afferents [82]. Using improved methods, studies later reported a reduction in presynaptic inhibition in patients with spastic multiple sclerosis [80, 83]. Similar findings were also reported in those with spinal cord injury but not in those post-stroke [84] suggesting that presynaptic inhibition is reduced

in some spastic populations, but not in all. Whether the same results exist in children with CP, remains unclear.

2.2.2 Clinical assessments of spasticity

The measurement of spasticity is typically quantified using either clinical or quantitative evaluation methods. Clinical methods include validated clinical assessments such as the Modified Ashworth Scale (MAS)[85] or the Modified Tardieu Scale (MTS)[86]. The MAS builds on the original Ashworth scale by adding an extra classification level to the scale in order to increase sensitivity [87]. Since then, the MAS has become the most accepted clinical tool used to measure the increase of muscle tone [88] and has been applied in clinical settings to grade muscle spasticity [85]. The MAS is composed of a 6-point scale where a grade of 0 indicates no increase in muscle tone. A grade of 1 indicates a slight increase in muscle tone, with a catch and release or minimal resistance at the end of the range of motion (ROM) when an affected part(s) is moved in flexion or extension. A grade of 1+ identifies a slight increase in muscle tone, manifested as a catch, followed by minimal resistance through the remainder (less than half) of the ROM. A grade of 2 is provided when a marked increase in muscle tone throughout most of the ROM is observed, but affected part(s) are still easily moved. A grade of 3 is identified as a considerable increase in muscle tone, paired with difficult passive movement. Finally, a grade of 4 observes the affected part(s) rigid in flexion or extension [85].

The MTS is another clinical scale used to assess spasticity. The MTS is also composed of a 6-point scale and although its application is not as widespread as the

MAS, it has recently been recommended as a more reliable, effective, and suitable alternative for the measurement of muscle spasticity [89, 90]. The MTS uses standardized procedures to measure quality of muscle reaction to passive movement at specified velocities (V1-V3), providing advantages over the MAS when assessing spasticity in children with CP. Velocities are defined where V1 refers to a speed "as slow as possible" specifically, slower than the natural drop of the limb segment under gravity. Velocity V2 describes speed to be equal to that of the limb segment falling under gravity and finally, V3 describes speed to be "as fast as possible" or faster than the rate of the natural drop of the limb segment under gravity. Additionally, the MTS determines two angles (R1 and R2). The angle of muscle reaction (R1) is defined as the point in the joint range in which a velocity-dependent ''catch'' or clonus is felt during a quick stretch of the muscle. The angle describing full ROM is equivalent to passive ROM (R2) and the difference between R1 and R2 describes the dynamic component [91]. A grade of 0 describes no resistance throughout the course of the passive movement. A grade of 1 is described by slight resistance through the course of passive movement with no clear ''catch'' at a precise angle. A grade of 2 identifies a clear catch at a precise angle, interrupting the passive movement, followed by release. A grade of 3 refers to a fatigable clonus (< 10s, when maintaining the pressure) appearing at a precise angle contrary to a grade of 4, an unfatigable clonus (>10 s when maintaining the pressure) at a precise angle. Finally, a grade of 5 describes the joint to be immovable [91].

Although these clinical assessments are widely and commonly used, the measurement of spasticity remains a difficult and unresolved problem, partly due to the complex pathophysiology of spasticity [92]. The inter-rater reliability of these scales have shown

mixed results [89, 91, 93-95] and their inability to differentiate neural from non-neural components [96] has led to much of their criticism. The literature suggests caution when applying and interpreting results based on these scales in children with CP [91, 97, 98].

2.2.3 Quantitative measurement of spasticity

In the last years, efforts to provide objective measures of spasticity has led to progress in translating instrumented spasticity measurement systems to clinical practice [72, 96]. Although these systems still leave the issue of differentiating between neural and non-neural components of spasticity partly unresolved, measurements have proven to be more valid and reliable than commonly used clinical assessment alternatives [94, 99, 100]. In this section, we will discuss biomechanical, neurophysiological, and newly proposed methods which have been applied in the literature to produce quantitative outcome measures estimating the severity of spasticity.

Biomechanical measures assessing spasticity generally observe and calculate the resistance of a muscle from passive joint movement [100]. One method commonly used is the pendulum test [101-103]. The pendulum test is based on the oscillation features of an extremity in free circulation. Upon release of the extremity of interest in the extension position, sinusoidal patterns are observed with the use of electrogoniometers assessing motion and tachometers assessing movement rate [104]. However, consistency between researchers has shown to be limited suggesting the need for standardized protocols when implementing the pendulum test for spasticity evaluation [102]. Additionally, the pendulum test is limited, as it may only be used to evaluate spasticity in the knee muscles. But most importantly, the pendulum test does not readily indicate whether

neural factors or non-neural factors, such as alterations in muscular viscoelastic properties, dampen the swing movement [94, 100].

Isokinetic dynamometry serves as an advantageous alternative as it allows for the standardization of protocols [102] with acceptable mechanical reliability and validity [105]. Isokinetic dynamometry measures resistance to movement of a rested and loose extremity. As the extremity of interest is moved at specific velocities, resistance can be measured as “torque”, “peak torque” or “threshold angle”. Spasticity therefore, can be assessed by observing increases in resistance or “torque”, as a result of simultaneous increases in speed. Studies assessing spasticity using isokinetic dynamometry have highlighted its feasibility and reproducibility [94], resulting in significant differences in resistance between healthy and clinical population such as stroke [106, 107], spinal cord lesions [108, 109] and children with CP [110-112]. However, similar to the pendulum test, biomechanical measures fail to readily dissociate increased resistance in the muscle due to non-neural factors from the velocity-dependent resistance due to spasticity [94]. Considering the importance of non-neural components and their contribution to spastic hypertonia [72], adopting methods which illustrate passive muscle properties, such as ultrasound imaging, may complement instrumented spasticity assessment.

Surface electromyography (sEMG) is another method which has been used to assess the neural pathophysiological mechanisms of spasticity [94, 113]. When using sEMG, electrical current generated in the muscles during contraction, results in evoked signals, which can be used to represent the activity of a given muscle [114]. Since prominent clinical signs of spasticity include an exaggerated stretch reflex and co-contraction, sEMG can be used to quantify both during isometric and dynamic conditions [115]. The

use of sEMG has become particularly popular due to its noninvasive, convenient, and low-cost nature [100]. Therefore, sEMG has been used to evaluate spastic components in clinical populations including patients post-stroke [107, 116], patients with spinal cord injury [117] and in children with CP [43, 118, 119]. Study results have shown that despite high variability in sEMG measurements, reflexes are typically larger in spastic populations compared to age-matched healthy controls but show low correlation to the severity of spasticity assessed by the MAS [94]. Therefore, it is important to recognize, once more, the multidimensional composition of spasticity. Although sEMG has shown to provide insight on stretch reflex thresholds, the use of sEMG in conjunction with biomechanical techniques may serve as a better alternative than sEMG alone when evaluating the full scope of the spastic syndrome [119-121].

2.2.4 Spasticity in children with CP

In children with spastic CP, spasticity is manifested primarily by an exaggeration of stretch reflex, which increases in intensity as movement velocity also increases [18, 72, 73]. As a result, abnormal movement and postural control in children with CP are commonly observed [122]. Studies have shown that hypertonia in spastic patients can result from both increased stretch reflex and from intrinsic muscular and other spinal control mechanisms [76, 123]. Therefore, in spastic patients, hypertonia can be divided into two components: hypertonia mediated by the stretch reflex, which corresponds to spasticity, and hypertonia due to soft tissue changes, otherwise known as intrinsic hypertonia [72, 73]. However, clinical tests have typically been unable to differentiate

between spastic and intrinsic hypertonia, leading to the terms “spasticity” and “hypertonia” often being used interchangeably [72].

2.2.5 Treatment of spasticity and motor impairments in children with CP

The primary goal of any intervention related to spasticity and children with CP should be to improve function. Although there is no cure, management of symptoms can help increase social interaction, locomotion and overall, a better quality of life. There are various approaches to treatment including physical therapy, medication and surgical treatments [124]. The specific type of treatment often depends on individual symptoms and range of impairment. Typically, children with CP receive physical therapy. Although physical therapy can span across a wide range of approaches and techniques, popular interventions commonly adopt muscle strengthening and fitness programs [124, 125]. The literature highlights that fitness training seems to be more appropriate to improve functional levels compared to strengthening techniques [126] but information related to optimal intensity, duration and frequency of cardiac and muscular physical therapy continues to be limited. Further evidence-based research is needed in order to conclude the effectiveness of these therapeutic techniques [125].

Botulinum toxin is the most widely used medical intervention in children with CP to treat spasticity [127]. Of the seven major BoNT serotypes, only BoNT type-A (BoNT-A) and BoNT type-B have been used in children with CP with BoNT-A returning better results in children with CP [128]. The primary mechanism of BoNT-A involves the inhibition of acetylcholine release at the neuromuscular junction [129]. After injection, the overall effects can be described as localized muscle denervation [128]. There exists

very little evidence that BoNT-A has direct central effects, with any signs of central effects resulting from peripheral denervation influencing neuroplasticity [129]. Injection of BoNT-A is dose-dependent with little systemic spread of toxin due to high and rapid affinity binding at the local muscles. Primary effects include the reduction of muscle strength due to acute muscle atrophy resulting in secondary effects such as the reduction of muscle spasticity in children with CP [130]. Clinical effects typically last from 3-6 months but have been observed to last up to or longer than 12 months with adverse effects however, such as muscle atrophy, lasting longer than clinical effects such as muscle relaxation [130]. Therefore, the need to individualize the use of BoNT-A remains although, in principle, the use of BoNT-A seems simple.

Selective dorsal rhizotomy (SDR) is also a recognized neurosurgical intervention for spasticity in children with CP with compelling evidence from systematic reviews of its effectiveness [126]. In patients with spastic diplegia, including children with CP, SDR involves the division of selected afferent nerve roots between L1-S2, targeting specific reflex arcs which contribute to the increased spasticity of the lower limbs [131]. Throughout the procedure, a multilevel lumbar laminectomy allows for easy visualization of the nerve roots [132, 133]. The motor roots in the ventral horn are protected while the dorsal roots are typically sectioned into a 50-70% proportion although the literature it mixed, with some centers advocating for a 25-40% of rootlets sectioned [134]. Results between both approaches have suggested similar efficacy in tone reduction without the side effects that a sectioning of 50-70% proportion might have, such as scoliosis, kyphosis, lumbar lordosis, spondylolysis, and spinal stenosis [134]. Although short-term efficacy is evident, long-term outcomes of SDR remain unclear in the literature [134,

135]. Short-term improvements include increased gross motor function abilities, gait quality and reduced spasticity [134, 136]. However, patient selection criteria remains controversial [134]. Typically, children with CP who are classified as GMFCS II-III tend to benefit more from SDR and although children who are considered GMFCS-I may also benefit, the benefits may be too small to justify a surgical procedure [136]. In summary, the literature highlights the short-term effectiveness of SDR [134, 136-138]. However, more studies are required to evaluate the long-term effects of SDR and addressing the cause of spasticity rather than just the symptoms should be prioritized.

2.3 Physical activity

2.3.1 Assessment of physical activity

Physical activity is defined as any bodily movement that results in energy expenditure [139]. Habitual physical activity specifically encompasses occupationally related activities, leisure and sport [12]. Energy expenditure is commonly expressed as a rate (i.e. kcal per minute) or by using a metabolic equivalent of task, otherwise known as MET [140]. One MET is defined as the energy expenditure level at rest. The MET value for a specific task is calculated by dividing the metabolic rate of said task, divided by the energy expenditure at rest and it typically presented as a ratio [141]. Various methods of calculating energy expenditure are available in the literature. Historically, these have included questionnaires and activity logs. However, limitations inherent to these methods include the over- or under-estimation of physical activity levels. Therefore, the literature suggests alternatives such as accelerometers, heart rate monitors and pedometers as

methods to obtain improved estimates of exercise volume, intensity and energy expenditure [142].

Accelerometers are small, wearable monitors that record acceleration in gravitational units on one or more planes at sampling rates above 1 time/second (usually 40-100 Hz). Subsequently, the recorded accelerations are then processed to a lower resolution (i.e., epoch) and calibrated to a known criteria measure such as oxygen consumption [142]. Commonly, calibration studies rely on unitless intensity metrics, or "counts". These metrics are typically applied to thresholds which output the data into intensity categories such as sedentary, light, moderate and vigorous [142]. Accelerometers have been used in numerous studies and have been found to be a reliable and valid tool to assess physical activity in various stages of life ranging from children to the elderly [143, 144]. One of the most commonly used accelerometers is the ActiGraph GT9X Link (ActiGraph, Pensacola, FL) [145]. The ActiGraph GT9X Link displays raw physical activity data as mean counts per minute, a commonly used accelerometer metric [146]. The sum of activity counts for a valid day is divided by the number of minutes of wear time in that day across all valid days to get the mean counts per minute [146].

However, despite the improvements that accelerometer-based activity monitors inherently provide, such as increased reliability and validity, decreased subjectivity and decreased human error [142], there are some limitations to consider. These limitations include the proprietary nature of many algorithms to quantify PA, lack of sensitivity on sedentary and light-intensity range of the activity spectrum, and inability to detect non-ambulatory activities such as cycling and weight-lifting [144].

2.3.2 Classification of physical activity

Physical activity can be performed under various intensities ranging from sedentary behavior to vigorous physical activity [147]. Using METs as reference thresholds for absolute intensities, physical activity can be categorized as light, < 3.0 METs, moderate, 3.0-5.9 METs, vigorous ≥ 6.0 METs [148]. Light intensity activities require the least amount of effort (light walking or stretching) while vigorous physical activities require the most oxygen consumption to participate (running ≥ 5 mph, basketball, volleyball) [147].

2.3.3 Physical activity in children with CP

It is well known that children with CP are at risk of reduced habitual activity and increased sedentary time [149] primarily due to the physical impairments which characterize CP such as, impaired posture and movement but also to environmental and psychological factors [67]. Research has reported that levels of physical activity are related to the level of impairment (GMFCS) in children with CP [150] and that 89% of children with CP do not participate in sufficient physical activity [151]. Furthermore, Maher et al. also reported that children with CP were found to be less physically active compared to typically developing children and that the decline in physical activity was positively related to age [150].

2.3.4 Clinical importance of physical activity in children with CP

The observed decreases in habitual physical activity in children with CP can result in an underdevelopment of gross motor skills [12] and an increased risk for secondary

health problems such as cardiovascular disease, osteoporosis, obesity and type II diabetes [11]. Research shows that children with CP display underdeveloped bones [152, 153]and muscles [154, 155] which can be attributed, in part, to low physical activity levels [156]. Since children with CP are less likely to develop bones, muscles and cardiorespiratory systems to adequate capacities [157], functional ability may be jeopardized by limiting physical activity participation [150] putting those with CP at higher risk of low independence and increased sedentary behavior [158]. Fortunately, the low physical activity levels in children with CP are reversible. Previous studies have observed that habitual physical activity can be increased in those with CP [11]. The ability to do so makes physical activity levels important to consider when developing and assessing the efficacy of therapeutic interventions aiming to improve functional ability in children with CP.

2.4 Physical fitness and muscular strength

Physical fitness is defined as a set of attributes that people have or can attain that relate to the ability to perform physical activity. Physical fitness is characterized by an ability to perform daily activities with vigor and a demonstration of traits and capacities that are associated with a low risk of premature development of hypokinetic diseases [139, 159]. The health-related components which make up physical fitness are: cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility [139]. Muscular strength, endurance, and flexibility make up a specific type of fitness referred to as musculoskeletal fitness [160]. Muscle strength, under dynamic conditions, is defined as the maximum force that a muscle or muscle group is

able to generate at a specific velocity [160]. Muscle strength is an important component of health and has a role which is relevant to the performance of daily activities [161]. In addition, muscle strength is known to be the most important predictor of function and is inversely related to the degree of disability [160].

2.4.1 Muscle weakness in children with CP

It is well known that children with CP demonstrate a reduced amount of muscle strength compared to typically developing peers [14, 17, 45]. This holds true even in children with CP who have mild impairments (GMFCS I-II) [162]. Wiley and Damiano conducted a study which assessed muscle weakness in 30 ambulant children with CP (15 hemiplegic, 15 diplegic) and 16 typically developing controls [14]. Children with CP were weaker in all of the 8 assessed lower limb muscle groups. This was true not only for the affected limb, but also for the unaffected limb compared to typically developing peers. Several factors contributing to muscle weakness in children with CP are highlighted in the literature. These include both neurological and musculoskeletal components [45].

2.4.2 Neurological contributors to muscle weakness in CP

From a neurological standpoint, muscle weakness in children with CP can be attributed to central neurological damage, the primary lesion in children with CP. Damage to the pyramidal tracts often leads to reduced central input to motor neurons [162] resulting in a decreased ability to properly activate agonist muscles [163]. This can lead to patterns of abnormal movement which are subject to reinforcement as

development progresses. As maturation of the central nervous system (CNS) occurs, neural circuits are reinforced by repetition. Through myelination and apoptosis, the neural circuits producing abnormal movement in children with CP can become stronger [164]. In addition, studies have also demonstrated that children with CP have abnormal recruitment of motor units compared to typically developing children [165]. Stackhouse et al. reported a slower rate of force production in children with CP (n = 12) compared to typically developing controls (n = 12) suggesting inefficient motor unit recruitment. Lastly, damage to inhibitory pathways, specifically reciprocal inhibition, can lead to apparent muscle weakness in children with CP [162]. Damage to these neural pathways can result in pathological co-contraction, where an increase in antagonistic drive restrains proper agonist activation in children with CP. Pathological co-contraction has shown to increase energy expenditure, impeding movement [166]. Similar results have been reported in children with CP [15]. These negative consequences have been reported to result in increased cost of walking [167], which could influence the reduced levels of physical activity observed in children with CP.

In summary, neural factors which can contribute to muscle weakness in children with CP include reduced agonist ability, abnormal neural circuit reinforcement, and impaired reciprocal inhibition.

2.4.3 Musculoskeletal contributors to muscle weakness in CP

Research has also highlighted musculoskeletal components which can lead to muscle weakness in children with CP. Historically, muscle tissue was thought to remain unchanged in individuals post-cerebral lesion [168]. However, it is now well established

that individuals with CP typically experience significantly altered skeletal muscle, contributing to the clinically observed muscle weakness [169]. These alterations include: increased sarcomere length, decreased whole muscle length, decreased cross-sectional area (CSA), and changes to passive tissue properties of muscle [45].

The production of muscle torque is essential in order to properly carry out desired movement(s). Maximal torque is dependent on an optimal overlap of actin and myosin filaments. As a result, muscle strength is dependent on the total number of in-series sarcomeres and the length of each sarcomere [169]. In theory, the optimal sarcomere length falls within a range of 2.30 to 2.47 microns (μm) [109]. However, studies assessing sarcomere length in children with CP have reported a pathological increase in sarcomere length resulting in the inability to produce maximal force due to a reduced amount of cross-bridges formed [170]. A potential mechanism leading to this structural abnormality is thought to result from insufficient muscle growth compared to bone growth during development in individuals with CP [164].

Furthermore, children with CP also often display shorter muscle belly length compared to typically developing peers [171]. This decrease in muscle belly length can further reinforce suboptimal force production by limiting the amount of sarcomeres available in order to produce torque. Affected muscles in children with CP, which rest in a shortened position, can also affect the non-spastic opposing muscle. Specifically, due to the chronic shortening of the affected muscle, the opposing muscle rests at a longer, disadvantageous length which can result in the inability to shorten to necessary lengths in order to properly fulfill functional movement.

It is also well established that muscle force is strongly correlated to both muscle physiological and anatomical CSA [172], although the correlation with physiological CSA is slightly better. Previous studies have reported that growth and development lead to increases in strength per unit of CSA and that these increases continue through adolescence in typically developing individuals [173]. Children with CP, however, tend to have a smaller muscle CSA compared to controls. Elder et al. conducted a study that compared 28 children with CP to typically developing controls and results demonstrated that children with CP had a reduced CSA in conjunction with reduced ability to generate torque compared to controls [17]. Similar results were also reported by Marbini et al. [174].

Finally, changes in muscle passive properties are also thought to contribute to muscle weakness in children with CP. Interestingly, there is evidence that changes to passive tissue properties may actually be of greater relevance compared to altered reflexes regarding functional limitation [175]. The viscoelastic properties of muscle are influenced by both the type and amount of collagen [45], which has been reported to increase in children with CP [176]. This increase in collagen content is suggested to play a key role in the increase of muscle stiffness that children with CP commonly experience. An increase in muscle stiffness of the spastic muscle can lead to increased resistance during passive movement which may lead to the apparent muscle weakness observed [45].

It is important to note that muscle strength is related to several factors other than the factors recently mentioned. Due to individual differences in anthropometrics, sex, and age, muscle strength is expected to also vary in developing children [173]. Nevertheless,

increased attention and research should continue to focus on factors such as physical activity, which are known to impact a child's strength [67]. Given that CP is a chronic disorder, early intervention is of essence so that the abnormal maturation in both neural and muscle tissue components affecting muscle strength are managed before complete maturation is reached by children with CP.

2.5 Muscle co-contraction in motor control and adaptation

Throughout life, individuals are constantly presented with unique physical environments. As a way to adapt, the CNS relies on two major mechanisms of motor control. The first mechanism involves learning an internal model which generates motor commands to create appropriate forces specific to certain movements. The second mechanism involves control of the joints and limbs through the regulation of muscle co-contraction [177]. Muscle co-contraction provides stability against external disturbances and can be used as a compensation technique for inaccuracies that may exist in the internal model mentioned in the first mechanism [48]. As motor skills and performance improves, muscle co-contraction has shown to decrease [178]. Depending on the task, the level of co-contraction will vary in order to provide the necessary mechanical stability [179]. Franklin et al. was able to identify three phases during adaptation to a novel physical environment in typically developing individuals. First, as a new environment is presented abruptly, an initial increase in muscle co-contraction is observed providing increased stiffness and stability around the joint of interest. Second, as learning progresses, the internal model is improved by the CNS and reduces the dependency on muscle co-contraction resulting in a decrease of co-contraction levels. Third, muscle co-

contraction continues to decrease after improved accuracy of the internal model is achieved in the last phase of adaptation [177]. Franklin et al. later suggested that this continued decline in phase three is part of a mechanism aimed to reduce the metabolic cost of movement [179].

2.5.1 Quantification of muscle co-contraction

With the use of electromyography (EMG), researchers have been able to quantitatively estimate co-contraction [180, 181]. Although computational methods vary, the use of EMG magnitude to generate a co-contraction index has been found to be a reliable method when observing co-contraction during movement [13]. However, the literature consistently suggests caution when interpreting results of co-contraction indices or ratios (CCR). Therefore, it is important to highlight some inherent limitations when interpreting CCR. For example, during movements which require very low or very high levels of force, CCR could yield similar results [13] but have entirely different functional implications. In addition, high CCR theoretically reflect an increase of antagonist contribution during movement. However, in clinical populations, such as children with CP, a high ratio could also reflect decreased agonist ability to generate the required level of force rather than an increase in antagonist resistance [182]. For these reasons, it is important to scrutinize data used to generate CCR. Furthermore, it is important to assess CCR in relation to functional impairment. With the use of functional assessments, conclusions can be further supported or dismissed regarding the influence that co-contraction may have on functional ability in children with CP.

2.5.2 Pathological co-contraction in children with CP

Given the importance that co-contraction has on motor control and adaptation [48], co-contraction has been a topic of interest in clinical populations with functional deficits. This includes co-contraction in elderly populations [37-39], in those post-stroke [40, 41, 183], and in children with CP [13, 15, 16, 119]. Results of these studies suggest that co-contraction may be positively related to age and risk of falling even after adaptation is acquired [37-39]. In children with CP, many studies have focused on the effects that co-contraction may have on the abnormal gait patterns typically experienced by this population. Unnithan et al. conducted a study between 9 children with CP and able-bodied controls. Study results demonstrated that higher levels of co-contraction were highly related to increased metabolic cost during locomotion [15]. It has been suggested that a potential mechanism behind this continuation of high levels of co-contraction is a result of spasticity in individuals with CP [18] impeding natural adaptation mechanisms observed in healthy populations [48]. Increased muscle co-contraction in individuals with spasticity is mainly originated from deficient supraspinal input [184]. However, it can also be influenced by damaged spinal functions such as reduced presynaptic and reciprocal inhibition [74].

In a later study, Pinto et al. also reported that co-contraction is a significant predictor of metabolic cost during gait [185]. Moreover, Pinto et al. and others have reported that gait speed can also be predicted by levels of co-contraction [185, 186]. However, no clear consensus has been described in the literature regarding the specific role of co-contraction in metabolic cost or locomotion speed [13, 185]. It remains unclear if increased co-contraction is a compensatory functional adaptation unique to

neurologically impaired populations, including children with CP. Therefore, continued research is warranted to assess the functional implications of co-contraction and the mechanisms through which co-contraction can, or cannot, modulate functional performance in children with CP.

2.6 Principles of near-infrared spectroscopy

2.6.1 Diffuse optical imaging

Diffuse optical imaging is a method that relies on the interaction of near-infrared light, through absorption and elastic scattering of light, with biological tissue to measure differences in concentration of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR). Near-infrared light is a type of electromagnetic wave between 700 nm to 900 nm which is slightly beyond what is visible to the human eye. Using near-infrared spectroscopy, the molecule dependent differences of near infrared light absorption of HbO and HbR are what allow for the concentration of each, within a given biological tissue, to be calculated. These data can then be further processed to produce spatially resolved images containing information about physiological factors, such as blood volume and oxygenation of a particular region of interest [53, 187].

Functional near-infrared spectroscopy (fNIRS) is known to have a high temporal resolution as a result of high sampling rates. Although typical sampling rates are around 12.5 Hz, devices reach up to 100 Hz as technological advancements have been made. This high temporal resolution makes it easier to filter and isolate physiological artifacts such as those from respiration and cardiac pulsations, which occur at different ranges of frequencies than those of task-related measures of brain activity [55, 188]. Furthermore,

the spatial resolution of fNIRS is adequate enough to allow for the coverage of areas not involved in the stimulation of interest. Doing so can provide insight on the contrast between cortical areas of interest and its surroundings.

2.6.2 Optical window

The optical window refers to the range between ~700-900 nm, where biological tissue, including bone, are relatively transparent to near-infrared light. Most biological tissue contain water as a major component, which absorb very little energy at these wavelengths. However, the chromophores in HbO and HbR absorb a significantly contrasting amount of near-infrared light in this range. As photons are introduced to the scalp via light sources, they travel through the cortical tissue and are either absorbed or scattered. After interacting with the tissue of interest, photons can be measured using detectors after the photons have followed a banana shaped path back to the surface of the scalp or skin [53]. Wavelengths in the optical window can be chosen in order to optimize the absorption of HbO and HbR, with HbO absorbing more strongly above 790 nm and HbR absorbing more strongly below 790 nm [188]. In biological tissue, HbO and HbR are the main absorbers of light. Both HbO and HbR are also strongly linked to metabolic demands and tissue oxygenation.

2.6.3 Determining oxygen levels using NIRS

Functional near infrared-spectroscopy measures changes in optical density, mediated by optical absorption. Changes in optical density are assumed to be small and can be modeled using the modified Beer-Lambert law. The modified Beer-Lambert law

provides empirical, optical attenuation data in a highly scattering medium [189]. The modified Beer-Lambert law builds on the original Beer-Lambert law by introducing a scattering dependent light intensity loss parameter. The law describes the loss of light intensity (I) in tissue (OD) as a function of chromophore concentrations (c, units [M]), molar extinction coefficients (ε, [M− 1 cm− 1]), differential path length factor (DPF, unitless; which accounts for the increase in distance the light travels due to the light scattering coefficient (μ_s')), source-detector separation distance (d, [cm]) and G (unitless) [190]. Furthermore, the index i indicates all of the investigated chromophores of interest, typically HbO and HbR while I_0 denotes the intensity of emitted light. Assuming that the change in light scattering vs light absorption is small, G can be considered time-invariant, therefore neglected when determining change in optical density (ΔOD) for a time point (t_1) against an initial time point (t_0).

The modified Beer-Lambert law is valid when measuring change in homogenous tissue, which is not the case for measurements in the brain [191]. However, since the inhomogeneous nature of brain tissue is constant and covered mostly by the constant G, it no longer poses a problem for quantification purposes. However, it must be noted that this does lead to a strong underestimation of concentration size changes in HbO and HbR. In principle, the error can be corrected by taking into account partial differential path lengths [192]. However, the correction is not essential, and often not performed, as the trend of the signals are correct and comparable across different locations and stimulation paradigms [190]. Recommended values for ε and DPF can be found in the literature [193, 194]. Previous studies have shown that DPF is sex, age and wavelength dependent with an estimated 15% variability between subjects [195]. This between-subject error can be

corrected using time-resolved instrumentation. However, time resolved instrumentation is expensive [190]. However, most of the literature reports results in terms of group averages and not individual results. In doing so, DPF error can be averaged out [190] but would require larger sample sizes. Paired comparisons within individuals could help further reduce this effect. However, when describing methodologies, DPF values used should be reported in order to ensure comparability between publications [190].

2.6.4 Neurovascular coupling

Functional near-infrared spectroscopy captures hemodynamic changes in the cortical tissue in response to external stimuli or movement [52], through the use of a process known as neurovascular coupling [53, 54]. Neurovascular coupling is described as the process by which regional cerebral blood flow is modulated due to an increase in metabolic demand of oxygen consumption [196]. Based on this theory, active cortical regions would demonstrate higher levels of HbO and a paired, inverse response from HbR levels. However, in order to properly capture a hemodynamic response, the external stimuli must be sustained long enough to provoke an increase of oxygen demand to the regions involved, typically after 2 seconds [197]. When the external stimuli is removed, a return to baseline levels, observed as a decrease in HbO an increase of HbR will be evident.

2.6.5 Functional near infrared-spectroscopy systems

There are three main types of fNIRS systems. These include continuous wave (CW), time domain (TD) and frequency domain (FD) systems [198]. The oldest and most

commonly used systems are CW-NIRS systems [190]. These devices employ the use of multiple wavelength sources and a steady-state light source, from either laser or light emitting diodes, with emitted intensity constant with time [199] to measure attenuation of light via source-detector pairs. Compared to other systems, CW-NIRS systems are advantageous due to their simplicity of use, size, weight, and cost [198]. However, as previously mentioned, when using CW-NIRS systems, differentiation between attenuation and absorption or scattering is not possible [190].

Time resolved fNIRS instrumentation or TD-NIRS systems use a steady-state laser which emits picosecond pulses of light into the tissue [200]. Following the injection of light pulses, detectors measure the arrival time of single photons. These arrival times of individual photons can be used to estimate tissue optical properties such as absorption and scattering, unlike CW-NIRS which only acquires intensity of light. The estimation of scattering and absorption makes it possible to characterize absolute HbO and HbR concentrations [201]. However, out of the three system types, TD-NIRS is the most expensive, complex and the system with the least amount of channels and sampling frequency possibilities [202].

Lastly, FD-NIRS uses laser sources which provide intensity-modulated input of light by a sinusoidal function [201]. As a result, measurements of amplitude of modulation, average intensity and phase shift are collected. The phase shift represents the delay between the emitted and detected waves of light and changes with the optical path length of the light through the tissue. From the absorption and scattering coefficients, absolute Hb concentrations can be calculated [203]. There remains much progress to be made in regards to the use of fNIRS. However, the progress made in recent years has led

to its increased use in neuroscience research [190] and novel applications in neurorehabilitation.

2.6.6 Functional near-infrared spectroscopy in neurorehabilitation research

In recent years, fNIRS has been introduced into the field of rehabilitation medicine. Specifically, fNIRS systems have been used in neurorehabilitation settings both as a monitoring tool and as a therapeutic tool [204]. As a monitoring tool, fNIRS can be used to assess neural mechanisms during gait and postural control. Studies assessing cortical activity during gait using fNIRS have reported symmetrical cortical activity in the supplementary motor areas (SMA) during treadmill walking [205]. Additionally, studies also reported the involvement of the prefrontal cortex (PFC) during the acceleration phase of locomotion suggesting that the PFC is involved in the adaptation of locomotion and that the sensorimotor cortex (SMC) is involved in the stabilization of gait [206]. Other studies have also noted the involvement of the PFC during gait in elderly, stroke and Parkinsonian populations [207-210]. Studies have also noted the role of the SMA in voluntary postural control [211] displaying a relationship between individual postural ability and cortical activation in the SMA, as well as a significant correlation between SMA cortical activity and longitudinal balance recovery in stroke patients [212, 213]. As a therapeutic tool, fNIRS has been used to provide real-time neurofeedback in efforts to enhance brain plasticity [204, 212]. Results from previous studies seem promising, reporting evidence that suggests that real-time neurofeedback, provided by fNIRS, can help improve cortical activation patters in both healthy and clinical populations [214, 215]. However, despite the increased use of fNIRS in rehabilitation medicine, few studies

have assessed cortical activation in children with CP using fNIRS. There remains a need for further research assessing globalized cortical activity in children with CP in order to investigate and understand the neural underpinnings related to functional tasks and therapeutic interventions.

2.6.7 Functional near-infrared spectroscopy in children with CP

The literature is limited when it comes to research involving the use of fNIRS to assess cortical activity in children with CP. Studies that have used fNIRS in children with CP have mainly assessed cortical activation during upper extremity tasks. From those studies, reports showed increased cortical activity during squeezing tasks in the sensorimotor area [65, 216] with a more pronounced activation in children with CP compared to typically developing children during bimanual squeezing tasks compared to single handed squeezing tasks, irrespective of hand dominance. Two studies that assessed the sensorimotor areas in children with CP during finger tapping tasks were able to detect differences in activation patterns in the sensorimotor areas, compared to typically developing children [61, 217]. In lower extremity studies using fNIRS in children with CP, the sensorimotor areas showed a relationship between activation and muscle activity not required, in theory, for the instructed task suggesting that cortical organization inefficiency in children with CP can be a primary culprit for loss of selective voluntary motor control in the lower extremities [218]. Lastly, one gait study using fNIRS to assess cortical activity reported increased activation in the somatosensory and superior parietal cortices associated with increased error in gait kinematics of children with CP [66]. To our knowledge, this is the extent of the literature assessing cortical activity patterns using

fNIRS in children with CP, confirming the need for fNIRS studies in this population in efforts to assess and understand the effects that therapeutic interventions may have on cortical activity and the neuromuscular pathways which may help improve functional ability in children with CP.

2.7 Specific aims

The overall objective of this project is to further the understand underlying mechanisms influencing physical activity participation and altered neuromuscular pathways in children with CP. Specifically, this project aims to assess the relationships between physical activity, muscle strength and measures of pathological muscle impairment such as co-contraction in children with CP. In a more exploratory manner, this also project aims to assess the relationships between central and peripheral pathologies observed in children with CP. My central hypotheses are 1) muscle co-contraction is negatively related to functional strength and physical activity in children with CP and 2) differences in brain hemodynamic activation levels between children with CP and typically developing children will be significantly and inversely related to muscle co-contraction in children with CP. The rationale for this project is that it will allow for increased understanding of factors limiting children with CP to participate in physical activity and increase understanding of the functional implications that muscle co-contraction may have in children with CP. Additionally, this project will provide insight into the pathological symptoms observed in the neuromuscular pathways of children with CP.

I plan to test my central hypotheses by using the following specific aims:

Specific aim 1. To evaluate the effects of muscle co-contraction on lower limb functional strength and its relationship to physical activity participation in children with CP.

Hypothesis 1.1. Children with CP will display reduced physical activity participation, lower limb functional strength, assessed by lateral step-up test performance, and higher levels of co-contraction compared to typically developing children.

Hypothesis 1.2. Levels of co-contraction and repetitions completed during a lateral step-up test, reflecting functional muscle strength, will have a significant negative and clinically relevant relationship in both children with CP and typically developing children.

Hypothesis 1.3. Physical activity and will have a significant positive and clinically relevant relationship with repetitions completed during a lateral step-up test, reflecting functional strength, and a significant inverse relationship with co-contraction ratios.

Specific aim 2. To assess the relationship between prefrontal hemodynamic activity and muscle co-contraction in children with CP during a lateral step-up test.

Hypothesis 2.1. Children with CP will have lower prefrontal hemodynamic activation and higher co-contraction ratios compared to typically developing children.

Hypothesis 2.2. Prefrontal hemodynamic activation and muscle co-contraction will have a significant inverse and clinically relevant relationship in children with CP.

Findings from this project will allow for a deeper understanding of the underlying mechanisms reducing physical activity participation in children with CP. Additionally, results from this project could also provide further insight into the underlying

mechanisms of muscle pathology observed in children with CP and could begin to evaluate its relationship to central pathologies also observed in children with CP.

CHAPTER 3

MUSCLE CO-CONTRACTION, MUSCLE WEAKNESS AND PHYSICAL ACTIVTIY IN CHILDREN WITH CEREBRAL PALSY

3.1 Introduction

Muscle weakness is a symptom commonly observed in children with CP [219]. Muscle weakness refers to the inability to produce or maintain an anticipated level of force [26]. Children with CP experience limited function and participation due to muscle weakness [33]. Therefore, understanding the underlying mechanisms of muscle weakness in children with CP could provide important insight for proper intervention. According to previous studies, co-contraction, also referred to as co-activation [34], has shown to be a potential mechanism behind muscle weakness in children with CP [13, 182]. Co-contraction refers to the simultaneous activity of agonist and antagonist muscles across the same joint [41, 220]. Co-contraction is a normal motor control strategy observed in healthy individuals during various motor tasks [18]. As environmental and task demands of voluntary movement change, so does the need for stability and joint stiffness, resulting in an increase or decrease of co-contraction. When presented with new environments, which cause disturbances to balance and/or posture, an increase in co-contraction can be observed as an early response [221]. Therefore, co-contraction may enhance or impede functional performance, depending on the motor task requirements and the individual's ability to modulate co-contraction in the central nervous system (CNS). Generally,

studies have reported higher levels of co-contraction in individuals with CP compared to controls [42, 44, 222, 223]. The general consensus is that co-contraction during volitional movement may be attributable to several factors, including abnormal supraspinal input from the motor cortex and decreased Ia reciprocal inhibition in the antagonistic muscle [17, 43, 224, 225]. However, these studies only assessed co-contraction and its relationship to force production under isometric conditions. Studies which assessed co-contraction in clinical populations under dynamic conditions, such as gait, also found increases in co-contraction levels [13, 186, 226]. However, to our knowledge, only one study assessed the relationship between co-contraction and muscle weakness in children with CP. Damiano et al. [13] observed no relationship between the increase in co-contraction levels and muscle strength, assessed by isometric knee extensions, in children with CP. This is consistent with other studies which have assessed the relationship between muscle strength and co-contraction in both children with CP and individuals post-stroke [227-229]. However, to our knowledge, no studies have evaluated the relationship between co-contraction and lower limb functional strength in children with CP during a highly dynamic lower limb functional strength assessment, such as the LSUT, which progressively increases requirements of strength and balance [230]. Therefore, the literature remains unclear about the functional implications that co-contraction may have in children with CP when functional tasks require both an increase in muscle strength and stability.

Additionally, there is evidence that co-contraction can be reduced by chronic changes in physical activity participation [231, 232]. Since children with CP tend to participate in less physical activity compared to typically developing children [10, 12],

the risk for developing secondary health problems is a major concern [11]. Therefore, assessing the relationships between physical activity and co-contraction is warranted to better understand the role that physical activity may have on pathological co-contraction during functional movement in children with CP. Unfortunately, studies assessing the relationship between physical activity participation and co-contraction during highly dynamic functional tasks, such as the LSUT, are lacking.

Therefore, the purpose of this study was 1) to determine whether children with CP had higher levels of co-contraction during a lower limb functional strength test (i.e. LSUT) compared to typically developing children and 2) to determine the relationships between CCR and functional strength (LSUT repetitions) in children with CP compared to typically developing children and 3) to assess relationships between CCR and physical activity participation in children with CP and typically developing children. We hypothesized that 1) children with CP would have higher CCR in all of the assessed muscle pairs compared to typically developing children across all LSUT step heights 2) Co-contraction ratios would correlate negatively with LSUT and 3) physical activity counts would correlate negatively with levels of co-contraction during the LSUT.

3.2 Methods

Participants

Children with CP and typically developing control children matched to children with CP for age (± 1.5 y) sex and race were recruited from schools, physician offices, rehabilitation centers, and social media groups using flyers, and through advertisements in local newspapers. Inclusion criteria for children with CP included those who were 5 to

11 years of age, had spasticity, and were able to ambulate without an assistive device. Inclusion criteria for typically developing children included no history of neurological or motor disorders, and not taking medications that affect musculoskeletal health. The study was approved by the Institutional Review Board of the University of Georgia. Informed consent was obtained from the parent or legal guardian and assent was obtained from the participant, if able, before data collection was initiated.

Gross Motor Functional Classification System (GMFCS)

Gross motor function in children with CP was assessed using the gross motor classification system (GMFCS), which is based on a five-point scale. There is a progressive increase in motor function deficit with higher ratings [70]. Briefly, a GMFCS I classification indicates an ability to walk indoors and outdoors and climb stairs with no limitations. Activities involving running and jumping can be performed, but with limited speed, balance and coordination. A GMFCS V classification indicates severe limitations and an inability to ambulate [233]. In order to properly classify each participant, children with CP were asked to complete a series of tasks including running, jumping and stair climbing.

Anthropometrics

Height and body mass were measured while the children were wearing shorts and a teeshirt, and were without socks, shoes, or braces. Height was measured using a stadiometer (Seca 217; Seca GmbH & Co. KG., Hamburg, Germany) to the nearest 0.1 cm. Body mass was measured using a digital scale (Detecto, 6550, Cardinal Scale, Webb

City, MO) to the nearest 0.1 kg. Body mass index (BMI) was calculated as body mass (kg)/ height (m^2).

Physical activity

Physical activity was assessed using the Actigraph GT9X (Pensacola, FL) accelerometer-based physical activity monitor. Among brands that are commercially available, Actigraph accelerometers are the most frequently used in research [234]. The Actigraph GT9X utilizes a gyroscope, magnetometer, a triaxial MEMS accelerometer, and measures acceleration between ± 8 g at a sampling rate of 30 to 100 Hz. Participants were asked to wear two monitors on the lateral aspect of the ankle and two monitors on the hip of the more affected side in children with CP and on the non-dominant side in controls. Physical activity data was recorded during 3 weekdays and 1 weekend day, for a total of 4 days, while the participants wore these monitors continuously for a 24-hour period. Participants and participant's families were asked to take the monitors off during bathing, showering, or swimming. This was confirmed by reviewing activity logs kept by the children with assistance from their parent and by visually examining the graphical output generated using software provided by the manufacturer. If participants did not wear the monitors on any of the days, they were asked to re-wear the monitors to make up for missed days. The total activity counts per day averaged from the two monitors are reported.

Lateral step-up test (LSUT)

The LSUT procedure was explained to participants prior to testing. At the start of the test, feet were approximately shoulder-width apart. The more affected lower

extremity in children with CP and the non-dominant lower extremity in typically developing children were considered the tested limb. Participants were instructed to lift the resting limb and place it next to the tested limb, which was the concentric phase and then return the resting limb to its original position, which was the eccentric phase. Participants were also asked to keep their hips, knees, and feet facing forward and not rotate while performing the test.

The LSUT consisted of 4 trials, 20 seconds per trial, and a progressive increase in step height for each successive trial (0, 10, 15, and 20 cm, respectively). For the 10, 15, and 20 cm trials, the foot of the more affected lower extremity in children with CP and the non-dominant lower extremity in typically developing children was placed on a step platform. Participants were instructed to perform as many repetitions as possible without any support. Repetitions were only considered successful if the heel of the non-tested limb touched the floor and a return to the original position was accomplished with no support. Steps that required assistance were counted, but as an unsuccessful repetition. Participants were allowed to perform one or two practice bouts prior to each trial to ensure that they understood the test protocol. Physical demonstration of optimal performance was also provided to the participants by test administrators. Each LSUT trial lasted 20 seconds and was preceded by a rest period of 20 seconds, in which the child was instructed to stand in their testing position “as still as possible”, while focusing on an “X” sign on the wall located at eye level and 4.5 meters away. A graphical representation of the LSUT is presented in Figure 1A. The single-trial block paradigm design of the LSUT is presented in Figure 1B.

Performance results of the LSUT were calculated using a weighted scoring system, based on difficulty (i.e. step height) and accounting for all attempts. Steps that required assistance or were done incorrectly were counted, but adjusted down by a multiplier. Assisted or incorrect steps at 0 cm were multiplied by 0.05, 10 cm by 0.10, at 15 cm by 0.15, and assisted or incomplete steps at 20 cm were multiplied by 0.20 and added to the total steps for each height, respectively.

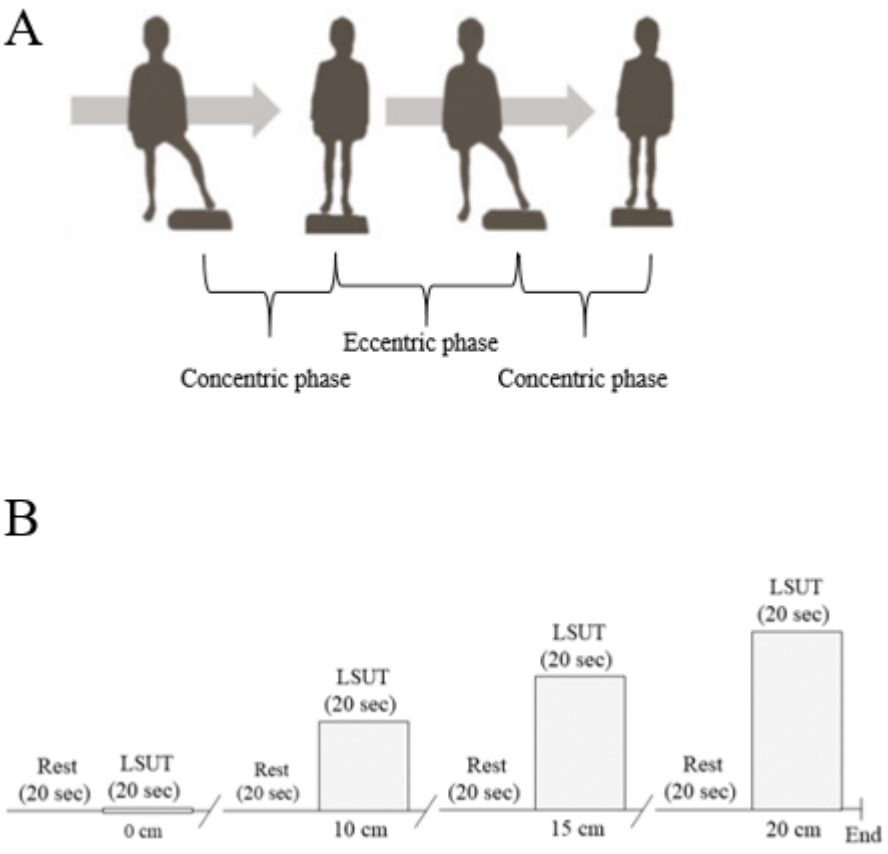

Figure 1. A graphical representation of two successful repetitions during the LSUT (A). Concentric and eccentric phases are outlined for reference. A graphical description of the progressive LSUT block paradigm used for the experimental task (B). The LSUT

included single trials at 0, 10, 15, and 20 cm step heights. The block paradigm began with 20 seconds of rest.

Electromyography (EMG) data collection

Each participant had the skin beneath the location of the EMG sensor abraded and cleaned with an alcohol prep pad to ensure proper contact with the corresponding electrode. Electromyography (EMG) sensors (Delsys Inc., Natick, MA) were placed according to each target muscle. For this study, the tibialis anterior (TA), soleus (SOL), lateral gastrocnemius (LG), biceps femoris (BF) and vastus lateralis (VL) muscles were assessed. Electrodes corresponding to the TA were placed at 1/3 of the line between the tip of the fibula and the tip of the medial malleolus. The SOL sensor was placed at 2/3 of the line between the medial condyle of the femur to the medial malleolus. For the LG, electrodes were placed at 1/3 of the line between the head of the fibula and the calcaneus. The BF electrodes were placed at 50% of the line between the ischial tuberosity and lateral epicondyle of the tibia. Lastly, the VL electrodes were placed at the 2/3 of the line from the anterior superior iliac spine to the superior lateral side of the patella in the direction of the muscle fibers. The sample frequency used for data collection as set at 2000 Hz. Electromyography activity was described as the average amplitude within the concentric and eccentric time frames for each LSUT repetition.

Electromyography (EMG) data processing

EMG data were mean offset, band-pass filtered (fourth order Butterworth, cut-off frequency of 20-400 Hz), rectified, low-pass filtered (fourth order Butterworth, cut-off

frequency of 10 Hz) [235]. A mean offset normalization was chosen based on recommendations found in the literature [236]. This type of EMG normalization sets the amplitude normalization to the mean value found within each trial, in this case, each LSUT repetition. The main effect of this type of EMG normalization is reduced variability and reduced standard deviation range. A maximum voluntary contraction normalization was not found to be suitable considering our studied population. Maximum voluntary contraction normalization is recommended only in studies done with healthy and trained subjects [236].

Quantification of muscle co-contraction

A co-contraction ratio (CCR) was calculated for both the concentric and eccentric phases of the LSUT for each of the four LSUT step heights (0, 10, 15 and 20 cm, respectively) across three muscle pairs: TA/SOL, TA/LG and BF/VL using the following formula [237]:

$$CCR = 2 * \frac{sEMGantagonist}{sEMGagonist + sEMGantagonist} * 100$$

Where *sEMGantagonist* represents the EMG signal with lower average magnitude and *sEMGagonist* represents the EMG signal with the higher average magnitude. In this formula, the antagonist activity is normalized in relation to the mean total muscle activity. Next, the resulting value is multiplied by two to counterbalance the activity of the agonist muscle [220]. A CCR of 100 would represent equal activity of both the agonist and antagonist muscles while a CCR of 0 would represent agonist activation only.

Electromyography (2000 Hz, Delsys Inc.) data were synced with kinematic data via motion capture software (100 Hz, Qualisys, Lincolnshire, IL) which used the CAST Full Body model (Qualisys, Lincolnshire, IL). Data were further processed using Visual 3D (C-motion, Ontario, Canada) in order to identify the heel strike and push-off events of the non-tested limb for each participant. The identified events were then used to discriminate between the concentric and eccentric phases of the LSUT. The concentric phase of the LSUT represents the time of foot push-off from the ground to the time the foot lands on the step. The eccentric phase represents the time from stepping off of the platform until contact of the heel is made with the floor. A graphical representation of the concentric and eccentric phases can be found in figure 1A.

Statistical analysis

All statistical analyses were conducted using SPSS Statistics 24 (IBM Corp., Armonk, NY). Data were checked for normality by examining skewness, kurtosis, and the Shapiro-Wilk test. Group differences in physical characteristics were determined using an independent t-test if the data were normally distributed and a Mann-Whitney *U* test if the data were non-normally distributed. One sample t-tests were used to determine whether the height, body mass, and BMI percentiles were different from the 50^{th} age- and sex-based percentiles in the children with CP and in the controls. Values are presented as mean ± SD unless stated otherwise.

A univariate generalized linear model (GLM) was used to assess group effects between CCR of each muscle pair and LSUT repetitions across all four step heights. The GLM was also used to assess LSUT step height effects on the CCR of each muscle pair

in both the concentric and eccentric LSUT phases, and LSUT step height effects on the number of repetitions completed between groups. Mann-Whitney *U* tests were used to assess group differences in CCR at specific LSUT step heights. Spearman correlations were conducted to assess relationships between CCR and LSUT repetitions. For all statistical tests, the alpha level was set at 0.05. The magnitude of the effects was determined using Cohen's d (*d*), with 0.2, 0.5, and 0.8 representing small, medium, and large effect sizes, respectively [238].

3.3 Results

Physical characteristics, LSUT performance and physical activity

Twenty-two children with spastic CP (all GMFCS level I-II) and 22 typically developing children participated in the study. There were no significant group differences in age, height, body mass, BMI, height percentile, body mass percentile, or BMI percentile ($p > 0.10$) (Table 1). Furthermore, height percentile, body mass percentile, and BMI percentile were not different from the 50th age- and sex-based percentiles in either group.

Table 1. Physical characteristics of children with cerebral palsy (CP) and typically developing children (Con).

	CP (n = 22)	Con (n = 22)	*d*	*p*
Age (years)	8.3 ± 2.0	8.1 ± 2.1	0.10	0.80
Sex (M/F)	12/10	12/10	—	—
Height (m)	1.30 ± 0.14	1.29 ± 0.14	0.07	0.80
Height (%)*	56 ± 35	56 ± 27	0.00	0.81
Body mass (kg)*	29 ± 9	28 ± 11	0.10	0.64
Body mass (%)	50 ± 31	50 ± 29	0.00	0.97
BMI*	16.5 ± 2.7	16.4 ± 2.8	0.04	0.89
BMI (%)	46 ± 32	49 ± 32	0.09	0.78
GMFCS (I/II)	18/4	—	—	—

Values are mean ± SD. GMFCS, Gross Motor Function Classification System, BMI, body mass index. % for height, body mass, and BMI reflect the percentile relative to age- and sex-based norms. *Non-normally distributed and analyzed using a Mann-Whitney *U* test.

There was a significant step-height effect during the LSUT with fewer repetitions completed as step height increased ($p < 0.001$) (Figure 2). There was also a significant group effect with children with CP completing fewer repetitions than controls across all step heights ($p < 0.001$) (Figure 2).

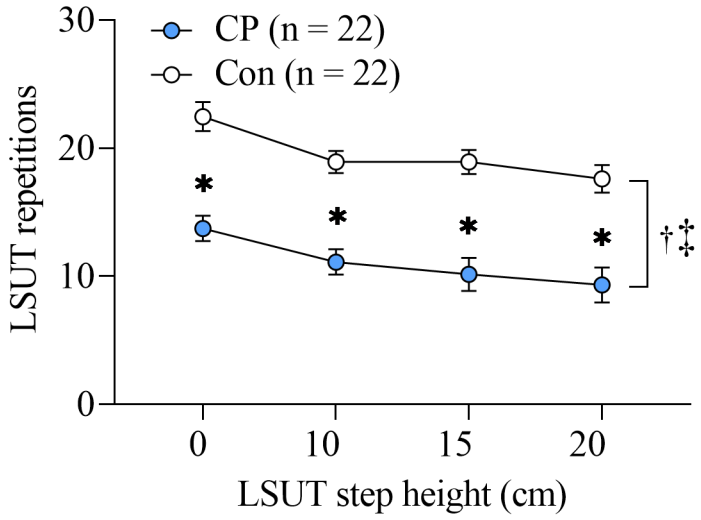

Figure 2. Repetitions at each step height of the lateral step-up test (LSUT) in children with cerebral palsy (CP) and in typically developing children (Con). Values are mean ± SE. †Group effect, $p = < 0.001$; ‡LSUT step height effect $p < 0.05$; *Difference between groups at a specific height, $p < 0.001$.

Furthermore, children with CP had lower counts of physical activity compared to controls at the ankle ($p = 0.02$), but not at the hip ($p = 0.22$) (Figure 3).

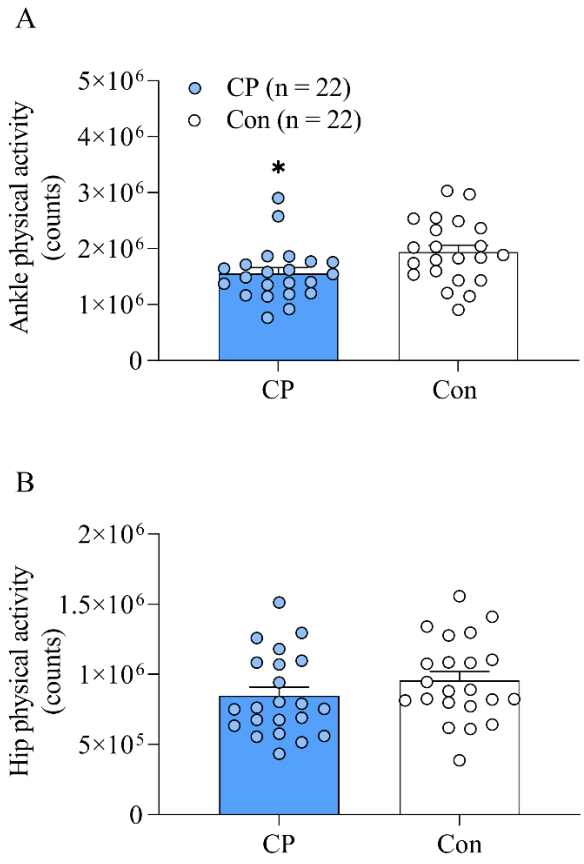

Figure 3. Bar graphs demonstrate group comparisons of A) ankle physical activity counts and B) hip physical activity counts in children with cerebral palsy (CP) and typically developing children (Con). Values are means ± SE. *Different from controls, $p < 0.05$.

Evaluation of muscle co-contraction during the LSUT

Concentric phase

Electromyography activity of the TA, SOL, BF and VL muscles was significantly lower in children with CP compared to controls during the LSUT (Figure 4) (all $p <$

0.05). Specific differences were observed between groups at all LSUT step heights in the SOL and VL, where children with CP had lower EMG activity compared to controls (Figure 4) (all $p < 0.05$). Furthermore, EMG activity was lower in children with CP during the 0, 10 and 20 cm step heights for the TA, and during the 0 and 10 cm step heights for the BF (Figure 4) (all $p < 0.05$).

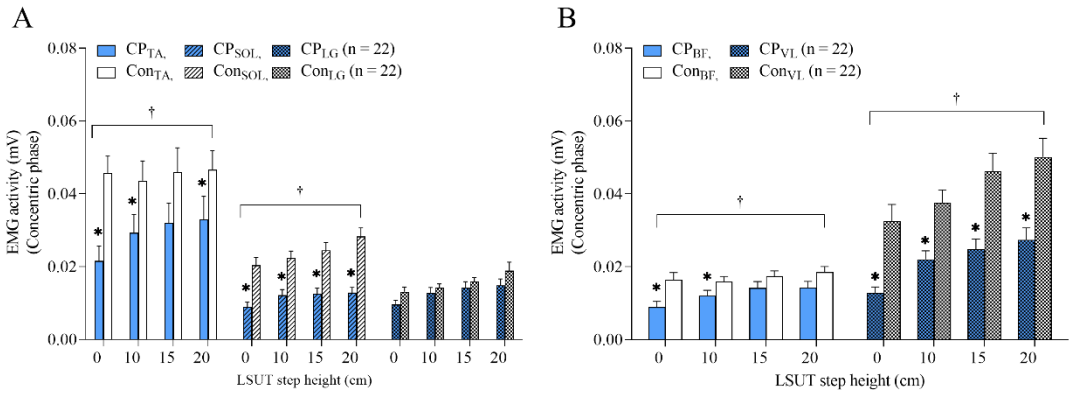

Figure 4. Bar graphs demonstrate electromyography (EMG) activity of the A) leg muscles and B) thigh muscles across all lateral step-up test (LSUT) step heights during the concentric phase of the LSUT. Values are mean ± SE. †Group effect, $p < 0.05$; *Different from controls (Con), $p < 0.05$.

Muscle CCR of the TA/SOL muscle pair were significantly lower in children with CP compared to controls during the LSUT (Figure 5A) ($p < 0.05$). However, CCR were significantly higher in children with CP compared to controls in the BF/VL muscle pair. Specific differences were only observed between children with CP and controls in the TA/SOL muscle pair at the 15 and 20 cm LSUT step heights (Figure 5A) (all $p < 0.05$). No significant CCR group effects were observed in the TA/LG muscle during the LSUT (Figure 5B) ($p > 0.05$).

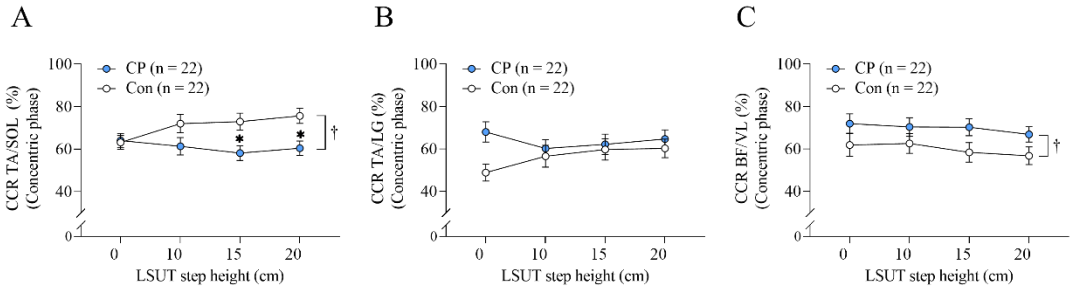

Figure 5. Line plots display muscle co-contraction ratios (CCR) for each muscle pair in the leg (A & B) and thigh (C) across individual LSUT step heights during the concentric phase of the LSUT. Values are mean ± SE. †Group effect, $p < 0.05$; *Different from controls (Con), $p < 0.05$.

Eccentric phase

Electromyography activity of the TA, SOL, and VL muscles was significantly lower in children with CP compared to controls during the LSUT (Figure 6) (all $p < 0.05$). Specific differences were observed between children with CP and controls at all LSUT step heights in the TA, SOL and VL muscles, where children with CP had significantly lower EMG activity compared to controls (Figure 6) (all $p < 0.05$).

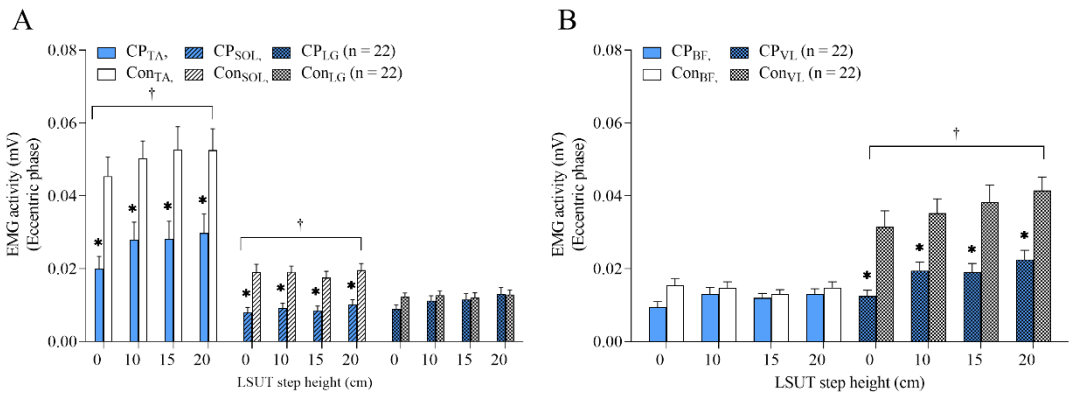

Figure 6. Bar graphs demonstrate electromyography (EMG) activity of the A) leg muscles and B) thigh muscles across all lateral step-up test (LSUT) step heights during the eccentric phase of the LSUT. Values are mean ± SE. †Group effect, $p < 0.05$; *Different from controls (Con), $p < 0.05$.

Muscle CCR of the TA/LG and BF/VL muscle pairs were significantly higher in children with CP compared to controls during the LSUT (Figures 7B & C) (all $p < 0.05$). Specific differences were observed in the TA/LG at all LSUT step heights compared to controls (Figure 7B) (all $p < 0.05$). Specific differences were observed in the BF/VL at the 0, 15 and 20 cm LSUT step heights compared to controls (Figure 5C) (all $p < 0.05$). No significant CCR group effects were observed in the TA/SOL muscle pair during the LSUT (Figure 5A) ($p > 0.05$).

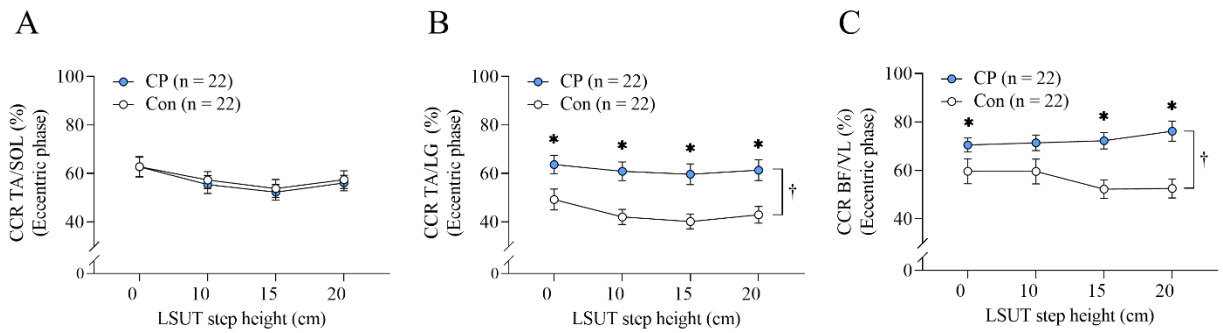

Figure 7. Line plots display muscle co-contraction ratios (CCR) for each muscle pair in the leg (A & B) and thigh (C) across individual LSUT step heights during the eccentric phase of the LSUT. Values are mean ± SE. †Group effect, $p < 0.05$; *Different from controls (Con), $p < 0.05$.

Muscle co-contraction and its relationship to LSUT performance

During both the concentric and eccentric phases of the LSUT, CCR were not significantly related to LSUT performance in any muscle pair in children with CP or in controls (all $p > 0.05$).

Muscle co-contraction and its relationship to physical activity

Concentric phase

Physical activity at the ankle was significantly and negatively correlated to CCR of the TA/LG muscle pair at the 15 cm (Figure 11C) ($r_s = -0.42$, $p = 0.05$) and 20 cm (Figure 8D) ($r_s = -0.46$, $p = 0.03$) LSUT step heights.

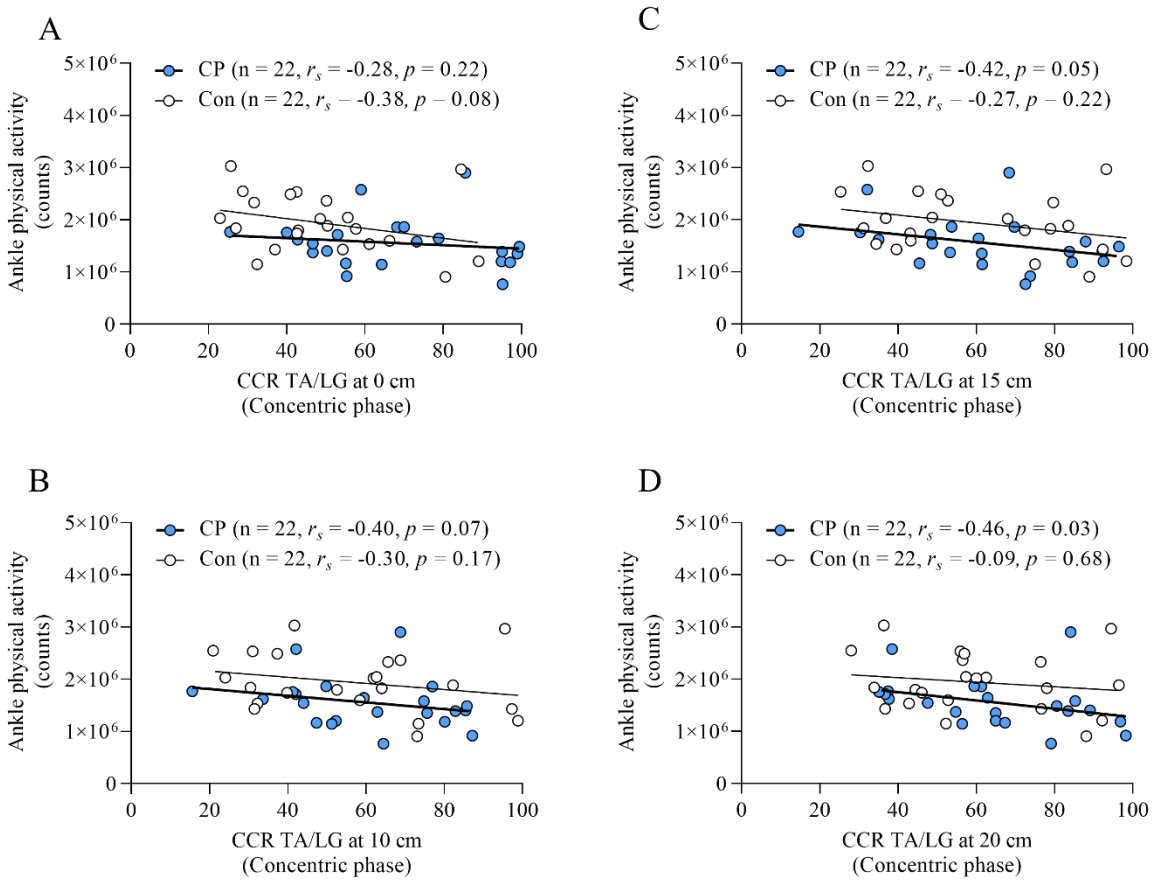

Figure 8. Relationships between tibialis anterior (TA) and lateral gastrocnemius (LG) co-contraction ratios (CCR) during the concentric phase of the lateral step-up test (LSUT) and physical activity at the ankle in children with cerebral palsy (CP) and typically developing children (Con).

Eccentric phase

Children with CP had a significantly negative relationship between physical activity counts at the ankle and CCR of the TA/SOL muscle pair at the 15 cm (Figure 9C) (r_s = -0.42, p = 0.05) and 20 cm (Figure 9D) (r_s = -0.45, p = 0.04) LSUT step heights. In addition, children with CP showed significant and negative relationships between

physical activity at the ankle and CCR of the TA/LG muscle pair at the 20 cm LSUT step height (Figure 10D) (r_s = -0.45, p = 0.04). Finally, controls only showed significant and negative relationships between physical activity counts at the ankle and CCR of the TA/LG muscle pair at the 15 cm (Figure 10C) (r_s = -0.51, p = 0.01) and 20 cm (Figure 10D) (r_s = -0.51, p = 0.02) LSUT step heights. No significant relationships between physical activity counts at the ankle and CCR of the BF/VL muscle pair were observed during the LSUT.

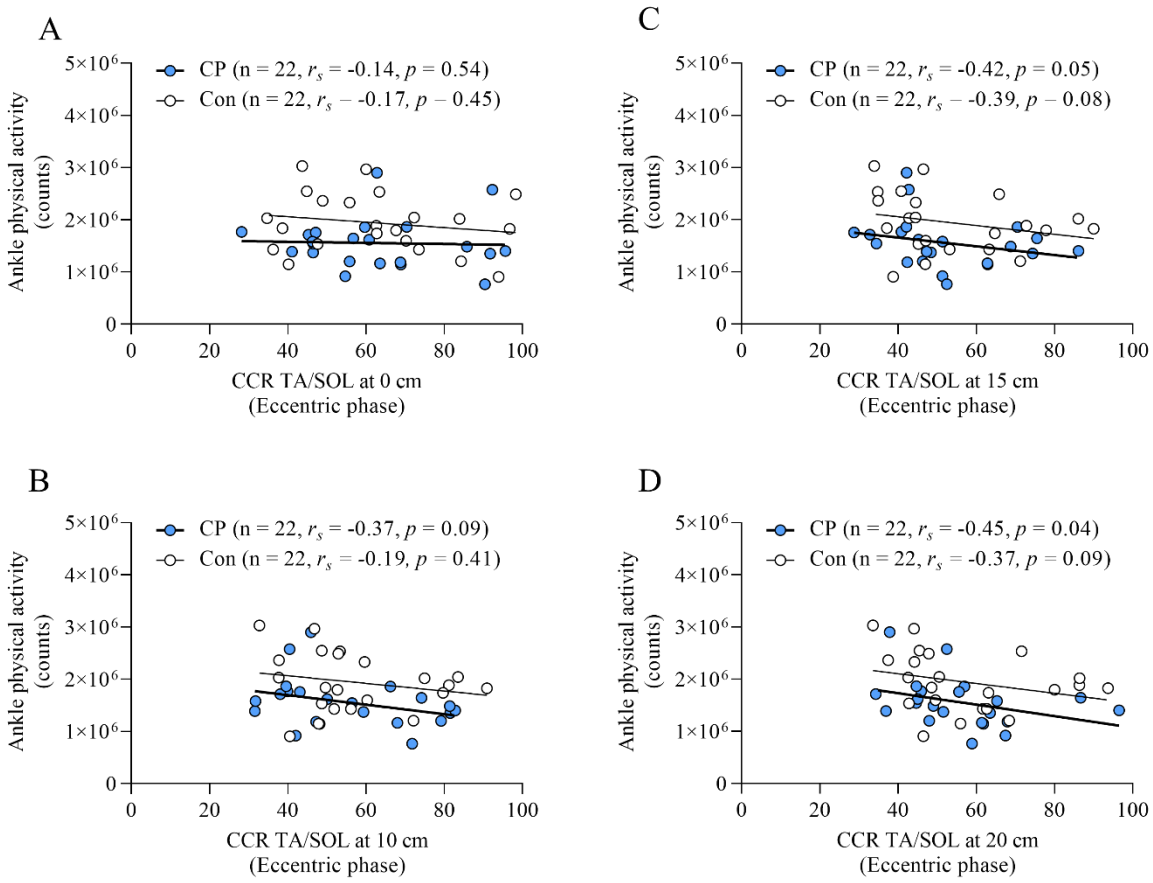

Figure 9. Relationships between tibialis anterior (TA) and soleus (SOL) co-contraction ratios (CCR) during the eccentric phase of the lateral step-up test (LSUT) and physical

activity at the ankle in children with cerebral palsy (CP) and typically developing children (Con).

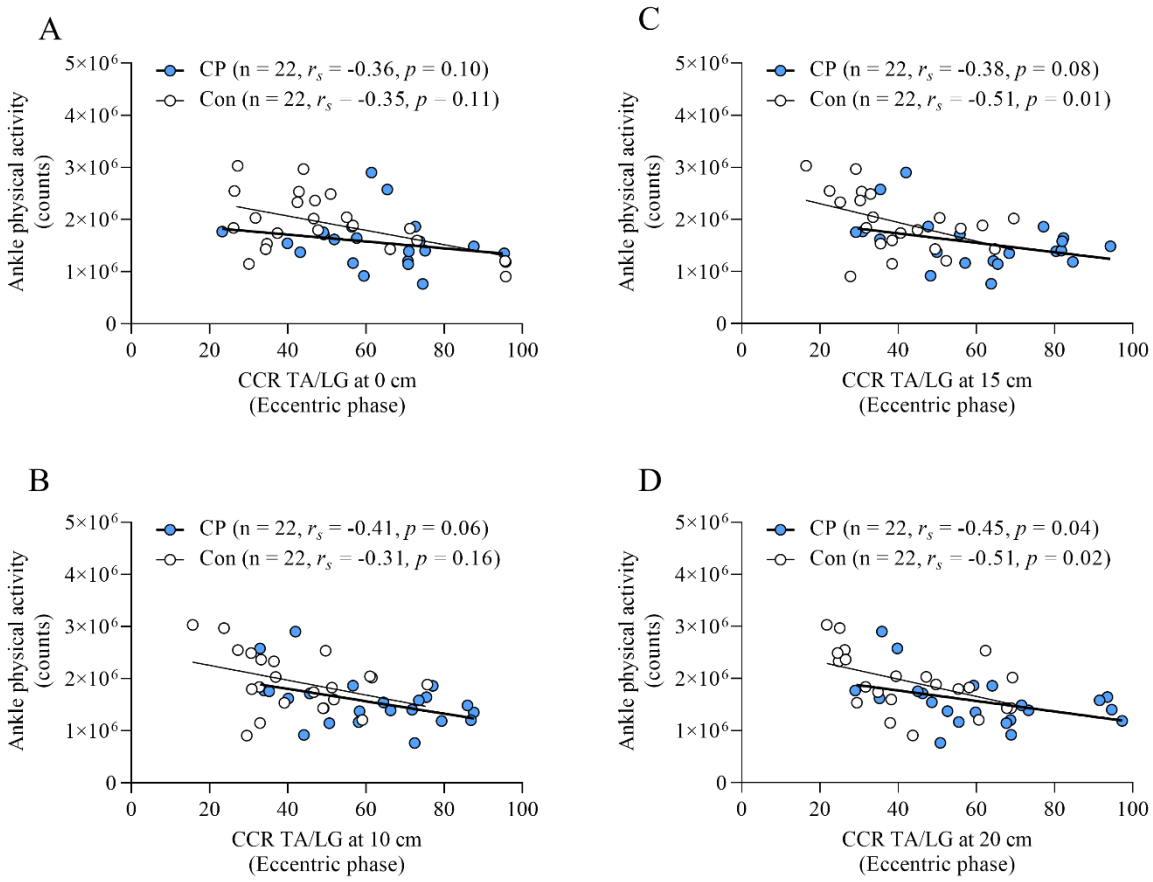

Figure 10. Relationships between tibialis anterior (TA) and lateral gastrocnemius (LG) co-contraction ratios (CCR) during the eccentric phase of the lateral step-up test (LSUT) and physical activity at the ankle in children with cerebral palsy (CP) and typically developing children (Con).

3.4 Discussion

In this study, the relationships between co-contraction, dynamic functional strength and physical activity were assessed in children with CP and typically developing children. One of the primary findings was that children with CP had a lower CCR during the concentric phase of the LSUT in the TA/SOL muscle pair and a higher level of CCR during the eccentric phase of the LSUT in the TA/LG muscle pair. However, both ankle plantar flexor muscle groups displayed increased CCR between the concentric and eccentric phases of the LSUT. Similar to other results, the involvement of both the ankle plantar flexor (TA/SOL and TA/LG) muscle pairs becomes of increased importance during eccentric movement [239]. The same study also suggested that eccentric plantar-flexion strength may be an important contributor to functional ankle instability [239]. More research is needed to confirm whether this is similar in children with CP.

Additionally, children with CP had a higher level of co-contraction in the BF/VL muscle pair during both the concentric and eccentric phases of the LSUT. This could be due to a compensatory mechanism to properly adjust stiffness during the LSUT [240]. In order to compensate for ankle plantar flexor weakness [241, 242], increased co-contraction around the knee joint may serve to increase overall leg stiffness. It has been shown that increased knee co-contraction is positively related to increased gait speed, although metabolically inefficient, in children with CP [185]. It could be that a similar response is provoked during a LSUT and that optimization parameters in children with CP revolve around the accomplishment of a functional demand (i.e. a LSUT repetition) and not on energy efficiency, as previously suggested in the literature [243, 244]. However, further research is needed to confirm this observation.

The CCR results of this study partially support those of previous studies [42, 44, 222, 223] but also shed light on the inherent limitations that CCR contain. If interpretations were to be made according to the general consensus, that is, that an increase or decrease in CCR results from a paired increase or decrease in antagonistic muscle activity, one would assume that the unexpected decrease in CCR in children with CP in the TA/SOL muscle pair during the concentric phase of the LSUT is due to a decrease in antagonistic muscle activity. After assessing the EMG data of both the TA and the SOL, we found this to be true, supporting the theoretical frameworks regarding CCR calculations. The TA/SOL muscle pair does, in fact, show a significant decrease in antagonistic muscle activity compared to typically developing children. However, the same does not apply for the differences in CCR observed during the eccentric phase of the LSUT. In the TA/LG muscle pair, antagonist muscle activity is consistently and significantly lower in children with CP compared to typically developing children (Figure 6A). Nevertheless, CCR is significantly higher during all four of the LSUT step heights in children with CP (Figure 7B). Similar results are observed in the BF/VL muscle pair (Figures 6B & 7C). These results reinforce concerns and precautions found in the literature which should be considered when interpreting CCR [13, 245-247]. It seems that the increase in the CCR observed in this study are influenced in children with CP, to a greater degree, by the lack of ability of agonist muscles to meet a certain level of force rather than the traditional idea of a pathologically derived increase of antagonist muscle activity. This is evident in cases where agonistic activity is significantly lower in children with CP but antagonistic activity does not significantly differ between groups. However, the resulting CCR remain significantly higher in children with CP. Without knowledge of

underlying muscle activity, results would be left up to assumption. Fortunately, EMG data were made available and insight on individual muscle activity allowed for better and more accurate interpretation of results.

Similar to recent studies, our current study agrees that co-contraction may not be a strong indicator of neuromotor pathology as earlier literature has conditioned us to believe [248]. Using the LSUT as a measure of lower limb functional strength and functional ability has been previously supported [249]. In our current study, children with CP were found to be less functionally capable compared to typically developing peers. Contrary to our hypothesis performance outcomes (LSUT repetitions) during the LSUT did not significantly correlate to CCR across any muscle pair or study group. Despite the novelty of the current study, where functional strength was assessed in a dynamic fashion, results seem to be in accordance with previous studies assessing the relationship of co-contraction and muscle strength [227-229]. However, our current study provides implications related to dynamic functional strength which remain limited in the literature [13, 250] and therefore, provides important clinical relevance.

As counterintuitive as these results may seem, it is important to note the heterogeneity of suggestions in the literature. Previous studies have suggested that a primary source of muscle weakness in CP is not increased co-contraction (antagonistic restraint) but rather, that muscle weakness is primarily driven by the inability of the agonist muscles to produce a sufficient level of force [182, 251]. Though the CCR presented in this study do not adequately translate this proposed mechanism underlying functional muscle weakness in children with CP, CCR are clearly influenced by agonist muscle activity. In addition, our current study clearly demonstrates the presence of

functional muscle weakness and lack of functional ability in children with CP compared to typically developing children when evaluating EMG data and performance outcomes during the LSUT. We can assume that these limitations then, inherent to CCR calculations, serve as a major factor in the lack of relation that may still exist between muscle activation patterns and functional strength measures in children with CP. Furthermore, it reinforces the need for further research surrounding the neurophysiology of pathological co-contraction in children with CP. Specifically, the functional benefits of successfully reducing co-contraction levels in children with CP.

Significant negative relationships were, however, observed between physical activity at the ankle and CCR during the LSUT. Individuals with higher CCR participated in less physical activity. Interestingly, significant negative relationships were only observed during the more difficult stages of the LSUT (15 and 20 cm LSUT step heights). The current results suggest that reduced levels of physical activity are associated, to a greater degree, by the deficiencies in agonist muscle activity compared to higher levels of co-contraction in children with CP. Specifically, when the task demands increase such as in the more difficult stages of the LSUT. However, although significant, the correlations were only found to be moderate ($-51 < r_s < -42$). This suggests that physical activity participation is only partially influenced by the ability or inability to properly activate agonist muscles in children with CP. Additionally, irrespective of the underlying mechanisms behind higher CCR in children with CP, higher co-contraction is suggested to result in increased energy expenditure in older populations [166] and in children with CP [15]. The combination of both agonist deficiency and higher energy expenditure as a result of increased CCR, could be a why significant positive

relationships were only observed during the more difficult stages of the LSUT, where the abnormalities are provoked to a greater degree compared to the less difficult stages. In order to further assess these relationships, it is important to classify physical activity participation into intensity categories. If similar results are observed during higher levels of physical activity intensity (vigorous-very vigorous), the results of our current study can be further supported.

As treatments and interventions aim to reduce co-contraction in children with CP, it remains important to determine whether higher levels of co-contraction in children with CP is a primary impairment or simply a form of compensation [119, 248, 250]. Our results provide the opportunity to discuss the functional implications of higher co-contraction in children with CP and whether co-contraction is an effective treatment target in children with CP.

The current study has notable strengths. First, participants were matched for age, sex and race. Therefore, the potential influence of these factors on group differences is minimized. Furthermore, the height, body mass, and BMI of the typically developing children were not different from the 50^{th} age- and sex-based percentiles suggesting that the children were reasonable representatives of the general population. Second, the ability to synchronize kinematic data with EMG data allowed for an accurate discrimination between concentric and eccentric phases for each participant.

The limitations of this study also require discussion. First, the order of step heights during the LSUT was not randomized. Therefore, the effects that LSUT step-heights may have on levels of muscle co-contraction could be confounded by an adaptation effect. It has previously been demonstrated that adaptations in dynamic

stability to perturbations are observed in studies conducting as little as five repeated trials [252]. Whether similar effects are observed during a LSUT remains unclear. Secondly, the use of MEG has inherent limitations. The placement of electrodes, skin resistance and subcutaneous fat can all contribute to variations in EMG response [94]. Although these factors were controlled for as best as possible, possible influence could be present in resulting data.

3.5 Conclusions

The results of this study do not support the idea that muscle co-contraction is a significant contributor to functional muscle weakness in children with CP. Instead, our results suggest that CCR should continue to be interpreted with caution. In this study, CCR were influenced, to a greater degree, from the inability of agonist muscles to meet a required level of force production in children with CP, rather than a pathological increase of antagonist muscle activation. Hence, the idea that CCR accurately depict pathological changes in antagonist muscle activity, is not completely supported by the results of this study. In addition, physical activity was significantly and negatively related to CCR during the more difficult stages of the LSUT. Individuals with higher CCR participated less in physical activity. Considering that CCR were influenced, to a greater degree, by the inability of agonist muscles to properly activate, it can be inferred that physical activity participation is partially mediated by agonist failure rather than increased levels of muscle co-contraction in children with CP. Results of this study also warrant further research in order to evaluate the potential, if any, functional benefits that may result from successfully reducing pathological co-contraction in children with CP.

3.6 Acknowledgment

We thank all the participants and their families for their support. JL and CMM designed the study; JL, SJ and SW conducted the data collection; JL, SJ, SW and CMM analyzed the data; JL and CMM wrote the manuscript. All authors edited and approved the final manuscript. The authors declare that they have no conflicts of interest. This study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Center for Medical Rehabilitation Research (grant numbers HD050530, HD071397 and HD090126), and the University of Georgia Athletic Association.

CHAPTER 4

PREFRONTAL HEMODYNAMIC ACTIVITY AND MUSCLE CO-CONTRACTION IN CHIDLREN WITH CEREBRAL PALSY

4.1 Introduction

Throughout daily living, individuals are presented with novel environments requiring motor learning and motor adaptation. Muscle co-contraction is one of the primary mechanisms that the human body relies on to adapt to these new conditions [48]. In fact, certain levels of muscle co-contraction are essential during locomotion even after adaptation to certain motor tasks has been achieved [179]. The degree of muscle co-contraction is then dependent on the specific demands of the motor task and is modulated by the central nervous system (CNS) [253]. However, children with CP have previously demonstrated excessive co-contraction during movement compared to typically developing controls [42, 44, 222, 223]. Due to the etiology of their brain injury [2], children with CP are found to be less capable of effectively controlling co-contraction. Disruption to the neural pathways responsible for reciprocal inhibition are thought to be a major cause of the abnormal regulation observed [74]. This pathological impairment, along with other symptoms, typically induces significant limitations on the ability to carry out daily activities in children with CP [7].

Although it is observed peripherally, it is well understood that muscle co-contraction is centrally mediated [48]. Milner et al. observed the presence of cerebellar-

parietal-frontal networks regulating muscle co-contraction [254]. Although the cerebellum is a primary component, it is plausible that other brain areas are associated with motor adaptation mechanisms including muscle co-contraction, especially areas which have been observed to correlate strongly with cerebellar activity such as the prefrontal cortex (PFC). Previous research has revealed the presence of a strongly coordinated cerebello-prefrontal pathway during sensorimotor learning and adaptation [255, 256]. Although the functional co-participation of the cerebrellum and prefrontal cortex is clear, less is known about the mechanisms through which they interact. Nevertheless, the joint operation of these two brain structures can only result as advantageous in terms of hastening overall motor learning, when learning is defined as improved task performance [256]. Understanding the role that the PFC has can potentially shed light on the mechanisms regulating sensorimotor adaptation processes such as muscle co-contraction.

Using fNIRS, brain activity of the prefrontal cortex (PFC) can effectively be assessed during dynamic conditions [56] with a better temporal resolution (12.5 Hz, typically) compared to fMRI (0.3-0.6 Hz) [55]. During abnormal motor function, the PFC is suggested to have an important role [257-259]. More specifically, the PFC becomes more involved as motor task complexity and the need to modulate locomotion speed increases [206, 260]. This has been observed to be especially true in clinical populations, where the need for compensation strategies and/or selective attention results in altered patterns of activation of brain areas, such as the PFC [261]. Interestingly, the literature has also proposed that the increase of muscle co-contraction primarily serves as a compensatory strategy in clinical populations [262, 263] including children with CP [13].

However, the relationship between the PFC and muscle co-contraction, to our knowledge, has not yet been explored. Understanding the underlying mechanisms of this centrally-mediated peripheral behavior is therefore warranted. Findings could provide useful information on the neurophysiological basis of excessive co-contraction in CP, the implications that it may have on functional ability and whether successfully reducing co-contraction is necessary in children with CP.

Therefore, the purposes of this study are 1) to determine the relationship between PFC cortical hemodynamic activation and muscle co-contraction during a LSUT in children with CP and typically developing children, and 2) to determine the relationship between PFC hemodynamic activation and LSUT performance in children with CP and typically developing children.

4.2 Methods

Participants

Fifteen children with spastic CP who were able to ambulate without an assistive device, and who were recruited to participate in a clinical trial were recruited to participate in this study. The clinical trial examined the effect of mild vibration on muscle, balance, and physical activity in children with CP. For the clinical trial, children with CP were recruited from physician offices, rehabilitation centers, schools, and social media groups using flyers, and through advertisements in local newspapers. Typically developing children age- (± 1.5 y) and sex-matched to children with CP and between the 5th and 95th age-and sex-based percentiles for height and body mass were recruited to participate as controls from schools using flyers and by word-of-mouth. Inclusion criteria

for children with CP included those who were 5 to 11 years of age, had spasticity, and were able to ambulate without an assistive device. Inclusion criteria for controls included no history of neurological or motor disorders, not taking medications that affect musculoskeletal health and not participating in high level sports. The study was approved by the Institutional Review Board of the University of Georgia. Informed consent was obtained from the parent or legal guardian and assent was obtained from the participant, if able, before data collection was initiated.

Gross Motor Classification System (GMFCS)

Gross motor function in children with CP was assessed using the gross motor classification system (GMFCS), which is based on a five-point scale. There is a progressive increase in motor function deficit with higher ratings [70]. Briefly, a GMFCS I classification indicates an ability to walk indoors and outdoors and climb stairs with no limitations. Activities involving running and jumping can be performed, but with limited speed, balance and coordination. A GMFCS V classification indicates severe limitations and an inability to ambulate [233]. In order to properly classify each participant, children with CP were asked to complete a series of tasks including running, jumping and stair climbing.

Anthropometrics

Height and body mass were measured while the children were wearing shorts and a tee shirt, and were without socks, shoes, or braces. Height was measured using a stadiometer (Seca 217; Seca GmbH & Co. KG., Hamburg, Germany) to the nearest 0.1

cm. Body mass was measured using a digital scale (Detecto, 6550, Cardinal Scale, Webb City, MO) to the nearest 0.1 kg. Body mass index (BMI) was calculated as body mass (kg)/ height (m^2).

Lateral step-up test (LSUT)

The LSUT procedure was explained to participants prior to testing. At the start of the test, feet were approximately shoulder-width apart. The more affected lower extremity in children with CP and the non-dominant lower extremity in typically developing children were considered the tested limb. Participants were instructed to lift the resting limb and place it next to the tested limb, which was the concentric phase and then return the resting limb to its original position, which was the eccentric phase. Participants were also asked to keep their hips, knees, and feet facing forward and not rotate while performing the test.

The LSUT consisted of 4 trials, 20 seconds per trial, and a progressive increase in step height for each successive trial (0, 10, 15, and 20 cm, respectively). For the 10, 15, and 20 cm trials, the foot of the more affected lower extremity in children with CP and the non-dominant lower extremity in typically developing children was placed on a step platform. Participants were instructed to perform as many repetitions as possible without any support. Repetitions were only considered successful if the heel of the non-tested limb touched the floor and a return to the original position was accomplished with no support. Steps that required assistance were counted, but as an unsuccessful repetition. Participants were allowed to perform one or two practice bouts prior to each trial to ensure that they understood the test protocol. Physical demonstration of optimal

performance was also provided to the participants by test administrators. Each LSUT trial lasted 20 seconds and was preceded by a rest period of 20 seconds, in which the child was instructed to stand in their testing position "as still as possible", while focusing on an "X" sign on the wall located at eye level and 4.5 meters away. A graphical representation of the LSUT is presented in Figure 1A. The single-trial block paradigm design of the LSUT is presented in Figure 1B.

Performance results of the LSUT were calculated using a weighted scoring system, based on difficulty (i.e. step height) and accounting for all attempts. Steps that required assistance or were done incorrectly were counted, but adjusted down by a multiplier. Assisted or incorrect steps at 0 cm were multiplied by 0.05, 10 cm by 0.10, at 15 cm by 0.15, and assisted or incomplete steps at 20 cm were multiplied by 0.20 and added to the total steps for each height, respectively.

Electromyography (EMG) data collection

Each participant had the skin beneath the location of the EMG sensor abraded and cleaned with an alcohol prep pad to ensure proper contact with the corresponding electrodes. Electromyography (EMG) sensors (Delsys Inc., Natick, MA) were placed according to each target muscle. For this study, the tibialis anterior (TA), soleus (SOL), lateral gastrocnemius (LG), biceps femoris (BF) and vastus lateralis (VL) muscles were assessed. Electrodes corresponding to the TA were placed at 1/3 of the line between the tip of the fibula and the tip of the medial malleolus. The SOL sensor was placed at 2/3 of the line between the medial condyle of the femur to the medial malleolus. For the LG, electrodes were placed at 1/3 of the line between the head of the fibula and the calcaneus.

The BF electrodes were placed at 50% of the line between the ischial tuberosity and lateral epicondyle of the tibia. Lastly, the VL electrodes were placed at the 2/3 of the line from the anterior superior iliac spine to the superior lateral side of the patella in the direction of the muscle fibers. The sample frequency used for data collection as set at 2000 Hz.

Electromyography (EMG) data processing

EMG data were mean offset, band-pass filtered (fourth order Butterworth, cut-off frequency of 20-400 Hz), rectified, low-pass filtered (fourth order Butterworth, cut-off frequency of 10 Hz) [235]. A mean offset normalization was chosen based on recommendations found in the literature [236]. This type of EMG normalization sets the amplitude normalization to the mean value found within each trial, in this case, each LSUT repetition. The main effect of this type of EMG normalization is reduced variability and reduced standard deviation range. A maximum voluntary contraction normalization was not found to be suitable considering our studied population. Maximum voluntary contraction normalization is recommended only in studies done with healthy and trained subjects [236].

Quantification of muscle co-contraction

A co-contraction ratio (CCR) was calculated for both the concentric and eccentric phases of the LSUT for each of the four LSUT step heights (0, 10, 15 and 20 cm, respectively) across three muscle pairs: TA/SOL, TA/LG and BF/VL using the following formula [237]:

$$CCR = 2 * \frac{sEMGantagonist}{sEMGagonist + sEMGantagonist} * 100$$

Where *sEMGantagonist* represents the EMG signal with lower average magnitude and *sEMGagonist* represents the EMG signal with the higher average magnitude. In this formula, the antagonist activity is normalized in relation to the mean total muscle activity. Next, the resulting value is multiplied by two to counterbalance the activity of the agonist muscle [220]. A CCR of 100 would represent equal activity of both the agonist and antagonist muscles while a CCR of 0 would represent agonist activation only.

Electromyography (2000 Hz, Delsys Inc.) data were synced with kinematic data via motion capture software (100 Hz, Qualisys, Lincolnshire, IL) which used the CAST Full Body model (Qualisys, Lincolnshire, IL). Data were further processed using Visual 3D (C-motion, Ontario, Canada) in order to identify the heel strike and push-off events of the non-tested limb for each participant. The identified events were then used to discriminate between the concentric and eccentric phases of the LSUT. The concentric phase of the LSUT represents the time of foot push-off from the ground to the time the foot lands on the step. The eccentric phase represents the time from stepping off of the platform until contact of the heel is made with the floor. A graphical representation of the concentric and eccentric phases can be found in figure 1A.

fNIRS data acquisition

Two, portable, continuous wave fNIRS devices (Portalite, Artinis Medical Systems, Einsteinweg, The Netherlands) using two different wavelengths (~750 and ~850

nm) were used for this study. Data were sampled at 50 Hz. Each system consisted of three LED optode sources placed at fixed distances of 30, 35, and 40 mm, respectively from a single optode receiver. For this study, only data from the 30 mm source-detector pair was used, consistent with previous literature [264], and in accordance with the manufacturer recommendations. Both devices were placed on the children's forehead, approximately 10% of the nasion-inion distance from the nasion and 7% of the head circumference to the right and left of the midline. These areas correspond roughly to Brodmann's areas 9 and 10 or 10-20 EEG locations left frontal pole (Fp1) and right frontal pole (Fp2) [265]. The PFC hemispheres were identified as ipsilateral and contralateral based on the lower limb dominance of each participant. The devices were secured in place using double-sided adhesive tape and were covered using black felt to ensure minimal intrusion of external light and loss of system-emitted light during data collection. Oxysoft software (version 3.2.51 x 64, Artinis Medical Systems, Einsteinweg, The Netherlands) was used for data collection and real-time data visualization. Start-of-trial, end-of-trial, and rest-period events were manually marked for each trial according to a standardized protocol for all participants. The fNIRS data collection setup is presented in Figure 11.

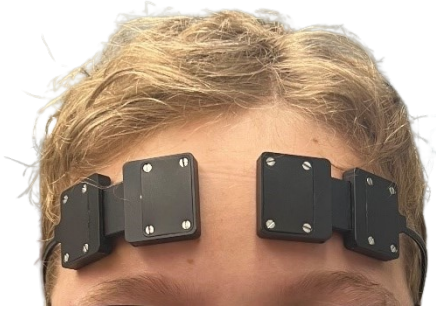

Figure 11. An example of the fNIRS placement over the participants' forehead to assess hemodynamic activation of the prefrontal cortex in each hemisphere.

fNIRS data processing

The data collected from the fNIRS systems were analyzed using MATLAB (MathWorks, Natick, MA, United States of America) and the HOMER3 package [266] prior to statistical analyses. First, raw light voltage intensities were converted to changes in optical density. Next, correction for motion artifacts was performed using a hybrid technique, SplineSG, as described by Jahani et. al. [267]. This hybrid method takes advantage of different correction algorithms. The method first identifies the baseline shifts and corrects them using a spline interpolation technique, as described by Scholkmann et. al. [268]. The remaining spikes are corrected by smoothing techniques: Savitzky–Golay (SG) filtering or robust locally weighted regression and smoothing. After correcting for motion artifacts, the optical density values were filtered using a low-pass filter set at 0.5 Hz to account for physiological noise, such as heart rate [269]. After filtering the data, optical densities were converted into relative oxygenated hemoglobin (HbO) concentration changes using the modified Beer-Lambert Law, with a constant partial path-length factor of 1. All trials were baseline corrected using the last 5 seconds of rest preceding each trial. Relative HbO concentration changes (Δ HbO) were averaged

across the entire 20-second trial duration for each of the four LSUT trials. The signal processing techniques were performed in accordance to recommended practices for fNIRS studies [270]. Finally, the Δ HbO averages obtained for each trial and hemisphere were used for further statistical analysis. For a graphic representation of the fNIRS processing steps, please refer to Figure 12.

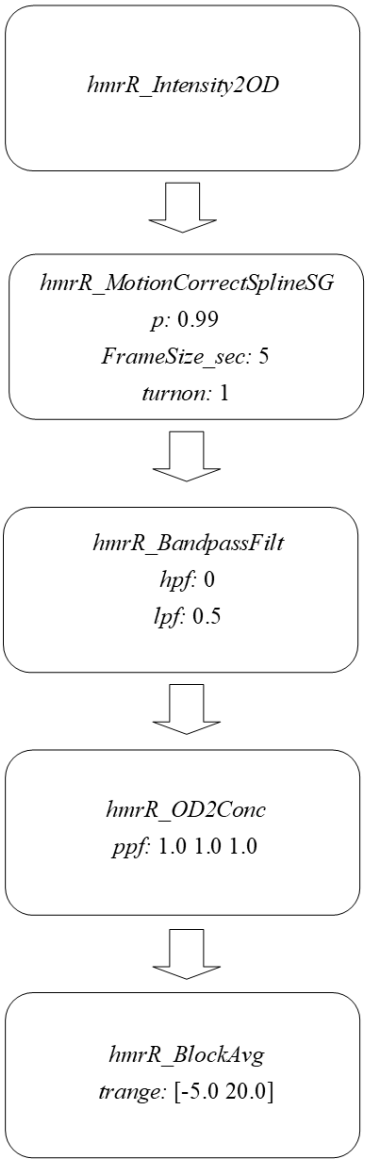

Figure 12. A flowchart of the fNIRS data processing using the HOMER3 software.

Statistical analysis

All statistical analyses were conducted using SPSS Statistics 24 (IBM Corp., Armonk, NY). Data were checked for normality by examining skewness, kurtosis, and the Shapiro-Wilk test. Group differences in physical characteristics were determined using an independent t-test if the data were normally distributed and a Mann-Whitney *U* test if the data were non-normally distributed. One sample t-tests were used to determine whether the height, body mass, and BMI percentiles were different from the 50th age- and sex-based percentiles in the children with CP and in the controls. Values are presented as mean ± SD unless stated otherwise.

A univariate generalized linear model (GLM) was used to assess group effects between PFC hemodynamic activation (Δ HbO) in the ipsi- and contra-lateral hemispheres, CCR of each muscle pair and LSUT repetitions across all four step heights. The univariate GLM was also used to assess LSUT step height effects on the degree of PFC activation between groups in both PFC hemispheres and LSUT phases, LSUT step height effects on the CCR of each muscle pair in both LSUT phases, and LSUT step height effects on the number of repetitions completed between groups. Independent t-tests were conducted to assess group differences in LSUT repetitions and PFC hemodynamic activation in the contra- and ispi-lateral hemispheres at specific LSUT step heights. Mann-Whitney *U* tests were used to assess group differences in CCR at specific LSUT step heights. Spearman correlations were conducted to assess relationships between CCR and LSUT repetitions, and PFC hemodynamic activity and CCR in children with CP and controls. Pearson correlations were conducted to assess PFC hemodynamic activity and LSUT repetitions in children with CP and controls. For all

statistical tests, the alpha level was set at 0.05. The magnitude of the effects was determined using Cohen's d (*d*), with 0.2, 0.5, and 0.8 representing small, medium, and large effect sizes, respectively [238].

4.3 Results

Participant characteristics and LSUT performance

Fifteen children with spastic CP (GMFCS level I-II) and 15 typically developing children participated in the study. There were no significant group differences in age, height, body mass, BMI, height percentile, body mass percentile, or BMI percentile ($p > 0.05$) (Table 2). Furthermore, height percentile, body mass percentile, and BMI percentile were not different from the 50th age-and sex-based percentiles in either group.

Table 2. Physical characteristics in children with cerebral palsy (CP) and in typically developing children (Con).

	CP (n = 15)	Con (n = 15)	*d*	*p*
Age (years)	9.3 ± 2.0	9.4 ± 1.9	0.03	0.94
Sex (M/F)	8/7	8/7	—	—
Height (m)	1.33 ± 0.13	1.38 ± 0.12	0.03	0.37
Height (%)*	44 ± 33	62 ± 25	0.61	0.11
Body mass (kg)	30.2 ± 7.6	33.5 ± 11.0	0.35	0.34
Body mass (%)	44 ± 33	56 ± 32	0.37	0.35
BMI	16.8 ± 2.2	17.3 ± 3.3	0.18	0.61
BMI (%)	48 ± 33	50 ± 35	0.06	0.83
Dominant limb (L/R)	7/8	1/14	—	—
GMFCS (I/II)	13/2	—	—	—

Values are mean ± SD. GMFCS, Gross Motor Function Classification System, BMI, body mass index. % for height, body mass, and BMI reflect the percentile relative to age-

and sex-based norms. *Non-normally distributed and analyzed using a Mann-Whitney *U* test.

There was a significant step-height effect during the LSUT with fewer repetitions completed as step height increased ($p < 0.001$) (Figure 13). There was also a significant group effect with children with CP completing fewer repetitions than controls across all step heights ($p < 0.001$) (Figure 13).

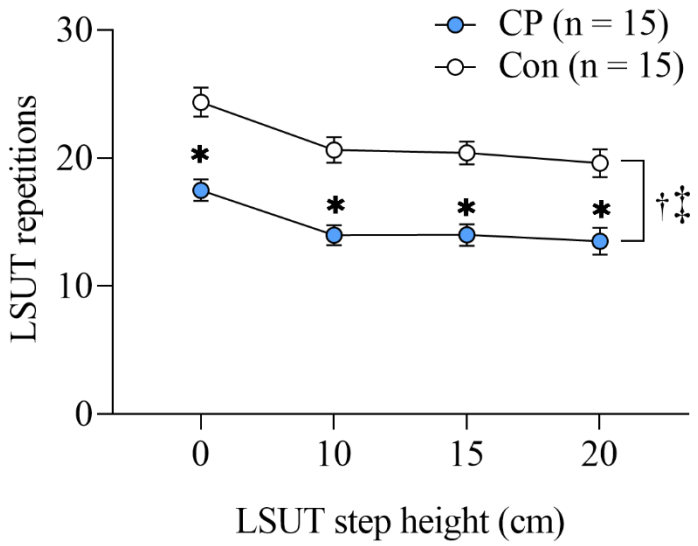

Figure 13. Repetitions at each step height of the lateral step-up test (LSUT) in children with cerebral palsy (CP) and in typically developing children (Con). Values are mean ± SE. †Group effect, $p = < 0.001$; ‡LSUT step height effect $p < 0.05$; *Difference between groups at a specific height, $p < 0.001$.

Evaluation of muscle co-contraction during the LSUT

Concentric phase

Muscle CCR of the BF/VL muscle pair were significantly lower in children with CP compared to controls during the LSUT (Figure 14C) ($p < 0.01$). Specific differences were only observed between children with CP and controls in the BF/VL muscle pair at the 20 cm LSUT step heights (Figure 14C) ($p = 0.03$). No significant CCR group effects were observed in the TA/SOL or the TA/LG muscle pairs during the LSUT (Figure 14A & B) (all $p > 0.05$).

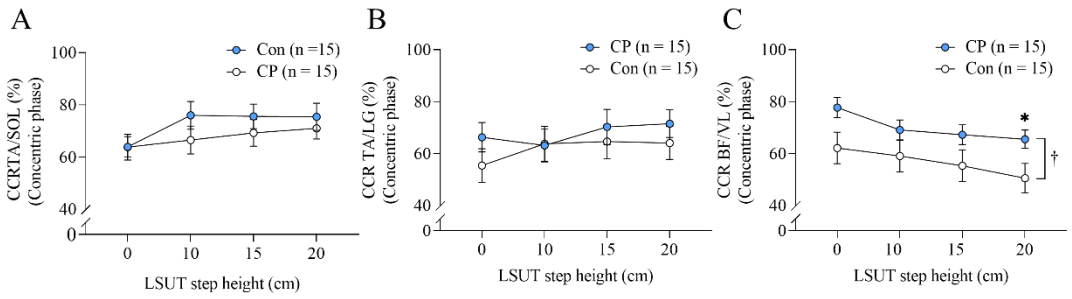

Figure 14. Line plots display muscle co-contraction ratios (CCR) for each muscle pair in the leg (A & B) and thigh (C) across individual LSUT step heights during the concentric phase of the LSUT. Values are mean ± SE. †Group effect, $p < 0.05$; *Different from controls (Con), $p < 0.05$.

Eccentric phase

Children with CP had significantly higher muscle CCR compared to controls in the TA/LG and BF/VL muscle pairs during the eccentric phase of the LSUT (Figures 15B & C) (all $p < 0.01$). Additionally, a significant step height effect was observed in the BF/VL muscle pair where CCR were decreased as LSUt step height increased (Figure

15C) ($p < 0.05$). Specific differences were observed between groups in the CCR of the TA/LG at the 10, 15 and 20 cm LSUT step heights (Figure 15B) (all $p < 0.05$). Specific differences in BF/VL CCR were also observed at the 15 and 20 cm step heights (Figure 15C) (all $p < 0.05$).

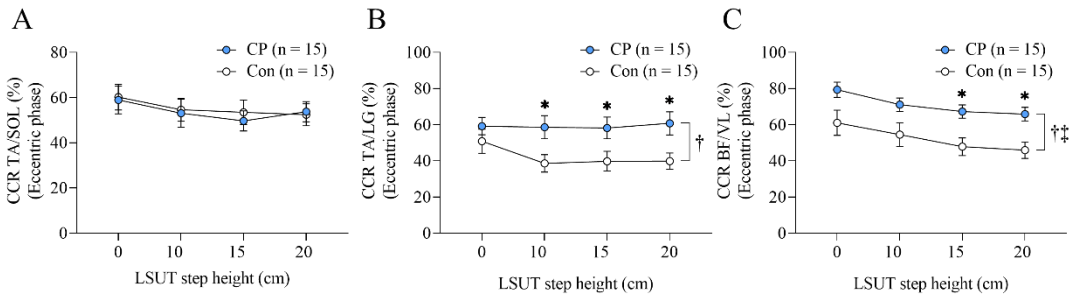

Figure 15. Line plots display muscle co-contraction ratios (CCR) for each muscle pair in the leg (A & B) and thigh (C) across individual LSUT step heights during the eccentric phase of the LSUT. Values are mean ± SE. †Group effect, $p < 0.05$; *Different from controls (Con), $p < 0.05$.

Evaluation of prefrontal hemodynamic activity during the LSUT

A significant group effect was observed in prefrontal hemodynamic activity of the contralateral hemisphere ($p < 0.01$) and ipsilateral hemisphere ($p = 0.05$), across all LSUT step heights (Figure 16). Children with CP had significantly lower PFC hemodynamic activation (60.65 ± 148.68 uM.mm) compared to controls (137.59 ± 161.96 uM.mm) in the contralateral hemisphere of the PFC (Figure 16A) ($p < 0.01$). Similarly, children with CP also had significantly lower PFC hemodynamic activation in

ipsilateral hemisphere of the PFC (106.08 ± 168.31 uM.mm) compared to controls (169.80 ± 184.13 uM.mm) (Figure 16B) ($p = 0.05$). Specific differences in PFC hemodynamic activity between groups were only observed at the 20 cm LSUT step height in the contralateral hemisphere (Figure 16A) ($p = 0.05$).

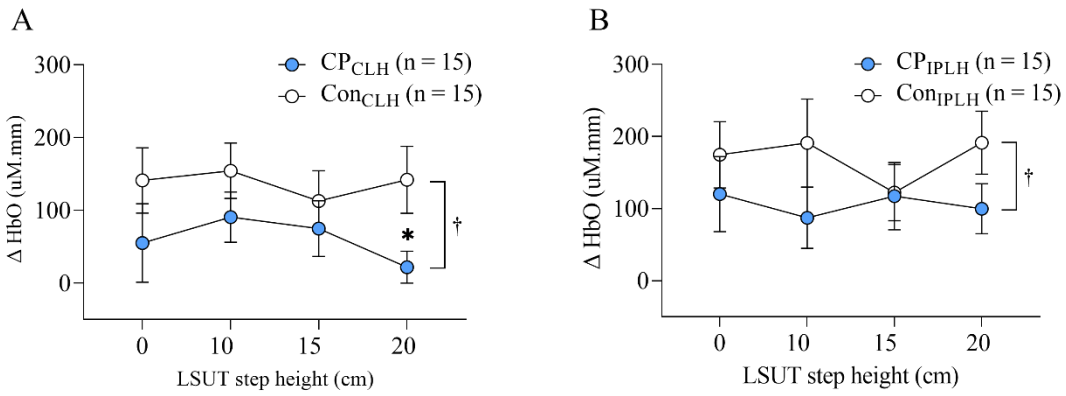

Figure 16. Prefrontal cortex oxygenated hemoglobin (Δ HbO) in children with cerebral palsy (CP) and in typically developing children (Con) at each step height of a lateral step-up test (LSUT) in the A) contralateral hemisphere (CLH) and B) ipsilateral hemisphere (IPLH). Values are mean ± SE and are corrected for HbO at rest. † Group effect, $p < 0.01$; *Difference between groups at a specific height, $p = 0.04$.

Prefrontal hemodynamic activity and its relationship to LSUT performance

Typically developing children only had significant relationships between the number of LSUT repetitions completed and contralateral PFC hemodynamic activation at the 10 ($r = -0.63$, $p = 0.02$) and 20 cm ($r = 0.56$, $p = 0.04$) LSUT step heights (Figure 17B & D) (all $p < 0.05$). Children with CP only had significant and positive relationships

between ipsilateral PFC hemodynamic activation and LSUT repetitions during the 0 cm step height (Figure 18A) ($r = 0.55$, $p = 0.03$).

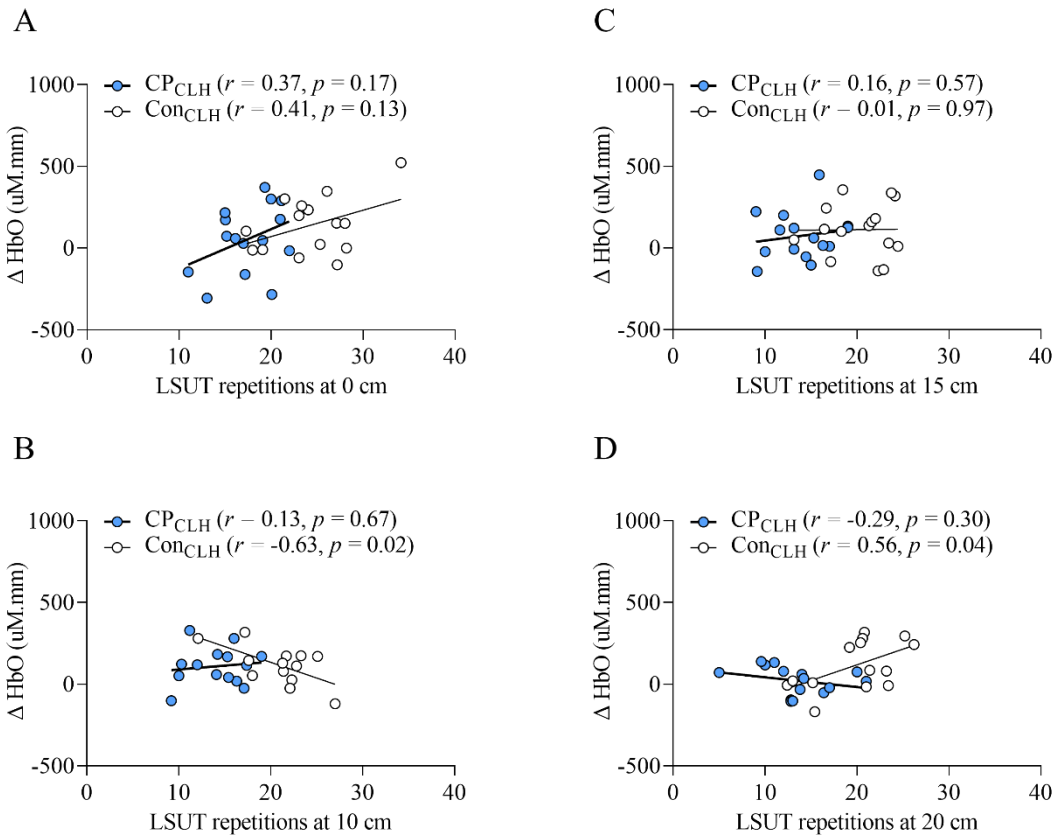

Figure 17. Comparison of contralateral (CLH) prefrontal hemodynamic activation (Δ HbO) and LSUT repetitions completed in children with cerebral palsy (CP) and in typically developing children (Con).

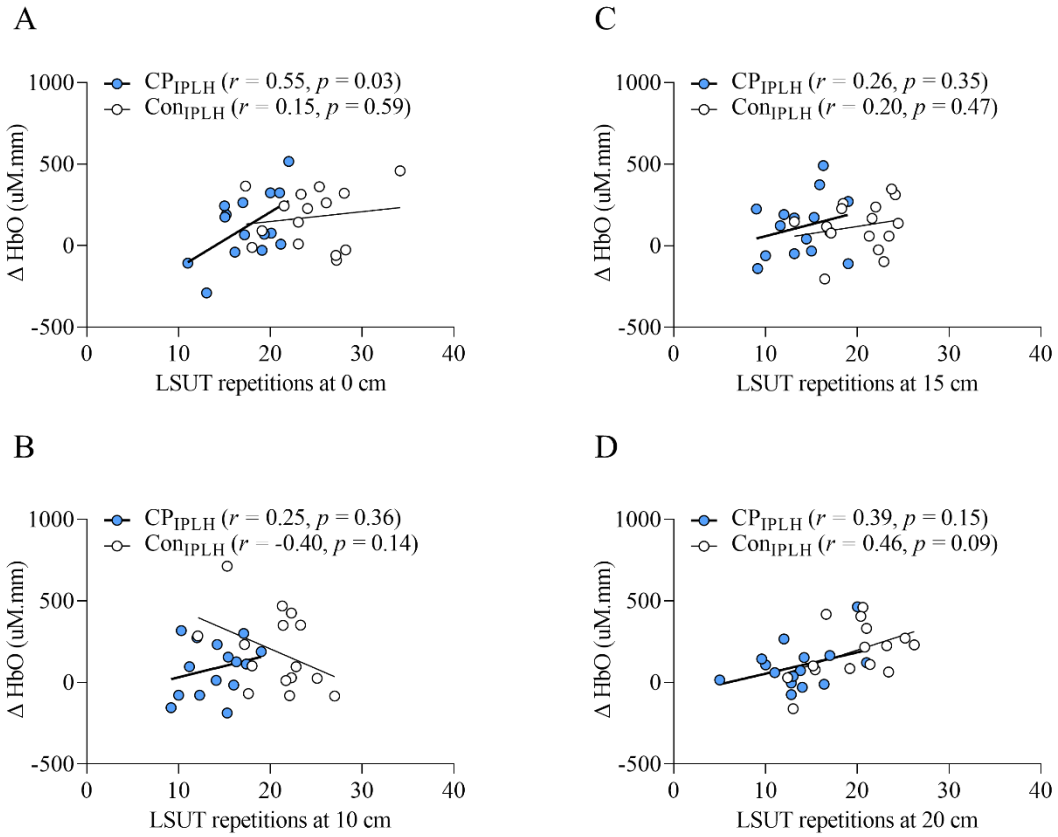

Figure 18. Comparison of ipsilateral hemisphere (IPLH) prefrontal hemodynamic activation (Δ HbO) and LSUT repetitions completed in children with cerebral palsy (CP) and in typically developing children (Con).

Relationships between prefrontal hemodynamic activation and lower limb muscle co-contraction during the LSUT

Concentric phase

Children with CP showed a positive relationship between prefrontal hemodynamic activation of the ipsilateral hemisphere and BF/VL CCR which grew stronger as the LSUT progressed in difficulty (Figures 19 A-D). Children with CP had

significant and positive relationships between prefrontal hemodynamic activation of the ipsilateral hemisphere and BF/VL CCR at the 15 cm (r_s = 0.64, p = 0.01) and 20 cm (r_s = 0.59, p = 0.02) LSUT step heights (Figures 19C&D)

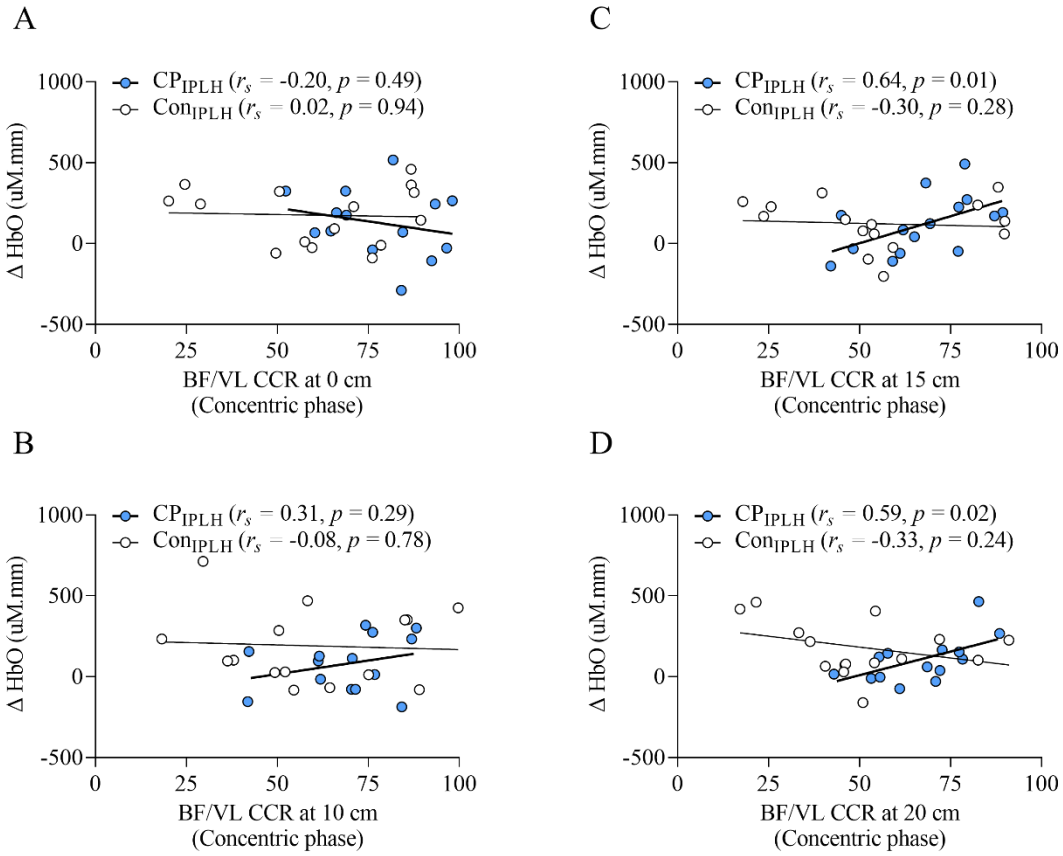

Figure 19. Comparison of prefrontal hemodynamic activation (Δ HbO) in the ipsilateral hemisphere (IPLH) and muscle co-contraction (CCR) in the biceps fermoris/vastus lateralis (BF/VL) muscle pair during the concentric phase of the lateral step-up test (LSUT) in children with cerebral palsy (CP) and typically developing children (Con).

Eccentric phase

Controls had a significantly positive relationship between prefrontal hemodynamic activation of the contralateral hemisphere and CCR of the TA/LG muscle pair at the 10 cm step height (Figure 20B) (r_s = 0.58, p = 0.04).

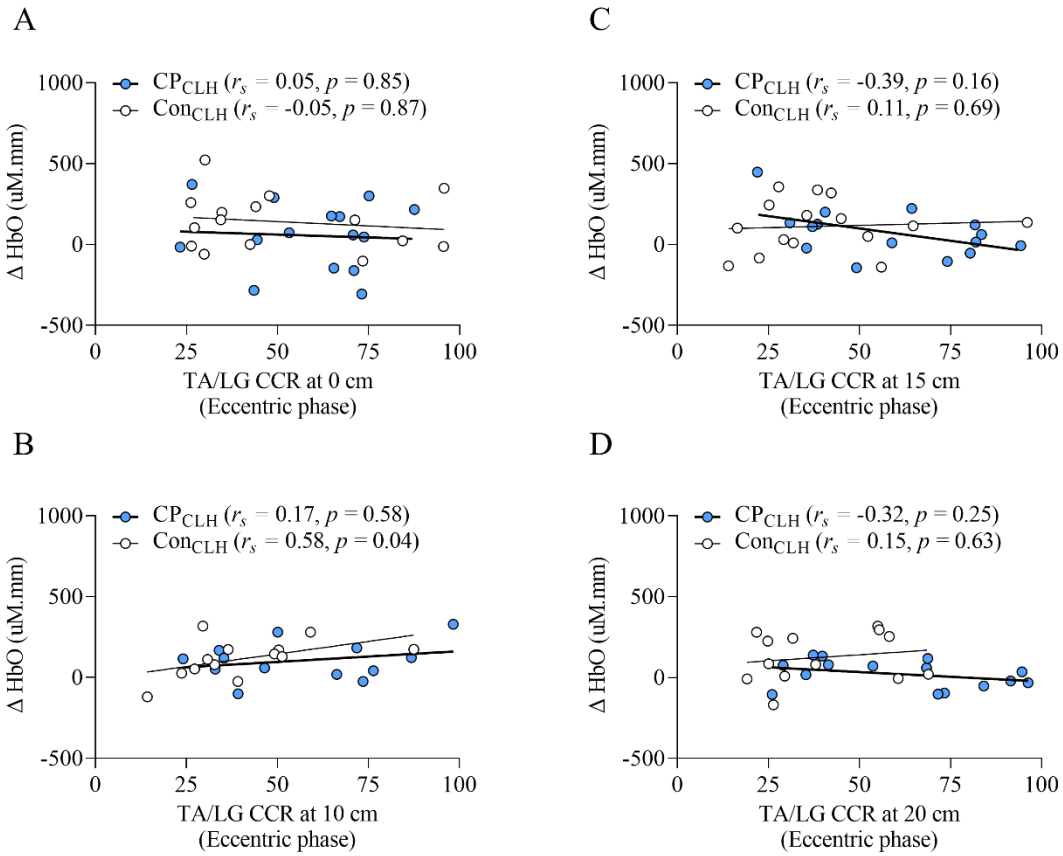

Figure 20. Comparison of prefrontal hemodynamic activation (Δ HbO) in the contralateral hemisphere (CLH) and muscle co-contraction (CCR) in the tibialis anterior/lateral gastrocnemius (TA/LG) muscle pair during the eccentric phase of the lateral step-up test (LSUT) in children with cerebral palsy (CP) and typically developing children (Con).

Children with CP had a significantly positive relationship between prefrontal hemodynamic activation of the contralateral hemisphere and CCR of the BF/VL at the 15 cm step height (Figure 21C) (r_s = 0.51, p = 0.05). No significant relationships were observed between prefrontal hemodynamic activation of the ipsilateral hemisphere and muscle co-contraction in children with CP or controls during the eccentric phase of the LSUT (all $p < 0.05$).

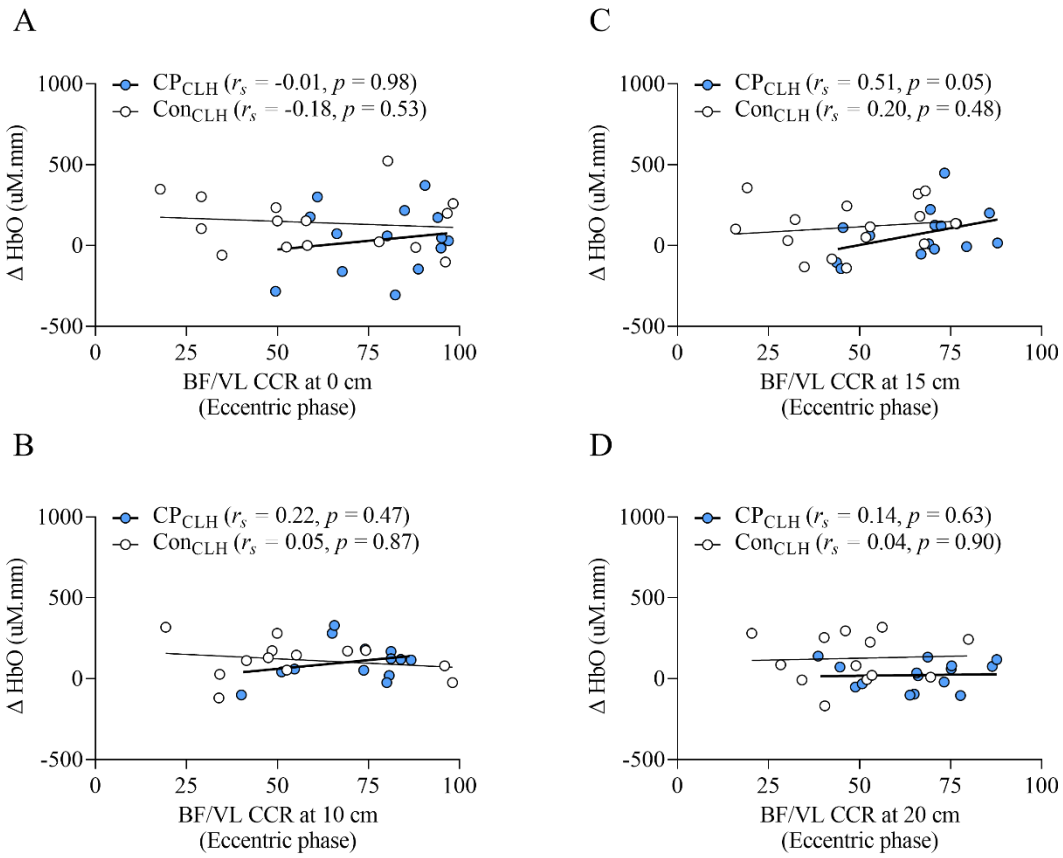

Figure 21. Comparison of prefrontal hemodynamic activation (Δ HbO) in the contralateral hemisphere (CLH) and muscle co-contraction (CCR) in the biceps femoris/vastus lateralis (BF/VL) muscle pair during the eccentric phase of the lateral

step-up test (LSUT) in children with cerebral palsy (CP) and typically developing children (Con).

4.4 Discussion

A primary aim of this study was to assess the relationships between prefrontal hemodynamic activation and lower limb functional strength in children with CP compared to typically developing children. One of the primary findings was that both children with CP and typically developing children showed positive relationship between prefrontal hemodynamic activation and functional strength, reflected by LSUT repetitions completed. However, significant positive relationship was observed during the less difficult stages of the LSUT in children with CP and during the most difficult stages in typically developing children.

The transient hypofrontality hypothesis [271] can begin to help understand potential mechanisms involved in this observed differences in prefrontal hemodynamic activation between groups. According to the transient hypofrontality hypothesis, extensive neural activation is required to run motor patterns, assimilate sensory inputs, and coordinate autonomic regulation during sustained movement. The increase in demand for neural resources results in a decrease in cortical activity in brain structures, such as the PFC, that are not directly involved in controlling motor output [271]. Results of this study would suggest that typically developing children present sufficient neural resources or enough previously acquired motor control to reject the need for PFC recruitment until the more difficult stages of the LSUT, where perturbations may provoke a need for error feedback learning. On the contrary, children with CP seem to depend to a

greater degree on prefrontal resources during the early, less difficult stages of the LSUT. It could be that the perturbations even during the less difficult stages of the LSUT are enough to begin an error feedback loop in the prefrontal cortex in children with CP but as task difficulty increases, so does the need for other, primary motor, areas of the brain causing a shift in neural resource recruitment even though motor control may not fully be acquired. Interestingly, children with CP only had significant positive relationship between PFC hemodynamic activity of the ipsilateral hemisphere while typically developing children showed significant positive relationship in the contralateral hemisphere. The observations of our current study suggest that children with CP not only depend on cognitive resources during different task difficulties compared to typically developing children, but that resources within the PFC, when required, also differ. Further research is needed to better understand the underlying mechanisms behind the differences of prefrontal recruitment.

This study also demonstrated that CCR and prefrontal hemodynamic activity were significantly and positively related in both study groups. Furthermore, significant positive relationships were observed during the more difficult stages of the LSUT in children with CP and during the less difficult stages in typically developing children. Previous neuroimaging studies have demonstrated that the cerebellum is a primary mediator of muscle co-contraction [48] and that the PFC works in conjunction during the adaptation phase of motor learning which is dominated by feedback error learning [272]. It can therefore be speculated that children with CP depend, to a greater degree, on cognitive brain structures, such as the PFC, compared to typically developing children in order to reach adequate motor adaptation during the LSUT. This dependency becomes stronger as

the task demands of the LSUT increase. The fact that typically developing children demonstrate similar patterns but during the early, less difficult stages of the LSUT, suggests that muscle co-contraction is being regulated as expected [48], where muscle co-contraction is properly regulated and the requirement for it decreases as the LSUT progresses.

Moreover, the significant positive relationships between CCR and prefrontal hemodynamic activation demonstrated to differ between the concentric and eccentric phases of the LSUT. Both children with CP and typically developing children had significant relationship in the contralateral hemisphere during the eccentric phase of the LSUT. On the contrary, typically developing children typically developing children had significant relationships in the ipsilateral hemisphere during the concentric phase of the LSUT. The observed results further support the idea that children with CP and typically developing children rely on different neural resources within the PFC during the same motor task. However, further research is needed to properly evaluate these differences.

Furthermore, the results of this study also demonstrated that PFC activation in children with CP is lower compared to typically developing children. Previous literature has suggested that the observed hemodynamic response in children with CP compared to typically developing children may be attributed to physiological factors [271, 273]. Due to lower cardiorespiratory levels [274] and increased energy expenditure while walking [275] in children with CP compared to typically developing children, the hemodynamic effects resulting in reduced PFC hemodynamic activation should be more pronounced in children with CP, as our current results demonstrate. Since cardiorespiratory fitness, energy expenditure and physical activity are known to be interrelated in children with CP

[275], these factors could further help explain the relationship between PFC hemodynamic activation and functional muscle weakness or fatigue in children with CP. However, a multi-dimensional approach using alternative methods to assess dynamic muscle and cardiorespiratory response markers during movement is required in order to further understand the relationship observed between PFC hemodynamic activity and peripheral abnormalities in children with CP.

The current study has notable strengths. First, a wireless fNIRS system was used to acquire hemoglobin concentration changes. Thus, it allowed us to assess the effect of a highly dynamic functional test (i.e., LSUT) on PFC activation in children with CP. Previously, fNIRS systems were designed using wired fiber optic bundles, making it difficult to observe a hemodynamic response to dynamic movement due to the considerable weight, limited flexibility, and restricted length of the fiber optic bundles [201]. Second, the region of the brain studied (i.e., PFC) is not subject to fNIRS signal distortion. Areas of the scalp that contain dense hair have been known to reduce signal quality and optode-to-scalp coupling [276]. Third, participants were matched for age and sex. Therefore, the potential influence of these factors on group differences is minimized. Furthermore, the height, body mass, and BMI of the typically developing children were not different from the 50^{th} age- and sex-based percentiles suggesting that the children were reasonable representatives of the general population.

The limitations of this study also require discussion. First, the fNIRS device used restricted coverage to a single channel over each PFC hemisphere. Therefore, the response patterns of other brain regions during the LSUT remain unclear. Further research is needed to understand whether different response patterns are present in other

brain areas, including the primary motor, premotor, and supplementary motor areas. Second, our small sample size prevented the assessment of potential confounders, including age and brain lesion type and timing. While the study sample was matched for age, supplementary data for brain injury type and timing were not collected. These factors have previously been shown to influence functional outcomes in the upper extremities of children with CP [277]. Lastly, measures of peripheral fatigue, central fatigue, and cardiorespiratory indicators of task intensity were not assessed. It is understood that physiological factors, including blood pressure, heart rate, and dermal blood flow, can confound fNIRS signals. However, practices reducing the influence of these confounding factors are also established and were applied accordingly during this study [278]. The benefit of assessing physiological factors during a LSUT include the possibility of an objective quantification of cardiovascular intensity, which has been shown to influence PFC activation. Specifically, higher cardiovascular fitness has correlated positively with PFC activation during cognitive and balance tasks [279, 280]. Whether similar effects are present during a LSUT remains unclear. Furthermore, the order of step heights during the LSUT was not randomized. Therefore, the effects that LSUT step-heights may have on levels of muscle co-contraction could be confounded by an adaptation effect. It has previously been demonstrated that adaptations in dynamic stability to perturbations are observed in studies conducting as little as five repeated trials during gait [252]. Whether the same is true during a LSUT remains unclear.

4.5 Conclusions

It was demonstrated that prefrontal hemodynamic activity is lower in children with CP compared to typically developing children. Additionally, this study demonstrated that CCR are positively related to physical activity participation levels in both children with CP and typically developing children. Results of this study also suggest that recruitment of prefrontal resources differs between children with CP and typically developing children depending on the loading phase of movement. Moreover, it was demonstrated that children with CP rely on different prefrontal neural resources compared to typically developing children during the same motor task. Furthermore, physiological factors in children with CP could further influence the reduced prefrontal hemodynamic activations patterns observed in this study. Further research is warranted to better understand the underlying mechanisms observed.

4.6 Acknowledgment

We thank all the participants and their families for their support. JL and CMM designed the study; JL, SJ, OK and SR conducted the data collection; JL, SJ, OK and SR analyzed the data; JL and CMM wrote the manuscript. All authors edited and approved the final manuscript. The authors declare that they have no conflicts of interest. This study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Center for Medical Rehabilitation Research (grant numbers HD050530, HD071397 and HD090126), and the University of Georgia Athletic Association.

CHAPTER 5

CONCLUDING SUMMARY

The overall objectives of this dissertation were 1) to evaluate the effects of muscle co-contraction on lower limb functional strength and its relationships to physical activity participation in children with CP and typically developing children and 2) to assess the relationship between prefrontal hemodynamic activity, muscle co-contraction, and functional strength and ability in children with CP and typically developing children. The specific aims are briefly summarized below.

Summary of specific aim 1: Results demonstrated that muscle co-contraction does not play a major role in lower limb functional strength in children with CP. Reduced agonist activation played an important role in the modulation of peripheral activation patterns in children with CP and in the successful performance of a lower limb functional strength assessment compared to typically developing children. Furthermore, physical activity participation significantly and positively related to muscle co-contraction during the more difficult stages of the LSUT in both children with CP and typically developing children.

Future directions: The quantification methods of muscle co-contraction have been previously criticized in the literature. Future studies should aim to determine whether the functional implications of successfully reducing muscle co-contraction in children with CP is of significant functional benefit. Additionally, physical activity should be categorized to further support the findings of this study.

Summary of specific aim 2: It was demonstrated that children with CP experience lower prefrontal hemodynamic activity during a lateral step-up test compared to typically developing children. Children with CP experience different prefrontal and muscle activation patterns during the same motor task compared to typically developing children. Muscle CCR relate significantly and positively to prefrontal hemodynamic activity in both children with CP and typically developing children. Results suggest that prefrontal recruitment is sensitive to task intensity and loading phase of movement.

Future directions: This study only observed on region of interest. Future studies should aim to assess other areas of the brain related to movement together with prefrontal areas. In addition, studies should aim to assess cardiometabolic markers during assessment to provide further understanding of underlying mechanisms resulting in decreased PFC hemodynamic activation in children with CP.

In both studies, children with CP completed fewer repetitions during a LSUT compared to typically developing children. Co-contraction ratios were not observed to significantly relate to LSUT performance. However, prefrontal recruitment patterns did show significant positive relationships with LSUT repetitions completed in children with CP. Considering the importance of cognitive structures such as the PFC during postural control [210, 281], deficiencies in performance during a LSUT could be related to deficiencies in control mechanisms in children with CP. In order to effectively evaluate postural control during a LSUT, future studies should consider measures of dynamic postural stability including center of mass and center of pressure. Postural stability, which can be described as balance, is the ability to maintain and regain the center of mass

within the base of support [282]. Muscle weakness in children with CP has demonstrated to negatively affect postural control [283] but the results of this dissertation suggest that agonist deficiency did not significantly result in reduced LSUT performance. Therefore, the assessment of the LSUT under a postural control framework rather than a functional strength perspective, is of interest for future studies. Previous research has highlighted the need to assess postural control under dynamic conditions [284] making the LSUT a reasonable approach. However, it is important to note that the LSUT can only be reliably used in children with mild impairment (GMFCS I-II) due to functional limitations in those with greater impairment (GMFCS III-V).

Nevertheless, the results of this dissertation shed light into potential mechanisms, both central and peripheral, regulating functional ability in children with mild spastic CP. Importantly, results demonstrated that increased levels of co-contraction in children with mild CP may be better addressed as a compensatory mechanism rather than a pathological symptom during functional tasks such as the LSUT. Attention to other areas, instead of increased co-contraction, of functional ability a can further enhance programs aiming to improve functional deficits in children with mild CP. Future studies should consider controlling for the number of repetitions completed during a LSUT and using time needed to successfully complete the required repetitions as the performance outcome. This way, postural control rather than functional strength becomes the primary focus of the assessment. Additionally, future studies should continue to assess co-contraction in CP under dynamic functional conditions. Ultimately, the ability to increase functional ability should be the goal of any intervention in those with CP. Being able to

directly assess functional measures with observed pathologies can help better understand mechanisms adopted pre and post interventions.

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Appendix A

Institutional Review Board Approval Letter

UNIVERSITY OF GEORGIA

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Office of Research
Institutional Review Board

APPROVAL OF PROTOCOL

August 28, 2018

Dear Christopher Modlesky:

On 8/28/2018, the IRB reviewed the following submission:

Type of Review:	Modification
Title of Study:	Effect of a high-frequency, low-magnitude vibration on muscle properties, physical activity and balance in children with cerebral palsy
Investigator:	Christopher Modlesky
Co-Investigator:	Katherine Collins
IRB ID:	MOD00006312 (STUDY00004873)
Funding:	NATIONAL INSTITUTES OF HEALTH
Grant ID:	AWD00007725
Review Category:	Expedited – Minor Modification

Modification: Added Joel Licea to the study team

Materials Reviewed: Modification form

The IRB approved the protocol from 8/28/2018 to 4/3/2019 inclusive. Before or within 30 days of study closure, whichever is earlier, you are to submit a continuing review with required explanations. You can submit a continuing review by navigating to the active study and clicking Create Modification / CR. If continuing review approval is not granted before the expiration date of 4/3/2019 approval of this study expires on that date.

Please close this study when all human subject research activities and data analysis of identifiable information is complete.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103).

Sincerely,

Kate Pavich, IRB Analyst
Human Subjects Office, University of Georgia