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Can muscle synergies shed light on the mechanisms underlying motor gains in response to robot-assisted gait training in children with cerebral palsy?

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Abstract

Background Children with cerebral palsy (CP) often experience gait impairments. Robot-assisted gait training (RGT) has been shown to have beneficial effects in this patient population. However, clinical outcomes of RGT vary substantially from patient to patient. This study explored the hypothesis that clinical outcomes are associated with changes in muscle synergies in response to RGT.

Methods Thirteen children with CP and Gross Motor Function Classification Scale (GMFCS) levels I–IV were recruited in the study. Children participated in a 6 week-RGT intervention and underwent clinical evaluations and gait studies—with focus on the analysis of electromyographic (EMG) data—pre- and post-training. Lower-limb muscle synergies were derived from the EMG recordings. Pre- vs. post-RGT clinical outcomes and muscle synergies were compared to explore potential relationships.

Results Three and, less often, two muscle synergies were detected in study participants pre-RGT. Linear mixed effect models showed that composition of the muscle synergies and their temporal activation coefficients present deviations from normative data proportional to the severity of functional limitations (i.e., GMFCS levels, $p < 0.01$). At a group level, changes in muscle synergies pre- vs. post-RGT did not significantly correlate with changes in clinical outcomes ($p > 0.05$). However, it was observed that participants who displayed prominent changes in muscle synergies also displayed large improvements in clinical scores.

Conclusions Gait impairments in children with CP were associated with muscle synergies that deviated from normative. Participants who demonstrated the most substantial improvements in clinical scores following RGT exhibited multiple changes in the muscle synergies. However, no statistically significant correlations were identified at the group level. Future studies relying on larger datasets are needed to further investigate this observation and potential underlying mechanisms.

Keywords Cerebral palsy, Electromyography, Gait, Muscle synergies, Rehabilitation robotics

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Introduction

Cerebral palsy (CP) is formed by a group of disorders affecting movement, development, and posture that cause significant functional limitations, and it is the most common cause of motor disability in children [1]. Its estimated prevalence has been reported in the range between 1.5 and 3 per 1000 live births [1]. Its clinical features include muscle weakness, spasticity, and impairment of selective motor control [2].

Children with CP often experience gait impairments with a negative impact on mobility and quality of life [3–6]. Gait deviations in CP display large variability in their characteristics, are often complex, and can evolve during development, sometimes causing muscle contractures and joint deformities due to an imbalance in the forces generated by agonist–antagonist muscles and in muscle tone [7]. Interventions to improve gait are an important component of the treatment of children with CP [5]. Rehabilitation can minimize complications and improve gait, thus enhancing function [5].

Robot-assisted gait training (RGT) has been used as an efficient way to deliver high-dosage, high-intensity, task-specific interventions. These are “training ingredients” believed to maximize motor gains. While several studies have shown positive clinical outcomes in response to RGT at the group level [8–17], careful examination of the results of studies that provided data on a subject-by-subject basis reveals that significant variability marks the response to RGT in children with CP [8, 18–22]. It is unclear why children with CP display such a variability in their response to RGT. Are there individual patient characteristics that make RGT suitable for some children with CP and not for others? If clinicians knew why some children respond prominently to RGT whereas others do not, they would be able to prescribe RGT when a clinically important response is expected (based on the patient’s characteristics) and consider alternative treatments otherwise.

Muscle synergies represent muscle coordination patterns used to generate motor outputs. Their analysis provides a window of observation on how the nervous system generates movement patterns [23]. Several studies have shown that muscle synergies during gait are altered in children with CP [24]. Compared to typically developing children, children with CP display fewer muscle synergies marked by co-activations of agonist and antagonist muscles [25–27]. Changes in muscle synergies have been studied in children with CP in response to selective dorsal rhizotomy [28–31], orthopedic surgery [28, 30–32], botulinum toxin type A injections [28, 30, 33], and conservative treatment (i.e., physical therapy) [30], but changes in lower limb muscle synergies in response to RGT have only been reported in a study by Conner et al.

[34] focused on assessing the effects of a robotic system developed by the authors that was used to deploy resistance training in children with CP. Because gait deviations in children with CP are associated with a variety of aberrant patterns of muscle activation [35, 36], we decided to explore the relationship between the characteristics of such patterns and the response to RGT in children with CP hoping to shed light on what causes the above-mentioned variability in the response to the intervention. To achieve this goal, we relied on the analysis of muscle synergies [37–39].

In the study herein presented, we performed an exploratory investigation in a group of children with CP who underwent RGT using a robotic system (LokomatPro by Hocoma AG, Volketswil, Switzerland) most often used in clinical sites that provide pediatric patients with access to RGT. We evaluated their muscle synergies pre- and post-training with the overall objective of investigating the relationship between changes in muscle synergies and clinical outcomes (including functional measures and quality of movement as described in the Methods section of the manuscript). Metrics derived to quantify changes in muscle synergy characteristics in response to RGT served as the primary outcomes of the study. More specifically, the cosine similarity was used to compare the weights of the muscle synergies and the zero-lag cross-correlation (ZLCC) was used to compare their temporal coefficients. Functional measures and measures of quality of movement pre- vs post-training served as the secondary outcomes. To achieve the above-stated overall objective of the study, we tested three hypotheses: (1) there is a correlation between the degree of disarrangement of muscle synergies and the functional ability of children with CP; (2) muscle synergies change in response to RGT in a way that makes them more similar to normative synergies (i.e., positive changes); and (3) changes in muscle synergies correlate with changes in clinical outcomes. Furthermore, we performed a qualitative analysis of the results to identify instances in which prominent changes in muscle synergy characteristics were accompanied by large motor gains.

Methods

Participants

A convenience sample of 13 children with CP and gait impairments were enrolled in the study. This sample size is comparable with the sample size used in previous exploratory studies with focus on muscle synergies [27, 40, 41]. All parents or guardians signed a consent form, and children signed an assent form. Both were approved by the Spaulding Rehabilitation Hospital Institutional Review Board (protocol # 2015P001482, clinical trial # NCT06156969). Children were eligible to participate

in the study if they were diagnosed with spastic CP, were between 6 and 18 years of age, were classified between levels I and IV of the Gross Motor Function Classification System (GMFCS) [42], had femoral length between 210 and 350 mm (as required to use the RGT system utilized in the study), and had the ability to communicate pain and discomfort. Individuals were excluded from the study if they had received RGT during the last 3 months, reported any contraindication to RGT (such as thromboembolic disease, progressive neurological disorder, cardiovascular or pulmonary contraindications), displayed aggressive behavior, had severe cognitive deficits, joint instabilities, bone fractures, osteoporosis, lower-limb joint fusion (i.e., arthrodesis), or skin ulcers affecting the trunk or lower limbs.

Experimental procedures

Figure 1 shows a schematic representation of the study procedures. Details are provided in the following.

Robot-assisted gait training protocol

Children were asked to undergo 18 gait training sessions using the LokomatPro (Hocoma AG, Volketswil, Switzerland) over a period of approximately 6 weeks. Each session included 30 min of walking assisted by the robot, allowing for rest breaks as needed. Training sessions were overseen by a clinician (a physical therapist or a physiatrist) trained in the use of the robotic system. Bodyweight support, walking speed, and guidance force

provided by the robot were adjusted during the training session as deemed appropriate by the clinician overseeing the session. Bodyweight support and guidance force were adjusted in a way that allowed the child to achieve nearly normative gait kinematics while maximizing the level of participants' engagement. In other words, the child was encouraged to put maximum effort toward generating the gait movements while the clinician overseeing the session decreased the bodyweight support and guidance force to the maximum extent possible without compromising the quality of the lower-body kinematics. This approach was adopted with the intention of achieving maximum engagement of the child during the training session (which is deemed relevant to motor learning) while avoiding aberrant movements (which are deemed detrimental to improving gait).

Surface EMG data during gait

Surface electromyographic (EMG) data was gathered pre- and post-RGT during overground gait using the Wave system (Cometa srl, Bareggio, Milan, Italy). The data was collected at 1800 Hz using wireless probes from the following muscles in both lower limbs: gastrocnemius (lateral head), soleus, tibialis anterior, peroneus longus, rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, and gluteus maximus. We followed the SENIAM 8 (Surface Electromyography for the Non-Invasive Assessment of Muscles) guidelines to place the electrodes. The guidelines provide instructions about

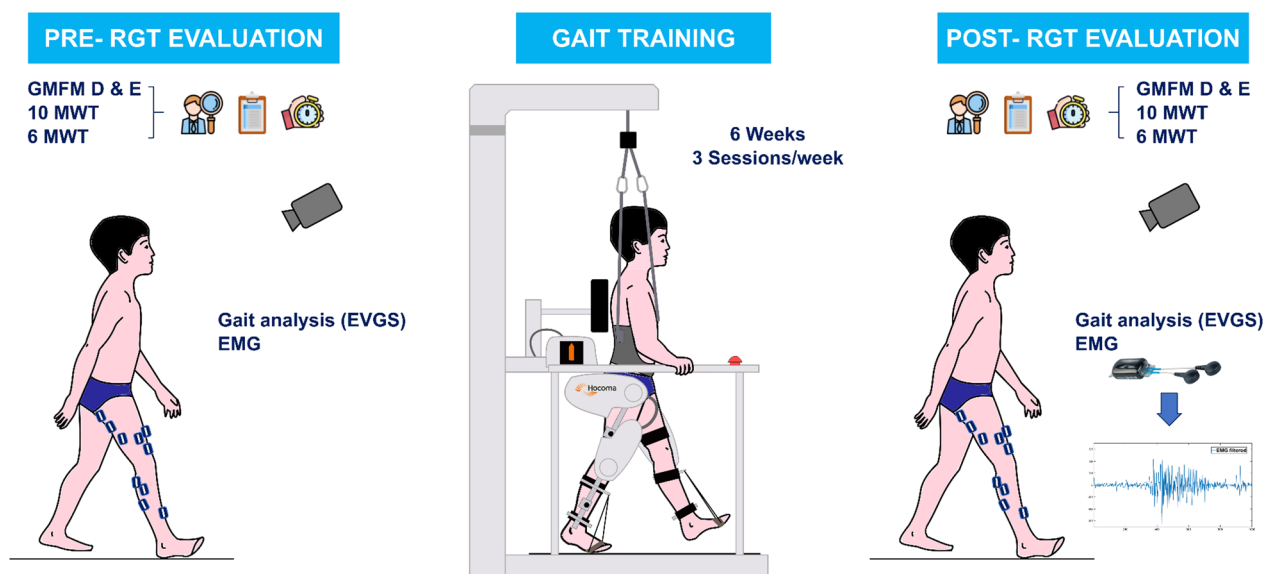


Fig. 1 Overview of the study procedures. Children underwent a 6-week Robot-assisted Gait Training (RGT) intervention (3 sessions per week) and pre- and post-RGT evaluations including sections D and E of the Gross Motor Function Measure (GMFM) scale, the 10-m walk test (10 MWT), the 6-min walk test (6 MWT), and a gait evaluation to collect surface electromyographic (EMG) data as well as perform a visual assessment of patterns of motion using the Edinburgh Visual Gait Score (EVGS)

how to position the EMG electrodes for each muscle as a point on a line between two anatomical landmarks [43]. The pre-amplification units of the EMG system were attached using double-sided tape and secured with Coban. During the baseline session, after the electrodes were placed, we measured the distance from each of the electrodes to two specific body landmarks according to the above-referenced guidelines (e.g., for the electrodes used to record the activity of the gastrocnemius muscle, we measured the distance between the two electrodes and the head of the fibula and the lateral malleolus, respectively). These measures were used to place the EMG electrodes in the same position during the post-RGT assessment session. The system used to collect the EMG data was integrated with a motion capture system (Vicon, Oxford Metrics, Yarnton, Oxfordshire UK) used in the study to segment the EMG data according to the gait cycles. A minimum of five walking trials were collected for each side (i.e., leg). Participants were tested in barefoot conditions. They were allowed to use assistive devices if they could not walk safely without.

Normative muscle synergies were derived from recordings gathered (using the same experimental setup) from nine adult healthy controls as part of a study approved by the Spaulding Rehabilitation Hospital Institutional Review Board (protocol # 2019P002419). The normative muscle synergies we obtained from the control group were consistent with those reported in previous studies in children of age comparable with our group [28]. Specifically, we identified four muscle synergies. The first synergy was active during early stance (load acceptance) and marked by a prominent activation of the gluteus maximus, vastus lateralis, vastus medialis, and rectus femoris muscles. The second muscle synergy was active during the push off phase of the gait cycle and was marked by a prominent activation of the gastrocnemius, soleus, and peroneus muscles. The tibialis anterior and rectus femoris muscles were the primary contributors to the third synergy, which was active during the swing phase and allowed for foot clearance. Finally, the fourth muscle synergy was primarily marked by the activation of the biceps femoris and semitendinosus muscles and accounted for the deceleration of the leg during the terminal swing phase of the gait cycle.

Clinical data

Demographic, anthropometric and clinical data including sex, age, race, ethnicity, dominant side, weight, height, characteristics of CP (i.e., topographic classification and GMFCS level [42]), other diagnoses, orthoses or assisted devices used for walking were collected at baseline. Assessments were performed before and after study participants underwent RGT. The clinical tests

performed by a clinician during the evaluation sessions included the standing (section D) and the walking, running and jumping (section E) sections of the *Gross Motor Function Measure* (GMF-M-88) scale [44], walking speed measured by the *10-m walk test* (10 MWT), and endurance using the *6-min walk test* (6 MWT). Video recordings were collected during the gait trials for the EMG studies. Standard cameras were utilized to provide coronal and sagittal views and derive *Edinburgh Visual Gait Scores* (EVGS) [45].

Data analysis

Analysis of muscle synergies

Figure 2 shows a schematic representation of how muscle synergies contribute to generating patterns of muscle activity [46]. In this schematic example, the EMG envelopes of four muscles are shown to be the result of combining three muscle synergies. The weights of each muscle synergy determine how much each of the four muscles contribute to that specific synergy. The temporal coefficients (often referred to as “temporal activations” or “temporal activation coefficients”) determine the level of activation of each synergy over time. This model provides the basis for the analysis approach utilized in the study as described below.

Raw surface EMG data were filtered using a 4th-order high-pass Chebyshev filter, with a cut-off frequency of 20 Hz, to attenuate movement artifacts. The output data were rectified and filtered using a 4th-order low-pass Chebyshev filter, with a cut-off frequency of 5 Hz, to obtain the EMG envelope for each EMG channel, which was normalized by the peak value observed for each subject for that given channel [47, 48]. The resulting time-series were segmented according to the gait cycles (i.e., intervals from foot-contact to foot-contact). The EMG envelope for each gait cycle was then resampled to 100 points. The first and last gait cycles of each trial were discarded.

Muscle synergies were extracted separately for each study participant [46]. The EMG data for a total of 20 gait cycles per study participant were used for the analyses herein described. The EMG envelope data for each subject were stored in a $m \times t$ matrix, “m” being the number of muscles (i.e., ten) and “t” being the total number of samples (20 gait cycles $\times$ 100 points per cycle = 2,000 samples). Data were analyzed separately for each leg. We used the non-negative matrix factorization (NNMF) [47, 48] function provided by MATLAB (MathWorks, Natick MA, USA). The algorithm factors the initial “A” matrix ($m \times t$) into two non-negative matrices denoted “W” ($m \times n$) and “T” ($n \times t$) by minimizing the root mean square value of the residual “D” defined by the following equation:

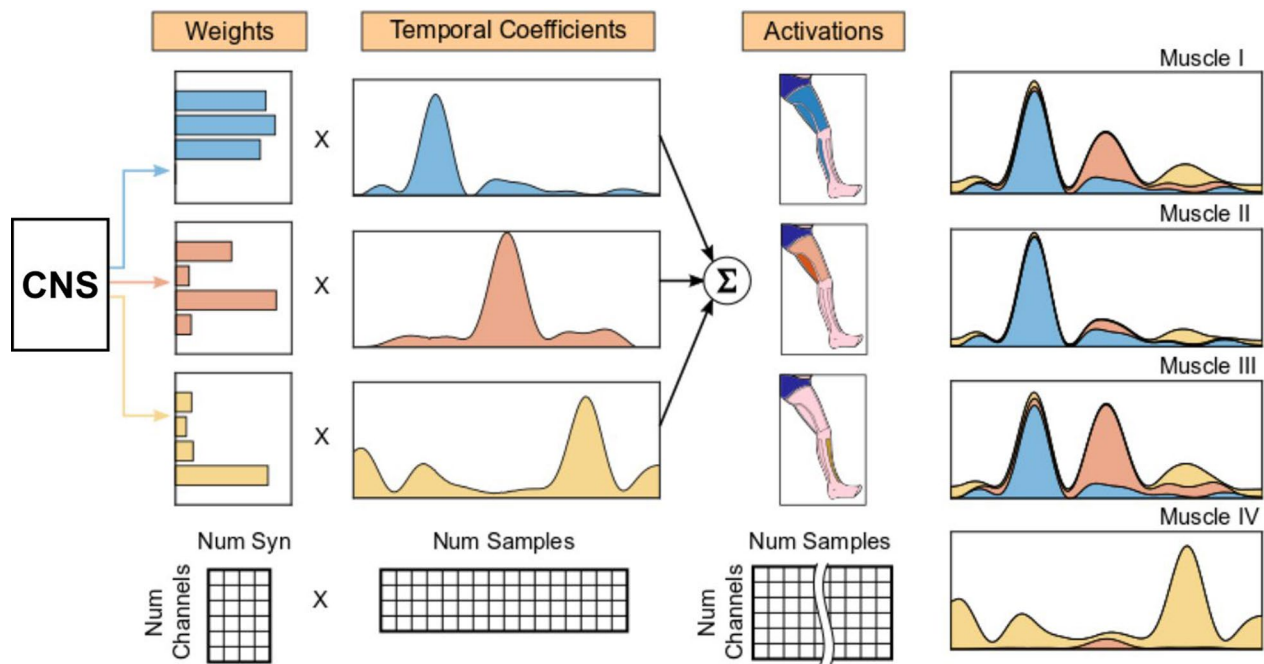


Fig. 2 Generation of muscle synergies. Muscle synergies are “modules” utilized by the central nervous system (CNS) to reduce the dimensionality of motor control during the performance of complex movements. The “modules” consist of weights (that determine the level of contribution of each muscle to a given synergy) and temporal coefficients (that determine the level of activation of each synergy over time). The combination of weights and temporal coefficients leads to the patterns of activation (and hence the EMG envelopes) of all monitored muscles

$$D = \frac{\|A - W * T\|_F}{\sqrt{(n * m)}}$$

where “n” is the number of synergies selected by the user, “m” the number of EMG channels, and F the Frobenius norm.

The W matrix identifies the contribution of each muscle to each synergy (i.e., weights). The T matrix defines the temporal activation of each synergy (i.e., temporal coefficients). The multiplicative update algorithm was utilized for these analyses. The number of replicates (number of times the algorithm is initialized to derive weights and temporal coefficients) was set to 5000 and the maximum number of iterations was set to 500 [49]. We identified the number of synergies by evaluating the difference, computed as R-squared (R^2) value, between the EMG envelopes and their synergy-based reconstructions [49]. We used a double-threshold approach to select the number of synergies by requiring an average $R^2 > 75\%$ and a minimum R^2 per channel $> 55\%$ [50].

Because prior work suggested that EMG data collected from children with CP display fewer muscle synergies than data collected from a normative sample [26, 28, 35, 41, 51], we evaluated if the synergies observed in children with CP could be considered the result of merging normative synergies. We applied the technique proposed

by Cheung et al. [39, 48]. Accordingly, we modeled the weights of each muscle synergy observed in children with CP using our healthy control reference synergies according to the following equation:

$$w_{CP_i} \approx \sum_{k=1}^{K_{ref}} p_k^i w_{REF_k}$$

where the “i-th” CP synergy “ w_{CP_i} ” was modeled, using a least square fit, as a linear combination of the four normative synergies “ w_{REF_k} ”. This generated four coefficients “ p_k^i ”, which represent how much each normative synergy contributed to “ w_{CP_i} ”.

The results of the above-described analyses allowed us to test the hypothesis that the degree of disarrangement of muscle synergies is correlated with the functional ability of children with CP (as captured by GMFCS levels). We used two metrics: (1) the cosine similarity to compare weights (i.e., to compare the composition of the muscle synergies in healthy controls with that observed in children with CP); and (2) the zero-lag cross-correlation (ZLCC) value to compare temporal coefficients (i.e., to compare the temporal activation of the muscle synergies in healthy controls with that observed in children with CP). Both the cosine similarity and the ZLCC parameters span the interval between 0 and 1, where the maximum

value represents a perfect match with the reference (i.e., average observation in healthy controls) [23, 52, 53]. For these analyses, we considered all the outputs of the muscle synergy algorithm that satisfied the above-stated R^2 criteria. It is worth noting that the cosine similarity has been used to compare the composition of different muscle synergies in previous studies as it is an effective metrics when one wants to capture changes in the weights that determine the contribution of different muscles to a synergy [54]. Also, the ZLCC has been extensively used to compare waveforms of a nature similar to the temporal coefficients that we compared in this study as it provides an effective way to measure differences in the shape of waveforms of interest [52]. To test the hypothesis that there is a correlation between the degree of disarrangement of muscle synergies and the functional ability of children with CP, we used mixed-effect regression models (for each individual synergy) with GMFCS levels as fixed effect and random effects to account for between-subjects and within-subject differences (i.e., “*SynergySimilarity* ~ 1 + *GMFMC_Level* + (1 | *SubID*)”).

Then, we focused on longitudinal analyses and investigated if muscle synergies change in response to RGT in a way that makes them more similar to normative synergies. We estimated changes in response to RGT in cosine similarity and ZLCC values (using normative muscle synergies as reference). For these analyses, we computed the mean and standard deviation of the distribution of similarity values obtained by comparing each synergy with the normative synergies. The results were examined for both the most affected and the contralateral leg. The range spanned by the observed changes in cosine similarity and ZLCC values was divided into intervals based on their magnitude. Results were reported in table format displaying participant-by-participant data. To assess the relevance of changes in muscle synergy characteristics, we used as reference the variability observed in our normative dataset (with typical standard deviation $\cong 0.015$). We reasoned that, if a change (pre- vs post-training) was comparable with the variability that marks the normative dataset, it should not be considered significant. Accordingly, we considered positive changes < 0.02 as not significant; changes ≥ 0.02 but < 0.04 as moderate improvements and highlighted them in light green; changes ≥ 0.04 but < 0.06 as large improvements and highlighted them using a dark green color; and changes ≥ 0.06 as very large improvements and highlighted them using a darker green color. Negative changes of the same magnitudes were considered moderate, large, and very large worsening and highlighted in orange, light red, and dark red, respectively. A Chi Square test was performed on these data to test if the changes in muscle synergies in response to RGT were random changes.

Clinical outcomes and muscle synergies

Because we anticipated significant differences across study participants in both clinical outcomes and muscle synergies in response to RGT, we sought to investigate if the results of the muscle synergy analysis could be used to shed light on the response to RGT on a participant-by-participant basis.

Paired t-tests were first performed on the GMFM, 10 MWT, 6 MWT, and EVGS scores to assess if data collected in the study showed significant changes in clinical scores in response to RGT as previously observed in other studies [10, 16, 18, 19, 55, 56]. A 5% significance level was used for these analyses. Then, we considered the changes in response to RGT observed on a participant-by-participant basis and examined potential associations with changes in muscle synergies.

Changes in clinical scores on a participant-by-participant basis were identified as follows. Changes in sections D and E of the GMFM-88 that were ≥ 2 points were highlighted as exceeding the minimum clinically important difference (MCID) in standing (1.2 points) and walking (1.6 points) function as suggested by Oeffinger et al. [57]. The range of motor gains exceeding this value was divided into three equal intervals. Data falling in these three intervals was labeled as “moderate”, “large”, and “very large” motor gains, respectively.

The choice of MCID values for the 10 MWT and 6 MWT in children with CP has been a matter of debate [58]. In absence of well-established reference values, criteria consistent with clinical experience as reported by Storm et al. [59] were used in this study. Accordingly, changes in 10 MWT and 6 MWT values in response to RGT that fell between 10 and 30% of the baseline value were labeled as “moderate”; changes between 30 and 50% of the baseline value were labeled as “large”; and changes exceeding 50% of the baseline value were labeled as “very large”.

The EVGS scores of the two legs were used to determine the most affected leg of each participant. The EVGS scores were then averaged to generate a total EVGS score (i.e., combining the scores of both legs). Changes exceeding the MCID threshold value of 1.9 points [60] were highlighted and the range of observed EVGS scores exceeding the MCID threshold value was divided into three equal intervals as described above for the GMFM scores.

Finally, we tested the hypothesis that positive changes in muscle synergies correlate with positive clinical outcomes. We used the above-stated definitions of positive and negative changes in clinical outcomes and muscle synergies and derived accordingly the Kendall correlation and its significance. In addition, qualitative observations were made based on visual observation of the summary

tables of changes in muscle synergies and clinical outcomes in response to RGT.

Results

Table 1 provides a detailed description of the participants' characteristics. Participants were 13.1 ± 3.4 years old (mean $\pm$ standard deviation). Eight out of the thirteen participants were females. Most participants had diplegia (9 children), two had quadriplegia, one had triplegia, and one had hemiplegia. Participants used different types of ankle-foot orthoses. Some of them used a mobility assistive device (e.g., one used a cane, three of them crutches, and three a walker). Eight subjects participated in 18 RGT sessions, four completed 17 sessions, and one completed 12 sessions.

Muscle synergies in children with CP

The composition of the muscle synergies pre- and post-RGT in all study participants is shown in Fig. 3. Herein we show the composition of the muscle synergies as the linear combination of the four normative synergies. The color-coded graphical representation indicates the percentage contributions of the normative synergies to each of the synergies observed in children with CP.

Almost all the participants showed three muscle synergies, both pre- and post-RGT. Two participants displayed two muscle synergies pre-RGT. When we identified three muscle synergies, their composition was typically characterized as follows. The first muscle synergy (Syn 1) most often displayed the “load acceptance” and “leg deceleration” normative synergies as its dominant components.

The “push-off” normative synergy also contributed to this synergy to a degree that varied across study participants. The second muscle synergy (Syn 2) mostly resembled the “push-off” normative synergy but included components from other normative synergies (most often the “load acceptance” and “leg deceleration” normative synergies). Finally, the third muscle synergy (Syn 3) displayed high similarity with the “foot clearance” normative muscle synergy but included components from other normative synergies (most prominently the “push-off” normative synergy) to a variable degree across participants.

A qualitative observation of the temporal activation coefficients (not shown in Fig. 3) highlighted a less prominent modulation of the muscle synergies than typically observed in control subjects. In a clinical context, this is often referred to as “non-phasic activity”. The lack of prominent modulation was more apparent in children with more severe functional limitations (i.e., GMFCS levels III and IV compared to levels I and II).

Muscle synergies and GMFCS levels

To quantify the relationship between the characteristics of the muscle synergies and the GMFCS levels, we used the cosine similarity value to compare the weights of the normative muscle synergies and the muscle synergies of children with CP [23, 52, 53]. We used the zero-lag cross-correlation (ZLCC) value as the metric for comparison of the normative and the participants' temporal coefficients. Figure 4 shows the cosine similarity and the ZLCC for both legs combined and grouped by GMFCS levels [23, 52, 53]. Data for the control group (which also displayed

Table 1 Subject-by-subject demographic and clinical data at baseline

Subj#	Age (yrs)	Gender	Topographic classification	GMFCS	Dominant Side	Most affected side	Orthoses/walking aids
Sub01	11	Male	Diplegia	2	Right	Left	SMO bilaterally
Sub02	18	Male	Diplegia	3	Right	Left	Post. AFO bilaterally, two crutches
Sub03	15	Female	Diplegia	2	Right	Right	Post. AFO (left)
Sub04	8	Female	Quadriplegia	2	Left	Right	Post. AFO bilaterally
Sub05	14	Female	Diplegia	3	Right	Left	Two crutches
Sub06	12	Female	Diplegia	2	Right	Left	Post. AFO bilaterally, 1 cane
Sub07	6	Female	Diplegia	3	Right	Right	Assistance of a person/posterior walker
Sub08	15	Male	Diplegia	2	Right	Right	Post. AFO bilaterally
Sub09	14	Female	Diplegia	1	Left	Left	Insoles
Sub10	13	Male	Hemiplegia	1	Right	Left	Carbon fiber AFO (left)
Sub11	17	Female	Quadriplegia	4	Left	Left	Post. AFO bilaterally, posterior Walker/manual wheelchair
Sub12	12	Female	Triplegia	3	Right	Left	Post. AFO bilaterally, posterior walker
Sub13	16	Male	Diplegia	3	Left	Left	Post. AFO bilaterally, crutches

GMFCS Gross motor function classification system, SMO Supramalleolar orthosis, AFO Ankle-foot orthosis, Assistance of a person: the subject walked holding someone's hand

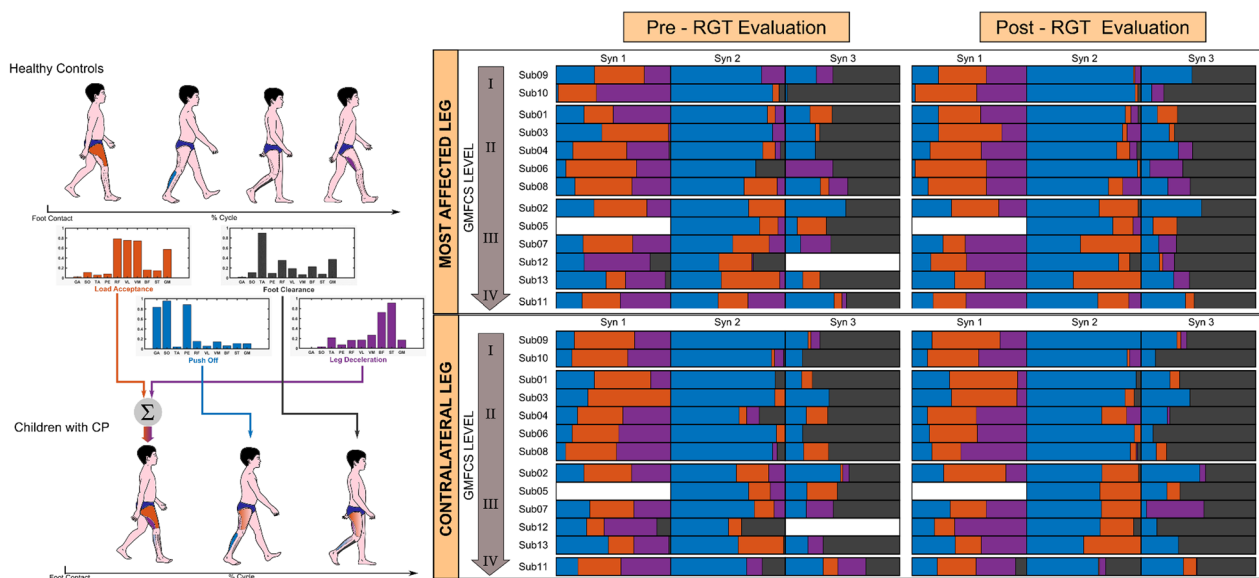


Fig. 3 Muscle synergies Pre- vs Post-RGT. Left panel: the gait cycle of healthy volunteers (top), the weights of the normative (i.e., observed in healthy volunteers) muscle synergies (middle), and the gait cycle of children with CP (bottom) showing an example of merging of muscle synergies. The main muscles active in each phase of the gait cycle are highlighted in the representation of both the healthy child and the child with CP. Right panel: a representation of the percentage contribution of each normative synergy to the muscle synergies observed in children with CP in the most affected leg (top) and contralateral leg (bottom). Color code: red—load acceptance synergy, blue—push off synergy, black—foot clearance synergy, and purple—leg deceleration synergy. *CP* cerebral palsy, *RGT* Robot-assisted Gait Training

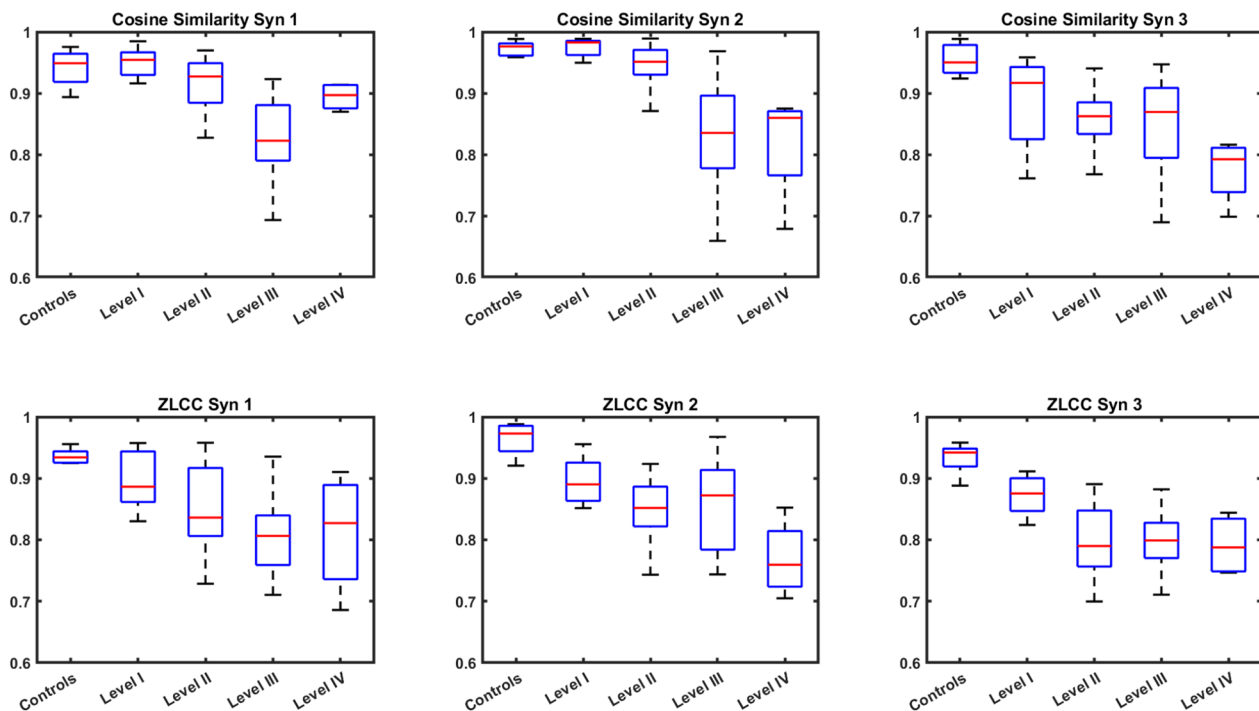


Fig. 4 Cosine similarity and ZLCC of muscle synergies. Boxplots are shown for controls and for different GMFCS levels (Level I–IV). Boxplots combine values for both legs and for pre- and post-RGT recordings. *GMFCS* Gross motor function classification system, *Syn* Synergy, *ZLCC* zero-lag cross-correlation, *RGT* Robot-assisted Gait Training. Marked with an asterisk symbol the groups that shown significant difference in the Dunn's post hoc comparisons ($p < 0.05$)

variability across individuals) is shown in the figure to provide a reference value. GMFCS levels III and IV were associated with muscle synergies that appeared to deviate from the normative muscle synergies more than for GMFCS levels I and II in both their composition (i.e., weights) and temporal activations (i.e., temporal coefficients). We performed a statistical analyses using mixed-effects regression models with GMFCS levels as fixed effect. Separate models were fitted for the cosine similarity values and for the ZLCC values of each synergy. Significance was achieved for the cosine similarity values and ZLCC values of all three synergies ($p < 0.01$). These results imply that the correlation between GMFCS levels and cosine similarity values as well as ZLCC values observed by visual inspection of the results (Fig. 4) is statistically significant. Visual observation of the muscle synergies in study participants suggested that this result was due to a higher incidence of co-activations of agonist

and antagonist muscles in the composition of the muscle synergies with an increase in GMFCS levels. Besides, a less prominent modulation of the temporal coefficients was observed for higher GMFCS levels. The differences between muscle synergies for level II and level III participants appear to be mostly captured by the weights rather than the temporal coefficients of the muscle synergies.

Changes in muscle synergies in response to RGT

Tables 2 and 3 show the cosine similarity and ZLCC values pre- and post-RGT for the most affected and the contralateral leg, respectively. The cells of these tables are highlighted in different colors according to the magnitude of the change observed in response to RGT as explained in the Methods section. We performed Chi Square tests and despite the small sample size, this analysis highlighted significant changes in response to RGT in the cosine similarity values for Syn

Table 2 Cosine similarity and ZLCC for each muscle synergy of most affected leg pre- and post-RGT

Most Affected		Cosine Similarity (Weights)			Zero-Lag Cross-Correlation (Temporal Coefficients)		
GMFCS	ID #	Syn 1	Syn 2	Syn 3	Syn 1	Syn 2	Syn 3
Level I	Sub09	0.86(0.06)-0.92(0.08)	0.91(0.02)-0.97(0.01)	0.83(0.02)-0.76(0.08)	0.90(0.02)-0.95(0.04)	0.87(0.03)-0.91(0.04)	0.87(0.03)-0.88(0.05)
	Sub10	0.96(0.01)-0.98(0.02)	0.99(0.01)-0.98(0.00)	0.96(0.02)-0.93(0.03)	0.86(0.02)-0.87(0.02)	0.86(0.01)-0.90(0.01)	0.91(0.02)-0.90(0.02)
Level II	Sub01	0.83(0.03)-0.88(0.03)	0.94(0.02)-0.92(0.01)	0.83(0.00)-0.90(0.01)	0.81(0.02)-0.81(0.02)	0.89(0.01)-0.88(0.01)	0.75(0.03)-0.79(0.04)
	Sub03	0.84(0.07)-0.89(0.07)	0.94(0.04)-0.94(0.06)	0.87(0.03)-0.87(0.03)	0.96(0.02)-0.94(0.05)	0.85(0.05)-0.72(0.06)	0.71(0.02)-0.70(0.02)
	Sub04	0.93(0.03)-0.95(0.03)	0.96(0.02)-0.96(0.04)	0.86(0.03)-0.83(0.06)	0.79(0.02)-0.84(0.03)	0.84(0.04)-0.83(0.05)	0.80(0.03)-0.84(0.04)
	Sub06	0.93(0.03)-0.96(0.03)	0.92(0.02)-0.99(0.00)	0.86(0.03)-0.86(0.04)	0.85(0.02)-0.81(0.05)	0.74(0.02)-0.84(0.01)	0.87(0.01)-0.88(0.01)
	Sub08	0.95(0.02)-0.95(0.02)	0.87(0.05)-0.94(0.02)	0.77(0.03)-0.84(0.02)	0.81(0.02)-0.83(0.02)	0.85(0.03)-0.81(0.02)	0.75(0.03)-0.76(0.02)
Level III	Sub02	0.82(0.02)-0.82(0.02)	0.88(0.03)-0.81(0.02)	0.71(0.05)-0.71(0.03)	0.71(0.02)-0.77(0.02)	0.77(0.06)-0.80(0.08)	0.73(0.02)-0.79(0.03)
	Sub05		0.94(0.01)-0.92(0.00)	0.93(0.01)-0.95(0.00)		0.85(0.01)-0.87(0.00)	0.87(0.00)-0.88(0.00)
	Sub07	0.89(0.06)-0.87(0.03)	0.80(0.11)-0.69(0.03)	0.88(0.01)-0.90(0.02)	0.84(0.05)-0.94(0.03)	0.74(0.08)-0.85(0.05)	0.80(0.01)-0.80(0.03)
	Sub12	0.79(0.03)-0.92(0.03)	0.75(0.01)-0.97(0.01)	-0.92(0.01)	0.83(0.01)-0.81(0.02)	0.95(0.01)-0.97(0.02)	-0.75(0.07)
	Sub13	0.69(0.03)-0.79(0.03)	0.68(0.05)-0.66(0.03)	0.87(0.05)-0.86(0.01)	0.76(0.04)-0.78(0.03)	0.91(0.05)-0.88(0.02)	0.85(0.02)-0.80(0.01)
Level IV	Sub11	0.87(0.04)-0.91(0.02)	0.68(0.11)-0.85(0.05)	0.78(0.05)-0.81(0.02)	0.69(0.02)-0.79(0.04)	0.70(0.10)-0.74(0.04)	0.75(0.02)-0.75(0.03)

The results are reported as mean and standard deviation (in parenthesis) of the parameter values estimated from the recordings carried out pre- and post-RGT. Changes are highlighted using different colors according to their magnitude (see text for details)

GMFCS Gross motor function classification system, Syn Synergy, ZLCC Zero-lag cross-correlation, RGT Robot-assisted gait training

Table 3 Cosine similarity and ZLCC for each muscle synergy of the contralateral leg pre- and post-RGT

Contralateral		Cosine Similarity (Weights)			Zero-Lag Cross-Correlation (Temporal Coefficients)		
GMFCS	ID #	Syn 1	Syn 2	Syn 3	Syn 1	Syn 2	Syn 3
Level I	Sub09	0.94(0.03)-0.95(0.04)	0.99(0.00)-0.95(0.01)	0.90(0.02)-0.82(0.02)	0.83(0.01)-0.86(0.03)	0.88(0.01)-0.85(0.01)	0.77(0.03)-0.82(0.04)
	Sub10	0.97(0.02)-0.96(0.02)	0.98(0.01)-0.98(0.01)	0.95(0.02)-0.94(0.02)	0.96(0.01)-0.94(0.01)	0.96(0.01)-0.95(0.02)	0.90(0.03)-0.87(0.04)
Level II	Sub01	0.83(0.07)-0.89(0.04)	0.96(0.01)-0.97(0.01)	0.94(0.01)-0.87(0.01)	0.87(0.01)-0.89(0.01)	0.92(0.01)-0.92(0.02)	0.85(0.04)-0.80(0.03)
	Sub03	0.94(0.02)-0.89(0.05)	0.97(0.00)-0.94(0.06)	0.86(0.01)-0.81(0.05)	0.95(0.00)-0.93(0.01)	0.91(0.01)-0.70(0.06)	0.81(0.02)-0.78(0.02)
	Sub04	0.93(0.04)-0.96(0.02)	0.87(0.04)-0.90(0.04)	0.80(0.02)-0.88(0.01)	0.80(0.04)-0.82(0.04)	0.85(0.02)-0.87(0.01)	0.73(0.04)-0.77(0.03)
	Sub06	0.97(0.02)-0.96(0.02)	0.99(0.01)-0.99(0.01)	0.93(0.01)-0.92(0.01)	0.93(0.01)-0.91(0.01)	0.89(0.02)-0.90(0.02)	0.78(0.02)-0.79(0.02)
	Sub08	0.91(0.03)-0.86(0.03)	0.97(0.01)-0.98(0.00)	0.83(0.01)-0.89(0.01)	0.73(0.01)-0.74(0.01)	0.84(0.03)-0.80(0.03)	0.89(0.03)-0.87(0.02)
Level III	Sub02	0.86(0.02)-0.82(0.01)	0.83(0.07)-0.84(0.03)	0.72(0.09)-0.69(0.04)	0.74(0.04)-0.74(0.02)	0.77(0.08)-0.76(0.07)	0.75(0.02)-0.79(0.02)
	Sub05		0.90(0.01)-0.89(0.00)	0.87(0.01)-0.91(0.01)		0.87(0.00)-0.89(0.00)	0.82(0.01)-0.77(0.00)
	Sub07	0.89(0.05)-0.82(0.09)	0.93(0.03)-0.88(0.05)	0.86(0.01)-0.80(0.04)	0.80(0.02)-0.86(0.08)	0.77(0.02)-0.80(0.04)	0.83(0.01)-0.84(0.04)
	Sub12	0.88(0.03)-0.91(0.02)	0.81(0.01)-0.89(0.01)	-0.95(0.01)	0.76(0.02)-0.84(0.04)	0.92(0.02)-0.89(0.01)	-0.71(0.05)
	Sub13	0.70(0.02)-0.79(0.04)	0.81(0.03)-0.75(0.02)	0.90(0.01)-0.85(0.01)	0.82(0.03)-0.88(0.02)	0.94(0.03)-0.92(0.02)	0.80(0.06)-0.81(0.04)
Level IV	Sub11	0.91(0.05)-0.88(0.03)	0.88(0.07)-0.87(0.03)	0.70(0.07)-0.82(0.06)	0.87(0.04)-0.91(0.01)	0.78(0.03)-0.85(0.03)	0.84(0.03)-0.82(0.03)

The results are reported as mean and standard deviation (in parenthesis) of the parameter values estimated from the recordings carried out pre- and post-RGT. Changes are highlighted using different colors according to their magnitude (see text for details)

GMFCS Gross motor function classification system, Syn Synergy, ZLCC Zero-lag cross-correlation, RGT Robot-assisted gait training

1 which displayed patterns closer to normative post-RGT ($p=0.042$). Visual inspection of these tables suggested that changes in cosine similarity values for the most affected leg (Table 2) is marked by a more consistent pattern of improvement for the first muscle synergy (Syn 1) compared to the second (Syn 2) and third (Syn 3) synergies. In fact, when a change was observed for Syn 1, it was always an improvement in similarity with the normative data. The largest improvements in cosine similarity for Syn 1 were observed for two of the GMFCS level III participants (i.e., Sub 12 and 13). More variability was observed in changes in cosine similarity for Syn 2, with some participants displaying very large improvements (such as Sub 11 and 12) and others displaying a considerable worsening in cosine similarity (such as Sub 7). Highly variable results were observed for Syn 3. Changes in cosine similarity for the contralateral leg (Table 3) appeared to be less consistent across participants for all three muscle synergies. Changes in ZLCC values for the most-affected (Table 2) and the contralateral leg (Table 3) in response to RGT displayed patterns similar to the ones displayed by the changes in cosine similarity values. More consistent improvements in ZLCC values were generally observed for Syn 1. In contrast, Syn 2 and 3 showed a less consistent ZLCC change in response to the intervention.

Clinical outcomes of RGT

To explore a potential association between changes in muscle synergies in response to RGT and clinical outcomes, we examined the clinical outcome data pre- and post-RGT shown in Table 4 and then compared changes in the outcomes shown in this table with those observed in the above-discussed tables summarizing the results of the muscle synergy analysis (i.e., Tables 2 and 3).

Group-level analysis of pre- vs post-RGT clinical outcomes showed improvements in sections D ($p \cong 0.02$) and E ($p < 0.01$) of the GMFM-88, and in EVGS scores ($p < 0.01$). Nearly significant improvements were observed in the 6 MWT scores ($p \cong 0.06$), whereas no group change was observed in the 10 MWT scores ($p \cong 0.46$). These results appear to be consistent with previous reports on the effects of RGT in children with CP [16, 19, 55, 61].

A closer look at Table 4 shows a large variability in the response to RGT across subjects. Elements of the table are highlighted in different colors according to the magnitude of the observed change and its direction (i.e., improvement vs. worsening in clinical scores according to the criteria described in the Methods section). Participants displayed improvements across different clinical dimensions: eight participants showed an improvement in section D of the GMFM-88, ten showed an improvement in section E of the GMFM-88, four in gait speed,

Table 4 Clinical outcomes and EVGS scores, Pre- and Post-RGT

GMFCS	ID #	GMFM-88 D	GMFM-88 E	10 MWT	6 MWT	EVGS
Level I	Sub09	32-32	61-65	6.9-5.5	374-390	9.0-6.0
	Sub10	38-37	68-69	6.6-5.6	376-607	5.5-4.5
Level II	Sub01 ^a	31-28	42-56	8.5-8.7	275-310	12.5-10
	Sub03	29-34	54-59	10.8-10.4	301-276	10-8.5
	Sub04	34-36	60-64	6.0-6.7	505-540	9-7.5
	Sub06	32-35	47-59	8.7-4.6	298-300	14-10
	Sub08 ^b	28-33	44-45	14.8-15.3	187-211	11-11
Level III	Sub02	29-28	31-40	10.4-7.6	332-410	17.5-12
	Sub05 ^b	28-28	36-49	10.8-14.0	403-395	11-11.5
	Sub07 ^b	6-12	12-14	7.7-12.8	244-192	19-17
	Sub12	22-29	25-48	7.0-6.4	296-437	17.5-11.5
	Sub13	12-14	12-12	16.3-16.5	150-220	19-17
Level IV	Sub11	3-8	4-10	59.0-69.7	57-68	14-13.5

^a12 sessions of RGT completed; ^b17 sessions of RGT completed

Changes are highlighted using different colors according to their magnitude (see text for details). GMFCS Gross motor function classification system, GMFM-88 D Gross motor function measure section D (standing), GMFM-88 E Gross motor function measure section E (walking, running and jumping), 10 MWT 10-m walk test (walking speed), 6 MWT 6-min walk test (endurance), EVGS Edinburgh visual gait scores, RGT Robot-assisted gait training

seven in gait endurance, and seven in gait quality (i.e., EVGS scores). Some participants displayed an improvement only in one clinical dimension, such as Sub 05, who displayed an improvement in section E of the GMFM-88 from 36 to 49 points and a worsening in walking speed (as captured by the 10 MWT). In contrast, others showed large improvements in several clinical outcomes. For instance, Sub 12 showed improvements in sections D and E of the GMFM-88, in the 6 MWT score, and in the EVGS score.

Exploring the relationship between muscle synergies and clinical outcomes of RGT

We estimated the Kendall correlation between the changes in muscle synergies in response to RGT (Tables 2 and 3) and clinical outcomes (Table 4) and obtained p-values ranging between 0.11 and 0.45 (i.e., not significant) and correlation values ranging between 0.06 and 0.12 (i.e., low correlation) for different clinical outcomes. However, visual inspection of the tables showed that some participants displayed a large change in muscle synergy characteristics in response to RGT as well as large motor gains.

For instance, Sub 12 showed two muscle synergies pre-RGT and three muscle synergies post-RGT for both the most affected and the contralateral leg. The two synergies that were present pre-RGT showed positive changes in cosine similarity for both the most affected and the contralateral leg. This participant displayed motor gains across four clinical dimensions. Sub 05 also displayed two muscle synergies pre-RGT. However, the number of muscle synergies did not change post-RGT. No noticeable changes in cosine similarity and ZLCC values for the synergies of the most affected leg were observed. This participant showed an improvement only in one clinical outcome (i.e., section E of the GMFM scale). These observations suggest that, at least in some patients, a prominent change in muscle synergy characteristics leads to large motor gains. Vice versa, small changes or no change in muscle synergy characteristics appear to be associated with marginal motor gains.

When we attempted to extend such a consideration to the rest of the study group, we observed that great variability across individuals in the relationship between changes in muscle synergies in response to RGT and motor gains. All the remaining study participants displayed three muscle synergies, both pre- and post-RGT. All of them showed clinical improvements in at least two of the clinical outcomes tracked in the study. Because we had observed different muscle synergy characteristics for different GMFCS levels (Fig. 4), we explored potential relationships between changes

in muscle synergy characteristics in response to RGT and clinical outcomes separately for each GMFCS level. Also, because we observed more consistent changes in response to RGT for the most-affected leg, we focused on the data for this leg.

The two level I study participants (i.e., Sub 09 and 10) displayed different changes in muscle synergies in response to RGT. Sub 09 showed improvements in cosine similarity and ZLCC values for both Syn 1 and Syn 2. In contrast, Sub 10 did not show improvements in cosine similarity in response to RGT and showed a moderate improvement in ZLCC for Syn 2. Sub 09 showed improvements in three clinical scale scores, whereas Sub 10 displayed improvements in only two clinical scale scores.

Five of the study participants (i.e., Sub 01, 03, 04, 06, and 08) were classified as level II according to the GMFCS. Sub 01, 06, and 08 showed improvements in response to RGT in cosine similarity for two synergies, whereas Sub 04 did not show any improvements in cosine similarity but displayed improvements in ZLCC for two synergies. Sub 03 displayed an improvement in cosine similarity for one synergy and no improvements in ZLCC values. Changes in the GMFM scale results were fairly consistent in these study participants (i.e., all five participants displayed an improvement in at least one of the two GMFM sections considered in the study, with Sub 03, 04, and 06 showing improvements in both). Sub 06 showed gains across the greatest number of clinical dimensions (four out of five) and was the only one who displayed improvements in cosine similarity for both Syn 1 and Syn 2.

Three of the study participants classified as level III according to the GMFCS displayed three muscle synergies both pre- and post-RGT. In response to RGT, only Sub 13 showed an improvement in cosine similarity (for Syn 1), whereas Sub 02 showed improvements in ZLCC for all three synergies, and Sub 07 showed improvements in ZLCC for two out of three synergies. All three participants showed improvements in at least one of the sections of the GMFM tracked in the study and in EVGS. Changes in 10 MWT and 6 MWT were less consistent across level III participants, with Sub 07 displaying a worsening in these outcomes (possibly because of difficulties experienced by the child with following instructions during the post-RGT session). Sub 02 showed improvements in both. Sub 13 showed an improvement in 6 MWT, but not in 10 MWT.

Finally, we had one level IV participant (i.e., Sub 11). Improvements in response to RGT were observed in three clinical scales (sections D and E of the GMFM scale and 6 MWT). The clinical response was accompanied by changes in cosine similarity for all three

synergies and ZLCC values for two out of three synergies of the most affected leg.

Discussion

We carried out this study to investigate if changes in the characteristics of the muscle synergies pre- vs. post-RGT could account for the variability in the outcomes of RGT that our research group and others observed in previous studies [8, 18–22]. The great majority of the literature has largely neglected consideration of the variability in the response to RGT among children with CP. Most studies have been focused on comparing different intervention modalities based on the average effects observed in samples of the target patient population [62]. Herein we took a radically different approach, namely we focused on a single intervention modality (i.e., RGT) and attempted to analyze differences in the response to RGT across study participants. We performed group analyses to assess if a group response could be detected. This provided us with confidence that our sample of children with CP was representative of the CP population. Then we explored individual differences in the response to RGT.

First, we assessed if we could identify relationships between the characteristics of the muscle synergies in children with CP and the severity of their functional limitations as captured by the GMFCS levels. Such a relationship was previously suggested by Tang et al. [26] based on a qualitative analysis of the muscle synergies. In this study, we took a quantitative approach based on the cosine similarity between the composition of normative muscle synergies and the synergies observed in children with CP. In addition, we estimated the ZLCC between the temporal coefficients of normative muscle synergies and those of the synergies observed in children with CP. We observed a decrease in cosine similarity and in ZLCC with an increase in the severity of functional limitations, namely an increase in GMFCS level. By fitting a mixed-effects regression model to the data of each synergy, we showed a statistically significant correlation between muscle synergy characteristics and GMFCS level for all the parameters considered in the study. In other words, we showed that the severity of functional limitations is associated with the degree of disarrangement of the muscle synergies, both in their composition and in their temporal activation. This finding is consistent with previous studies by Steele's group based on the Walking Dynamic Motor Control (Walk-DMC) index [31, 35]. However, our work shows that functional limitations affect individual muscle synergies. In contrast, the Walk-DMC index is meant to account for the characteristics of all the muscle synergies at once. In line with previous work by Safavynia et al. [63], we argue that the analysis of individual synergies could be highly relevant to the clinical decision

process concerning the design of RGT interventions. Such analysis could allow clinicians to target specific muscle groups and the timing of their activation during the gait cycle.

Subsequently, we analyzed the changes in muscle synergies observed in response to RGT. Changes in muscle synergies (although often modest in magnitude) were previously observed in children with CP pre vs. post orthopedic surgery [28, 30–32], botulinum toxin type A injections [28, 30, 33], selective dorsal rhizotomy [28–31], and conservative treatment (physical therapy) [30]. In our study with focus on RGT, we observed different patterns of change in muscle synergies among study participants. In one participant, we observed a change in the number of muscle synergies from two to three and a dramatic improvement in clinical outcomes pre- vs. post-intervention. In most cases, we observed three muscle synergies at baseline and changes in the synergy composition and/or temporal coefficients. These changes varied from participant to participant showing highly complex response across individuals and GMFCS levels. However, our analysis of the results based on a Chi Square test highlighted a statistically significant improvement in the composition of the Syn 1 pre vs post-RGT.

Albeit no significant association was detected via Kendall correlation tests, we observed several instances in which motor gains across multiple clinical outcomes occurred together with changes in several muscle synergies that displayed an improvement either in cosine similarity with the normative synergies or in ZLCC values. To further explore the relationship between changes in muscle synergies and clinical outcomes, we suggest carrying out future studies using a sample size of sufficient magnitude to allow one to explore if clusters of individuals displaying a similar association between muscle synergies and clinical outcomes could be identified. In other words, we suggest that cluster analysis techniques might be able to identify stereotypic responses to RGT in subsets of children with CP. Furthermore, we suggest carrying out future studies by monitoring the muscle synergies recruited by study participants during RGT and encouraging the use of synergies that are as close as possible to normative synergies. This could be achieved by processing EMG recordings collected during RGT, estimating the muscle synergies recruited by each participant, estimating the cosine similarity and ZLCC using normative synergies as reference, and generating feedback accordingly. Feedback could be provided to therapists with oversight of the RGT session so that training parameters (e.g., level of bodyweight support provided by the robotic system [64]) could be adjusted accordingly. Also, feedback could be provided to participants by generating visual and/or auditory feedback or forces generated by the

robot to resist movement when participants recruit synergies with low cosine similarity and ZLCC values and to facilitate movement when participants recruit synergies with high cosine similarity and ZLCC values. This could be particularly suitable in children with CP displaying severe selective motor control impairment. The above-mentioned feedback modalities could help “break” aberrant synergies (associated with severe selective motor control impairment) while encouraging the recruitment of “physiological” (i.e., normative) synergies.

The main limitations of this study include the small sample size, the heterogeneity of the participants, and the fact that the normative muscle synergies were not derived from a sample of individuals matching the age and gender of the children with CP undergoing RGT. Furthermore, due to the limited sample size, the heterogeneity of the participants, and the large number of tests required to investigate the characteristics of the muscle synergies, we opted for not adjusting for multiple comparisons the p-values obtained from the performed statistical tests. These limitations should be considered when designing future clinical trials to further explore the relationship between muscle synergy characteristics and clinical outcomes of RGT. For instance, it is possible that the heterogeneity of the sample used in our study might have played a confounding factor. However, it should be noted that the inclusion of a heterogeneous population provided us with some advantages in the context of our exploratory study. Whereas it made more difficult to achieve statistical significance on a group basis (e.g., for the Kendall correlation analyses), it provided access to a larger variety of muscle synergy characteristics and hence maximized the likelihood of identifying individual cases in which changes in muscle synergies were associated with large motor gains. Future studies will need to rely on a larger sample size to expand upon the analyses performed in this preliminary trial and enable the analysis of covariates as well as the use of the clustering techniques mentioned above. Furthermore, whereas we believe that the use of data collected from healthy adults was appropriate in the context of the preliminary study herein reported, an appropriate sample of pediatric data should be used to generate the normative synergies in future studies.

Conclusions

The results of our study showed a significant variability in motor gains observed in the response to RGT among children with CP. Our findings also highlighted that, at least in a subset of children with CP, motor gains in response to RGT are associated with changes in muscle synergies leading to an increase in their similarity to normative synergies. Future studies should be performed to explore the relationship between motor gains and

changes in muscle synergies in response to RGT using a large sample size hence enabling statistical analyses that explore covariates and the application of clustering techniques to identify subgroups of children with CP that display a similar response to RGT hence enabling within-cluster statistical analyses. The identification of baseline characteristics of the patient’s muscle synergies that are predictive of a large response to RGT could be enabled by such analyses and lead to personalized intervention strategies, which we hope would lead to better motor gains.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12984-025-01550-x>.

Supplementary Material 1.

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Author contributions

G.V.D., S.S., J.F.D., G.S., and P.B. contributed to the design of the study. G.V.D., J.F.D., E.F., C.A.D., D.N., and P.B. contributed to the implementation of the research protocols. S.S., G.V.D., E.F., and P.B. curated and analyzed the data. G.V.D., S.S., J.F.D., G.S., V.C., C.E.R.V., D.N., and P.B. contributed to the interpretation of the data. G.V.D., S.S., and P.B. wrote the manuscript. All the authors contributed substantially to the critical revision of the manuscript and approved its final version.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The research study presented in the manuscript was approved by the Spaulding Rehabilitation Hospital Institutional Review Board (protocol # 2015P001482, clinical trial # NCT06156969). All parents or guardians signed a consent form, and children signed an assent form.

The research study carried out to gather normative muscle synergies was also approved by the Spaulding Rehabilitation Hospital Institutional Review Board (protocol # 2019P002419). All participants signed a consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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