Evaluation of muscle synergies in individuals with cerebral palsy

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Abstract

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Cerebral palsy (CP) originates from a brain injury, causing impairments in motor control specific to the individual. These motor impairments manifest themselves differently between individuals, resulting in altered and highly heterogeneous gait patterns. Interventions aimed at improving motor function produce highly variable results between individuals, with some benefiting greatly and others seeing little or even negative impacts. Electromyography (EMG) recordings allow muscle activity to be measured, giving an opportunity to see how the brain is controlling and coordinating movement. Muscle synergies provide a tool to quantify motor control by finding lower-dimensional groups of weighted muscles which are commonly activated during an activity such as walking. In individuals with neurologic impairments such as stoke, spinal cord injury, and CP synergy complexity is reduced, and synergy organization is altered. The goals of this dissertation were to evaluate how motor control is altered in individuals with

CP and address some of the challenges in translating muscle synergies into a useful clinical measure.

There are many methodologies for pre-processing EMG data prior to calculating synergies, and these choices can impact clinical interpretations. We found that synergy complexity was sensitive to EMG pre-processing, but that these effects could be mitigated by normalizing to typically-developing (TD) synergies. When a consistent number of synergies was evaluated the muscles recruited within synergies and synergy activations were similar across a range of filtering conditions. In order to use synergies as a measure of motor control, we sought to determine whether muscle synergies were repeatable between days and between centers. We found similar levels of repeatability for both TD children and children with CP, for both synergy complexity and structure of synergy weights when measured across two separate days. We also found similar associations between pre-treatment synergy complexity and post-treatment outcomes in CP at two separate institutions. Across a variety of common interventions, children with motor control closer to that of their TD peers were associated with greater improvements in kinematics and walking speed. These results suggest that synergies provide a repeatable measure of motor control which may be useful in treatment planning.

Common treatments which aim to improve walking function may also impact motor control, either by directly targeting the nervous system or by indirectly targeting the biomechanical constraints of the system. We evaluated changes in muscle synergies after treatment and rehabilitation and found only small changes that were inconsistent between individuals. While current treatments do not consistently alter synergies, we found that those children whose synergy activations that more closely matched TD post-treatment were associated with improved treatment outcomes.

We also applied muscle synergies as an individual model of motor control to musculoskeletal simulation techniques in an effort to improve estimation of muscle activations. Muscle force, and thus muscle activations are used to evaluate a range of clinical questions including muscle contributions to gait and joint loadings. We compared experimental EMG to muscle activations computed using standard musculoskeletal optimization methods and to activations constrained to synergy groupings and for both TD and CP children. We found that constraining modeled activations to muscle synergies did not improve predication of muscle activations for either group. These results suggest that generic musculoskeletal parameters including activation dynamics and musculoskeletal geometry may limit predictions of muscle activations during gait and that constraining muscle activations to synergistic patterns cannot alone improve these estimations.

This dissertation examines methodological considerations pertaining to the calculation of muscle synergies, including demonstrating that muscle synergies can be robustly measured across days and processing decisions. This work provides important evidence for the clinical utility of muscle synergies in CP, demonstrating associations with treatment outcomes across treatments, centers, and muscles measured. This work also suggests that synergies may be a promising target for future treatments in an effort to improve mobility in children with CP.

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Chapter 1. AIMS OVERVIEW

AIM 1: Electromyography data processing impacts muscle synergies during gait for unimpaired children and children with cerebral palsy.

In neuromuscular disorders, such as stroke and cerebral palsy, muscle synergies are being used to evaluate motor control. However, prior to synergy analysis, processing of electromyography data varies between studies and the impacts of these processing decisions on synergy analysis is unclear. We processed electromyography data from three groups of children with CP and a typically developing (TD) control group across a range of low-pass filtering conditions and two amplitude scaling methods found in the literature. We analyzed how synergy outputs changed for each group across these processing decisions. Synergy complexity measured by number of synergies or the total variance accounted for by one synergy ($tVAF_1$) was sensitive to processing choices. Scaling to a z-score of complexity, walk-DMC, minimized reduced the sensitivity to filtering conditions. Synergy structure and activations were less sensitive to processing decisions suggesting similar patterns in muscle activations are found.

AIM 2: Repeatability of muscle synergies within and between days for typically developing children and children with cerebral palsy.

Muscle synergies are being increasingly used to evaluate neuromuscular control. However, the repeatability of synergies between trials and between days had not been evaluated. We analyzed the repeatability of muscle synergies both within and between days for TD and

children with CP. The repeatability of synergy complexity, measured by the total variance accounted for (tVAF), and structure, measured by the correlation of synergy weighting vectors, was similar for both groups, both between gait cycles and between two days. This work suggests that synergies found from multiple gait cycles is repeatable for both TD and children with CP.

AIM 3: Associations between synergies and treatment outcomes in cerebral palsy are robust across clinical centers.

In children with CP, recent research showed that muscle synergy complexity (walk-DMC) was associated with treatment outcomes at a single center. Clinical protocols, treatments, and decision making can vary between centers. The goal of this study was to replicate the first study's findings at a second clinical center. We analyzed gait analysis and electromyography data from children across three treatment groups, botulinum toxin injections (BTA), selective dorsal rhizotomy (SDR), and single-event multi-level orthopaedic surgery (SEMLS). We used two outcome measures: non-dimensionalized walking speed and the gait deviation index, a summary measure of kinematics. We found similar associations between walking speed and synergy complexity but a reduced, although still significant, association with kinematics. These association were robust when synergy complexity was calculated for the same muscle set used in the original study and for three alternate muscle sets, including an expanded unilateral muscle set and bilateral sets of the original and expanded muscles. The results of this study suggest that synergy analysis can provide additional information not captured in traditional gait analysis, which may be useful for treatment planning.

AIM 4: Changes in muscle synergies following common treatments in cerebral palsy.

Although the previous aim helped demonstrate that synergy-based measures may be useful for treatment planning the goal of this study was to determine to what extent common treatments can alter synergies in CP, and whether those changes would also be associated with treatment outcomes. We analyzed the children from the previous aim who had data collected both before and after treatment with BTA, SDR, or SEMLS. We evaluated changes in synergy complexity, measured by number of synergies and $tVAF_1$, and synergy organization of the weights and activations. We did not find a trend towards increasing number of synergies, nor did either synergy weights or activations become closer to TD peers for any treatment groups. We did find a significant trend toward reduced synergy complexity measured with $tVAF_1$ for the BTA and SDR treatment groups. Individual changes in synergies were variable for all measures. Changes in synergy complexity and synergy weights were not associated with treatment outcomes. Only synergy activation patterns that more closely match TD after treatment were significantly associated with improved kinematics and walking speed.

AIM 5: Determine whether muscle synergies improve muscle activation estimates in musculoskeletal modeling.

Muscle activations estimated using inverse musculoskeletal modeling frequently fail to match with experimental EMG recordings. However, accurate estimation of muscle forces, and thus muscle activations, are important to evaluate many important questions such as joint loadings and muscle contributions during gait. The goal of this study was to determine whether subject specific synergies, could improve estimated muscle activations relative to experimentally

measured activations by adjusting the optimization function to minimize the sum of synergy activations squared. We analyzed walking simulations during single leg stance for six TD and six children with CP. Although we were able to constrain the model to commonly activate muscles within the framework of muscle synergies, we did not find consistent improvements in estimated activation patterns relative to EMG signals. This suggests that constraining estimated activation patterns to synergies alone is insufficient to improve musculoskeletal models muscle activations relative to EMG.

Chapter 2. BACKGROUND

2.1 CEREBRAL PALSY

Cerebral palsy (CP) is a non-progressive neurologic disorder causing a wide range of movement impairments, originating from a lesion or injury to the brain at or near the time of birth [1]. CP is one of the most common causes of physical disability in childhood, affecting roughly three out of every thousand live births [2,3]. The diagnosis of CP is limited to covering motor impairments, but due to its neural origin, CP is commonly co-occurring with other impairments such as intellectual disabilities or epilepsy [3]. Even without co-occurring intellectual disabilities the estimated medical costs are 10 times per year as a typically developing child [4], with an estimated lifetime cost of over $900,000 [5].

Every brain injury in CP is unique, altering motor control on an individual basis. Broadly speaking, individuals with CP are grouped into four general types of neurological impairment: spastic, dyskinetic, ataxic, and roughly 10% demonstrate a mixture of the other three [6]. Spastic CP is the most common type [7,8], with four primary neuromuscular deficits: muscle weakness, shortened muscles, spasticity (heightened stretch reflex), and impaired selective motor control [9]. This dissertation focuses on children with spastic CP and altered motor control. Additional classifications group individuals by which limbs are impaired, overall movement function, and walking patterns [10]. Classification by limb includes hemiplegia or hemiparesis, when one side is predominantly involved, or diplegia when both sides are impaired. Scales such as the Gross Motor Functional Classification System (GMFCS), Functional Assessment Questionnaire (FAQ), or Gross Motor Function Measure (GMFM) are frequently used to assess movement. Altered walking patterns common in CP include intoeing, excessive hip flexion, equinus (characterized by toe walking), and crouch gait (characterized by increased knee flexion) [11].

Given the heterogeneous nature of motor impairment, treatment in CP is extremely complicated and must be customized to the individual. The treatments prescribed are based upon physical exams, functional assessments, visual or 3D gait analyses, electromyography (EMG), and various imaging modalities. Treatments include surgical procedures, pharmacology, assistive devices, and physical therapy including strength and gait training. Treatments such as selective dorsal rhizotomy (SDR) target the nervous system directly while botulinum toxin type A (BTA) injections provide short-term changes in muscle activity. Orthopedic surgeries largely target the biomechanical constraints of the system, and include procedures such as tendon lengthening, muscle transfers, and correction of skeletal deformities. Physical therapy and gait training are aimed at improving strength and improving coordination patters. Gait analysis has impacted the ability to prescribe surgical interventions, generally improving treatment outcomes [12–14]. However, treatment outcomes are still highly variable with many individuals failing to improve after surgery [15], spasticity management treatments [16], or strength training [17]. Thus, despite the many metrics and scales currently used to target treatments, there remains a need for new and better methods which can improve treatment outcomes in CP.

2.2 EMG

Clinically, lower limb selective motor control in CP is assessed using scales such as the Boyd and Grahram selective motor control test, Trost selective motor control test (for dorsiflexion) or the Selective Control Assessment of the lower extremity (SCALE, for hip, knee, ankle, subtalar, and toes) which rate a child’s ability to move a specified joint in insolation [18,19]. One method to examine the underlying motor control is through EMG. EMG records the electrical activity produced during the activation of muscles, and has long been used

experimentally in gait analyses and is often used to determine the timing of muscles. Surface EMG is measured using a pair of electrodes placed on the skin over the muscle to be recorded from. Placement guidelines suggest placing the sensor over the muscle belly in line with the muscle fibers [20]. EMG records the net difference in potential between the two electrodes caused by the depolarization of many individual motor units within a muscle [21]. The recorded potential difference gives an approximation of the overall muscle activation but is limited by a number of factors including crosstalk from other muscles, cancellation between motor units, subcutaneous tissue thickness, conduction velocities of muscle fibers, and environmental contamination. Surface EMG is also limited to superficial muscles, being unable to record from deeper muscles. These factors limit the ability to use EMG amplitude as a direct measure of force and make comparisons between individuals challenging [22]. Further, the manner in which motor units are recruited can vary over time and under fatigue [23]. Despite these challenges research has shown that EMG waveforms are repeatable within and between days, for unimpaired subjects [24,25].

In general the pipeline for processing EMG is as follows: 1) initial high-pass or band-pass filtering to reduce movement artifacts and noise, 2) full wave signal rectification, 3) smoothing of the signal to obtain an envelope of the muscle activation, 4) amplitude scaling, and 5) time scaling, such as normalizing to a gait cycle (Figure 2.1) [10,21,22,25,26].

EMG provides a wealth of information, but can be hard to interpret and is inconsistently used in clinical practice for children with CP [27]. EMG has been used in research to assess the timing of specific muscles over various speeds [10,28–30], as a measure of spastic catch [31,32], and co-contraction ratios [33,34]. A study by Cappelini et al. [28] found that EMG bursts tend to be wider in children with CP and toddlers compared to older TD children. Zwaan et al. [34]

found that the co-contraction ratio between the vasti and gastrocnemius were higher in CP during gait and that this measure correlated with selective motor control scores (modified Trost SMC), suggesting that EMG during gait is associated with clinical scales of motor control. The above methods generally involve looking at individual EMG patterns or the relation between pairs of muscles. As there are many muscles involved with walking, interpreting muscles in isolation provides limited understanding of the underlying motor control. One method to gain a broader understanding of motor control using EMG from many muscles is the theory of muscle synergies.

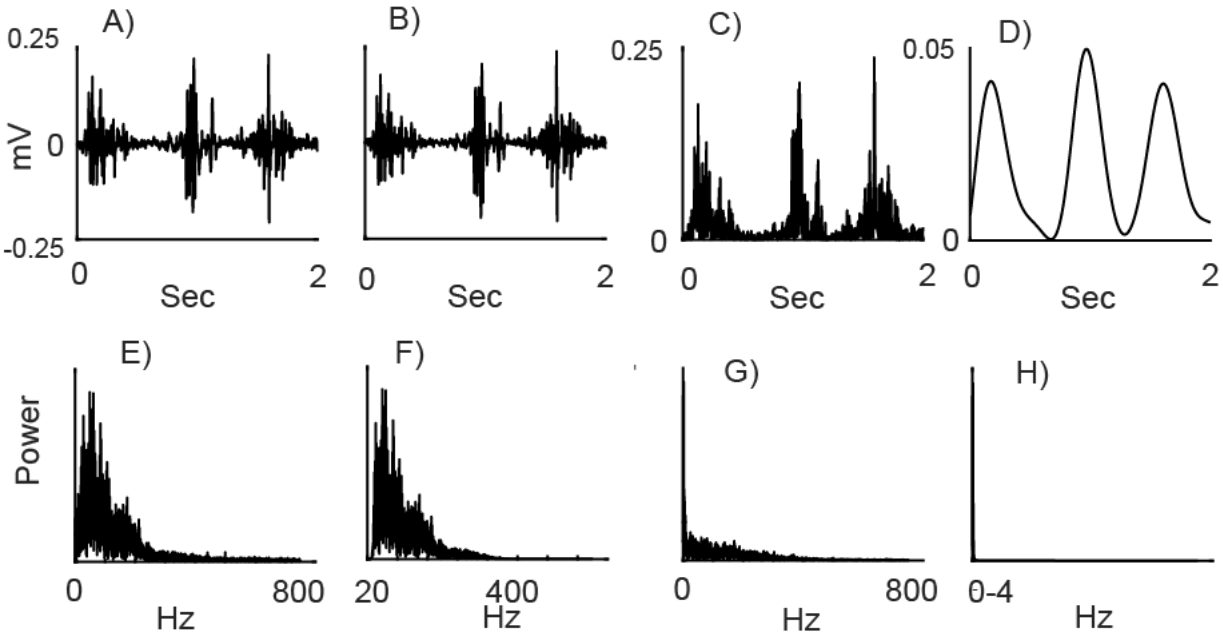

Figure 2.1. Processing of EMG data. A-D) time domain. E-H) frequency domain. First raw EMG data (A, E) is high pass filtered, in this case between 20 and 400 Hz (B, F), then full wave recitfied (C, G), and smoothed (D,H), in this case using a 4hz low pass filter. The smoothed data would then be normalized by amplitude and gait events.

2.3 MUSCLE SYNERGIES

The theory of muscle synergies originates from the observation that there are fewer degrees of freedom (joints) in movement then there are muscles to control, resulting in an overdetermined system. Synergies suggests that the central nervous system does not control each muscle independently, which would be computationally expensive, but instead operates in a lower dimensional space of fixed activity patterns (synergies) of groups of muscles. These synergies are then combined to flexibly produce a range of coordinated actions. Evidence for this lower dimensional space has been found in the analysis of spinal stimulation in frogs where stimulation of specific sites in the spine produced a set of muscle activations in the limb. Stimulating multiple sites resulted in muscle forces that could be represented by a vector summation of the muscle forces from individual stimulation sites [35,36]. In mammals, decerebrate cats can walk on a treadmill using only sensory feedback from the limbs, although the movements become highly stereotyped [37]. Scratching specific locations in spinalized frogs can elicit a range muscle activations which can be explained with only four weighted groupings of muscles (i.e. synergies) [38]. Cheung et al. [39] found that the same synergies could explain frog behavior both before and after spinalization suggesting that synergies may be activated by descending central commands but also activated by feedback in the peripheral nervous system. Similar experiments carried out in rhesus monkeys found that synergies extracted from voluntary behavior matched synergies extracted during spinal stimulation [40,41].

In humans synergies have been calculated from experimental EMG for a wide range of behaviors including walking, running, cycling, and balance, which can generally be represented with 4-6 synergies in healthy adults [42–44]. Synergies are calculated with matrix factorization algorithms which finds a set of synergy weights (W_{mxn}) and synergy activations (C_{nxt}), such

that $EMG_{mxt} = W_{mxn} \times C_{nxt} + error$, where *m* is the number of muscles measured, *t* is the number of time points, and *n* is the a priori defined number of muscle synergies. A number of factorization algorithms have been used to identify muscle synergies in simulated and experimental data, including principle component analysis (PCA), independent component analysis (ICA), non-negative matrix factorization (NMF), and factor analysis (FA) [45]. Of these, NMF [46] has gained traction as the preferred algorithm, due to the non-negativity constraints, eliminating any negative muscle weights which lack physiological meaning for muscle recordings (Figure 2.2).

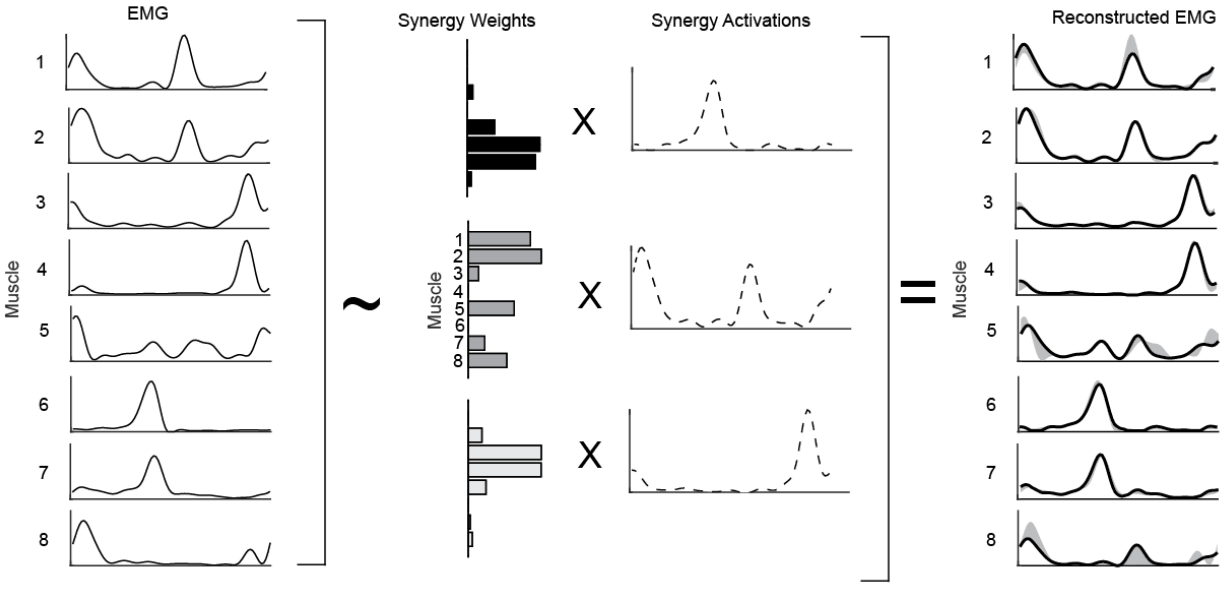

Figure 2.2. Example of non-negative matrix factorization (NMF). Here, a set of three synergies (synergy weights) are activated over time (synergy activations) to approximate the origional EMG data. The reconstructed EMG is shown with errors from the original EMG pattern in grey.

Unlike PCA, the solution from NMF is numerical and thus care must be taken that locally optimal solutions are found. In the work presented here we use settings developed by Jessica Allen which have been shown to produce repeatable results. One effect of the non-negativity

constraints is that individual synergies are not independent from one another. Thus, it is important to note that the three synergy solution is not equivalent to the two synergy solution with the addition of a third synergy.

2.4 Muscle Synergies in Neurologic Impairment

Reduced motor control hinders movement and has been suggested as an important factor influencing treatment outcomes [47]. Muscle synergies as a measure of impaired muscle control has been examined in stroke [48–51], Parkinson's [52,53], spinal cord injury [54,55], and CP [28,56–59]. One of the most common methods to evaluate synergies is to determine the number of synergies an individual has during an experimental task. The number of synergies is determined through a variety of methods depending on the study but generally include a threshold on the total variance accounted for by the identified number of synergies and may include thresholds on the variance accounted for in individual muscles [54]. Common thresholds include 80, 90, and 95% variance accounted for across all muscles [57,58,60]. An alternate method finds the number of synergies such that one additional synergy would increase the r^2 value by less than a threshold (e.g. $<10^{-4}$) [28,61]. Studies using a variance threshold have consistently found that the number of synergies is reduced across neurologically impaired populations and scales with impairment [49,58,60] while the linear fit methods (r^2) may identify similar numbers of synergies as unimpaired individuals [28]. Studies in individuals with chronic stroke have found that the impaired synergies are predominantly found on the impaired side, with the unaffected side frequently demonstrating synergies similar to heathy controls [49,60].

In gait, four synergies have been typically identified during unimpaired walking [49,62]. The first synergy (C1) is active in early stance and provides support during weight acceptance. The second synergy (C2), consists of the plantarflexors and acts to support and propel the body

during late stance and swing initiation. The third synergy (C3) serves to extend the knee and lift the foot during swing and after heel strike. The fourth synergy (C4) uses the hamstrings to propel the body during stance and decelerate the leg at the end of swing (Figure 2.3). Impaired individuals with chronic stroke were found to have 2-4 synergies. It has been suggested that the reduction in synergies frequently represents a merging and fracturing of unimpaired synergies [60]. Merged synergies are identified by finding linear combinations of unimpaired synergies which reconstruct the impaired synergy. Fractured synergies are identified by combining the impaired synergies to make a single unimpaired synergy. The least impaired individuals with four synergies demonstrated weights and activation patterns similar to unimpaired, suggesting more intact motor control. It is interesting to note that when four synergies were extracted, regardless of the number identified, Clark et al. [49] found similar weightings with the unimpaired controls but altered timings. Gizzi et al. [63] found that activation patterns were conserved but synergy weights reorganized in mildly affected stoke subjects with no reduction in number of synergies. These studies demonstrate that neurologic impairment can alter the complexity and organization of synergies and that the alterations can vary between individuals.

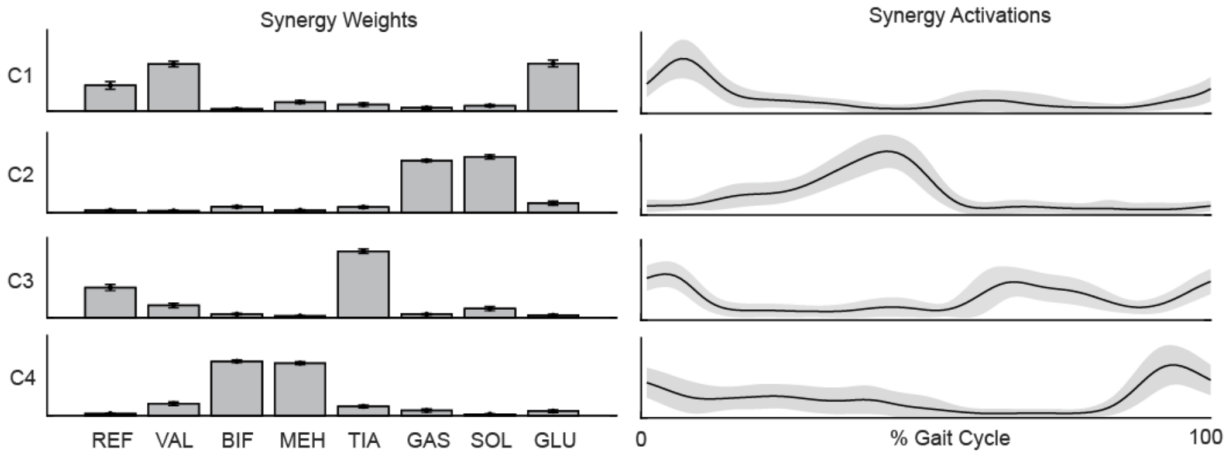

Figure 2.3. Average (SD) four synergy solution for 31 TD individuals.

Studies evaluating synergies in CP have followed a similar pattern of investigation as stroke [28,56–59]. Li et al. [56] found that the number of synergies was generally reduced in CP. In individuals with similar numbers of synergies as the control group, one or more synergies demonstrated altered muscle weightings suggesting impaired motor control. Tang et al. [57] expanded this work finding that synergies tended to be highly symmetric between legs in unimpaired individuals. However, in diplegic CP, there was also a reduction in similarity between limbs, suggesting that synergy alterations are frequently different between legs. An extensive study of over 549 individuals with CP, found that a summary measure of synergy complexity, the total variance accounted for by one synergy ($tVAF_1$) was higher in CP, and related to the number of synergies identified in an individual [58]. Moreover, $tVAF_1$ correlated with existing clinical scales rating walking function, strength, spasticity, and selective motor control. Higher synergy complexity (e.g. closer to TD generally) was correlated with higher walking function, higher strength, lower spasticity, and higher selective motor control. Beyond being a surrogate for existing measures in CP, synergy complexity was shown to be associated with treatment outcomes after adjusting for pre-treatment values of kinematics and walking speed [64]. This suggests that muscle synergies provide additional information about a child's walking pattern beyond what is captured with other measures.

Chapter 3. ELECTROMYOGRAPHY DATA PROCESSING IMPACTS MUSCLE SYNERGIES DURING GAIT FOR UNIMPAIRED CHILDREN AND CHILDREN WITH CEREBRAL PALSY

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ABSTRACT

Muscle synergies calculated from electromyography (EMG) data identify weighted groups of muscles activated together during functional tasks. Research has shown that fewer synergies are required to describe EMG data of individuals with neurologic impairments. When considering potential clinical applications of synergies, understanding how EMG data processing impacts results and clinical interpretation is important. The aim of this study was to evaluate how EMG signal processing impacts synergy outputs during gait. We evaluated the impacts of two common processing steps for synergy analyses: low pass (LP) filtering and unit variance scaling. We evaluated EMG data collected during barefoot walking from five muscles of 113 children with cerebral palsy (CP) and 73 typically-developing (TD) children. We applied low pass (LP) filters to the EMG data with cutoff frequencies ranging from 4 to 40 Hz (reflecting the range reported in prior synergy research). We also evaluated the impact of normalizing EMG amplitude by unit variance. We found that the total variance accounted for (tVAF) by a given number of synergies was sensitive to LP filter choice and decreased in both TD and CP groups with increasing LP cutoff frequency (*e.g.* 9.3 percentage points change for one synergy between 4 and 40 Hz). This change in tVAF can alter the number of synergies selected for further analyses. Normalizing tVAF to a z-score (*e.g.*, dynamic motor control index during walking, walk-DMC) reduced sensitivity to LP cutoff. Unit variance scaling caused comparatively small changes in tVAF. Synergy weights and activations were impacted less than tVAF by LP filter choice and unit variance normalization. These results demonstrate that EMG signal processing methods impact outputs of synergy analysis and z-score based measures can assist in reporting and comparing results across studies and clinical centers.

3.1 INTRODUCTION

Muscle synergies have been used to describe the low-dimensional sets of weighted muscle groups that are recruited during functional tasks [36,65]. Prior research has theorized that the nervous system uses these synergies as a simplified method of control, rather than controlling each muscle individually. Recent research has applied muscle synergies as a framework to evaluate altered neuromuscular control in individuals with neurologic disorders. Research on individuals with stroke and CP have shown that fewer synergies are required to describe EMG data during functional tasks compared to unimpaired individuals, and this reduction in activation complexity may contribute to movement impairments [48,49,51,58,66–68]. However, despite the general agreement that synergy complexity is reduced in stroke and CP, there is no consistent methodology for calculating muscle synergies. Prior to calculating muscle synergies, raw EMG data are processed to generate linear envelopes describing the activation of each muscle during a task such as walking. In general, this process consists of an initial filtering (e.g., high pass or band pass filtering), full wave rectification, low pass (LP) filtering, and amplitude scaling. As researchers investigate potential clinical applications of synergy analyses, such as in clinical gait analysis, understanding the impact of EMG preprocessing is important to compare across studies or clinical centers.

Prior synergy research has used a wide variety of EMG preprocessing methods. In particular, a wide range of LP filters have been used to smooth EMG data, with LP cutoff frequencies ranging from 1 Hz [69] to 40 Hz [42], and including many intermediate values including 4 Hz [49], 10 Hz [58], 20 Hz [70], 30 Hz [71], or 35 Hz [72]. Despite this, there has been little research examining how muscle synergy calculations are impacted by these LP filter choices. Kleissen [73] showed large differences in smoothness and cycle-to-cycle variability in

EMG envelopes from the gluteus medius during gait when LP filtered at 3.4 or 25 Hz. For synergies, Van der Krogt et al. [74] showed that the total variance accounted for (tVAF) by a given number of synergies was reduced with increasing LP cutoff frequency in children with CP for EMG data LP filtered between 2 and 25 Hz. Since tVAF is commonly used to pick or choose the number of synergies for further analysis (*e.g.,* the number of synergies required for tVAF > 90 or 95%), impacts of LP filtering on tVAF can further impact conclusions about muscles that are activated together or differences in synergies between control and clinical populations. Hug et al. [75] noted that the number of synergies required to explain 90% of the variance in EMG data changed between 4, 10 and 15 Hz LP filters. However, it has not been shown how LP filters can affect calculated synergy weights, which describe muscles commonly activated together, or synergy activation curves, which describe how each synergy is activated over time.

After filtering, the processed EMG data amplitudes are often scaled through one of several methods. These include peak measured amplitude [49,58], maximum voluntary contractions [76,77], or median trial maximums [48]. Additionally, for synergy analyses, prior research has scaled the amplitude so that each muscle has unit variance [51,71,72]. Unit variance scaling has been applied to avoid larger representations of high-variance muscles in the output synergy weights [70]. As with filter cutoff, the effects of amplitude scaling on synergy outputs remains unclear.

To reduce potential impacts of EMG preprocessing on synergy results and facilitate comparison across studies or clinical centers, some prior research has suggested normalizing data to a z-score. For example, the dynamic motor control index during walking (walk-DMC) provides a summary measure of synergy complexity by normalizing tVAF by one synergy to the average and standard deviation of a group of unimpaired individuals [58,64]. By normalizing to a

group of controls from a given clinic or research lab, walk-DMC may help to reduce the impacts of different equipment, muscles, or EMG preprocessing methods across institutions. Walk-DMC differs between typically-developing (TD) children and children with CP and is associated with treatment outcomes for children with CP [64]. The impact of EMG processing on walk-DMC has not been investigated.

The goal of this research was to examine how EMG processing, specifically the choice of LP filter cutoff frequency and amplitude scaling, affects synergy analyses for TD children and children with CP. We evaluated how processing choices impact synergy complexity, in terms of tVAF and walk-DMC. We also evaluated how synergy weights and synergy activation curves change with processing choices. We hypothesized that walk-DMC would be more consistent across EMG processing conditions than tVAF, and that synergy weights and activations would change across processing parameters. Further, we hypothesized that both the TD and CP children's synergies would be similarly impacted by processing choices. Understanding the impact of EMG data processing on synergy outputs will help inform comparisons between studies and guide future clinical applications of synergy analyses.

3.2 METHODS

Human subjects' approval was obtained from both the University of Washington and the University of Minnesota for this study.

We retrospectively analyzed individuals who previously received gait analysis at Gillette Children's Specialty Healthcare. For this study, we sought to identify 40 individuals with diplegic CP, belonging to each of the Gross Motor Function Classification System (GMFCS) Levels I, II, and III (120 total participants), who had EMG data collected from five muscles during routine clinical gait analysis. For GMFCS Level III, only 33 individuals met these

inclusion criteria. Data for TD children were obtained from the control database at Gillette Children's Specialty Healthcare. Table 4.1 summarizes the demographic data for all participants in this study.

Table 4.1. Study population.

	N	Sex F:M	Age (yr)	Height (m)	Mass (kg)
TD	73	30:43	10.5 ± 3.5	1.44 ± 0.20	40.3 ± 13.3
GMFCS I	40	22:18	10.4 ± 4.8	1.35 ± 0.19	33.6 ± 15.6
GMFCS II	40	14:26	10.9 ± 5.8	1.34 ± 0.22	33.5 ± 15.9
GMFCS III	33	17:16	12.2 ± 9.4	1.28 ± 0.18	32.8 ± 21.9

N, number of participants; F, Female; M, Male; GMFCS, Gross Motor Function Classification System

3.2.1 *Electromyography Data*

Surface EMG data (Motion Laboratory Systems, Baton Rouge, LA, USA) were collected at 1080 Hz for five muscles (rectus femoris, medial hamstrings, lateral hamstrings, gastrocnemius, and tibialis anterior) during barefoot walking at a self-selected speed. For each individual, one limb was randomly selected for analysis. We took the middle 80% of the entire gait trial to avoid transient accelerations and decelerations near the beginning and end of the trial and maximize data for analysis (Oliveira et al., 2014). Raw EMG data were band pass filtered between 35 and 500 Hz upon collection.

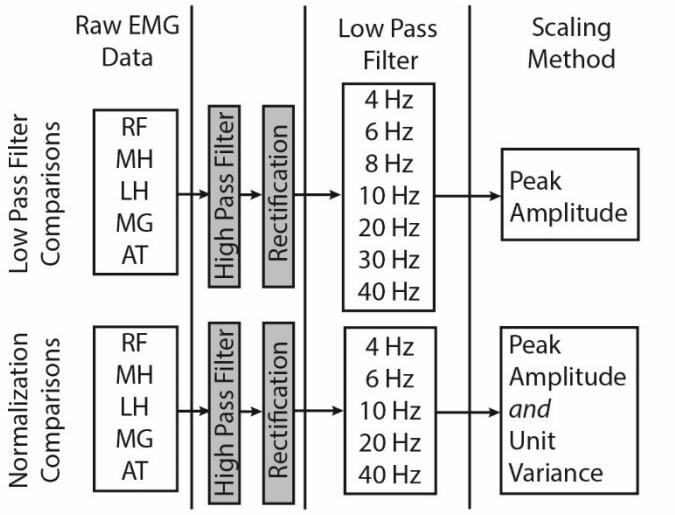

Figure 3.1. Processing steps and filter parameters used in this study to evaluate the impact of LP filter choice and amplitude normalization methods on the results of synergy analyses. RF, rectus femoris; MH, medial hamstring; LH, lateral hamstring; MG, medial gastrocnemius; AT, anterior tibialis.

EMG data for each child were digitally processed with a high pass (HP) filter and a set of varying LP filters (Figure 3.1). The filter parameters were based upon prior studies of synergies during gait [42,49,58,70,71]. The pipeline for processing EMG data for synergy analysis involves the following sequence (1) HP filtering (40 Hz) to eliminate DC drift and movement artifacts, (2) full wave rectification, and (3) LP filtering to create a linear envelope of muscle activity. For both filtering steps, we used 4th order Butterworth filters, which have commonly been used in synergy analyses [49,62,66,68]. The specific LP cutoff frequencies evaluated were: 4, 6, 8, 10, 20, 30, and 40 Hz. Since maximum voluntary contractions are not collected as part of clinical care at Gillette, EMG data were scaled to the peak amplitude for each muscle. Since some prior synergy analyses scale EMG data to unit variance, we also investigated the impact of unit variance scaling with varying filter parameters. Each EMG channel was scaled to unit variance across the walking trial. After filtering and amplitude scaling, the EMG envelopes were down-sampled to 100 Hz to reduce synergy computation time.

3.2.2 *Synergy Analysis*

Synergies were calculated from the EMG data processed with each filtering condition using non-negative matrix factorization (NMF) (Figure 3.2). This method calculates a set of synergy weights ($\boldsymbol{W_{mxn}}$) and synergy activations ($\boldsymbol{C_{nxt}}$), such that $\boldsymbol{EMG = W \times C + error}$ where *n* is the number of synergies (1-4 in this study), *m* is the number of muscles (5 in this study), and *t* is equal to the number of EMG data points. The error term is defined as the difference between the filtered EMG data and the EMG data reconstructed from the product of the synergy weights and activations. We calculated synergies with NMF in Matlab (Statistics and Machine Learning Toolbox, MathWorks, Inc., Natick, Massachusetts, United States) using the following parameters: 50 replicates, 1000 maximum iterations, a $1x10^{-4}$ minimum threshold for convergence, and a $1x10^{-6}$ threshold for completion. Note that specific synergies were calculated separately for each number of synergies specified. In other words, a synergy from a 2-synergy solution may be different than all of the synergies from a 3-synergy solution.

We used three measures to evaluate synergy complexity: (1) the total variance accounted for (tVAF), (2) the number of synergies required for tVAF>90%, and (3) a z-score of tVAF (walk-DMC). The tVAF by n synergies was defined as one minus the ratio of the sum of squared errors to the sum of filtered EMG data over all muscles (eq. 3.3, [78]). Traditionally, tVAF is used to define the number of synergies to evaluate in synergy analyses. For each LP filter, we used a t-test to compare tVAF and a Mann-Whitney U-test was used to compare the number of synergies between CP and TD groups.

$$tVAF_n = \left(1 - \frac{\left[\sum_j^t \sum_i^m (error)^2\right]}{\left[\sum_j^t \sum_i^m (EMG)^2\right]}\right) \times 100\% \tag{3.1}$$

Walk-DMC is a z-score based upon tVAF by one synergy ($tVAF_1$, eq. 3.4), and uses the average and standard deviation of $tVAF_1$ ($tVAF_{AVG}$ and $tVAF_{SD}$) from unimpaired controls. Thus, the average walk-DMC score for the TD group is 100, and each 10-point deviation represents one standard deviation from the TD controls. Note that a higher $tVAF_1$ score results in a lower walk-DMC score. For example, a walk-DMC of 80 indicates that an individual's synergy complexity during walking is two standard deviations below the TD group, suggesting simplified control.

$$walk\text{-}DMC = 100 + 10\left[\frac{tVAF_{AVG} - tVAF_1}{tVAF_{SD}}\right] \tag{3.2}$$

To evaluate the effect of filter parameters on synergy weights and activations, we calculated the correlation coefficients comparing synergy weights and activations across all filter conditions. We computed the average correlation coefficient between the *W* matrices output by NMF for each of the LP filtering conditions. Similarly, we computed the average correlation coefficient for synergy activations between the *C* matrices output by NMF from each of the LP filtering conditions.

Since some prior studies [70,71] scale EMG data for each muscle to unit variance before running NMF, we also evaluated the impact of unit variance scaling on the resulting synergies. We compared the outputs of synergy analyses performed with EMG scaled by unit variance and by peak activation. We calculated the change in average $tVAF_1$ and walk-DMC with each LP filter condition to examine the impact of unit variance scaling on synergy complexity. Similarly, we calculated the correlation coefficients in synergy weights (*W*) and activations (*C*) with each LP filter condition between the unit variance and peak activation scaling methods. Note that EMG may be scaled directly to unit variance [51,70] or scaled to peak amplitude and then to unit

variance [71,72,79] with equivalent synergy outputs. In this paper, we first scaled to peak amplitude and then to unit variance.

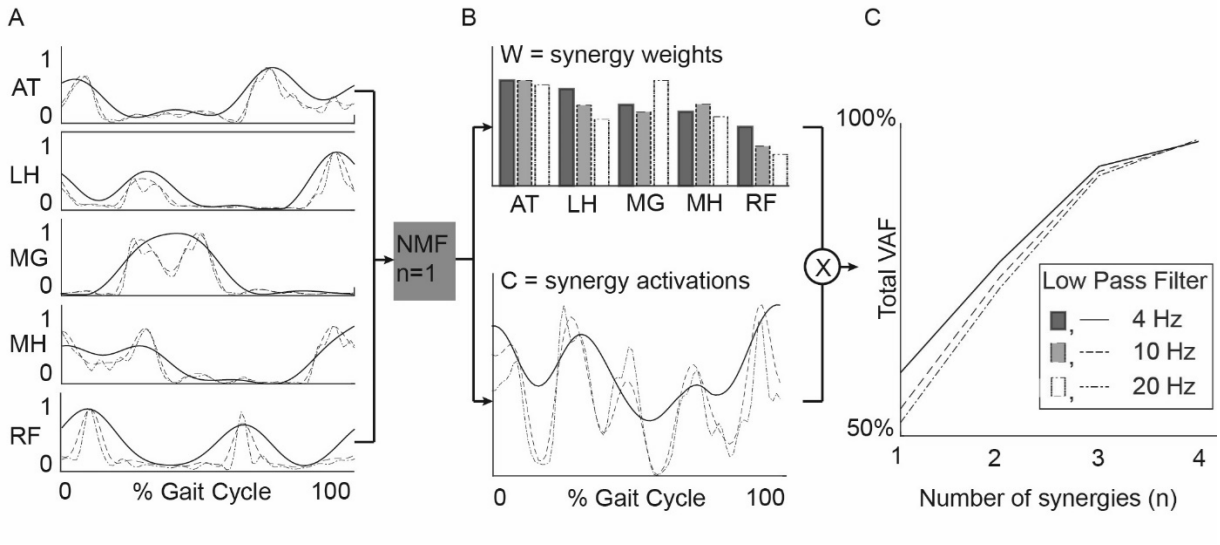

Figure 3.2. Example data from a representative TD participant. (A) EMG data was processed with varying LP filter cutoffs. (B) Synergy weights (*W*) and activations (*C*) were calculated for n= 1 to 4 synergies. (C) Total variance accounted for by *n* synergies provides a measure of synergy complexity and is often used to select a number of synergies for further analysis (*e.g.*, tVAF > 90%). RF, rectus femoris; MH, medial hamstring; LH, lateral hamstring; MG, medial gastrocnemius; AT, anterior tibialis.

3.3 RESULTS

3.3.1 *Synergy Complexity*

LP filter cutoff frequency impacted synergy complexity, as measured by tVAF. Varying the LP cutoff frequency from 4 Hz to 40 Hz decreased $tVAF_1$ by 9.6 percentage points (i.e. from 72.0% to 62.4%) for the unimpaired group, and 9.4, 8.9, and 9.1 percentage points for the GMFCS Level I, II, and III groups, respectively (Figure 3.3A). For individual participants, changes in $tVAF_1$ ranged from 2.2 to 15.1 percentage points across LP filtering conditions. For more than one synergy, $tVAF_{2\text{-}4}$ also decreased with increasing LP cutoff frequency with an average absolute reduction in tVAF of 6.5 percentage points for $tVAF_2$, 3.8 percentage points for $tVAF_3$, and 1.6 percentage points for $tVAF_4$, across all participants. Despite changes in $tVAF_n$

with LP cutoff frequency, tVAF was still significantly greater in CP compared to TD across all LP cutoff frequencies and numbers of synergies (t-test, $p < 0.01$ for all comparisons).

Changes in tVAF influenced the choice of number of synergies (Figure 3.3B). When we applied a threshold of tVAF > 90% to identify the number of synergies, only 27% of individuals with CP and 52% of TD had the same the number of synergies across all LP cutoff frequencies (Figure 3.4). The average number of synergies during walking with the 90% tVAF threshold was 2.12 (0.58) and 2.89 (0.36) for CP and TD groups when we applied a 4 Hz LP cutoff frequency, versus 2.88 (0.43) and 3.37 (0.49) with a 40 Hz LP cutoff frequency. However, the number of synergies was significantly less in CP compared to unimpaired controls across all LP cutoff frequencies (Mann-Whitney U-test, $p < 0.01$ for all cutoff frequencies). A total of 69% individuals with CP and 44% of controls increased the number of synergies by one with increasing LP cutoff frequency, while 4% and 4% increased by two synergies, respectively. Increasing LP cut-off frequency did not always lead to a greater number of synergies; four TD children decreased the number of synergies with increasing LP cutoff frequency.

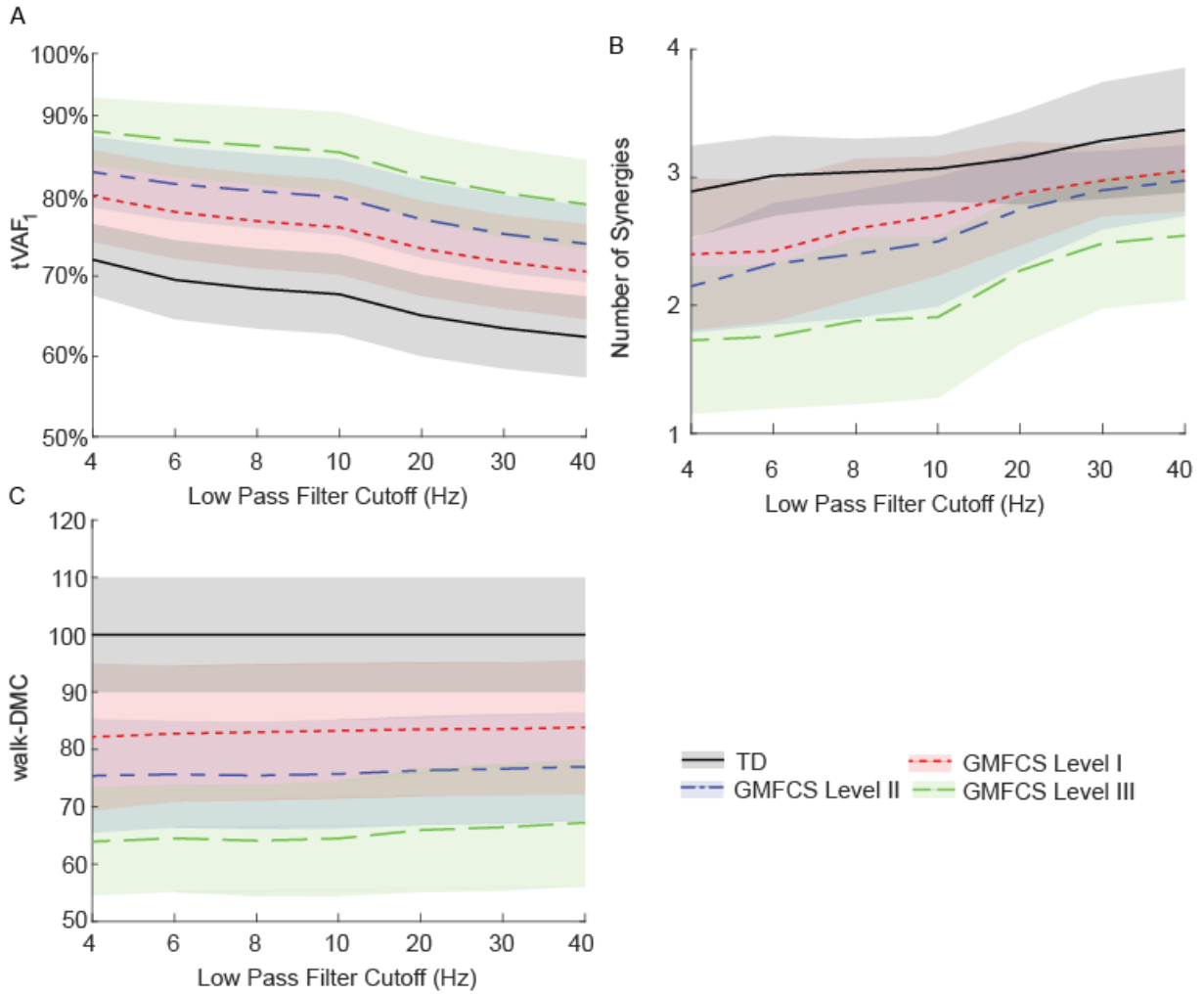

Figure 3.3. Average +/- one standard deviation of (A) total variance accounted for by one synergy ($tVAF_1$), (B) number of synergies for tVAF > 90%, and (C) walk-DMC across LP cutoff frequencies for TD and CP groups. As LP filter cutoff frequency increased, tVAF decreased and number of synergies increased for all groups. Average walk-DMC scores had minimal changes across LP cutoff frequencies.

Walk-DMC reduced the impact of LP cutoff frequency on synergy complexity. Between 4 Hz and 40 Hz, GMFCS Levels I, II, and III average walk-DMC scores increased by 1.7, 1.6, and 3.3 points, respectively (Figure 3.3C). Since walk-DMC normalizes $tVAF_1$ based upon the mean and standard deviation of the unimpaired group, the unimpaired group's average walk-DMC does not change (average of 100 with a 10 point standard deviation). For individual

participants, the change in walk-DMC with LP cutoff frequency ranged from <0.01 points to 15.4 points with an average change of 4.0 points. Some individual's walk-DMC increased with increasing LP cutoff frequency, while others decreased.

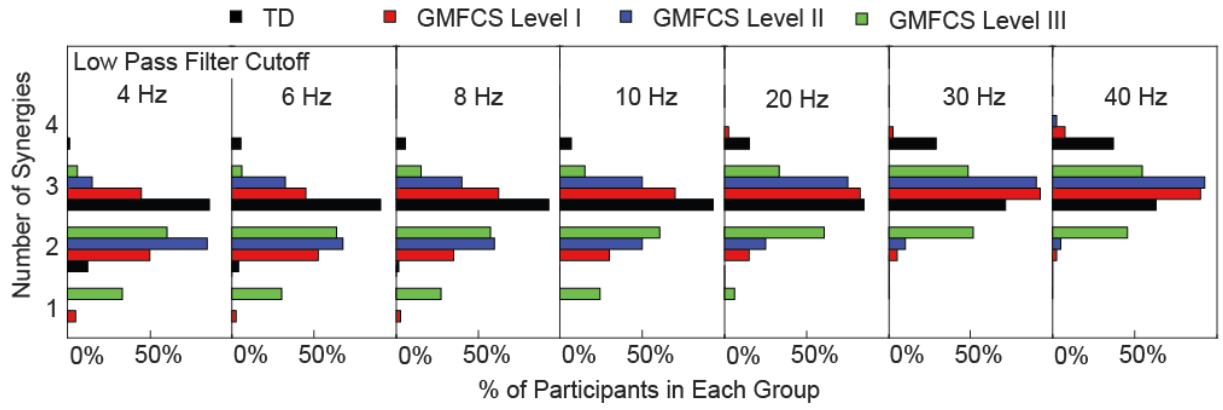

Figure 3.4. Number of synergies required for tVAF > 90%. Each TD and CP group is shown as the percentage of the total number of individuals in that group. As LP cutoff frequency increased the number of synergies increased for all groups.

3.3.2 *Synergy Weights*

Similar to tVAF, changes in LP cutoff frequency also impacted synergy weights. Synergy weights calculated with a 4 Hz and 40 Hz LP filter had an average correlation coefficient of 0.66, 0.87, 0.93, and 0.92 for 1 to 4 synergies, respectively (Figure 3.5). The average correlation coefficient by group were 0.68, 0.89, 0.94, and 0.93 for the TD children for 1 to 4 synergies, respectively; 0.69, 0.86, 0.94, and 0.92 for GMFCS Level I; 0.63, 0.85, 0.92, and 0.91 for GMFCS Level II; and 0.68, 0.86, 0.90, and 0.90 for GMFCS Level III. For an individual participant, the minimum correlation coefficient of synergy weights across LP cutoff frequencies was <0.01, 0.09, 0.47, and 0.57 for 1 to 4 synergies. Between 4 Hz and 40 Hz, the correlation coefficient was less than 0.8 for 56%, 20%, 11%, and 17% of all individuals for 1 to 4 synergies.

3.3.3 *Synergy Activations*

Synergy activations calculated with 4 or 40 Hz LP filters had an average correlation coefficient of 0.79, 0.78, 0.78, and 0.74 across all participants for 1 to 4 synergies, respectively (Figure 3.5). The average correlation coefficients were 0.79, 0.81, 0.81, and 0.78 for the TD children for 1 to 4 synergies, respectively; 0.79, 0.78, 0.79, and 0.74 for GMFCS Level I; 0.79, 0.76, 0.76, and 0.72 for GMFCS Level II; and 0.79, 0.75, 0.74, and 0.70 for GMFCS Level III. For an individual participant, the minimum correlation coefficient of synergy activations across LP cutoff frequencies was 0.51, 0.23, 0.40, and 0.45 for 1 to 4 synergies.

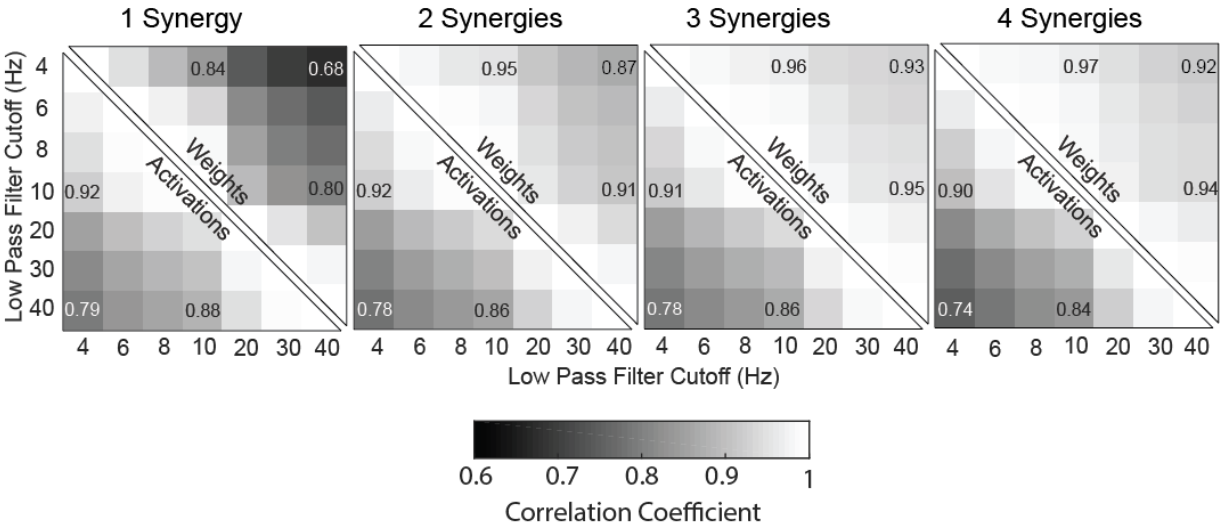

Figure 3.5. Correlation coefficients of synergy weights and synergy activations between LP cutoff frequencies, averaged across all subjects (TD and CP) for one to four synergies.

3.3.4 *Unit Variance*

Scaling EMG data to unit variance impacted synergy complexity, structure, and activations. Scaling to unit variance had a variable impact on $tVAF_1$, increasing $tVAF_1$ for some children and decreasing $tVAF_1$ for others when compared to peak amplitude scaling (average

difference across all participants: 1.7, SD 1.6 percentage points). However, group average $tVAF_1$ changed only slightly with unit variance scaling, with a maximum change of 1.3 percentage points for TD with a 4 Hz LP filter (Figure 3.6A). Changes in walk-DMC due to unit variance scaling were largest with a 4 Hz LP filter with increases of 4.0, 5.4, and 6.2 points for GMFCS Levels I, II, and III and smallest with a 40 Hz LP with group changes of 1.0, 1.1, and -0.7 points, respectively (Figure 3.6B). The synergy weights correlation coefficients calculated with and without unit variance scaling were lowest for one synergy and decreased with greater LP cutoff frequency. Synergy activations were similar between scaling methods and correlation coefficients slightly decreased with increasing LP filter cutoff.

For EMG data scaled to unit variance, LP cutoff frequency caused slightly larger changes in $tVAF_1$, with an average change of 10.5 percentage points between 4 Hz and 40 Hz LP filters. When we applied a threshold of tVAF > 90% to choose the number of synergies, 12% of children with CP and 11% of TD children had the same the number of synergies across all LP cutoff frequencies. Changes in walk-DMC were similar with changes of 1.2, 2.8, and 3.7 points for GMFCS Levels I, II, and III, respectively. The correlation coefficients of synergy weights were higher with unit variance scaling than EMG data normalized by peak amplitude, with average correlation coefficients of 0.90, 0.94, 0.95, and 0.96 for 1- 4 synergies comparing 4 Hz and 40 Hz LP filters (Figure 3.6C). The correlation coefficients of synergy activations were also slightly higher than EMG data normalized by peak amplitude, with average correlation coefficients of 0.81, 0.81, 0.79, and 0.77 for 1- 4 synergies comparing 4 Hz and 40 Hz LP filters (Figure 3.6D).

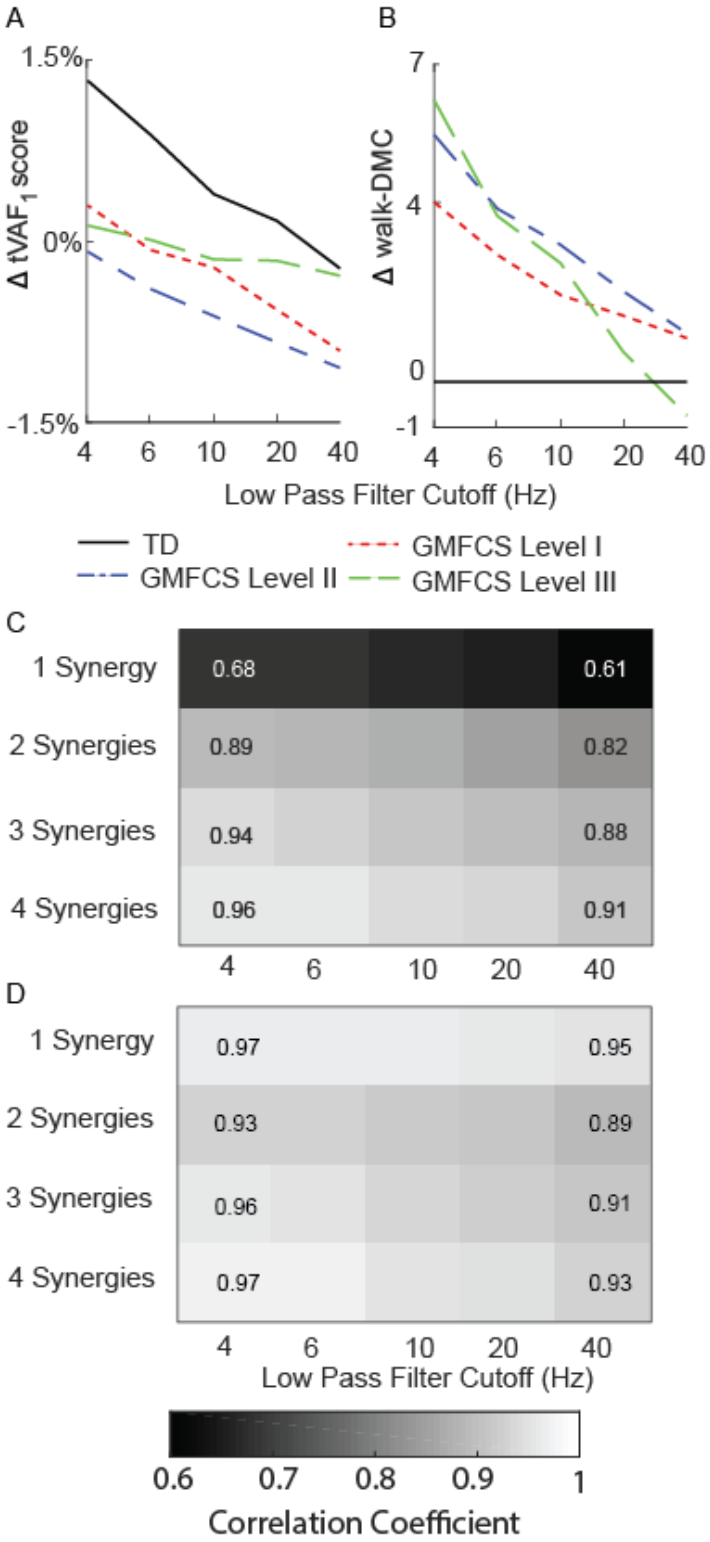

Figure 3.6. Average change in (A) tVAF and (B) walk-DMC for synergies calculated with EMG data scaled by peak activation or unit variance. Positive values indicate that results from unit variance scaling were greater than peak activation scaling. Average correlation coefficients of (C) synergy weights and (D) synergy activations between EMG data scaled by peak activation or unit variance.

3.4 DISCUSSION

A z-score normalized measure of synergy complexity, walk-DMC, was more stable across LP filter parameters than tVAF or number of synergies. For both TD and CP children, tVAF decreased with increasing LP cutoff. Amplitude scaling of EMG data had smaller effects than LP filter choice on synergy complexity. These results highlight one disadvantage of using tVAF thresholds (*i.e.*, tVAF > 90%) to identify the number of synergies for further analyses. Since tVAF is sensitive to filtering parameters, different studies may report different synergy numbers and co-activation patterns, depending on their choice of LP cutoff frequency. Despite the sensitivity of tVAF to LP cutoff, the TD and CP groups were significantly different across all LP filters for all measures of synergy complexity. These results suggest that z-score measures may be useful for comparing synergy results across studies or clinical centers. However, z-score normalization requires EMG data from TD or control participants, which may not be available at all institutions. Similarly, caution should be exercised when picking a single tVAF threshold for selecting number of synergies or comparing number of synergies across studies.

The choice of LP filter also affected individual muscle contributions (muscle weights) within each synergy. Synergy weights for solutions with fewer synergies (*e.g.*, $n = 2$ synergies) were more sensitive to LP cutoff. Increasing the number of synergies increased similarity of synergy weights since fewer muscles were activated together in each synergy. In this study we used a clinical dataset with EMG data from five muscles. We anticipate that the impacts of LP filter choice on synergy weights may be greater for datasets that have more muscles, since more muscles would be activated together in each synergy [80]. Our results support work by Chvatal & Ting [81] who demonstrated that further smoothing EMG data LP filtered at 40 Hz by subsequently averaging across bins ranging from 10 ms to 200 ms resulted in similar synergy

weights (similarity > 0.85 for the selected number of synergies with a threshold of tVAF > 85%). The correlation coefficients of the synergy activation curves also decreased with increasing LP filter cutoff. The decrease in correlation with increasing LP cutoff for the activation curves is reflective of the input EMG data, which retains additional high frequency components when processed with a higher LP filter (Figure 3.2).

The choice of amplitude scaling between unit variance and peak amplitude also impacted the individual muscle weights within each synergy. Synergy weights and activations were more similar across LP filter conditions for EMG data scaled to unit variance than peak amplitude, since scaling by unit variance reduces differences between muscles that may impact synergy weights and activations. All amplitude scaling methods involve applying a unique scaling factor to each EMG channel, which impacts the scaling of calculated synergy weights. Note that scaling to unit variance negates the effects of any previous scaling (*e.g.,* peak amplitude or maximum voluntary contraction). As with LP filter choice, analyses that calculated fewer synergies (*e.g., n* = 2 synergies) were more sensitive to amplitude scaling. The stronger influence of EMG processing methods on synergy solutions with fewer synergies is especially important for evaluations of clinical populations, which typically have reduced synergy complexity compared to control populations.

Just as we found a range of LP filters used in prior research, we also found a range of HP filters used before rectification, including 40 Hz [49,68,82], 35 Hz [42,72], and 20 Hz [74,75]. We could not explore the effects of HP filter choice with our dataset since our data were originally recorded with an on-board 35 Hz HP filter. However, the international society of Electrophysiology and Kinesiology (ISEK) currently recommends a HP filter from 5-10 Hz [83] and De Luca [26] found that a 20 Hz HP filter was the best compromise between eliminating

movement artifacts and retaining EMG power. HP filters primarily act to reduce DC drift in the EMG signal due to motion artifact and other nonphysiological signals. Consequently, we do not expect large impacts from HP filters on synergies, but the precise impacts of HP filtering on synergy analyses remain an open question.

Beyond filter cutoff frequency and amplitude scaling methods, there are other EMG preprocessing choices we did not explore, including filter type and filter order. Devaprakah et al. [84] compared a 2nd order critically damped filter to a 2nd order Butterworth filter with consistent cutoff frequencies and found only small differences in the EMG data that did not affect clinical interpretation. De Luca [26] found less than a 1% difference in root mean square difference between EMG profiles processed with 2nd or 3rd order Butterworth filters. Taken together, these results suggest that filter choice and order are less significant than LP cutoff frequency for EMG and synergy analyses.

Given the wide variety of EMG data processing methods used in prior research, exploring and discussing the underlying biological mechanisms that should inform the choice of filters and synergy analyses methods would be useful for future research. Current EMG data processing methods are largely based upon technical specifications. Prior work has found that LP filters should be tailored to the specific task [23,85]. However, there is a need to explore the neurophysiology underlying synergy analyses, especially considering some of the limitations of surface EMG data [21]. For example, if synergies are driven by an underlying central pattern generator, what are the rates of these reflex loops, and how can these biological processes inform data preprocessing and interpretation of synergy analyses? If central pattern generators are driven by low-frequency mechanisms, then perhaps low-frequency LP cutoff frequencies are more

appropriate. Future research, such as newly developed methods with direct central nervous system recordings and surface EMG data may assist in understanding these relationships [86].

Output measures of synergy analyses including tVAF, synergies weights, and synergy activations were sensitive to EMG processing methods. We found that increasing LP filter cutoff frequency decreased synergy complexity, as measured by tVAF. Since tVAF is commonly used to identify the number of synergies, LP filter choice can impact conclusions about the number of synergies and muscle co-activation patterns from synergy analyses. Synergy weights and activations are less sensitive to LP cutoff frequency when calculated for two or more synergies. Future studies of synergy analyses and potential clinical applications should carefully consider and report EMG processing methods to enable comparisons across studies and institutions. As synergy analysis is adopted in clinical gait analysis to inform treatment planning, these results highlight the importance of carefully considering EMG processing methods and the utility of a control database. We found that z-score based measures, such as walk-DMC, that compare to control populations can reduce sensitivity to LP filter choice and facilitate comparisons between studies and clinical centers with different EMG protocols.

Chapter 4. REPEATABILITY OF MUSCLE SYNERGIES WITHIN AND BETWEEN DAYS FOR TYPICALLY DEVELOPING CHILDREN AND CHILDREN WITH CEREBRAL PALSY

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ABSTRACT

Muscle synergies are typically calculated from electromyographic (EMG) signals using nonnegative matrix factorization. Synergies identify weighted groups of muscles that are commonly activated together during a task, such as walking. Synergy analysis has become an emerging tool to evaluate neuromuscular control; however, the repeatability of synergies between trials and days has not been evaluated. The goal of this study was to evaluate the repeatability of synergy complexity and structure in unimpaired individuals and individuals with cerebral palsy (CP). EMG data were collected from eight lower-limb muscles during gait for six typically developing (TD) children and 5 children with CP on two separate days, over three walking speeds. To evaluate synergy complexity, we calculated the total variance accounted for by one synergy (tVAF1). On a given day, the average range in tVAF1 between gait cycles was 18.2% for TD and 19.1% for CP. The average standard deviation in tVAF1 between gait cycles was 4.9% for TD and 5.0% for CP. Average tVAF1 calculated across gait cycles was not significantly different between days for TD or CP participants. Comparing synergy structure, the average within day correlation coefficients of synergy weights for two or more synergies were 0.89 (0.15) for TD and 0.88 (0.15) for CP. Between days, the average correlation coefficient of synergy weights for two or more synergies was greater than 0.89 for TD and 0.74 for CP. These results demonstrate that synergy complexity and structure averaged over multiple gait cycles are repeatable between days in both TD and CP groups.

4.1 INTRODUCTION

How the human body controls muscle activity to coordinate complex movements remains an open question and an important area of research. In cyclic motions, such as walking, prior

research has theorized that the nervous system controls a lower dimensional system composed of weighted groups of muscles, rather than controlling each muscle individually [65]. These weighted groups of muscles are commonly referred to as synergies or modes. Synergies are commonly estimated from experimental electromyography (EMG) using matrix factorization algorithms [45], such as nonnegative matrix factorization (NNMF). These algorithms identify groups of muscles that are consistently activated together during a given task [42,87].

In unimpaired individuals, only a small set of synergies (e.g., n=4-6) are required to reproduce measured EMG signals during balance, walking, and various other tasks [42,44,87,88]. Recent research has used synergies as a framework to evaluate altered neuromuscular control in individuals with neurologic disorders, such as stroke or cerebral palsy (CP) [48,49,56]. These studies have demonstrated that individuals with neurologic disorders use fewer synergies during walking compared to unimpaired individuals, suggesting a simplified control strategy that may contribute to impaired movement [49,56,66]. Synergies may be clinically useful for evaluating impaired neuromuscular control or predicting patient-specific responses to treatment [36,51,67,68]. For example, Routson et al. [89] found that synergies measured before a treadmill training program in adult stroke survivors were associated with changes in synergy structure, complexity, and timing after training and were also related to improvements in gait.

These studies suggest that synergies may be clinically useful for diagnosis and treatment planning. However, before the clinical potential can be evaluated, the repeatability of synergies needs to be quantified. Repeatability of synergies between steps and between days has not yet been investigated among individuals with neurologic disorders such as stroke or CP. Natural variability between steps may cause significant changes in muscle activity [90], and may impact

the clinical utility of synergy analyses. Past studies have used a number of methods to address this variability, including averaging EMG data over multiple trials [43,91,92], or concatenating EMG from multiple gait cycles prior to calculating synergies [49,63,87]. Oliveira et al. [90] found concatenation of EMG from multiple gait cycles improved synergy representation of muscle activity in subsequent gait cycles compared to EMG averaged over multiple gait cycles.

In this study, our goal was to examine the repeatability of synergies, for both typically developing (TD) children and children with CP. We hypothesized synergies would be repeatable between days for both TD and CP. Further, we hypothesized that, due to neuromuscular impairments, children with CP would display less repeatability between steps compared to TD. The results of this study will help inform how synergies can be used to evaluate neuromuscular control for potential clinical applications.

4.2 METHODS

We retrospectively analyzed repeatability of synergies for a group of six TD children and five children with CP who had previously received repeated gait analyses with EMG (Table 3.2). The children with CP had mild impairment, Gross Motor Function Classification System (GMFCS) Level I. Three of the children with CP had a primary diagnosis of spastic diplegia and two of the children with CP had a primary diagnosis of spastic hemiplegia (one left and one right side impairment). Kinematics at the self-selected speed were with the normal range except for P9 (apparent equinus per Rhodda et al. [93]) and P11 (group 0 hemiplegic per Riad et al. [94]).

For each individual, retrospective EMG and motion capture data was analyzed for nine trials on two separate days (*i.e.,* 18 total trials). The second data collection occurred an average of 8.5 days after the initial data collection (range 2 to 23 days). For children with CP, this time interval normally corresponded to a follow-up visit discuss the results of the gait analysis. Each

individual walked at three walking speeds: self-selected walking pace, a fast pace, and as fast as possible without running. The number of gait cycles collected over the trials on each day varied between participants due to differences in walking speed, step length, and quality of marker data. The average number of gait cycles analyzed for TD participants on a day was 44.8 (SD: 15.9), with a range of 25-78 cycles, and 47.5 (19.6), with a range of 24-81 for CP participants. Two trials for one TD participant from the first day contained missing marker data and were excluded from analyses.

Table 3.2. Study population.

Subject	Gender	Age (years)	Mass (kg)	Height (m)	Diagnosis
Typically developing					
P1	M	6	24.7	1.25	–
P2	M	13	47.6	1.60	–
P3	F	13	63.4	1.66	–
P4	M	15	59.0	1.79	–
P5	M	6	20.2	1.20	–
P6	F	9	26.9	1.31	–
Avg (SD)	–	10.3 (3.5)	40.3 (17.1)	1.5 (0.2)	–
Cerebral palsy					
P7	M	11	54.8	1.56	Sp D
P8	F	11	33.6	1.30	Sp D
P9	F	13	45.0	1.60	Sp D
P10	M	10	28.3	1.35	H-L
P11	M	6	21.0	1.22	H-R
Avg (SD)	–	10.2 (2.3)	46.5 (12.0)	1.4 (0.1)	–

Sp D = Spastic diplegia; H-L = Hemiplegia with left affected limb; H-R = Hemiplegia with right affected limb.

Electromyography (EMG) data were recorded at two laboratories within the same hospital using a 16-channel system (Wave Wireless EMG, Cometa, Milan, Italy) at either 1000 or 1500 Hz and were synchronized with a 10- or 15-camera motion analysis system (VICON, Oxford Metrics, Oxford, UK) recording at 100 Hz. The EMG data were high pass filtered with a 4th order Butterworth with a 40 Hz cut-off, rectified, and low pass filtered at 4 Hz [49]. EMG

data were collected from eight muscles per leg including the gluteus medius, lateral hamstrings, medial hamstrings, vastus lateralis, rectus femoris, gastrocnemius (lateral head), soleus, and tibialis anterior. Both legs were analyzed for the TD participants and participants with diplegic CP, while only the affected side was analyzed for the participants with hemiplegic CP. Some trials contained poor EMG signal quality for a single muscle, which was excluded from the analysis for both days for those participants (impacting the right vastus lateralis for P1-P4, P8 and P11 and the left gluteus medius for P10). EMG for each muscle was normalized to the maximum on a given day and segmented into gait cycles for each limb (measured heel strike to heel strike from motion analysis data). Each gait cycle was normalized to 101 data points.

Synergies were calculated from the EMG data using NNMF [45,46]. Briefly, NNMF decomposes experimental EMG data into a set of synergy weights (W_{mxn}) and synergy activations (C_{nxt}), such that $EMG = W*C + error$, where n is the number of synergies, m is the number of muscles measured (7 or 8 in this study) and t is equal to the number of time points (101 over the normalized gait cycle for this study). Error is defined as the difference between the experimental EMG and the reconstructed EMG calculated by synergies. We calculated synergies with NNMF in Matlab (MathWorks, Inc., Natick, Massachusetts, United States) using the following parameters which produced repeatable synergies between trials of NNMF: 50 replicates, 1000 max iterations, $1x10^{-4}$ minimum threshold for convergence, and a $1x10^{-6}$ threshold for completion. For each gait cycle, we calculated both the synergy complexity, which describes the total variance accounted for ($tVAF_n$) in the muscle activity reproduced by synergies (n=1 to 5), and the synergy weights or structure, which describe muscles commonly activated together.

For each participant, we evaluated synergy complexity by calculating the average and standard deviation of $tVAF_n$ (for 1 to 5 synergies) for each limb and each day (TD: 6 participants x 2 limbs x 2 days = 24 samples; CP: 3 diplegic participants x 2 limbs + 2 hemiplegic participants x 1 limb, x 2 days = 16 samples). Total variance accounted for was calculated as:

$$tVAF_n = \left(1 - \frac{\left[\sum_j^t \sum_i^m (error)^2\right]}{\left[\sum_j^t \sum_i^m (EMG)^2\right]}\right) \times 100\% \quad (4.3)$$

To determine repeatability of $tVAF_n$ between gait cycles, we evaluated the range and standard deviation of $tVAF_n$ values for both TD and CP groups. To determine the repeatability of $tVAF_n$ between days and with varying speeds, we used a linear mixed effects (LME) model to examine the fixed effects of group (*i.e.*, TD versus CP), day, and cycle speed normalized by leg length, and random effects on intercept for each participant. The resulting LME equation was of the form:

$$tVAF_n \sim C_1 \times Group + C_2 \times Day + C_3 \times Cycle\ Speed + (1|Subject) \quad (4.4)$$

To evaluate the repeatability of synergy structure, we compared the repeatability of the synergy weights, *W*, between gait cycles and between days. The order of synergies returned from NNMF is not consistent between runs. For example, the first synergy returned from one trial may correspond to the fourth synergy returned from another trial. Thus, to compare synergies, we first had to identify similar synergies. We used K-means cluster analysis to identify the similar synergies between gait cycles and days for each individual [95]. Briefly, K-means cluster analysis plots an observation as a point in *m*-dimensional space and then groups them into K clusters by minimizing the sum of the squares of the distances between all points and the cluster center. For this study, each observation was a measured synergy from a gait cycle and K was the number of synergies (n = 1 to 5). We used the centers of clusters from the K-means analysis as the average synergy weights.

We compared the repeatability of synergy weights between gait cycles by computing the correlation coefficient between the measured synergies from each gait cycle at the participants' self-selected speed to the average set of synergies identified from K-means analysis. For each day, the average and standard deviation of the correlation coefficient was also found for each participant and cycle speed. We used a Wilcoxon sign-rank test to assess significant differences in the average, standard deviation, and coefficient of variation (COV) of the correlation coefficient between days within both the TD and CP groups for the self-selected speed gait cycles. The average and standard deviations in correlation coefficients were calculated across both the TD and CP groups and compared using a Mann-Whitney test for the self-selected speed gait cycles.

To inform future studies, we also estimated how many gait cycles are needed on a given day to reduce the expected error in estimates of synergy complexity. We evaluated how the standard deviation in total variance accounted for by one synergy ($tVAF_1$), calculated from all measured gait cycles and speeds stabilized as the number of gait cycles increased. We calculated the margin of error (MOE) for a 95% confidence interval for each participant, limb, and day as $MOE = 1.96\left(\sigma/\sqrt{N}\right)$ where N equals the number of gait cycles and σ equals the standard deviation in $tVAF_1$ computed from those N gait cycles. Starting with N=2 gait cycles, we calculated the MOE and evaluated changes in the MOE as additional gait cycles were included. We approximated the number of gait cycles required to achieve a specified MOE in $tVAF_1$ from 2-4%. In other words, we estimated how many gait cycles would be required to be 95% confident that the true mean $tVAF_1$ would be contained within a defined MOE. We estimated the number of gait cycles as $N = \left[1.96\left(\sigma/MOE\right)\right]^2$ and assumed a static standard deviation calculated over all measured gait cycles for each participant.

4.3 RESULTS

The LME model identified a significant difference in synergy complexity, as measured by total variance accounted for ($tVAF_n$), between TD and CP for n = 1 to 5 synergies (Figure 4.1.A). Across all gait cycles, $tVAF_1$ described on average 77.2% (SD: 4.1%) of the variance in muscle activity for the children with CP compared to 68.4% (2.3%) for TD. The LME model estimated a coefficient of 10.0% (standard error, SE: 0.02) difference in $tVAF_1$ between groups ($p<0.001$). Thus, even though this study included CP children with mild impairment, fewer synergies described a greater variance in muscle activity in CP children compared to TD children, similar to prior research [58].

There was no significant difference in $tVAF_n$ between gait cycles. Between all measured gait cycles, the average standard deviation in total variance counted for by one synergy ($tVAF_1$) was 4.9% for TD (range of 3.7% to 6.5%) and 5.0% for CP (range of 2.5% to 7.5%). The average maximum difference in $tVAF_1$ between gait cycles from a single day was 18.2% for TD and 19.1% for CP.

Between days, there was also no significant differences in $tVAF_n$ for the LME, except for $tVAF_2$ which had a significant difference of 0.54% (SE: 0.003) between days ($p= 0.03$). Looking specifically at the variance accounted for by one synergy, TD participants had an average $tVAF_1$ of 68.4% (5.0%) on day 1 and 68.4% (4.7%) on day 2. In CP, average $tVAF_1$ was 77.4% (5.3%) on day 1 and 76.9% (4.8%) on day 2. Of the participants with CP, participant 7 showed a distinctly lower $tVAF_n$ than any of the other children with CP, which was more similar to the TD children (Figure 4.2), which demonstrates some of the heterogeneity in CP. These results suggest that synergy complexity as measured by $tVAF_n$ is repeatable between days.

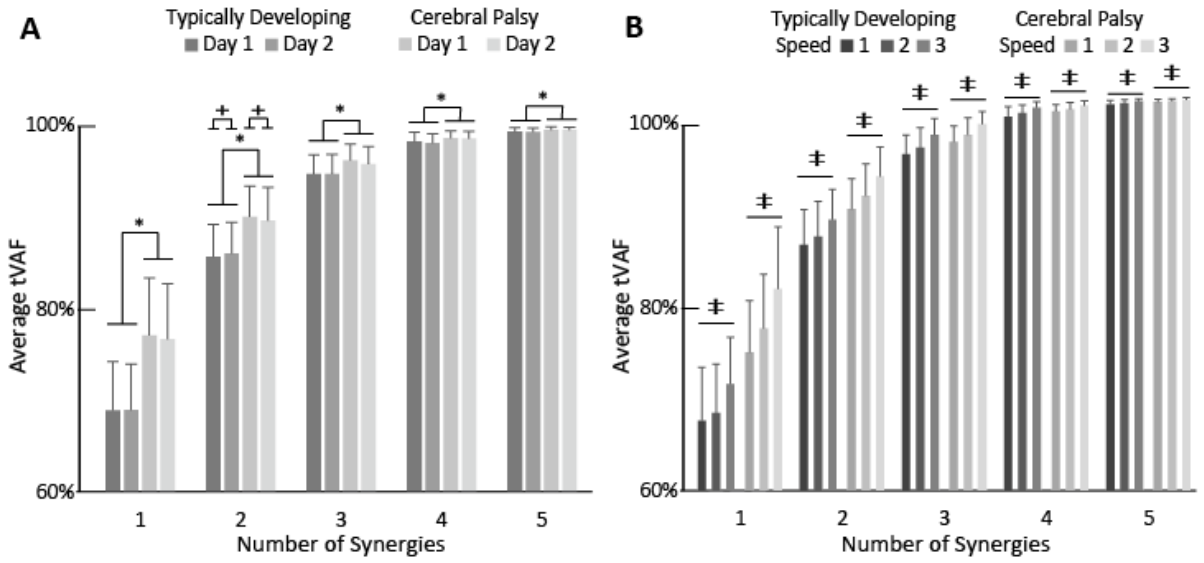


Figure 4.1. (A) Average tVAFn for day 1 and day 2 in TD and CP calculated from all measured gait cycles (including all three walking speeds). * indicates a significant difference in tVAFn with $p<0.05$ comparing between TD and CP groups. + indicates a significant difference between days in tVAFn with $p<0.05$. (B) Average tVAFn for each of the three walking speeds in TD and CP from both days. ‡ indicates a significant difference in tVAFn with $p<0.05$ comparing between walking speeds.

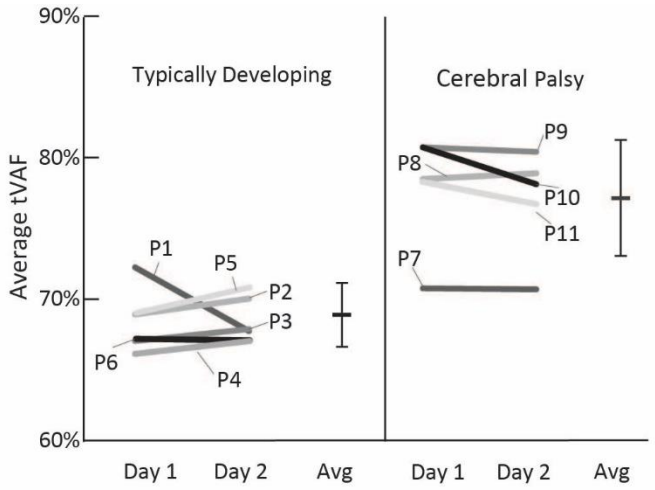


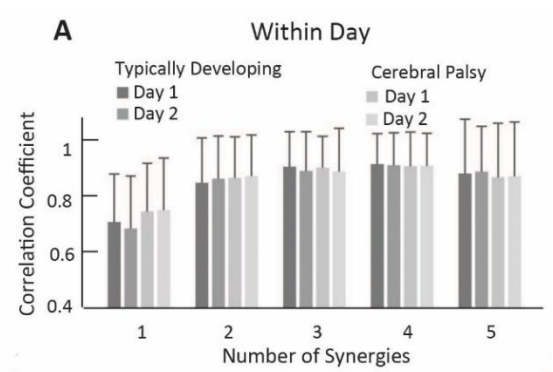
Figure 4.2. Average $tVAF_1$ across all gait cycles for each participant (P) on day 1 and day 2. Overall group averages and standard deviations are shown to the right. Participant P7 had $tVAF_1$ measurements in the range of the TD group. There was a significant difference in $tVAF_1$ between TD and CP groups, but there were no signficant difference in $tVAF_1$ between days within either the TD or CP groups

In the LME, walking speed had a significant effect on synergy complexity for $tVAF_n$ of 1 to 5 synergies (slope = 5.0, SE 0.004, $p < 0.001$ for $tVAF_1$). At the self-selected speed, $tVAF_1$ was 74.0% (5.2%) for CP and 67.1% (5.4%) for TD compared to 80.5% (6.3%) and 70.8% (4.8%) respectively at the fastest walking speed (Figure 4.3 B).

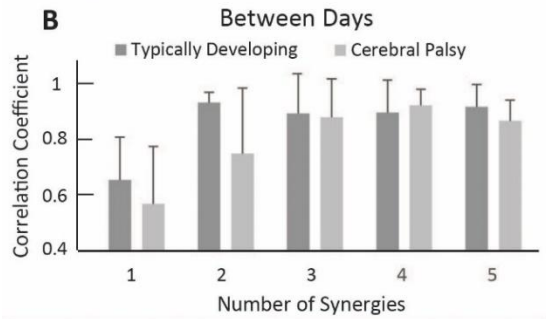
Synergy weights, W, also varied between gait cycles on a given day. TD children had an average within day correlation coefficient at their self-selected speed of 0.71 (0.17) for one synergy on day 1 and 0.68 (0.18) on day 2 (Figure 4.3). Children with CP had an average within day correlation coefficient of 0.74 (0.17) on day 1 and 0.75 (0.19) on day 2 for one synergy. Correlation coefficients increased to greater than 0.85 for both TD and CP groups when 2 to 5 synergies were compared. Synergies calculated from the faster walking speeds also differed from the self-selected walking speeds. The correlation coefficients compared to the self-selected speed synergies decreased with increasing walking speed: 0.45 (0.24) and 0.41 (0.24) for the fast and fastest speed for TD and 0.51 (0.22) and 0.40 (0.22) for the fast and fastest speeds for CP. This indicates changes in synergy structure with increasing speed for both groups.

Between days, there were no significant differences in the average, standard deviation, or COV in the synergy structure correlation coefficients for 1 to 5 synergies in either the TD or CP groups at self-selected speeds (*e.g.*, TD: p=0.844, p=0.688, p=0.563 for 1 synergy; CP: p=0.813, p=0.625, p=0.813 for 1 synergy). There were also no significant differences in repeatability of synergy weights between the TD and CP groups, including the average, standard deviation, or COV in correlation coefficients for 1 to 5 synergies (p=0.339, p=0.818, p=0.621 respectively for 1 synergy). The average correlation coefficients for synergy weights between days were 0.65 (0.15) for TD and 0.57 (0.20) for CP for one synergy. The average between day correlation coefficients for 2 to 5 synergies increased to between 0.89 and 0.93 for TD and between 0.75 and

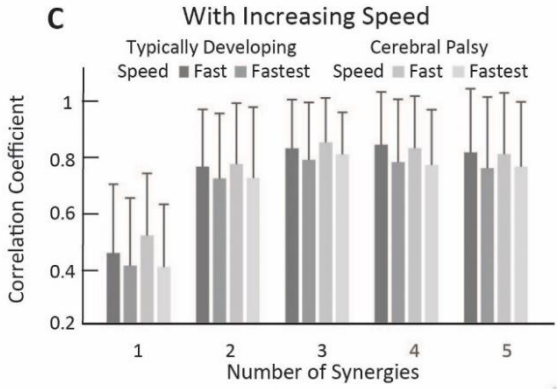
0.92 for the CP group at self-selected speeds. There was also no significant difference in the average between day correlation coefficients between the TD and CP groups. These results demonstrate that synergy complexity and synergy weights can vary between gait cycles, but have good repeatability when averaged across gait cycles for a given day at a participant's self-selected



Within Day Correlation Coeffcients					
Synergies:	1	2	3	4	5
TD	.69± 0.18	.85± 0.16	.90± 0.13	.97± 0.17	.88± 0.18
CP	.75± 0.19	.87± 0.15	.89± 0.13	.91± 0.12	.87± 0.19



Between Day Correlation Coeffcients					
Synergies:	1	2	3	4	5
TD	.65± 0.15	.93± 0.04	.89± 0.14	.90± 0.12	.92± 0.08
CP	.57± 0.20	.75± 0.23	.88± 0.14	.92± 0.06	.87± 0.07



Faster Speed Correlation Coeffcients					
Synergies:	1	2	3	4	5
TD Fast	.45± 0.24	.75± 0.20	.82± 0.17	.83± 0.19	.81± 0.23
Fastest	.41± 0.24	.72± 0.23	.78± 0.20	.77± 0.22	.75± 0.25
CP Fast	.51± 0.22	.76± 0.22	.84± 0.16	.82± 0.18	.80± 0.22
Fastest	.40± 0.22	.72± 0.25	.80± 0.15	.76± 0.20	.76± 0.23

Figure 4.3. (A) Within Day correlations between average synergies for each day for TD and CP groups for the self-selected walking speed only. There were no significant differences between days within the TD and CP groups nor between the TD and CP groups for n = 1-5 synergies. (B) Correlations between average synergies of the self-selected speed from day 1 and day 2 for TD and CP groups. There were no significant differences between days within the TD and CP groups nor between the TD and CP groups for n = 1-5 synergies. (C)

Correlations between average synergies of the self-selected speed and the fast and fastest walking speeds. Both TD and CP showed decreasing synergy structure similarity with increasing walking speeds.

walking speed.

To estimate the effect of number of gait cycles on confidence intervals for $tVAF_1$ we calculated the MOE of each participant, limb, and day using all measured gait cycles (Figure 4.4). As expected, with increasing number of gait cycles the MOE decreases and stabilizes. The maximum number of gait cycles required for $tVAF_1$ to stabilize to within a MOE of 2%, 3%, and 4% was 41, 18, and 11 gait cycles across all TD participants and 43, 19, and 11 cycles across all CP participants. Among all TD and CP participants, the average number of gait cycles for $tVAF_1$ to stabilize within a MOE of 2%, 3%, and 4% was 24, 11, and 6 gait cycles, respectively.

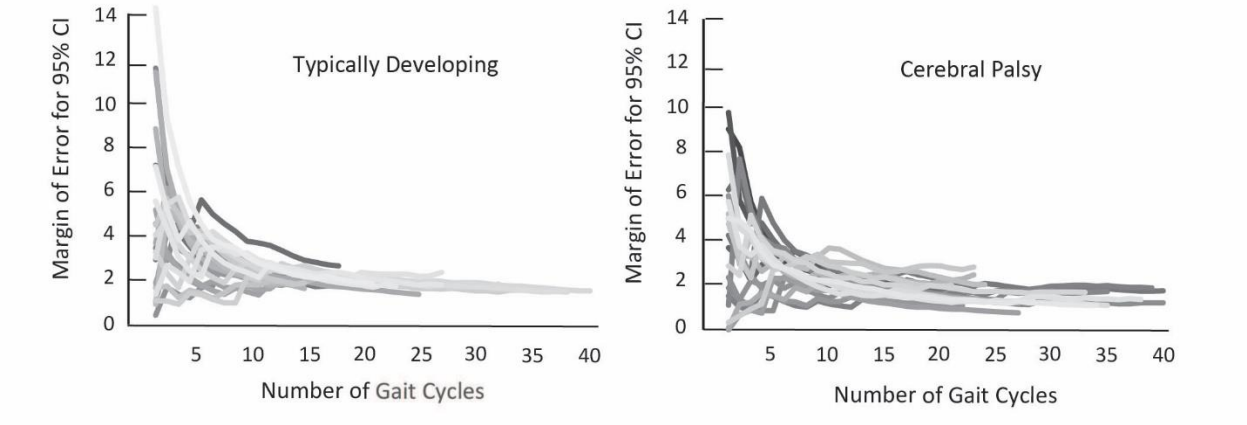


Figure 4.4. Margin of error in a 95% confidence interval based upon experimentally measured standard margins of error for the first N gait cycles for each participant and day. All gait cycles, from all walking speeds were used for this calculation. When calculated for small numbers of gait cycles the expected margin of error can change dramatically as a result of step-to-step variability. As the number of gait cycles increases, the margin of error decreases and stabilizes.

4.4 DISCUSSION

This study aimed to evaluate repeatability of synergies between steps and days. for TD individuals and individuals with CP. We determined that synergy complexity, $tVAF_n$, and

synergy weights, *W* vary between gait cycles in both TD individuals and individuals with CP, and are affected by walking speed. The level of step-to-step variability was similar between TD and CP groups. Despite the step-to-step variability, average synergy complexity and structure were repeatable between days. These results demonstrate that synergies can provide a consistent measure of neuromuscular control between days but the step-to-step variability also highlights the risks of using synergies measured from only a few gait cycles and demonstrates the need to record sufficient data as part of clinical routine. Walking speed also needs to be monitored between days, since it influences both synergy complexity and structure.

The results of this study will support future research that use synergies as a clinical tool in the evaluation of impairments amongst individuals with CP or stroke during gait, with applications toward both diagnosis and assessing longitudinal changes resulting from rehabilitation treatments, similar to a prior study in stroke [89]. Our work corroborates previous findings showing that individuals with neurologic disorders demonstrate a simplified control strategy, even though the individuals included in this study had mild impairments [48,49,66].

This study examined the repeatability of muscle synergies during gait measured from seven or eight lower limb muscles. It has been previously shown that the number and choice of muscles analyzed will impact both synergy weights and $tVAF_n$ [80]. In this study, we tested the impact of including seven or eight muscles due to the poor EMG signal quality of a few muscles, but found that the results and conclusions were similar between analyses with seven or eight muscles. The selection of muscles to be measured may also change the repeatability of synergy analyses.

Similarly, synergy repeatability may be affected by other factors such as choice of task or impairment level. This study included a limited number of participants who were all GMFCS

Level I, in which only impaired limbs were analyzed. We also did not have a large enough sample size to examine differences between patients with bilateral involvement (diplegia) and unilateral involvement (hemiplegia). These results demonstrate promise that synergy complexity and weights are repeatable between days, but further research will be required to confirm if these results are consistent across CP subtypes, in other clinical populations, or for other tasks beyond walking.

In summary, synergy complexity and weights were repeatable between days and repeatability of synergy analyses were similar between TD and CP groups. Both synergy complexity and weights were affected by walking speed. Increasing the number of gait cycles improved the estimates of synergies for comparison between days. The repeatability of synergy complexity with 20 gait cycles was sufficient to evaluate $tVAF_1$ with an average MOE within 3% for all participants in this study. Experimental protocols that include sufficient gait cycles and monitor walking speed will be important for future studies that aim to use synergy analyses to compare neuromuscular control between individuals or days.

Chapter 5. ASSOCIATIONS BETWEEN SYNERGIES AND TREATMENT OUTCOMES IN CEREBRAL PALSY ARE ROBUST ACROSS CLINICAL CENTERS.

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ABSTRACT

Objective: To determine whether patient-specific differences in motor control quantified using muscle synergy analysis were associated with changes in gait after treatment in cerebral palsy across two clinical centers with different treatments and clinical protocols.

Design: Retrospective Cohort Study.

Setting: Clinical Medical Center.

Participants: Center 1: 473 children with cerebral palsy and 84 typically-developing children. Center 2: 163 children with cerebral palsy and 12 typically-developing children.

Interventions: Standard clinical care at each center.

Outcome Measures: The dynamic motor control index during walking (walk-DMC) was computed from electromyography data during gait using muscle synergy analysis. Regression analysis was used to evaluate whether pre-treatment walking speed or kinematics, muscle synergies, treatment group, prior treatment, or age were associated with post-treatment changes in gait at both clinical centers.

Results: Walk-DMC was significantly associated with changes in speed and kinematics after treatment with similar regression models at both centers. Children with less impaired motor control were more likely to have improvements in walking speed and gait kinematics after treatment, independent of treatment group.

Conclusions: Dynamic motor control evaluated with synergy analysis was associated with changes in gait after treatment at both centers, despite differences in treatments and clinical protocols. This study further supports the finding that walk-DMC provides additional information, not captured in traditional gait analysis, that may be useful for treatment planning.

5.1 INTRODUCTION

Poor motor control often arises after neurologic injury, such as in cerebral palsy (CP). Reduced motor control hinders movement and has been suggested as an important factor influencing treatment outcomes [47]. Recent research has suggested that measures derived from muscle synergy analysis, such as the Dynamic Motor Control Index during Walking (walk-DMC), may provide a clinical tool to quantify poor motor control and inform treatment planning [58,64]. These studies also suggested that individuals with less impaired motor control, or higher walk-DMC scores, have greater improvements in walking ability after treatment than individuals with poor motor control. These results support the common clinical belief that poor motor control can contribute to worse treatment outcomes. Despite these initial promising results, the relationship between walk-DMC and treatment outcomes has only been evaluated at 1 center. Reproducibility is critical to understand the generalizability and potential impact of new measures in the clinic, especially when considering that many published biomedical findings fail to be reproduced [96].

Whether walk-DMC's association with treatment outcomes extends across clinical centers remains an open question, especially considering differences in clinical protocols and treatments between centers. For example, between centers, the dosage and number of muscles treated with botulinum toxin type A (BTA) injection [97], amount of transection in selective dorsal rhizotomy (SDR) [98], and choice of procedures in single-event multi-level orthopedic surgeries (SEMLSs) for children with CP [99] can a vary. In clinical gait analyses, the number of muscles monitored with electromyography varies between centers which may impact calculations of synergies and walk-DMC. Thus, it is important to determine whether differences

between centers in procedures, outcomes, or collected data, refute or alter conclusions about whether walk-DMC is a useful measure to inform treatment planning.

Walk-DMC leverages the theory of muscle synergies to create an objective measure of motor control that quantifies an individual's complexity of neuromuscular control during walking [58,100]. Synergy analysis uses electromyography data and matrix factorization algorithms to identify a small set of weighted muscles groups (synergies) that are recruited together during functional tasks [62,65,90]. After neurologic injury (e.g. stroke and CP), even fewer synergies are required to describe the electromyography data, suggesting a simplified control strategy that may contribute to impaired movement [28,49,57,89,101]. Since electromyography data are collected as part of standard care in clinical gait analysis laboratories, synergy methods are attractive for quantifying patient-specific deficits in neuromuscular control. Walk-DMC represents a summary measure of an individual's synergy complexity.

The aim of this research was to investigate whether walk-DMC is associated with treatment outcomes across clinical centers. A secondary goal was to determine whether differences in clinical treatment or data collection protocols (*e.g.* the number of muscles included in synergy analysis) impact these results. Determining if walk-DMC is associated with changes in kinematics and walking speed following treatment will help determine the clinical utility and generalizability of walk-DMC as a measure of motor control for treatment planning in CP.

5.2 METHODS

The data used in this study received ethical approval by the Commissie Medische Ethiek (KU Leuven) and the University of Minnesota.

5.2.1 *Participants*

Children with CP from 2 clinical centers with pre-treatment electromyography (EMG) and kinematic data, collected as standard clinical care, were retrospectively analyzed. For Center 1, 473 children (Table 5.1) from Gillette Children's Specialty Healthcare, St. Paul, MN were analyzed across the following treatment groups: selective dorsal rhizotomy, SEMLS, single-level orthopedic surgery, or conservative treatment (physical therapy, excluding BTA injection). Full details on the collection methodology from Center 1 can be found in the article by Schwartz et al [64].

Table 5.1. Subject Demographics, average (one standard deviation).

Treatment	N	GMFCS	Age	Gender	Speed	Speed	GDI	GDI	Follow-up Time
		I / II / III	y+mo	F: M	Pre	Post	Pre	Post	y+mo
Center 1									
CONS	76	22/28/26	6+8 (2+7)	35:41	0.33 (0.11)	0.36 (0.12)	71.3 (11.4)	73.7 (12.2)	1+7 (0+7)
ORTHO-1	39	16/15/8	6+11 (3+4)	16:23	0.34 (0.11)	0.36 (0.12)	71.5 (9.7)	75.7 (10.7)	1+6 (0+4)
SEMLS	176	25/85/66	10+0 (3+5)	77:99	0.31 (0.11)	0.29 (0.11)	67.4 (9.7)	76.3 (10.2)	1+5 (0+5)
SDR	182	35/76/71	5+7 (2+0)	82:100	0.32 (0.12)	0.35 (0.11)	69.5 (9.4)	75.1 (8.5)	1+6 (0+4)
Center 2									
BTA	60	20/20/20	6+9 (2+11)	20:40	0.31 (0.14)	0.29 (.015)	73.3 (12.1)	74.1 (10.8)	0+2 (0+2)
SEMLS	59	20/19/20	12+1 (3+1)	24:35	0.28 (0.11)	0.25 (.013)	66.1 (11.7)	76.7 (12.0)	1+1 (0+2)
SDR	44	12/28/4	9+1 (2+0)	23:21	0.33 (0.11)	0.31 (.010)	72.1 (10.5)	74.0 (13.9)	1+1 (0+5)

BTA: Botulinum Toxin Type A Injection, CONS: Conservative Treatment, F: Female, GDI: Gait Deviation Index,
N: number of participants, M: Male, ORTHO-1: Single-Level Orthopaedic Surgery, Post: Post Treatment, Pre: Pre Treatment,
SDR: Selective Dorsal Rhizotomy , SEMLS: Single-Event Multi-Level Orthopedic Surgery,
Speed: Non-Dimensional Walking Speed, y+mo: Years + Months.

For Center 2, we analyzed motion analysis data (Vicon) from 163 children with CP (Table 5.1), collected at the Clinical Motion Analysis laboratory of the University Hospitals Leuven, Belgium, distributed between 3 treatment groups: BTA, SDR, and SEMLS. We selected a roughly even distribution between Gross Motor Function Classification System Levels I to III

for the BTA and SEMLS groups. The SDR group was selected based upon data availability (fewer individuals, mostly Gross Motor Function Classification System Level II). Participants walked barefoot at their self-selected speed. Data from 12 typically-developing (TD) children were included for comparison to the CP groups.

5.2.2 *Electromyography*

Surface EMG data (Wave Wireless EMG) were collected at either 1000 or 1500 Hz from 4 muscles (rectus femoris, medial hamstrings, gastrocnemius, and tibialis anterior). Four additional muscles (gluteus medius, vastus lateralis, lateral hamstrings, and soleus) were recorded from 147 children with CP and the TD children at Center 2. Because we were using retrospective clinical data, some walking trials contained one or more poor or missing electromyography channels. In some cases, clinicians switched electrodes between walking trials such that each muscle was recorded in at least 1 trial. We analyzed each child's more impaired side, when indicated by clinician assessment, or otherwise selected a random side. Electromyography data from the middle 80% of each trial were used to avoid transient accelerations and decelerations near the beginning and end of each trial, and maximize data for synergy analysis [90].

Raw electromyography data were band-pass filtered between 20 and 500 Hz upon collection, then digitally pre-processed with a 20 Hz high-pass filter, rectified, and low-pass filtered at 10 Hz [102]. Each electromyography channel's amplitude was scaled to its maximum across all trials. Electromyography data were then down-sampled to 100 Hz and concatenated from all available trials for each individual to maximize the number of steps for analysis.

5.2.3 *Synergy Analysis*

We used walk-DMC to evaluate whether synergies were associated with treatment outcomes. Walk-DMC converts total variance accounted for in the 1-synergy solution ($tVAF_1$) to a z-score using the average and standard deviation of $tVAF_1$ from the TD group ($tVAF_{AVG}$ and $tVAF_{SD}$). The average walk-DMC of the TD group is 100, and each 10 point change in walk-DMC represents one standard deviation from the TD group (eq. 1). A higher $tVAF_1$ results in a lower walk-DMC score, suggesting a simplified neuromuscular control strategy. Walk-DMC was created in a manner similar to other common clinical scales that enable easy comparison with TD controls, such as the Gait Deviation Index (GDI) [103].

$$walk\text{-}DMC = 100 + 10\left[\frac{tVAF_{AVG} - tVAF_1}{tVAF_{SD}}\right] \quad (5.5)$$

The 1-synergy solution was calculated for each child from EMG data using weighted non-negative matrix factorization [104,105]. Non-negative matrix factorization [45,64] finds a set of synergy weights (W_{mxn}) and activations (C_{nxt}) such that EMG=W × C + error, where *n* is the number of synergies (1 in this study), *m* is the number of muscles (4, 8, or 16 in this study), and *t* is the number of electromyography data points. Weighted non-negative matrix factorization extends non-negative matrix factorization by assigning each data point a weight, allowing us to assign a weight of zero to all missing or corrupted electromyography channels (Figure 5.1). We calculated synergies in Matlab using the following parameters: 50 replicates, 1000 maximum iterations, a $1x10^{-4}$ minimum convergence threshold, and a $1x10^{-6}$ completion threshold.

5.2.4 *Outcome Measures*

Changes in walking ability were assessed after treatment using 2 measures: GDI [103] and non-dimensional walking speed [106]. GDI measures an individual's deviation in kinematics

compared to an unimpaired dataset using 9 joint angles. GDI is scaled such that the average ± standard deviation of the control group is 100 ±10 points (each child was analyzed with respect to his/her center's control kinematic database). Dimensionless walking speed was calculated as $walking\ speed\ (m/s)/\sqrt{leg\ length * gravity}$ to account for differences in speed due to leg length [106].

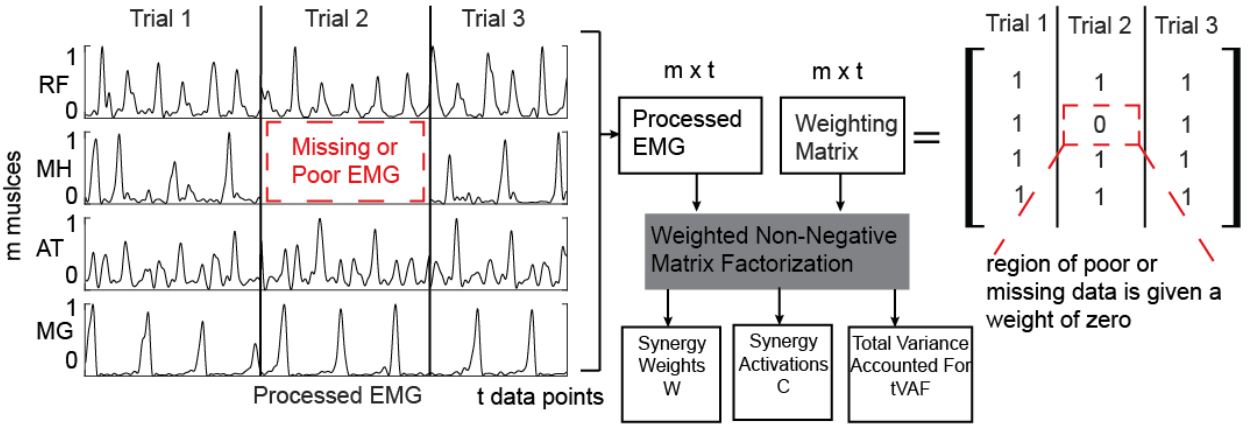

Figure 5.1. Data from multiple walking trials are concatenated together. In some trials there is poor or missing data for some channels. When weighted non-negative matrix factorization is used, the regions of poor or missing data are given zero weight and not incorporated into the update rules for non-negative matrix factorization. This approach allowed us to maximize the amount of data for analysis. As with traditional non-negative matrix factorization, synergy weights, activations and total variance accounted for by a given number of synergies are the outputs. Abbreviations: AT, tibialis anterior; MG, medial gastrocnemius; MH, medial hamstrings, RF, rectus femoris.

To determine whether walk-DMC was associated with treatment outcomes, stepwise linear regression models were created for each outcome measure (posttreatment GDI and walking speed), starting with a constant model to identify the fewest explaining factors. The 4-muscle set was used to replicate the methods from Center 1 [64]. The initial potential regressors supplied to this model were the pretreatment outcome measure (pretreatment GDI or walking speed), walk-DMC, treatment group, age, and whether the limb had undergone prior surgery (yes/no). Regressors were added into the model such that the sum of squared errors was

minimized using an F statistic at an alpha of .05 and critical P<.05. To minimize the effect of outliers, robust fitting using a bi-square weighting algorithm was applied to the model output from the stepwise regression. Additionally, we applied the linear regression models originally identified from Center 1 [64] to compare the regression coefficients between the 2 centers.

To examine sensitivity of the prior results to clinical protocols, we analyzed the impact of number of muscles on the regression results by including 4 or 8 muscles in the synergy analysis. These represent two of the most common muscle sets used in clinical gait analyses. Since inter-limb effects may be important [107,108], we also calculated bilateral walk-DMC using either the 4- or 8-muscle sets from both legs. The same methods for the linear regression models were applied to each set of synergy outputs. Of the 163 individuals from Center 2 with electromyography data for 4 muscles unilaterally, 152 had data bilaterally, and 147/136 had data for eight muscles unilaterally/ bilaterally.

To examine the robustness of the resulting models (across muscle sets for GDI and walking speed) a 10-fold cross-validation [109] was performed by replicating regressions on a random 90% of the data and testing the resulting models on the remaining 10% of observations. Model robustness was assessed by examining the cross-validated errors in relation to the original model errors.

5.3 RESULTS

5.3.1 *Gait Deviation Index*

At Center 2, the average pre/posttreatment GDI scores were 73/74, 72/74, and 66/77 for the BTA, SDR, and SEMLS treatment groups, respectively. Pretreatment GDI was significantly lower in the SEMLS group compared to the BTA or SDR groups (1-way ANOVA, Tukey Kramer post-hoc P<.001). For each treatment group, GDI increased more than 5 pts (minimum

clinically significant difference) [110] in 28% (BTA), 27% (SDR), and 68% (SEMLS) of individuals. The percentage of individuals whose GDI decreased more than 5 pts was 25% (BTA), 16% (SDR), and 5% (SEMLS).

Pretreatment GDI, walk-DMC, and treatment group were significantly associated with post-treatment GDI, with an interaction between pre-treatment GDI and treatment group (Table 5.2). This exactly matches the form of the model identified at Center 1 [64]. The effect sizes (95% confidence interval) were 43.2 (±7.7) for pretreatment GDI, 7.4 (±7.2) for walk-DMC, and 8.0 (±3.6) for treatment group (Figure 5.2). Both centers' models indicated a positive coefficient for walk-DMC, (higher walk-DMC scores corresponded to higher posttreatment GDI), but the slope magnitude was smaller at Center 2 (.11 vs .26 at Center 1).

5.3.2 *Walking Speed*

The average pre/posttreatment dimensionless walking speeds at Center 2 were .31/.29, .28/.25, and .33/.31 for the BTA, SDR, and SEMLS treatment groups, respectively. Pretreatment dimensionless speeds were not significantly different between treatment groups (1-way ANOVA, P=.18). After treatment, 17% (BTA), 27% (SDR), and 27% (SEMLS) increased their walking speed by more than 10%, while 50% (BTA), 36% (SDR), and 51% (SEMLS) decreased walking speed by more than 10%.

Stepwise linear regression indicated that pretreatment dimensionless walking speed and walk-DMC were significantly associated with posttreatment walking speed at Center 2 (Table 5.2). The effect sizes were .42 (±.06) for pre-treatment walking speed and .12 (±.07) for walk-DMC (Figure 5.2). The coefficient for walk-DMC was similar between centers (.0019 vs .0023 at Center 1), with the positive slopes indicating higher walk-DMC scores were associated with faster post-treatment walking speeds. The model at Center 1 also found treatment group and age

to be significant predictors. Applying the model at Center 1 model to the data of Center 2 described 66% of the variance in post-treatment walking speed (vs 67% with the Center 2 model), with effect sizes of .41 (±.07) for pretreatment walking speed, .13 (±.07) for walk-DMC, -.03 (±.07) for age, and .01 (±.03) for treatment group (Figure 5.2).

5.3.3 *Muscle Sets*

Children with CP had lower walk-DMC than TD children across 4- or 8-muscle sets, and unilateral or bilateral muscle sets (1-way Anova, Tukey Kramer Post-hoc $p<0.001$). Walk-DMC was significantly associated with posttreatment GDI and walking speed for all muscle sets, although after applying robust fitting, the coefficient between posttreatment GDI and walk-DMC was no longer significant for the unilateral 8-muscle set ($p=.12$). The effect sizes for posttreatment GDI were similar across all muscle sets for walk-DMC (range: 5.4-8.3), pretreatment GDI (41.0-42.5), and treatment (6.8-7.4). The effect sizes for posttreatment dimensionless walking speed were similar across muscle sets (.42-.43 pretreatment speed and .12-.13 walk-DMC).

5.3.4 *Cross Validation*

Cross-Validation errors (Table 5.3) were similar to the original errors for all models at both centers. On average 10-fold validation errors between the modeled and measured outcomes were smaller than the model calculated from the full dataset at Center 2.

Table 5.2. Regression models of post-treatment GDI and walking speed at two centers.

GDI

Regression Model*

				GDI Post =	GDI Pre x Treatment		+ Treatment Intercept		+ walk-DMC	
			treatment group		estimate	p	estimate	p	estimate	p
Center 1 **	R^2	0.42	Cons		0.74	<.01	-0.68	0.91		
	RMSE	7.8	SEMLS		0.51	<.01	20.87	<.01	0.26	<.01
			SDR		0.38	<.01	27.49	<.01		
			Ortho-1		0.61	<.01	8.94	0.37		
Center 2	R^2	0.52	BTA		0.57	<.01	24.44	<.01		
	RMSE	8.7	SEMLS		0.65	<.01	25.57	<.01	0.11	<.05
			SDR		0.99	<.01	-6.60	0.49		

Non- Dimensional Speed

Center 1 Regression Model

				Speed Post =	Speed Pre		+ Treatment Intercept		+ walk-DMC		+ Age	
			treatment group		estimate	p	estimate	p	estimate	p	estimate	p
Center 1 **	R^2	0.53	Cons				-0.010	0.81				
	RMSE	0.081	SEMLS		0.62	<.01	-0.037	0.36	0.0023	<.01	-0.0044	<.05
			SDR				-0.009	0.82				
			Ortho-1				-0.011	0.8				
Center 2	R^2	0.66	BTA				-0.073	<.05				
	RMSE	0.078	SEMLS		0.72	<.01	-0.075	0.07	0.0021	<.01	-0.0018	0.42
			SDR				-0.0606	0.12				

Center 2 Regression Model

				Speed Post =	Speed Pre		+ Intercept		+ walk-DMC	
			treatment group		estimate	p	estimate	p	estimate	p
Center 2	R^2	0.67								
	RMSE	0.077	All		0.74	<.01	-0.08	<.05	0.0019	<.01

BTA: Botulinum Toxin Type A Injection, CONS: Conservative Treatment, GDI: Gait Deviation Index,
ORTHO-1: Single- Level Orthopaedic Surgery, Post: Post Treatment, Pre: Pre Treatment, SDR: Selective Dorsal Rhizotomy,
SEMLS: Single-Event Multi-Level Orthopedic Surgery, Speed: Non-Dimensional Walking Speed,
Walk-DMC: Dynamic Motor Control Index during Walking

* For GDI, the stepwise regression identified the same model for Center 1 and Center 2 data

** Data reproduced from Schwartz et al. 2016 [64]

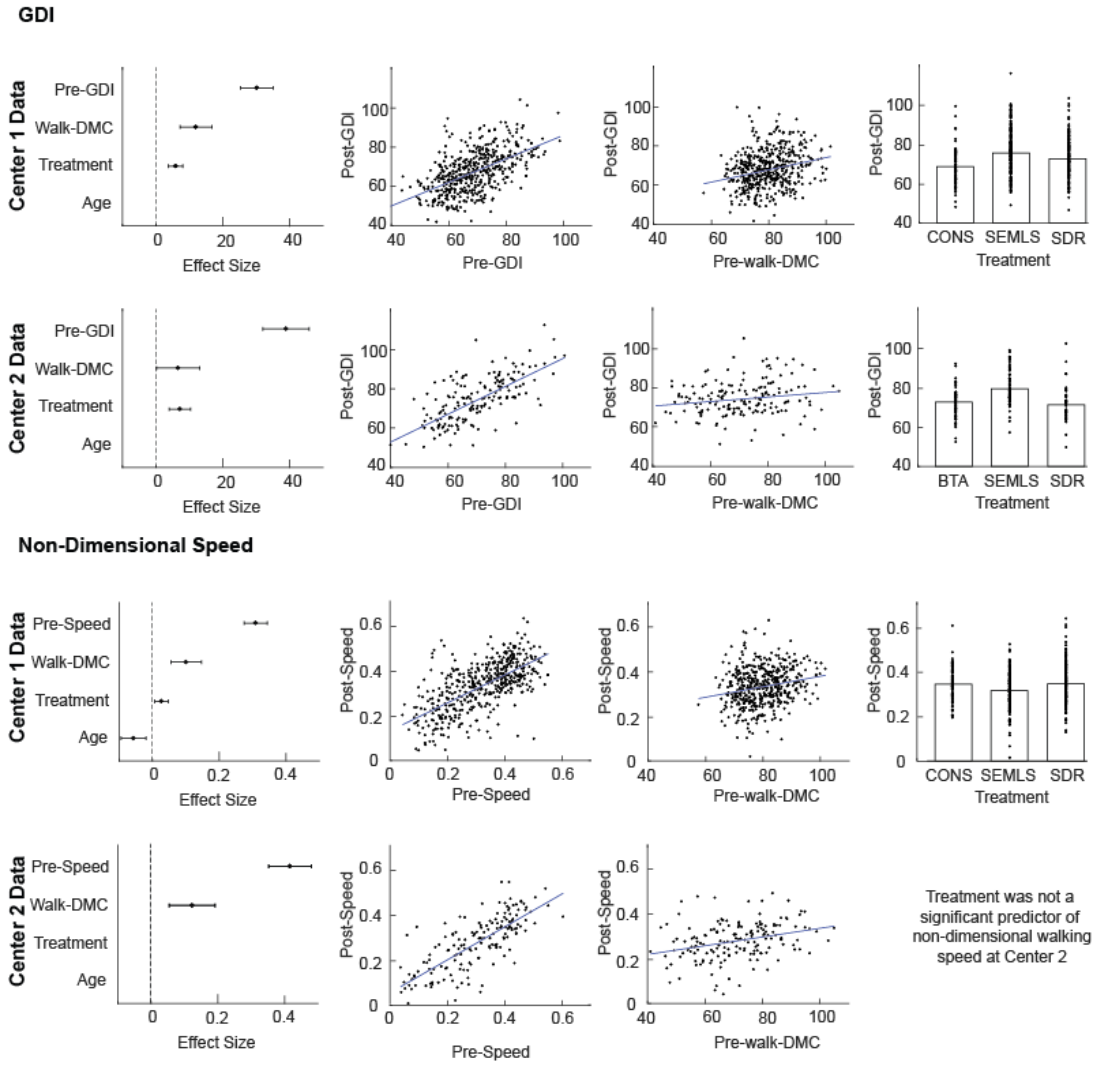

Figure 5.2. Adjusted response plots and effect sizes are shown for statistically significant regressors for GDI and nondimensional walking speed models. Models are identified by the stepwise regression after applying robust fitting from the original article (Schwartz et al, 2016) and the data from Center 2 (4 muscles). The estimated effect sizes and 95% confidence interval show which regressors are present in the Center 1 and Center 2 models. Adjusted response plots show the relation between the outcome (posttreatment GDI or nondimensional walking speed) and each predictor after removing the effect of the other predictors. For GDI, walk-DMC, treatment group, and pretreatment GDI were significant regressors in the Center 1 data (top row, reproduced from Schwartz) and Center 2 data (second row). For nondimensional walking speed, treatment and age (not shown) were significant regressors in the Center 1 data (third row, reproduced from Schwartz), but not in the Center 2 data (bottom row) Walk-DMC and pretreatment walking speed were present in both models.

Table 5.3. Cross-Validation Results

	Root Mean Square Errors			
	GDI		Non-Dimensional Walking Speed	
	Original Model	Cross Validation	Original Model	Cross Validation
Four Muscle model				
Center 1	7.8	7.7	0.08	0.08
Center 2	8.7	8.7	0.08	0.08
Alternate Muscle Sets				
Center 2 (8 muscles)	8.9	8.4	0.08	0.07
Center 2 (4 muscles bilateral)	9.0	8.6	0.08	0.07
Center 2 (8 muscles bilateral)	9.2	8.3	0.08	0.07

GDI: Gait Deviation Index

5.4 DISCUSSION

Walk-DMC was associated with changes in GDI and walking speed after treatment at a second clinical center, and showed results strikingly similar to those found at the first clinical center. Walk-DMC was positively associated with posttreatment walking speed, such that individuals with less impaired motor control pretreatment (higher walk-DMC) had greater increases in walking speed after treatment. A change in walking speed of roughly 10% represents a clinically important difference [111], which corresponds to a preoperative difference of 16 pts walk-DMC at Center 1 or 15 pts walk-DMC at Center 2. Walk-DMC was also positively associated with changes in walking kinematics, as measured with GDI, but was weaker at Center 2. A change of 5 points GDI represents a clinically important difference [110] which corresponds to a preoperative difference of 19 points in walk-DMC at Center 1 and 45 points in walk-DMC at Center 2. These differences may be due to differences in clinical outcomes and treatment groups between centers, as discussed below.

For both walking speed and GDI, children with lower walk-DMC scores generally had worse outcomes after treatment compared to children with higher walk-DMC scores. These findings contrast with other pretreatment variables. For example, kinematics or spatiotemporal measures have previously been used to predict treatment outcomes, and have indicated that greater impairments were generally associated with better treatment outcomes [15,112]. Similarly, in this study, lower pretreatment walking speed and GDI were associated with greater improvements after treatment. The positive slope of walk-DMC with treatment outcomes suggests that walk-DMC can provide unique information about a child's walking pattern that is not reflected by other measures.

Children with less impaired motor control (higher walk-DMC) but greater impairments in walking (low GDI or speed) had the best outcomes across treatments at both clinical centers. Synergies have been theorized to reflect simplified control strategies, such as from central-pattern generators or other lower-levels of control in the central nervous system [107]. While these hypotheses are challenging to verify in humans, the results of this research suggest that walk-DMC may serve as a warning sign to identify children who are more dependent on lower-level control and may have smaller improvements in walking after treatment.

There were several differences between the analysis of walk-DMC and outcomes at the 2 centers. In comparison to Center 1, we grouped all orthopedic surgeries together (versus separating single or multiple orthopedic surgeries) and there was no conservative treatment group. Instead, a BTA group was included. Center 2 included a higher percentage of children with Gross Motor Function Classification System Level I (32% vs 21% at Center 1). Importantly, we also noted smaller changes in GDI after SDR at Center 2 (2 pts) compared to Center 1 (5 pts). These differences in outcomes following SDR from the 2 centers highlights the

need to evaluate differences in protocols between centers. A separate examination by Huenaerts et al [113] of patients at Center 2 who received SDR showed that small changes in the gait profile score (similar to GDI) were due to improved knee kinematics combined with worsening hip flexion and anterior pelvic tilt. The differences in SDR outcomes impacted our regression models at Center 2 by increasing the effect sizes of treatment and pretreatment GDI, while decreasing the effect size of walk-DMC. Re-computing the linear models without the SDR treatment group caused all effect sizes to more closely match Center 1.

The muscles measured with electromyography were dictated by the current standard of care at both centers. This study demonstrated that walk-DMC was significantly associated with treatment outcomes regardless of choice of muscles (*i.e.*, unilateral/bilateral and 4/8-muscle sets). The similarity of unilateral and bilateral walk-DMC also suggests that these methods provide a more global, rather than limb-specific, measure of motor control. A further methodological difference was the application of weighted nonnegative matrix factorization to the Center 2 data (versus nonnegative matrix factorization at Center 1), increasing the amount of electromyography data available for analysis by including trials with missing or corrupted channels (11% of trials for 4 muscles). Tests on data sets with no missing electromyography data showed no differences in synergy outputs between the 2 algorithms.

5.4.1 *Study Limitations*

The results of this study were limited by the use of retrospective data, which affects our ability to prospectively evaluate the use of walk-DMC or other measures of motor control in treatment planning. The other variables included in the model were selected to match the prior study, which focused on variables previously suggested to be associated with treatment outcomes in CP. Other variables (e.g., metabolic costs, physical exam measures, or neurologic injury) may

also be important predictors of treatment outcomes in CP. In this study, we used GDI as a global measure of improvements in gait. However, improving GDI is not the only goal targeted by interventions in CP. For the BTA treatment group, a series of repeated treatments shifts the focus from altering kinematics to maintaining improvements [114] and most subjects included in this study had received prior BTA treatments (68%). Additional clinical measures, such as spasticity, (which is targeted by BTA and SDR treatments) were not included in this analysis. Specific details of the treatments including which muscles were targeted with BTA, or what specific surgical procedures were administered during SEMLS were also not included. The heterogeneity in treatments in CP remains a challenge in predicting patient-specific improvements in walking ability after treatment.

5.4.2 *Conclusions*

This study demonstrated that walk-DMC was associated with treatment outcomes at two separate centers across a variety of treatments. These associations were not sensitive to which muscles were included in the analysis, demonstrating robust patterns that can help inform the use of motor control to determine which children are more likely to benefit from treatments to improve gait in CP.

Chapter 6. MUSCLE SYNERGIES DEMONSTRATE ONLY MINIMAL CHANGES AFTER TREATMENT IN CEREBRAL PALSY

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ABSTRACT

Background: Children with cerebral palsy (CP) have altered synergies compared to typically-developing peers, reflecting different neuromuscular control strategies used to move. While these children receive a variety of treatments to improve gait, whether synergies change after treatment, or are associated with treatment outcomes, remains unknown.

Methods: We evaluated synergies for 147 children with CP before and after three common treatments: botulinum toxin type-A injection (n=52), selective dorsal rhizotomy (n=38), and multi-level orthopaedic surgery (n=57). Changes in synergy complexity were measured by the number of synergies required to explain >90% of the total variance in electromyography data and total variance accounted for by one synergy. Synergy weights and activations before and after treatment were compared using the cosine similarity relative to average synergies of 31 typically-developing (TD) peers.

Results: There were minimal changes in synergies after treatment despite changes in walking patterns. Number of synergies did not change significantly for any treatment group. Total variance accounted for by one synergy increased (*i.e.*, moved further from TD peers) after botulinum toxin type-A injection (1.3%) and selective dorsal rhizotomy (1.9%), but the change was small. Synergy weights did not change for any treatment group (average 0.001 ± 0.10), but synergy activations after selective dorsal rhizotomy did change and were less similar to TD peers (-0.03 ± 0.07). Only changes in synergy activations were associated with changes in gait kinematics or walking speed after treatment. Children with synergy activations more similar to TD peers after treatment had greater improvements in gait.

Conclusions: While many of these children received significant surgical procedures and prolonged rehabilitation, the minimal changes in synergies after treatment highlight the

challenges in altering neuromuscular control in CP. Development of treatment strategies that directly target impaired control or are optimized to an individual's unique control may be required to improve walking function.

6.1 BACKGROUND

Cerebral palsy (CP) is caused by an injury to the brain at or near the time of birth [1]. Individuals with CP have impaired control and coordination of their muscles, as well as a variety of secondary musculoskeletal impairments. Muscle synergies have recently been used to evaluate and quantify impaired motor control in CP. Synergies are calculated from electromyography (EMG) data to identify weighted groups of muscles commonly activated together. Children with CP have altered synergies during gait compared to typically-developing (TD) peers [28,56–58,101,115], similar to other clinical populations such as stroke [48,49,60,66,82], spinal cord injury [55,79,116], and Parkinson's Disease [52,53]. Fewer synergies are required to describe muscle recruitment during dynamic tasks in CP, which is thought to contribute to impaired movement [55,58,82].

Recent research has suggested that synergies measured prior to treatment are associated with changes in gait after treatment in CP [64,117,118]. A summary measure of synergy complexity, the dynamic motor control index during walking (Walk-DMC), measured before treatment, has been shown to be associated with changes in gait kinematics and walking speed at two clinical centers [64,118]. Children with greater synergy complexity, meaning synergies more similar to TD peers, are more likely to have improvements in gait kinematics and walking speed after single-event multi-level orthopaedic surgery (SEMLS), selective dorsal rhizotomy (SDR), or botulinum toxin injections type-A (BTA). While this research has suggested that synergy-based measures may be useful for treatment planning, the impact of these treatments on

synergies is an open question. Researchers have proposed that treatments that can modify synergies may be clinically useful and contribute to improvements in movement [9,100,119]. However, whether or to what extent treatments can alter synergies or how those changes relate to functional outcomes remains unknown.

Few prior investigations have examined whether synergies can be altered as a result of an treatment [89,120,121]. Focusing mainly on rehabilitation after stroke, these studies have found mixed results, but have demonstrated that treatments have the potential to alter muscle synergies. For example, after rehabilitation therapies in stroke, synergy complexity has been found to increase [89], or have minimal changes [120], while in Parkinson's, synergy complexity has been found to decrease [121]. All of these studies found some reorganization of synergy weights and/or timings after treatment [89,120,121]. In CP, preliminary research has suggested that there are minimal changes in synergies following treatment. For example, van der Krogt et al. (2016) reported a slight reduction in synergy complexity (*i.e.*, further from TD peers) following BTA, while Oudenhoven et al. (2016) and Loma-Ossorio Garcia (2015) reported little change in synergy complexity following SDR or SEMLS, respectively [74,122,123]. Changes in synergy weights or activations after treatment have not been examined in CP.

The aim of this research was to examine whether common treatments in CP result in changes to synergy complexity, weights, or activations. Individuals with CP present a compelling population in which to examine changes in synergies due to the variety of treatments, often including extensive rehabilitation. Treatments, such as SDR, target the nervous system directly, while orthopedic surgery largely targets the musculoskeletal system. Injections of BTA provide short-term changes in muscle activity versus the long-term neuromuscular changes from SEMLS or SDR. If synergies change after SEMLS, SDR, or BTA, this could suggest that

intensive rehabilitation or targeted treatments may be able to modify impaired control in children with CP. In contrast, if treatments do not alter synergies, these results could suggest that motor control is relatively fixed in CP.

6.2 METHODS

6.2.1 *Participants*

We retrospectively analyzed pre- and post-treatment EMG and kinematic data collected at UZ Pellenberg, Belgium, during clinical motion analysis for 147 children with spastic CP (**Error! Reference source not found.**). The children with CP were distributed between three treatment groups: BTA, SDR, and SEMLS. All children were in Gross Motor Function Classification System (GMFCS) Levels I-III. We also evaluated gait for 31 typically-developing (TD) children for comparison to the children with CP. Apart from two TD children who had one walking trial, all participants completed a minimum of two barefoot, self-selected speed walking trials. Some of the children with more severe impairments (GMFCS Level III) walked with support, either from a therapist or assistive device. Marker trajectories were tracked using a 10 to 15 camera VICON system (Nexus 1.8.4, Vicon-UK, Oxford, UK), sampled at 100Hz. Joint kinematics were calculated using the marker set of the lower limb Plug-in-Gait (PiG) model.

6.2.2 *Electromyography*

Surface EMG data (Wave Wireless EMG, Cometa, Bareggio, Italy) were collected at either 1000 Hz or 1500 Hz from eight muscles bilaterally (gluteus medius, rectus femoris, vastus lateralis, medial hamstrings, lateral hamstrings, tibialis anterior, gastrocnemius, and soleus) during clinical gait analysis. Raw EMG data were band-pass filtered between 20 and 500 Hz upon collection. EMG data were analyzed from the more impaired side, when clinically

indicated (n =33, hemiplegic children and diplegic children with a more impaired side), and otherwise from a random side for each child (n=114, diplegic children). All trials with EMG data (range = 1 to 12 trials, IQR = 2 to 4 trials) were concatenated within a session (pre- or post-treatment) for each child to maximize the number of steps for analysis [90]. For each trial, we excluded the first and last 10% of the EMG data at the beginning and end of each trial to avoid periods of acceleration and deceleration [102]. A linear envelope was calculated for each muscle using the following EMG data processing steps: high-pass filtered at 20 Hz, rectified, low-pass filtered at 10 Hz, amplitude scaled to the muscle's maximum activation across all trials from a session, and down-sampled to 100 Hz [102].

Table 6.1. Participant Demographics

Treatment	N	GMFCS I / II / III	Age y+mo	Gender F:M	Height meters	Mass kg
BTA	52	18/19/15	6+10 (2+11)	19:33	1.15 (0.16)	21.3 (8.7)
SDR	38	11/23/4	9+4 (2+0)	20:18	1.33 (0.10)	29.7 (6.2)
SEMLS	57	20/17/20	12+2 (3+1)	23:34	1.45 (0.16)	39.3 (14.8)
TD	31	-	9+3 (2+9)	17:14	1.38 (0.17)	33.8 (13.3)

NOTE. Values are average (1 SD) or as otherwise indicated
N: Number of participants, GMFCS: Gross Motor Function Classification System, y+mo: Years + Months, F: Female, M: Male, BTA: Botulinum Toxin Type-A Injection, SDR: Selective Dorsal Rhizotomy SEMLS: Single Event Multi-Level Orthopaedic Surgery, TD: Typically-Developing Children

6.2.3 *Synergy Analysis*

We calculated synergies using weighted non-negative matrix factorization (WNMF) in Matlab (MathWorks Inc., Natick, Massachusetts, United States) using the Matrix Factorization Toolbox [104,105]. As with traditional non-negative matrix factorization (NMF), WNMF finds a

set of synergy weights (W_{mxn}) and activations (C_{nxt}) such that EMG=W × C + error, where, *m* is the number of muscles (8 in this study), *t* is the number of EMG data points, and *n* is the number of synergies. WNMF differs from traditional implementations of NMF in that it assigns each data sample a weight (1 = EMG present, 0 = EMG absent). We selected the WNMF algorithm to accommodate our clinical data set, which contained poor or missing EMG channels for 15% of all trials. For example, in some individuals there was missing data from one muscle and between trials the electrode was switched with another muscle's electrode such that EMG data for each muscle was recorded in at least one trial. In each concatenated session, all eight muscles were recorded in at least one trial, ensuring that each muscle was represented in the synergy outputs for each child. The following settings were used for WNMF: 50 replicates, 1000 maximum iterations, $1x10^{-4}$ minimum threshold for convergence, and $1x10^{-6}$ threshold for completion.

6.2.4 *Synergy Complexity*

To evaluate synergy complexity, the total variance accounted for by *n* synergies ($tVAF_n$) was calculated as [71,78]:

$$tVAF_n = \left(1 - \frac{\left[\sum_j^t \sum_i^m (error)^2\right]}{\left[\sum_j^t \sum_i^m (EMG)^2\right]}\right) \times 100\% \quad (6.6)$$

We calculated the number of synergies required for $tVAF_n$>90% (N_{90}). Number of synergies has been used extensively to evaluate synergies in both unimpaired individuals and clinical populations [43,49,89], with prior research indicating that children with CP require fewer synergies than TD peers [57,58].

The total variance accounted for by a single synergy solution ($tVAF_1$) provides a summary measure of synergy complexity that has been shown to be related to function and treatment

outcomes in CP [64,118]. To contextualize the magnitude of changes in $tVAF_1$ relative to TD peers and compare to prior research, the Dynamic Motor Control Index during Walking (Walk-DMC) was calculated as a scaled z-score of $tVAF_1$, where $tVAF_{AVG}$ and $tVAF_{SD}$ are the average and standard deviation of $tVAF_1$ of the TD individuals. Walk-DMC is scaled such that the average score is 100 for TD peers with a 10-point change representing one standard deviation of the TD group.

$$walk\text{-}DMC = 100 + 10\left[\frac{tVAF_{AVG} - tVAF_1}{tVAF_{SD}}\right] \tag{6.7}$$

6.2.5 *Synergy Composition*

We also examined whether synergy weights or activations changed after treatment [89]. To provide context, we compared synergy weights and activations to TD peers. For the TD group, four synergies explained over 90% of the variance in EMG data for 81% of individuals (19% required five synergies). Thus, the average synergy weights and activations for four synergies was calculated for the TD group to define the archetype synergies. The archetype synergies had similar weights as previously published analyses of TD adults and children: C1 consisted primarily of extensor activity (gluteus medius, rectus femoris, and vastus lateralis); C2 consisted primarily of the plantarflexors (gastrocnemius and soleus); C3 consisted primarily of the tibialis anterior and rectus femoris; and C4 consisted primarily of the medial and lateral hamstrings [28,49,107]. We calculated the four-synergy solution for each child with CP and computed the cosine similarity (un-centered correlation coefficient) with the archetype synergy weights and activations. As both synergy weights and activations from WNMF are purely positive, cosine similarity constrains the correlation coefficient between 0 and 1, where a higher

similarity indicates synergies that are more similar to TD peers. We evaluated whether similarity to TD peers changed after treatment, comparing the similarity of synergy weights and activations to the TD archetypes before and after each treatment [124]. We also evaluated whether the similarity of synergies to the TD archetypes differed between treatment groups pre-treatment.

6.2.6 *Changes in Gait*

In addition to EMG data, kinematic data from the clinical gait analyses were used to assess changes in gait post-treatment using two measures: walking speed and the gait deviation index (GDI). Walking speed was calculated from the average fore-aft velocity of the sacral marker for each trial and non-dimensionalized [106] as $walking\ speed\ (m/s)/\sqrt{(leg\ length\ (m) * gravity(m/s\text{^}2))}$ to account for differences in leg lengths or growth between visits. The GDI is a summary measure of an individual's deviation from a TD control population for nine kinematic joint angles (pelvis: flexion/extension, internal/external rotation, adduction/abduction; hip: flexion/extension, internal/external rotation, adduction/abduction; knee: flexion/extension; and ankle: dorsiflexion/plantarflexion, foot progression angle) [103]. Similar to Walk-DMC, GDI is a scaled z-score such that the average of the clinic's control kinematic database is 100, and every standard deviation from the average is represented by a 10-point decrease. Note that the clinic's control kinematic database (n=55, age: 10+7 (3+11) y + mo, mass: 40.0 (17.7) kg, height: 1.48 (0.21) m) is separate from the TD group with EMG data available that was used for comparing synergies. To align results with the standards of the clinic and use the full set of TD kinematics, we used the separate databases for these analyses. However, we did compare the databases and found the kinematics were similar and did not cause significant changes in the reported kinematic results.

6.2.7 *Statistical Analyses*

Descriptive statistics included the calculation of the average and standard deviation for synergy and gait metrics. One-way analysis of variance (ANOVA) with t-test post-hoc were used to evaluate differences between groups pre-treatment on all continuous measures ($tVAF_1$, synergy weights, synergy activations, GDI, and walking speed) [124]. A Kruskal-Wallis with rank-sum post hoc was used to evaluate differences between groups pre-treatment on the ordinal measure, N_{90} [124]. Paired t-tests (for continuous data) and a Wilcoxon signed-rank test (for ordinal data) were used to evaluate changes between pre- and post-treatment [124]. To adjust for multiple comparisons in this study a Benjamini-Hochberg multiple comparison correction was applied to α=0.05 [125].

To determine whether changes in synergies were associated with changes in gait post-treatment, we performed stepwise linear regressions for each outcome measure (*e.g.*, speed and GDI). Stepwise regression started with a constant model, and regressors were added such that the sum of squared errors was minimized using an F-statistic at an alpha of 0.05 and critical $p<0.05$. Initial potential regressors were pre-treatment GDI or walking speed, age, treatment group, and changes in synergies. These were chosen based on previous research suggesting their importance in gait outcomes [64]. Changes in synergies were measured with (1) $tVAF_1$, (2) changes in synergy weights relative to the TD archetype, and (3) changes in synergy activations relative to the TD archetype. The model identified by the stepwise regression was recomputed with robust fitting using a bi-square weighting algorithm to minimize the effect of outliers in our regressions [126]. The impact of each regressor was assessed using effect sizes. Effect sizes were estimated from the adjusted response, computed by allowing each regressor to vary after averaging out the effects of the other regressors.

Model robustness was examined by performing a 10-fold cross-validation and comparing the resultant errors to the original model errors. Cross-validation was performed by replicating the regressions 10 times with 90% of the data and testing the resultant model on the withheld 10%, where each observation appears in a test set exactly once [109].

6.3 RESULTS

6.3.1 *Synergy Complexity*

There were no significant differences in number of synergies (N_{90}) pre-treatment between groups ($p=0.60$) and N_{90} did not change significantly post-treatment for any treatment group ($p>0.10$ for all groups). Similar to prior research, N_{90} was significantly smaller in the children with CP pre-treatment (average (SD): 2.78 (0.64)) compared to TD peers (4.19 (0.40), $p<0.001$, Figure 6.1). Number of synergies did change for some children: N_{90} changed for 33%, 40%, and 49% of individuals in the BTA, SDR, and SEMLS treatment groups, respectively. However, these changes were variable: 10% (BTA), 13% (SDR), and 18% (SEMLS) had an increase in N_{90}, while 23% (BTA), 26% (SDR), and 32% (SEMLS) had a decrease in N_{90}.

The total variance accounted for by a single synergy did not change for the SEMLS group (+0.3%, $p = 0.69$), but $tVAF_1$ had a small, but significant change after BTA (+1.3%, $p = 0.005$) and SDR (+1.9%, $p < 0.001$, Figure 1). Note in both cases $tVAF_1$ increased, indicating that synergy complexity was further from TD peers post-treatment. Changes in $tVAF_1$ corresponded to a 0.9, 4.1, and 6.2 point decreases in Walk-DMC for SEMLS, BTA, and SDR groups, respectively. The average (SD) $tVAF_1$ pre-treatment was 79.1% (6.2%) for BTA, 80.1% (4.9%) for SDR, and 80.2% (5.9%) for SEMLS, which were all significantly greater than the average $tVAF_1$ for the TD group of 64.4% (3.1%) ($p<0.001$, Figure 1). There was no significant difference in $tVAF_1$ between groups pre-treatment ($p=0.46$).

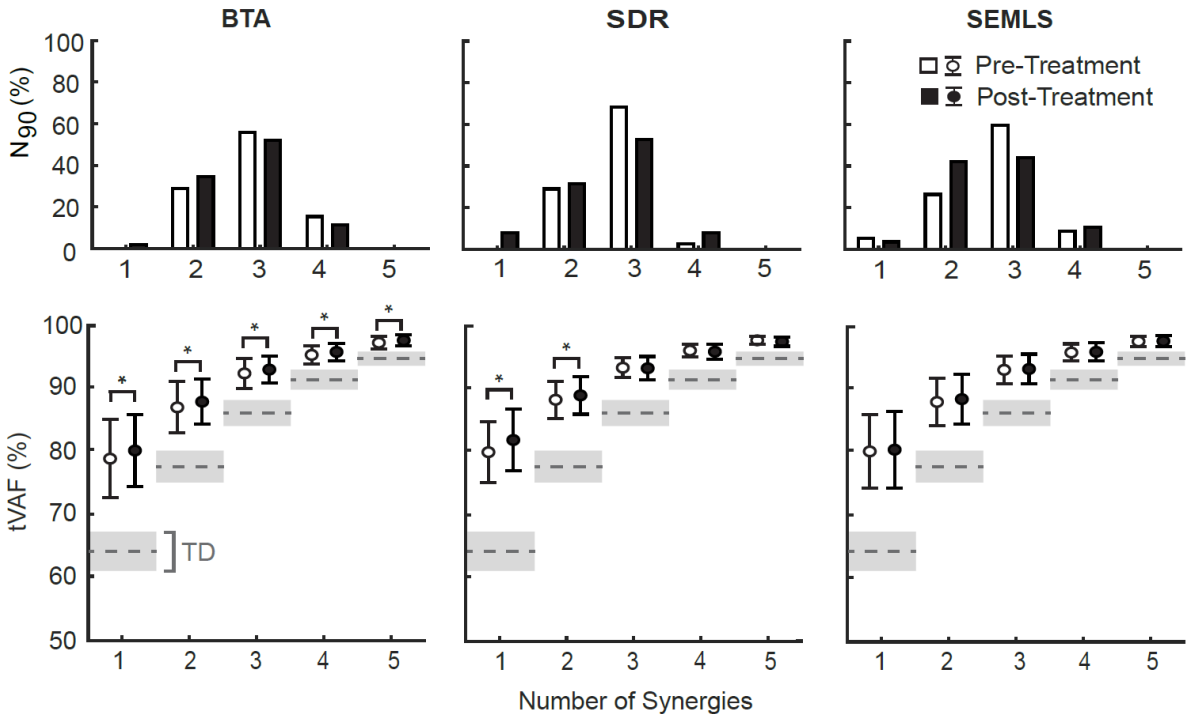

Figure 6.1. (Top) Histogram of the number of synergies to account for greater than 90% of the variance in EMG data (N90) for the children with CP (pre-treatment and post-treatment). (Bottom) Average (+/- 1 SD) total variance accounted for (tVAF) by one to five synergies for the children with CP (pre-treatment and post-treatment). The TD tVAF is shown in grey (average +/- 1 SD) for comparrison. *indicates significant change in tVAFn following treatment ($p<0.05$). BTA: Botulinum Toxin Injection Type-A; SDR: Selective Dorsal Rhysotomy; SEMLS: Single Event Multi-Level Surgery; TD: Typically-Developing Children.

6.3.2 *Synergy Composition*

Synergy weights did not change significantly post-treatment (Figure 6.2. (Top Left) Average (± SD) synergy weights and activations for the typically developing children. Average TD weights and activations define the synergy archetypes that were used to compare synergies before and after treatment for the children with CP. Comparison of the average (± SD) pre- and post-treatment synergy weights and activations for BTA (Top Right), SDR (Bottom Left), and SEMLS (Bottom Right). BTA: Botulinum Toxin Injection Type-A; SDR: Selective Dorsal Rhysotomy; SEMLS: Single Event Multi-Level Surgery; TD: Typically-Developing Children; RF: Rectus Femoris; VL: Vastus Lateralis; MH: Medial Hamstrings; LH: Lateral Hamstrings; TA: Tibialis Anterior; GAS:

Medial Gasterocnemius; SOL: Soleus; GLU: Gluteus Medius..). The average similarity of the CP synergy weights to the TD archetypes pre-treatment were 0.77 (0.17), 0.88 (0.11), 0.90 (0.07), and 0.92 (0.10) for C1, C2, C3, and C4, respectively, and were not different between treatment groups (p=0.73). After treatment, the average change in similarity to the TD synergy weights was 0.01 (0.08), -0.03 (0.14), and 0.02 (0.10) for the BTA, SDR and SEMLS groups, respectively and not statistically significant (p>0.10 for all groups).

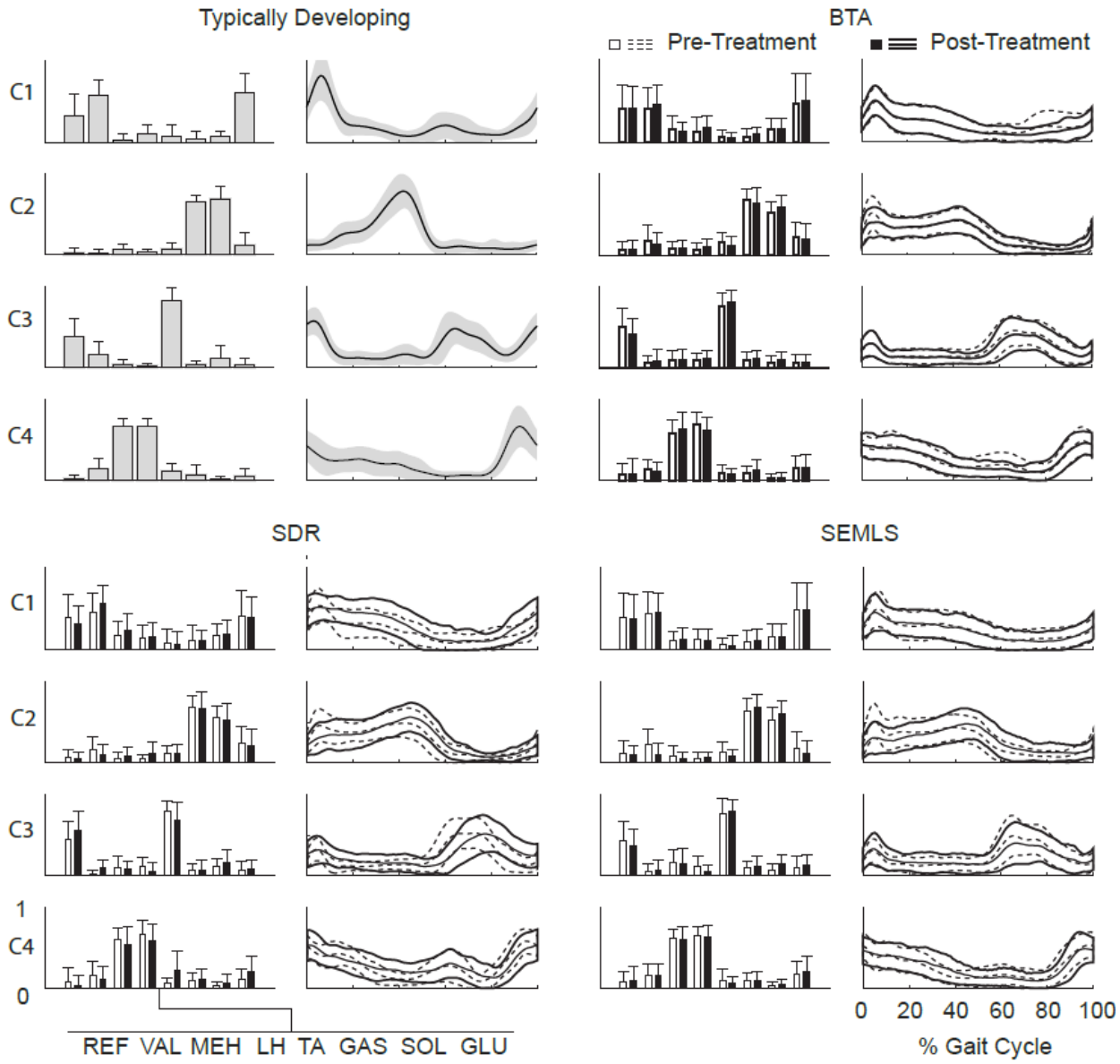

Figure 6.2. (Top Left) Average (± SD) synergy weights and activations for the typically developing children. Average TD weights and activations define the synergy archetypes that were used to compare synergies before and after treatment for the children with CP. Comparison of the average (± SD) pre- and post-treatment synergy weights and activations for BTA (Top Right), SDR (Bottom Left), and SEMLS (Bottom Right). BTA: Botulinum Toxin Injection Type-A; SDR: Selective Dorsal Rhysotomy; SEMLS: Single Event Multi-Level Surgery; TD: Typically-Developing Children; RF: Rectus Femoris; VL: Vastus Lateralis; MH: Medial Hamstrings; LH: Lateral Hamstrings; TA: Tibialis Anterior; GAS: Medial Gasterocnemius; SOL: Soleus; GLU: Gluteus Medius.

Synergy activations also did not change significantly after BTA or SEMLS, but there was a significant decrease in similarity to TD synergy activations after SDR. The average cosine similarity to the TD archetypes was similar between treatment groups pre-treatment ($p=0.08$) and was 0.81 (0.12), 0.81 (0.09), 0.82 (0.07), and 0.86 (0.07) for C1, C2, C3, and C4, respectively. After treatment the average change in synergy activations was not significant at 0.01 (0.05) and -0.01 (0.09) for the BTA and SEMLS groups, respectively, but was statistically significant at -0.03 (0.07) for the SDR group ($p=0.01$).

6.3.3 *Changes in Gait*

There were significant improvements in gait kinematics (Table 6.2. Participant outcomes.) following SEMLS (pre/post GDI = 66/77, $p<0.001$), but smaller changes after SDR (74/77, $p=0.06$) and BTA (74/75, $p=0.91$). After treatment 23%, 32% and 67% of BTA, SDR, and SEMLS children increased their GDI scores by more than 5 points (minimum clinically significant difference, [110]), while 37%, 11%, and 5% decreased by more than 5 points, respectively. There were significant decreases in walking speed after SEMLS (0.29/0.24, $p<0.001$) but smaller changes after BTA (0.32/0.30, $p=0.08$) and SDR (0.34/0.30, $p=0.03$, non-significant after multiple comparison correction). After treatment 15%, 21% and 25% of the BTA, SDR, and SEMLS groups increased their dimensionless walking speed by more than 10%

(clinically significant difference, [111]), while 50%, 42%, and 53% decreased by more than 10%, respectively.

Changes in gait kinematics and walking speed after treatment were significantly associated with changes in synergy activations (Table 6.3. Regression models of post-treatment GDI and walking speed., Figure 6.3. Effect size and adjusted response plots of significant regressors for post-treatment GDI and walking speed identified from stepwise regression. The estimated effect sizes and 95% confidence interval show which regressors are present in each model. Adjusted response plots show the relation between each outcome measure (post-treatment GDI or non-dimensional walking speed) and each predictor after removing the effect of the other predictors. Synergy activations that became closer to the TD archetypes were associated with better kinematics and faster walking speeds post-treatment. BTA: Botulinum Toxin Injection Type-A; GDI: Gait Deviation Index; SDR: Selective Dorsal Rhysotomy; SEMLS: Single Event Multi-Level Orthopaedic Surgery; TD: Typically Developing.), such that individuals whose synergy activations were more similar to TD peers after treatment had better outcomes. Neither changes in $tVAF_1$ nor synergy weights were associated with changes in GDI or walking speed post-treatment. The average cross-validated model errors were less than 3% higher than the original model for GDI and within 1% of the original model for walking speed.

6.4 DISCUSSION

Treatments for children with CP are often assumed to make dramatic changes to an individual's musculoskeletal and neuromuscular systems. SEMLS and other orthopaedic surgeries alter the musculoskeletal system, reorienting bones, altering muscles paths, or lengthening tendons. BTA injections temporarily block muscle action potentials. SDR permanently removes some afferent feedback. After all of these treatments, children also receive extensive rehabilitation. While these treatments can induce significant changes in movement, our

findings suggest that they have minimal impact on the underlying strategies that an individual uses to control and coordinate their muscles, suggesting that motor control is relatively fixed in CP.

Table 6.2. Participant outcomes

Treatment	N	Speed		GDI		N_{90}		$tVAF_1$	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
BTA	52	0.32 (0.14)	0.30 (.015)	74.4 (12.2)	74.6 (11.2)	2.87 (0.66)	2.73 (0.69)	0.79 (0.06)	0.80 (0.06)
SDR	38	0.34 (0.12)	0.30 (.011)	73.8 (10.2)	76.6 (13.1)	2.74 (0.50)	2.61 (0.75)	0.80 (0.05)	0.82 (0.05)
SEMLS	57	0.29 (0.11)	0.24 (.013)	66.4 (11.7)	76.8 (12.2)	2.72 (0.70)	2.61 (0.73)	0.80 (0.06)	0.80 (0.06)
TD	31	0.50 (0.09)	-	93.6 (9.3)	-	4.19 (0.40)	-	0.64 (0.03)	-

NOTE. Values are average (1 SD) or as otherwise indicated
N: Number of participants, Post: Post-Treatment, Pre: Pre-Treatment,
Speed: Non-Dimensional Walking Speed, GDI: Gait Deviation Index, N_{90}: Number of Synergies,
$tVAF_1$: Total Variance Accounted for By One Synergy, BTA: Botulinum Toxin Type-A Injection,
SDR: Selective Dorsal Rhizotomy, SEMLS: Single Event Multi-Level Orthopaedic Surgery,
TD: Typically-Developing Children.

Table 6.3. Regression models of post-treatment GDI and walking speed.

	Speed (r^2=0.70)			GDI (r^2=0.50)		
Term	Estimate	Standard Error	p	Estimate	Standard Error	p
Intercept*	0.02	0.02	0.16	-	-	-
				BTA: 21.33	4.92	<.001
				SDR: 24.16	5.01	<.001
				SEMLS: 29.28	4.42	<.001
Pre-Treatment	0.83	0.05	<.001	0.71	0.06	<.001
Change in Synergy Activations	0.49	0.09	<.001	22.27	10.50	0.036

* Treatment effect only for GDI
GDI: Gait Deviation Index, Speed: Non-Dimensional Walking Speed, BTA: Botulinum Toxin Type-A Injection, SDR: Selective Dorsal Rhizotomy, SEMLS: Single Event Multi-Level Orthopaedic Surgery.

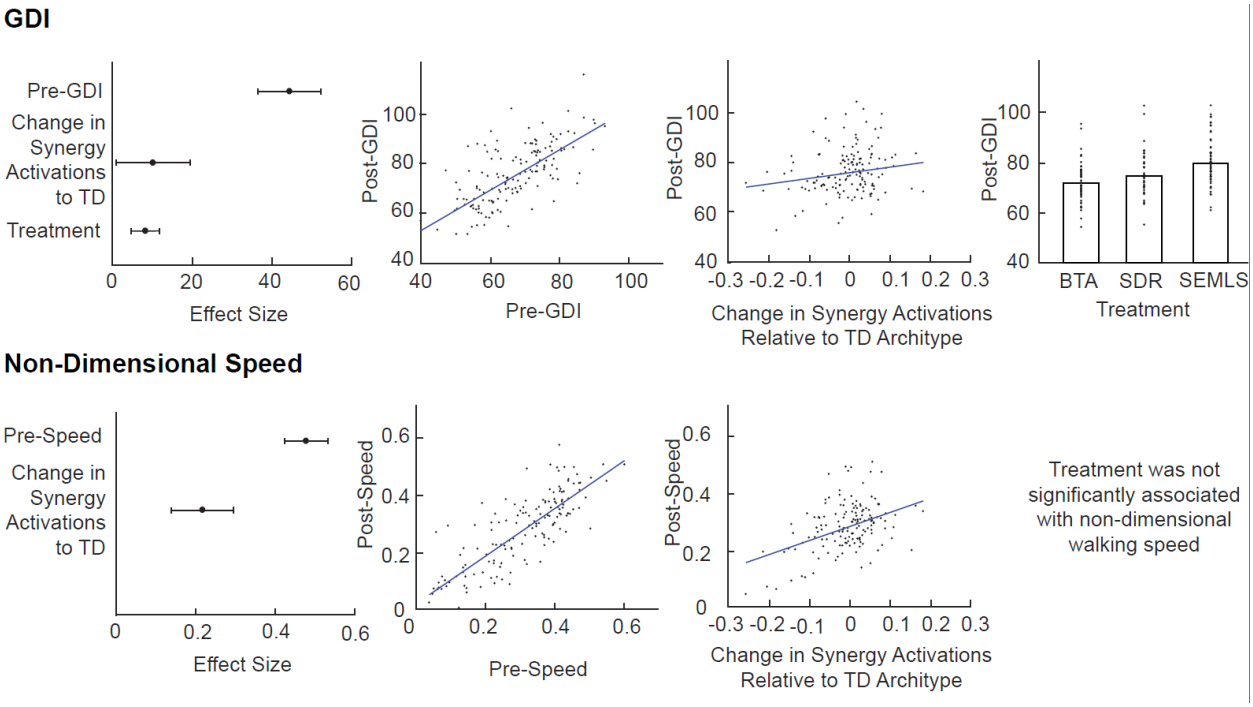

Figure 6.3. Effect size and adjusted response plots of significant regressors for post-treatment GDI and walking speed identified from stepwise regression. The estimated effect sizes and 95% confidence interval show which regressors are present in each model. Adjusted response plots show the relation between each outcome measure (post-treatment GDI or non-dimensional walking speed) and each predictor after removing the effect of the other predictors. Synergy activations that became closer to the TD archetypes were associated with better kinematics and faster walking speeds post-treatment. BTA: Botulinum Toxin Injection Type-A; GDI: Gait Deviation Index; SDR: Selective Dorsal Rhysotomy; SEMLS: Single Event Multi-Level Orthopaedic Surgery; TD: Typically Developing.

While research has consistently demonstrated that individuals with neurologic injuries use a simplified control strategy compared to unimpaired individuals during locomotion [57,58,82,89,121], we found minimal changes in synergies after treatment. Although there was a small, but significant, increase in $tVAF_1$ for BTA and SDR treatment groups, this change was in the opposite direction than desired: $tVAF_1$ increased, creating a larger gap between the children with CP and TD peers. Both BTA and SDR treatments block or inhibit signals in the nervous system, potentially explaining this reduction in synergy complexity. In prior conference

proceedings, van der Krogt and colleagues (2016) similarly reported a trend toward increasing $tVAF_1$ after BTA, while Oudenhoven (2016) found no significant changes in $tVAF_1$ following SDR. In all cases, the average change in $tVAF_1$ has been less than 2%, suggesting minimal changes after treatment in CP [74,122]. Moreover, a post-hoc analysis of the data found an average range in $tVAF_1$ of 2.8% between trials within a session, roughly 1.5 times larger than the changes we see after SDR. Number of synergies (N_{90}) demonstrated a similar trend of minimal changes. Although N_{90} changed after treatment for 41% of individuals, there were no significant changes for any treatment group. Rather these changes demonstrate that the number of synergies, an ordinal measure, may be inappropriate to evaluate changes in synergy complexity. For example, if an individual has a $tVAF_n$ of 89% at one visit and 90% at another visit, their number of synergies would change despite only a small change in $tVAF_n$. While both measures suggest minimal changes in synergy complexity after treatment in CP, we prefer to use tVAF versus N_{90} for greater granularity.

Synergy weights did not change after treatment, suggesting that similar groups of muscles were activated together. Synergy activations did change after SDR only, but again they were less similar to TD peers. Across all treatments, improvements in gait after treatment were only associated with changes in synergy activation that became more similar to TD peers. These findings highlight that even if coordination (*i.e.*, which muscles are being activated together) stays constant after treatment, changing patterns of recruitment (*i.e.*, synergy activations) can lead to improvements in gait. The importance of synergy activations was also demonstrated by Routson and colleagues (2013), who found that synergy activations, especially plantarflexor timing (synergy C2), were associated with improvements in kinematics and walking speed.

The lack of changes in synergy composition contrasts with research in unimpaired adults, where highly trained individuals have been found to have altered synergies compared to novices [72,127,128]. Further, interventions such as powered exoskeletons have been shown to alter synergy weights and activations [129–131]. Whether future innovations in treatments such as feedback training [129,132,133], forced exploration of new movement patterns [134], or electrical stimulation of the spinal cord [135] can induce similar changes in synergies for individuals with CP remains unknown. However, children with CP have been shown to have synergies more similar to neonates or toddlers [28,107], and the altered maturation process of the brain and descending pathways may limit neural plasticity [136]. A reduction in neural plasticity could explain the small changes in synergies observed in this study even after drastic surgeries and extensive rehabilitation. Understanding the plasticity and impacts of treatments specifically targeted at neural control represent an important area of future research in CP.

As a retrospective study, this research was limited by clinical protocols. Children in this study walked without assistive devices when possible, but we did not exclude children who used them. However, walkers and other assistive devices can alter biomechanics and muscle activity [137–139], and understanding the impact of assistance on synergy complexity and structure represents an important area for future research. Although synergies have been shown to be repeatable between days for both TD and CP individuals [101,140], the amount of time before and after treatment varied. Participants received therapy per their individual treatment plans as part of the standard of care. Thus, observed changes in synergies are due to the treatments analyzed in this study, along with a combination of rehabilitation [89,120,121], growth, and development [28,107]. While the EMG data used to analyze synergies included the large muscles commonly targeted with treatment, it is possible that there are greater changes in activations or

synergies for muscles not evaluated with EMG recordings as part of standard clinical gait analysis. Similarly, the amount and quality of data varied between individuals and sessions. Prior research has shown that number of gait cycles can impact synergies, especially for small numbers of gait cycles [90]. Thus, we chose to use all available trials in our analysis, accounting for as much variability between gait cycles as possible. Missing data in some individuals necessitated the use of WNMF to calculate synergies, which could cause some changes in the synergy outputs. A post-hoc comparison between synergies calculated using the WNMF algorithm on sessions with complete data and the same sessions where data was omitted (up to 70% of one EMG channel and 30% of a second EMG channel, with non-overlapping portions) found an average change in $tVAF_n$ of <1% for n = 1-5 synergies and an average cosine similarity >0.95 for synergy weights and activations.

6.4.1 *Conclusions*

This study demonstrated that common treatments in CP, including extensive rehabilitation, resulted in minimal changes in muscle synergies. There were decreases in synergy complexity after BTA and SDR, but these changes were small and resulted in synergy complexity less similar to TD peers. Changes after treatment were variable across participants, emphasizing the heterogeneity of movement patterns in CP that necessitate better methods to quantify patient-specific differences in motor control and movement. Across treatments, changes in synergy activations were associated with changes in gait. Children whose synergy activations were more similar to TD peers after treatment had greater improvements in kinematics and walking speed. These results highlight that, although synergy complexity and weights are challenging to change in CP, synergy activations may provide a target for rehabilitation to improve gait.

Chapter 7. IMPACT OF MUSCLE SYNERGY CONSTRAINTS ON STATIC OPTIMIZATION DURING GAIT FOR UNIMPAIRED CHILDREN AND CHILDREN WITH CEREBRAL PALSY

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Kaat Desloovere

Michael H. Schwartz

Katherine M. Steele

ABSTRACT

Musculoskeletal models are frequently used to estimate muscle activations by minimizing muscular effort. However, estimated activations often fail to match muscle activations recorded experimentally through electromyography (EMG). Research has theorized that the nervous system may simplify the range of possible muscle activations by constraining the activations to weighted groups of muscles or muscle synergies. Moreover, research has shown that synergies can be altered in groups with neurological impairments, such as cerebral palsy (CP). The aim of this study was to test whether constraining the estimation of muscle activations in a musculoskeletal model to synergistic patterns can improve the correlation with EMG data. We evaluated modeled muscle activations during gait for six typically developing children and six children with CP using 1) static optimization (SO), minimizing muscle activations squared, and 2) synergy static optimization (SynSO), minimizing the synergy activations squared. For SynSO, estimated muscle activations were computed using the weights identified from two, three, four, and five synergy solutions. SynSO caused changes in estimated activations compared to SO. However, the correlation (cosine similarity) to EMG data was not higher over the gait cycle for SynSO than for SO in either TD or CP groups. SynSO improved estimated activations during single-limb stance, but not during the swing phase of gait. Correlation of estimated activations to EMG was variable between muscles and individuals. Cosine similarity between estimated activations and EMG data was higher in CP than TD for both SO and SynSO. Constraining activations to SynSO caused the simulated muscle stress to increase compared to SO for all individuals and was largest when constrained to the fewest (two) synergies. These results suggest that constraining modelled activations to subject specific synergies alone cannot improve estimation of muscle activations during gait for generic musculoskeletal models.

7.1 INTRODUCTION

Muscle synergies have been used as a method to understand how muscles are commonly activated during tasks such as walking by identifying a low dimensional space of weighted muscle groupings [36]. These weighted groups of muscles have been shown to be altered among individuals with neurologic injuries, such as stroke or cerebral palsy (CP) [48,49,57,58,101]. Although calculation of synergies has been used to describe muscle activation patterns in experimental data, these patterns have only begun to be applied to support musculoskeletal modeling.

Estimating muscle forces and activations is key to many questions asked with musculoskeletal modeling [141]. Examples include contributions of specific muscles to gait [142–145] loads acting upon joints [146,147], and use of orthotic devices [148,149]. However, when muscles activations are calculated using optimization based methods, there are large variations in estimated muscle activations across studies [150]. Comparisons of modeled muscle activations to experimental data from electromyography (EMG) recordings are frequently performed only qualitatively, broadly assessing timing and amplitudes [74,141,147,151–154]. Quantitative assessments on unimpaired subjects revealed only moderate correlations between experimental and modeled muscle activations [154–156]. A recent study by Veerkamp found similar levels of between individuals with CP and TD individuals [157]. Other prior studies of individuals with CP often used constraints, specifying when a muscle must be on and off, or other strategies to try to get better agreement between simulated activations and experimental measures from EMG data [142,158,159] Muscle synergies may provide a framework to improve estimation of computed muscle activations by providing an alternate method to constrain which muscles are simultaneously activated based upon an individual's EMG data [160].

Static optimization is a common algorithm used to estimate muscle activity that minimizes an objective function, such as minimizing the sum of squared muscle activations while satisfying the system equations of motion. Current optimization methods have been shown to be related to minimizing muscle stress and tend to minimize modeled co-contraction [146,161]. However, a recent study by Simpson [162] found that individual muscle activations could be adjusted to almost any level at any point in the gait cycle while still satisfying kinematic and kinetic constraints, suggesting that shapes of modeled activation patterns are driven predominantly by the choice of optimization function, rather than required by the joint torques. As high levels of co-contraction are a hallmark of gait in CP [10,163], other optimization criteria may be more appropriate when modeling pathologic gait [145,164]. It has previously been theorized that the central nervous system may be constrained to search for muscle activation patterns by combining a limited number of factors or muscle synergies [65]. If synergies are a within the range of kinetically feasible activations, constraining to individualized synergy structures may help capture subject-specific activations patterns.

Muscle synergies have previously been used to constrain muscle activity for musculoskeletal simulations, most prominently in forward dynamic simulations [62,165–169]. Forward dynamic simulations describe how internal forces (muscles) are activated and calculate the resulting kinematics and kinetics. Two studies have employed synergies with musculoskeletal modeling in pathologic gait of adult stroke survivors [66,170]. Most of these simulation studies have focused on tracking ideal synergy activation patterns as part of the optimization [66,166,167,170,171], which has allowed for performance similar to EMG tracking forward dynamics while reducing the number of input parameters. Accurate EMG/synergy tracking requires extensive model calibration achieved by adjusting model parameters of each

muscle including muscle activation delays, EMG scale factors, and tendon slack lengths such that the models closely match experimental kinematics and kinetics. These procedures are extremely time and computationally expensive. One study applied synergy controls without EMG tracking and found better calculation of joint loads than individual EMG alone; however, like the previously mentioned studies, this model was highly calibrated for a single individual [172]. Another study in the upper limb used optimization of synergy activations to model muscle activations during three-dimensional force generation and found that synergies better represented EMG data than independent muscle optimization [173].

The goal of this research was to compare simulated muscle activations with synergy constraints to experimental EMG data of gait in typically developing individuals (TD) and individuals with CP. We hypothesized that the similarity between EMG data and activations minimizing the stress of individual muscles would be lower in CP, due to altered motor control. We hypothesized that by activating muscles together in the musculoskeletal models using subject specific synergies, we would reduce the possible modeled muscle activation to better match experimental EMG, providing better estimates of muscle dynamics compared to using optimized individual muscle control.

7.2 METHODS

7.2.1 *Participants*

We retrospectively analyzed clinical motion analysis data collected at UZ Pellenberg, Belgium for six children with CP and six TD children (Table 1). All children with CP were in Gross Motor Function Classification System (GMFCS) Levels I or II. Marker trajectories were tracked using a 10 to 15 camera VICON system (Nexus 1.8.4. Vicon-UK, Oxford, UK) sampled

at 100Hz. Ground reaction forces were collected using two AMTI force plates sampled at either 1000 Hz or 1500 Hz.

Table 7.1. Participant Demographics (average (SD)).

Participant	Age	Gender	Height	Weight	GMFCS
	y+mo	m/f	mm	kg	
CP_01	8+11	f	1308	24.4	2
CP_02	15+9	m	1710	49.1	2
CP_03	9+3	f	1235	32.6	2
CP_04	7+9	m	1163	20.4	2
CP_05	6+6	m	1204	22.2	2
CP_06	11+8	m	1574	50.6	1
CP Avg	**10+0 (3+4)**	**4/2**	**1366 (223)**	**33.2 (13.6)**	
TD_01	10+0	f	1314	28.6	-
TD_02	7+7	m	1319	27.2	-
TD_03	8+7	m	1340	31.9	-
TD_04	8+6	m	1340	27.5	-
TD_05	8+3	f	1288	29.6	-
TD_06	10+4	f	1404	30.3	-
TD Avg	**8+11 (1+1)**	**3/3**	**1334 (39)**	**29.2 (1.8)**	

7.2.2 *Electromyography*

Surface EMG data (Wave Wireless EMG, Cometa, Bareggio, Italy) were collected at either 1000 Hz or 1500 Hz from eight muscles bilaterally (gluteus medius, rectus femoris, vastus lateralis, medial hamstrings, lateral hamstrings, tibialis anterior, gastrocnemius, and soleus) during clinical gait analysis. Because we were using retrospective clinical data, not all muscles were recorded for every trial and, for some individuals, a single muscle was missing from all trials (right vastus lateralis in CP03, CP04, and CP05; left tibialis anterior in TD02, and left rectus femoris in TD04). Raw EMG data were band-pass filtered between 20 and 500 Hz upon collection. We calculated a linear envelope for each muscle by high-pass filtering at 20 Hz,

rectifying the data, and low-pass filtering at 6 Hz [102]. Prior to calculating synergies, we concatenated the middle 80% of EMG data for all available trials for each participant to maximize the amount of data for synergy analysis while removing periods of transient acceleration or deceleration near the beginning and end of each trial [90,102]. The concatenated data was down-sampled to 100 Hz and scaled to a peak amplitude of one for each muscle.

7.2.3 *Synergy Analysis*

We calculated synergies with weighted non-negative matrix factorization (WNMF) using the Matrix Factorization Toolbox [104,105] in Matlab (MathWorks, Inc., Natick, Massachusetts). We have previously used WMNF to accommodate clinical EMG data with poor or missing channels by assigning a weight of zero to those data points, allowing us to maximize data for synergy analysis [118,174]. Aside from the missing EMG channels noted above, all muscles were recorded in at least two trials within the concatenated session. WNMF finds a set of synergy weights (W_{mxn}) which are activated (C_{nxt}) such that $EMG = W \times C + error$, where m is the number of muscles (7 or 8), n is the number of synergies (2 to 5), and t is the number of time points in the concatenated session. Synergies were calculated for each side (unilaterally) using the following WNMF settings: 50 replicates, 1000 maximum iterations, $1x10^{-4}$ minimum threshold for convergence, and $1x10^{-6}$ threshold for completion. Synergy weights and activations were scaled such that the maximum weight in a synergy was one. Similar to prior research, reconstruction of the EMG data by n synergies was higher in CP for all numbers of synergies compared to TD (Figure 7.1) [58].

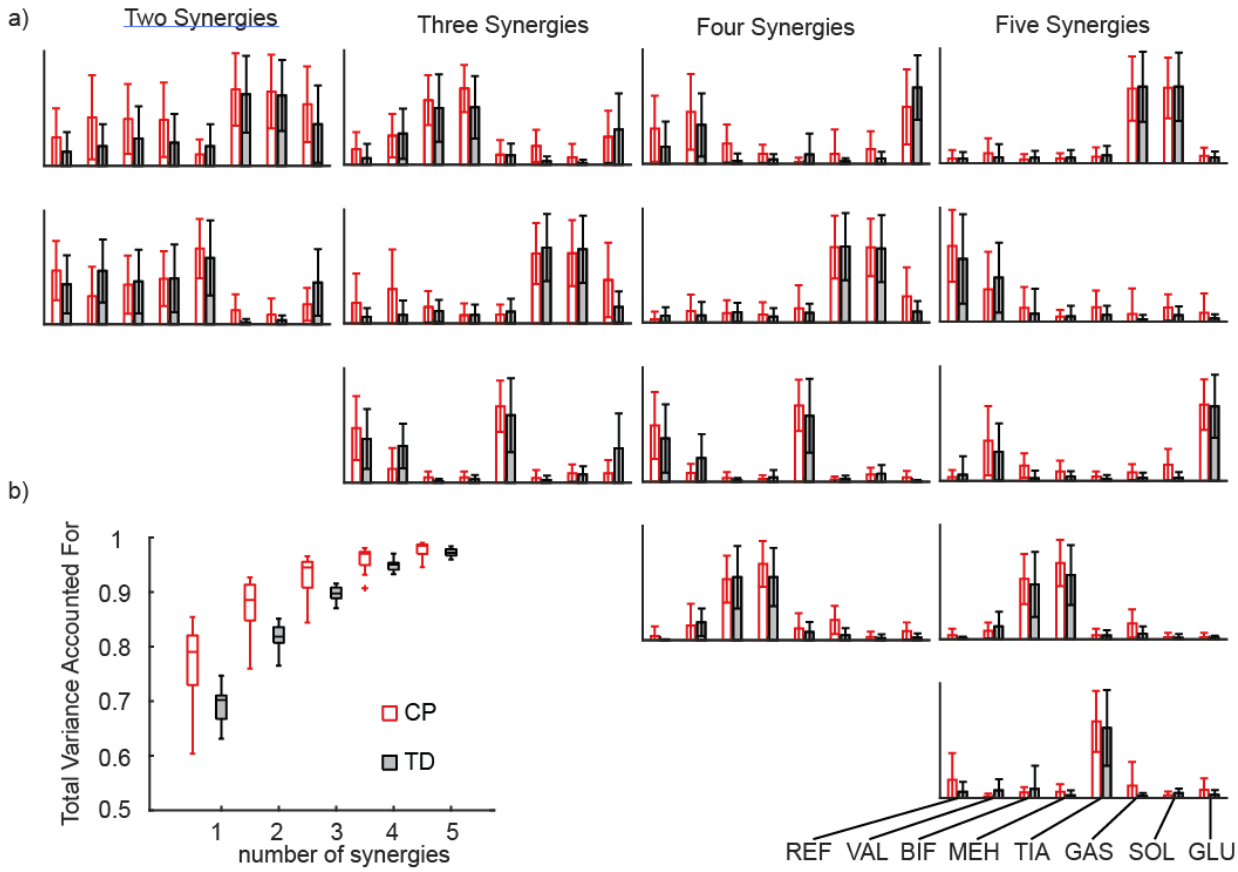

Figure 7.1. Muscle synergies calculated from EMG data: a) Muscle weights for 2 to 5 synergies for CP and TD. b) The total variance in EMG data accounted for a given number of synergies was greater for children with CP than TD peers.

7.2.4 *Musculoskeletal Modeling*

We used marker trajectories from an extended marker set, based upon the Plug-in-Gait (PiG) model, to scale a generic 19 degree-of-freedom and 92 musculotendon actuator model in OpenSim version 3.2 [175–177]. We used inverse kinematics to calculate joint angles by minimizing the error between the experimental markers and virtual model markers. The average RMS marker error was 0.92 ±0.19 cm and the average maximum marker error was 2.64 ±0.97 cm [141]. The force plate data used in this study had a threshold applied upon collection where

forces under 25N were not recorded. Thus, to avoid dynamic inconsistencies in our models occurring near heel strike and toe off, we limited our investigation to single-limb stance. We performed a residual reduction analysis to improve dynamic consistency in our models by making small adjustments to the position of the torso center of mass and joint angles [178]. A total of 88 simulations of single-limb stance phase (44 CP, 44 TD) were generated. The number of simulations per individual ranged between 3 and 13 for CP and 5 and 10 for TD.

We calculated simulated muscle activations using two methods (Figure 7.2). First, we used the standard static optimization (SO) algorithm in OpenSim [179]. SO estimates muscle forces that satisfy joint dynamics at each point in time while accounting for muscle force-length properties. The cost function employed by SO minimizes muscle stress as the sum of squared muscle activations [179–181]. To evaluate whether constraining to synergies improved estimates of muscle activity, we used the synergy optimization (synSO) plug-in previously described by Steele et al. (2015). SynSO allows the user to specify weighted groups of muscles to be commonly activated while minimizing the sum of squared synergy activations. For each synergy, the synergy weights we calculated from experimental EMG data were applied to the corresponding musculotendon actuators for each muscle. Thus, synergy weights for the gastrocnemius were applied to both the medial and lateral gastrocnemius actuators, weights for the medial hamstrings were applied to both semimembranosus and semitendinosus actuators, weights for the lateral hamstrings were applied to both biceps femoris long head and short head actuators, and weights for the rectus femoris, vastus lateralis, tibialis anterior, and soleus were all applied to their individual musculotendon actuators. As only 26 of the model's 92 musculotendon actuators were accounted for with EMG data, the remaining 66 musculotendon actuators were independently activated as in SO. We evaluated SynSO for sets of two to five

synergies for each participant. Similar to prior research, synergies were calculated and applied independently for each leg (*e.g*. in a four-synergy simulation we calculated and used four synergies for the right leg and four synergies for the left leg). Constraining activations through SynSO to fewer synergies reduced the number of successful simulations. For all numbers of synergies, more simulations were successful in CP than TD (e.g. 95% vs 86%, five synergies; 45% vs 34%, two synergies).

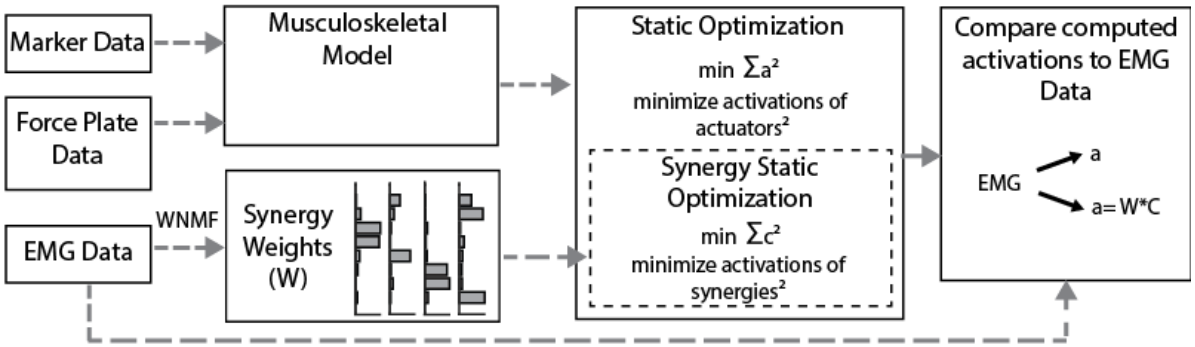

Figure 7.2. Musculoskeletal modeling framework: Musculotendon activations are computed from the musculoskeletal model using the static optimization algorithm or the synergy static optimization algorithm and compared to measured EMG data. Static optimization minimizes the sum of all 92 actuators squared. Synergy static optimization groups muscles together using synergy weights from the measured EMG data and minimizes the sum of the activations of those synergies squared.

7.2.5 *Outcome Measures*

To determine whether constraining to synergies resulted in simulated muscle activations that were more similar to measured EMG data, we calculated the cosine similarity between the filtered EMG data and simulated muscle activations for SO and SynSO. We determined that the similarity due to chance was 0.55, which we calculated as the average cosine similarity across all individuals and EMG channels to 1000 random vectors with a truncated Laplacian distribution

[45]. Thus, cosine similarity was normalized such that the similarity due to chance was given a value of zero. We examined the similarity for each muscle by concatenating the simulated activations from all trials and calculating the cosine similarity to the corresponding measured EMG data. For muscles modeled with multiple musculotendon actuators, we calculated and compared the average activation for SO. In SynSO, the synergy weightings constrained all musculotendon actuators within a modeled muscle to have the same activation. We calculated the average similarity for each participant across all muscles. We compared the average similarity of estimated activations to EMG data between SO and SynSO, and between single-limb stance and swing for each algorithm. We compared the simulated activations between SO and SynSO by computing the normalized similarity. We also computed the change in summed muscle stress (overall and by muscle) and peak activation of muscles.

7.3 RESULTS

The similarity of estimated activations and experimental EMG data was similar between SO and SynSO, but generally poor for both algorithms. The normalized similarity (median (IQR)) between EMG and simulated muscle activations from SO was higher in CP (0.48 (0.17)) than in TD (0.36 (0.18)) (Figure 7.3). Normalized similarity for SynSO in CP was less for fewer synergies, with values of 0.37 (0.10), 0.38 (0.09), 0.48 (0.17), and 0.47 (0.19) for two to five synergies, respectively. In TD, similarity from SynSO was less than in CP and was lower than SO with a similarity of 0.24 (0.21), 0.19 (0.16), 0.27 (0.24), 0.26 (0.19) for two to five synergies.

We found a better representation of EMG data during stance phase (during single limb support) for SynSO across all numbers of synergies (CP: 0.59 to 0.65, TD: 0.48 to 0.51) When only stance phase (during single limb support) was evaluated compared to SO (CP: 0.39 (0.26), TD: 0.34 (.16)). However, we did not find increased similarity to EMG during swing for either

CP or TD using SynSO. Similarity to EMG during swing phase was 0.38 (0.26) for SO and varied between 0.36 and 0.61 for SynSO in CP. For TD, the median similarity to EMG was 0.33 (0.21) for SO and ranged between 0.26 and 0.32 for syn SO.

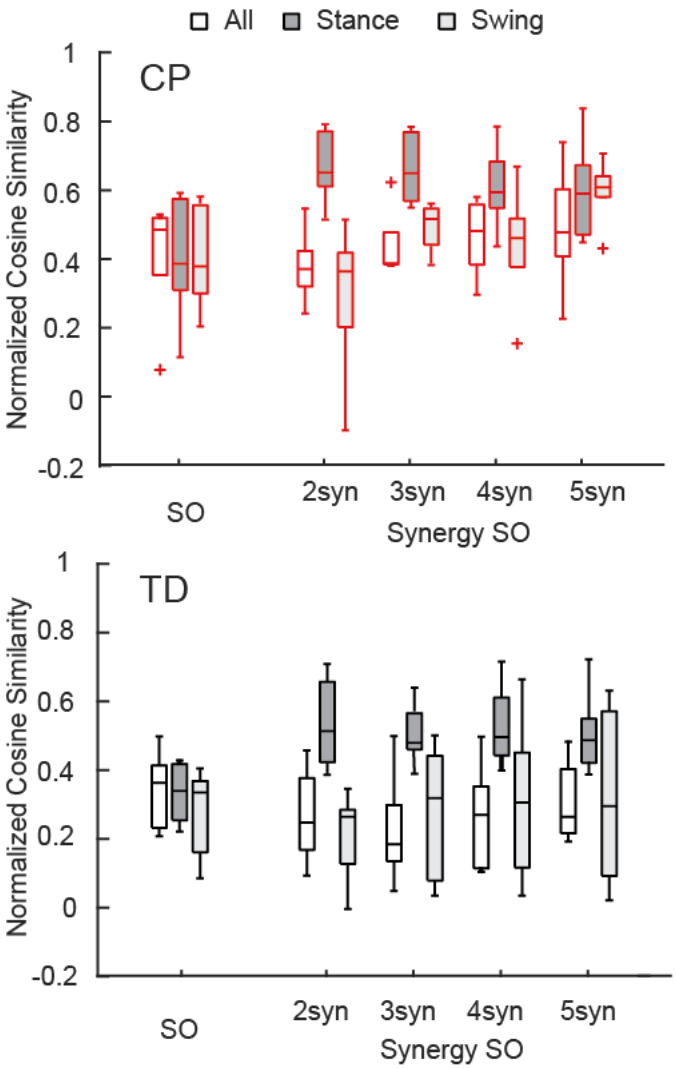

Figure 7.3. Normalized similarity of simulated activations and EMG data: Cosine similarity was used to examine how well estimated activations from simulation represented experimental EMG data for the TD and CP groups during single-limb stance and/or swing. Similarity was normalized such that zero equals similarity due to random chance and one equals perfectly similarity. Median similarity was better than chance for both CP and TD for SO and SynSO. Single-limb stance phase was better represented by SynSO than SO.

Similarity to EMG data was highly variable between individuals. The plantarflexors (gastrocnemius, and soleus) and tibialis anterior were the most similar muscles to EMG using SO (Figure 7.4). Constraining the simulated activations to SynSO tended to improve the similarity to EMG for the plantarflexors (CP: median soleus similarity increased from 0.65 for SO to 0.76 for three SynSO) and decreased the similarity to EMG for the tibialis anterior (TD: median

similarity decreased from 0.57 for SO to -0.24 for three SynSO). The similarity of the gluteus medius to EMG was higher in CP (SO: 0.72 (0.22)) than TD (0.37 (0.30)) but did not become more similar when SynSO was employed. The hamstrings and rectus femoris tended to become less similar to EMG when constrained to SynSO for the TD group and had only small changes in CP. The vastus lateralis tended to be only as similar as chance using SO and became more similar to EMG for all numbers of synergies in CP, but was still poorly represented in the TD group (SO: -0.16; five SynSO 0.19). Examination of the activation patterns between SO and SynSO showed that most muscles were recruited to higher amplitudes in single-limb stance (Figure 7.5).

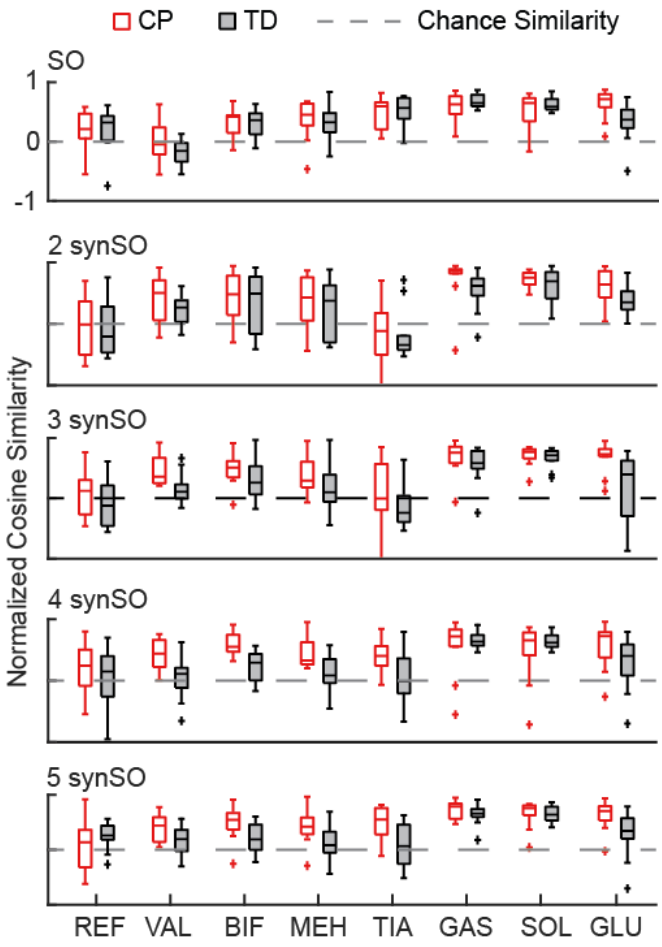

Figure 7.4. Similarity of individual muscles: The similarity of each muscle was compared for SO and SynSO for CP and TD groups. Similarity was normalized such that zero equals similarity due to random chance and one equals perfectly similarity. Activations computed with SO had the lowest similarity to EMG data for the rectus femoris (REF), vastus lateralis (VAL), and biceps femoris (BIF). Activations computed with SynSO had poor similarity to EMG data for the tibialis anterior (TIA), REF, and BIF (for the TD group). The gastrocnemius (GAS) and soleus (SOL) had the greatest similarity to EMG data for both algorithms.

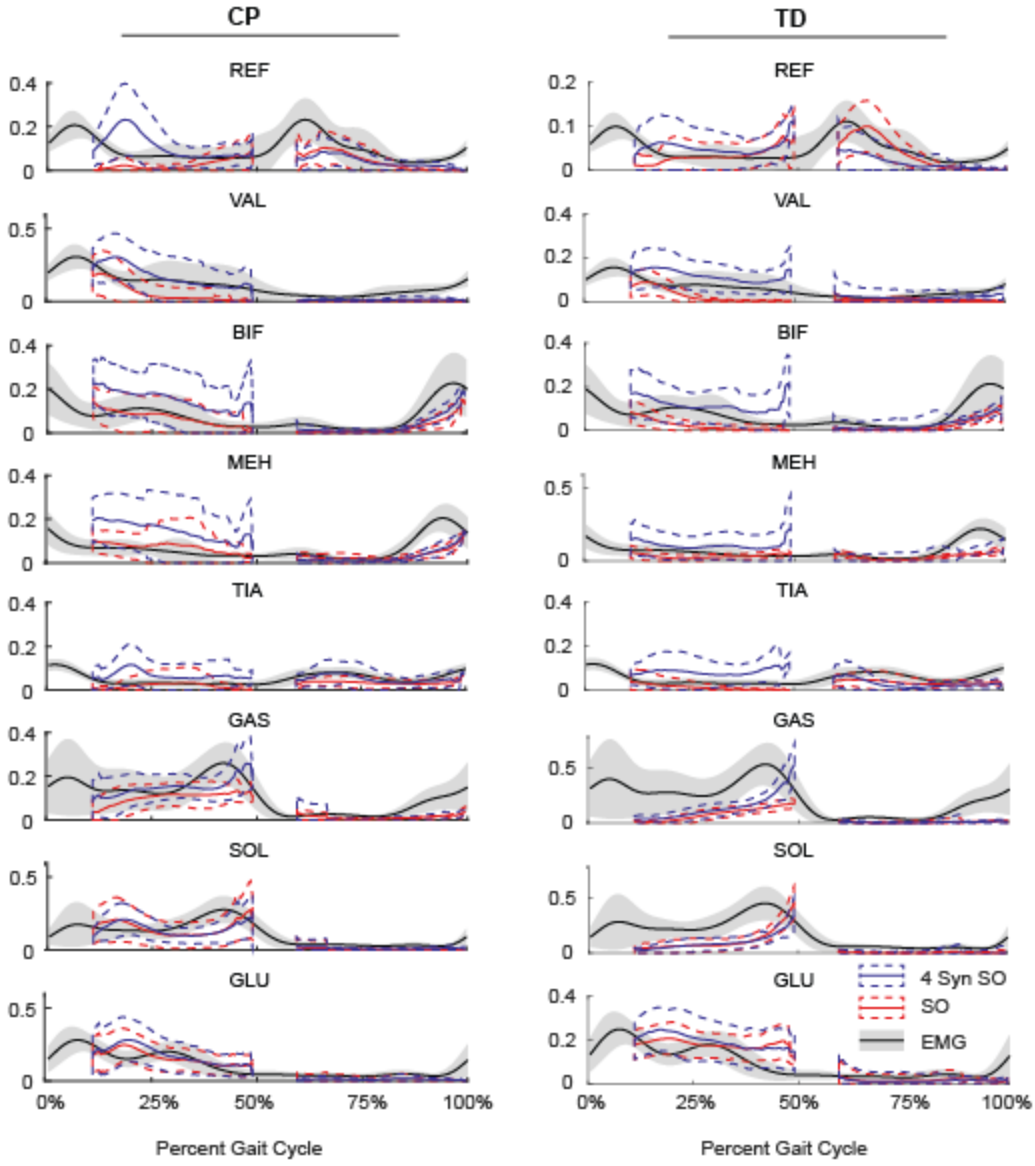

Figure 7.5. Average SO, 4SynSO and EMG activation patterns for CP and TD: The modeled activation tended to be higher for SynSO than SO for most muscles in both TD and CP during single-limb stance. EMG activations are scaled to the maximum activation in either SynSO or SO.

Simulated muscle stress increased in SynSO relative to SO for all individuals and was highest for the two synergy solutions (Figure 7.6) with an increase of 157% (72%). As simulated muscle stress is a rough estimate of energetic cost, indicating that the constraints of

SynSO finds solutions requiring greater effort. Muscle activated within a synergy had increases in muscle stress of 72% (61%) for two synergies and 64% (45%) for five synergies. For muscles that were independently activated, stress increased by 323% (235%) for two synergies and 147% (98%) for five. Despite the large changes in summed muscle stress, changes in peak activation were less than 10% for over 60% of the muscles across all numbers of synergies in SynSO.

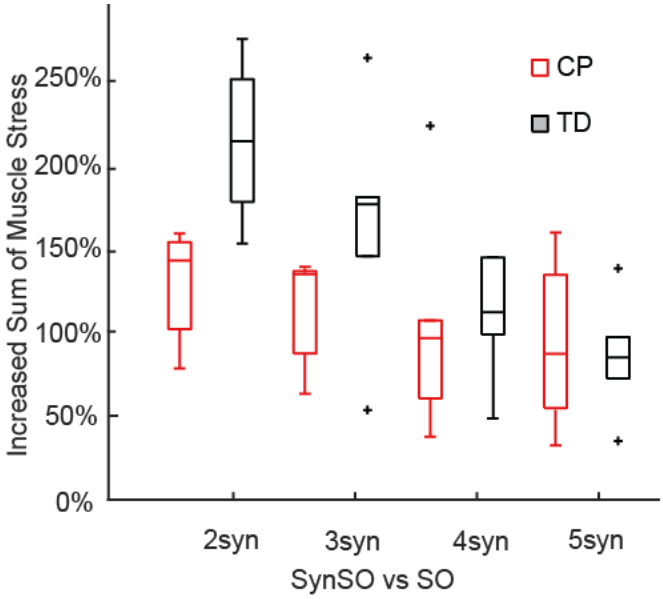

Figure 7.6. Increased sum of muscle stresses for SynSO: Muscle stress measured as the muscle activations squared increased for both TD and CP across all number of synergies. Increases in muscle stress were highest for two synergies and lowest for five synergies.

SynSO caused changes in simulated activations both for muscles included in a synergy and muscles that were independently controlled that did not have EMG data (Figure 7.7). Muscles that were constrained to synergies demonstrated the largest changes, with a normalized similarity between SO activations and SynSO of 0.17 (0.22) for two synergies and 0.54 (0.16)

for five synergies. Muscles that were independently controlled had smaller changes than those within synergies, with a normalized similarity between SO and SynSO activations of 0.52 (0.09) for two synergies and 0.60 (0.14) for five synergies.

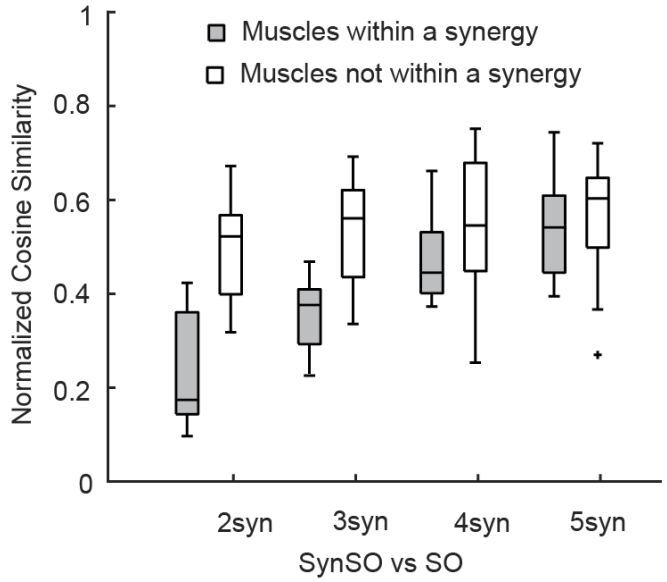

Figure 7.7. Similarity of activations computed with SO and SynSO: Activations computed with SynSO were different than those calculated from SO, for both muscles that were constrained to a synergy and muscles that did not have EMG data and were independently activated. Similarity was normalized such that zero equals similarity due to random chance and one equals perfectly similarity.

7.4 Discussion

We investigated whether constraining musculoskeletal simulations to subject-specific synergies could improve estimations of muscle activation during gait. Across all subjects, using static optimization incorporating synergies (SynSO) caused changes in estimated muscle activation patterns compared to traditional SO. Compared to SO, estimated muscle activations using SynSO tended to better match EMG data during single-limb stance phase for both TD and CP individuals. However, SynSO also tended to estimate activations that were less similar to

EMG data during swing, such that overall SynSO did not better estimated EMG data than SO. For both algorithms the similarity to experimental EMG data for both CP and TD groups was generally poor, emphasizing the need for new methods to model muscle activity for analyses of human movement.

The correlations found in this study between EMG and SO were similar to those previously reported [154–157]. These four studies demonstrate variability both between individuals and across muscles, similar to our results. The best-represented muscles during gait were the plantarflexors, consistent with our results for both CP and TD [154–156]. The worst-represented muscles were the knee extensors and hamstrings which is also consistent with our findings for TD and CP [154–156].

Selection of an appropriate number of synergies is challenging for this type of problem. To avoid biasing our results based upon and ad hoc threshold, we computed our results over a range of two to five synergies. We chose to apply a minimum of two synergies, as a minimum representation of gross flexion and extension which has been previously been found to well represent data in infants and individuals with cerebral palsy [58,107]. As additional synergies were added, muscle activation patterns within each synergy became more independent (e.g. the tibialis anterior was largely independent in the five-synergy solution for CP and TD), more closely representing the conditions in static optimization (Figure 1). Constraining to a smaller number of synergies led to higher levels of overall muscle stress, indicating an overall less optimal solution. As SynSO did not tend to improve correlation with EMG data for any number of synergies, we were unable to find an optimal number of synergies needed for either group.

Our results using synergies to improve estimations of muscle activation during gait contrasts with previous studies [170–173] which found generally good estimation of EMG with

synergies. The differences between the previous work and our results here broadly fit into three categories: the optimization criteria, the challenge of relating EMG amplitudes to neural excitations, and generic musculoskeletal properties. In the prior studies of Walter [172], Meyer [170], and Serrancoli [171], EMG shape tracking was used as part of the optimization algorithm which constrains the modelled activations to the EMG profile. In this study we sought to model muscle activations through a modified static optimization cost function which minimized synergy activations squared, consistent with the optimization previously implemented by Borzelli [173] and Mckay [183]. This cost was motivated by the traditional physiologically motivated cost functions which seek to minimize fatigue or load in individual muscles [179,180,184], while constraining the space of allowable muscle activations to specified patterns of coactivation. The constrained search space resulted in higher muscle stresses than what is found with independent actuation, consistent with prior studies [173,183]. We note that minimizing synergy activations squared alters the cost function, removing the direct physiological relationship to muscle stress. A prior investigation by Mckay [183] in cats suggests that minimizing synergy activations squared, as performed in this study, results in higher muscle stress than minimizing muscle stresses squared subject to synergy constraints. A further difference is that, unlike the prior studies [173,183], we did not have EMG data for all muscles in the model and instead allowed the unmeasured muscles to have their activations optimized independently as it is unclear how to scale the unmeasured muscles within a synergy.

The challenges in directly comparing EMG to musculoskeletal modelling has been well documented [21,164] and include methods scaling EMG to peak neural excitations [160,173], electromechanical delays [185], as well as interpretation of EMG stemming from inter-step variability, crosstalk, cancelation, measurement orientation, and pre-processing decisions

[21,102]. In this study, we modelled activations using subject specific synergies whose weights were derived from EMG data normalized by peak measured EMG amplitude during walking. This choice was necessitated by our use of retrospective data and represents the simplest implementation of synergies into musculoskeletal modelling. To compensate for the uncertain scaling parameters between EMG and neural activation, previous forward dynamic simulations have tracked activation patterns but allowed the relative weights of the modelled muscles to vary either through a minimization of muscle stress with synergy activation tracking [62,165], or as part of the initial EMG tracking calibration process [170–172]. Alternate methods of scaling synergies experimentally, such as by a maximum voluntary contraction or the use of force-to-EMG measurements [173], require the collection and integration of additional data, significantly complicating the implementation. Although the choice of amplitude scaling prior to calculating synergies can impact the relative weights of muscles within a given synergy [102], a recent investigation by Kieliba et al. (2018) found nearly identical synergy structures between EMG data normalized by maximum voluntary contractions or peak activations in healthy adults. The consistency of these synergy structures suggests that the relative weights of muscles within a synergy scaled by experimental data may only have a small impact on our results.

A key limitation of our ability to model muscle activations using SynSO is the lack of any electromechanical delay, which neglects activation/deactivation dynamics. In those studies that used EMG shape tracking, the electromechanical delay was also uniquely scaled for each muscle [170,172] or applied from the literature [171]. In a post-hoc analysis we evaluated the impacts of including a delay between EMG and modelled activations of 10 to 100ms but found inconsistent impacts on similarity between phases of the gait cycle number of synergies included in the optimization. For the previous studies which used a static optimization-based algorithm,

the investigations were limited to examining muscle activity during a isometric force generation task across a variety of directions [173,183], negating the impact of activation dynamics. Conversely, for dynamic tasks such as walking, in which a gait cycle may take approximately one second, even a 50ms delay may have substantial impacts on the similarity between simulated muscle activity and experimental EMG. This is likely the defining difference in the good estimation of EMG patterns found in those studies and the lack thereof in this study.

Generic musculoskeletal models also include sample-based assumptions about geometry (e.g. muscle attachment points, bone geometry) and muscle properties (e.g. activation delays, maximum muscle forces, and tendon lengths) which can have large impacts on estimated muscle activations [164,171,187–189] and may not represent individual properties [190], especially in children or individuals with CP [191–193]. Again, those studies that use EMG shape tracking tune musculotendon properties as part of the model calibration [170–172], but these parameters are difficult to validate for individuals. Despite these challenges, generic models have the advantage of minimizing the amount of data that must be collected for any individual. In this study, we sought to investigate the effects of constraining to synergies alone on estimates of muscle activity.

This study demonstrated that muscle activations estimated from static optimization using musculoskeletal modelling does not well predict EMG profiles. Constraining activation patterns to experimentally measured synergies increased estimated muscle stresses but did not improve the estimation of muscle activations for either CP or TD individuals. These findings suggest that constraining muscle activations to synergistic patterns alone cannot improve estimation of muscle activations during gait for generic musculoskeletal models.

Chapter 8. CONCLUSION.

8.1 SUMMARY

This dissertation provides an important contribution toward developing the clinical utility of muscle synergies as a measure of motor control in cerebral palsy. The findings in this study were achieved only through the interdisciplinary collaboration between engineering research and clinical partners.

The first objective of this dissertation (Chapter 3) was to evaluate the impacts on muscle synergies of common EMG pre-processing methodologies. The results of this objective found that measures of synergy complexity based upon the variance reconstructed by a given number of synergies were sensitive for to filtering conditions both unimpaired children and children with CP. While the impacts on synergy structure and timings are less pronounced for filtering than complexity, amplitude scaling caused changes in the relative weightings of muscles within synergies. Pre-processing decisions can impact the interpretation of muscle synergies, impeding the ability to compare results across studies. Normalization to an unimpaired control population was presented as a method to reduce the sensitivity of these choices.

The second objective (Chapters 4 and 5) were to examine the repeatability of muscle synergies. This work established that muscle synergies calculate similar structures and complexity across days in children with cerebral palsy and typically developing children. Further, this work replicated and generalized prior findings that synergy complexity is associated treatment outcomes in cerebral palsy across a common treatments and clinical centers. However, inter-center differences in procedures and choice of outcome measures impacted the strength of those associations.

The third objective (Chapter 6) examined whether synergies can change as a result of common treatments in cerebral palsy. This research found small and inconsistent changes,

indicating that current treatments do not consistently alter synergy complexity, structure, or timings. However, this analysis also demonstrated that when synergy timings did improve, those improvements were associated with improved kinematics and walking speeds across treatments. Thus, suggests that improving synergy timings may be a potential target for future rehabilitation protocols.

Finally, the last objective of this dissertation (Chapter 7) incorporated subject-specific muscle synergies into the optimization of muscle activations in musculoskeletal modeling. The results of this analysis demonstrated that incorporating synergies into the existing generic musculoskeletal modeling framework cannot alone improve estimation of muscle activations relative to EMG data. Additional information including, scale factors on muscle weights, choice of optimization criteria, and subject specific muscle properties may be required to generate better estimations of muscle activations.

This work contained in this dissertation has addressed several fundamental questions surrounding both the science and clinical application of muscle synergies. This work provides context to synergy calculations across processing decisions. By demonstrating that synergies are repeatable between days this dissertation has shown that muscle synergies can be reliably computed from both unimpaired children and children with CP. Similarly, this work has demonstrated robust clinical associations with treatment outcomes, confirming clinical value of these measurements. Moreover, this dissertation has demonstrated that synergies are not easily modifiable despite changes in kinematics, indicating that synergies may represent a static control architecture.

8.2 FUTURE WORK

The work contained in this dissertation provides a foundation upon which further investigations can build upon, potentially extending the clinical utility of muscle synergies in cerebral palsy. The following sections outline some important directions for future research building on each of the objectives presented here.

- **How can synergy processing choices be further refined by insights from neuroscience?**

  Despite the contributions presented in this dissertation in examining the impacts of processing decisions there remains a need to develop methods to select physiologically correct filtering conditions and scaling factors. Variable frequency cutoff methods have been utilized as a method to normalize filtering to the speed of an activity, although the impacts of these methods on synergies has not been fully investigated. Other potential avenues of investigation may include extending synergies into additional sources of bioelectric recordings such as recording directly from spinal cord or from the peripheral nervous system with electroneurography.

- **Can long-term EMG monitoring be combined with synergies to better understand modularity across a wide range of tasks?**

  Most studies examine synergies during a single task. Those that examine multiple tasks frequently indicate shared synergies[44,72,194,195]. However, these studies only provide snapshots of human activity. Long-term EMG data may provide a more holistic

understanding of how synergies are organized across tasks and provide insights regarding how the nervous system is organized. For example, it has been proposed that there may be more synergies than muscles but that only a subset are activate during an activity and constraining the neural system. Answers to these questions may enable new metrics for evaluating impaired synergies in individuals with neurologic disorders.

- **Can synergies be altered using targeted treatments?**

  Research presented in this dissertation suggest that current treatments, including extensive physical therapy do not consistently alter synergies. However, other modalities should be investigated for efficacy in altering synergies including biofeedback training, pattern exploration, or electrical stimulation

- **Can synergies be used to examine neuro-maturation?**

  Past research has shown that synergies are simplified in neonates and gains complexity with development, such that toddler synergies resemble those of adults. Longitudinal tracking of synergies may help elucidate how the nervous system maturates, both in typically developing children and children with neurological disorders. This may also provide insights as to whether and when there are critical periods when the nervous system is most receptive to specific interventions.

The overarching goal of this work was to advance the ability to manage and treat children with cerebral palsy. This dissertation provided several key contributions, demonstrating the

robust associations with treatment outcomes across processing decisions. The possible research directions outlined are intended to further advance these goals by providing a better understanding of altered motor control and hopefully providing new interventions that can improve movement and quality of life.

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