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The effect of prolonged walking on muscle fatigue and neuromuscular control in children with cerebral palsy

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ABSTRACT

Background: Muscle fatigue of the lower limbs is considered a main contributor to the perceived fatigue in children with cerebral palsy (CP) and is expected to occur during prolonged walking. In adults without disabilities, muscle fatigue has been proposed to be associated with adaptations in complexity of neuromuscular control.

Research question: What are the effects of prolonged walking on signs of muscle fatigue and complexity of neuromuscular control in children with CP?

Methods: Ten children with CP and fifteen typically developing (TD) children performed a standardised protocol on an instrumented treadmill consisting of three stages: six-minutes walking at preferred speed (6 MW), moderate-intensity walking (MIW, with two minutes at heart rate > 70% of predicted maximal heart rate) and four-minutes walking at preferred speed (post-MIW). Electromyography (EMG) data were analysed for eight muscles of one leg during three time periods: 6 MW-start, 6 MW-end and post-MIW. Signs of muscle fatigue were quantified as changes in EMG median frequency and EMG root mean square (RMS). Complexity of neuromuscular control was quantified by total variance accounted for by one synergy (tVAF1). Muscle coactivation was assessed for antagonistic muscle pairs.

Results: EMG median frequency was decreased at 6 MW-end and post-MIW compared to 6 MW-start in children with CP ($p < 0.05$), but not in TD children. In both groups, EMG-RMS ($p < 0.01$) and muscle coactivation ($p < 0.01$) were decreased at 6 MW-end and post-MIW compared to 6 MW-start. tVAF1 decreased slightly at 6 MW-end and post-MIW compared to 6 MW-start in both groups ($p < 0.05$). Changes were most pronounced from 6 MW-start to 6 MW-end.

Significance: Children with CP presented signs of muscle fatigue after prolonged walking, while no effects were found for TD. Both groups showed minimal changes in tVAF1, suggesting signs of muscle fatigue are not associated with changes in complexity of neuromuscular control.

1. Introduction

Many children with cerebral palsy (CP) report limitations in walking duration due to fatigue during daily activities [1,2]. Fatigue during walking can be associated with a deterioration of the walking pattern [3], for instance reflected by loss of balance control and tripping. It is assumed that muscle fatigue of the lower limbs is a main contributor to the perceived fatigue in children with CP [4] which can be expected to be most likely to occur during prolonged walking and/or walking at moderate intensity. Muscle fatigue has been described as any exercise-induced reduction in force-generating capacity [5], and can be separated into two components; central and peripheral fatigue [6–8].

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Central fatigue has been defined as a reduction in voluntary activation, whereas peripheral fatigue is described as a reduction in the force generating capacity of a muscle due to processes near the neuromuscular junction and the muscle fibre [9]. Peripheral muscle fatigue is often accompanied by decreased conduction velocity of muscle fibre action potentials, associated with a decreased median frequency of the surface electromyogram (EMG) [10]. Moreover, since muscle fatigue is associated with force reduction, a larger part of the muscle needs to be activated in order to maintain force output. Therefore, voluntary activation increases, presented as an increased root mean square (RMS) of the EMG signal [5]. Therefore, a decrease in EMG median frequency and an increase in EMG-RMS have been used as indirect measures of muscle fatigue (Eken et al., 2020; Parent et al., 2019).

It has been proposed that the effects of muscle fatigue can be counteracted by modifications in neuromuscular control [11], such as increased muscular activation and changes in activation patterns across groups of muscles [12], in order to maintain force output and to stabilise the joints [13]. For instance, some previous studies indicated that the development of muscle fatigue in adults without disabilities during reaching and grasping tasks might be related to a simplification of neuromuscular control [14–16]. Authors of these studies suggested the central nervous system decreases its complexity during fatiguing conditions, by limiting the number of elements it has to control due to movement reorganization in muscles and joints, i.e. consistently activating one group of muscles together instead of activating each muscle individually [14–16]. However, current knowledge on the effect of muscle fatigue on neuromuscular control is limited and mainly concerns non-cyclic movements in adults, approaching neuromuscular control at the level of the individual muscles and joints. Since neuromuscular control is known to be already simplified in many children with CP [17], it can be questioned whether similar effects would occur in children with CP during the development of muscle fatigue, for instance during functional activities such as prolonged walking.

Therefore, the aim of this study was to investigate the effects of prolonged walking on signs of muscle fatigue and complexity of neuromuscular control in children with CP and typically developing (TD) children. A novel exercise protocol was used that allowed to assess prolonged walking in a testing environment and within a reasonable time frame. In this way, further insight in possible limiting factors during prolonged walking in children with CP could be obtained. We hypothesised that signs of muscle fatigue would occur in both groups of children after prolonged walking, and complexity of neuromuscular control would reduce in both groups as a result of muscle fatigue, with the effects being more pronounced in children with CP.

2. Methods and procedures

2.1. Participants

10 children with a spastic paresis (9 children with CP and 1 child with hereditary spastic paraparesis with comparable motor impairments), and 15 TD children participated in this study. Inclusion criteria for both groups were *a)* 6–18 years of age; *b)* being able to walk independently without walking aids for at least 10 min; and *c)* having sufficient cognitive ability to follow instructions. All parents and children (only when aged 12 years and older) provided written informed consent prior to the measurements. The protocol was approved by the medical ethics committee of the VU University Medical Center Amsterdam and the ethics committee of the VU University Amsterdam.

2.2. Procedures

The protocol described below was part of a larger protocol also including collection of 3D motion capture as well as breath-by-breath oxygen consumption. A brief description of the protocol is described below and a schematic overview is provided in Fig. 1.

All participants walked on an instrumented treadmill placed in a virtual reality environment (GRAIL, Motek Medical BV, Houten, The Netherlands). A safety harness without weight support was worn to prevent falling while walking on the treadmill. Prior to the start of the experiments, participants completed a period of 10-minutes of habituation to walking on the treadmill, followed by six-minutes of overground walking to determine overground preferred walking speed (PWS). This was followed by a 30-minute preparation phase during which participants could rest and recover from these previous walking bouts.

Thereafter, participants performed a prolonged walking protocol on the treadmill, which was developed to reflect a daily life situation in which fatigue-complaints are reported in children with CP [18], within a reasonable time frame. First, children walked at PWS and a slope of 0° for 6 minutes (6 MW). Second, since normal walking was expected not to evoke signs of muscle fatigue in all children, an exercise protocol was added if 6 MW could not be considered to be of moderate intensity. Moderate intensity was defined as heart rate $>$ 70% of the predicted maximal heart rate (HRmax) of 195 bpm [19] for both CP and TD, as this has been reported not to differ between groups [20]. If this threshold was already reached during 6 MW, participants continued to walk for 2 more minutes at this moderate intensity (MIW). If the threshold was not reached, speed and slope of the treadmill were increased during a 5-minutes exercise protocol (adapted from Kotte et al. [21]), to gradually reach the 70% HRmax threshold set for MIW, after which participants walked for two minutes at the final step of the exercise protocol. Heart rate was continuously monitored and treadmill speed and slope were adapted accordingly if needed, to ensure that heart rate did not drop below 70% HRmax. Finally, all participants walked at PWS and a slope of 0° again for another four minutes (post-MIW).

EMG data (Zerowire, Cometa, Milan, Italy) were collected bilaterally at 1000 Hz of 8 muscles of the lower leg: rectus femoris, vastus lateralis, semitendinosus, gastrocnemius medialis, gastrocnemius lateralis, peroneus longus, tibialis anterior and soleus muscles following SENIAM guidelines [22]. To measure heart rate as an indicator of walking intensity, a heart rate monitor (Garmin Ltd., Olathe, KS, USA) was placed on the chest.

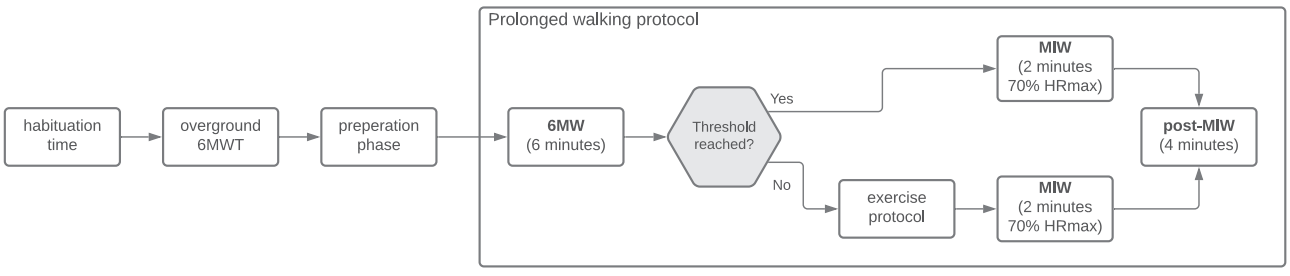

Fig. 1. Schematic overview of the prolonged walking protocol. 6MWT: six-minute walk test; 6MW: six-minutes walking; MIW: moderate-intensity walking; HRmax: predicted maximal heart rate.

2.3. Data analysis

Data was analysed for the most affected leg in children with CP, based on clinical observation. For TD children, data was analysed for a randomly selected leg. EMG data was band-pass filtered (2nd order Butterworth, bidirectional between 20 and 250 Hz). Gait cycles in which the EMG signal of at least one muscle deviated at least eight standard deviations from the average EMG signal were removed from analysis, as well as data of the first five gait cycles of the walking trial. All study outcomes were evaluated over the remaining cycles during the following three periods: the first 35 gait cycles at baseline (6 MW-start), the last 35 gait cycles of 6 MW (6 MW-end) and the final 20 gait cycles of the measurement (post-MIW). The effect of prolonged walking was evaluated by comparing 6 MW-end and post-MIW to 6 MW-start. Data analysis was performed using Matlab R2020a (The Mathworks, USA).

For each gait cycle, EMG median frequency of the power spectrum was determined using fast Fourier transformation. Thereafter, EMG signals were rectified and low-pass filtered (2nd order Butterworth, bidirectional, 5 Hz) to obtain smooth, rectified envelopes from which the EMG-RMS was calculated. For muscle synergy analysis, rectified EMG data were low-pass filtered (4th order Butterworth, bidirectional, 10 Hz). EMG data from each muscle was normalised to the average peak value over all included gait cycles in 6 MW-start. Muscle synergies were quantified using non-negative matrix factorization (NNMF) for each gait cycle separately, which is a mathematical algorithm commonly used for condensing measured muscle activation into sets of muscle synergies [23,24]. How well the extracted synergies could describe EMG activity was determined by the total variance accounted for (tVAF) for solutions with 1–4 synergies. Complexity of neuromuscular control was quantified by the average tVAF for the first synergy solution (tVAF1) [17].

To allow for comparison of synergy structures and weightings, the four-synergy solution was further investigated, since four muscle synergies have been reported sufficient to describe at least 90% of tVAF in TD children given the number of analysed muscles and data acquisition [23]. Synergies were grouped by functional muscle group weightings, starting with the synergy that could explain the highest percentage of tVAF, similar to the method used by Booth et al. [23]. The first synergy was defined as the one weighing highest towards gastrocnemius medialis, followed by semitendinosus, rectus femoris, and tibialis anterior muscles.

As secondary outcome of neuromuscular control, muscle coactivation was assessed to obtain further insight in the synergistic activation of specific muscle pairs. Muscle coactivation was assessed for the lower leg between the soleus and tibialis anterior muscles and for the upper leg between the semitendinosus and vastus lateralis muscles, using the normalized smooth rectified EMG data. Coactivation was defined as the simultaneous activation of two muscles and calculated as the ratio between the less and more active muscle, multiplied by the sum of activity found in both muscles [25]. Coactivation was calculated for individual strides, i.e. the same strides as used for muscle fatigue and synergy analysis, and subsequently averaged over each of the three evaluation phases (6 MW-start, 6 MW-end, post-MIW).

2.4. Statistics

All parameter distributions were checked for normality using a Kolmogorov-Smirnov test. Differences in patient characteristics between children with CP and TD children were identified using Mann-Whitney U tests. For EMG median frequency, EMG-RMS, tVAF1 and muscle coactivation, differences in actual values between groups (CP, TD) and evaluation phases (6 MW-start, 6 MW-end, post-MIW), as well as their interactions, were assessed using repeated measures analysis of variance (RM-ANOVA) over all muscles combined with Bonferroni adjustment using SPSS version 26 (IBM Corp., USA). 1D Statistical parametric mapping (SPM) RM-ANOVA was used to compare synergy activation patterns over the evaluation phases and groups, performed in Matlab. For all outcome measures, significance level was set at $p < 0.05$.

3. Results

No differences were found for age, height and weight between CP and TD ($p > 0.05$) (Table 1). Two children with CP were classified as level I on the gross motor function classification scale (GMFCS) and eight as level II. Details about participant characteristics and the protocol are provided in Table 1. In 5 children with CP, the threshold for MIW was already reached during 6 MW and the exercise protocol did not have to be applied. In 5 other children with CP and all TD children, treadmill speed and slope were increased according to the exercise protocol. Two children with CP used the handrail for extra balance during walking. In two children with bilateral CP, the least affected leg was analysed, as EMG electrodes lost connection on the affected leg. One TD child was excluded from analysis, as EMG channels lost connection on both legs. One child with CP was not able to complete the protocol. Since the heart rate of this participant was > 150 bpm during 6 MW, data of 6 MW-end were used to quantify post-MIW.

EMG median frequency averaged over all muscles was higher in CP (95.1 ± 2.6 Hz) than in TD (76.4 ± 2.3 Hz, $p < 0.001$) and was decreased at 6 MW-end (−3.30 Hz) and post-MIW (−4.21 Hz) compared to 6 MW-start ($p = 0.03$) in CP, but not in TD (−0.29 Hz at 6 MW-end, +0.16 Hz at post-MIW compared to 6 MW-start, interaction $p = 0.03$, Fig. 2). EMG-RMS was lower in CP (29.2 ± 2.0 μV, averaged over all muscles) than in TD (35.7 ± 1.7 μV, $p = 0.02$). EMG-RMS averaged over

Table 1
Characteristics of typically developing (TD) children and children with cerebral palsy (CP).

	TD (n = 14)	CP (n = 10)	p-value
Sex (F/M)	7/7	3/7	
Age (years)	10.8 ± 2.3	11.6 ± 2.7	0.53
Height (cm)	148.0 ± 14.8	154.8 ± 17.6	0.14
Weight (kg)	39.7 ± 11.1	45.5 ± 18.9	0.09
Treadmill speed (m s^{-1})	1.21 ± 0.17	0.99 ± 0.24	0.01
Number of children with CP with unilateral or bilateral involvement (unilateral/bilateral)	N.A.	1/9	
Number of children with CP classified as GMFCS level I/II	N.A.	2/8	
Number of children with CP classified as Children's Rehabilitation Activities Profile type 1/2/3/4/5[42]	N.A.	0/3/0/5/2	
Incrementing exercise protocol applied (yes/no) i.e. HR > 70% predicted HR-max not achieved during 6 MW	14/0	5/5	
Duration exercise protocol (minutes)	3.1 ± 0.9 (2.0–5.0)	2.8 ± 0.84 * (2.0–4.0)	
Maximal slope during exercise protocol ()	2.7 ± 1.1 (1.5–4.7)	0.9 ± 1.0 * (0.0–2.1)	
Maximal speed during exercise protocol (m s^{-1})	1.6 ± 0.7 (1.4–4.0)	1.1 ± 0.3 * (0.5–1.3)	

Data are mean ± standard deviation (range). F, female; M, male; N.A., not applicable; GMFCS, Gross Motor Function Classification System; HR, heart rate; * this value only includes the children with CP that performed the exercise protocol (N = 5)

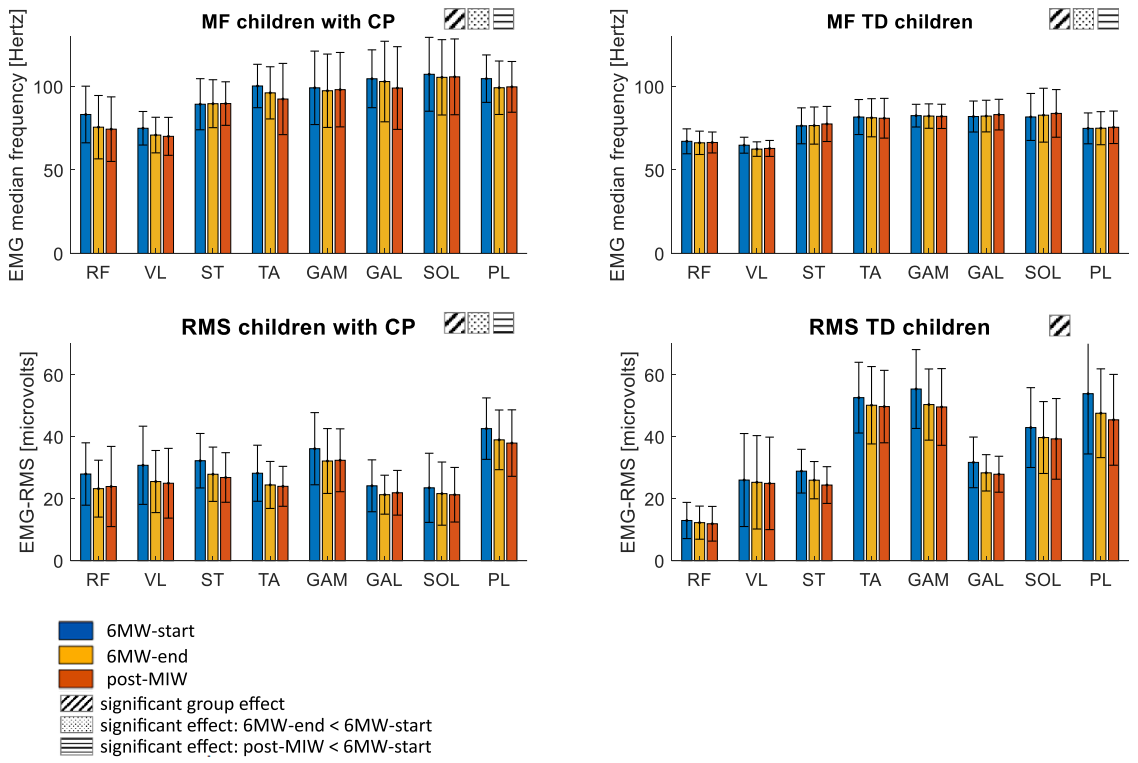

Fig. 2. EMG median frequencies (MF, top) and EMG root mean square (RMS, bottom) for children with CP (left) and TD children (right). Significance boxes are determined across all muscles combined. Error bars represent standard deviations. RF: rectus femoris; VL: vastus lateralis; ST: semitendinosus; TA: tibialis anterior; GAM: gastrocnemius medialis; GAL: gastrocnemius lateralis; SOL: soleus; PL: peroneus longus.

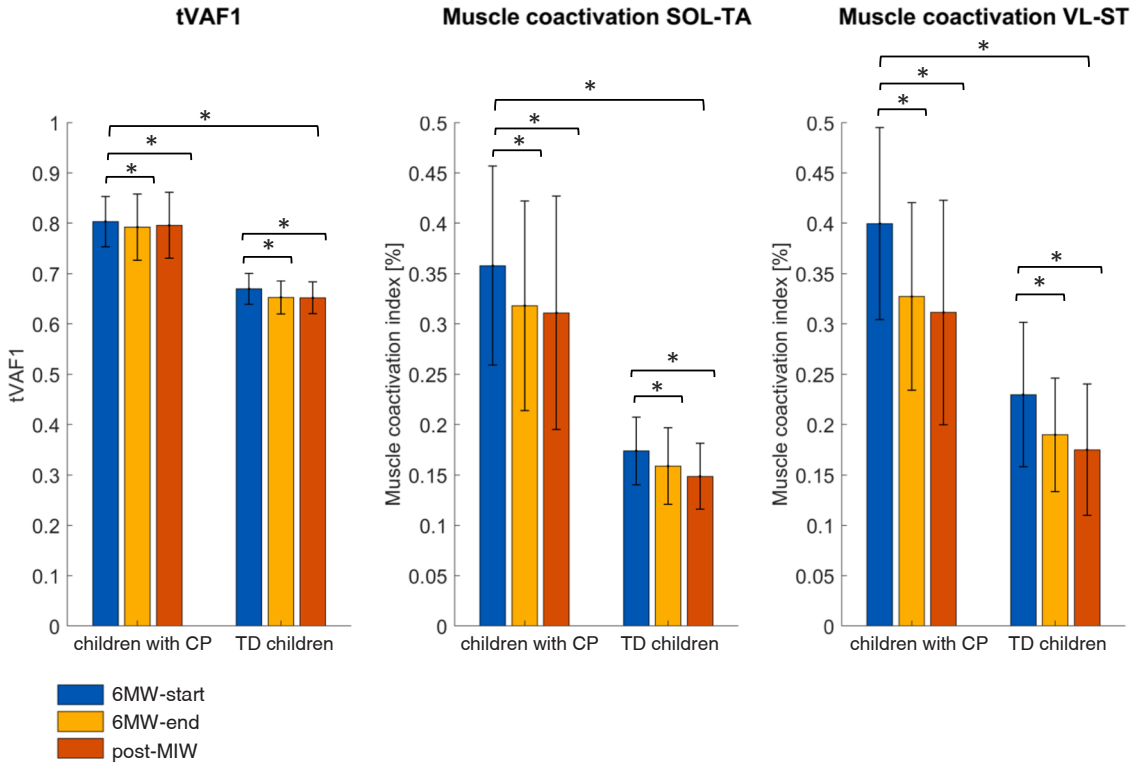

Fig. 3. Total variance accounted for by one muscle synergy (tVAF1, A) and muscle coactivation outcomes for children with CP and TD children (B and C). SOL: soleus; TA: tibialis anterior; VL: vastus lateralis; ST: semitendinosus. Significant effects between evaluation phases and groups are indicated with an asterisk (*) ($p < 0.05$).

all muscles was decreased at 6 MW-end and post-MIW compared to 6 MW-start ($p < 0.001$) in both groups (CP: −3.45 μV at 6 MW-end, −3.76 μV at post-MIW; TD: −3.09 at 6 MW-end, −3.90 at post-MIW compared to 6 MW-start), but no interaction effect between group and evaluation phase was found ($p > 0.05$). EMG median frequency and EMG-RMS for all eight muscles at all evaluation phases are provided in Appendix 1.

tVAF1 was higher in CP (0.80 ± 0.01) than in TD (0.66 ± 0.01) ($p < 0.001$, Fig. 3). tVAF1 was reduced equally in both groups at 6 MW-end and post-MIW compared to 6 MW-start ($p = 0.01$; CP: - 0.01 at 6 MW-end, −0.01 at post-MIW; TD: −0.01 at 6 MW-end, −0.01 at post-MIW compared to 6 MW-start). tVAF4 was 0.97 ± 0.01 for CP and 0.95 ± 0.01 for TD during all evaluation phases. Coactivation indices were higher for CP than for TD for both muscle pairs ($p < 0.05$, Fig. 3) and were lower at 6 MW-end and post-MIW compared to 6 MW-start in both groups ($p < 0.001$). Coactivation was more reduced in CP than in TD (interaction $p = 0.03$).

For synergy patterns, several significant but small changes were found between evaluation phases. For the first synergy (based on gastrocnemius medialis), activation decreased with evaluation phase during the early stance phase, and increased during the late swing phase (Fig. 4). Synergy activation differed between groups during midstance and terminal stance. A significant interaction effect between evaluation phase and group was also found. Activation of the second synergy decreased with evaluation phase and differed between groups during stance phase. Activation of the third synergy decreased during late stance and mid-swing and differed between groups mainly during the swing phase. A significant interaction was also found. Also for the third and fourth synergy, small effects of group, evaluation phase and their interaction were found (Fig. 4).

4. Discussion

The aim of this study was to investigate the effects of prolonged walking on signs of muscle fatigue and complexity of neuromuscular control in children with CP. We found signs of muscle fatigue in children with CP, but not in TD children. In contrast to our expectations, prolonged walking did not lead to reduced complexity of neuromuscular control.

Similar to findings by Eken et al. [26], children with CP showed a decrease in EMG median frequency already within six minutes of walking at comfortable speed, while signs of muscle fatigue were not

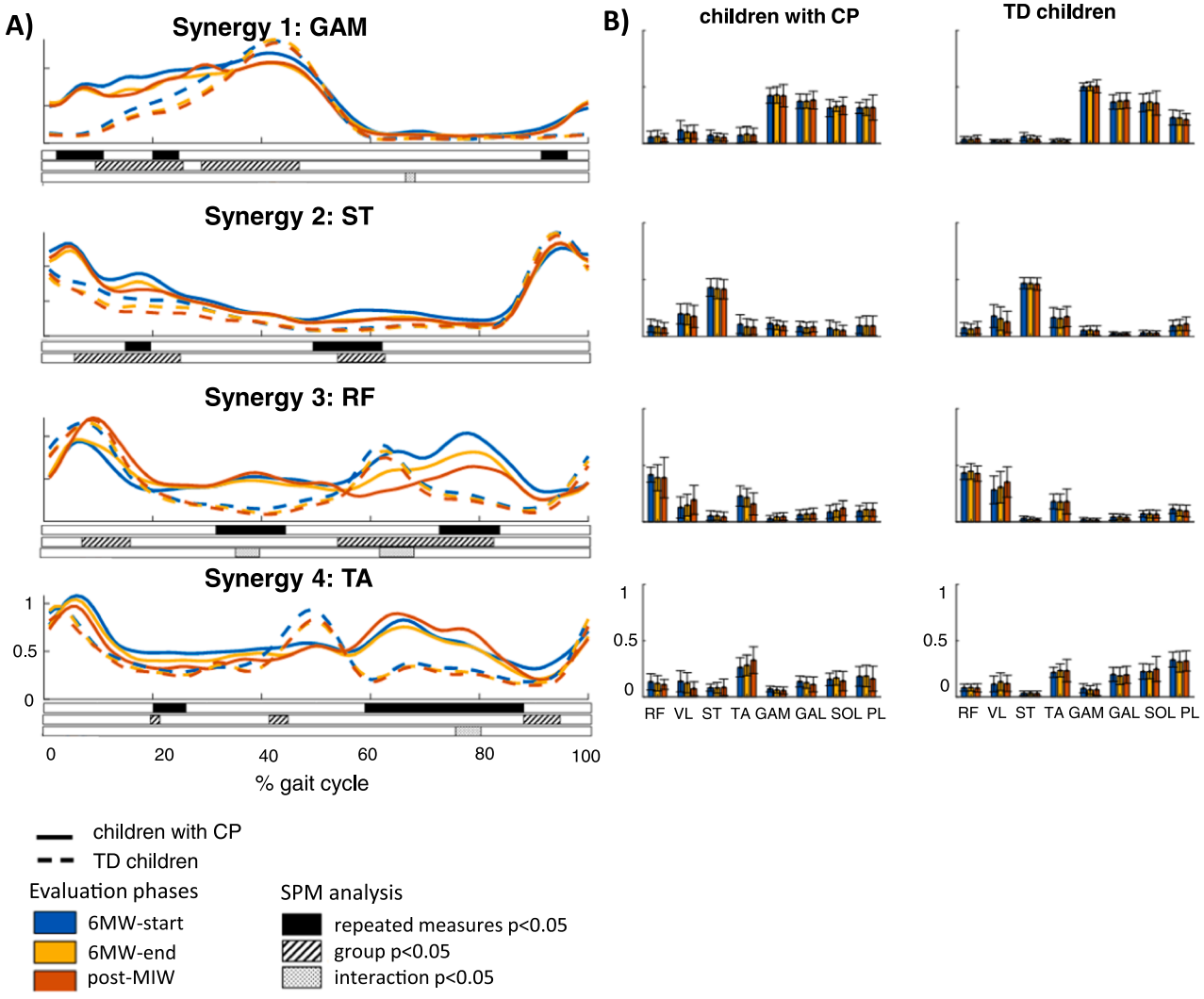

Fig. 4. A: Muscle synergy activation patterns for children with CP (solid line) and TD children (dashed line). From top to bottom: synergy activations based on highest activation in gastrocnemius medialis, semitendinosus, rectus femoris and tibialis anterior. Black solid, dashed and dotted boxes show the part of the gait cycle in which a significant difference is present ($p < 0.05$) between evaluation phases, groups or their interaction, respectively, according to SPM. B: Muscle synergy weighting factors for children with CP (left) and TD children (right). RF: rectus femoris; VL: vastus lateralis; ST: semitendinosus; TA: tibialis anterior; GAM: gastrocnemius medialis; GAL: gastrocnemius lateralis; SOL: soleus; PL: peroneus longus.

present in TD children. For children with CP, signs of muscle fatigue persisted until the end of the walking protocol, but in contrast to our hypothesis, signs of muscle fatigue did not increase further at post-MIW, and differences were most pronounced from 6 MW-start to 6 MW-end. Reported values were comparable to those of Parent et al. [3]. TD children did not even show signs of muscle fatigue after performance of the exercise protocol to provoke MIW. Since all children performed the walking exercise at moderate intensity, our results indicate that children with CP might experience signs of muscle fatigue earlier than TD children. The early onset of muscle fatigue in children with CP can partly be explained by reduced muscle strength [27,28]. Children with CP may have performed the protocol on a higher relative demand in terms of their neuromuscular system, i.e. on a higher level of their maximal muscle strength in comparison to TD children. Secondly, increased muscle coactivation levels in CP observed throughout the walking protocol may also explain an early onset of muscle fatigue, since excessive muscle coactivation is considered a strong contributor to muscle fatigue, as it is associated with an elevated oxygen consumption, in children with CP [29]. Moreover, the early onset of muscle fatigue in children with CP may be due to a deterioration of gait patterns with prolonged walking, such as an increasing crouch pattern [3], which could increase the load on the muscles during specific phases of a gait cycle.

In contrast to previous studies [26,30], our results showed a decrease in EMG-RMS after prolonged walking, which could indicate that fatigue did not occur. In these previous studies, participants did not walk at constant speed during overground [26] and treadmill [30] walking, suggesting increased EMG-RMS in these studies might be partly due to increased walking speeds and not solely through the development of muscle fatigue. One explanation for reduced EMG-RMS in our study could be habituation to treadmill walking. It has been shown that walking on a treadmill can be associated with elevated EMG activity and muscle coactivation compared with overground walking [31,32]. Indeed, co-activation levels also decreased over time in our study. Another explanation for decreased EMG-RMS could be reduced signal transmission due to accumulation of sweat under EMG electrodes. Accumulation of sweat is known to decrease the amplitude of the EMG signal, while EMG median frequency remains unaffected [33].

While we expected simplified motor control after prolonged walking, we found a small decrease in tVAF1 instead, comparable to previously reported values [17]. Although a decreased tVAF1 could be interpretated as more complex motor control, given its small magnitude it is questionable whether these differences reflect a clinically relevant improvement in motor control. Since we found signs of muscle fatigue only in children with CP and reduced tVAF1 and muscle coactivation in both groups of children, it is likely that these changes in tVAF1 are also partly due to habituation to treadmill walking. On the other hand, the reduced muscle coactivation is in line with previous studies that showed reduced muscle coactivation levels under fatigue conditions in adults without disabilities [34,35]. These authors described this decrease as a coping strategy for muscle fatigue and suggested fatigue-induced reductions in movement performance can be a result of reduced muscle coactivation [34,35]. However, further research is needed to obtain better insights in the complex relationship between muscle fatigue and motor control.

The results of the current study, with only small changes in tVAF1 and activation patterns, contribute to the idea that muscle synergies are robust and consistent over functional tasks [23,36–38]. Previous research showed that similar muscle synergies are activated during different types of activities, such as walking, running and cycling [36]. Moreover, it has been shown that changes in muscle synergies are minimal across different conditions, for instance during treadmill walking at a range of speeds in TD children [37] and during walking with biofeedback in both TD children and children with CP [23]. It has also been found that CP-related treatments can alter the gait pattern in children with CP, but do not change muscle synergies [38]. Our results provide further evidence that human neuromuscular control is relatively fixed, especially in children with CP, using the same sets of muscle synergies in different conditions, even during the onset of muscle fatigue.

This study has some limitations to consider for interpretation. First of all, it should be mentioned that this study could not provide direct evidence for the development of muscle fatigue as we did not measure force-generating capacity of the muscles, but only looked at signs of muscle fatigue as quantified by EMG median frequency and EMG-RMS. These outcome measures could be affected by multiple factors other than fatigue, such as fibre type and changes in recruitment of motor units [39]. Secondly, the definition of moderate-intensity walking was based on estimated group effects, while an individual threshold would have been more accurate, but this was not considered feasible within our protocol. Thirdly, the sample size of this study was rather small and one child with CP could not complete the full protocol, which may limit the ability of the analyses to detect significant differences between variables. In addition, including one child with hereditary spastic paraplegia in this group of children with CP could have influenced the outcomes, although it is not expected to change the overall conclusion of this study, as both disorders manifest in comparable symptoms [40] and muscle characteristics [41]. Another limitation is that data of only one leg could be analysed, whereas analysis of both legs in children with CP would provide more insight in their motor impairments. Finally, since post-MIW outcomes were assessed only at the end of the protocol, it is unknown whether muscles may have recovered to some extent immediately after the MIW exercise protocol. Therefore, we may have underestimated signs of muscle fatigue in some children, and an interesting next step would be to further investigate differences in recovery between children.

5. Conclusions

This study shows that children with CP experience signs of muscle fatigue during prolonged walking, whereas no signs of muscle fatigue were found in TD children even though both groups walked for at least two minutes at $>70\%$ of predicted maximal heart rate. Both groups showed only minimal changes in complexity of neuromuscular control with prolonged walking, which were likely to be related to decreased muscle coactivation levels throughout the protocol. In contrast to our hypothesis, our results show that complexity of neuromuscular control is not reduced during the development of muscle fatigue in children with CP.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gaitpost.2022.01.004.

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