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Yngvild Gagnat

Evaluation of gait function in children with cerebral palsy

New insights into commonly used methods

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of Philosophiae Doctor
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Evaluering av gongfunksjon hos barn med cerebral parese
Ny innsikt i ofte brukte metodar

Å gå er ein essensiell motorisk ferdigheit for dagleg aktivitet og sosial deltaking. Motoriske sjukdommar, som cerebral parese (CP), kan gi endra muskelaktivitet med auka samaktivering av musklane, avvik i gongmønster og auka asymmetri. Dette kan føre til auka energikostnad under gonge, som igjen kan redusere aktivitetsnivået og evne til deltaking. For å kunne ta kliniske avgjerder om behandling og oppfølging er det viktig å kunne evaluere faktorar relatert til både typisk og patologisk gonge. Og for det er det nødvendig med objektive og kvantitative metodar. Det blir ulike metodar for å evaluere gongfunksjon. Det gjer det utfordrande å samanlikne mellom studiar, og å danne eit godt grunnlag for avgjerder. Målet med dette doktorgradsarbeidet var difor å auke innsikta i metodar som ofte blir brukt for å evaluere muskelaktivitet, gongmønster og energikostnad, sjå korleis desse faktorane påverkar kvarandre og kva konsekvensar val av metode har for resultata og tolkinga av desse.

Barna med CP som var inkludert i dette arbeidet var ei homogen og velfungerande gruppe, men dei viste avvik i muskelaktivitet, samaktivering og gongmønster samanlikna med typisk utvikla barn. For å betre kunne vurdere om, og i kva måte, det er avvik i muskelaktivitet og samaktivering, kan det tilrådast å bruke både absolutte og normaliserte data. Både total energikostnad og om ein trekk frå energiforbruket under kvile, var påverka av gonghastigheit og kroppsstørrelse hos typisk utvikla barn. Total energikostnad var meir robust mot individuelle endringar i hastigheit, og kan difor vere fordelaktig å bruke når ein evaluerer effekt av behandling. Hos barna med CP viste asymmetri og samaktivering ingen samanheng med energikostnad under gonge, men auka avvik i gongmønster hadde ein sterk samanheng med auka energikostnad.

Oppsummert viste resultata frå dette arbeidet at val av metode påverka resultata og følgjeleg tolkinga av både muskelaktivitet, samaktivering og energikostnad. Og sjølv dei minst ramma barna med CP kan ha variasjonar og avvik som kan vere av betydning for dagleg aktivitet og deltaking.

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Abbreviations

BSA	Body surface area
CP	Cerebral palsy
MVC	Maximal voluntary contraction
RER	Respiratory exchange ratio
RMS	Root mean square
sEMG	Surface electromyography
VO_2	Oxygen uptake
VCO_2	Carbon dioxide production
Q-Q plot	Quantile-quantile plot
3DGA	3-dimensional gait analysis
5MWT	5-minute walk test

Definitions of terms

Ambulant – Being able to walk

Bony deformities – A malposition of the bone (1)

Cadence – Step rate per minute

Contralateral – The opposite side of the body

Contracture – Loss of joint range due to shortening of the fibrous connective tissue (1)

Electrode – Device used to record myoelectric signals

Energy – The capacity to perform work (1)

Extension – Straightening of joint

Flexion – Bending of the joint

Gait cycle – The sequence between two following foot strikes by the same limb (1)

Gait phase – Divisions of the gait cycle representing specific functional patterns (1)

Ipsilateral – The same side of the body

Markers – Small balls positioned on designated anatomical landmarks, to segment the body when conducting a 3DGA (1)

Spasticity – An involuntary over-reaction of a rapid stretch (1)

Steady state – A plateau, free of acceleration or deceleration (1)

The WE-study – Does botulinum toxin A make walking easier in children with cerebral palsy

Lists of publications

Paper I *Surface electromyography normalization affects the interpretation of muscle activity and coactivation in children with cerebral palsy during walking*.

Gagnat Y., Brændvik S.M., Roeleveld K.

Paper II *Energy cost of gait in children and its effect of speed, age, and body size.*

Gagnat Y., Oudenhoven L.M., Brændvik S.M., Bardal E.M., Roeleveld K.

Paper III *The relation of energy cost of walking with gait deviation, asymmetry, and lower limb muscle co-activation in children with cerebral palsy: a retrospective cross-sectional study.*

Gagnat Y., Brændvik S.M., Ringheim I., Roeleveld K.

Abstract

Walking is an essential motor skill for daily living and social participation. The neuromuscular system is vital in achieving support, stability, and progression during walking. Motor disorders, such as cerebral palsy (CP) may cause deviations in gait pattern, asymmetry, and altered muscle activity with excessive muscle co-activation, affecting gait function. In children with CP, impaired gait function may be seen through increased energy cost of walking compared to typically developing children, which in turn may limit activity level and participation. Evaluation of factors related to both typical and pathological gait function is important for clinical decision making. For such, objective and quantitative methods are needed.

A 3-dimensional gait analysis (3DGA) describes the gait pattern by providing kinetic, kinematic, and spatiotemporal information. Global measures, such as the gait deviation index (GDI), may be extracted from the 3DGA data, providing an overall score of gait pathology. Surface electromyography (sEMG) provide information about muscle activity and muscle co-activation during walking. However, there are unwanted factors affecting the sEMG signal, and various ways to deal with this, which complicates the interpretation. Moreover, various methods are used to calculate the co-activation index. Energy cost of walking represents the overall gait function and may be presented as total (gross energy cost) or in addition to resting energy expenditure (net energy cost). Gross energy cost is considered more reliable, while net energy cost is reported less affected by between-subject variations in speed and growth-related subject characteristics. However, the effect of the within-subject variation in speed on energy cost is less established. Additionally, to what extent energy cost is affected by a deviating and more asymmetric gait with increased muscle co-activation, is still deficient. Therefore, this thesis aimed to gain further insight into commonly used methods for evaluating gait function in ambulant children with CP.

Paper I evaluated how the interpretation of muscle activity and co-activation was affected by the normalisation of the sEMG-amplitudes, and compared two methods of calculating the co-activation index. The findings showed that the overall muscle activity pattern did not change after normalisation, but the between-subject variation was reduced. However, relevant physiological variation may have also been eliminated. The children with CP showed deviations in muscle activity from the typically developing children in different phases of the gait cycle using absolute and normalised amplitudes. Consequently, some of the phases with

increased co-activation index deviated between the two methods. But in common they showed that an increase in the muscle co-activation index mostly was attributed reduced muscle activity rather than increased antagonist muscle activity. The two methods of calculating the co-activation index showed similar deviations between the groups, but one method was considered less applicable due to greater between-subject variation and non-normal distribution.

Paper II evaluated gross and net energy cost in typically developing children, and the effect of speed and growth-related subject characteristics. The findings showed that gross energy cost was less affected by within-subject variations in speed compared to net energy cost, where an increase in speed showed increased energy cost. Gross energy cost had a strong, negative relation to between-subject variation in speed, age, and body size. Although reduced, these relations were not eliminated for net energy cost, and they followed a concave shape.

Paper III evaluated how gross energy cost of walking in children with CP was affected by gait pattern, gait asymmetry, and lower limb muscle co-activation. The findings showed that deviations in gait pattern, reflected through the GDI, in addition to body size, had a strong, positive relation to energy cost. Gait asymmetry and co-activation were not related to energy cost.

To summarise, the interpretation of muscle activity and co-activation was affected by normalisation method when evaluating group differences. Thus, using both absolute and normalised amplitudes for a complete interpretation of the sEMG data is recommended. Moreover, when interpreting the co-activation index, the methodological approach and the underlying muscle activity must be considered before drawing conclusions on abnormal co-activation levels and the cause of this. Although normalised to speed and body size, both gross and net energy cost of walking in typically developing children were still affected by those factors. However, gross energy cost may be beneficial when evaluating treatment effect, as improvements in energy cost due to improvements in gait function and consequently speed, may be concealed using net energy cost. Moreover, increasing deviations in gait pattern among children with CP was related to increase in gross energy cost of walking.

Introduction

Walking is an essential motor skill learned at an early stage of life. It is an important skill for daily living activities and social participation (2). During walking, the neuromuscular system aims to attain bodyweight support, dynamic stability, forward progression, and foot clearance from the ground (3). To successfully achieve this, a complex system of multiple degrees of freedom in the motor system involving various muscles is necessary. The muscles are activated through the central nervous system and produce forces that apply necessary moments at the joints to support the body against gravity and move the body limbs to the desired position. However, this may be disrupted by motor disorders causing various deviations in movements and gait function (3, 4).

A persons' gait function includes the underlying factors; gait pattern and muscle activity and is overall reflected through the energy cost of walking (Figure 1). A quantitative description of gait pattern includes information regarding kinetics, i.e., the forces applied during gait; kinematics, i.e., the angles of the pelvis, hip, knee and ankle joints; and spatiotemporal characteristics such as walking speed, cadence and step length (2). Muscle activity describes whether and how much the muscles are active, and energy cost represents the amount of energy used to move the body. To gain better insight in these factors of gait function, it is important to conduct research on both typical and pathological gait. Increased knowledge about gait function may contribute to the improvement of gait among populations with motor disorders by better adapting the course of treatment and rehabilitation. This in turn may result in a more active, independent life with social participation, both during childhood and throughout adult life.

1.1. Gait function of children with cerebral palsy

The most common motor disorder in childhood is cerebral palsy (CP), with an overall prevalence varying between 1.5 and 3 per 1000 live births (5-8). Cerebral palsy is a neurodevelopmental condition, comprising a group of permanent disorders of the development of movement and posture (9). It is caused by a non-progressive lesion of the cerebral motor cortex, occurring prior to, during, or within two years after birth (7, 10). Cerebral palsy is characterised by a combination of various motor impairments (10-12). Loss of connections to the lower motor neurons causes negative features, that is insufficient motor activity. This appears as reduced selective motor control, reduced muscle strength, and poor balance and coordination of movements. Loss of inhibition of the lower motor neurons causes positive

features, that is increased motor activity. This appears as spasticity and excessive muscle co-activation. Secondary musculoskeletal impairments such as muscle contractures and bony deformities are also common characteristics (2).

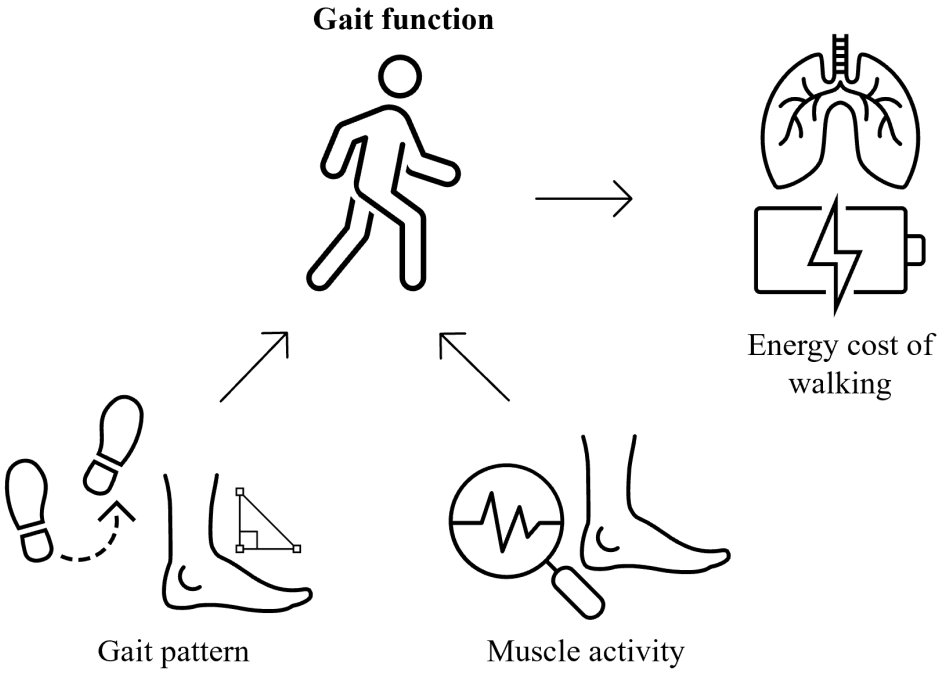

Figure 1. Illustration of the underlying explanatory factors of gait function; gait pattern and muscle activity, and the overall describing factor; energy cost of walking.

Based on the main neuromotor impairments, CP may be categorised into the subtypes: spastic, dyskinetic, and ataxic CP (8, 9). The subtypes may further be categorised based on anatomical distribution of the impairment. The spastic subtype is the most common type of CP, accounting for approximately 70-90 % of the cases (8, 13). Spastic CP may be divided into unilateral or bilateral, referring to whether limbs on one side or both sides of the body are affected (6, 8). Moreover, based on functional mobility or activity limitation, CP may be categorised into one out of five levels of the Gross Motor Function Classification System (GMFCS, Figure 2) (14, 15). In short, level I includes walking without restrictions, level II includes walking without

assistive devices, level III includes walking with assistive mobility devices, level IV includes limited self-mobility and the use of assistance or power mobility for transport, and level V includes severely limited self-mobility with the use of assistive technology (14). According to the Norwegian Quality and Surveillance Registry of Cerebral Palsy (NorCP) approximately 70 % of all children diagnosed with CP are categorised as level I or II (13). Of the children diagnosed with spastic unilateral CP, approximately 100 % are within these two levels, and approximately 50 % of the children diagnosed with spastic bilateral CP. These children are relatively well functioning and comprises the majority of children diagnosed with cerebral palsy. This thesis will hereafter focus on ambulant children with spastic CP (level I-II).

The characteristic features of children with CP impair motor function in general, and gait function in particular. There are various gait deviations presented for children with CP and, overall, they are reported to walk slower with a more asymmetric and variable gait compared to typically developing children (16-18). More specifically, the gait pattern is characterised by deviations in joint kinematics of both the pelvis, hip, knee, ankle and foot (19). Moreover, the children with CP may have difficulties in voluntarily activating their muscles, and are reported to be weaker than typically developing children (20, 21). Reduced muscle strength in the plantar flexor muscles may, for instance, reduce propulsion during gait (22). In addition, spasticity, an involuntary stretch response of the muscles, is suggested to be one of the main contributors to impaired gait function (23, 24). Spasticity of the hamstrings and plantar flexor muscles may respectively reduce knee extension causing knee-flexed gait and reduce ankle dorsiflexion causing toe-walking (25, 26). This in turn may decrease walking speed and step length. Spasticity may in addition lead to contractures and pain (10).

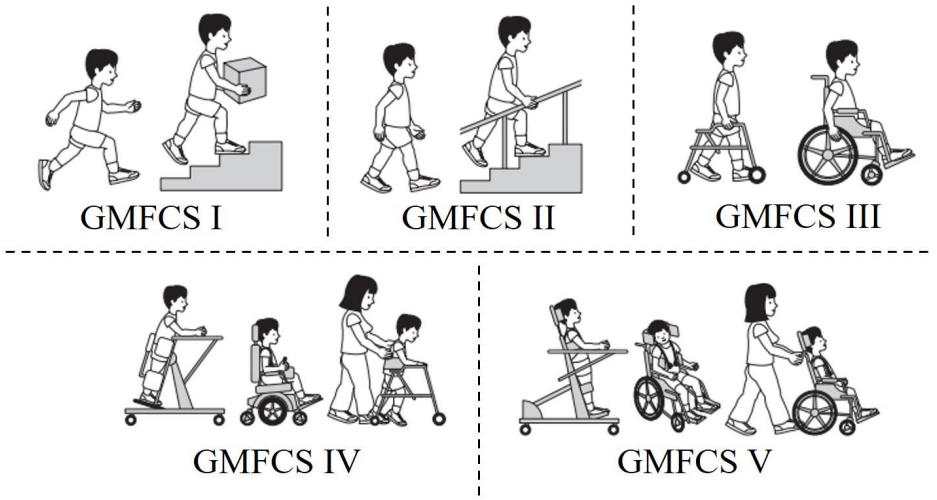

Figure 2. Illustration of the five levels of the Gross Motor Function Classification System (GMFCS) of children with cerebral palsy. Adapted, with permission, from resources at The Royal Children's Hospital, Melbourne, Australia, https://www.rch.org.au/clinicalguide .

Muscle co-activation is defined as simultaneous activity of opposing muscles crossing the same joint (27). During complex tasks, such as walking, muscle co-activation occurs at certain phases during the gait cycle as a normal control strategy, ensuring stability of the joint and coordination, allowing for efficient walking (27-29). Among children with CP, increased levels of muscle co-activation have been reported (30-33). This excessive muscle co-activation is thought to cause inefficient movements, by increasing the load of the joints and reducing flexibility and adaptability (28, 30). However, what underlies these increased levels are rarely considered, and the influence of excessive muscle co-activation on functional ability is not established (27, 28, 34-36). Whether it is acting pathologically by restricting movement, or physiologically by compensating for reduced muscle strength, is not completely known.

Children with CP are also reported to have increased energy expenditure of walking compared to typically developing children (37-39). This increase is reported to further increase with decreasing functional level and may be attributed various underlying factors (39-41). As mentioned earlier, the gait pattern of children with CP is characterised by deviations in joint kinematics, asymmetry and altered muscle activity with increased levels of muscle co-

activation. Specific kinematic deviations have shown to be related to increased energy cost of walking in children with CP (42). And although an asymmetric gait pattern is reported to be more energy demanding in a healthy, adult population and in patients after stroke (43-45), it is still uncertain what effect it may have in children with CP. Furthermore, there are inconsistencies in the literature with regards to how the excessive muscle co-activation is related to energy expenditure of walking. Increased co-activation of the lower limb muscles have shown to be related to an increased (31) or decreased (46) walking energy expenditure, or not to have a relation (47). However, various methods have been used both for measuring muscle co-activation and energy expenditure during walking, which makes comparisons and interpretations challenging.

1.2. Evaluation of gait function

Evaluation of gait function in children with CP is of importance to define functional level, and to aid treatment prescriptions. A common treatment course of children with CP is to improve gait function by targeting factors that increase the energy expenditure of walking (10, 40, 48, 49). This in turn may lead to increased daily activity and social participation. There are various types of treatments available, targeting spasticity, contractures and/or muscle weakness (50). The treatments may be non-operative, including physical therapy to maintain range of motion and increase muscle strength, the use of orthosis to address muscle contractures and bone deformity and pharmacological treatment to reduce muscle stiffness and spasticity (2, 19). Surgical treatments such as intrathecal baclofen and selective dorsal rhizotomy is used to reduce spasticity and orthopaedic surgery addresses muscle contractures and bony deformities.

As one of the primary focus areas of the treatment of children with CP is to make walking easier, it is important to evaluate the underlying factors of gait function affecting the energy expenditure of walking. For instance, such knowledge could aid decisions on whether a muscle should be treated with botulinum toxin-A to reduce spasticity, or whether one should undergo surgery to improve gait function. In order to evaluate factors affecting and describing gait function, objective and quantitative measures are needed, of both typical and pathological gait. However, in the clinical evaluation of children with CP various methods are used, and increased knowledge of the most commonly used methods is important to aid clinical decision making and development of an appropriate treatment course.

1.2.1. Gait pattern

There are various methods available for evaluation of gait pattern. The application of body-worn sensors is a validated method that can be used to evaluate gait characteristics related to spatiotemporal parameters and balance (18, 51, 52). Moreover, it is a time-efficient, low-cost method that can be used outside the laboratory environment. The use of an electrical walkway is another portable method, which is easy to administer and provides reliable information related to spatiotemporal gait characteristics (53, 54). However, the most comprehensive method is the use of a camera-based 3-dimensional gait analysis (3DGA) (55). This method provides information about not only spatiotemporal characteristics of gait, but also kinetics and kinematics. The kinetic data represents the ground-reaction forces, and the moments and powers of the joints and the kinematic data represents changes in the angles of the different joints or segments; trunk, pelvis, hip, knee and/or ankle (2). A 3DGA is a widely used method to determine functional level, evaluate changes over time and effect of interventions in children with CP (55, 56).

To more precisely describe and identify functional significance of different movements, gait may be divided into cycles and phases (Figure 3) (1). A gait cycle starts as one foot touches the ground and lasts until the same foot touches the ground again (2). Further, a gait cycle may be divided into a stance and a swing phase. The stance phase consists of a first double support, where both feet are on the ground, followed by a single support phase where the opposite foot is in swing phase, before a second double support. Spatial and temporal characteristics may be calculated based on the gait cycle, and are widely used to document changes in gait, such as walking speed, cadence, and length of the stride (2, 57). These variables are commonly normalised to leg length to correct for differences in size, which allows for comparisons between subjects (58).

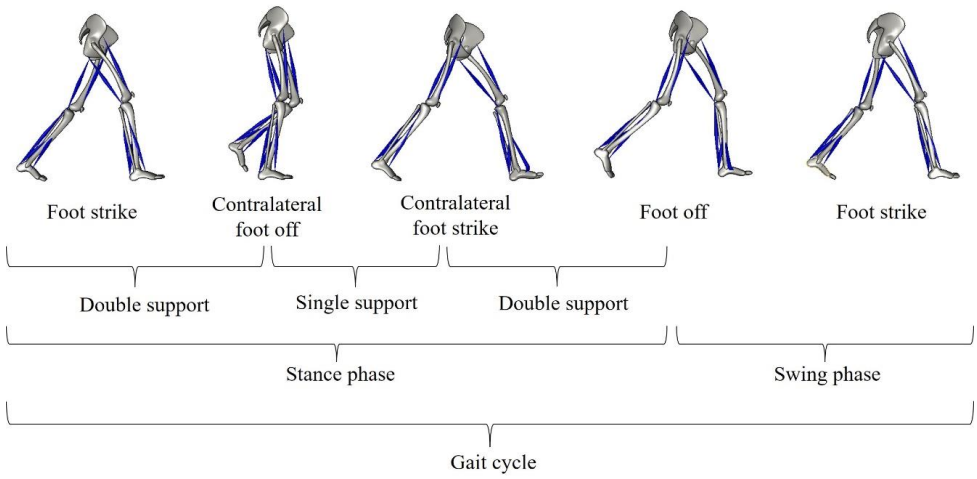

Figure 3. Illustration of a right leg's gait cycle with divisions into phases.

Overall, a 3DGA generates a large amount of data containing complex information that needs to be interpreted. Thus, different global measures have been proposed, such as the Gillette Gait Index (GGI), Gait Deviation index (GDI) and Gait Profile Score (GPS) (59-61). These measures are designed to provide a single, numeric score to represent overall gait pathology and are commonly used. They are all reported to be valid in describing and evaluating children with CP (62, 63). While the GGI and GDI only provide a score representing the overall pathology, the GPS may be decomposed into Movement Analysis Profiles (MAPs) allowing for analysis of the individual kinematic components included (63). However, although these measures are highly validated, and correlated, the GDI has been proposed superior as a more sensitive measure when it comes to comparing to typically developing children, and when evaluating treatment effects.

1.2.2. Muscle activity

Evaluation of neuromuscular activity, measured through surface electromyography (sEMG), is useful to gain further insight into the underlying, explanatory factors of gait function (64). When sEMG measurements are included to the 3DGA, comprehensive information about the simultaneous activation patterns of the involved muscles during gait is available (3). The use of sEMG measurements provides an objective evaluation of whether, or how much, a muscle is active during a given task. With careful and thorough interpretation, the use of sEMG

measurements to evaluate muscle activity may provide valuable information to better understand both typical gait and the state of a motor disease.

The sEMG amplitude represents muscle activity through the number of recruited motor units, the firing rate and firing pattern (65). Due to possible influencing factors, which may be technical, such as the size, shape, and material of the electrodes; and/or physiological, such as subcutaneous fat layer, the sEMG is commonly normalised in order to compare between individuals, sessions or muscles. When normalising, the absolute sEMG amplitude from the specific task of interest is divided by a reference amplitude of the same muscle, which gives a relative value of the sEMG amplitudes. The reference amplitude may be retrieved from either a maximal voluntary contraction (MVC) or during the specific task of interest. Normalising to a peak amplitude obtained during an MVC, is commonly used as it ensures high repeatability in a healthy population (66-68). Through this method, the percentage of total muscle activation capacity, represented by the sEMG amplitudes from the specific task, can be evaluated. However, the peak obtained during an MVC may not always represent the maximum activation capacity. As for instance, in children, and particularly in children with neurological conditions, who may find it challenging to voluntary activate their muscles to the maximum. Therefore, when evaluating dynamic movements, normalising to the peak amplitude obtained during the specific task of interest is considered a good alternative for this group (4, 69, 70). Moreover, this method is suggested superior to reduce between-subject variation (67, 71). However, during a dynamic task such as walking, the peak sEMG amplitude may occur at different phases of gait for typically developing children compared to children with neurological conditions, due to spasticity or reduced muscle strength. This may affect the normalised sEMG amplitudes of the other gait phases, which may subsequently affect the interpretation of muscle activity. Therefore, it is also suggested not to normalise the sEMG data (4, 46, 71-74).

Muscle co-activation is defined as the simultaneous activity of muscles crossing the same joint (27). At this individual joint, at least two muscles are acting opposite to each other, defined as the agonist and antagonist muscle (34). The agonist muscle is acting in one direction by producing force and/or moment, prescribed by the desired task, while the antagonist muscle opposes this. Muscle co-activation may act across single muscle pairs, or across large muscle groups, named muscle synergies. However, in this thesis, the former type of co-activation will be addressed.

To quantify muscle co-activation, calculations of a co-activation index is used. This index is based on the sEMG amplitudes of the agonist and antagonist muscles (34). In the literature, different methods of calculating the co-activation index have been used (34, 69). The antagonist muscle activity is compared to either the agonist muscle activity solely or to the total muscle activity of both the antagonist and agonist. However, there is no consensus on which calculation method is superior, and the use of different methods makes it difficult to state an overall picture of the mechanism.

As different approaches for handling sEMG data and calculations of the co-activation index are used, it may complicate the investigation and interpretation of the results (69). Using normalised sEMG amplitudes to calculate the coactivation index is the most common approach (30, 31, 33, 46, 75). However, using absolute amplitudes avoids unnecessary data transformation, and has therefore been suggested to be a more beneficial approach (72). For example, using normalised sEMG amplitudes in a ratio to calculate the co-activation index will thus normalise the data twice. Moreover, using absolute amplitudes has been suggested to be preferable when calculating the co-activation index in populations with weak muscles (73). In cases where the sEMG amplitudes are potentially low throughout the entire task, normalising to a peak value may thus cause an overestimated co-activation index, misleading the interpretation.

1.2.3. Energy cost of walking

The overall gait function is often quantified through measuring energy expenditure of walking (40). Energy expenditure may be evaluated using a variety of methods and equipment (76). The use of gas-exchange measurements of oxygen uptake (VO_2) and carbon dioxide production (VCO_2) is considered a gold standard, and is commonly used (77). The amount of VO_2 consumed is dependent on body size, and is therefore normalised to bodyweight to better allow for comparisons between individuals (78). Clinical evaluation with energy expenditure measurements is usually conducted at self-selected, comfortable walking speed. However, energy expenditure increases with speed, and is therefore often normalised to speed and referred to as energy cost (40, 79). Even though it is an objective and quantitative measure, several methodological challenges have been presented (80). This is especially evident when evaluating children during growth, as energy cost is still reported to be affected by speed, age, and body size (80-82). This may partly be attributed to the resting energy expenditure, which changes with growth (40, 82). The resting energy expenditure includes the basal metabolic rate and the resting muscular consumption of sitting or standing position. Gross energy cost covers

the total cost required for movement, including the resting energy expenditure, while net energy cost only covers the cost required for movement, i.e., the resting energy expenditure is deducted. There are certain challenges measuring resting energy expenditure, especially in children, and high within-subject variations have been reported (38, 83). Due to this, gross energy cost has shown better reproducibility compared to net energy cost. However, using net energy cost has shown to better reduce the effect of age and body size (37). Moreover, a non-dimensional normalisation of net energy cost has also been suggested to eliminate the effect of anatomical and physiological variables (84). However, as it is dimensionless, it is more difficult to interpret, and the only difference from net energy cost is driven by a constant factor that is the gravitational force. Therefore, the relation to speed and body size is similar to the relation of net energy cost (37). The advantage of using gross energy cost due to high reproducibility and using net energy cost due to less dependence on age and body size seems to be established knowledge. However, although impaired gait function may affect both speed and energy cost of walking, the ways in which individual variations in gait speed potentially affect energy cost are less established.

1.3. Rationale for the thesis

Conducting research on gait function in patients with motor disorders is important to better understand the nature of the disease, as well as the underlying mechanisms (3). Moreover, it is important in order to develop and improve rehabilitation approaches and to evaluate the effect of treatment. Ambulant children with CP show impaired gait function with deviating gait pattern and muscle activity, and increased energy cost of walking. Thus, a common treatment goal for these children is to make walking easier by reducing the energy cost of walking. The treatment is therefore often aimed directly at factors affecting the energy cost, such as the gait pattern and muscle activity. However, various methods are used in when evaluating gait function, both for handling sEMG data and for calculating the co-activation index and energy expenditure of walking. It is therefore challenging to synthesise existing research as well as conducting new comparisons. Thus, there is a need for increased knowledge regarding methods used to evaluate gait function in order to better interpret the deviations, decide on a proper treatment course and evaluate treatment effect.

1.4. Aims of the thesis

The overall purpose of this thesis was to gain further insight into commonly used methods for evaluating gait function in ambulant children with CP. More specifically by evaluating methods

used to measure explanatory and descriptive factors of gait function, how they interact, and the consequences of methodological choices for interpretation.

This was addressed through the specific aims of the following three papers:

Paper I: Evaluate the effect of sEMG normalisation on the interpretation of muscle activity and co-activation. More specifically, this was evaluated by comparing between-subject variation and group differences between healthy legs of typically developing children and the affected legs of ambulant children with CP. Differences between two methods of calculating the co-activation index were also examined.

Paper II: Evaluate how two different methods of calculating energy cost of walking was affected by within-subject variations in speed as well as between-subject variations in speed and growth-related subject characteristics, in typically developing children.

Paper III: Evaluate to what extent variations in gross energy cost of walking in ambulant children with CP was related to gait pattern, gait asymmetry and lower limb muscle co-activation.

2. Methods

This thesis comprises three cross-sectional studies. Paper I and II are methodological studies, which evaluated how various methods of handling sEMG data, and calculating the co-activation index and energy cost of walking, affected the results. The study of Paper III was evaluating how underlying factors of gait function affected the energy cost of walking.

Data for all three studies included in this thesis were affiliated the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway (Table 1). The data used in the studies of Paper I and III was conducted as part of the WE-study; Does botulinum toxin A make walking easier in children with CP (85) and was collected at the gait lab of NeXtMove core facility, NTNU, Trondheim, Norway. For the study of Paper III, data was, in addition, collected at two collaborating clinical sites in the WE-study; the clinical gait analyses facility at Vestfold Hospital Trust, Norway and the Mazovian neurorehabilitation and Psychiatry Center in Zagorze, Wiazowna, Poland. The studies of Paper I and III are based on baseline data, prior to injection of botulinum toxin-A or saline water, and the study of Paper III includes, in addition, data 24 weeks post injection. The study of Paper I also includes clinical data from regular outpatient follow up at St.Olavs Hospital, Trondheim university Hospital, Trondheim, Norway, in addition to data of typically developing children from the reference base at the gait lab of NeXtMove core facility, NTNU. The study of Paper II includes data of typically developing children collected at a local elementary and junior high school in Trondheim, Norway, with equipment from the NeXtMove core facility, NTNU.

The data collection for the studies of Paper I and III was conducted between October 2015 and October 2021, and the data collection for the study of Paper II was conducted in October and November 2017.

Table 1. Description of where the data collections took place and which data was included in the three papers included in this thesis.

	Paper		
Sites of data collection	I	II	III
The gait lab of NeXtMove core facility, NTNU, Trondheim, Norway	X		X
The clinical gait analyses facility at Vestfold Hospital Trust, Norway			X
Mazovian neurorehabilitation and Psychiatry Center, Wiazowna, Poland			X
Local elementary and junior high school, Trondheim, Norway		X	
Type of data included			
Baseline data of the WE-study	X		X
Data of the WE-study, 24 weeks post treatment			X
Clinical data from outpatient follow up, St.Olavs Hospital, Trondheim, Norway	X		
Data of typically developing children from the reference base at the gait lab of NeXtMove core facility, NTNU, Trondheim, Norway	X		

NTNU = Norwegian University of Science and Technology; WE-study = Does botulinum toxin A make walking easier in children with CP.

2.1. Ethics

As part of the WE-study, the studies of Paper I and III were approved by the Regional Committee for Medical and Health Research Ethics in Middle Norway (REK Central). The study of Paper II was approved by the Norwegian Centre for Research Data (NSD). Written consent was signed by the children's parents or guardians prior to participation. All studies were performed in accordance with the Declaration of Helsinki.

2.2. Participants

Distribution of age and gender of the participants in each paper is presented in Table 2. The primary target group in the studies of Paper I and III was ambulant children with CP. They were diagnosed with unilateral or bilateral spastic CP, with GMFCS level I or II. Exclusion criteria were if the children were treated with botulinum toxin-A in the lower limb muscles preceding the last three months prior to inclusion. Additionally, the children should not have undergone surgery in the legs preceding 24 months prior to inclusion. Typically developing children, without physical disability or medical conditions affecting their gait, were included in the studies of Paper I and II. All children included were between the age of 4.5 and 17 years old.

Table 2. Distribution of age and gender of the three papers included in this thesis.

Paper	Population	Age, years		Boys	N
		Mean ± SD	95 % CI	N (%)	
I	Children with CP	12 ± 3 y	10 – 13 y	16 (70 %)	23
	Typically developing children	9 ± 1 y	9 – 10 y	4 (36 %)	11
II	Typically developing children	11 ± 3 y	10 – 11 y	23 (53 %)	42
III	Children with CP	10 ± 3 y	9 – 10 y	21 (53 %)	40

CI = confidence interval; CP = Cerebral palsy; N = number of participants; SD = Standard deviation; y = years.

2.3. Procedures, equipment, and data analyses

Characteristics of the children, including age, height and bodyweight were recorded prior to testing. Body surface area (BSA, m^2) was calculated according to Equation 1 (86):

Equation 1: $BSA\ (m^2) = \sqrt{\frac{height\ (cm) \times bodyweight\ (kg)}{3600}}$

BSA = Body surface area

2.3.1. Three-dimensional gait analysis (Paper I and III)

A 3-dimensional gait analysis (3DGA) was used to evaluate gait pattern. The 3DGA was conducted using the Vicon Motion System (Ltd, Oxford, UK, Paper I and III) or using the Qualisys Motion Capture System (Qualisys AB, Gothenburg, Sweden, Paper III). Dependent on the system used, a total of ten or seven cameras were located around the gait lab. The sampling frequencies were 200 and 150 Hz, respectively. Additionally, two AMTI force plates (Watertown, USA) with a sampling frequency of 1000 Hz, were integrated into a 7-8-metre walkway. Reflective markers (16, 20 or 28) were placed on anatomical landmarks on the lower limbs, according to the Vicon Plug-in-Gait model (Paper I) (87), the Istituti Ortopedici Rizzoli (IOR) lower body marker set (Paper III) (88) or the Qualisys CAST lower body marker set (Paper III) (89), respectively. The children walked barefoot at a self-selected, comfortable walking speed, and conducted a minimum of three trials.

Kinematic data derived from the Vicon Motion System and the Qualisys Motion Capture System were respectively processed in the Nexus software (Oxford Metrics, Oxford, UK, Paper I) and the Qualisys Gait module (Qualisys AB, Gothenburg, Sweden, Paper I and III). Gait cycles were defined, events detected, and spatiotemporal gait parameters were calculated. Data from the 3DGA was exported as c3d-files and a customized Matlab program (R2020b, MathWorks, Inc., Natick, MA, USA), written using the Biomechanical Toolkit (Btk Development Core Team, Version 0.3.0), was used for consecutive processing and calculations. The gait cycle was normalised to a 100 %. Data was visually inspected and averaged over the included trials.

In Paper I, the gait cycle was divided into six phases in order to evaluate muscle activity throughout the whole gait cycle (Figure 4). The detected events were used to define four gait phases. The weight acceptance phase lasted from ipsilateral foot strike to contralateral foot off. The stance phase followed to contralateral foot strike before the swing phase continued until ipsilateral foot strike. Additionally, the stance and swing phases were divided into two, based on where ipsilateral knee moment changed from external flexion to extension and where peak knee flexion occurred, respectively.

Walking speed, cadence and step length were normalised to leg length (m) according to Equation 2 - 4 (58):

Equation 2: $Normalised\ speed = \frac{speed\ (m/s)}{\sqrt{leg\ length\ (m) \times 9.81\ m/s^2}}$

Equation 3: $Normalised\ cadence = \frac{cadence}{\sqrt{leg\ length\ (m) \times 9.81\ m/s^2}}$

Equation 4: $Normalised\ step\ length = \frac{step\ length\ (m)}{leg\ length\ (m)}$

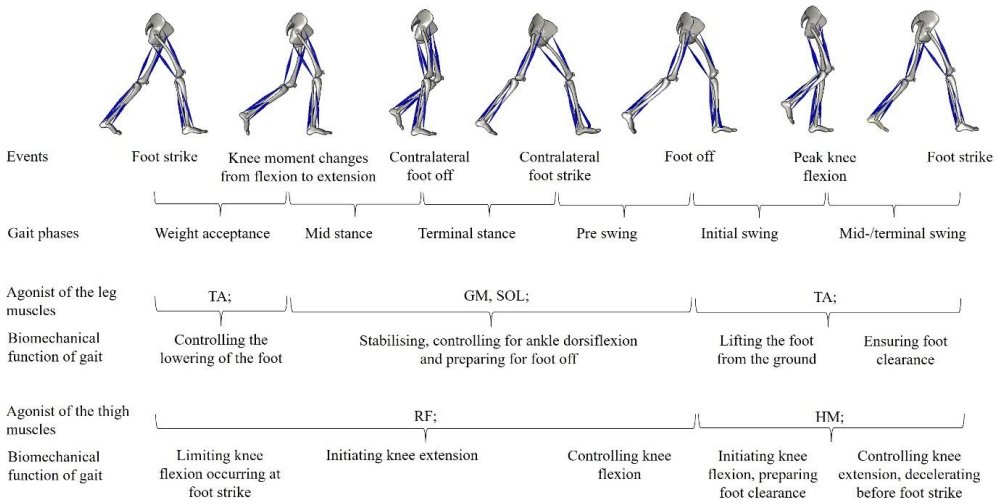

Figure 4. Illustration of a right leg's gait cycle with events separating the six gait phases. Below follows the definition of the agonist muscles of the leg and thigh, based on their biomechanical function during the different gait phases (72).

TA = Tibialis anterior; GM = Gastrocnemius medialis; SOL = Soleus; RF = Rectus femoris; HM = Hamstring medialis

2.3.1.1. Gait deviation index and asymmetry (Paper III)

Based on 3DGA data, the gait deviation index (GDI) (60) was calculated to represent the children's gait pattern. From every 2 % of the normalised gait cycle the kinematic variables pelvic anterior/posterior tilt, hike/drop, internal/external rotation, hip adduction/abduction, flexion/extension, internal/external rotation, knee flexion/extension, ankle dorsi-/plantarflexion and foot progression were extracted. Kinematic data from 26 typically developing children, obtained at the gait lab of NeXtMove core facility, NTNU, Trondheim, Norway, were used as reference material. The GDI's of the children with CP were obtained by comparing individual kinematics to the reference material. Mean GDI across legs were used for consecutive analyses. A GDI of 100 or above indicates absence of gait pathology, whereas every ten points below 100 corresponds to one standard deviation from the average typical gait.

Asymmetry was calculated according to Equation 5 using the GDI of the left and right leg (90). An asymmetry score of zero indicates perfect symmetry, whereas higher values reflect higher degrees of asymmetry.

Equation 5: $GDI\ asymmetry = \left(abs\left(\ln\left(\frac{GDI\ left}{GDI\ right} \right) \right) \right) \times\ 100$

Abs = absolute; GDI = gait deviation index; ln = logarithm.

2.3.2. Surface electromyography (Paper I and III)

Muscle activity was measured using surface electromyography (sEMG) concurrent with the 3DGA. Preparation of the skin and electrode placement were conducted according to the SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) guidelines (91). Myon wireless sEMG (Myon AG, Switzerland, Paper I and III), Cometa MiniWave sEMG (Bareggio, Italy, Paper III) or DelSys Trigno Avanti wireless sEMG system (DelSys Inc, Natick, MA, USA, Paper III) were used to record muscle activity bilaterally of the m. tibialis anterior (TA), m. soleus (SOL), m. gastrocnemius medialis (GM), m. rectus femoris (RF) and m. hamstring medialis (HM). The sEMG data was amplified by a 1000 gain with a sampling frequency of at least 1000 Hz. Data was visually inspected for artefacts and noise, and data of not satisfactory quality were excluded from the analyses regarding muscle activity. The raw sEMG data was band-pass filtered using an 8th order Butterworth filter with cut-off frequency at 30 and 300 Hz. The sEMG root mean square (RMS) values were computed with a 50 ms moving window. The highest RMS value throughout the gait cycle was used for normalisation. The sEMG-RMS amplitudes were extracted for every percent of the normalised gait cycle. Both absolute sEMG-RMS amplitudes (in µV) and normalised amplitudes (in %) were included in Paper I. Normalised amplitudes were included in Paper III.

2.3.2.1. Co-activation index (Paper I and III)

The co-activation index was calculated across three muscle pairs (TA/GM, TA/SOL, and RF/HM). In Paper I, two different methods for calculating the co-activation index were used, as shown in Equation 6 (29) and Equation 7 (92). These methods were chosen on the basis that they are commonly used in the literature when evaluating co-activation during walking in children with cerebral palsy. The co-activation index was calculated for each of the six gait phases and averaged across the included trials.

Equation 6: $Co - activation\ index\ I = 2 \times \frac{sEMG_{antagonist}}{sEMG_{agonist} + sEMG_{antagonist}} \times 100$

$sEMG_{antagonist}$ = lowest sEMG-RMS amplitude; $sEMG_{agonist}$ = highest sEMG-RMS amplitude.

Equation 7: $Co-activation\ index\ II = \frac{sEMG_{antagonist}}{sEMG_{agonist}} \times 100$

$sEMG_{antagonist}$ = lowest sEMG-RMS amplitude; $sEMG_{agonist}$ = highest sEMG-RMS amplitude.

In co-activation index I by Falconer and Winter (Equation 6) (29), the antagonist activity is normalised in relation to the total muscle activity, while in co-activation index II by Ikeda and colleagues (Equation 7) (92), the antagonist activity is expressed as a percentage of the agonist activity only. For both methods, a co-activation index of 100 % represents equal agonist and antagonist activity, while 0 % represents solely agonist activity. Definition of the agonist and antagonist muscles were based on the biomechanical function of the muscles during each gait phase (1, 72). Definitions of the agonist muscles of the leg and thigh and their functional role for each gait phase are presented in Figure 4.

Although commonly used, there are some limitations to both co-activation index I and II. They do not handle periods of low muscle activity well and may report on high levels of co-activation where both the agonist and antagonist muscles have high activity or low activity. Thus, the co-activation index poorly reflects level of muscle activity. In Paper III, another method for calculating the co-activation index was used, as shown in Equation 8 (93). This index is defined as the ratio between the agonist and antagonist muscles, multiplied by the sum of activity of both muscles. Thus, it better reflects on how the level of activity of the muscles is in relation to each other. The index can range between zero and 200, and a high co-activation index represents high levels of activity of both muscles, while a low co-activation index represents low levels of both muscles, or high levels of activity of one muscle along with a low level of activity of the other (93).

Equation 8: $Co-activation\ index\ III = \frac{1}{100}\sum_{p=1}^{p=100} \frac{RMS_{low}(p)}{RMS_{high}(p)} \times \left(RMS_{low}(p) + RMS_{high}(p)\right)$

RMS_{low} = lowest sEMG-RMS amplitude, i.e., the antagonist muscle; RMS_{high} = highest sEMG-RMS amplitude of each muscle pair, i.e., the agonist muscle, p = percentage of the normalised gait cycle; sEMG = Surface electromyography; RMS = Root mean square.

The index was calculated for every percent of the normalised gait cycle, providing a time series, before an overall average of the gait cycle was obtained, and subsequently averaged over the included trials and the three muscle pairs.

2.3.3. Energy expenditure during walking (Paper II and III)

Energy expenditure was measured during a 5-minute walk test (5MWT) (38). Speed (m/s) was calculated for each gait condition, dividing distance walked (m) over duration (s), and normalised according to Equation 2 (58). For the study of Paper II, this was conducted around a handball field of 40 times 20 meters or on a 400-meter track, and the children were instructed to walk as they normally do (i.e., self-selected, comfortable walking speed), slower and faster than normal, to jog and run. In addition, energy expenditure was measured during three minutes of rest, while sitting and standing. For the study of Paper III, the test was conducted on a 45-metre pathway and only during self-selected, comfortable walking. A portable indirect calorimeter, Metamax version II or IIIb (Cortex Biophysik GmbH, Leipzig, Germany) was carried on the children's back and was used to measure oxygen uptake (VO_2) and carbon dioxide production (VCO_2). The calorimeter was calibrated prior to testing according to the manufacturer's instructions. A facemask was placed over the mouth and nose of the child, carefully inspected for leakage.

In Paper II, the VO_2 and VCO_2 from the resting test and the 5MWT were averaged over a two-minute visually inspected steady state period. In Paper III, the VO_2 and VCO_2 from the 5MWT were averaged over a one-minute visually inspected steady state period during the last two minutes of the test. The respiratory exchange ratio (RER) was calculated over the corresponding period, dividing VO_2 by VCO_2. Resting and gross energy expenditure (J/kg/min) was calculated according to Equation 9 (94).

Equation 9: $Energy\ expenditure\ (J/kg/min) = (4.940 \times\ RER + 16.040)\ \times VO_2\ (ml/kg/min)$

RER = Respiratory exchange ratio; VO_2 = Oxygen uptake.

The lowest energy expenditure from the two resting test was subtracted gross energy expenditure to obtain net energy expenditure (J/kg/min). Gross and net energy cost (J/kg/m) were calculated by dividing gross and net energy expenditure by speed (m/min).

2.4. Statistical analysis

Normality distribution of the data was evaluated by Q-Q-plots prior to statistical analyses. The level of significance was set to $p < 0.05$, and borderline significance to $p < 0.1$. Statistical analyses were conducted using Matlab (R2018b, MathWorks, Inc., Natick, MA, USA) in Paper I and using SPSS (IBM Statistics for Windows, Version 27.0., Armonk, NY: IBM Corp) in Paper II and III. The statistical analyses of the main outcome measures for each of the three papers included in this thesis are described below.

2.4.1. Paper I: Deviations in muscle activity and co-activation in children with CP from typically developing children

Mixed model analyses were conducted to evaluate differences between the healthy legs of typically developing children and the affected legs of children with CP. The sEMG-RMS amplitudes and the co-activation index were set as dependent variables. Type of leg was set as a fixed effect and subject as a random effect to account for repeated measurements. Where the residuals were not normally distributed, data was log-transformed.

2.4.2. Paper II: The effect of speed, age, and body size on energy cost of walking

Mixed model analyses were conducted to evaluate the effect of within-subject variations of normalised speed on energy cost. In two separate models, gross and net energy cost were set as dependent variables and speed as independent variable. Subject was set as a random factor to account for repeated measures. Univariate regression analyses were conducted to evaluate the effect of between-subject variation of speed, age, and body size on energy cost for each gait condition. Gross and net energy cost were set as dependent variables, and speed, age, height, bodyweight, and BSA as independent variables. For curvilinear relations, quadratic terms of the independent variables were included. To ease comparisons to linear relations, separate linear regressions were conducted for ascending and descending parts of the quadratic curves.

2.4.3. Paper III: Relations between energy cost, gait pattern, gait asymmetry, and muscle co-activation

Mixed model analyses were conducted to evaluate the relation between the energy cost of walking and the GDI, GDI asymmetry, and the co-activation index. Subject was set as a random factor to account for repeated measures. Separate analyses with energy cost as dependent variable and age, height, bodyweight, BSA, GDI, GDI asymmetry, and co-activation index as independent variables were conducted. Secondly, analysis with energy cost as dependent variable and the highest correlating growth-related subject characteristic and GDI, GDI

asymmetry, and co-activation index was conducted. Thirdly, separate analyses with energy cost as dependent variable, the highest correlating growth-related subject characteristic together with GDI, GDI asymmetry, or co-activation index were conducted.

3. Results

The main findings of Paper I-III will be presented in the following section.

3.1. Paper I

The main aim of Paper I was to evaluate the effect of sEMG normalisation on the interpretation of muscle activity and co-activation, and to compare two methods of calculating the co-activation index. Differences in muscle activity and co-activation indices between healthy legs of typically developing children and affected legs of children with CP were examined using both absolute and normalised sEMG-RMS amplitudes.

First to describe the groups in general, the children with CP showed significantly reduced normalised walking speed, cadence, and step length compared to the typically developing children ($p < 0.02$). Visual inspection of the kinematic curves showed increased hip flexion during terminal stance and pre-swing for the children with CP, increased knee flexion during all gait phases other than pre- and initial swing. At foot strike and mid-/terminal swing, the ankle of the typically developing children was in neutral, whereas in plantarflexion for the children with CP. However, the children with CP showed increased dorsiflexion during late weight acceptance phase, midstance and the beginning of initial swing.

The findings showed that the overall average muscle activity pattern did not differ between using absolute and normalised sEMG-RMS amplitudes (Figure 5). However, the between-subject variation in both groups was more evenly distributed after normalisation. Both absolute and normalised amplitudes showed significant differences between typically developing children and children with CP in all muscles except in HM. However, in these four muscles, the deviations of children with CP were different using absolute and normalised amplitudes in 13 out of 24 cases (i.e., muscles times phases).

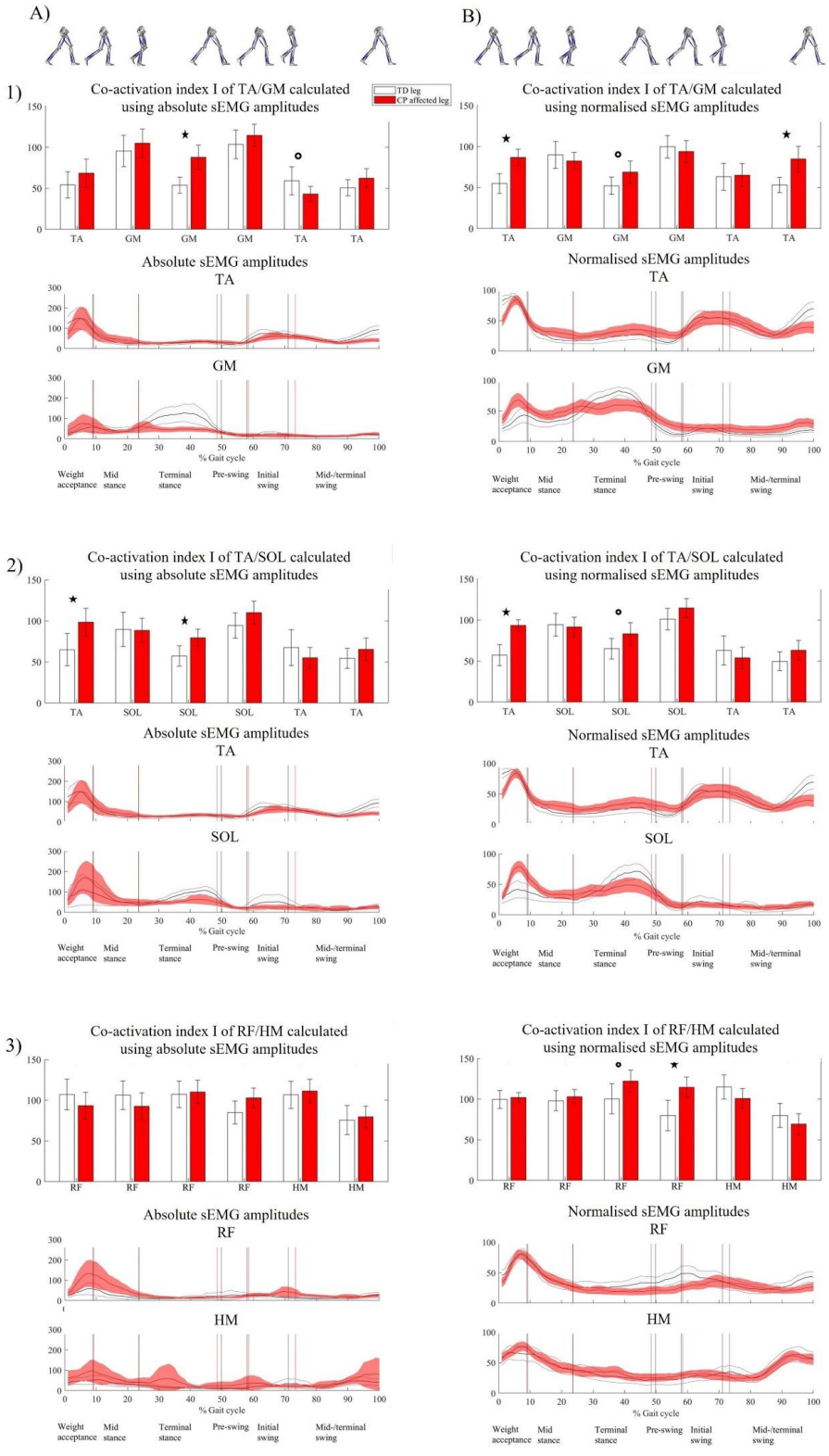
A)
B)
1)
Co-activation index I of TA/GM calculated using absolute sEMG amplitudes
TD leg
CP affected leg
Co-activation index I of TA/GM calculated using normalised sEMG amplitudes
TA
GM
Absolute sEMG amplitudes
Normalised sEMG amplitudes
% Gait cycle
Weight acceptance
Mid stance
Terminal stance
Pre-swing
Initial swing
Mid-/terminal swing
2)
Co-activation index I of TA/SOL calculated using absolute sEMG amplitudes
Co-activation index I of TA/SOL calculated using normalised sEMG amplitudes
SOL
3)
Co-activation index I of RF/HM calculated using absolute sEMG amplitudes
Co-activation index I of RF/HM calculated using normalised sEMG amplitudes
RF
HM

Figure 5. Graphical overview of the muscle activity and co-activation index I. Root mean square surface electromyographic amplitudes (sEMG-RMS, µV, A) and sEMG-RMS amplitudes normalised to peak sEMG-RMS obtained during the gait cycle (%, B) for each of the five muscles (TA (1 and 2), GM (1), SOL (2), RF and HM (3)). Time normalised to 0-100 % of the gait cycle. Presented as mean (solid line) with 95 % confidence interval (shaded area). The vertical lines represent the mean timing of the events dividing the gait cycle into six gait phases. The co-activation index of each of the three muscle pairs (TA/GM (1), TA/SOL (2) and RF/HM (3)) is presented for each of the six gait phases, presented as mean with 95 % confidence interval. The agonist muscle is indicated for each gait phase. The right legs' gait cycles are illustrated at the top. The six gait phases are named in the bottom of each subplot.
TA = Tibialis anterior; GM = Gastrocnemius medialis; SOL = Soleus; RF = Rectus femoris; HM = Hamstring medialis. Grey = typically developing children, red = children with cerebral palsy.

During weight acceptance phase, the RF muscle activity of the affected legs of children with CP was significantly increased using absolute sEMG-RMS amplitudes ($p = 0.04$). Using normalised sEMG-RMS amplitudes showed borderline significantly reduced TA muscle activity ($p = 0.07$), and significantly increased GM and SOL muscle activity ($p < 0.02$). During mid-stance, absolute sEMG-RMS amplitudes showed borderline significantly increased RF muscle activity ($p = 0.08$). During terminal stance there was a significantly reduced GM and SOL muscle activity using absolute sEMG-RMS amplitudes. Using normalised sEMG-RMS amplitudes showed significantly reduced GM and RF muscle activity ($p < 0.02$). There was borderline significantly reduced SOL muscle activity ($p = 0.06$). During pre-swing, normalised sEMG-RMS amplitudes showed significantly increased TA muscle activity and significantly reduced RF muscle activity ($p < 0.05$). During initial swing, absolute sEMG-RMS amplitudes showed significantly reduced TA, GM, and SOL muscle activity ($p < 0.05$). Significantly reduced SOL muscle activity was also seen using normalised sEMG-RMS amplitudes, in addition to significantly reduced RF muscle activity ($p < 0.05$). During mid-/terminal swing, absolute sEMG-RMS amplitudes showed significant reduced TA muscle activity ($p = 0.001$). This was also seen using normalised sEMG-RMS amplitudes, in addition to significantly reduced RF muscle activity ($p < 0.05$).

Both methods used for calculating the co-activation index and based on using both absolute and normalised sEMG-RMS amplitudes, showed increased values for the affected legs of children with CP compared to healthy legs of typically developing children (Co-activation

index I presented in Figure 5). Using absolute sEMG-RMS amplitudes calculating co-activation index I by Falconer and Winter (29) showed significantly increased co-activation index of TA/SOL for children with CP during weight acceptance phase ($p = 0.02$). This was also seen using normalised sEMG-RMS amplitudes for TA/SOL in addition to TA/GM ($p < 0.001$). During terminal stance, the co-activation index of TA/GM and TA/SOL were significantly increased using absolute sEMG-RMS amplitudes ($p < 0.01$), but these increases did not reach statistical significance using normalised sEMG-RMS amplitudes ($p < 0.08$). The co-activation index of RF/HM was borderline significantly increased during terminal stance using normalised sEMG-RMS amplitudes ($p = 0.053$). During pre-swing, using normalised sEMG-RMS amplitudes, the co-activation index of RF/HM was significantly increased ($p = 0.004$). During initial swing, there was a borderline significant reduction in the co-activation index of TA/GM using absolute sEMG-RMS amplitudes ($p = 0.099$). Using normalised sEMG-RMS amplitudes showed significant increase during mid-/terminal swing for TA/GM ($p = 0.002$).

Calculating the co-activation index II by Ikeda and colleagues (92) using absolute sEMG-RMS amplitudes showed significantly increased co-activation index of TA/SOL for children with CP during weight acceptance phase ($p = 0.03$), while the co-activation index of RF/HM showed a borderline significant decrease ($p = 0.08$). Using normalised sEMG-RMS amplitudes, the co-activation index of TA/GM and TA/SOL was significantly increased ($p < 0.001$). During terminal stance, there was a significantly increased co-activation index of TA/GM and TA/SOL using absolute sEMG-RMS amplitudes ($p < 0.01$). Using normalised sEMG-RMS amplitudes, the increased co-activation index of TA/SOL and RF/HM was borderline significant ($p < 0.09$). During pre-swing and mid-/terminal swing, the co-activation index of RF/HM and TA/GM respectively showed a significant increase using normalised sEMG-RMS amplitudes ($p < 0.004$).

3.2. Paper II

The aim of Paper II was to evaluate how two different methods of calculating energy cost of walking was affected by speed and growth-related subject characteristics.

Gross energy cost significantly decreased with increase in age, height, bodyweight, and BSA during all gait conditions ($p < 0.009$, Figure 6 A). For net energy cost, the relation to growth-related subject characteristics followed quadratic, concave shapes, and were mainly present during comfortable and fast walking (Figure 6 B). Separate analyses on the ascending and

descending parts of the curves showed that during slow walking, an increase in bodyweight was significantly related to increase in net energy cost up to the turning point of the curve at approximately 40 kg ($p = 0.048$). During slow, comfortable, and fast walking, an increase in height and BSA was significantly related to decrease in net energy cost after the turning point of the curve at approximately a height of 141 cm or a BSA of $1.21 m^2$ ($p < 0.05$). This was also seen during comfortable walking and jogging for age after the turning point of the curves at approximately ten years of age ($p < 0.03$) and during fast walking for bodyweight after the turning point at approximately 41 kg ($p = 0.007$).

Although non-significant, the relation between gross energy cost and within-subject variation in normalised speed followed a quadratic, convex shape with the turning point around comfortable/fast walking speed ($p = 0.2$, Figure 7 A1). Net energy cost showed a significant, positive linear relation to within-subject variation in normalised speed ($p < 0.001$ Figure 7 B1). Gross energy cost was more dependent on between-subject variation in normalised speed compared to net energy cost in all gait conditions. Gross energy cost significantly decreased with increase in speed during slow walking, jogging, and running ($p < 0.007$, Figure 7 A2). Net energy cost significantly decreased with increase in speed during running ($p = 0.02$ Figure 7 B2).

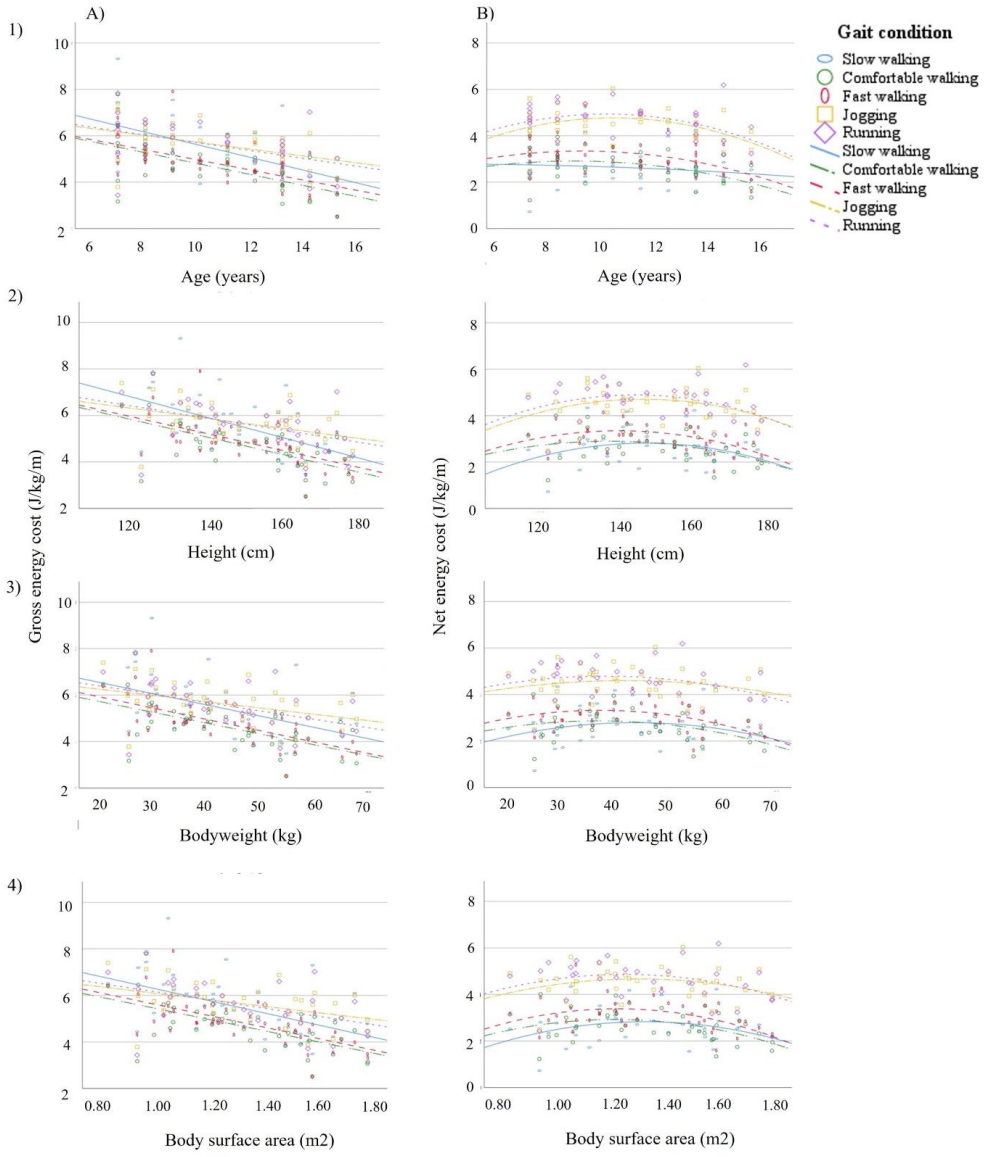

Figure 6. Gross energy cost (A) and net energy cost (B, both in J/kg/m) as a function of age (1), height (2), bodyweight (3), and body surface area (BSA, 4). Presented for the five gait conditions with fit lines of each condition.
Blue = slow walking, green = comfortable walking, red = fast walking, yellow = jogging, and purple = running.

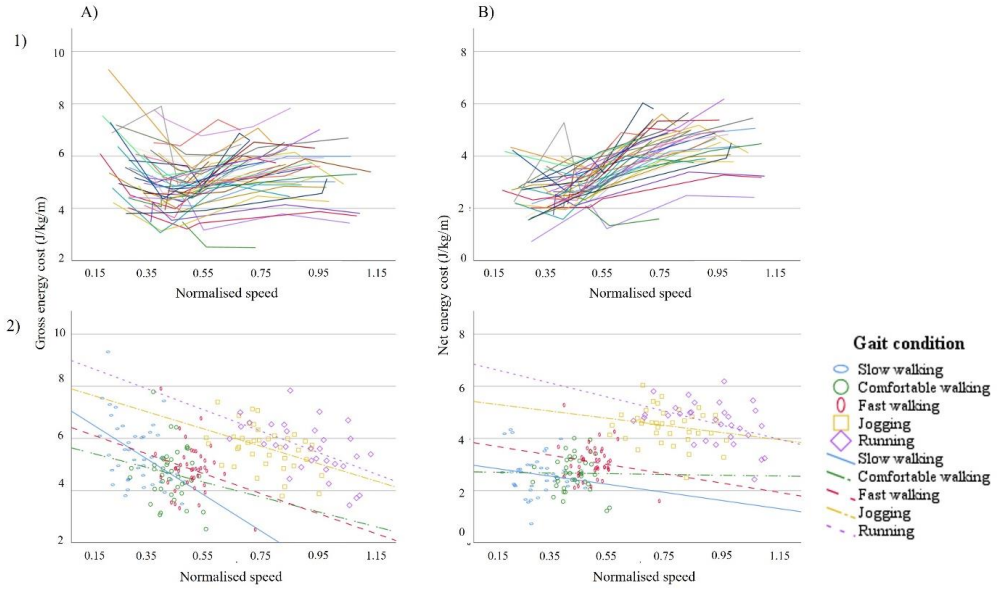

Figure 7. Gross energy cost (A) and net energy cost (B, both in J/kg/m) as a function of normalised speed, at individual level where each line represents one child (illustrating within-subject variation, 1) and for the five gait conditions with fit lines of each condition (illustrating between-subject variation, 2).
Applies to row 2: Blue = slow walking, green = comfortable walking, red = fast walking, yellow = jogging, and purple = running.

3.3. Paper III

The aim of Paper III was to evaluate the relation between energy cost of walking and gait pattern, gait asymmetry, and lower limb muscle co-activation in children with CP.

Of the growth-related subject characteristics age, height, bodyweight, and BSA, height was strongest related to energy cost, explaining 26 % of the variance ($p < 0.001$, Figure 8 A). Gait pattern and asymmetry were reflected through the GDI, where a decrease in GDI (i.e., increasing deviations in gait pattern) and increase in GDI asymmetry was significantly related to increase in energy cost, explaining 24 and 7 % of the variance, respectively ($p < 0.02$, Figure 8 B and C). The positive relation between the co-activation index and energy cost did not reach statistical significance ($p = 0.2$, Figure 8 D).

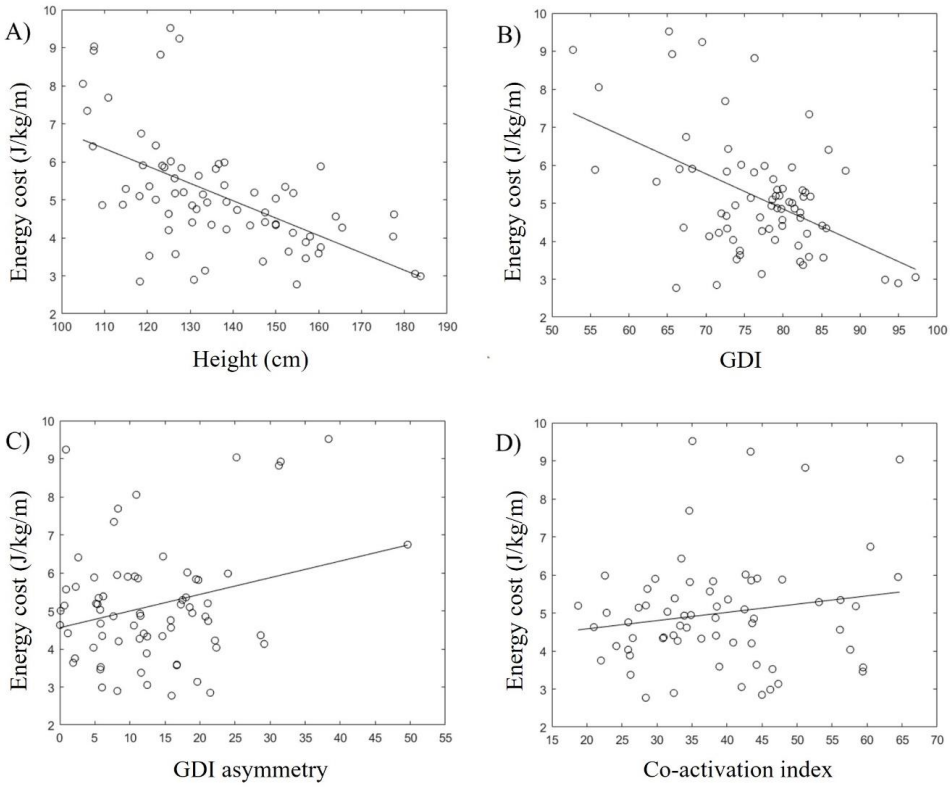

Figure 8. Energy cost (J/kg/m) as a function of height (A), gait deviation index (GDI, B), GDI asymmetry (C), and co-activation (CoA) index (D).

Including the highest correlating growth-related subject characteristic height to a multivariable analysis with GDI, GDI asymmetry, and co-activation index explained 38 % of the variance in energy cost ($p < 0.001$). Height and GDI were significant independent predictors ($p < 0.002$). Separate analyses for the dependent variables adjusting for height showed that GDI was significantly related to energy cost, explaining 43 % of the variance ($p < 0.001$). GDI asymmetry was borderline significantly related ($p = 0.09$).

4. Discussion

The overall purpose of this thesis was to gain further insight in commonly used methods for evaluating gait function in ambulant children with CP. The three papers included in this thesis aimed to evaluate various methods measuring explanatory and descriptive factors of gait function, how these factors interacted and consequences the methodological choices had for interpretation of the results.

The findings of Paper I showed that whether using absolute or normalised sEMG-RMS amplitudes affected the results and thus also the interpretation of muscle activity and co-activation index when evaluating group differences. However, the overall muscle activity pattern did not change between the two methods. Normalising the sEMG-RMS amplitudes reduced the between-subject variation but could also have reduced potentially relevant physiological variation. Although the two methods used to calculate the co-activation index, showed similar findings of increased co-activation index in children with CP compared to typically developing children, the deviations reached statistical significance during different gait phases using absolute and normalised sEMG-RMS amplitudes in the calculations.

The findings of Paper II showed that in typically developing children, gross energy cost was highly affected by between-subject variations in speed and growth-related subject characteristics compared to net energy cost. However, using gross energy cost may be more beneficial when evaluating treatment effect in clinical practice, as net energy cost may conceal changes in energy cost due to changes in gait function and thus speed. Although energy cost is normalised to bodyweight, the effect of growth-related subject characteristics was still present for both gross and net energy cost.

The findings of Paper III showed that gross energy cost of walking in children with CP was highly affected by gait deviation, reflected through the GDI, adjusted for height as the highest correlating growth-related subject characteristic. Neither gait asymmetry nor muscle co-activation were related to gross energy cost of walking.

A general discussion of the most important findings of Paper I-III will be given in the section below, followed by methodological and ethical considerations.

4.1. Main results

4.1.1. Normalisation of surface electromyography (Paper I)

Evaluating muscle activity during walking is useful in clinical practice when evaluating gait function, for treatment prescriptions, and evaluation of treatment effect (3). Therefore, the use of sEMG measurements is commonly included as part of the 3DGA. The sEMG amplitudes represent the action potentials produced by the muscle, but several unwanted factors may affect the measurements and cause non-physiological between-subject variation (3, 65). These factors are related to the specifications regarding the electrodes used, or the muscle tissue. In an attempt to reduce this unwanted variation and be able to compare physiological differences between groups, individuals or sessions, the sEMG-RMS amplitudes were normalised to the peak amplitude obtained during walking. The findings of Paper I showed that the overall average muscle activity pattern between the absolute, non-normalised sEMG-RMS amplitudes and the normalised amplitudes did not change. Although normalising the amplitudes in general reduced the between-subject variation, potential clinically relevant physiological variability were reduced. This has also been reported in previous research as a consequence of normalising to a peak obtained during a dynamic task such as walking (68). Large between-subject variation was seen during the weight acceptance phase and terminal stance for the typically developing children, and during the weight acceptance phase for children with CP using absolute sEMG-RMS amplitudes (Figure 5). This variability was eliminated after normalisation (Figure 5). However, the rest of the non-normalised gait cycle showed relatively low between-subject variation, which may indicate low non-physiological variation in the measurements.

As mentioned, the overall average muscle activity pattern did not change after normalisation, which is in correspondence with findings previously reported in healthy adults (70, 72, 73) and patients after stroke (72, 73). Despite this, using absolute and normalised sEMG-RMS amplitudes showed different deviations of CP from typically developing children, which should be considered when interpreting the results clinically. Increased amplitudes during one gait phase for children with CP using absolute sEMG-RMS changed to reduced amplitudes in another gait phase after normalisation, and vice versa (Figure 5). An example of this is the muscle activity of TA being somewhat reduced in the children with CP from the initial swing phase to early weight acceptance using both absolute and normalised amplitudes, but the deviations reached statistical significance during different phases. Where both initial and mid-/terminal swing phase were significantly decreased using absolute sEMG-RMS amplitudes, this shifted using normalised amplitudes towards mid-/terminal swing, and a borderline

significance during the weight acceptance phase. Additionally, TA muscle activity was significantly increased during pre-swing after normalisation. This could either be a result of normalisation, or a physiological compensation for the reduced activity seen during swing phase. Moreover, in typically developing children, the calf muscles (GM and SOL) were particularly active during the weight acceptance phase, terminal stance, and initial swing. The calf muscle activity in children with CP seemed somewhat increased during weight acceptance phase, but this was only statistically significant after normalisation. During terminal stance and initial swing, the calf muscle activity was significantly decreased for children with CP using absolute amplitudes. However, after normalisation, only GM during terminal stance and SOL during initial swing remained significantly decreased. The normalisation process should be kept in mind when interpreting data. Solely using sEMG-RMS amplitudes indicates reduced activity of the calf muscles during terminal stance, while normalised amplitudes indicate increased activity during weight acceptance phase. This then poses the question of whether we should treat overactivity of the muscles with botulinum toxin or muscle weakness with strength training?

4.1.2. Calculations and interpretations of the co-activation index (Paper I and III)

There are various methods used to calculate the co-activation index, and a total of three different methods were included in the work of this thesis. In Paper I, comparisons of two commonly used methods were conducted, using both absolute and normalised sEMG-RMS amplitudes. Both methods showed the same significant deviations of CP from the typically developing children. However, compared to co-activation index I by Falconer and Winter (29), co-activation index II by Ikeda and colleagues (92) showed, in general, considerably higher values. Further, these values were often above 100 %, indicating higher antagonist muscle activity compared to the agonist muscle. In co-activation index I by Falconer and Winter, the antagonist activity is expressed as a percentage of the total muscle activity, and multiplied by two to counterbalance the activity of the agonist muscle activity (29). In co-activation index II by Ikeda and colleagues, the antagonist activity is expressed as a percentage of agonist muscle activity (92). This explains the higher values of co-activation index II. The between-subject variation was greater using co-activation index II, and the variables had to be log transformed prior to analyses. On this basis, co-activation index I by Falconer and Winter (29) was considered more applicable.

However, a potential shortcoming with the use of both these methods is that during dynamic movements, such as walking, they are largely affected by periods where both the agonist and

antagonist muscles have low activity. Therefore, the different gait phases were investigated separately in Paper I. Although a co-activation index of 100 % indicate equal activity of the agonist and antagonist muscles, it may be attributed to high levels of activity in both muscles as well as low activity. This may be exemplified in the findings of Paper I, where relatively low muscle activity in TA, GM, and SOL during pre-swing phase resulted in high values of the co-activation index (Figure 5 1 and 2). Moreover, in periods with low activity in both muscles, a small increase in antagonist activity would cause an increased co-activation index. To interpret these methods requires a thorough evaluation of the simultaneous underlying muscle activity, in order to decide whether the increased co-activation is of clinical relevance.

Co-activation index III proposed by Rudolph and colleagues (93) was included in Paper III. This index provides a time-varying value and expresses the antagonist activity as a percentage of total activity, in addition to the agonist activity. Thus, a high value would represent high activity levels of both agonist and antagonist muscles. In contrast, a low value would represent low activity levels of both muscles, or high activity level of one muscle along with low activity level of the other muscle. This index is therefore better to use when calculating an overall co-activation index. An overall index was considered more appropriate when conducting a correlation study, as in Paper III, in order to reduce the number of variables included. The findings related to co-activation index I by Falconer and Winter (29) and co-activation index III by Rudolph and colleagues (93) will be discussed below.

Although the co-activation values of Paper I and III are not directly comparable as two different methods were used, both studies showed abnormal levels of co-activation index in children with CP. The findings of Paper I showed that there were phases where the typically developing children had low agonist activity and high co-activation index. In these phases, even higher co-activation index in children with CP cannot be expected. During weight acceptance phase, terminal stance, initial and mid-/terminal swing, the typically developing children showed a clear burst in the agonist sEMG-RMS amplitudes of TA/GM and TA/SOL muscle pair and relatively low co-activation indices (below 75 %, Figure 5). This was seen using both absolute and normalised amplitudes. For children with CP, the co-activation index was increased for approximately 50 % of these gait phases, which is in accordance with previous research on co-activation during walking in children with CP (30, 33). In Paper III, the co-activation index ranged between 19 and 65, with an average of 39. These values correspond to previously reported findings of leg and thigh muscle co-activation in children with CP, which were reported as being significantly higher compared to typically developing children (32).

The findings of Paper I showed that the interpretation of group differences of the co-activation index during separate gait phases was affected by the handling of the sEMG data. The different deviations seen using absolute and normalised sEMG-RMS amplitudes, affected the calculations of the co-activation index and provided different pictures on how and when children with CP deviated from typically developing children. Using both absolute and normalised sEMG-RMS amplitudes to calculate the co-activation index showed increased co-activation of the calf-muscles (TA/GM and TA/SOL) in children with CP during weight acceptance. This increase did not, however, reach statistical significance for TA/GM using absolute amplitudes. Although no deviations in the underlying muscle activity was seen using absolute amplitudes, significantly increased antagonist muscle activity (GM and SOL) was seen after normalisation, in addition to somewhat decreased agonist activity (TA). These findings indicate, at least for some of the children, that the increased index was due to increased co-activity of the calf-muscles. During terminal stance, however, using both absolute and normalised amplitudes increased co-activation index was seen, together with decreased agonist muscle activity (GM and SOL). There was no increased antagonist activity (TA), indicating that the increased index was due to muscle weakness rather than increased co-activity. This was also seen using normalised amplitudes during terminal stance and pre-swing for the co-activation index of RF/HM and during mid-/terminal swing for the co-activation index of TA/GM, where increased co-activation index was seen together with reduced agonist muscle activity (RF and TA) and not increased antagonist muscle activity (HM and GM). Approximately 90 and 70 % of the significant deviations in absolute and normalised sEMG-RMS amplitudes, respectively, were attributed decreased amplitudes. This indicates that reduced muscle strength is an important contributor to the altered muscle activity and increased values of the co-activation index. Moreover, these findings highlight that without knowledge of the underlying muscle activity, it is challenging to interpret causes and implications of an increased co-activation index.

In Paper I, the co-activation index was calculated for each muscle pair and for each gait phase and aimed to get a detailed insight into how muscle co-activation and the underlying muscle activity deteriorated during the different phases of a gait cycle. It has been argued that it is beneficial to evaluate gait pattern by phases, especially when evaluating abnormalities, as the implication of one joint's motion compared to another joint's motion will vary among the gait phases (1). Based on the findings of Paper I, evaluating the co-activation index during separate gait phases appeared appropriate, as the deviations of CP from typically developing children

differed between the gait phases. In Paper III, an overall co-activation index averaged across all muscle pairs was reported, as the aim was to get insight into how co-activation in its entirety affected energy cost of walking. If an effect would have been detected, it would have been of interest to break down the co-activation index to see whether, and which, specific gait phases were crucial and for which muscles.

4.1.3. Calculations of energy cost of walking (Paper II)

The overall gait function was reflected through energy cost of walking. In children with CP, the energy cost of walking is often increased, and treatment is therefore commonly aimed at reducing this (37, 41, 48, 49, 95). However, the different methods of calculating the energy cost of walking have different challenges, which affects the results and must be considered when interpreting them.

The challenges regarding growth-related subject characteristics, such as age and body size, will be discussed in this section. The findings of Paper II showed that gross energy cost of typically developing children was highly affected by age and body size. This is in accordance with previously reported findings of children with CP and typically developing children, where gross energy cost decreased as age and body size increased (37, 82, 96). Compared to gross energy cost, net energy cost has previously been reported to show a similar, but weaker relation to age and height for both children with CP and typically developing children (37). The findings of Paper II showed that net energy cost was less affected, but the relation followed a concave shape. This quadratic relation indicates that, until a given age or body size, the energy efficiency of walking decreases. Similar findings have been reported for children with CP, suggesting that gait is least efficient around the age of 12 (97). In the study of Paper II, the turning point of the curve was shifted somewhat to the left, around the age of ten. Performing analyses on ascending and descending parts of the curves showed that the effect of age and body size was approximately between 25 – 50 % less for net energy cost compared to gross energy cost for the older, taller, and heavier children. For the younger, smaller children, the effect of age and body size was minimal, but there was a large spread in the data, which may reflect the challenges of measuring resting energy expenditure.

Although energy cost is normalised to speed, the findings of Paper II showed that there still was an effect. And a question is whether we really want to eliminate all effect of speed. By measuring energy expenditure during different gait conditions, it is possible to evaluate how different speeds potentially affect the different measures of energy cost. In the study of Paper

II, the typically developing children were able to comply with the speed instructions, as the speed significantly increased between the five gait conditions: slow, comfortable, and fast walking, jogging, and running. Walking at a self-selected, comfortable walking speed is thought to be most energy efficient with an appropriate combination of step length, frequency, and width (98). Energy expenditure is expected to increase with increasing deviations of these parameters, which the findings of gross energy cost confirmed. Gross energy cost was significantly higher during slow walking, jogging, and running, compared to comfortable walking. Net energy cost on the other hand increased from slow walking up to running. Which indicates that comfortable walking speed was not the most energy efficient. The reason for this can be explained by the fact that gross energy cost includes resting energy expenditure, which has a more prominent contribution during slow walking, and the relative contribution of cost required for movement increases with increasing speed. Clinical evaluations and gait tests are usually conducted at self-selected, comfortable walking speed. Net energy cost has been reported to be less affected of speed during this condition, and has therefore been recommended over gross energy cost (79). However, walking speed is related to functional ability, and an effect of treatment in children with CP is precisely improved walking speed (99-101). The findings of Paper II indicate that where improvements in gait function lead to improvements in walking speed, and thus reductions in energy cost, this may potentially be concealed using net energy cost. The use of gross energy of walking may therefore be recommended when evaluating clinically relevant changes in children with CP, as it was less affected of individual variations in speed. This is supported by previous research, arguing gross energy cost is a more sensitive measure with higher reproducibility compared to net energy cost (38, 83).

4.1.4. Factors of gait function affecting energy cost of walking (Paper III)

Overall, results from Paper I showed that children with CP had lower normalised walking speed and shorter normalised step length compared to typically developing children. This is in accordance with previous research (16, 102). Further, although not statistically tested, the children with CP showed increased hip flexion during terminal stance and pre-swing, increased knee flexion during the entire stance phase and mid-/terminal swing, increased plantarflexion at foot strike and during mid-/terminal swing, which are also in accordance with previous reported findings (102). In Paper III, children with CP showed a mean GDI of 77 (95 % CI: 75-79), which agrees with the kinematic deviations seen during walking. This GDI corresponds to approximately two standard deviations away from the typical gait pattern, similar to previously reported results for children with CP at this functional level (103-105). Previous

research has reported significant decreases in GDI with increasing movement disability, reflected through increase in GMFCS levels and reduced motor capacity in standing evaluated by the Gross Motor Function Measure (GMFM) (39, 103-105). There were no differences in GDI between GMFCS level I and II in our study sample, but this could be explained by the fact that only five out of 40 children were classified with GMFCS level II. However, the findings of Paper III showed that GDI in combination with height, explained 40 % of the variation in energy cost. These findings indicate that the GDI is a valid method to detect differences in gait function, even among the least affected and well-functioning children with CP. In support of our findings of deviating gait pattern being related to increments in gross energy cost, significant relations between increased net energy cost and reduced knee and hip extension in children with CP have been reported (42). Moreover, the findings of Paper II showed that for typically developing children, with an increase in self-selected speed within the five different speed conditions, gross energy cost decreased. This is in agreement with research on children with CP, reporting that better gait function is related to reduced gross energy cost of walking and increased walking speed (39, 41).

In Paper III, gait asymmetry was reflected through the natural logarithm of the difference between the right and left leg's GDI. Asymmetry may be quantified using various measures, but they are highly correlated and choice of measure would thus probably not have affected the results (106). The gait asymmetry ranged between 0 and 50, where the mean score was 13 (95 % CI: 11-16). Previous research on a healthy, adult population and stroke patients have reported that asymmetric gait was related to increase in energy expenditure of walking (43-45). However, this was not seen in children with CP. An explanation for this could be that the mean gait asymmetry score was close to the score of 10, which is considered to be the limit of clinical relevance (107).

Although excessive muscle co-activation has been reported in children with CP, there is no agreement on the role or significance for daily function (28, 69). The findings of Paper III agrees with a study reporting no relation between thigh muscle co-activation and oxygen uptake (47), but are contrary to a study reporting a positive relation between increased leg and thigh muscle co-activation and oxygen uptake (31). Direct comparisons between studies are challenging, as different methods were used for calculating the co-activation index and to express energy expenditure of walking. However, it emphasizes the complexity of using the co-activation index and the uncertainties regarding excessive co-activation and how it affects gait function. Nevertheless, the findings of Paper I indicated that reduced muscle strength was

an important factor for the increased co-activation index, whereas the findings of Paper III showed no relation to energy cost of walking. Thus, based on the findings of this thesis, it appears as the excessive muscle co-activation acts as a physiological mechanism rather than a pathological one.

4.2. Methodological considerations

Methodological considerations of the work included in this thesis will be discussed in the following section.

In this thesis, the main target group was ambulant children with CP. These children were recruited as part of a randomized controlled trial (85) and from the regular outpatient follow-up at the local hospital. Children with GMFCS level I and II were part of the studies of Paper I and III included in this thesis. The relatively homogeneous group of children represents a large party of the ambulant children diagnosed with spastic CP. Both children diagnosed as unilateral and bilateral were included, and visual inspection did not discover systematic differences between the groups in any of the outcome measures. Moreover, in Paper III, gait asymmetry showed no effect on energy cost, supporting the choice of merging the groups.

There were some challenges with regards to the sEMG measurements. Although proper skin preparations and electrode placements were done according to the guidelines (91), some sEMG data were excluded due to poor signal quality. In some cases, the movement artefact was easier to detect as simultaneously video recordings could identify external disturbances affecting the signal. However, in other cases it was challenging to distinguish between movement artefacts and spastic activity. For this, thorough investigations, and evaluations of the sEMG signal was conducted before the decision whether to include or exclude was made. It is difficult to know whether the decisions were made on the correct basis as we do not know the truth, but this highlights the challenges of conducting sEMG measurements and the importance of visually controlling data prior to analyses.

Conducting gas-exchange measurements includes wearing a face mask for a longer time period, which may feel uncomfortable. In addition, the equipment was carried on the children's back, which altogether potentially could affect the gait as it may feel unnatural. However, the walk test lasted for five minutes, which allowed some time for familiarisation with the equipment and to ensure that a steady state condition in the measurements of VO_2 and VCO_2 was reached.

High within-subject variation has been reported for both typically developing children and children with CP doing resting energy expenditure measurements (38, 83). The advised

procedure with abstinence from food 10-12 hours prior to testing, 5-10 minutes of rest and familiarization before 12-16 minutes of measurements in order to ensure high reproducibility (108) was not followed in the study of Paper II. This may have affected the results, but it is not feasible to follow the standard conditions when testing children. However, to provide valid resting energy expenditure measurements in Paper II, two protocols were conducted, one sitting and one standing, where the test with the lowest value was used for subsequent analyses.

In Paper III, data from three different labs with different equipment was merged. Prior to analyses data was visually inspected. And no differences in kinematic variables or energy cost measurements were revealed between the three different marker setups of the 3DGA nor between the two version of the Metamax portable calorimeter.

4.3. Ethical considerations

Prior to inclusion, the parents or guardians of the children had to provide written consent. All data were unidentified using participant codes. The children's participation was based on interest and not on referral. The responsible personnel were all trained and experienced using the test procedures. All children were carefully observed during the testing sessions to detect any discomfort. Where children reported discomfort, the testing was paused. The responsible personnel asked if, and when, the child wanted to continue, and it was accepted if the child wanted to end the test. A few children became too tired and lost motivation during the session and were therefore unable to complete it. This was accepted and managed by the responsible personnel. The children could withdraw from the studies at any time, without justification. Given the purpose of the studies, the scope of the testing sessions and requirements of the participants were considered acceptable.

5. Clinical implications

Despite a homogenous group of well-functioning children with CP, the work of this thesis reported findings of relevance for this specific group. The findings of Paper I and III support previous research reporting that children with CP have a deviating gait pattern, altered muscle activity, and increased co-activation index. Moreover, even within the least affected children with CP, gait deviations may be of significance for daily activity and participation.

However, the findings also showed that one must be careful in drawing conclusions and comparisons without considering the method that underlies. Using sEMG measurements is useful for evaluating muscle activity during specific phases of gait, but when evaluating differences between groups or evaluating changes after treatment, the choice of method for handling the sEMG data affect the results. To make decisions on whether the measured muscle activity is deviating and in which manner, to use both absolute and normalised data is recommended. Particularly since normalisation potentially also reduce relevant physiological variation that could be of clinical relevance. Further, the increased co-activation index was for the most explained by the inability to sufficiently activate the agonist muscle, suggesting a focusing area of treatment should be strength training rather than reducing overactivity by the use of botulinum toxin-A. Moreover, as the co-activation index showed no relation to energy cost of walking, suggest that muscle co-activation not necessarily should be treated or considered as a pathological mechanism, hampering and restricting movement.

To use gross energy cost when evaluating changes in gait function over time among children appears to be a favourable method. Both gross and net energy cost were affected by age and body size to a greater or lesser extent, but gross energy cost was less affected of the individual child's variation in speed and may thus better detect changes in energy cost due to changes in gait function and thus speed. Moreover, increasing deviations in gait pattern were strongly related to increases in gross energy cost. Which also suggests that the GDI can be a useful method to detect differences in gait function in children with CP, GMFCS level I and II.

6. Future research

Research within the field of children with cerebral palsy is commonly related to the ability of walking and daily activity. Which is an important area as gait function has impact on the children's social participation and quality of life. However, making proper interpretations is essential for proper clinical decision making. Therefore, increased knowledge of the methodology is necessary.

The work of this thesis has aimed to gain further insight into commonly used methods for evaluating gait function in children with CP. The findings have contributed to the development of the research field and provided information and recommendations that is useful in order to formulate and answer relevant future research questions.

Paper I introduced the consequences normalisation of the sEMG data has for interpretation of muscle activity and co-activation. However, to conclude whether to normalise the data or not is challenging, and future research should aim to relate the use of both methods to functional outcomes to better answer which method is more beneficial in interpreting altered muscle activity and co-activation.

Paper II showed that gross and net energy cost are affected differently by within- and between-subject variations in speed and body size. In future research, longitudinal studies should be conducted evaluating how short- and long-term changes in body size affects the interpretation of both gross and net energy cost. Moreover, how individual changes in gait function and speed affects energy cost of walking in children with CP should also be evaluated in future research.

Paper III showed that only deviations in gait pattern was related to increased energy cost, while neither gait asymmetry nor co-activation were related. However, it cannot be concluded that treatment induced improvements in gait function, indeed would reduce energy cost of walking, nor that reducing gait asymmetry and muscle co-activation would not make walking easier. Thus, future research should aim to conduct longitudinal studies evaluating changes in gait function with changes in energy cost to better evaluate how they are related. This would add new and valuable knowledge to the field.

7. The role of the Ph.D. candidate

This Ph.D. project was part of the WE-study, which is a double blinded, randomised control trial (85). The data collection of the WE-study began in September 2015, and I started my Ph.D. in October 2017. The data collection that formed the basis of this Ph.D. project was developed by the project management, including my supervisors, Karin Roeleveld and Siri Merete Brændvik. I designed and conceptualised scientific problems for three papers in collaboration with my supervisors. I was the main author of the three papers included in this thesis and I performed statistical analyses, interpreted the results, wrote the first draft of the manuscript, was responsible for the revisions and submissions of the papers. Originally, the focus area was to evaluate factors of gait function in relation to treatment effects of botulinum toxin-A. I have adjusted and created new research questions along the way, as challenges have arisen. First due to delays in the recruitment of participants for the WE-study, and subsequently as the global pandemic struck in 2020, the data collection was put on hold and caused further delays. A challenge resulting from this is that the data material used for the different papers were not designed to address those specific aims. However, the work of this thesis has contributed to increasing insight that will be useful at a later stage of the WE-study, evaluating the effect of botulinum toxin-A treatments on gait function in ambulant children with CP.

Regarding my contribution to the WE-study, I received training so I could contribute to the data collection at one of the test sites of the study, the gait lab of NeXtMove core facility at NTNU, Trondheim. Further contribution to the project included data processing and management. Moreover, I developed a program used to automate the transfer and extraction of 3DGA data, performing signal processing and calculations. I have gained very good experience with the procedures of all studies included, and of operating equipment used, and handling various software.

8. Conclusions

The work of this thesis contributes to increased knowledge regarding methods used for evaluating gait function in ambulant children with CP. In summary, the findings have demonstrated that the interpretation of both muscle activity and co-activation was affected by whether absolute or normalised sEMG data were used, when evaluating group differences. But independent of normalisation or method used for calculating the co-activation index, children with CP showed increased values compared to typically developing children. The deviations did, however, occur at different phases of gait using absolute and normalised sEMG data. Moreover, evaluating the underlying muscle activity of the increased co-activation index showed that the increase was mainly due to decreased agonist muscle activity, rather than increased antagonistic co-activity. These findings indicate that the cause of co-activation could be a physiological function, compensating for the reduced muscle strength. This may explain why there was no relation between co-activation index and gross energy cost of walking in children with CP. Gait asymmetry was also not related, while an increase in gait pattern deviation, reflected through the GDI, was significantly related to an increase in gross energy cost of walking. The study sample consisted of a homogeneous group of well-functioning children with CP, and the GDI proved to be an applicable method for detecting differences in gait function even within the least affected children. However, when evaluating changes over time, changes in growth-related subject characteristics must be considered. Both net and gross energy cost showed to be affected of age and body size in typically developing children. And although net energy cost was less affected, the relation was quadratic, suggesting gait becomes less energy efficient up to a certain age and body size. Gross energy cost was more affected by between-subject variations in speed compared to net energy cost, implying that with decreasing gait function and walking speed, the energy cost of walking increases. Net energy cost was more affected by within-subject variation in speed, and a consequence is that a decrease in energy cost due to improvements in gait function and thus walking speed, would potentially be concealed.

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Paper I

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METHODS
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Surface Electromyography Normalization Affects the Interpretation of Muscle Activity and Coactivation in Children With Cerebral Palsy During Walking

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Investigating muscle activity and coactivation with surface electromyography (sEMG) gives insight into pathological muscle function during activities like walking in people with neuromuscular impairments, such as children with cerebral palsy (CP). There is large variation in the amount of coactivation reported during walking in children with CP, possibly due to the inconsistent handling of sEMG and in calculating the coactivation index. The aim of this study was to evaluate how different approaches of handling sEMG may affect the interpretation of muscle activity and coactivation, by looking at both absolute and normalized sEMG. Twenty-three ambulatory children with CP and 11 typically developing (TD) children participated. We conducted a three-dimensional gait analysis (3DGA) with concurrent sEMG measurements of tibialis anterior, soleus, gastrocnemius medialis, rectus femoris, and hamstring medialis. They walked barefoot at a self-selected, comfortable speed back and forth a 7-m walkway. The gait cycle extracted from the 3DGA was divided into six phases, and for each phase, root mean square sEMG amplitude was calculated (sEMG-RMS-abs), and also normalized to peak amplitude of the linear envelope (50-ms running RMS window) during the gait cycle (sEMG-RMS-norm). The coactivation index was calculated using sEMG-RMS-abs and sEMG-RMS-norm values and by using two different indices. Differences between TD children's legs and the affected legs of children with CP were tested with a mixed model. The between-subject muscle activity variability was more evenly distributed using sEMG-RMS-norm; however, potential physiological variability was eliminated as a result of normalization. Differences between groups in one gait phase using sEMG-RMS-abs showed opposite differences in another phase using sEMG-RMS-norm for three of the five muscles investigated. The CP group showed an increased coactivation index in two out of three muscle pairs using sEMG-RMS-abs and in all three muscle pairs using sEMG-RMS-norm. These results were independent of index calculation method. Moreover, the increased coactivation indices could be explained by either reduced agonist activity or increased antagonist activity. Thus, differences in muscle activity and coactivation index between the groups change after normalization. However, because we do not know the truth, we cannot conclude whether to normalize and recommend incorporating both.

Keywords: surface electromyography, muscle activity, coactivation, cerebral palsy, gait, amplitude normalization

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INTRODUCTION

Surface electromyography (sEMG) is used to measure muscle activity and may be used clinically to investigate muscle function during activities such as walking in conditions affecting the neuromuscular system (1). In children with cerebral palsy (CP), three-dimensional gait analysis (3DGA) with simultaneous sEMG measurements is often conducted to get insight into muscle activity as part of treatment prescriptions and evaluation of treatment effect. Cerebral palsy, the most common cause of physical disability in childhood, is characterized by insufficient motor activity such as reduced muscle strength and poor balance, but also increased motor activity such as spasticity and excessive muscle coactivation (2, 3). Those features of children with CP may impair function in general and gait in particular. Compared to typically mature gait, children with CP have shown deviations in different gait phases and greater physiological variability during walking (4, 5).

Muscle coactivation, defined as simultaneous activity of agonist and antagonist muscles crossing the same joint, is a normal motor control strategy to increase joint stability and coordination (6, 7). During complex tasks, such as walking, coactivation occurs prominently at certain phases during the gait cycle, ensuring stability and allowing efficient walking (8). Excessive and/or prolonged coactivation, however, may cause inefficient movements by reducing flexibility and adaptability and increasing the loading of the joints, and thus, energy cost (6, 7, 9, 10). Therefore, a main treatment goal for ambulatory children with CP is to make walking easier, through, for example, normalizing altered muscle activity and coactivation (11). However, the role of the increased coactivation in children with CP has been questioned in several studies, and the findings are conflicting (9, 12–14). Coactivation may be quantified using a coactivation index, which is a value calculated to represent the amount of coactivation between the given muscles. Potential challenges when it comes to investigating and interpreting muscle activity and coactivation, which also may explain the diversity of findings, could be choice of approach for handling the sEMG data and calculations of the coactivation index (15).

The amplitude of the sEMG represents the number of motor units recruited and their firing rate and pattern (16). However, the amplitude is affected by several other factors, such as the size, shape, and material of the electrode and the distance between the electrodes and the active muscle tissue, largely determined by the subcutaneous fat layer, causing nonphysiological between-subject variability. To adjust for this variability and allow for comparison between participants, sEMG signals are commonly normalized to a standard value, usually peak sEMG obtained during a maximal voluntary isometric contraction (MVIC) (15). Children, and especially children with neurological conditions, such as CP, may have difficulties in performing an MVIC because it is challenging to voluntarily produce maximal muscle activation (12, 13, 17). In this case, normalizing to peak sEMG obtained during the specific task to be evaluated, that is during walking, is considered a feasible and appropriate approach (15, 18). However, the peak sEMG during walking may occur at different phases of gait for typically developing (TD) children and children with CP, for example, because of reduced muscle strength or spasticity. This may have consequences for the normalized sEMG in the other phases of gait, which in turn could affect the interpretation of muscle activity. Therefore, in people with neurological conditions, it is also suggested to not normalize the sEMG data (13, 19–22).

The different ways of normalizing sEMG data are used interchangeably when investigating muscle coactivation. Although the majority of the studies in the literature usually normalize the sEMG data prior to calculating the coactivation index (9, 12, 13, 23, 24), using absolute data has been suggested to be beneficial because it prevents unnecessary data transformation (19). Calculations are often done using a ratio, and therefore, normalizing the sEMG data prior may normalize the data twice. In addition, Lamontagne et al. (20) argue for using absolute values when calculating the coactivation index in populations with weak muscles, because the sEMG values could be low during walking, and normalizing to a percent of a peak value before coactivation index calculations in such cases may lead to an overstated index.

Similar to this lack of standardization of sEMG normalization, different indices are used for calculating the coactivation index. For instance, the muscle activity of the antagonist could be compared either to the muscle activity of the agonist only or to the total muscle activity of both the agonist and the antagonist (25). Comparisons between studies are difficult, and it is challenging to form an overall picture of the mechanism when different approaches are used (15).

Therefore, the overall aim of this article was to investigate the effect of sEMG normalization on the interpretation of muscle activity and coactivation. The specific aim was to evaluate the between-subject variability and group differences between the healthy legs of TD children and the affected legs of ambulatory children with CP. In addition, differences between two indices used for calculating the coactivation index were examined.

MATERIALS AND METHODS

This is a retrospective cross-sectional study, based partly on baseline data from an ongoing randomized controlled trial (26) and partly on clinical data from regular outpatient follow-up at St. Olavs University Hospital, Trondheim, Norway.

Participants

In total, 23 ambulatory children diagnosed with unilateral or bilateral spastic CP and classified with Gross Motor Function Classification System level I or II were included in this study. Ages ranged between 6 and 17 years. Exclusion criteria were botulinum toxin A treatment in the lower limb muscles in the preceding last 3 months, and surgery in the legs in the preceding 24 months prior to inclusion. Eleven typical developing (TD) children, within the same age range, were included as reference. Participant characteristics are presented in **Table 1**. The study was approved by the Regional Committee for Medical and Health Research Ethics in Middle Norway (REK Central), and a written consent in accordance with the Declaration of Helsinki was signed by the parents or guardians prior to participation.

TABLE 1 | Descriptive data presented as number (n) or as mean ± standard deviation (SD) for the different groups.

	TD	CP
N	11	23
Unilateral right/left/bilateral (n)	—	9/8/6
GMFCS I/II (n)	—	17/6
Gender, female/male (n)	7/4	7/16
Age, years (mean ± SD)	9.4 ± 1.3	11.7 ± 3.1
Height, cm (mean ± SD)	136.4 ± 9.3	147.7 ± 18.1
Weight, kg (mean ± SD)	33.6 ± 8.3	42.1 ± 18.2
Left leg length, cm (mean ± SD)	70.6 ± 6.4	77.2 ± 9.9
Right leg length, cm (mean ± SD)	70.9 ± 6.4	77.5 ± 9.7

TD, typically developing children; CP, children with cerebral palsy; GMFCS, Gross Motor Function Classification System.

Procedure and Equipment

Walking was assessed using 3DGA (Vicon Motion Systems, Ltd., Oxford, UK). Ten cameras with a sampling frequency of 200 Hz and three AMTI force plates (Watertown, MA, USA), with a sampling frequency of 1,000 Hz were positioned along a 7-m walkway. Sixteen reflective markers were placed on anatomical landmarks on the lower limbs, according to the Vicon Plug-in-Gait model (27). Participants were instructed to walk barefoot back and forth the walkway at a self-selected, comfortable walking speed. A minimum of three trials with at least two clean foot strikes on the force plates for each leg were obtained.

During the 3DGA, concurrent sEMG of m. tibialis anterior (TA), m. soleus (SOL), m. gastrocnemius medialis (GM), m. rectus femoris (RF), and m. hamstring medialis (HM), was recorded bilaterally using wireless sEMG (Myon AG, Schwarzenberg, Switzerland). Skin preparation and sEMG electrode placement were done according to the SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) guidelines (28). The sEMG recordings were amplified by a 1,000 gain with a sampling frequency at 1,000 Hz.

Data Analysis

From the TD children and the children with bilateral CP, both legs were included in the analysis. From the children with unilateral CP, only the affected leg was included. The healthy legs from TD children and the affected legs from children with CP henceforth will be referred to as TD and CP, respectively.

Nexus software (Oxford Metrics, Oxford, UK) was used to process kinematic data, define gait cycles, detect events, and calculate the spatiotemporal parameters walking speed (m/s), cadence (steps/min) and step length (m), and export c3d-files with data from the 3DGA. Raw sEMG signals were visually inspected for artifacts and noise using Myon ProEMG (Myon AG, Baar, Switzerland). A customized MATLAB program (R2018b; MathWorks, Inc., Natick, MA, USA), written using the Biomechanical Toolkit (Btk Development Core Team, version 0.3.0.), was used for processing the c3d-files.

Walking speed, cadence, and step length were normalized to leg length (m) as in Hof (29), using the following equations:

$$\begin{aligned} \textit{Normalized walking speed} &= \textit{speed}/\sqrt{(\textit{leg length} \times 9.81\, m/s^2)} \\ \textit{Normalized cadence} &= \textit{cadence}/\sqrt{(\textit{leg length} \times 9.81\, m/s^2)} \\ \textit{Normalized step length} &= \textit{step length}/\textit{leg length} \end{aligned}$$

The gait cycle was divided into six phases based on detected events (**Figure 1**). The first of these phases was the weight acceptance phase, lasting from ipsilateral foot strike to contralateral foot off. This was followed by midstance, continuing to the point where ipsilateral knee moment changed from external flexion to extension. If this change did not occur, as the external knee moment was continuously in flexion, the mean timing of this event for the equal leg in the respective group was used (i.e., healthy leg in TD/affected leg in CP unilateral or CP bilateral). From this event, terminal stance started and continued to the contralateral foot strike, before preswing lasting to ipsilateral foot off. Then initial swing started and continued to ipsilateral peak knee flexion, preceding midswing/terminal swing lasting to ipsilateral foot strike.

Hip flexion/extension, knee flexion/extension, and ankle dorsi/plantarflexion were time-normalized to the gait cycle. The angles at each percentage of the gait cycle were estimated by using a spline fit.

The raw sEMG data were band-pass filtered using an eighth-order Butterworth filter with cutoff frequency at 30 and 300 Hz. After visually inspecting the data, for all sEMG channels and each percentage of the gait cycle, an sEMG root mean square (RMS) value was calculated with a window of 50 ms. For each sEMG channel, the highest RMS value (peak RMS) was obtained and used for normalization. In addition, the RMS of each sEMG channel was calculated for each of the six gait phases as defined above and illustrated in **Figure 1**. To evaluate the effect of normalization, both absolute sEMG-RMS amplitudes (μV) and normalized to the peak RMS obtained during the complete gait cycle were included in the analyses, henceforth referred to as sEMG-RMS-abs and sEMG-RMS-norm, respectively.

After visually inspecting the data and assurance of low intrasubject variability, spatiotemporal gait parameters, kinematics, and sEMG-RMS amplitudes were averaged over the included trials to obtain each leg's mean value.

The coactivation index was calculated for all six gait phases, across three muscle pairs (TA/GM, TA/SOL, and RF/HM) using the following two indices (1, 8):

$$\begin{aligned} CoA1 &= 2 * \frac{sEMG_{antagonist}}{sEMG_{agonist} + sEMG_{antagonist}} * 100 \\ CoA2 &= \frac{sEMG_{antagonist}}{sEMG_{agonist}} * 100 \end{aligned}$$

In coactivation index 1 (CoA1), the antagonist activity was normalized in relation to the mean total muscle activity and multiplied by two to counterbalance the activity of the agonist (8). In coactivation index 2 (CoA2), the antagonist was expressed as a percentage of agonist muscle activity only. For both indices,

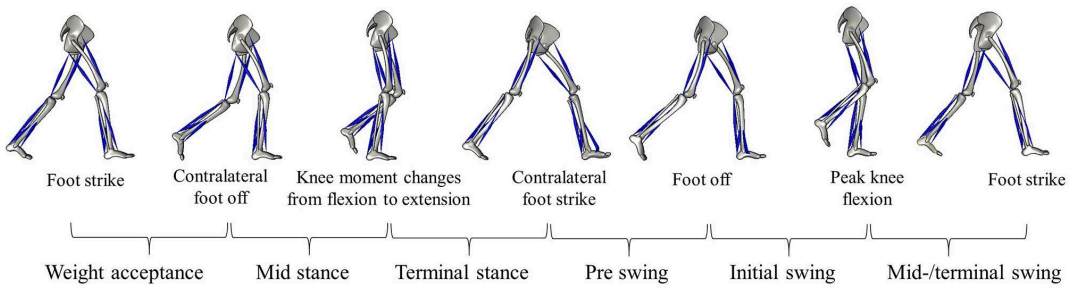

FIGURE 1 | Illustration of a complete gait cycle with the right leg's events, separating the six gait phases: weight acceptance, midstance, terminal stance, preswing, initial swing, midswing/terminal swing.

a coactivation index of 100% represents equal activity of the agonist and antagonist muscles, whereas 0% represents solely agonist activation.

The definitions of agonist and antagonist muscles are often based on the magnitude of the sEMG amplitude, where the higher signal is assigned to the agonist (19). However, this presumption may not hold in a population with altered muscle activity, especially during complex tasks such as walking. It is therefore necessary to allow for changes in the agonist and antagonist roles throughout the gait cycle, based on the biomechanical function of the muscles around the knee and ankle (19, 30). For TA/GM and TA/SOL coactivation, TA was defined as agonist during the weight acceptance phase, working to control lowering of the foot and during initial and midswing/terminal swing, lifting the foot from the ground, and ensuring foot clearance. Gastrocnemius medialis and SOL were defined as agonists during midstance, terminal stance, and preswing, where they are main contributors to stabilize, control for ankle dorsiflexion, and prepare for foot off. For RF/HM coactivation, RF was defined as agonist during weight acceptance, limiting the magnitude of flexion occurring as the foot strikes the ground, midstance and terminal stance, initiating knee extension, and preswing, controlling for knee flexion. Hamstring medialis was defined as agonist during initial and midswing/terminal swing, initiating knee flexion and preparing for foot clearance, and controlling for knee extension and decelerating the swinging leg, respectively.

Statistical Analysis

Statistical analyses were carried out using MATLAB (R2018b; MathWorks, Inc.). From the kinematic data (hip, knee, and ankle joint angles) and sEMG-RMS amplitudes per percentage of the gait cycle, group (TD and CP) averages and 95% confidence interval (CI) were calculated and displayed. For each percentage of the gait cycle, the CP group data were defined as different from TD when the average of the group did not overlap with the 95% CI of the other group.

Between-group (TD vs. CP) differences in the spatiotemporal gait parameters, sEMG-RMS amplitudes, and coactivation indices for the six different gait phases were tested using linear mixed models. The spatiotemporal gait parameter, muscle or coactivation muscle pair of interest was set as dependent variable, leg as fixed effect, and subject as random effect. Normality of residuals was checked by visual inspection of QQ plots. Where residuals were not normally distributed, analysis was additionally carried out using log-transformed data. In case of similar results, p values from the analysis with non–log-transformed data, henceforth referred to as original analysis, are presented. Mean with 95% CI values for TD and mean with 95% CI deviations of the CP group from TD are retrieved from the original analyses in all cases. Significance was set at $p < 0.05$, and trends are reported where $p < 0.1$.

TABLE 2 | Spatiotemporal gait parameters of the healthy legs of typically developing children (TD) and the deviation of the affected legs of children with cerebral palsy (CP) from TD, presented as mean with 95% confidence interval (CI).

	TD			Deviations of CP from TD		
	Mean	95% CI		Mean	95% CI	
Normalized walking speed	0.46	0.43	0.49	**−0.08**	**−0.11**	**−0.05**
Normalized cadence	48.7	45.0	52.4	**−5.7**	**−10.3**	**−1.2**
Normalized step length	0.81	0.77	0.86	**−0.11**	**−0.16**	**−0.06**
Time in single support (%)	40.7	39.7	41.8	**−1.36**	**−2.7**	**−0.1**
Time in double support (%)	17.9	16.2	19.7	1.1	−1.1	3.3

Significant group differences ($p < 0.05$) presented in bold.

RESULTS

Twenty-two healthy legs from TD children and 29 affected legs from children with CP were included for the analyses. Spatiotemporal gait characteristics are presented in **Table 2**. The CP group had significantly lower normalized walking speed and normalized cadence ($p < 0.01$) and shorter normalized step length ($p = 0.02$) compared to the TD group. The percentage time in single support (midstance and terminal stance combined) was significantly shorter for the CP group ($p < 0.04$), whereas there was no difference between the groups in percentage time in double support (weight acceptance and preswing combined, $p = 0.3$). The relative duration of the different gait phases varied between the groups, where the CP group had significantly longer

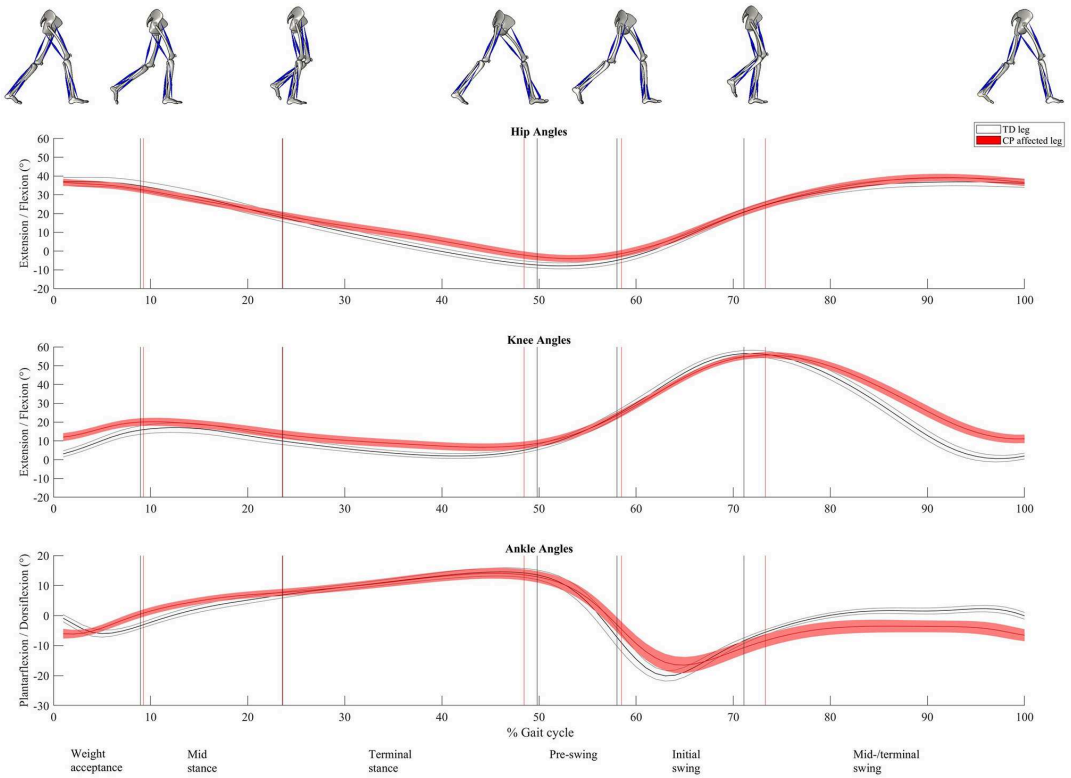

FIGURE 2 | Sagittal-plane joint kinematics. At the top hip extension/flexion; in the middle, knee extension/flexion; and at the bottom, ankle plantarflexion/dorsiflexion. Time normalized to 0 to 100% of the gait cycle. Presented as mean (solid line) with 95% confidence interval (shaded area). The vertical lines represent the mean timing of the different events dividing the gait cycle into six gait phases (named at the bottom line). Gray color is used for the healthy legs of typically developing children and red for the affected legs of children with CP. Illustrations of the right leg's events, separating the different phases, are seen at the top.

time in preswing and initial swing compared to TD ($p = 0.002$ and $p < 0.001$). The differences in mean timing of the detected events separating the gait phases are illustrated as vertical lines in **Figures 2**, **3**. The CP group had increased hip flexion of ∼7 degrees during terminal stance and preswing (**Figure 2**). During the majority of the gait cycle, the CP group had increased knee flexion, except for during preswing and initial swing. The difference was largest (∼10 degrees) during weight acceptance and midswing/terminal swing. The CP group had ∼6 degrees plantarflexion at foot strike, while the TD group was in a neutral position. This was also seen during midswing/terminal swing. However, late in the weight acceptance phase, during midstance and start of the initial swing, the CP group had increased dorsi flexion of about the same size.

Effect of Normalization on Muscle Activity

Figure 3 shows muscle activity during the complete gait cycle for TA, GM, SOL, RF, and HM using sEMG-RMS-abs and sEMG-RMS-norm for the TD and CP groups. In both groups, the average gait pattern was very similar when presented as sEMG-RMS-abs or sEMG-RMS-norm, because the gait phases with high and low amplitudes hardly changed (**Figure 3**). However, it seems that the between-subject variability (thickness of the shaded area) in both the TD and CP groups is more evenly distributed during the gait cycle after normalization than before (**Figure 3**). However, for TA, GM, SOL, and RF, the between-subject variability is less from terminal stance phase and throughout the gait cycle prior to normalization.

The residuals from the linear mixed model either were not normally distributed or had an outlier for the majority (26 of 30) of the sEMG-RMS-abs variables and for 13 of 30 variables of the sEMG-RMS-norm. These variables were log transformed, and the results were similar to the original analysis for 35 of the 39 variables in total. The four variables with changed results are marked with α in **Table 3**. One variable (HM sEMG-RMS-abs during preswing) had an outlier that remained following log transformation. We conducted the analysis both with and without this outlier, and it did not change the statistical results;

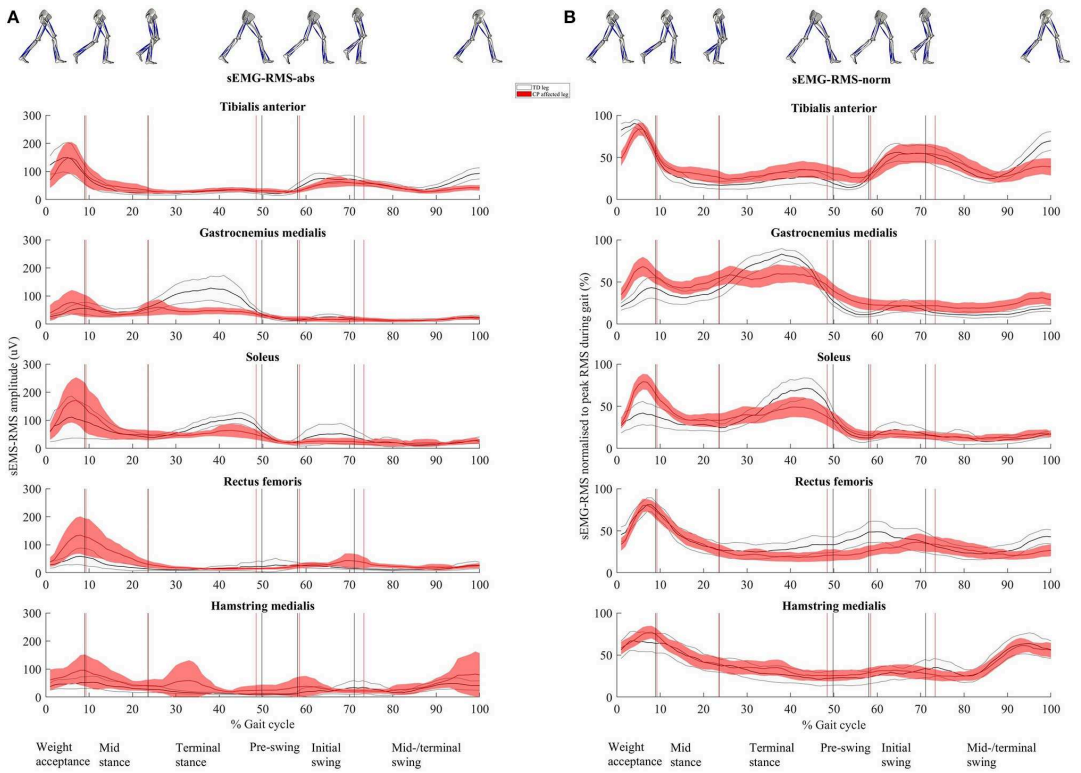

FIGURE 3 | (A) Root mean square (RMS) surface electromyographic (sEMG) amplitude (μV, sEMG-RMS-abs) and **(B)** RMS of sEMG normalized to peak RMS obtained during the gait cycle (%, sEMG-RMS-norm) for the five muscles. Time normalized to 0 to 100% of the gait cycle. Presented as mean (solid line) with 95% confidence interval (shaded area). The vertical lines represent the mean timing of the different events dividing the gait cycle into the six gait phases (named in the bottom line). Gray color is used for the healthy legs of typically developing children and red for the affected legs of children with CP. Illustrations of the right leg's events, separating the different phases, are seen at the top.

thus, results from the original analysis are presented. **Table 3** shows gait phase averaged sEMG-RMS-abs and sEMG-RMS-norm amplitudes for the six gait phases for the TD group and for the deviation of the CP group from TD.

For sEMG-RMS-abs amplitudes (column A, **Figure 3** and **Table 3**), in all muscles, both the TD and CP groups had similar values during at least four of the six gait phases. Tibialis anterior was, however, significantly reduced for the CP group during initial and midswing/terminal swing ($p = 0.05$ and $p = 0.001$, respectively). Gastrocnemius medialis and SOL were significantly reduced for the CP group during terminal stance ($p = 0.002$ and $p = 0.001$, respectively) and initial swing ($p = 0.03$ for both). Rectus femoris was significantly increased for the CP group during weight acceptance ($p = 0.04$). During midstance, this increase was borderline significant ($p = 0.08$). Although the average HM amplitude for the CP group was above the TD group during almost the whole gait cycle, no significant group differences were found in this muscle.

For sEMG-RMS-norm (column B, **Figure 3** and **Table 3**), the CP group showed similar amplitudes as the TD group in only two to three of the six gait phases, except for HM where no significant group differences were observed. Tibialis anterior was borderline significantly reduced for the CP group compared to the TD group during weight acceptance phase ($p = 0.07$) and significantly reduced during midswing/terminal swing ($p = 0.04$). During preswing, TA was significantly increased for the CP group ($p = 0.05$). Gastrocnemius medialis and SOL were significantly increased for the CP group during weight acceptance phase ($p = 0.02$ and $p = 0.001$, respectively). During terminal stance, GM was reduced for the CP group ($p = 0.01$), and there was a trend toward a reduction in SOL ($p = 0.06$). During initial swing, SOL was significantly reduced in the CP group ($p = 0.05$). Rectus femoris was significantly reduced for the CP group during terminal stance ($p = 0.02$), preswing ($p = 0.003$), initial ($p = 0.05$), and midswing/terminal swing ($p = 0.04$).

TABLE 3 | Muscle activity for healthy legs of typically developing children (TD) during six gait phases and the deviation of the affected legs of children with cerebral palsy (CP) from TD, presented as mean with 95% confidence interval (CI).

	(A) sEMG-RMS-abs (μV)						(B) sEMG-RMS-norm (%)					
	TD			Deviation of CP from TD			TD			Deviation of CP from TD		
Phases	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
TIBIALIS ANTERIOR												
Weight acceptance[β]	150.8	85.0	216.5	−10.3	−94.6	74.0	95.6	84.6	106.6	*−13.1*	*−27.3*	*1.0*
Midstance	59.1	33.2	85.0	1.3	−32.3	35.0	40.9	29.2	52.6	−1.4	−16.7	13.8
Terminal stance	37.3	28.3	46.2	−3.6	−15.0	7.7	32.0	20.9	43.0	1.8	−12.4	15.9
Preswing	27.0	17.9	36.1	5.8	−6.3	17.8	20.3	12.9	27.7	**9.7**	**0.1**	**19.4**[α]
Initial swing[β]	81.8	62.3	101.2	**−16.9**	**−42.1**	**8.3**[α]	64.8	50.3	79.3	−7.3	−26.1	11.5
Midswing/terminal swing[β]	74.2	61.7	86.7	**−28.1**	**−44.4**	**−11.9**	59.5	47.7	71.2	**−16.0**	**−31.4**	**−0.5**
GASTROCNEMIUS MEDIALIS												
Weight acceptance	51.4	4.2	98.6	18.3	−43.8	80.3	42.5	28.9	56.2	**21.0**	**3.3**	**38.7**
Midstance[β]	64.7	33.6	95.9	−3.2	−43.7	37.2	49.6	39.0	60.1	5.6	−8.2	19.3
Terminal stance[β]	112.4	87.2	137.6	**−53.9**	**−86.5**	**−21.2**	81.5	71.0	92.1	**−18.2**	**−32.2**	**−4.1**
Preswing[β]	40.8	16.5	65.1	−15.9	−46.6	14.9	25.1	14.5	35.8	*6.0*	*−7.6*	*19.6*
Initial swing	39.5	24.4	54.7	**−22.0**	**−41.3**	**−2.8**	33.0	21.8	44.2	−10.7	−25.4	4.1
Midswing/terminal swing	26.3	16.2	36.5	−6.3	−19.4	6.8	19.5	14.1	24.9	6.9	−0.3	14.1
SOLEUS												
Weight acceptance	107.9	16.7	199.1	42.7	−70.4	155.8	43.9	32.1	55.8	**26.3**	**10.7**	**41.8**
Midstance[β]	85.3	39.1	131.5	−2.9	−60.4	54.6	43.7	33.7	53.7	2.8	−10.4	16.1
Terminal stance[β]	96.1	78.9	113.4	**−38.6**	**−61.1**	**−16.1**	67.1	52.3	81.9	*−18.1*	*−37.3*	*1.1*
Pre–swing[β]	36.7	22.6	50.9	−11.0	−28.7	6.7	25.7	14.6	36.9	−4.6	−18.6	9.4
Initial swing	66.1	36.3	95.9	**−41.3**	**−78.2**	**−4.4**	32.7	21.3	44.1	**−14.8**	**−29.4**	**−0.2**
Mid–/ terminal swing	30.9	18.2	43.6	−6.6	−22.9	9.7	18.8	13.4	24.2	−1.7	−8.8	5.4
RECTUS FEMORIS												
Weight acceptance[β]	55.0	9.9	100.1	**55.6**	**−2.8**	**113.9**[α]	78.3	68.7	87.9	−6.8	−19.2	5.6
Midstance[β]	42.6	2.4	82.8	*55.2*	*4.2*	*106.2*[α]	61.3	49.3	73.3	−5.0	−20.4	10.3
Terminal stance[β]	24.0	11.9	36.1	0.3	−15.3	15.8	39.4	30.1	48.6	**−14.7**	**−26.6**	**−2.9**
Preswing[β]	40.2	13.8	66.5	−20.2	−54.9	14.4	45.7	34.3	57.1	**−23.5**	**−38.5**	**−8.5**
Initial swing	28.8	12.1	45.6	12.9	−8.7	34.6	53.6	41.8	65.4	**−15.8**	**−31.2**	**−0.3**
Midswing/terminal swing	23.5	14.1	32.9	3.3	−8.7	15.3	42.0	32.0	52.1	**−13.7**	**−26.7**	**−0.7**
HAMSTRING MEDIALIS												
Weight acceptance	62.3	28.6	95.9	18.4	−25.6	62.5	86.7	73.1	100.3	−10.2	−28.2	7.8
Midstance	49.0	14.2	83.7	17.9	−26.7	62.6	62.8	52.6	73.1	−6.1	−19.7	7.5
Terminal stance	24.2	−5.5	53.8	22.6	−16.4	61.6	40.0	29.7	50.2	−0.3	−13.6	13.0
Preswing	15.3	−4.2	34.8	15.6	−10.3	41.4	30.5	19.9	41.1	−0.9	−14.4	12.6
Initial swing[β]	38.8	10.8	66.9	−7.9	−43.5	27.7	40.3	29.4	51.2	−5.8	−19.9	8.2
Midswing/terminal swing[β]	49.9	16.6	83.2	6.8	−36.7	50.3	59.9	51.1	68.6	−8.0	−19.6	3.6

Muscle activity presented as (A) RMS of sEMG amplitude (μV, sEMG-RMS-abs) and (B) RMS of sEMG normalized to peak RMS obtained during the gait cycle (%, sEMG-RMS-norm). Negative values indicate lower values for the CP group compared to TD. Significant group differences ($p < 0.05$) presented in bold and $p < 0.1$ presented in italic. [α]Analysis conducted on log-transformed data. [β]Gait phases where the given muscle is defined as agonist. RMS, root mean square; sEMG, surface electromyography.

Effect of Normalization on Calculations of the Coactivation Index

Both absolute (column A, **Figure 4**) and normalized (column B, **Figure 4**) CoA1 values (CoA1-abs and CoA1-norm, respectively) were, in general, higher than 50% for both the TD and CP groups. The CoA1 values in RF/HM were relatively high and often ∼100% (**Figure 4**), indicating equal activity of the agonist and antagonist muscles. Absolute CoA2-values (CoA2-abs, column A, **Figure 5**) were higher than 100% in three and six of 18 muscle pairs and gait phases in the TD and CP group, respectively, indicating higher activity of the antagonist than the agonist muscles. For normalized CoA2 values (CoA2-norm, column B, **Figure 5**), this was only seen once in TD and in five of 18 muscle pairs and gait phases in the CP group.

For CoA2, only TA/GM CoA2-abs during midswing/terminal swing and TA/GM CoA2-norm during weight acceptance phase were normally distributed. The rest of the variables were log transformed, resulting in normally distributed residuals. For 27 of the 34 variables, the results were similar for the log-transformed analysis as the original analysis. For the

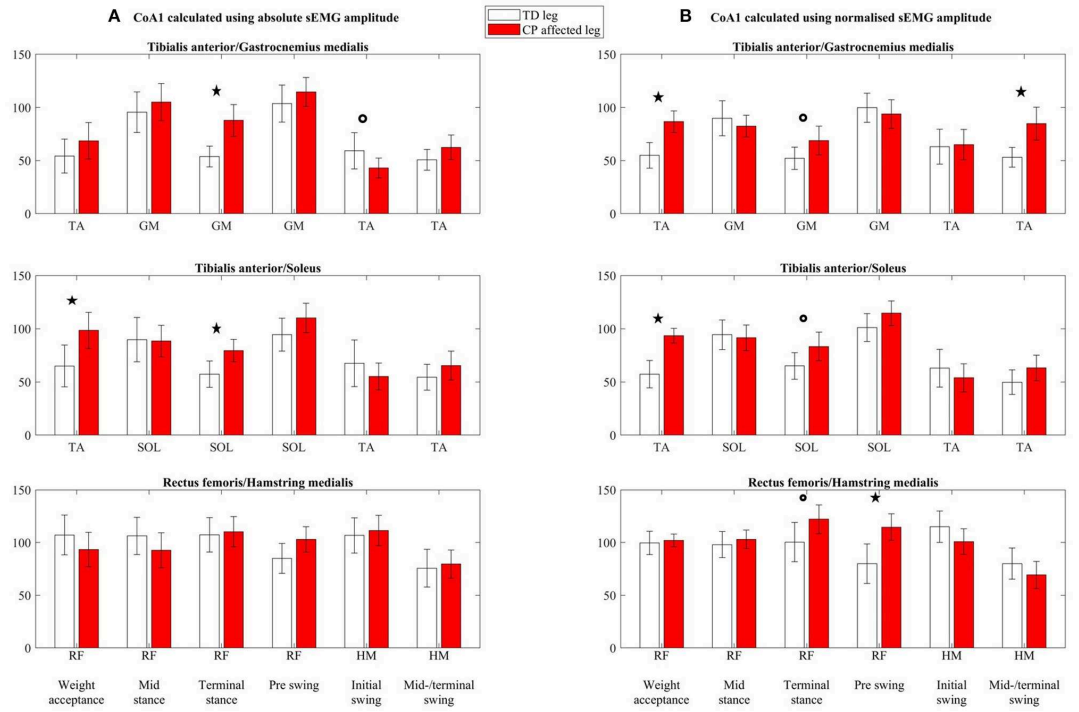

FIGURE 4 | Coactivation index 1 (CoA1) calculated using **(A)** absolute sEMG-RMS amplitudes (CoA1-abs) and **(B)** using normalized sEMG-RMS amplitudes (CoA1-norm), presented as mean with 95% confidence interval. Calculated for three coactivation muscle pairs: tibialis anterior/gastrocnemius medialis, tibialis anterior/soleus, and rectus femoris/hamstring medialis, for each of the six gait phases (named in the bottom line). The agonist in the coactivation index muscle pair is indicated for each gait phase below each subplot. TA, tibialis anterior; GM, gastrocnemius medialis; SOL, soleus; RF, rectus femoris; HM, hamstring medialis. *Significant group differences ($p < 0.05$), $^{\circ}p < 0.1$.

seven remaining, p values from the log-transformed analysis are presented.

For CoA1-abs (column A, **Figure 4**), TA/GM was increased in the CP group compared to the TD group during terminal stance ($p < 0.01$), had a trend to be reduced in the CP group during initial swing ($p = 0.1$), and was similar for both groups in the other four phases. Tibialis anterior/SOL was increased in the CP group during weight acceptance ($p = 0.02$) and terminal stance ($p < 0.01$) and was similar between the groups in the other four phases. Rectus femoris/HM showed no significant differences between the TD and CP groups (all $p > 0.1$).

For CoA1-norm (column B, **Figure 4**), TA/GM was increased in the CP group compared to TD during weight acceptance ($p < 0.001$), and midswing/terminal swing ($p = 0.002$), and there was a trend toward an increase in terminal stance ($p = 0.06$). In the other three phases, there were no differences between the groups. Tibialis anterior/SOL was increased in the CP group during weight acceptance ($p < 0.001$), there was a trend towards an increase in terminal stance ($p = 0.08$), and was similar for the groups in the other four phases. Rectus femoris/HM had a trend to be increased in the CP group during terminal stance ($p = 0.05$), and the increase was significant during preswing ($p = 0.004$). In the other four gait phases, there were no differences between the groups.

For CoA2-abs (column A, **Figure 5**), TA/GM was increased in the CP group compared to TD during terminal stance ($p = 0.002$), but was similar between the groups in the other five gait phases. Tibialis anterior/SOL was increased in the CP group during weight acceptance phase ($p = 0.03$) and during terminal stance ($p = 0.01$) but were similar between the groups in the other four phases. A borderline significant decrease was seen in the CP group for RF/HM during weight acceptance phase ($p = 0.08$), but no differences between the TD and CP groups were seen for the rest of the gait phases.

For CoA2-norm (column B, **Figure 5**), TA/GM was increased in the CP group compared to TD during weight acceptance phase ($p < 0.001$) and during midswing/terminal swing ($p = 0.002$). In the four gait phases in between, there were no differences between the groups. Tibialis anterior/SOL was increased in the CP group during weight acceptance phase ($p < 0.001$), and there was a

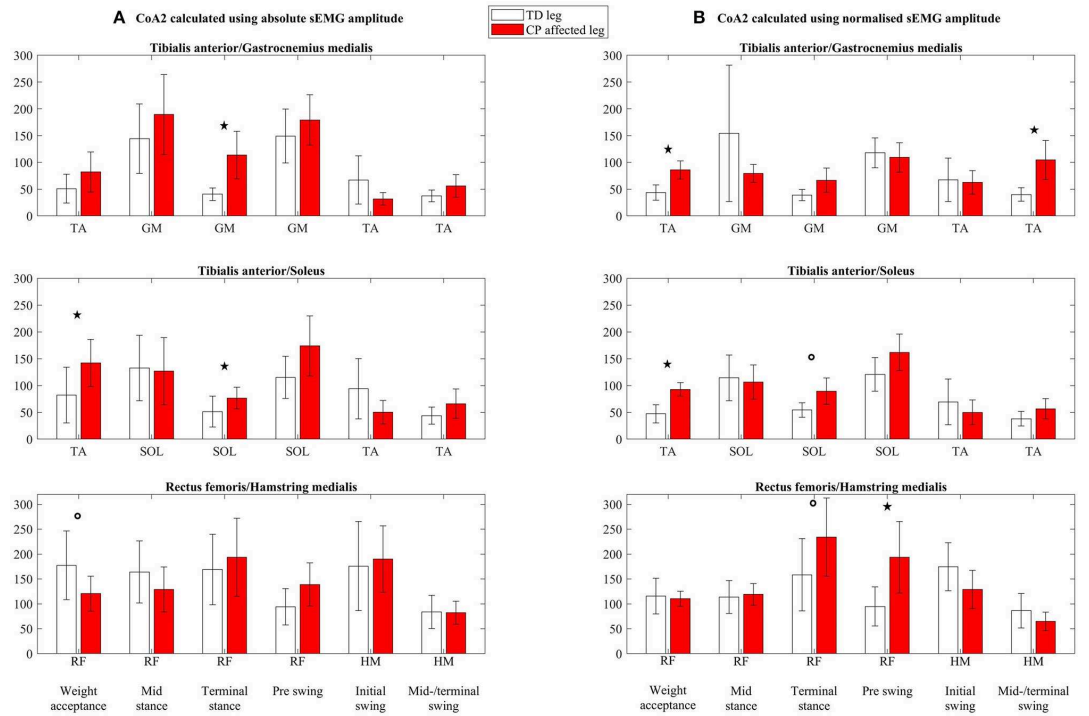

FIGURE 5 | Coactivation index 2 (CoA2) calculated using **(A)** absolute sEMG-RMS amplitudes (CoA2-abs) and **(B)** using normalized sEMG-RMS amplitudes (CoA2-norm), presented as mean with 95% confidence interval. Calculated for three coactivation muscle pairs: tibialis anterior/gastrocnemius medialis, tibialis anterior/soleus, and rectus femoris/hamstring medialis, for each of the six gait phases (named in the bottom line). The agonist in the coactivation index muscle pair is indicated for each gait phase below each subplot. TA, tibialis anterior; GM, gastrocnemius medialis; SOL, soleus; RF, rectus femoris; HM, hamstring medialis. *Significant group differences ($p < 0.05$), $^{\circ}p < 0.1$.

trend toward an increase during terminal stance ($p = 0.09$). There were no differences between groups in the other four gait phases. Rectus femoris/HM had a borderline significant increase in the CP group during terminal stance ($p = 0.05$). During preswing, the increase in the CP group was significant ($p = 0.004$). In the remaining gait phases, there were no differences between the TD and CP groups.

DISCUSSION

The aim of this article was to investigate the effect of sEMG normalization on the interpretation of muscle activity and coactivation. Therefore, differences in muscle activity and coactivation indices between the healthy legs of TD children and the affected legs of ambulatory children with CP were examined using both absolute and normalized sEMG-RMS amplitudes (sEMG-RMS-abs and sEMG-RMS-norm, respectively). A secondary aim was to evaluate differences between two indices for calculating the coactivation index.

Muscle Activity

Our results showed that normalization did not affect the average muscle activity pattern during gait within the TD or CP group but affected the between-subject variability within the groups and the difference in muscle activity between groups. Moreover, muscle activity deviations of the CP group from TD varied across the five investigated muscles.

Normalization of sEMG amplitudes is used to reduce between-subject variability caused by nonphysiological factors in order to compare physiological differences between muscles, individuals or sessions (16, 22, 31). However, it has been argued that as a consequence of normalizing the clinically relevant physiological variability could also be reduced (31). Our results show that the large between-subject variability seen in sEMG-RMS-abs during one to two specific gait phases is entirely equalized after normalization (**Figure 3**). This was seen in both groups. In the TD group, large between-subject variability in sEMG-RMS-abs was seen during weight acceptance phase for TA and SOL and during terminal stance for GM. In the CP group, TA, GM, SOL, and RF all showed large variability during

weight acceptance phase only. The remainder of the gait cycle (∼85%) showed low variability in sEMG-RMS-abs, suggesting low nonphysiological between-subject variability. This may indicate that the children have clinically relevant variation in muscle activity during some gait phases, which are diminished by normalization.

The overall muscle activity pattern in both groups was very similar across the two approaches of handling the sEMG data, because the gait phases with high and low amplitudes barely changed (**Figure 3**). This is in accordance with previous research evaluating the methods of sEMG normalization on healthy controls (18–20) and patients with stroke (19, 20). However, the deviations of the CP group from TD varied between the two approaches applied in this article. Increased sEMG-RMS-abs for CP in one gait phase, for instance, changed to reduced amplitude after normalization in another gait phase, or the other way around. Specifically, as seen in **Figure 3** and quantified in **Table 3**, TA showed some reduced activity in the CP group compared to TD from initial swing to early weight acceptance phase for both sEMG-RMS-abs and sEMG-RMS-norm. However, these deviations reached statistical significance in different phases for the two approaches (both swing phases for sEMG-RMS-abs, whereas only the midswing/terminal swing for sEMG-RMS-norm, in addition to bordeline significance at weight acceptance phase; **Table 3**). Moreover, the TA amplitude during preswing seemed somewhat increased in the CP group but was only significantly increased after normalization. This could be a physiological compensation for the reduced activity during swing, or a result of normalization.

In the TD group, GM and SOL were especially active during three gait phases: the end of weight acceptance phase, terminal stance, and initial swing (**Figure 3**). During the end of weight acceptance, GM and SOL seemed somewhat increased in the CP group. However, they were significantly increased only after normalization. During terminal stance, GM and SOL activity in the CP group was decreased using sEMG-RMS-abs, but after normalization only GM was still significantly decreased. Similarly, during initial swing, GM and SOL activity in the CP group was decreased using sEMG-RMS-abs, but only SOL remained significantly decreased after normalization. In the CP group, RF activity was increased using sEMG-RMS-abs during weight acceptance and possible during midstance, but there were no differences between the groups for the last four gait phases. After normalization, the amplitudes were decreased for the CP group from terminal stance to midswing/terminal swing, but no differences were seen for the first two phases.

Despite these alterations in deviating amplitudes of the CP group from TD, in a clinical perspective, evaluating the overall muscle activity pattern may often be more essential in detecting phasic abnormalities rather than relative to TD amplitudes (22). Our results showed that the overall picture of the muscle activity pattern within each group did not seem to be so different between absolute and normalized sEMG amplitudes. However, details can be of clinical relevance. To only base interpretations on absolute or normalized sEMG could have consequences for treatment prescriptions. Should we, for instance, interpret the results as mainly overactivity of the calf muscles (GM and SOL) during weight acceptance and treat with botulinum toxin A, or as reduced activity during terminal stance and treat with strength training?

Muscle Coactivation

There are several approaches for calculating the coactivation index, and in this article, we have looked closer at two indices commonly used. Our results showed statistically increased coactivation indices in the CP group compared to TD in three and four of 18 investigated muscle pairs and gait phases using absolute (CoA1-/CoA2-abs) and normalized (CoA1-/CoA2-norm) sEMG values, respectively. Although the two indices showed the same significant deviations in the CP group from TD, the values in CoA2 (**Figure 5**) were in general substantially higher than CoA1 values (**Figure 4**). Additionally, the between-subject variability was greater in CoA2 compared to CoA1, and as the variables of CoA2 had to be log transformed prior to analysis, CoA1 may therefore be more easily used when testing group differences. Hence, the following paragraphs will be based on CoA1.

In phases where there is low agonist activity and already very high coactivation indices in TD, even higher indices in CP cannot be expected. The TD group show clear agonist sEMG burst during weight acceptance, initial and midswing/terminal swing for TA, during terminal stance for SOL and GM and thus low coactivation indices (<75%) for both absolute and normalized values. Our findings indicate increased coactivation index in the CP group in 60% of these gait phases. These increased coactivation indices are in line with expectations and previous studies evaluating coactivation during walking in children with CP (9, 12).

However, there is no general agreement on the role of the coactivation in populations with neurological disorders, beyond abnormal levels that have been reported (15, 32). Potential explanations for our increased coactivation indices will be discussed below. During weight acceptance, the calf muscles–based coactivation indices (TA/GM and TA/SOL) were increased in the CP group for both CoA1-abs and CoA1-norm (although not statistically significant for TA/GM with CoA1-abs). For CoA1-abs, neither the agonist TA was decreased, nor the antagonist calf muscles (GM and SOL) increased, but for CoA1-norm, the antagonist calf muscles were increased in addition to somewhat decreased agonist TA. Using CoA1-norm, it seems that at least some of the children with CP showed increased index due to increased coactivation of the calf muscles. During terminal stance, however, the increased coactivation index accompanied by a largely reduced agonist calf muscle activity without increased antagonistic TA activity weakens the hypothesis of increased TA coactivation. Similarly, the increased coactivation index for the normalized TA/GM muscle pair during midswing/terminal swing was accompanied by reduced agonist TA activation and not increased antagonistic GM activity. Likewise, the increased coactivation index of the normalized RF/HM muscle pair during terminal stance and preswing was not accompanied by increased antagonistic HM, but by decreased agonistic RF activity. It is difficult to know if increased coactivation is due to excessive antagonist activity or

due to muscle weakness in the agonist, without any knowledge of the underlying muscle activity. Moreover, a coactivation index of 100% represents equal activity of the agonist and antagonist muscle but does not say anything about the amount of activity. Both muscles could potentially be highly active or somewhat active, and the latter with a slight increase in antagonist muscle activity would lead to a highly increased coactivation index. To decide whether the increased coactivation index is of clinical relevance, it is crucial to consider the underlying muscle activity at the same time.

Additionally, the interpretation of the coactivation index is closely related to the handling of the sEMG data. Using absolute or normalized sEMG-RMS amplitudes in the calculations gives different pictures of which gait phases the CP group deviate from TD, which emphasizes the complexity of the coactivation index.

CONCLUSION

This article showed that the interpretation of muscle activity and coactivation was affected by normalization approach when evaluating group differences. Although the overall muscle activity pattern did not differ between absolute and normalized sEMG-RMS amplitudes, normalization eliminated variability that could be interpreted as physiological variation within the children and deviating sEMG-RMS amplitudes were found in different phases after normalization. Taken together, these results emphasize the importance of being able to use absolute sEMG-RMS amplitudes in addition to the dynamic peak normalized values and to have knowledge about the underlying physiology in order to interpret sEMG data.

When interpreting the coactivation index, it is important to be aware of the methodological approach in order to understand the origin and function, before drawing conclusions on abnormal coactivation levels and making comparisons between different studies. Our findings suggest that increased coactivation index may be explained by other factors than excessive antagonist coactivation, such as the inability to sufficiently activate the agonist.

Because we do not know the truth, we cannot conclude whether to normalize the data and recommend considering both absolute and normalized data for a complete interpretation. However, future research should relate to functional outcomes, to better answer whether absolute or normalized sEMG-RMS amplitudes are favorable in the interpretations of altered muscle activity and coactivation index.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available due to Norwegian legislation. Questions regarding the datasets can be sent to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics in Middle Norway (REK Central). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YG, SB, and KR contributed conception and design of the study. YG and KR performed the statistical analysis. YG wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Paper II

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Energy cost of gait in children and the effect of speed, age, and body size

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ABSTRACT

Background: Energy cost (EC) of comfortable walking is often used in clinical evaluation of children with altered gait function. EC is presented as energy expenditure per kg bodyweight per meter, either in total (grossEC) or in addition to resting energy expenditure (netEC). GrossEC is considered more reliable and netEC less affected by between-subject variations in speed, age, and body size. However, the effect of the individual child's speed on EC is rarely considered, while altered gait function may affect both speed and EC.
Research question: To what extent are grossEC and netEC affected by within-subject variation in speed and between-subject variations in speed, age, and body size?
Methods: Forty-two typically developing children (7–15 y) were included in this cross-sectional study. Age, height, and bodyweight were obtained. Breath-to-breath gas-exchange measures of VO_2 and VCO_2 were conducted during rest and five over-ground gait conditions: walking at slow, comfortable, and fast speed, jogging and running. All conditions lasted 3–5 min. Body surface area, non-dimensional speed, grossEC, and netEC were calculated. Regression analyses and mixed model analyses were conducted to explain the effect of speed, age, and body size on variations in EC.
Results: GrossEC showed a non-significant, concave up relation to within-subject variation in speed, with a minimum around comfortable/fast walking speed. NetEC had a strong positive linear relation to within-subject variation in speed. For each gait condition, grossEC was more affected by between-subject variations in speed, age, and body size compared to netEC. However, the effect of age and body size was not eliminated for netEC but was quadratic.
Significance: Although normalised to speed and bodyweight, grossEC and netEC are still affected by those factors. However, they are affected differently for within- and between-subject variations. This must be considered when interpreting EC in children in relation to gait function.

1. Introduction

Energy expenditure during gait provides an indication of gait function and is often increased in children with movement disability [1–3]. Energy expenditure is regularly investigated for treatment evaluation as reducing energy expenditure during gait is a frequently used treatment goal [3–6]. Indirect calorimetry through gas-exchange measurements of oxygen (VO_2) and carbon dioxide (VCO_2) is considered the gold standard for investigating energy expenditure during gait [7]. To allow for comparison between individuals, energy expenditure is commonly normalised to body weight and presented in J/kg/min [8]. Energy expenditure measurements from indirect calorimetry requires at least one-minute steady state. To reach such a period with steady state during gait from rest, usually takes five minutes. Due to time limits and possibility of fatigue with longer periods of gait, clinical evaluation is usually performed at only one gait condition, commonly at self-selected,

Abbreviations: BSA, Body surface area; EC, Energy cost; EE, Energy expenditure; RER, Respiratory exchange ratio; VO_2, Oxygen uptake; VCO_2, Carbon dioxide production.

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comfortable speed. However, energy expenditure increases with speed and self-selected speed decreases with movement disability [2,3,9–11]. Therefore, to quantify gait efficiency in children with disabilities, energy expenditure is often normalised to speed and referred to as energy cost (EC, J/kg/m).

Although EC is an objective, quantitative measure, there are several methodological issues, especially when evaluating children in growth [12]. While EC of gait is commonly normalised to weight and speed, this normalised EC is still reported to be affected by speed and growth-related subject characteristics, such as age, height, bodyweight, and body surface area (BSA) [12–14]. This is partly thought to be caused by the resting energy expenditure (restEE) which changes with maturation [3,14]. RestEE consists of the basal metabolic rate and the resting muscular consumption during sitting or standing. While grossEC represents the total cost required for movement, including restEE, netEC represents the EC of gait after subtraction of restEE. Due to difficulties measuring restEE in children, grossEC has shown greater reproducibility compared to netEC [15,16]. However, subtracting restEE has shown to reduce the effect of growth-related subject characteristics [1]. In an attempt to remove the effect of anatomical and physiological variables, a non-dimensional normalisation of netEC has been proposed [17]. However, a dimensionless outcome is more difficult to interpret and, according to the normalisation scheme, the only difference between the netEC and the non-dimensional netEC is determined by a constant factor, the gravitational force. Thus, its relation to speed and growth-related subject characteristics is therefore the same as netEC [1].

Superiority of grossEC with respect to reproducibility and netEC with respect to its relative independency of growth-related subject characteristics seems to be largely accepted knowledge. However, the influence of individual variations in gait speed on EC is less systematically investigated. Gait function may affect both speed and EC independently, but the effect of the individual child's speed on EC is rarely considered. To establish a more complete basis for clinical interpretation of EC in children, this study aims to evaluate to what extent grossEC and netEC are affected by within-subject variations in speed, and by between-subject variations in speed and growth-related subject characteristics, in typically developing children.

2. Methods

2.1. Participants

The present study is part of a larger project evaluating activity and energy expenditure in children. The children in this project were recruited from a local elementary and junior high school. The tests were performed at the school premises and within school hours. Data from 42 typically developing children, aged between seven and 15 years old, without physical disability or medical conditions affecting their gait were analysed in this study.

2.2. Procedure and equipment

Characteristics of the children were recorded prior to testing, including age, height, and bodyweight. Body surface area (BSA, m^2) was calculated as follows [18]:

$$BSA\left(m^2\right) = \sqrt{\frac{bodyweight(kg) \times height(cm)}{3600}}$$

Energy expenditure was measured at rest and during gait tests. During rest, the children were sitting and standing for three minutes each. The gait tests lasted for five minutes each, and time of rest in between the tests was determined by the children themselves. The children wore shoes and were instructed to *walk as you normally do, walk slower than you normally do, walk faster than you normally do, jog, and run,* in that specific order. All speeds were self-selected, and the tests were conducted around a handball field of 40 times 20 m or on a 400-meter track. A portable indirect calorimeter, Metamax, version II (Cortex Biophysik GmbH, Leipzig, Germany) was carried as a backpack by the children and used to measure oxygen uptake (VO_2) and carbon dioxide production (VCO_2). Reliability and validity of this system as well as comparable systems have been reported before [19,20]. Prior to testing, the calorimeter was calibrated according to the manufacturer's instructions. The children wore a facemask placed over nose and mouth which was carefully inspected for leakage.

2.3. Data analyses

Speed (m/s) was calculated from the total distance over time during each gait test. Non-dimensional speed was calculated using the following equation [21]:

$$Non-dimensional\ speed = speed(m/s) \Big/ \sqrt{(9.81 m/s^2 \times leg\ length(m))}$$

From the resting and gait tests, VO_2 (l/min) and VCO_2 (l/min) were averaged over a two-minute visually inspected steady state period, where fluctuations in VO_2 and VCO_2 changed the least [1]. Respiratory exchange ratio (RER) was calculated by dividing VO_2 by VCO_2. The mean VO_2 relative to bodyweight (ml/kg/min) and RER were used to calculate resting and gross energy expenditure (restEE and grossEE, both in J/kg/min) using the following equation [22]:

$$EE(J/kg/min) = (4.940 \times RER + 16.040) \times VO_2(ml/kg/min)$$

Of the two resting tests, the test with the lowest restEE was subtracted grossEE to obtain net energy expenditure (netEE, J/kg/min). Gross and net energy cost (grossEC and netEC, J/kg/m) were calculated by dividing grossEE and netEE by speed (m/min).

2.4. Statistical analyses

Normal distributions of the included variables were evaluated and confirmed based on visual inspection of Q-Q-plots. To evaluate the differences in non-dimensional speed between gait conditions, a mixed model analysis was conducted with non-dimensional speed as dependent variable, gait condition was set as factor and subject as random factor to account for repeated measures. To evaluate the difference in grossEC and netEC between gait conditions, and the effect of within-subject variations of speed on grossEC and netEC, mixed model analyses were conducted. GrossEC and netEC were separately set as dependent variables and non-dimensional speed as independent variable. Gait condition was set as factor and subject as random factor to account for repeated measures. Univariate regression analyses were conducted to evaluate the relation between non-dimensional speed, growth-related subject characteristics, grossEC and netEC for each gait condition. Depending on the model, grossEC and netEC were set as dependent variables and non-dimensional speed, age, height, bodyweight and BSA as independent variables. Where visual inspections revealed curvilinear relations, quadratic terms were included in the specific models. The most appropriate model for each dependent variable is presented. Separate linear regression analyses were in addition conducted for the ascending and descending parts of the quadratic curves for growth-related subject characteristics, for comparisons to the linear relations.

Statistical analyses were carried out using SPSS version 27 (IBM Statistics). Statistical significance was set to $p < 0.05$.

3. Results

Characteristics of the children are reported in Table 1. Of the 42 participating children, 41 completed the gait conditions slow and comfortable walking, 42 fast walking, 39 jogging and 32 running. One child did not perform restEE measurements. Mean values, standard

Table 1
Characteristics of the participating children, presented as mean ± SD, 95% confidence interval (CI) and/or frequencies (N).

	Mean ± SD	95% CI	N
Gender (boys/girls)			23/19
Age (years)	10.6 y ± 2.6 y	10.2 y – 10.9 y	42
Height (cm)	149.7 ± 15.9	147.5 – 151.9	42
Bodyweight (kg)	43.4 ± 12.5	41.7 – 45.1	42
Body surface area (m^2)	1.34 ± 0.26	1.30 – 1.37	42

deviations, and the 95% confidence interval of restEE (J/kg/min), gait speed (m/min), grossEC (J/kg/m) and netEC (J/kg/m) are presented in Table 2.

Mixed model analyses showed that the non-dimensional speed significantly increased between the gait conditions, from an average of 0.33 during slow walking to an average of 0.94 during running ($p < 0.001$).

GrossEC showed a non-significant, concave up relation to within-subject variation in speed, with a turning point around comfortable/fast walking speed ($p = 0.2$, Fig. 1; Left column, Table 3). Testing between the gait conditions, did neither show a significant difference in grossEC between comfortable and fast walking ($p = 0.4$), nor between slow, walking, jogging, and running ($p < 0.4$). However, grossEC was significantly higher during the three latter conditions compared to comfortable and fast walking ($p < 0.01$).

NetEC showed a significant, linear relation to within-subject variation in speed, where non-dimensional speed explained 41% of the variance in netEC and increased from slow walking to running ($p < 0.001$, Fig. 1; Left column, Table 3). Testing between the gait conditions also showed a significantly higher netEC during fast walking, jogging, and running compared to slow and comfortable walking ($p < 0.006$), and during jogging and running compared to fast walking ($p < 0.001$). However, netEC was not significantly different between slow and comfortable walking ($p = 0.7$) nor between jogging and running ($p = 0.5$).

For each gait condition, grossEC was to a greater extent affected by the between-subject variation in speed compared to netEC (Fig. 1; Right column, Table 3). Linear regression analyses showed that non-dimensional speed explained between 3% and 29% of the variance in grossEC. With a one unit increase in non-dimensional speed, grossEC decreased with 6.75 J/kg/m during slow walking ($p = 0.006$), 3.23 J/kg/m during jogging ($p = 0.007$) and 3.97 J/kg/m during running ($p = 0.002$, Table 3). There were no significant relations between non-dimensional speed and netEC during slow, comfortable, or fast walking, nor jogging ($p > 0.2$). During running non-dimensional speed explained 18% of the variance in netEC, where an increase in speed was significantly related to decrease in netEC ($p = 0.02$).

Table 2
Speed and energy expenditure measures during rest and during the five gait conditions, presented as mean ± SD and 95% confidence interval (CI) with frequencies (N).

Condition	Mean ± SD	95% CI	N
	RestEE (J/kg/min)		
Rest	155.2 ± 47.1	140.3 – 170.1	41
	Speed (m/min)		
Slow walking	57.8 ± 14.9	53.1 – 62.5	41
Comfortable walking	79.7 ± 11.6	76.0 – 83.4	41
Fast walking	92.5 ± 13.4	88.3 – 96.7	42
Jogging	139.8 ± 23.6	132.1 – 147.4	39
Running	167.6 ± 30.5	156.6 – 178.6	32
	GrossEC (J/kg/m)		
Slow walking	5.46 ± 1.24	5.07 – 5.85	41
Comfortable walking	4.64 ± 1.01	4.32 – 4.96	41
Fast walking	4.81 ± 0.95	4.51 – 5.11	42
Jogging	5.64 ± 0.84	5.37 – 5.92	39
Running	5.60 ± 1.02	5.23 – 5.97	32
	NetEC (J/kg/m)		
Slow walking	2.61 ± 0.75	2.37 – 2.85	40
Comfortable walking	2.66 ± 0.66	2.45 – 2.88	40
Fast walking	3.08 ± 0.68	2.87 – 3.30	41
Jogging	4.48 ± 0.69	4.25 – 4.70	38
Running	4.61 ± 0.82	4.31 – 4.91	31

GrossEC was highly affected by growth-related subject characteristics, while netEC to a lesser extent, and with dissimilarity between the gait conditions (Fig. 2). Linear regression analyses showed that grossEC decreased with increase in age, height, bodyweight and BSA for all gait conditions (Fig. 2; Left column, Table 4).

For every year increase in age, there was a decrease in grossEC with the lowest value during jogging (0.15 J/kg/m) and the greatest value during slow walking (0.28 J/kg/m, $p < 0.006$). For every cm increase in height, there was a decrease in grossEC with the lowest value during jogging (0.02 J/kg/m) and the greatest value during slow walking (0.05 J/kg/m, $p < 0.009$). For every kg increase in bodyweight there was a decrease in grossEC with the lowest value during jogging (0.03 J/kg/m) and the greatest value during fast walking (0.05 J/kg/m, $p < 0.009$). Also, for every m^2 increase in BSA, there was a decrease in grossEC with the lowest value during jogging (1.4 J/kg/m) and the greatest value during slow walking (2.6 J/kg/m, $p < 0.007$). During slow walking, the growth-related subject characteristics explained between 25% and 35% of the variance in grossEC, during comfortable walking between 35% and 42%, during fast walking between 39% and 45%, during jogging between 17% and 23% and during running between 20% and 23%.

Quadratic regression analyses showed that significant relations between netEC and growth-related subject characteristics were mainly present during comfortable and fast walking (Fig. 2; Right column, Table 4). During comfortable walking, age and age^2, and BSA and BSA^2, explained 19% and 18% of the variance in netEC respectively ($p < 0.03$). Height and $height^2$, and bodyweight and $bodyweight^2$, explained 14% and 15% of the variance (borderline significant, $p < 0.06$). During fast walking, all growth-related subject characteristics in combination with their squared explained between 18% and 23% of the variance in netEC ($p < 0.03$). While during jogging, age and age^2 explained 15% of the variance (borderline significant, $p = 0.055$). The significant relations followed a concave down shape, where netEC increased until the turning point at approximately the age of ten years, height of 140 cm, bodyweight of 40 kg and BSA of 1.2 m^2. Linear regression analyses of the ascending and descending parts of the quadratic curves showed that netEC was barely affected of growth-related subject characteristics up to the turning points, while approximately half of the relations of the descending parts of the curves showed significant decreases in netEC with increases in age, height, bodyweight and BSA (Table 4).

4. Discussion

The aim of this study was to evaluate the effect of speed and growth-related subject characteristics on gross and net energy cost in typically developing children. Our findings show that grossEC was barely affected by within-subject variation in speed, but netEC was highly affected. Conversely grossEC was more affected by between-subject variations in speed compared to netEC. GrossEC decreased as age and body size increased, while this relation was less strong and non-linear for netEC.

The children participating in this study were instructed to walk slow, comfortable, and fast, and to jog and run. Our findings show that the speed significantly increased between the gait conditions, indicating that the speed instructions were consistent with the implementations. To walk at self-selected comfortable walking speed is thought to be close to an optimal, where the combination of step length, frequency and width diminishes the energy expenditure per meter [23]. Increasing deviations of these parameters are expected to increase the energy expenditure per meter and our findings of grossEC confirms this. Accordingly, grossEC was significantly higher during slow walking, jogging, and running

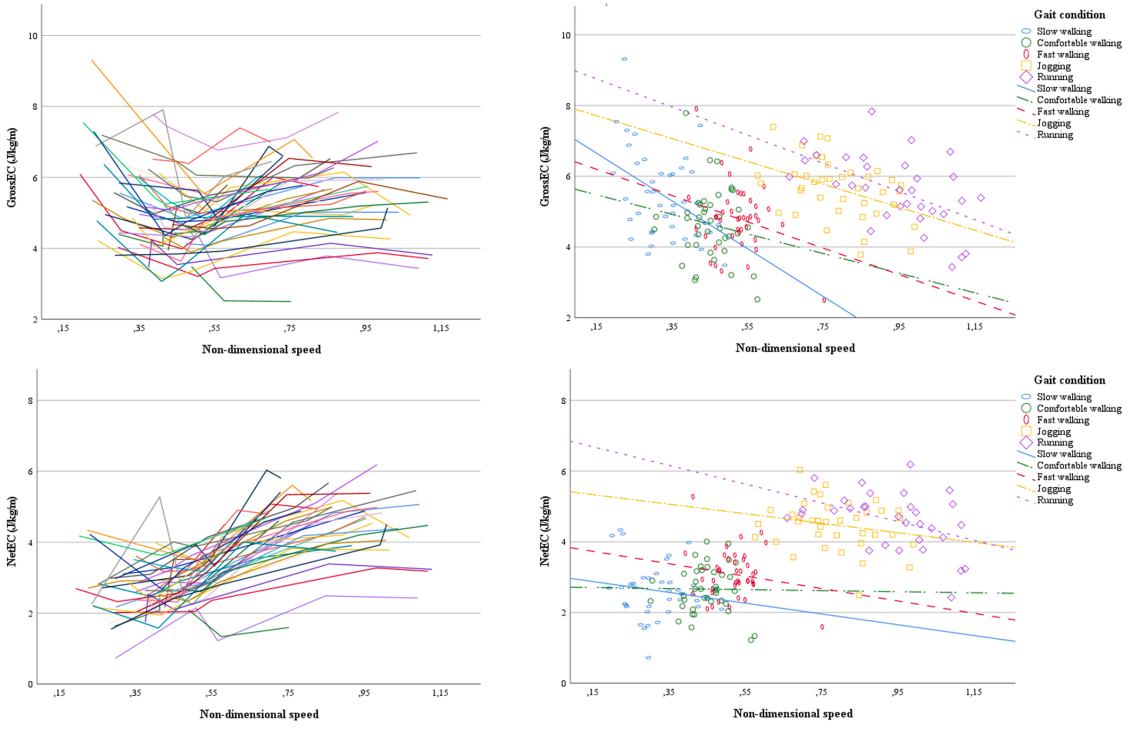

Fig. 1. GrossEC (top) and netEC (bottom, both in J/kg/m) as a function of non-dimensional speed, at individual level where each line represents one child (left column) and for the five gait conditions with fit lines of each condition (right column).

Table 3
Explained variance (R^2), statistical significance level (p-value) and slopes with standard errors (B (SE)) of regression models between gait speed and energy cost (EC). For the quadratic regression model of within-subject variation for grossEC, the B(SE) of the independent variable's squared is also presented. In addition, number of participants is presented (N). Significant relations are presented in bold (p-value <0.05).

	GrossEC (J/kg/m)				NetEC (J/kg/m)			
	R^2	p-value	B (SE)	N	R^2	p-value	B (SE)	N
Within-subject variation								
Non-dimensional speed	0.012	0.21	-2.02 (1.84)	42	**0.41**	**< 0.001**	**3.03 (0.27)**	**41**
Non-dimensional speed^2			1.74 (1.38)					
Between-subject variations								
Slow walking	**0.18**	**0.006**	**-6.75 (2.30)**	**41**	0.03	0.3	-1.53 (1.56)	40
Comfortable walking	0.03	0.3	-2.77 (2.66)	41	0.00	0.9	-0.15 (1.84)	40
Fast walking	0.06	0.1	-3.72 (2.25)	42	0.03	0.3	-1.76 (1.70)	41
Jogging	**0.18**	**0.007**	**-3.23 (1.14)**	**39**	0.05	0.2	-1.35 (1.03)	38
Running	**0.29**	**0.002**	**-3.97 (1.14)**	**32**	**0.18**	**0.02**	**-2.64 (1.03)**	**31**

compared to comfortable walking. NetEC on the contrary, increased from slow walking to running, implying comfortable walking speed is not the most beneficial energetically. These differences may be explained by the relative more prominent contribution of restEE to the total cost required for movement during slow walking, and the increasing relative contribution of cost required for movement with increasing speed [14].

Conducting energy expenditure measurements during various gait conditions makes it possible to evaluate how different gait speeds may affect the different measures of EC. NetEC has been recommended over grossEC due to its less effect of speed during comfortable walking [9]. However, gait speed is related to functional ability and may be a useful measure of disability [24]. Indeed, improvement in gait speed after treatment has been reported for children with cerebral palsy [25,26]. Our findings indicate that a potential decrease in EC as a result of increased gait speed, due to improved gait function, may be concealed using netEC when evaluating individual treatment effects. GrossEC may prove to be more robust against individual variations of speed and may therefore be expected to be more reliable. This agrees with previous studies, recommending grossEC as a more sensitive measure when evaluating clinically relevant changes at individual levels in children with cerebral palsy [15]. In addition, the observation that children with higher self-selected speed during specific gait condition have reduced grossEC, agrees with the expectation that children with better gait function have reduced EC of gait and increased speed [2,26,27].

Normalising energy expenditure to bodyweight should in theory allow for comparisons between different ages and body sizes, however our results indicate that this is not applicable for children in growth. Our

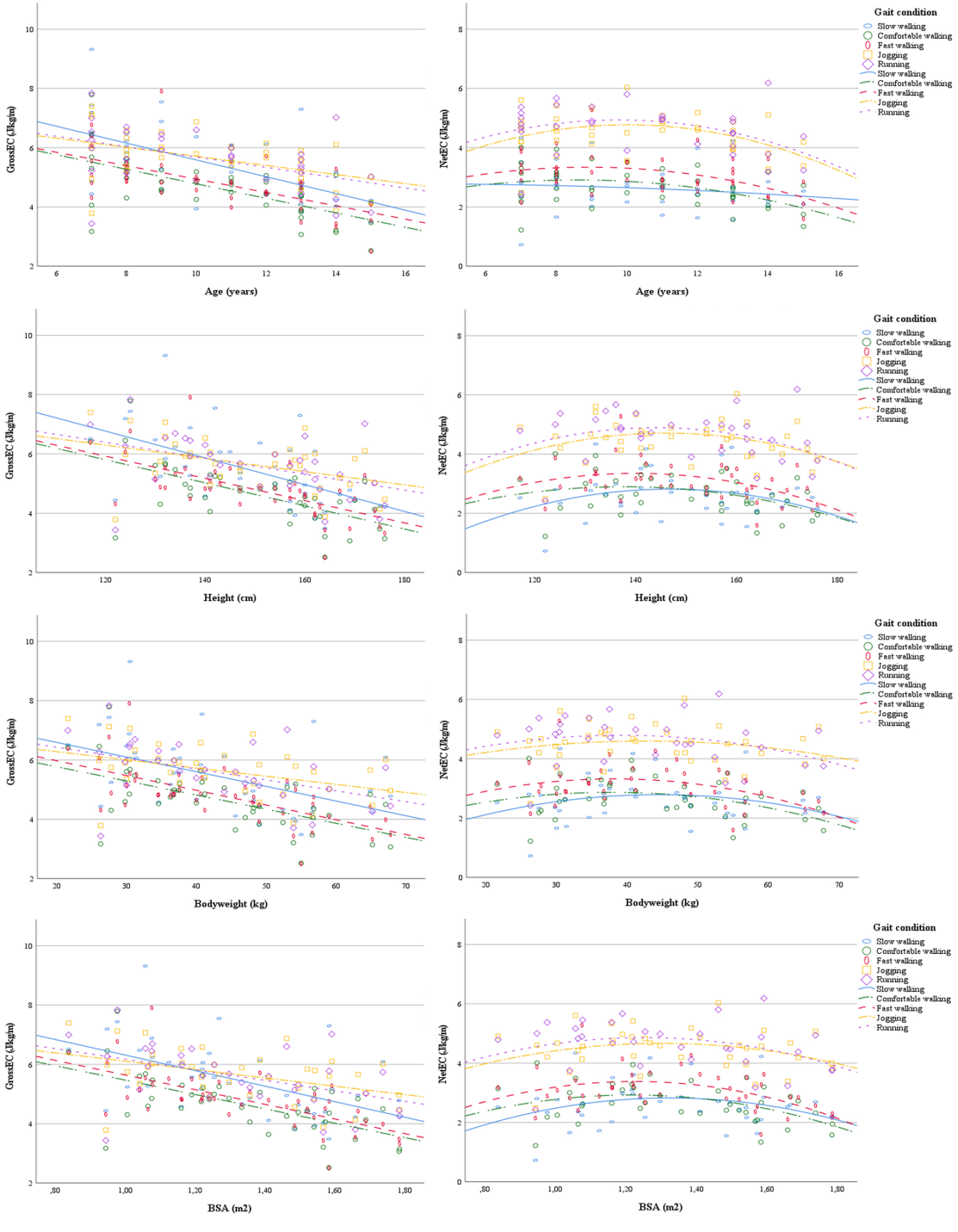

Fig. 2. GrossEC (left column) and netEC (right column, both in J/kg/m) as a function of age (top), height (second), bodyweight (third) and body surface area (BSA, bottom), for the five gait conditions with fit lines of each condition.

Table 4
Explained variance (R^2) and statistical significance level (p-value) of regression models between age, height, bodyweight, body surface area (BSA), and energy cost (EC). Slopes with standard errors of linear regression models are presented for grossEC (B (SE)). For illustration in comparison, slopes with standard errors of linear regression models for ascending (B_1 (SE_1)) and descending (B_2 (SE_2)) parts of the quadratic relations of netEC are presented. In addition, number of participants is presented (N). Significant relations are presented in bold (p-value <0.05) and borderline significant relations are presented in italic (p < 0.08).

	GrossEC (J/kg/m)				NetEC (J/kg/m)					
	R^2	p-value	B (SE)	N	R^2	p-value	B_1 (SE_1)	N	B_2 (SE_2)	N
Age (years)							<= 10 y		>=11 y	
Slow walking	**0.35**	**< 0.001**	**-0.28 (0.06)**	**41**	0.02	0.6	-0.05 (0.18)	*20*	-0.05 (0.12)	20
Comfortable walking	**0.42**	**< 0.001**	**-0.25 (0.05)**	**41**	**0.19**	**0.02**	0.02 (0.15)	20	**-0.20 (0.09)**	**20**
Fast walking	**0.39**	**< 0.001**	**-0.23 (0.05)**	**42**	**0.20**	**0.02**	0.08 (0.14)	20	-0.16 (0.09)	21
Jogging	**0.23**	**0.002**	**-0.15 (0.05)**	**39**	*0.15*	*0.055*	0.10 (0.17)	20	**-0.28 (0.09)**	**18**
Running	**0.23**	**0.006**	**-0.18 (0.06)**	**32**	0.13	0.1	0.14 (0.20)	16	-0.24 (0.15)	15
Height (cm)							<= 140 cm		>= 141 cm	
Slow walking	**0.33**	**< 0.001**	**-0.05 (0.01)**	**41**	0.07	0.2	0.03 (0.04)	13	**-0.03 (0.01)**	**27**
Comfortable walking	**0.39**	**< 0.001**	**-0.04 (0.01)**	**41**	*0.14*	*0.059*	-0.001 (0.04)	13	**-0.03 (0.01)**	**27**
Fast walking	**0.40**	**< 0.001**	**-0.04 (0.01)**	**42**	**0.18**	**0.03**	0.04 (0.03)	13	**-0.03 (0.01)**	**28**
Jogging	**0.19**	**0.005**	**-0.02 (0.01)**	**39**	0.11	0.1	0.04 (0.03)	13	-0.01 (0.01)	25
Running	**0.20**	**0.009**	**-0.03 (0.01)**	**32**	0.11	0.2	0.06 (0.04)	11	-0.02 (0.02)	20
Bodyweight (kg)							<= 40 kg		>= 41 kg	
Slow walking	**0.25**	**< 0.001**	**-0.05 (0.01)**	**41**	0.06	0.3	**0.07 (0.04)**	**20**	-0.02 (0.02)	20
Comfortable walking	**0.35**	**< 0.001**	**-0.05 (0.01)**	**41**	*0.15*	*0.052*	0.05 (0.03)	19	*-0.03 (0.02)*	*21*
Fast walking	**0.43**	**< 0.001**	**-0.05 (0.01)**	**42**	**0.19**	**0.02**	0.02 (0.03)	20	**-0.05 (0.02)**	**21**
Jogging	**0.17**	**0.009**	**-0.03 (0.01)**	**39**	0.04	0.5	0.04 (0.03)	19	-0.02 (0.02)	19
Running	**0.21**	**0.008**	**-0.04 (0.01)**	**32**	0.08	0.3	0.04 (0.05)	15	-0.03 (0.03)	16
BSA (m^2)							<=1.20 m^2		>= 1.21 m^2	
Slow walking	**0.29**	**< 0.001**	**-2.62 (0.65)**	**41**	0.08	0.2	1.91 (2.47)	14	**-1.53 (0.73)**	**26**
Comfortable walking	**0.39**	**< 0.001**	**-2.42 (0.49)**	**41**	**0.18**	**0.03**	0.80 (2.20)	13	**-2.09 (0.58)**	**27**
Fast walking	**0.45**	**< 0.001**	**-2.47 (0.43)**	**42**	**0.23**	**0.008**	1.73 (2.23)	14	**-1.85 (0.58)**	**27**
Jogging	**0.19**	**0.005**	**-1.41 (0.48)**	**39**	0.07	0.3	2.73 (2.22)	13	-0.94 (0.71)	25
Running	**0.22**	**0.007**	**-1.78 (0.61)**	**32**	0.11	0.2	3.35 (2.52)	12	-1.11 (1.01)	19

findings agree with previous research reporting a decrease in grossEC with increase in age and body size for children and adolescents [1,14,28]. Additionally, our study shows that this applies to different speeds of walking and running. Our findings confirm that grossEC is more affected by growth-related subject characteristics, compared to netEC [1,12,17]. Although less strong, linear inverse relations have been reported during self-selected comfortable walking speed for netEC, age and height [1]. However, even though the average speed, age and body size did not differ significantly from our study sample, we revealed quadratic relations, indicating that until a certain age and body size, gait gets less energy efficient.

Doing separate linear regression analyses on ascending and descending parts of the quadratic curves indicated that the older, taller, and heavier children changed their netEC with growth roughly in between 50% and 75% of the amount of grossEC (Table 4; comparing B_2 with B). Although this not always reached statistical significance, the amount would still be physiologically and clinically relevant. For the younger and smaller children, netEC was less affected by growth, but there was a greater spread in the data, like observed in other studies [1]. This may reflect the challenges of measuring restEE in the youngest children.

There are some considerations to highlight. There was no randomization of order of the conditions in the gait test, and the children themselves decided duration of rest in between the conditions. This could potentially have affected the energy expenditure measurements if they were more and more fatigued throughout the testing. However, the children were visually observed to ensure proper rest in between the conditions. Measuring resting energy expenditure in children may be challenging, and high within-subject variability has been reported both for typically developing children and children with cerebral palsy [15,16]. As an attempt to provide valid measurements, the resting protocol of the present study included both sitting and standing for three minutes each, where the lowest resting energy expenditure measure was used for subsequent calculations. Moreover, the procedures were carefully performed by ensuring the face mask was properly attached, giving explicit instructions, and monitoring of the measurements. However, this will be an element of uncertainty when it comes to using netEC measurements in children.

4.1. Conclusion

Evaluating grossEC and netEC during five different gait conditions showed that grossEC was less affected by within-subject variation in speed compared to netEC, indicating grossEC is favourable evaluating individual changes in EC. On the contrary, netEC was less affected by between-subject variations in speed. Where grossEC had a strong negative linear relation to growth-related subject characteristics during all gait conditions, netEC was less affected, but the relations were quadratic. NetEC showed the highest effect of growth-related subject characteristics during comfortable and fast walking. Our findings underpin the importance of being cautious when grossEC and netEC are used to evaluate children of different ages and body sizes, even during self-selected, comfortable walking speed.

Ethics approval and consent to participate

This study was approved by the Norwegian Centre for Research Data (NSD, Project nr: 469863). A written informed consent was signed by parents or guardians prior to participation and the study was performed in accordance with the Declaration of Helsinki.

Conflict of interest statement

The authors report no conflicts of interest.

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Paper III

Gagnat, Yngvild; Brændvik, Siri Merete; Ringheim, Inge; Roeleveld, Karin.
The relation of energy cost of walking with gait deviation, asymmetry, and lower limb muscle co-activation in children with cerebral palsy: a retrospective cross sectional study
.
This paper is awaiting publication and is therefore not included.

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