MOTOR CONTROL OF GAIT AND THE UNDERLYING NEURAL NETWORK IN PEDIATRIC NEUROLOGY

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MOTOR CONTROL OF GAIT AND THE UNDERLYING NEURAL NETWORK IN PEDIATRIC NEUROLOGY

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EDITORIAL
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Editorial: Motor Control of Gait and the Underlying Neural Network in Pediatric Neurology

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Keywords: gait, cerebral palsy, pediatric neurology, MRI, upper limb, ataxia, tDCS, Duchenne muscular dystrophy

Editorial on the Research Topic

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INTRODUCTION

Researchers around the world strive toward better understanding of the complexity and causes of movement disorders due to nervous system disease. Such research has mainly focused on adult neurological disorders such as stroke and Parkinson's disease, while significantly fewer studies have investigated pediatric populations. This may be caused by the complexity of nervous system diseases in children due to the combination of changes caused by disease and development. Therefore, within this research topic, we aimed at stimulating researchers to address important aspects of motor control and the underlying neural network in pediatric neurology.

Thirteen papers have been bundled in this eBook, including 1 review paper and 12 original research papers. Most of these papers focused on cerebral palsy (CP), which is not unexpected as CP is the most common developmental disorder associated with lifelong movement and posture disability (Aisen et al., 2011). One paper focused on Duchenne muscular dystrophy (DMD) and one on early-onset ataxia (EOA). We aimed to bundle papers on neural causes of movements disorders and their relation with motor function. Two included studies examined the link between brain lesions and motor control in CP (Grecco et al.,; Mailleux et al.,) and one review focused on the neural correlates of gait abnormalities in CP (Zhou et al.,). Understanding the neural control of movements in children with neurological disorders can help to improve existing or develop new rehabilitation strategies. Therefore, we also included papers that investigated (factors that influence) the control of movements, e.g., weakness, instability, and spasticity, which impact motor independence. None, however, focused on neuroimaging during gait.

CONTRIBUTIONS TO THE RESEARCH TOPIC

Two papers focused on upper limb reaching and grasping in CP. Mailleux et al. found a relation between structural brain damage and upper limb kinematics in unilateral CP. They found more aberrant patterns in children with cortical and deep gray matter lesions compared to children

with periventricular white matter lesions. Additionally, lesion location and extent had a greater influence on the kinematics in children with cortical and deep gray matter lesions. Importantly, damage to the posterior limb of the internal capsule was a predictor for the movement pattern. Simon-Martinez et al. estimated the impact of motor impairments on upper body kinematics. The results indicated that children with unilateral CP showed altered movement patterns in all joints during a large percentage of the movement cycle compared to typically developing (TD) children. Spasticity and muscle weakness had a negative effect on the movement pattern.

One contribution focused on gait in EOA. Lawerman et al. investigated the construct validity of the $SARA_{GAIT/POSTURE}$ subscales (Scale for Assessment and Rating of Ataxia) by relating these to existing balance scales (e.g., pediatric balance scale) and to a functional mobility classification system (GMFCS). They found a high construct validity for the $SARA_{GAIT/POSTURE}$ subscales. However, the scores discriminated insufficiently between the influence of ataxia and muscle weakness, which suggests the possible influence of ataxia (and muscle weakness) on the control of gait and posture in EOA.

Several contributions have identified important factors that influence gait in children with CP. Using muscle synergy analysis, Goudriaan et al. compared total variance accounted for by one synergy during gait in CP, which have neural and non-neural muscle weakness, with children with DMD, who have non-neural muscle weakness. They found that the complexity of the control of gait was not influenced by the non-neural constraints of muscle weakness, as the total variance accounted for by one synergy was similar between both groups. Contrarily, the importance of the influence of neural muscle weakness on the control of gait in CP was highlighted by a clear association between plantar flexor weakness and reduced synergy complexity in CP. This is in agreement with a paper by Nieuwenhuys et al. who examined the construct validity of a new gait classification system for CP. They were able to confirm that most joint patterns during gait are characterized by different patient-specific characteristics (such as age and GMFCS-level) and that they are often associated with muscle weakness and spasticity.

To reduce the negative effect of spasticity on gait, Botulinum Toxin treatment (BTX) may be an option. BTX, however, has been suggested to induce muscle weakness which may deteriorate gait in CP. Eek and Himmelmann found that voluntary plantar flexor muscle strength did not decrease after BTX-injections, but seemed to increase at 6-months follow-up. The muscle strength improvement and reduction of spasticity coincided with small improvements in gait kinematics.

A person's body weight may also influence gait in CP. To assess the effectiveness of interventions on gait in CP [as in (Eek and Himmelmann)], pre-post three-dimensional gait analyses are performed, usually with a considerable amount of time between measurements. Meyns et al. however, showed that clinical gait analysts should consider the negative effect of increased weight between pre-post measurements to avoid misinterpretation of interventions. They found that adding 10% body weight in children with CP, had detrimental effects on their spatio-temporal parameters, kinematics, and kinetics. As such, rehabilitation in CP should counteract overweight and obesity.

Also arm movements may have an effect on gait, as previous observational research indicated that children with CP show altered arm movements during walking related to instability (Meyns et al., 2011, 2012, 2016a). In the study by Delabastita et al. children with CP and TD children were required to walk with or without their arms free to swing while assessing trunk movements and gait stability. The results indicated that gait instability and trunk movements increased when arm swing was restricted in children with bilateral CP compared to TD children and children with unilateral CP. A related article by Meyns et al. focused on the possible contribution of the arm movements during gait on propulsion of the center of mass (CoM) in CP. They found that, even though it appeared that the contribution of the arm movements to propulsion of the CoM was larger in CP than in TD children, the contribution of the arms to forward propulsion was negligible compared to that of the legs and gravity. As such, the arms seem to have an important role in stability, but not in propulsion.

One contribution to the topic investigated neural correlates of gait in CP. Grecco et al. investigated the responsiveness to transcranial direct current stimulation combined with gait training. Their results revealed that the presence of a motor evoked potential in the quadriceps muscle was a predictor for gait velocity, while the presence of deeper (subcortical) injuries of the internal capsule was a predictor of gait kinematics and gross motor function.

Two contributions addressed motor learning in CP. Damiano et al. found that children with unilateral CP did not demonstrate poorer learning or retention of their gait pattern in a unilateral perturbation treadmill paradigm compared to TD children. In a follow-up paper by Bulea et al. they used a dynamical systems approach to provide insights in the complexity of the neural control of the legs in unilateral CP. The authors suggested that each leg and each type of walking has distinct neural circuits which can be adapted independently. As such, gait symmetry can be improved in the short term. This highlights the possible use of such paradigms in gait rehabilitation to increase step symmetry in unilateral CP.

Finally, Zhou et al. provided a comprehensive review on brain injuries in CP, associated neuromuscular deficits and gait abnormalities and their neural correlates with a focus on implications for rehabilitation. One of the findings was that only few studies (Meyns et al., 2016b) have examined the neural correlates of motor deficits and gait abnormalities in CP. Nevertheless, to truly assess the underlying neural networks of gait in pediatric neurology, future studies should implement neuroimaging techniques during gait (Makeig et al., 2009; Gwin et al., 2010; Wagner et al., 2012) in these populations which will provide good evidence for the motor control of gait.

With the current research topic, we stimulated researchers to focus on movement control and the underlying neural network in pediatric neurology. It has been shown that there are apparent changes in the relation between brain functional connectivity and the progression of walking and gross motor abilities from infancy to the toddler period (Marrus et al., 2018). Future research may focus on differences in the alterations of these network-level brain–behavior relationships between natural development or neurodevelopmental conditions. Given the scarcity of

research on the neural correlates and the underlying neural networks of gait in pediatric neurology, we urge researchers and funding agencies to invest time and resources on this topic as this will help to discover targeted treatment opportunities that can substantially improve functional outcomes for these children.

AUTHOR CONTRIBUTIONS

PM was topic editor of the Special Research Topic. MvdK, EO, and KD were co-editors of the Special Research Topic. PM wrote the paper. MvdB, KT, MvdK, EO, and KD edited and revised the paper.

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Non-neural Muscle Weakness Has Limited Influence on Complexity of Motor Control during Gait

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Cerebral palsy (CP) and Duchenne muscular dystrophy (DMD) are neuromuscular disorders characterized by muscle weakness. Weakness in CP has neural and non-neural components, whereas in DMD, weakness can be considered as a predominantly non-neural problem. Despite the different underlying causes, weakness is a constraint for the central nervous system when controlling gait. CP demonstrates decreased complexity of motor control during gait from muscle synergy analysis, which is reflected by a higher total variance accounted for by one synergy ($tVAF_1$). However, it remains unclear if weakness directly contributes to higher $tVAF_1$ in CP, or whether altered $tVAF_1$ reflects mainly neural impairments. If muscle weakness directly contributes to higher $tVAF_1$, then $tVAF_1$ should also be increased in DMD. To examine the etiology of increased $tVAF_1$, muscle activity data of gluteus medius, rectus femoris, medial hamstrings, medial gastrocnemius, and tibialis anterior were measured at self-selected walking speed, and strength data from knee extensors, knee flexors, dorsiflexors and plantar flexors, were analyzed in 15 children with CP [median (IQR) age: 8.9 (2.2)], 15 boys with DMD [8.7 (3.1)], and 15 typical developing (TD) children [8.6 (2.7)]. We computed $tVAF_1$ from 10 concatenated steps with non-negative matrix factorization, and compared $tVAF_1$ between the three groups with a Mann-Whiney *U*-test. Spearman's rank correlation coefficients were used to determine if weakness in specific muscle groups contributed to altered $tVAF_1$. No significant differences in $tVAF_1$ were found between DMD [$tVAF_1$: 0.60 (0.07)] and TD children [0.65 (0.07)], while $tVAF_1$ was significantly higher in CP [(0.74 (0.09)] than in the other groups (both $p < 0.005$). In CP, weakness in the plantar flexors was related to higher $tVAF_1$ ($r = -0.72$). In DMD, knee extensor weakness related to increased $tVAF_1$ ($r = -0.50$). These results suggest that the non-neural weakness in DMD had limited influence on complexity of motor control during gait and that the higher $tVAF_1$ in children with CP is mainly related to neural impairments caused by the brain lesion.

Keywords: cerebral palsy, Duchenne muscular dystrophy, motor control, muscle synergies, gait analysis, muscle weakness

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INTRODUCTION

Two of the most common neurological and neuromuscular diseases in childhood are cerebral palsy (CP) and Duchenne muscular dystrophy (DMD) (Sussman, 2002; Rosenbaum et al., 2007; Graham et al., 2016). CP is defined as "a group of permanent disorders of the development of movement and posture, causing activity limitations attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" (Rosenbaum et al., 2007). DMD is characterized by an altered gene on the X-chromosome, which codes for the protein dystrophin. Lack of dystrophin in muscles leads to a disbalance between damage and repair of the muscle fibers (Kobayashi and Campbell, 2012). This damage results in muscles that predominantly consist of fat and fibrous tissue (Sussman, 2002; Jones et al., 2010). Although CP and DMD have different origins and expressions, they have at least one symptom in common: muscle weakness. In both groups, muscle weakness is considered an important contributor to their pathological gait patterns (Sutherland et al., 1981; D'Angelo et al., 2009; Gage et al., 2009; Gaudreault et al., 2010; Doglio et al., 2011; Ganea et al., 2012; Steele et al., 2012).

There are only a small number of studies describing DMD gait (Sutherland et al., 1981; D'Angelo et al., 2009; Gaudreault et al., 2010; Doglio et al., 2011; Ganea et al., 2012; Ropars et al., 2016). Furthermore, none of these studies have verified to what extent these gait deviations were associated with muscle weakness (Sutherland et al., 1981; D'Angelo et al., 2009; Gaudreault et al., 2010; Doglio et al., 2011; Ganea et al., 2012; Ropars et al., 2016). In CP, several researchers have analyzed the relationship between muscle weakness and gait impairments, but their results are inconsistent (Damiano et al., 1995, 2010; Wiley and Damiano, 1998; Desloovere et al., 2006; Lee et al., 2008; Dallmeijer et al., 2011; Eek et al., 2011; Sagawa et al., 2013; Meyns et al., 2016; Shin et al., 2016). In DMD, muscle weakness is caused by non-neural changes in muscle morphology, whereas in CP, muscle weakness has neural as well as non-neural components. Neural components are considered the primary cause of weakness and are the result of the original brain injury (Gage et al., 2009). Examples include altered motor unit recruitment patterns and decreased selective motor control (Gage et al., 2009; Mockford and Caulton, 2010). Non-neural components are considered secondary causes of muscle weakness in CP (Gage et al., 2009), including changes in muscle morphology or lever-arm dysfunction due to bony deformities (Gage et al., 2009; Barrett and Lichtwark, 2010). The effect of these neural and non-neural changes on gait can be very different than their effect on strength assessments, such as maximal voluntary isometric contractions (MVICs). This could be an important reason for the discrepancies in previous studies analyzing the relationship between muscle weakness and altered gait in CP.

Despite the lack of consensus on how muscle weakness contributes to impaired gait, there is no doubt that it is a constraint the central nervous system (CNS) needs to deal with when initiating and controlling gait. Since children with CP and boys with DMD have different etiologies of weakness, the evaluation of how the CNS copes with muscle weakness in both populations has the potential to increase our understanding of the relationship between muscle weakness and gait deviations. In particular, it will help to differentiate between the relative effects of both neural and non-neural components of weakness on gait.

The regulation of human gait is not entirely understood, largely due to the abundant degrees of freedom (DOFs) and complexity of the human body (Latash, 2012). One of the theories for how humans control this abundance, is the use of muscle synergies instead of individual control of each muscle. Muscle synergies have been defined as the "consistent patterns of multi-muscle coordination that generate specific action" (Ting et al., 2015). Synergistic patterns of muscle recruitment have been well documented during various rhythmic tasks, including walking (d'Avella et al., 2003; Dietz, 2003; Nielsen, 2003; Barroso et al., 2013). Central pattern generators in the spinal cord and supra-spinal structures are thought to contribute to the regulation of these synergistic muscle activations (Lacquaniti et al., 1999; Dietz, 2002, 2003; Nielsen, 2003; Petersen et al., 2012). Synergies are flexible, thereby allowing to compensate for internal and external disturbances without affecting the outcome of the intended movement (Latash et al., 2002; Ting et al., 2015). This suggests that neural as well as non-neural components can affect synergies (Kutch and Valero-Cuevas, 2012; Bizzi and Cheung, 2013; Clark, 2015). In synergy analysis, evaluating the "total variance accounted for" (tVAF) by a given number of synergies can quantify the complexity of an individual's muscle activation patterns during dynamic tasks. The tVAF by one synergy ($tVAF_1$) can provide a summary measure of synergy complexity. When $tVAF_1$ is high, one synergy can explain a large part of the variance in muscle activity, representing a decrease in complexity of motor control during the analyzed task (Steele et al., 2015; Ting et al., 2015). Individuals with a CNS motor lesion, such as in CP or stroke, have higher $tVAF_1$ during gait than age-related healthy controls (Clark et al., 2010; Clark, 2015; Steele et al., 2015; Tang et al., 2015; Ting et al., 2015). Further, this decrease in complexity of motor control in children with CP was found to be related to muscle weakness (Steele et al., 2015). However, in these prior studies, muscle weakness was measured via a global summary score from manual muscle testing (MMT) (Steele et al., 2015). Not only does MMT have low reliability in young children with developmental disabilities (Mahony et al., 2009), but these analyses also limit our understanding of whether weakness of specific muscles affects control of gait.

If muscle weakness is a constraint for the CNS, it could limit the available degrees of freedom (DOFs) and negatively influence complexity of motor control, not only in CP, but also in boys with DMD. In children with CP, there is one confounding factor: the influence of the brain lesion on synergies and muscle weakness. Alterations in the CNS, such as the brain lesion in CP, affect a substantial part of synergy regulation (Lacquaniti et al., 1999; Dietz, 2002, 2003; Nielsen, 2003; Petersen et al., 2012). This brain lesion also underlies muscle weakness (its neural component) (Gage et al., 2009; Mockford and Caulton, 2010). The relationship between muscle weakness and $tVAF_1$ found in the previous study (Steele et al., 2015) could be caused by their mutual underlying source: the alterations in the CNS. This poses the research question: is muscle weakness contributing to higher

$tVAF_1$ during gait in children with CP or is the higher $tVAF_1$ a quantification of the underlying brain lesion?

The primary goal of this research was to compare and contrast the impact of muscle weakness on $tVAF_1$ extracted from synergy analysis during gait for children with CP and DMD. We evaluated $tVAF_1$ during gait at self-selected walking speed for three groups of children: children with CP, children with DMD, and TD children. We expected decreases in complexity of motor control (increase in $tVAF_1$) in both CP and DMD children when compared to a control group of TD children. However, in children with CP, due to the addition of a neural component of muscle weakness, a higher $tVAF_1$ was expected than in DMD. As a secondary goal, we also sought to analyze the effect of muscle weakness of four muscle groups (knee extensors, knee flexors, plantar flexors, and dorsiflexors) on complexity of motor control. Muscle weakness was assessed via MVICs with a standardized protocol, using a hand-held dynamometer (HHD) in a fixed position (Goudriaan et al., 2018). We hypothesized that of the four measured muscle groups, the plantar flexors would be largely responsible for higher $tVAF_1$ in both CP and DMD, because of their importance during gait (van der Krogt et al., 2012). For an overview of the complete study design we refer to **Table 1**.

MATERIALS AND METHODS

In preparation of this study, we performed a power analysis based on a pilot study (Goudriaan et al., 2016) to determine the sample size of the three groups (CP, DMD, and TD; **Table 1**). The pilot study indicated that for an effect size of $d = 1.23$, $\alpha = 0.05$, and power $(1\text{-}\beta) = 0.80$ a minimal sample size of 12 participants per group would be required to test our main hypothesis (GPower 3.1.9, Faul et al., 2007).

Subjects

We recruited 15 children with CP [median age (interquartile range): 8.9 (2.2)], 15 boys with DMD [8.7 (3.1)], and 15 typical developing (TD) children [8.6 (2.7)] (**Table 2**). Supplementary Tables 1–3 provide detailed subject characteristics. We asked the children with CP to participate at the time of their routine clinical gait analysis at the Clinical Motion Analysis Laboratory of the University Hospital of Pellenberg (CMAL-Pellenberg) or when they agreed to take part in a large European study, namely the MD-Paedigree project: A Model-Driven Pediatric European Digital Repository, partially funded by the European Commission under P7-ICT-2011-9 program (600932). Inclusion criteria were: (1) diagnosed with bilateral or unilateral CP without signs of dyskinesia, (2) Gross Motor Function Classification System (GMFCS) Levels I-II, (3) no Botulinum Toxin-A treatment within 6 months prior to the assessments, and (4) no history of lower limb surgery.

The children with DMD were recruited from the database of the neuromuscular reference center in the University Hospital of Gasthuisberg. If they agreed to participate in MD-Paedigree, we asked them to perform the additional strength measurements needed for the current study. For the DMD children the inclusion criteria were: (1) diagnosed with DMD and (2) no history of lower-limb surgery.

Colleagues and students working at the Clinical Motion Analysis Laboratory of the University Hospital of Pellenberg (CMAL-Pellenberg) assisted with the recruitment of the TD children. The inclusion criteria for the TD children was that they should not have any neurological or neuromuscular problems.

All children were evaluated at the CMAL-Pellenberg. The local ethics committee (Commissie Medische Ethiek KU Leuven) approved this study (S56041), under the Declaration of Helsinki. All the participants' parents or caretakers signed a written informed consent. All participants of 12 years of age or older also signed the informed consent.

Data Collection

We collected gait kinematics, kinetics, and muscle activity data at self-selected walking speed with 3D motion analysis. We used the marker set of the lower limb Plug-in-Gait (PiG) model and marker trajectories were tracked using a 10 to 15-camera VICON system (Nexus 1.8.4. Vicon-UK, Oxford, UK), sampled at 100 Hz. Muscle activity data were collected with surface electromyography (sEMG) bilaterally from the rectus femoris (REF), vastus lateralis (VAL), medial hamstrings (MEH), biceps femoris (BIF), medial gastrocnemius (GAS), soleus (SOL), tibialis anterior (TIA) and the gluteus medius (GLU), with a 16-channel telemetric sEMG system (Zerowire, Cometa, Italy) at 1,000 or 1,500 Hz. Based on the guidelines of Seniam, we attached circular Ag/AgCl electrodes with an area of 1 cm^2 and an interelectrode distance of 2 cm on the skin (Hermens et al., 1999).

All participants performed MVICs of the knee extensors (KE), knee flexors (KF), dorsiflexors (DF) and plantar flexors (PF) evaluated using a telemetric hand-held dynamometer (HHD) MicroFet® 2 (Hogan Health Industries, West Jordan, UT USA). To decrease compensatory mechanisms and influence of the assessor on MVIC-outcomes, we used a custom-made chair in which the participants were secured with straps around the pelvis and upper legs, and the HHD was fixed to the chair. We placed the HHD at 75% of the segment length (**Figure 1**) and applied a gravity correction for those MVICs where gravity influenced the output data (KF MVIC and PF MVIC), by subtracting the gravitational torque in rest position from the MVIC-outcomes (Boiteau et al., 1995; Goudriaan et al., 2018). The children first performed one test trial, followed by three actual MVICs, with a duration between 3 and 5 s. Between each trial, the children rested at least 10 s, and between each muscle group, they had a resting period of at least 2 min. During the measurements, the children had visual feedback and were verbally encouraged.

Data Analysis

In the children with CP and the boys with DMD, we first collected the gait analysis data and a standard clinical exam (range of motion, spasticity levels by Modified Ashworth and Tardieu scales, and strength by MMT) and then measured the MVICs by means of dynamometry. Based on the individual child's cooperation during and after the gait analysis and whether the child was fatigued, we decided to collect either bilateral or unilateral MVICs. In case of unilateral MVICs, we always chose the most involved side, based on the outcomes of the standard clinical exam. For the children with CP or DMD, we

TABLE 1 | Research design.

Research design		
Main research question	**Sub question**	
RESEARCH QUESTIONS		
Does muscle weakness contribute to higher $tVAF_1$ during gait in children with CP and boys with DMD compared to TD peers? Or is higher $tVAF_1$ in CP related to the underlying brain lesion in CP (expressing the reduction of available DOFs due to the lesion)?	Is weakness of individual muscle groups associated with $tVAF_1$ during gait?	
HYPOTHESES		
Complexity of motor control is influenced by muscle weakness, since muscle weakness could be considered a constraint decreasing the available degrees of freedom during gait	Muscle weakness in the plantar flexors is expected to have the largest influence on the complexity of motor control	
SUBJECTS		
cerebral palsy $N = 15$	Duchenne muscular dystrophy $N = 15$	Typically-developing children $N = 15$
3D gait analysis	**Maximal voluntary isometric contractions**	
DATA COLLECTION		
Kinematics and kinetics sEMG of rectus femoris, medial hamstrings, tibialis anterior, gastrocnemius (medial) and gluteus medius	Knee extension Knee flexion Dorsiflexion Plantar flexion	
DATA ANALYSIS		
Calculation of $tVAF_1$ using NNMF on sEMG data from 10 concatenated steps Non-dimensional walking speed	Calculation of torque normalized to bodyweight, averaged over three trials	
Main research question	**Sub question**	
STATISTICAL ANALYSIS		
Kruskal-Wallis *H*-test with *post-hoc* Mann-Whitney *U*-test to determine differences in $tVAF_1$, walking speed and maximal voluntary contractions between the three groups	Spearman's rank correlation coefficient with classification of Altman	

DOFs, degrees of freedom; N, number; NNMF, non-negative matrix factorization; sEMG, surface electromyography; $tVAF_1$, total variance accounted for by one synergy.

TABLE 2 | Subject characteristics.

	CP	DMD	TD
	Median (25–75%)		
Gender	**Boys: 7; Girls: 8**	**Boys: 15**	**Boys: 11; Girls: 4**
Diagnosis specifics	H: 8; D:7		
GMFCs level	I: 6; II:9		
Age (years)	8.9 (7.6–9.8)	8.7 (6.8–9.9)	8.6 (7.3–10.0)
Weight (kilograms)	29.0 (22.2–35.7)	23.7 (19.7–33.8)	27.4 (22.6–31.9)
Height (meters)	1.30 (1.20–1.39)	1.16 (1.10–1.29)	1.32 (1.26–1.36)

CP, cerebral palsy; D, diplegic; DMD, Duchenne muscular dystrophy; H, hemiplegic; TD, typical developing.

only included their most involved side in the analyses. In the TD children, MVICs were always collected bilaterally after the gait analysis. Based on the outcomes of the MVICs, we used the weakest leg for further analyses. All available clinical outcome measures are reported in Supplementary Tables 1–3.

We analyzed the sEMG data from five (REF, MEH, TIA, GAS, and GLU) of the eight muscles that were measured during gait. We excluded the VAL, the BIF, and the SOL from all analyses, because their activation patterns (and function) during gait are roughly the same as the REF, MEH, and GAS respectively (Winter, 1987). Also, these five muscles are the most common muscles to be evaluated during standard clinical gait and synergy analyses. For all participants, we selected 10 representative steps. The sEMG signals were filtered with a 6th order Butterworth bandpass filter with cut-off frequencies of 20 and 450 Hz. The signals were rectified and smoothed with a 4th order Butterworth lowpass filter with a frequency of 10 Hz (Shuman et al., 2017). We resampled the filtered sEMG signals of each step at 101 data points, representing 0–100% of a gait cycle. We then concatenated all resampled gait cycles and normalized the signals to the average amplitude of the 10 steps per muscle for each child.

We calculated synergies using non-negative matrix factorization (NNMF) (Lee and Seung, 1999; Ting and Macpherson, 2005; Oliveira et al., 2014; Shuman et al., 2016a) with the NNMF function in MATLAB (The Mathworks Inc., Natick, M.A., 2010) using the following settings: 50 replicates, 1,000 max iterations, $1*10^{-4}$ minimum threshold for convergence, and a $1*10^{-6}$ threshold for completion (Shuman et al., 2016a). NNMF decomposes the sEMG signals into two

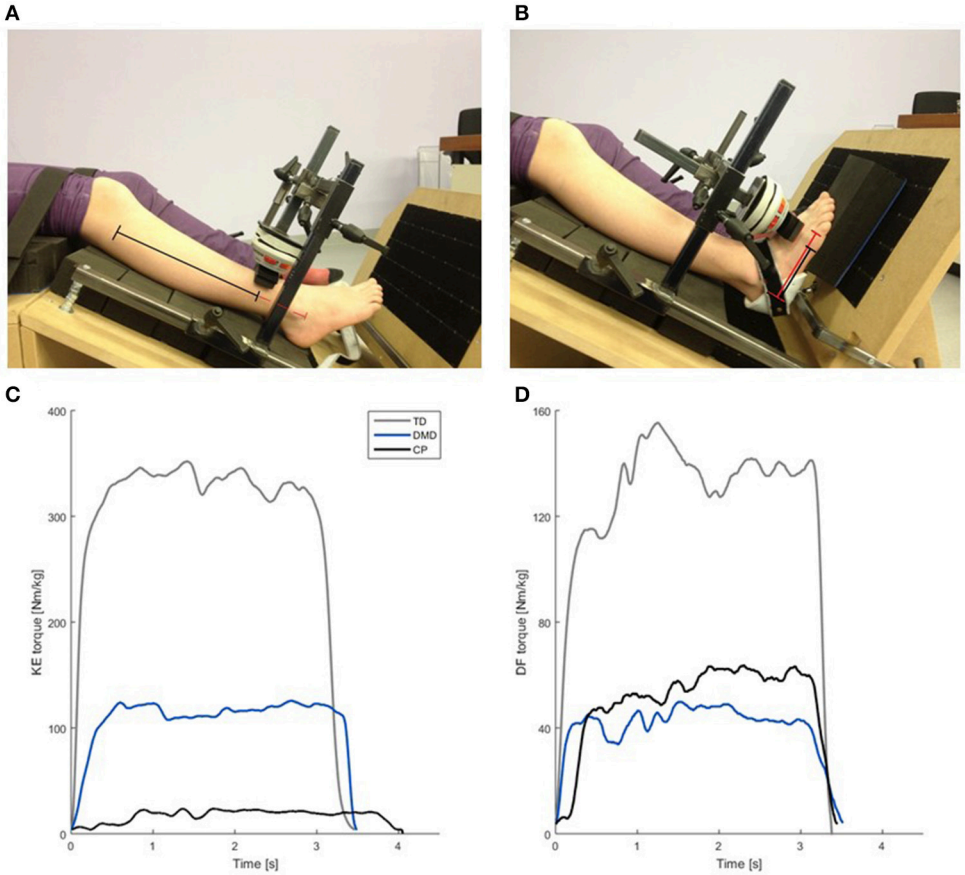

FIGURE 1 | Custom made chair used for the MVIC measurements **(A,B)**, including an example of the normalized net joint torque (Nm/kg) curves collected during the MVIC measurements **(C,D)**. **(A)** Test position for KE MVIC. The black + red lines represent the segment length (fibula head—lower border of lateral malleolus). The black line indicates the moment arm (75% of the segment length). **(B)** Test position for the DF MVIC. The red line represents the segment length (projection of lateral malleolus on lateral border of the foot—distal metacarpal head V). The black line indicates the moment arm (75% of the segment length). **(C)** Normalized knee extension torque (Nm/kg) of a representative KE MVIC of one child with TD (gray), a boy with DMD (blue) and a CP child (black) of similar age. **(D)** Normalized dorsiflexion torque in (Nm/kg) during a representative DF MVIC of the same children as used in **(C)**. Please note the scaling of the axes in **(C,D)** is not the same, due to difference between the knee extensors and the dorsiflexors in torque output. CP, cerebral palsy; DMD, Duchenne muscular dystrophy; DF, dorsiflexion; KE, knee extension; MVIC, maximal voluntary isometric contraction; Nm/kg, Newton meter per kilogram bodyweight; TD, typical developing; s, seconds.

matrices: W containing the synergy weights, which are the weighted contributions of each included muscle to each synergy, and C, the synergy activations, such that:

$$sEMG = (W_{m*n} * C_{n*t}) + error \quad (1)$$

In Equation (1), n is the number of synergies (one in this study), m is the number of muscles (five in this study), t is the number of data points (10*101 = 1,010 in this study), and *error* is the difference between the measured sEMG data and the reconstructed sEMG signals from the calculated synergies. The *error* value was then used to calculate tVAF as:

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

From an early age, contractile tissue of the muscles in children with DMD is replaced with fibrofatty tissue (Jansen et al., 2012). Fibrofatty tissue in the muscles might function as an additional lowpass filter (Farina et al., 2002), reducing $tVAF_1$ (van der Krogt et al., 2016; Shuman et al., 2017). We therefore calculated the power spectral density (PSD) of the bandpass filtered (20–450 Hz) sEMG signals with the PWELCH function in MATLAB using the following inputs: a window size of 1,024 samples, an overlap of 512 samples, 500 points to use in the Fourier transform, and the sample frequency of the sEMG signals (1,000 or 1,500 Hz). From the PSDs, we calculated the median frequency curves to compare group differences.

Walking speed (in m/s) was extracted from the gait data for each child and converted to a non-dimensional value with the formula of Hof (1996) to determine whether differences in walking speed could explain potential differences in $tVAF_1$ between the three groups (Ivanenko, 2005; Shuman et al., 2016a). Force data (in Newtons) from the MVICs was resampled to 100 Hz and the average maximal force out of three trials was calculated (Willemse et al., 2013; Goudriaan et al., 2018).

Subsequently, the net joint torque normalized to bodyweight (Nm/kg) was determined for all MVICs for each participant (Supplementary Tables 1–3).

Statistical Analysis

Since the data were not normally distributed, we used non-parametric tests in SPSS (SPSS Inc., Chicago, IL). We used a Kruskal-Wallis *H*-test and a *post-hoc* Mann-Whitney *U*-test with Bonferroni correction (resulting in the critical $p = 0.005$) to determine if there were significant differences in $tVAF_1$, non-dimensional walking speed, and MVICs between the three groups (CP, DMD, and TD). The PSD-plots were visually inspected for each muscle. We analyzed the relationship between $tVAF_1$ and muscle weakness in each individual muscle group with Spearman's rank correlation coefficients. We used the Altman classification (<0.20 = poor; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = good; 0.81–1.00 = very good) to interpret the correlation coefficients (Altman, 1991).

RESULTS

In the three study groups (CP, DMD, and TD), all five muscles showed good quality sEMG data for all 10 concatenated steps and could be included in the NNMF analysis, with the exception of the GLU for one of the TD children. The outcomes of the Kruskal-Wallis *H*-Test showed significant group differences for all assessed parameters (all $p < 0.005$). The results of the *post-hoc* Mann Whitney *U*-test on all parameters are plotted in **Figure 2**.

The $tVAF_1$ was significantly higher in the children with CP compared to DMD and TD children (both $p < 0.005$). No significant differences in $tVAF_1$ were found between the boys with DMD and the TD children. Median values for $tVAF_1$ were 0.74 in CP, 0.60 in DMD, and 0.65 in the TD children. The interquartile ranges (IQRs) were similar for the three groups, 0.09 for the children with CP, and 0.07 for both the boys with DMD and the TD children.

The children with CP and DMD walked slower than the TD children, but this was only significant for the children with CP ($p < 0.005$). Median values and IQRs for non-dimensional walking speed were: 0.40 (0.07) for the CP children, 0.42 (0.05) in the boys with DMD, and 0.48 (0.10) in the TD children.

The TD children were significantly stronger in all four muscle groups than the children in the other two groups (CP and DMD, all $p < 0.005$). The TD children showed more inter-subject variability in MVICs compared to CP and DMD, which was indicated by the larger IQRs. Median values and IQRs in Nm/kg of the knee extensors were: 0.62 (0.26) in CP, 0.72 (0.37) in DMD, and 1.29 (0.83) in TD. For the knee flexors, these values were: 0.43 (0.37) in CP, 0.50 (0.21) in DMD, and 1.04 (0.41) in TD. The dorsiflexors had the lowest MVIC values in all groups, with median values (IQRs) of 0.07 (0.07) in CP, 0.10 (0.04) in DMD, 0.27 (0.08) in TD. For the plantar flexors, median MVIC values of 0.22 (0.19), 0.33 (0.22), and 0.86 (0.45) were found for the CP, DMD, and TD groups, respectively.

Only two moderate-to-high correlations ($r \leq 0.41$) were found between muscle weakness and $tVAF_1$. Increased weakness in the plantar flexors was associated with higher $tVAF_1$ in the CP children ($r = -0.72$). In the boys with DMD, weaker knee extensors were associated with higher $tVAF_1$ ($r = -0.50$) (**Figure 3**).

When examining the PSD-plots of the three groups, they showed similar frequency bands, but in DMD the power was lower in the proximal muscle groups (**Figure 4**).

DISCUSSION

This study evaluated synergy complexity and strength in two common neuromuscular disorders to explore the impact of the neural and non-neural factors of muscle weakness on neuromuscular control during walking. Due to the differing etiology of these populations, this analysis helps to evaluate which factors serve as constraints to the CNS and influence impaired movement. We hypothesized that muscle weakness contributes to altered synergies and complexity of control during gait in children with CP and DMD, expressed by increased $tVAF_1$ during gait compared to TD children. Contrary to this hypothesis, our results suggested that the complexity of control was not influenced by the non-neural constraints of muscle weakness, since $tVAF_1$ was not significantly different between the children with DMD and the TD children. However, we confirmed that children with CP had reduced synergy complexity and that muscle weakness in the plantar flexors was related to higher $tVAF_1$ during gait. In children with DMD, increased weakness in the knee extensors influenced $tVAF_1$, although not enough to result in significantly different $tVAF_1$ between DMD and TD.

Similar to previously reported results, $tVAF_1$ was higher in the children with CP than in the group of TD children (Steele et al., 2015; Tang et al., 2015; Shuman et al., 2016a). The children with CP walked significantly slower than the TD children, which suggests that the differences in $tVAF_1$ between CP and the TD children might be more pronounced than expressed in our results, since a faster walking speed can result in higher $tVAF_1$ (Ivanenko, 2005; Shuman et al., 2016a). It could be that $tVAF_1$ gives an indirect representation of the child's neural capacity, with a higher $tVAF_1$ reflecting a higher level of involvement and increased muscle weakness. This agrees with the findings of Rose and McGill (2005) who determined that muscle weakness in children with CP is largely caused by neural factors. Further, the region on the motor cortex responsible for the distal muscle groups of the lower limb, is closer to the phylogenetic older parts of the brain (Volpe, 2000; Stiles and Jernigan, 2010) and it has been suggested that the older regions of the motor cortex are involved in synergy regulation (Bizzi and Cheung, 2013). Combined with the importance of the plantar flexors during gait, this might explain why we only found a strong correlation between weakness of the plantar flexors and $tVAF_1$ during gait and not between $tVAF_1$ and the other muscle groups in CP.

We checked if fibrofatty tissue in the muscles of the boys with DMD could act as an additional lowpass filter (Farina et al., 2002; Jansen et al., 2012) thereby reducing $tVAF_1$ (van der Krogt et al., 2016; Shuman et al., 2017). In DMD, the proximal muscle groups are more involved than the distal muscle groups, which was also represented in the PSD-plots. While the three groups

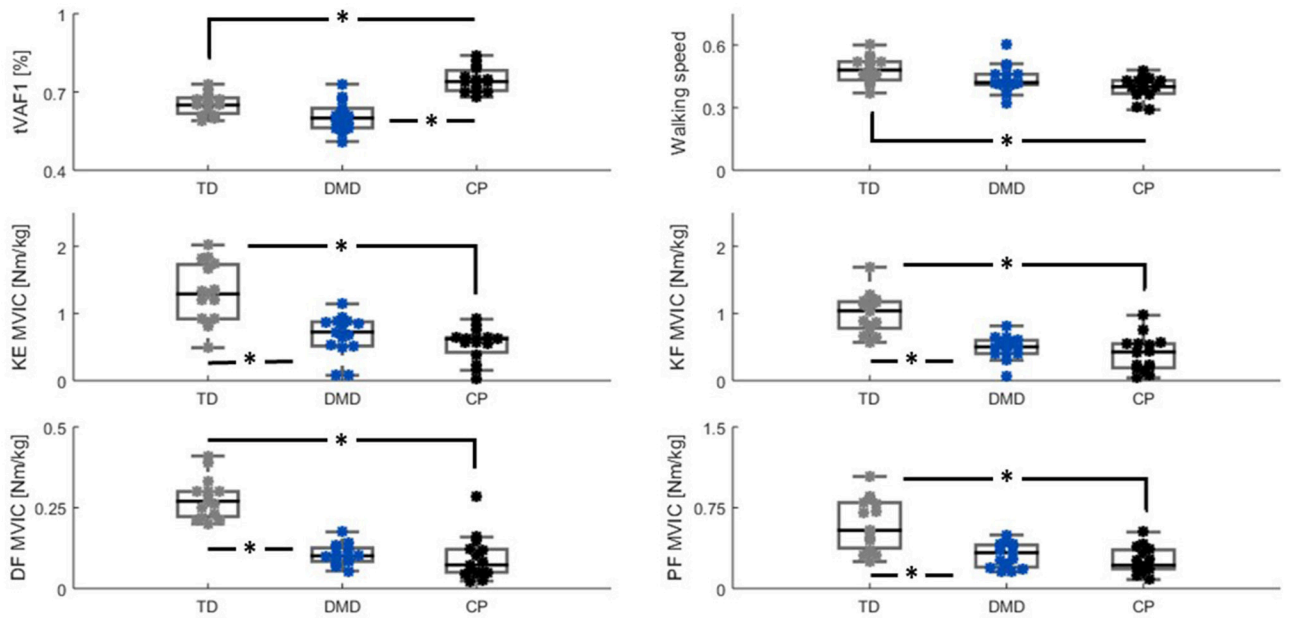

FIGURE 2 | Group differences (TD (gray), DMD (blue) and CP (black)) between $tVAF_1$, walking speed, and MVIC-outcomes. Significant differences ($p \leq 0.005$) based on the Mann-Whitney *U*-test are indicated with *. Please note the scaling on MVIC axes are not the same, due to differences in maximal net joint torque between muscle groups. CP, cerebral palsy; DMD, Duchenne muscular dystrophy; DF, dorsiflexion; KE, knee extension; KF, knee flexion; Nm/kg, Newton meter per kilogram bodyweight; MVIC, maximal voluntary isometric contraction; PF, plantar flexion; $tVAF_1$, total variance accounted for by one synergy; TD, typical developing.

A

Spearman's rho	$tVAF_1$		
	TD	DMD	CP
KE MVIC	0.19	**-0.50**	-0.09
KF MVIC	0.22	-0.07	-0.10
DF MVIC	0.19	0.06	-0.13
PF MVIC	-0.06	0.09	**-0.72**

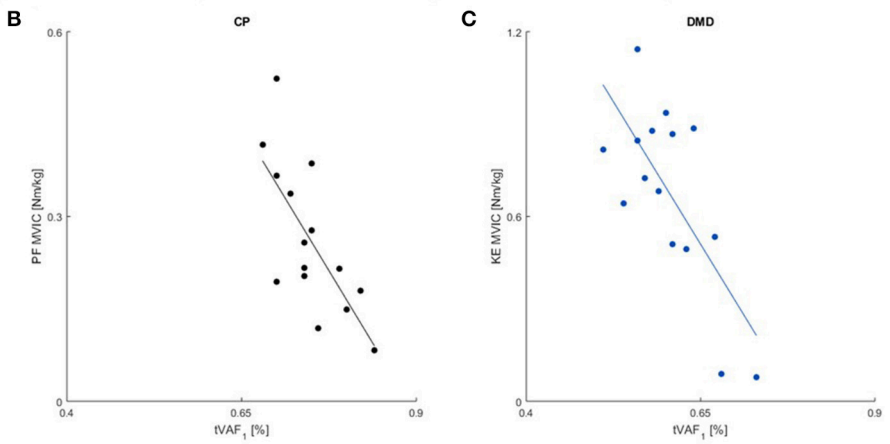

FIGURE 3 | (A) Spearman's rank correlation coefficients between MVIC outcomes and $tVAF_1$. Moderate or higher correlations ($r \leq 0.41$) are indicated in bold. There were significant associations between **(B).** PF MVIC and $tVAF_1$ in children with CP and **(C).** KE MVIC and $tVAF_1$ in children with DMD. Please note the scaling of the axes in **(B,C)** are not the same, due to differences in maximal net joint torque. CP, cerebral palsy; DMD, Duchenne muscular dystrophy; DF, dorsiflexion; KE, knee extension; KF, knee flexion; MVIC, maximal voluntary isometric contraction; PF, plantar flexion; TD, typical developing; $tVAF_1$, total variance accounted for by one synergy.

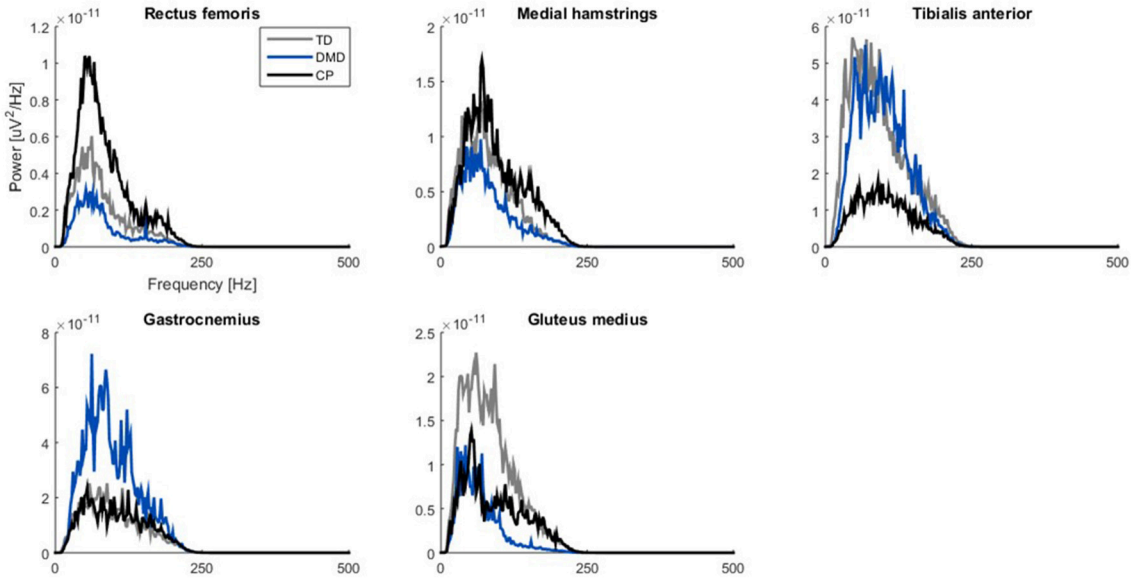

FIGURE 4 | Power spectrum density plots of filtered sEMG signals (20–450 Hz). Median curves are plotted for each group: TD (gray), DMD (blue) and CP (black). Please note the scaling of the axes is not the same, due to differences between muscles. CP, cerebral palsy; DMD, Duchenne muscular dystrophy; Hz, Herz; TD, typical developing; μV, microvolts.

showed similar frequency bands for all five muscles, the power was lower in the REF, MEH, and GLU muscles in the children with DMD. In children with DMD, fiber type IIb is the first fiber type to degenerate, which will have an influence on the frequency distribution, since these are the fast fibers connected to the motor units with the higher firing frequencies (Stackhouse et al., 2005; Jones et al., 2010).

In the children with DMD, the knee extensors are one of the most involved muscle groups (Sussman, 2002), which could explain the moderate negative correlation between the outcomes of the KE MVIC and $tVAF_1$. But, this non-neural weakness of the knee extensors did not sufficiently limit the complexity of control to create a difference in $tVAF_1$ between the children with DMD and the TD children. In other words, non-neural weakness appears to be only a small constraint for the CNS with respect to complexity of motor control.

Our results suggest that complexity of motor control, represented by $tVAF_1$, might be considered the neural capacity of a child, which could be difficult to alter with current treatments. Although $tVAF_1$ measured before treatment has been shown to be associated with changes in gait after treatment (Schwartz et al., 2016), prior research has also demonstrated that there are minimal changes in $tVAF_1$ after botulin toxin injections, selective dorsal rhizotomy, and single event multilevel surgeries among children with CP (Oudenhoven et al., 2016; Shuman et al., 2016b).

There are several important limitations in this research. First, we only correlated weakness with $tVAF_1$, whereas in children with CP and DMD, other clinical symptoms could have contributed to an increase in $tVAF_1$. Steele et al. (2015) determined that a higher level of spasticity and decreased selective motor control were also related to higher $tVAF_1$ in children with CP, although to a lesser extent than muscle weakness. Similar to muscle weakness, if a higher $tVAF_1$ indicates a higher level of involvement, this would not only be associated with more muscle weakness, but also with spasticity and decreased selective motor control (Ostensjø et al., 2004). In this study we focused on weakness, since DMD provides a comparison group to probe the relative impacts of non-neural factors that contribute to weakness on the results of synergy analysis. However, in children with DMD, other non-neurological symptoms besides muscle weakness are also present, such as decreased passive range motion due to contractures (Sussman, 2002). This only strengthens our conclusion that $tVAF_1$ represents the decreased DOFs in the CNS due to the brain lesion and that non-neural constraints have negligible influence on the complexity of motor control.

Further, due to the decreased selective motor control, an increase in level of co-contraction during strength assessments has been reported in children with CP (Mockford and Caulton, 2010). This increase in co-contraction has been suggested to be an important reason for the decrease in maximal torque output during a MVIC (Elder et al., 2003; Stackhouse et al., 2005). However, in a previous pilot study, while using the same protocol to measure MVICs, we determined that the levels of co-contraction were comparable between children with CP and TD children (Goudriaan et al., 2015). Similar results have been reported by Damiano et al. (2000), who determined that, although children with CP had higher levels of co-contraction during knee extension and knee flexion MVICs, this did not influence the outcomes of the MVICs.

Although the plantar flexors are important in maintaining a normal gait pattern, other muscle groups such as the hip abductors also play an important role (van der Krogt et al., 2012).

Unfortunately, our MVIC setup did not allow for standardized strength measurements of the hip muscles, thus the influence of weakness in these muscle groups on $tVAF_1$ during gait should be analyzed in the future. Finally, $tVAF_1$ outcomes in this study were only representative of the five muscles that were included in the analysis. If other muscles were to be analyzed or more muscles included, the value of $tVAF_1$ could differ since synergy analyses can be dependent on the number and choice of muscles (Steele et al., 2013). However, it is expected that the relative differences in $tVAF_1$ between the three groups (CP, DMD and TD) would be similar.

CONCLUSION

The lack of significant differences in $tVAF_1$ between boys with DMD and TD children suggests that non-neural muscle weakness has little influence on complexity of motor control during gait. Although, weakness in the plantar flexors was negatively correlated with $tVAF_1$ in the children with CP, this is most likely the result of the common underlying cause: alterations in the CNS. Our results imply that despite the predictive value of $tVAF_1$ on treatment outcomes, a child's baseline $tVAF_1$ (i.e., the child's neural capacity) could be difficult to influence with pre-surgery therapy or may require novel intervention strategies that more directly target neural capacity.

AUTHOR CONTRIBUTIONS

All authors contributed to the work either to the design, data collection, analysis, interpretation, writing, or editing. KD and MG designed the experiment. Patient recruitment was performed by MVdH, NG, and GM. Data collection was done by MG. BS and KS created the original software for synergy calculation, modifications were made by MG. MG and MVdH performed quality checks on the data. Data analysis was done by MG, BS, and KS. Statistical tests were run by MG. Interpretation of the results was done by KD, KS, BS, and MG. MG and KD wrote the paper, which was edited by KS, BS, MVdH, NG, and GM. The entire process supervised by KD.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2018.00005/full#supplementary-material

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frontiers in Human Neuroscience

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Construct Validity and Reliability of the SARA Gait and Posture Sub-scale in Early Onset Ataxia

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Aim: In children, gait and posture assessment provides a crucial marker for the early characterization, surveillance and treatment evaluation of early onset ataxia (EOA). For reliable data entry of studies targeting at gait and posture improvement, uniform quantitative biomarkers are necessary. Until now, the pediatric test construct of gait and posture scores of the Scale for Assessment and Rating of Ataxia sub-scale (SARA) is still unclear. In the present study, we aimed to validate the construct validity and reliability of the pediatric ($SARA_{GAIT/POSTURE}$) sub-scale.

Methods: We included 28 EOA patients [15.5 (6–34) years; median (range)]. For inter-observer reliability, we determined the ICC on EOA $SARA_{GAIT/POSTURE}$ sub-scores by three independent pediatric neurologists. For convergent validity, we associated $SARA_{GAIT/POSTURE}$ sub-scores with: (1) Ataxic gait Severity Measurement by Klockgether (ASMK; dynamic balance), (2) Pediatric Balance Scale (PBS; static balance), (3) Gross Motor Function Classification Scale -extended and revised version (GMFCS-E&R), (4) SARA-kinetic scores ($SARA_{KINETIC}$; kinetic function of the upper *and* lower limbs), (5) Archimedes Spiral (AS; kinetic function of the upper limbs), and (6) total SARA scores ($SARA_{TOTAL}$; i.e., summed $SARA_{GAIT/POSTURE}$, $SARA_{KINETIC}$, and $SARA_{SPEECH}$ sub-scores). For discriminant validity, we investigated whether EOA co-morbidity factors (myopathy and myoclonus) could influence $SARA_{GAIT/POSTURE}$ sub-scores.

Results: The inter-observer agreement (ICC) on EOA $SARA_{GAIT/POSTURE}$ sub-scores was high (0.97). $SARA_{GAIT/POSTURE}$ was strongly correlated with the other ataxia and functional scales [ASMK ($r_s = -0.819$; $p < 0.001$); PBS ($r_s = -0.943$; $p < 0.001$); GMFCS-E&R ($r_s = -0.862$; $p < 0.001$); $SARA_{KINETIC}$ ($r_s = 0.726$; $p < 0.001$); AS ($r_s = 0.609$; $p = 0.002$); and $SARA_{TOTAL}$ ($r_s = 0.935$; $p < 0.001$)]. Comorbid myopathy influenced $SARA_{GAIT/POSTURE}$ scores by concurrent muscle weakness, whereas comorbid myoclonus predominantly influenced $SARA_{KINETIC}$ scores.

Conclusion: In young EOA patients, separate $SARA_{GAIT/POSTURE}$ parameters reveal a good inter-observer agreement and convergent validity, implicating the reliability of the scale. In perspective of incomplete discriminant validity, it is advisable to interpret $SARA_{GAIT/POSTURE}$ scores for comorbid muscle weakness.

Keywords: early onset ataxia, SARA, gait, validity, myopathy, muscle weakness, coordination, balance

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INTRODUCTION

Pediatric ataxic gait and posture- assessment provides an important instrument to identify children and young adults with indisputable EOA (Brandsma et al., 2016a; Lawerman et al., 2016). The availability of validated gait and posture-biomarkers in children is also important for the entry of high quality data in international EOA databases (Durr, 2015; Brandsma et al., 2016a; Lawerman et al., 2016) and also for the evaluation of treatment (Romano et al., 2015), especially when the training of core-muscles is involved (such as by exergame-training) (van Diest et al., 2016; Schatton et al., 2017). In young, often disabled, EOA patients with limited concentration and physical endurance, optimally applicable gait and posture biomarkers are characterized as: non-invasive, quick and easy, compatible with adult parameters, reliable and also associated with a good construct validity (Schmidt and Embretson, 2003; Saute et al., 2012). Until now, insight in the validity of clinically available gait and posture- biomarkers is incomplete. The SARA is described as a reliable, quickly assessable, and non-invasive rating scale for patients with ataxia (Schmitz-Hubsch et al., 2006). SARA scores consist of summed: gait and posture- ($SARA_{GAIT/POSTURE}$ measuring gait, stance, sitting performances), kinetics ($SARA_{KINETIC}$) and speech ($SARA_{SPEECH}$) sub-scores (Schmitz-Hubsch et al., 2006). In EOA, we aimed to investigate the construct validity of the pediatric $SARA_{GAIT/POSTURE}$ sub-scale scores.

For the investigation of the EOA $SARA_{GAIT/POSTURE}$ construct validity, it is important to realize two points. First, it is important to realize that the SARA was originally designed and validated as a complete, total score in the domains of gait/posture, kinetics, and speech (Schmitz-Hubsch et al., 2006). However, under the assumption that the SARA sub-scale scores $SARA_{GAIT/POSTURE}$ and $SARA_{KINETIC}$ measure cerebellar functioning in different domains (i.e., vermis and anterior lobe and cerebellar hemispheres, respectively), we hypothesized that the $SARA_{GAIT/POSTURE}$ sub-scale could be separately validated. Second, it is important to realize that the SARA was originally designed and validated in adult patients with AOA (Schmitz-Hubsch et al., 2006). However, due to the short clinical assessment time and good score reproducibility, the scale was soon applied in children too (Brandsma et al., 2014a, 2016b; Hartley et al., 2015; Reetz et al., 2015). Before SARA scores can be analogously interpreted in AOA and EOA patients, it is thus important to take the effect of potential group differences into account. In comparison with the AOA patient group, EOA patients may reveal a large variety of disorders, with a heterogeneous phenotypic presentation and co-morbidity (such as myopathy and/or myoclonus). This explains why SARA score characteristics can differ between AOA and EOA patient groups (Sival and Brunt, 2009; Sival et al., 2011; Brandsma et al., 2014a, 2016b). For instance, in AOA patients, total SARA scores relate with ataxia as one single factor [i.e., 'ataxia' (Schmitz-Hubsch et al., 2006)]. This is contrasted by total SARA scores in EOA patients, which are also attributed to: (1) pediatric age (i.e., cerebellar maturation; Largo et al., 2003; Sival and Brunt, 2009; Brandsma et al., 2014a), (2) comorbid muscle weakness [in FA (Sival et al., 2011)], and (3) comorbid movement disorders (Brandsma et al., 2016b).

In children and young adults with EOA, we thus aimed to investigate the construct validity of the $SARA_{GAIT/POSTURE}$ sub-scale. Under the premise that parameters for $SARA_{GAIT/POSTURE}$ would depend on the integrated cerebellar processing of visual, vestibular, and sensory signals of the limbs and trunk (Sival, 2012; Delabasita et al., 2016; Takakusaki, 2017), $SARA_{GAIT/POSTURE}$ sub-scales would be expected to correlate with biomarkers for dynamic and passive balance, such as: the scale for ASMK [dynamic balance (Klockgether et al., 1998)] and the PBS (static balance; Franjoine et al., 2010). Additionally, we reasoned that clinically meaningful and effective $SARA_{GAIT/POSTURE}$ sub-scores would relate with a validated, age-related classification system for functional motility in children, such as the GMFCS (Palisano et al., 1997) – the extended and revised version (E&R; Palisano et al., 2008), which is originally designed for children with cerebral palsy. Furthermore, accurate kinematics for $SARA_{GAITPOSTURE}$ performances would also correlate with biomarkers for kinetic-limb function, such as: $SARA_{KINETIC}$ (upper and lower limbs) and AS [upper limb kinetic scores (Trouillas et al., 1997)]. Finally, effective EOA $SARA_{GAIT/POSTURE}$ scores would be expected to correlate with $SARA_{TOTAL}$. Strong and significant correlations would underpin a good convergent validity of $SARA_{GAIT/POSTURE}$ sub-scale scores. Absent influence by EOA co-morbidity factors (such as muscle weakness and/or myoclonus) on the scores would underpin sufficient discriminant validity of the $SARA_{GAIT/POSTURE}$ sub-scale.

In the present study, we thus aimed to elucidate the construct validity and reliability of EOA $SARA_{GAIT/POSTURE}$ sub-scale scores in children and young adults.

MATERIALS AND METHODS

The Medical Ethical Committee of the University Medical Center Groningen (UMCG), Netherlands, approved the study (METc 2011/165). According to the Dutch medical ethical law, both parents and children older than 12 years of age provided written informed consent. Children younger than 12 years of age provided assent. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the 'The Medical Ethical Committee of the University Medical Center Groningen

Abbreviations: AOA, adult onset ataxia; AS, Archimedes Spiral; ASMK, Ataxia Severity Measurement according to Klockgether; EOA, early onset ataxia (starting before the 25th year of life); FA, Friedreich's ataxia; GMFCS-E&R, Gross Motor Function Classification Scale- extended and revised version; ICARS, International Cooperative Ataxia Rating Scale; MF, muscle force; MF_{LE}, MF z-score of lower extremities; MF_{Prox}, MF z-scores of proximal muscles; MF_{TOTAL}, total MF z-score; MF_{UE}, MF z-score of upper extremities; MU, muscle ultrasound; PBS, Pediatric Balance Scale; SARA, Scale for Assessment and Rating of Ataxia; $SARA_{TOTAL}$, summed total SARA score; $SARA_{GAIT/POSTURE}$, the summed SARA sub-scores for gait, stance and sitting; $SARA_{KINETIC}$, SARA kinetic sub-score.

(UMCG), Netherlands'. In the absence of preceding pediatric data for a power calculation, we performed a prospective, explorative study.

Patients

Over a 5 year period (2011–2016), we have collected a complete cohort of EOA children that visited the pediatric neurology ward at UMCG (Brandsma et al., 2016b). From this cohort, we included patients that fulfilled the criteria for "distinct ataxia," characterized by: EOA (initiation of ataxia before the 25th year of life) and unanimous recognition of ataxia as the main movement disorder by three independent pediatric neurologists and/or unanimous recognition of ataxia as part of the movement disorder by three independent pediatric neurologists *and* confirmation of the ataxic phenotype by the OMIM database[1]. Patients were excluded when they were unable to understand the required motor function tasks for the present study.

We included 28 EOA patients [median age 15.5 (range: 6–34) years]. The response rate was 100%. In 24/28 (86%) patients, ataxia was independently recognized as the main movement disorder by all three pediatric neurologists. The other 4 of 28 (14%) patients were included on basis of unanimous phenotypic ataxia recognition (primary or secondary features) *and* diagnostic confirmation that ataxia is involved according to the OMIM database[1]. Underlying metabolic or genetic diagnoses (n = 24/28) included: FA (n = 8), GOSR2-mutation (n = 4), ataxia with vitamin E deficiency (AVED; n = 2), CACNA1A-mutation (n = 2), Ataxia Telangiectasia (n = 1), Joubert syndrome type 23 (n = 1), Kearns Sayre syndrome (KSS; n = 1), MHBD-deficiency (n = 1), NARP-mutation (n = 1), Niemann–Pick type C (n = 1), Poretti Bolthauser syndrome (n = 1), and SCA5 (n = 1). The remaining four patients remained undiagnosed, despite whole exome sequencing. We assigned patients to 'myopathic' or 'myoclonic' EOA subgroups, when myopathy or myoclonus was described in the medical records as major comorbid EOA pathology *and* when myopathic or myoclonic features are phenotypically described in the OMIM database[1]. The 'myopathic' co-morbidity subgroup ($EOA_{MYOPATHIC}$) involved 11 patients with FA (n = 8); KSS (n = 1); MHBD (n = 1); and NARP (n = 1) gene-mutations. The 'myoclonic' co-morbidity subgroup ($EOA_{MYOCLONIC}$) involved four GOSR2 patients with spontaneous, multifocal myoclonus and action-induced enhancement, at the upper extremities, face and lower extremities (van Egmond et al., 2014). In all four $EOA_{MYOCLONIC}$ patients, the medical records described clinical presence of comorbid myoclonus, which was also assessable during videotaped motor task performances (in 3 of 4 patients by 2 of 3 observers and in 1 patient by 1 of 3 observers). The remaining 'other' subgroup involved 13 patients, with neither 'myopathic' nor 'myoclonic' co-morbidity. In all patients, we reported the presence of secondary movement disorder features when at least 2 of 3 independent observers had assessed the same secondary feature, in accordance with the clinical phenotype. For patient characteristics, see **Table 1**.

Assessments

In pediatric EOA patients, we investigated the $SARA_{GAIT/POSTURE}$ construct validity by determining the: (1) inter-observer reliability, (2) convergent validity, and (3) discriminant validity.

Inter-Observer Reliability

For the inter-observer reliability, we determined the Interclass Correlation Coefficient (ICC) of the $SARA_{GAIT/POSTURE}$ video-ratings by three independent pediatric neurologists, according to the official SARA guidelines (Schmitz-Hubsch et al., 2006).

Convergent Validity

For convergent validity, we correlated $SARA_{GAIT/POSTURE}$ [i.e., summed gait, stance, and sitting sub-scale scores (Schmitz-Hubsch et al., 2006] with other rating scale scores for coordinated motor function, including ASMK [dynamic balance (Klockgether et al., 1998)]; PBS [static balance (Franjoine et al., 2010)]; GMFCS-E&R (Palisano et al., 1997, 2008), Dutch version[2]; $SARA_{KINETIC}$ (kinetic function of upper and lower limbs) (Schmitz-Hubsch et al., 2006); AS (kinetic function of the upper limbs (Trouillas et al., 1997) and, finally also $SARA_{TOTAL}$ [summed ataxia scores in gait/posture, kinetic, and speech domains (Schmitz-Hubsch et al., 2006)]. To prevent unnecessary test burden and exhaustion of the patient, we planned investigations during successive hospital visits for clinical reasons. For latent time intervals between tests, see Supplementary Table I.

For information about SARA, AMSK, PBS, GMFCS-E&R, and AS testing, see Appendix B. The ASMK (Klockgether et al., 1998) and GMFCS (Palisano et al., 2008) data were compiled from patient records and interviews. The PBS (Franjoine et al., 2010) scores were provided by one independent investigator, blinded for the results of the other test scores. In children, the reliability of this method was shown to be very high (ICC.997) (Franjoine et al., 2003).

Discriminant Validity

For discriminant validity, we determined the potentially confounding influence by comorbid EOA factors, consisting of (1) myopathic muscle weakness and (2) myoclonus on the $SARA_{GAIT/POSTURE}$ scores. We assessed MF by hand held dynamometry (CITEC; C.I.T. Technics, Haren, Groningen, Netherlands) (Beenakker et al., 2001). We determined summed total muscle force (MF_{TOTAL}), upper extremity muscle force

[1]Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD, United States), 24-12-2016. World Wide Web: http://omim.org/.

[2]Nederlandse vertaling 2009 NetChild Network for Childhood Disability Research, Utrecht, Netherlands, 15-10-2017. World Wide Web: https://canchild.ca/system/tenon/assets/attachments/000/000/067/original/GMFCS-ER_Translation-Dutch.pdf.

TABLE 1 | Patient characteristics.

	Age	EOA onset	EOA duration#	Ambulant *n* (%)	2ndMD features video 2/3 obs; *n* (%)	Disease co-morbidity	Medication^
Total group ($n = 28$)$	15.5 (6–34)	3 (0–11)	11 (3–25)	19 (68)			
$EOA_{MYOPATHIC}$ ($n = 11$)$	17 (8–27)^{ns}	4 (1–11)	7 (3–25)^{ns}	4 (36)		Hypertr cardiomyo ($n = 6$) Tachycardia ($n = 2$) Scoliosis ($n = 2$) Insulin deficiency ($n = 1$) AV-block ($n = 1$) Hypoparathyroidism ($n = 1$)	Idebenone ($n = 5$) Amiodaron ($n = 1$) Baclofen ($n = 1$) Magnesium ($n = 1$) Carbamazepine ($n = 1$)
EOA_{MYOCL} ($n = 4$)	15 (6–25)^{ns}	3 (1–3)	13 (3–22)^{ns}	4 (100)	3 (75) Myoclonus	Refractory epilepsy ($n = 3$)	Valproic acid ($n = 2$) Levetiracetam ($n = 2$) Clonazepam ($n = 3$) Clobazam ($n = 1$) Topiramate ($n = 1$)
EOA_{OTHER} ($n = 13$)	15 (8–34)	2 (0–11)	13.5 (8–23)	11 (85)	2 (15) Dystonia 2 (15) Chorea	IgA-deficiency ($n = 1$)	Miglustat ($n = 1$) Sultiame ($n = 1$) Levetiracetam ($n = 2$) Valproaic acid ($n = 1$) Clonazepam ($n = 1$) Dipiperon ($n = 1$) Melatonin ($n = 1$) Concerta ($n = 1$)
$EOA_{NON-MOYP}$ ($n = 17$)	15 (6–34)^{ns}	2 (0–11)	13.5 (3–23)^{ns}	15 (88)			
$EOA_{NON-MYOCL}$ ($n = 24$)	15.5 (8–34)^{ns}	3 (0–11)	11 (3–25)^{ns}	15 (63)			

EOA, early onset ataxia; EOA onset and duration: median value (range); # = scores are normally distributed; ambulant: number (%) ambulant patients; 2ndMD features video 2/3 obs = number (%) of secondary movement disorder features recognized by all 2 of the 3 observes; Medication^ = medication with published side effects on motor function; Hypertr cardiomyo, hypertrophic cardiomyopathy; $ = data about disease onset and disease duration missing in 1 patient; $EOA_{MYOPATHIC}$*, EOA with reported comorbid myopathy;* $EOA_{NON-MYOP}$*, EOA and absent comorbid myopathy (*$EOA_{MYOCLONUS} + EOA_{OTHER}$*);* EOA_{MYOCL}*, EOA with comorbid myoclonus;* $EOA_{NON-MYOCL}$*, EOA and absent comorbid myoclonus (*$EOA_{MYOPATHIC} + EOA_{OTHER}$*); ns, age and disease duration did not significantly differ between* $EOA_{MYOPATHIC}$ *and* $EOA_{NON-MYOP}$ *and between* EOA_{MYOCL} *and* $EOA_{NON-MYOCL}$ *(Mann–Whitney U; Student's t-test).*

(MF_{UE}), lower extremity muscle force (MF_{LE}), and proximal muscle force (MF_{PROX}). For detailed information of the tested muscles per item, see Appendix B. As the normality of pediatric MF depends on age, weight and sex, we expressed outcomes as Z-scores from the corrected normal values (Beenakker, 2005).

As 'ataxia' and/or 'myoclonus' could theoretically prohibit accurate muscle activation and/or MF assessment, we controlled whether paretic measurements (Z-scores < -2 SD) were consistent with MU abnormalities of the same muscles. MU images (of the biceps, rectus femoris, and tibial anterior muscles) were obtained in accordance with a standard protocol and settings (Sival et al., 2011; Brandsma et al., 2012). Two MU experts independently classified MU images as: 'myopathic,' 'neuropathic,' 'combined' (i.e., myopathic and neuropathic) or 'none' (in absence of myopathic or neuropathic abnormalities). In a previous publication, we have shown the reliability of this method (Brandsma et al., 2014b). Myopathic abnormalities are characterized by homogeneously increased MU density and/or muscle atrophy in a proximal to distal distribution. Neurogenic muscle abnormalities are characterized by MU inhomogeneity.

Correlations and Comparisons

For assessment of convergent validity, we correlated $SARA_{GAIT/POSTURE}$ (Schmitz-Hubsch et al., 2006) with the scores from: ASMK (dynamic balance), PBS (static balance), GMFCS-E&R, AS, $SARA_{KINETIC}$, and $SARA_{TOTAL}$. For the assessment of discriminant validity, we correlated $SARA_{GAIT/POSTURE}$ sub-scale scores with MF Z-scores. The correlations between $SARA_{GAIT/POSTURE}$ scores and MF Z-scores were subsequently stratified for EOA subgroups with and without comorbid myopathy. To evaluate the potential influence by myopathy and myoclonus on the $SARA_{GAIT/POSTURE}$ scores, we calculated the relative contribution of $SARA_{GAIT/POSTURE}$ to the total SARA scores (i.e., $SARA_{GAIT/POSTURE}$ %sub-score = [median gait score/median total score] × 100%), and we compared outcomes between myopathic versus non-myopathic and myoclonic versus non-myoclonic subgroups. For further insight, we also compared the $SARA_{KINETIC}$ sub-score percentages (i.e., $SARA_{KINETIC}$ %sub-score = [median kinetic score/median total score] × 100%) between all subgroups.

Statistical Analysis

We performed statistical analysis using SPSS statistics 22.0. We determined normality of age, time differences between assessments, median SARA scores, ASMK scores, PBS scores, GFMCS-E&R scores, AS scores and MF z-scores both graphically and by the Shapiro–Wilk test. Correlation results were interpreted by the Evans criteria [<0.20 very weak; 0.2 to 0.39 weak; 0.40 to 0.59 moderate; 0.6 to 0.79 strong, and 0.8 to 1 as very strong (Evans, 1996)]. All statistical tests were two-sided. p-values <0.05 were considered as statistically significant. We applied the Bonferroni correction to adjust the p-value for multiple comparisons on the same data.

RESULTS

Scale Descriptives and Inter-Observer Agreement

For descriptives of SARA, ASMK, PBS, GMFCS-E&R, and MF scores, see **Table 2**. The included patients revealed a binary distribution of ASMK scores (ASMK scores 1 and 3), corresponding with ambulant and non-ambulant function, respectively. There was no association between cross-sectional SARA scores and age or disease duration (Spearman's Rho, $r_s = 0.110$; $p = 0.58$; and $r_s = -0.108$; $p = 0.59$, respectively). For missing data, see Appendix A. The inter-observer agreement (ICC) of $SARA_{GAIT/POSTURE}$, $SARA_{TOTAL}$ and $SARA_{KINETIC}$ was high (0.97; 0.97; and 0.88, respectively).

Convergent Validity: The Association between SARA Scores, Ataxia Severity Measurement Scale (ASMK), Balance Performance (PBS), Gross Motor Functional Classification Scale (GMFCS-E&R), and Archimedes Spiral (AS)

$SARA_{GAIT/POSTURE}$ and $SARA_{TOTAL}$ scores were (very) strongly associated with ASMK, PBS, GMFCS-E&R, $SARA_{KINETIC}$, and AS scores; see **Table 3** and **Figure 1**. For comparison of SARA scores between the ambulant subgroup (AMSK score 1) and the non-ambulant subgroup (AMSK score 3), see Supplementary Table II. $SARA_{GAIT/POSTURE}$ sub-analysis for active balance ($SARA_{WALKING}$) and passive balance ($SARA_{STANCE/SITTING}$) revealed high correlations: (1) between $SARA_{WALKING}$ items and ASMK scores, and (2) between $SARA_{STANCE/SITTING}$ and PBS scores (Spearman's Rho: $r_s = 0.867$ and $r_s = 0.917$, respectively; $p < 0.001$). $SARA_{GAIT/POSTURE}$ was also correlated with $SARA_{KINETIC}$ (kinetic function of the upper *and* lower limbs; $r_s = 0.726$; $p < 0.001$) and with AS (kinetic function of the upper limbs; $r_s = 0.609$; $p = 0.002$). See **Table 3** and **Figure 1**.

Discriminant Validity

(a) Association between SARA scores and muscle force

In the *total EOA group*, $SARA_{GAIT/POSTURE}$ and $SARA_{TOTAL}$ revealed strong correlations with muscle weakness of the lower extremities (MF_{LE}) and proximal muscles (MF_{PROX}) (MF_{LE} and MF_{PROX}). In the 'myopathic' subgroup, $SARA_{GAIT/POSTURE}$ and $SARA_{TOTAL}$ revealed very strong correlations with muscle weakness of the lower extremities. For all r-values, see **Table 4** and **Figure 2**. In the myopathic subgroup, we controlled whether dynamometry and MU assessments corresponded with myopathic pathology (see **Table 5**). MU analysis revealed pure myopathic changes in 60% and combined myopathic/neurogenic changes in 30%. In the non-myopathic subgroup, the above mentioned correlations with muscle weakness were absent. This group revealed one child with neuropathic alterations and substantial muscle weakness, revealing a similar association between $SARA_{GAIT/POSTURE}$ scores and muscle weakness as the

myopathic group. For subgroup correlations, see **Table 4** and **Figures 2A–F**.

(b) Association between SARA scores, myopathy and myoclonus

Comparing EOA subgroups, revealed the highest %contribution of the $SARA_{GAIT/POSTURE}$ to the $SARA_{TOTAL}$ (i.e., $SARA_{GAIT/POSTURE}/SARA_{TOTAL} \times 100\%$) in the myopathic subgroup (Mann–Whitney U, $p = 0.038$), see **Figure 3**. Comparing the %contribution of the $SARA_{GAIT/POSTURE}$ to $SARA_{TOTAL}$ between myoclonic versus non-myoclonic subgroups, revealed a significantly lower %contribution of the $SARA_{GAIT/POSTURE}$ in the myoclonic subgroup

TABLE 2 | Rating scale scores per EOA group.

	Total group ($n = 28$)	$EOA_{MYOPATHIC}$ ($n = 11$)	$EOA_{NON-MYOP}$ ($n = 17$)	*p*-value	EOA_{MYOCL} ($n = 4$)	$EOA_{NON-MYOCL}$ ($n = 24$)	*p*-value
SARA scores							
Total							
Median (p25–p75)	14.5 (9.1–25.6)	27 (14.8–30.5)	11 (8.5–18)	0.022*	13.5 (10.1–18.8)	15.1 (8.7–27.8)	0.694
Min–max	5–34.5	5.3–34.5	5–29.8		9–20.5	5–34.5	
Gait/posture							
Median (p25–p75)	6 (4–14.5)	15 (5–18)	5 (3.3–6.5)	0.004**	5 (3.3–6.8)	6 (4–15)	0.306
Min–max	3–18	4–18	3–15		3–7	3–18	
Kinetic#							
Median (p25–p75)	5.3 (3.6–9.2)	8 (4.3–10)	5 (3.3–8)	0.144	6 (4.6–10.4)	5.3 (3.5–9.2)	0.469
Min–max	1.5–11.5	1.5–10.5	1.5–11.5		4.5–11.5	1.5–10.5	
ASMK scores							
Median (p25–p75)	1 (1–3)	3 (1–3)	1 (1–1)	0.009**	1 (1–1)	1 (1–3)	0.117
Min–max	1–3	1–3	1–3		1–1	1–3	
PBS scores							
Median (p25–p75)	42 (4–50)	3.5 (0–43.1)	45 (25.3–50.4)	0.005**	43.8 (34.6–48.8)	32.3 (3.8–50)	0.476
Min–max	0–55	0–50	4–55		32–50	0–55	
GMFCS-E&R							
Median (p25–p75)	1 (1–3)	4 (2–4)	1 (1–2)	0.000**	1,5 (1–2)	2 (1–4)	0.243
Min–max	1–5	2–5	1–4		1–2	1–5	
Archimedes spiral							
Median (p25–p75)	1.5 (1–2.9)	2 (0.8–3)	1 (1–2.9)	0.606	2.3 (1.3–3.6)	1 (1–2.8)	0.279
Min–max	0–4	0–4	0–4		1–4	0–4	
MF (z-scores)							
Median (p25–p75)	−1.2 (−3.5 to −0.4)	−3.2 (−4.8 to −1.3)	−0.6 (−1.3 to −0.2)	0.004**	−0.6 (−1.9 to −0.1)	−1.3 (−4.2 to −0.5)	0.245
Min–max	−5.9 to 0.4	−5.9 to −0.7	−4.5 to 0.4		−2.2 to −0.1	−5.9 to 0.4	

$SARA_{TOTAL}$, total score of the Scale for Assessment and Rating of Ataxia; ASMK, Ataxia Severity Measurement according to Klockgether; PBS, Pediatric Balance Scale; GMFCS-E&R, Gross Motor Function Classification Scale – extended and revised version; MF, total muscle force; $EOA_{MYOPATHIC}$, EOA with reported comorbid myopathy; $EOA_{NON-MYOP}$, EOA with absent comorbid myopathy ($EOA_{MYOCLONUS} + EOA_{OTHER}$); EOA_{MYOCL}, EOA with reported comorbid myoclonus; $EOA_{NON-MYOCL}$, EOA with absent myoclonus ($EOA_{MYOPATHIC} + EOA_{OTHER}$); p25–p75, lower and upper quartile; min, minimum; max, maximum; # = scores are normally distributed; p-values $^*p < 0.05$, $^{**}p < 0.01$ (Mann–Whitney U-test). The $EOA_{MYOPATHIC}$ subgroup reveals higher $SARA_{TOTAL}$, $SARA_{GAIT/POSTURE}$ and ASMK scores and lower PBS and muscle force scores than $EOA_{NON-MYOP}$. The EOA_{MYOCL} and $EOA_{NON-MYOCL}$ subgroups did not significantly differ.

TABLE 3 | Correlations between SARA scores and other measurements of coordination.

	$SARA_{GAIT/POSTURE}$	$SARA_{TOTAL}$	ASMK	PBS	GMFCS-E&R	$SARA_{KINETIC}$#	AS
$SARA_{GAIT/POSTURE}$	–	0.935*	0.815*	−0.943*	−0.862*	0.726*	0.609*
$SARA_{TOTAL}$	0.935*	–	0.772*	−0.911*	0.767*	0.887*	0.805*
ASMK	0.815*	0.772*	–	−0.817*	0.848*	0.474	0.489
PBS	−0.943*	−0.911*	−0.817*	–	−0.870*	−0.685*	−0.640*
GMFCS-E&R	−0.862*	0.767*	0.848*	−0.870*	–	0.510	0.461
$SARA_{KINETIC}$#	0.726*	0.887*	0.474	−0.685*	0.510	–	0.846*
AS	0.609*	0.805*	0.489	−0.640*	0.461	0.846*	–

*$SARA_{TOTAL}$, total score of the Scale for Assessment and Rating of Ataxia; $SARA_{GAIT/POSTURE}$, SARA gait and posture sub-scales; ASMK, Ataxia Severity Measurement according to Klockgether; PBS, Pediatric Balance Scale; GMFCS-E&R, Gross Motor Function Classification Scale – extended and revised version; AS, Archimedes Spiral; # = Scores are normally distributed; values represent Spearmans Rho; *correlations are considered statistically significant with $p \leq 0.002$ (Bonferroni correction for 21 comparisons). $SARA_{GAIT/POSTURE}$ and $SARA_{TOTAL}$ correlated strongly with other parameters for coordination measurement.*

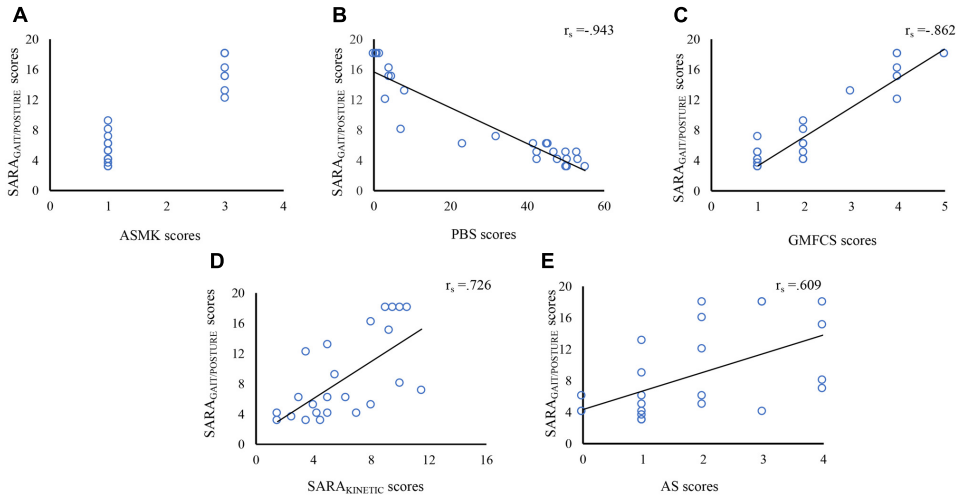

FIGURE 1 | Correlation between $SARA_{GAIT/POSTURE}$ sub-scores and ASMK, PBS scores, GMFCS-E&R, $SARA_{KINETIC}$, and AS. The x-axis indicates ASMK scores **(A)**, PBS scores **(B)**, GMFCS-E&R classification **(C)**, $SARA_{KINETIC}$ scores **(D)**, AS scores **(E)**. The y-axis indicates the $SARA_{GAIT/POSTURE}$ scores **(A–E)**. $SARA_{GAIT/POSTURE}$ scores were associated with ASMK, PBS scores, GMFCS-E&R, $SARA_{KINETIC}$, and AS scores. SARA, Scale for Assessment and Rating of Ataxia; ASMK, Ataxia Severity Measurement according to Klockgether; PBS, Pediatric Balance Scale; GMFCS-E&R, Gross Motor Function Classification Scale-the extended and revised version; AS, Archimedes Spiral.

(Mann–Whitney U, $p = 0.018$, see **Figure 3**). Conversely, we observed the highest %contribution of the $SARA_{KINETIC}$ to $SARA_{TOTAL}$ (i.e., $SARA_{KINETIC}/SARA_{TOTAL} \times 100\%$) in the myoclonic subgroup (Mann–Whitney U, $p = 0.028$), see **Figure 3**. For subgroup comparisons between myoclonic, myopathic, and other (non-myoclonic and non-myopathic), see **Figure 4**.

DISCUSSION

In children and young adults with EOA, we aimed to investigate the construct validity of $SARA_{GAIT/POSTURE}$ sub-scores. $SARA_{GAIT/POSTURE}$ sub-scores revealed a high inter-observer agreement (ICC) and were strongly associated with other quantitative scales for coordinative motor function, such as: active and static balance (ASMK, PBS), kinetic limb performances ($SARA_{KINETIC}$, AS) and total ataxia scores ($SARA_{TOTAL}$). Furthermore, we also observed a strong correlation between $SARA_{GAIT/POSTURE}$ sub-scores and the classification levels of the GMFCS (E&R), which is originally designed for the assessment of functional motility in children with cerebral palsy (Palisano et al., 1997, 2008). The discriminant validity of the $SARA_{GAIT/POSTURE}$ subscale between the measurement of ataxia and co-morbidity factors (muscle weakness and myoclonus) was incomplete. In children and young adults with EOA, we conclude that $SARA_{GAIT/POSTURE}$ scores are reliable. However, $SARA_{GAIT/POSTURE}$ parameters discriminate insufficiently between the influence by ataxia and muscle weakness. This implicates that gait and posture scores should be interpreted in homogeneous EOA subgroups that take comorbid muscle weakness into account.

TABLE 4 | Correlations between SARA scores and muscle force.

	Total group	$EOA_{MYOPATHIC}$	$EOA_{NON-MYOP}$
	r-values	*r*-values	*r*-values
$SARA_{Total}$-MF_{Total}^	−0.719**	−0.903**	−0.308
$SARA_{GAIT/POSTURE}$-MF_{LE}^	−0.724**	−0.882*	−0.320
$SARA_{GAIT/POSTURE}$-MF_{Prox}^	−0.690**	−0.894**	−0.248
$SARA_{KINETIC}$#-MF_{UE}#	−0.574*	−0.619	−0.410
$SARA_{KINETIC}$# -MF_{Prox}^	−0.516	−0.564	−0.293

*$EOA_{MYOPATHIC}$, EOA with reported comorbid myopathy; $EOA_{NON-MYOP}$, EOA with absent comorbid myopathy ($EOA_{MYOCLONUS}$ + EOA_{OTHER}); MF, muscle force; LE, lower extremities; UE, upper extremities; Prox, proximal muscles; $SARA_{TOTAL}$, total SARA score; $SARA_{GAIT/POSTURE}$, SARA gait sub-score; $SARA_{KINETIC}$, SARA kinetic subscore; # = Scores are normally distributed; ^ = Spearmans Rho (r-value = r_S-value); correlations are considered statistically significant with $p < 0.01$ (Bonferroni correction for five comparisons). *$p < 0.01$; **$p < 0.001$. In the $EOA_{MYOPATHIC}$ subgroup, $SARA_{TOTAL}$ and $SARA_{GAIT/POSTURE}$ scores correlate with MF.*

In previous EOA studies, we have shown that tools for the assessment of ataxic gait may contribute to the early recognition of indisputable EOA in young patients (Lawerman et al., 2016). Furthermore, well-validated clinical biomarkers for EOA gait and posture assessment are useful for the evaluation of pediatric treatment strategies, targeting at the training of core-muscle function (van Diest et al., 2016; Schatton et al., 2017). In the present study, we observed an excellent inter-observer agreement (ICC) on $SARA_{GAIT/POSTURE}$ sub-scores, which was in the same range as $SARA_{TOTAL}$ and $SARA_{KINETIC}$ sub-scores. These $SARA_{TOTAL}$ outcomes are in agreement with previously published ICC data in adult patients with predominantly AOA phenotypes (Schmitz-Hubsch et al., 2006).

We determined convergent validity of $SARA_{GAIT/POSTURE}$ sub-scores under the premise that all ataxic gait parameters for walking, standing, and balancing would depend on the

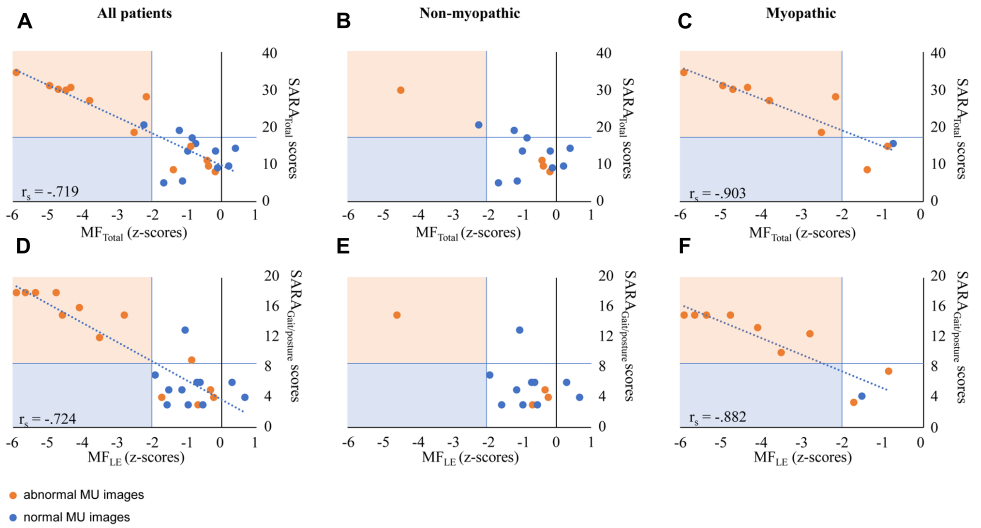

FIGURE 2 | Correlation between SARA scores and MF in EOA patients. **(A,D)** Represent outcome data in all patients. **(B,E)** Represent outcome data in non-myopathic patients. **(C,F)** Represent outcome data in myopathic patients. Orange markers represent patients with abnormal MU characteristics (by expert opinion). **(A–C)** The x-axis indicates MF_{TOTAL} z-scores; the y-axis indicates $SARA_{TOTAL}$ scores. **(D–F)** The x-axis indicates MF_{LE} z-scores; the y-axis indicates $SARA_{GAIT/POSTURE}$ scores. r_S values are presented in case of significant correlations. SARA, Scale for Assessment and Rating of Ataxia; MF, muscle force; LE, lower extremities. In heterogeneous EOA patients, the association between SARA scores and MF is attributed to outcomes of myopathic patients.

same integrated cerebellar processing of sensory, visual, and vestibular signals (Takakusaki, 2017) with upper- and lower-limb and trunk motor performances (Sival, 2012; Delabasita et al., 2016). We thus hypothesized that the construct validity of $SARA_{GAIT/POSTURE}$ could be reflected by the association with other coordinative motor function tests requiring cerebellar integration of multimodal signals. Accordingly, we observed that $SARA_{GAIT/POSTURE}$ sub-scores were strongly associated with the tested parameters for coordinated motor function. The $SARA_{GAIT/POSTURE}$ items for active and passive balance were strongly related with ASMK and PBS scores and also with GFMCS classifications, implicating that the closely associated test objectives have a functional significance. Furthermore, $SARA_{GAIT/POSTURE}$ scores were also correlated with kinetic functions of the upper and lower extremities, which can be understood by the fact that gait kinetics (including arm swing, turning, balance and tandem -stance and -gait performances) also require accurate limb kinetics. Finally, $SARA_{GAIT/POSTURE}$ scores appeared strongly associated with $SARA_{TOTAL}$ scores. Although correlated, $SARA_{GAIT/POSTURE}$ and AS scores revealed the lowest correlation. In perspective of the differences in tested cerebellar domains (vermis versus hemispheres) and the differences regarding motor function tasks (gross versus fine motor function tasks), the lower correlation is in accordance with our expectations. As focal cerebellar damage was excluded from the present study group inclusion, one could attribute the above mentioned correlations between different cerebellar domains and/or motor function tasks to global functional pathology of the cerebellum. In young, ataxic EOA patients without focal cerebellar lesions, these results may thus implicate that $SARA_{GAIT/POSTURE}$ scores can provide a global impression of the total ataxia-severity. When ambulant EOA children without focal lesions are too young (<4 years of age) or lack the motivation and/or concentration to complete all SARA motor task performances, $SARA_{GAIT/POSTURE}$ parameters could theoretically provide a fast and easy biomarker to estimate ataxia-progression. Altogether, in children and young adults with distinct EOA features, $SARA_{GAIT/POSTURE}$ can reliably measure 'ataxic' gait severity and may also provide a global impression of the total ataxia severity.

We obtained the above mentioned results under the premise that SARA and other coordination scales measure the same objective. However, as already stated for the AS, this is not necessarily correct, as the other biomarkers (such as for active and passive balance, and kinetic function) may measure more than the objective 'ataxia,' alone. This implicates

TABLE 5 | Muscle Ultrasound Abnormalities in myopathic and non-myopathic patients.

	$EOA_{MYOPATHIC}$ ($n = 10$)	$EOA_{NON-MYOP}$ ($n = 14$)
Myopathic muscle abnormalities	$n = 6$ (60%)	
Neurogenic muscle abnormalities		$n = 4$ (29%)*
Combined myopathic/neurogenic muscle abnormalities None of the above	$n = 3$ (30%) $n = 1$ (10%)	$n = 10$ (71%)

*$EOA_{MYOPATHIC}$, EOA with reported comorbid myopathy; $EOA_{NON-MYOP}$, EOA with absent comorbid myopathy ($EOA_{MYOCLONUS}$ + EOA_{OTHER}); *corresponding diagnoses were: ataxia telangiectasia (n = 1). Nieman–Pick's disease (n = 1) and unknown (n = 2).*

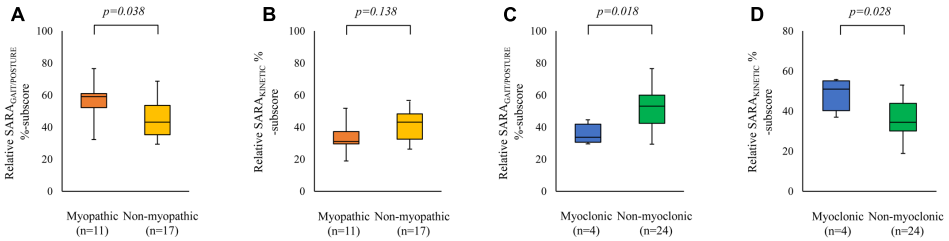

FIGURE 3 | Influence of myopathy and myoclonus on SARA %sub-scores. The x-axis represents the EOA phenotypes (myopathic versus non-myopathic, and myoclonic versus non-myoclonic). The y-axis represents the median $SARA_{GAIT/POSTURE}$ %sub-score (i.e., [$SARA_{GAIT/POSTURE}$ sub-score/median total score] × 100%, **A,C**); and the median $SARA_{KINETIC}$ %sub-score (i.e., [median $SARA_{KINETIC}$ score/median total score] × 100%, **B,D**). Boxes represent lower quartile, median and upper quartile; whiskers represent the minimum and maximum relative %sub-score. $SARA_{GAIT/POSTURE}$, SARA gait and posture sub-score; $SARA_{KINETIC}$, SARA kinetic sub-score. Comparing the %contribution of the $SARA_{GAIT/POSTURE}$ to $SARA_{TOTAL}$ between myopathic versus non-myopathic subgroups, revealed a significantly higher %contribution of the $SARA_{GAIT/POSTURE}$ in the myopathic subgroup **(A)**, whereas the %contribution of the $SARA_{KINETIC}$ was not significantly different between both groups **(B)**. Comparing the %contribution of the $SARA_{KINETIC}$ to $SARA_{TOTAL}$ between myoclonic versus non-myoclonic subgroups, revealed a significantly higher %contribution in the myoclonic subgroup **(C)**, whereas the %contribution of the $SARA_{GAIT/POSTURE}$ revealed a significantly lower %contribution in the myoclonic subgroup **(D)**.

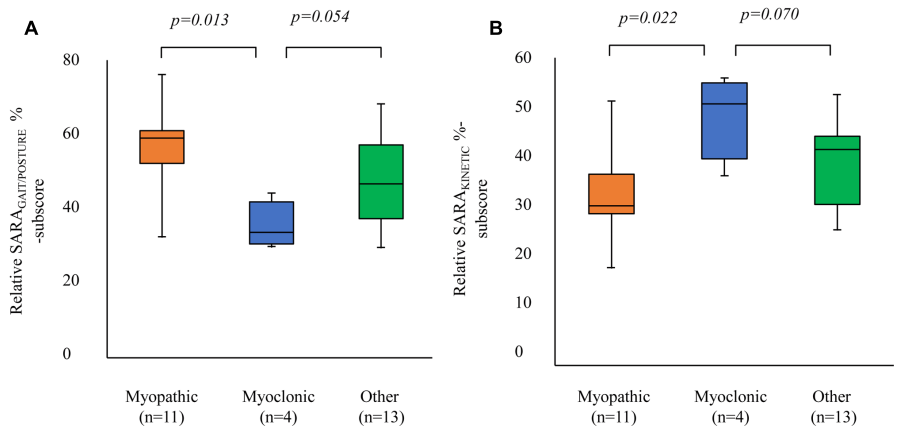

FIGURE 4 | Comparison of relative SARA %sub-scores between co-morbidity subgroups. The x-axis represents the EOA phenotypes [myopathic, myoclonic, and other (non-myopathic and non-myoclonic)]. The y-axis represents: **(A)** the median $SARA_{GAIT}$ %sub-score (i.e., [$SARA_{GAIT}$ score/median total score] × 100%) and **(B)** the median $SARA_{KINETIC}$ %sub-score (i.e., [median $SARA_{KINETIC}$ score/median total score] × 100%). Boxes represent lower quartile, median and upper quartile; whiskers represent the minimum and maximum relative %-sub-score. $SARA_{GAIT/POSTURE}$, SARA gait and posture sub-score; $SARA_{KINETIC}$, SARA kinetic sub-score. Myoclonic EOA phenotypes reveal a relatively smaller $\%SARA_{GAIT}$ than $\%SARA_{KINETIC}$ sub-scores compared to the other subgroups.

that other factors than ataxia could theoretically influence $SARA_{GAIT/POSTURE}$ scores. For instance, in previous studies, we have shown that the age of the child (i.e., cerebellar maturation) has an influence on SARA scores (Sival and Brunt, 2009; Brandsma et al., 2014a). Although mean age-related effects are comparatively small in relation to pathologic SARA scores in ataxic patients, the Childhood Ataxia and Cerebellar Group of the European Pediatric Neurology Society has recently shown that children younger than 8 years of life can also reveal considerable variation in $SARA_{TOTAL}$ scores, which may affect the interpretation of the longitudinal scores (Lawerman et al., 2017). However, as the variation of $SARA_{GAIT/POSTURE}$ sub-scores in young children appeared much smaller (Lawerman et al., 2017), one could use the $SARA_{GAIT/POSTURE}$ sub-scale as an internal control to discriminate between physiological age-related and ataxia effects on the $SARA_{TOTAL}$ scores. To elucidate the $SARA_{GAIT/POSTURE}$ test construct, we also investigated the potential effects of co-morbidity factors on the $SARA_{GAIT/POSTURE}$ sub-scores. $SARA_{GAIT/POSTURE}$ and $SARA_{TOTAL}$ scores revealed an incomplete discriminant validity between ataxia and comorbid 'muscle weakness.' Although this does not automatically implicate a causal relationship, absence of a relationship between muscle weakness and $SARA_{GAIT/POSTURE}$ and $SARA_{TOTAL}$ scores cannot be assumed, either. For instance, when the child has difficulties to raise an arm against gravity, or when the child has just sufficient MF to walk with support, muscle weakness is likely to affect the scores. Furthermore, in case of limiting muscle weakness to execute the SARA rating scale task, maximal scores should be given. In the latter case, ataxia itself has not determined the score, but limiting muscle weakness instead. This implicates that the discriminant validity of $SARA_{GAIT/POSTURE}$ sub-scores between muscle weakness and ataxia is incomplete.

Analyzing the patient inclusion of the myopathic EOA cohort, revealed a majority of patients with FA. This underpins our previously reported study data on the association between muscle weakness and ataxia scores in FA children (Sival et al., 2011). Interestingly, in another FA cohort, this association between SARA scores and muscle weakness was not reported (Bürk et al., 2009). However, in the latter study, MF Z-scores were not available, implicating that exact correlations cannot be made. Furthermore, one should be aware that correlations between muscle weakness and SARA scores would require patient sub-groups with sufficient variety in MF. For example, in homogeneous EOA groups with normal physiological muscle strength, the influence by muscle weakness on SARA scores would not be addressed. Similarly, in homogeneous EOA groups with severely progressed muscle weakness (represented by non-ambulant patients), plateauing SARA scores would also obscure an association with muscle weakness. These results implicate that it is advisable to obtain $SARA_{GAIT/POSTURE}$ scores in homogeneous EOA subgroups and to stratify outcomes for substantial variations in muscle weakness. Finally, we investigated the EOA influence of comorbid myoclonus on $SARA_{GAIT/POSTURE}$ sub-scores. In the comorbid myoclonus subgroup, the percentage (%) contribution of $SARA_{GAIT/POSTURE}$ to $SARA_{TOTAL}$ scores was low compared to non-myoclonus subgroup, reflecting a negative effect. Interestingly, the percentage (%) contribution of $SARA_{KINETIC}$ to $SARA_{TOTAL}$ scores was high in the comorbid myoclonus subgroup, compared to non-myoclonus subgroup, implicating a predominant effect of comorbid myoclonus on $SARA_{KINETIC}$, instead of $SARA_{GAIT/POSTURE}$ scores. As myoclonic jerks in GOSR2 patients may start at the upper extremities and increase during intended kinetic limb movements, these findings are understandable.

We are aware that this study has several limitations. First, the EOA patients fulfilling the requirements for patient inclusion are rare, implicating that the number of patients was limited. However, as the present data are obtained in a specialized movement disorder center over a study period of 5 years (with an inclusion rate of 100%), investigation of a larger patient cohort will not easily be accomplished. Second, we realize that statistically significant correlations do not necessarily implicate causality (Field, 2009). But, as significant correlations between $SARA_{GAIT/POSTURE}$ sub-scores and MF were consistently absent in patients without MF loss, our findings do not reject causality, either. Third, to avoid an unacceptable test burden and exhaustion for the patients, we planned different tests during successive medical visits to our outpatient clinic (see Supplementary Table I). However, as latent time intervals between tests would only exert a negative influence on the correlations, the positive inter-correlations between $SARA_{GAIT/POSTURE}$ and other ataxia biomarkers cannot be attributed to it. Fourth, we cannot exclude that other, yet unexplored confounders may also exist (such as neuropathy, concentration, behavior, and tiredness). Altogether, in the perspective of the presented findings, we conclude that $SARA_{GAIT/POSTURE}$ scores are associated with MF loss. In EOA patients with comorbid myopathy, it appears prudent to interpret $SARA_{GAIT/POSTURE}$ scores for the severity of muscle weakness.

CONCLUSION

The inter-observer agreement and convergent validity of $SARA_{GAIT/POSTURE}$ scores in EOA patients are high, implicating the reliability of the scores. Regarding the incomplete discriminant validity of the scores, it is advisable to interpret $SARA_{GAIT/POSTURE}$ scores for comorbid muscle weakness.

AUTHOR CONTRIBUTIONS

TL: draft of the manuscript, data acquisition, data analysis, interpretation of data. RB: data acquisition, revising the manuscript for important intellectual content. RV: data acquisition, interpretation of data, revising the manuscript for important intellectual content. JvdH: data acquisition, interpretation of data, revising the manuscript for important intellectual content. RL: data acquisition, revising the manuscript for important intellectual content. HK: data interpretation, drafting, and revising the manuscript for important intellectual content. DS: concept and design of the manuscript, data acquisition, interpretation of data, drafting, revising, and final version of the manuscript. All authors approved the final version and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2017.00605/full#supplementary-material

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frontiers in Human Neuroscience

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Structural Brain Damage and Upper Limb Kinematics in Children with Unilateral Cerebral Palsy

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Background: In children with unilateral cerebral palsy (uCP) virtually nothing is known on the relation between structural brain damage and upper limb (UL) kinematics quantified with three-dimensional movement analysis (3DMA). This explorative study aimed to (1) investigate differences in UL kinematics between children with different lesion timings, i.e., periventricular white matter (PWM) vs. cortical and deep gray matter (CDGM) lesions and (2) to explore the relation between UL kinematics and lesion location and extent within each lesion timing group.

Methods: Forty-eight children (age 10.4 ± 2.7 year; 29 boys; 21 right-sided; 33 PWM; 15 CDGM) underwent an UL 3DMA during a reach-to-grasp task. Spatiotemporal parameters [movement duration, (timing of) maximum velocity, trajectory straightness], the Arm Profile Score (APS) and Arm Variable Scores (AVS) were extracted. The APS and AVS refer to the total amount of movement pathology and movement deviations of the wrist, elbow, shoulder, scapula and trunk respectively. Brain lesion location and extent were scored based on FLAIR-images using a semi-quantitative MRI-scale.

Results: Children with CDGM lesions showed more aberrant spatiotemporal parameters ($p < 0.03$) and more movement pathology (APS, $p = 0.003$) compared to the PWM group, mostly characterized by increased wrist flexion ($p = 0.01$). In the CDGM group, moderate to high correlations were found between lesion location and extent and duration, timing of maximum velocity and trajectory straightness ($r = 0.53$–0.90). Lesion location and extent were further moderately correlated with distal UL movement pathology (wrist flexion/extension, elbow pronation/supination, elbow flexion/extension; $r = 0.50$–0.65) and with the APS ($r = 0.51$–0.63). In the PWM group, only a few and low correlations were observed, mostly between damage to the PLIC and higher AVS of elbow flexion/extension, shoulder elevation and trunk rotation ($r = 0.35$–0.42). Regression analysis revealed damage to the temporal lobe with lesion timing as interactor (27%, $p = 0.002$) and the posterior limb of the internal capsule (PLIC) (7%, $p = 0.04$) as the strongest predictors, explaining 34% of the variance in APS.

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Conclusion: UL kinematic deviations are more influenced by lesion location and extent in children with later (CDGM) versus earlier lesions (PWM), except for proximal movement pathology. Damage to the PLIC is a significant predictor for UL movement pathology irrespective of lesion timing.

Keywords: upper extremity, cerebral palsy, magnetic resonance imaging, brain injuries, biomechanical phenomena

INTRODUCTION

The ability to efficiently coordinate trunk, arm and hand movements is crucial in order to successfully reach and grasp and execute daily life activities such as eating, personal hygiene and self-care. In children with unilateral cerebral palsy (uCP), the presence of pathological movement patterns at the impaired upper limb (UL) has been shown to be associated with lower levels of unimanual capacity and bimanual performance impeding activities of daily life (Mailleux et al., 2017a). In these children, UL movement pathology is a common feature during the execution of various tasks, characterized by increased wrist and elbow flexion and elbow pronation accompanied by compensatory movements of the shoulder, scapula and trunk as assessed with three-dimensional movement analysis (3DMA) (Fitoussi et al., 2006; Jaspers et al., 2009, 2011a,c; Butler et al., 2010; Brochard et al., 2012; Butler and Rose, 2012; Klotz et al., 2014; Simon-Martinez et al., 2017). Still, virtually nothing is known about the underlying neuropathophysiology explaining UL movement pathology in children with uCP, while the relation between brain lesion characteristics and clinical outcomes of UL function has already been investigated (Feys et al., 2010; Holmström et al., 2010; Holmefur et al., 2013; Mackey et al., 2014; Mailleux et al., 2017b).

Brain lesions in children with uCP are often classified according to their presumed lesion timing: cortical maldevelopments (first and second trimester), periventricular white matter (PWM) lesions (early third trimester) and cortical and deep gray matter (CDGM) lesions (around term age) (Krägeloh-Mann and Horber, 2007). It has been shown that children with earlier lesions (i.e., PWM lesions) have a better UL function compared to children with lesions occurring later in life (i.e., CDGM lesions) (Feys et al., 2010; Holmström et al., 2010; Holmefur et al., 2013; Mackey et al., 2014). Apart from lesion timing, also lesion location and extent have been shown to relate with UL function, i.e., basal ganglia and/or thalamus involvement and more extended lesions are associated with a more impaired UL function (Feys et al., 2010; Holmström et al., 2010; Holmefur et al., 2013; Mackey et al., 2014; Shiran et al., 2014; Fiori et al., 2015; Baranello et al., 2016). We also recently demonstrated that lesion location and extent were more strongly related to UL function in children with CDGM lesions compared to children with PWM lesions (Mailleux et al., 2017b). Nevertheless, previous findings are based mainly on clinical outcomes, which do not provide information on selective anatomical motions at the individual joint levels. In contrast, an UL 3DMA can define movement deviations at joint level and provides an objective description of UL movement pathology.

So far, only Van Der Heide et al. (2005) investigated the relation between brain lesion severity and UL kinematics during a reaching task in children with both unilateral and bilateral CP. These authors demonstrated that more severe brain lesions were correlated with less straight hand trajectories. Nevertheless, in this study, kinematic outcomes were limited and brain lesions were visualized using ultrasound imaging, which has a lower spatial resolution and accuracy compared to MRI. In adult stroke patients, MRI research has shown that more severe cerebellar lesions (Konczak et al., 2010) and increasing brain activation in the ipsilesional motor cortex (Buma et al., 2016) correlate with poorer spatiotemporal parameters during reaching tasks. Interestingly, brain activation in the ipsilesional motor cortex was more strongly correlated with UL kinematics compared to clinical outcome measures of UL function (Buma et al., 2016). In addition, Meyns et al. (2016) also demonstrated the adverse impact of the underlying brain lesion on gait kinematics in children with CP. Together these findings point toward the benefits of UL 3DMA to further enhance our understanding of the complex interplay of structural brain damage and UL movement pathology in children with uCP.

Hence, this explorative study first aims to investigate whether UL kinematics differ between children with early (PWM) versus later lesions (CDGM) during a reach-to-grasp task. Secondly, we aim to explore the relation between lesion location and extent and UL kinematics within each lesion timing group. We hypothesize that children with CDGM lesions have more deviant UL kinematics than children with PWM lesions and that lesion location and extent impact more on UL movement pathology in children with CDGM compared to PWM lesions.

MATERIALS AND METHODS

Participants

Children were recruited via the CP-care program of the University Hospitals Leuven (Belgium). Children with a spastic type of uCP were enrolled in the study if they were aged between 5 and 15 years, able to comprehend test instructions, could at least actively grasp an object and had a brain MRI scan available taken after the age of 3 years. Additionally, only children classified with either PWM or CDGM lesions as defined by Krägeloh-Mann and Horber (2007) were included. Exclusion criteria were botulinum toxin-A injections 6 months prior to testing or a history of UL surgery. This study was carried out in accordance with the recommendations of the Medical Ethical Committee of the University Hospitals Leuven (S50480, S55555, and S56513). Written informed consent was obtained from all parents in accordance with the Declaration of Helsinki. In

addition, children aged older than 12 years were asked for their assent prior to participation.

Procedure

All children underwent an UL 3DMA at the Clinical Motion Analysis Laboratory of the University Hospitals Leuven. Children were assessed by well-trained physiotherapists routinely involved in the clinical evaluation of children with CP. Brain lesions were scored using a semi-quantitative MRI-scale (sqMRI scale, Fiori et al., 2014) by one pediatric neurologist (EO) who was blinded to the outcome of the UL 3DMA.

Three-Dimensional Movement Analysis

UL 3DMA was performed according to the protocol described by Jaspers et al. (2011b). Seventeen reflective markers were attached on the hand ($n = 3$), forearm ($n = 4$), humerus ($n = 4$), acromion ($n = 3$), and trunk ($n = 3$). The starting position was upright sitting with hips and knees in 90° flexion, ensured through a custom-made chair with adjustable foot and back support. Twelve to fifteen infrared Vicon-cameras were used for recordings, sampling at 100 Hz. First, static calibration trials were collected to identify the anatomical landmarks as described in Wu et al. (2005). Children were then asked to reach and grasp a vertically oriented cylinder (RGV). This cylinder was placed at shoulder height and arm length distance. The task RGV was chosen as it simultaneously requires elbow extension and supination, which adequately challenges the movement pattern of the UL in children with uCP. This task was executed twice with the impaired UL at self-selected speed. Each trial contained four movement repetitions, resulting in a total of eight movement repetitions. After data collection, two movement repetitions per trial were selected, depending on the child's task compliance and marker visibility (i.e., movement repetitions with marker occlusions >20% of the movement duration were excluded). Subsequently, start (i.e., hand on ipsilateral knee) and end positions (i.e., point of task achievement) of each movement repetition were identified using Nexus software (Oxford Metrics, Oxford, UK). Finally, UL kinematics were calculated in MATLAB using U.L.E.M.A. (v1.1.9, available for download[1]).

Spatiotemporal parameters and summary indices were extracted. Spatiotemporal parameters comprised movement duration, timing of maximum velocity, maximum velocity and trajectory straightness (i.e., calculated as the ratio of the actual length of the traveled hand path and the direct linear distance between start and endpoint). Summary indices included the Arm Profile Score (APS) and 13 Arm Variable Scores (AVS) and were determined as described in Jaspers et al. (2011c). The AVS was calculated for 13 joint angles as the root mean square error between the point-by-point comparison of each joint angle of the child with uCP and that same joint angle of a reference database (60 typically developing children, age 5–15 years). The root mean square error-average of all 13 joint angles equals the APS and represents the overall severity of UL movement pathology. The 13 AVS represent the deviating scores for the wrist (flexion/extension, ulnar/radial deviation), elbow (flexion/extension, pronation/supination), shoulder (elevation plane, elevation, rotation), scapula (anterior/posterior tilting, medial/lateral rotation, protraction/retraction) and trunk (flexion/extension, lateral bending, axial rotation).

[1]https://github.com/u0078867/ulema-ul-analyzer

Semi-Quantitative MRI Scale

The available MRI scan included at least one FLAIR sequence and was taken after the age of 3 years as described by Fiori et al. (2014). First, the lesion was drawn onto a graphical template, adapted from the CH2 atlas (Mazziotta et al., 2001) using a red pen. This template consisted of six axial slices containing the drawing of three lines: a cortical outline, a subcortical line dividing the gray from the white matter and a periventricular line bordering the periventricular white matter resulting in a cortico-subcortical, middle white matter and periventricular white matter layer. The boundaries of the frontal, parietal, temporal and occipital lobes were marked according to the Talairach atlas (Talairach and Tournoux, 1988). Secondly, for both hemispheres each layer in each lobe was scored, resulting in a lobar score (range 0–3) and summed up to obtain a hemispheric score (range 0–12). Next, damage to five subcortical structures, i.e., lenticular and caudate nucleus, thalamus, posterior limb of internal capsule (PLIC) and brainstem, was scored directly from the MRI scan as affected (score 1) or not affected (score 0) (subcortical score, range 0–5). Damage to the corpus callosum (anterior, middle and posterior section, range 0–3) and cerebellum (vermis, right and left hemisphere, range 0–3) were also scored directly from the MRI scan. Subsequently, a contralesional and ipsilesional total score (range 0–17) were obtained as the sum of the hemispheric and subcortical score of each respective hemisphere. Finally, the sum of all these scores led to the global score (range 0–40). Reliability and validity of the scale has already been established in children with CP (Fiori et al., 2014, 2015).

Lesion location was defined as damage to each of the four lobes, three layers, and five subcortical structures of the ipsilesional hemisphere. Lesion extent was determined by the ipsilesional hemispheric score, ipsilesional subcortical score, ipsilesional total score and the global score.

Statistical Analysis

Descriptive statistics were used to document demographic and kinematic characteristics. First, all kinematic parameters were tested for normality using the Shapiro-Wilk test. Differences in UL kinematics between the PWM and CDGM group were investigated using unpaired *t*-tests or Mann-Whitney *U*-tests depending on the type of data. Correlation coefficients were calculated for both lesion timing groups separately, between kinematic parameters and the scores of ipsilesional brain damage, the contralesional total score, the corpus callosum and the global score using spearman (r_s) or biserial (r_b) correlation coefficients depending on the type of data. The cerebellum was excluded for further analysis, since none of the participants showed damage to this region. Due to the explorative nature of the study, no correction for multiple testing was applied (Bender and Lange, 2001). Hence, correlations will be discussed according to their strength. Correlation coefficients <0.30 were considered as little or no correlation, 0.30–0.50 low, 0.50–0.70 moderate, 0.70–0.90

high, and >0.90 very high (Hinkle et al., 1998). Finally, a multiple regression analysis was used to identify the explained variance in UL movement pathology (APS). The variables entered into this model were selected via the Least Absolute Shrinkage and Selection Operator (LASSO) approach (Tibshirani, 1996). Variables entered in the LASSO approach were lesion timing, all ipsilesional scores for lesion location and extent, and age as well all ipsilesional scores with lesion timing as interacting variable. Two-sided 5% level of significance was used. Statistical procedures were carried out with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

Forty-eight children (29 males, 19 females; 21 right-sided, 27 left-sided; Manual Ability Classification System, Eliasson et al., 2006; I = 11, II = 22, III = 15) with a spastic type of uCP were included in this study. Thirty-three children had PWM lesions and 15 had CDGM lesions. UL clinical characteristics according to lesion timing are presented in Supplementary Material ST1. Average age at time of the UL 3DMA was 10 years and 4 months (SD ± 2 years and 7 months). Age did not differ significantly between the PWM and CDGM group ($p = 0.66$).

Differences in Upper Limb Kinematics between Lesion Timing Groups

Children with CDGM lesions had significantly longer movement durations ($p = 0.03$), earlier timings of maximum velocity ($p = 0.0005$) and less straight hand trajectories ($p = 0.005$) compared to children with PWM lesions (see **Table 1**). In addition, the scores for total movement pathology were higher in the CDGM group compared to the PWM group (APS, $p = 0.003$). Statistical comparison of the AVS further showed increased movement deviations of wrist flexion/extension ($p = 0.01$) and shoulder elevation ($p = 0.05$) and a trend for more deviating movement patterns of elbow pronation/supination ($p = 0.08$) in the CDGM group. The APS and 13 AVS for the PMW and CDGM group are presented in a bar chart, the Arm Movement Analysis Profile, which exhibits the contribution of each variable to the APS (A-MAP, **Figure 1**). Mean (standard deviation) and medians (interquartile ranges) per group can be found in Supplementary Material ST2.

TABLE 1 | Statistical comparison of the spatiotemporal parameters in the PWM (*N* = 33) compared to the CDGM (*N* = 15) group.

		PWM	CDGM	*p*-value
Duration (s)[a]	X (SD)	**1.56 (0.43)**	**1.94 (0.56)**	**0.03**
TimeVmax (%)[a]	X (SD)	**26.74 (5.09)**	**21.32 (4.25)**	**0.0005**
Vmax (m/s)[a]	X (SD)	1.05 (0.22)	1.15 (0.20)	0.12
TS[a]	X (SD)	**1.33 (0.23)**	**1.54 (0.23)**	**0.005**

[a] *unpaired t-test; X, mean; SD, standard deviation; TimeVmax, timing to maximum velocity; Vmax, maximum velocity; TS, trajectory straightness; PWM, periventricular white matter; CDGM, cortical and deep gray matter; bold indicates p<0.05.*

Relation between Lesion Location and Extent and Upper Limb Kinematics for Each Lesion Timing Group

Spatiotemporal Parameters

In the **PWM group**, no correlations were found for the spatiotemporal parameters, except for two low correlations. Damage to the middle white matter layer and the PLIC were associated with longer movement durations ($r_b = 0.31$) and less straight hand trajectories ($r_b = 0.33$), respectively. Interestingly, in the **CDGM group** several moderate to high correlations were found between lesion location and extent and movement duration, timing of maximum velocity and trajectory straightness ($r_b = 0.52$ to -0.79), indicating longer movement durations, earlier timings of maximum velocity and less straight hand trajectories with increasing brain damage (see **Table 2**). In addition, one high correlation was found between higher contralesional total scores and earlier timings of maximum velocity ($r_b = -0.71$.) Regarding maximum velocity, only one moderate correlation was found, i.e., with damage to the corpus callosum ($r_b = 0.62$).

Movement Pathology

In the **PWM group**, only a few and low correlations were found (**Table 3**). Damage to the PLIC was correlated with higher APS ($r_b = 0.36$) and increased movement deviations of elbow flexion/extension, shoulder elevation and trunk rotation ($r_s = 0.35$, 0.42, and 0.38, respectively). Low correlations were also found between higher subcortical scores and increased AVS of elbow flexion/extension ($r_s = 0.40$), between higher global scores and scapula medial/lateral rotation ($r_s = 0.39$) and between involvement of the thalamus and trunk rotation ($r_s = 0.44$). In contrast, damage to the brainstem was correlated with lower AVS of trunk flexion/extension ($r_s = -0.37$) and damage to the corpus callosum showed a negative correlation with AVS of scapula protraction/retraction and trunk lateral bending ($r_s = -0.42$ and $r_s = -0.45$, respectively).

In children with **CDGM lesions**, more and stronger correlations were found between the summary indices and brain lesion location and extent (**Table 4**). These correlations were most pronounced for the APS ($r_b = 0.36$–0.63) and the AVS of the wrist and elbow ($r_s = 0.34$–0.65). Proximally, correlations were rather scarce and mostly low. Regarding *lesion location*, damage to the temporal lobe and involvement of the cortico-subcortical layer correlated moderately with increased APS and AVS of wrist flexion/extension, elbow pronation/supination and elbow flexion/extension ($r_s = 0.50$–0.65). Further, positive, moderate correlations were found between involvement of the PLIC, thalamus and brainstem and higher AVS of wrist and elbow flexion/extension ($r_s = 0.50$–0.59). Proximally, positive moderate correlations were seen between damage to the corpus callosum and higher AVS of scapular protraction/retraction ($r_s = 0.53$) and between damage to the caudate nucleus and the AVS of trunk flexion/extension ($r_s = 0.59$). Regarding *lesion extent*, moderate correlations were found between higher ipsilesional hemispheric scores and increased AVS of elbow pronation/supination ($r_s = 0.54$). Higher ipsilesional subcortical

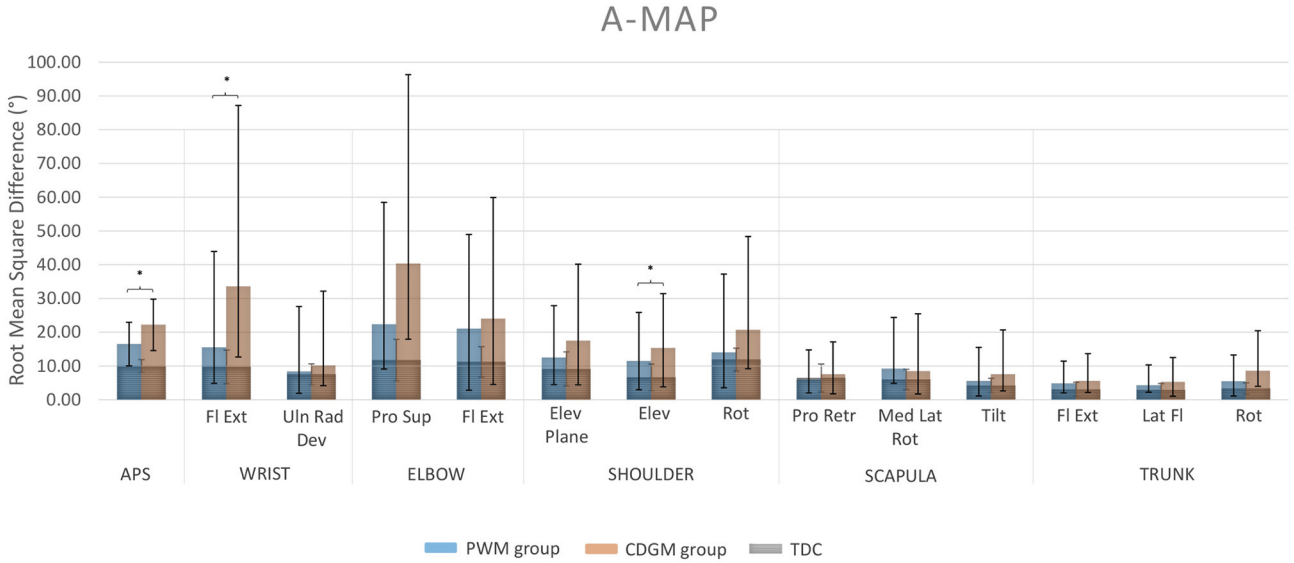

FIGURE 1 | Arm Movement Analysis Profile (A-MAP) of the PWM and CDGM group. Each column represents the AVS of one specific joint angle. The APS for total upper limb movement pathology is presented in the leftmost column. Blue columns represent the AVS and APS of the PWM group; orange columns of the CDGM group. The AVS and APS of the typically developing group overlay the columns of both the PWM and CDGM group in gray. APS, Arm Profile Score; AVS, Arm Variable Score; Fl Ext, flexion/extension; Uln Rad Dev, ulnar/radial deviation; Pro Sup, pronation/supination; Elev, elevation; Rot, rotation; Pro Retr, protraction/retraction; Med Lat Rot, medial/lateral rotation; Tilt, tilting; Lat Fl, lateral flexion; PWM, periventricular white matter; CDGM, cortical and deep gray matter; TDC, typically developing children; *significant difference between the PWM and CDGM group ($p < 0.05$).

scores were further moderately correlated with increased APS and AVS of wrist and elbow flexion/extension (r_s = 0.51–0.62). Higher ipsilesional total scores were moderately correlated with increased APS and AVS of elbow pronation/supination ($r_b = 0.51$ and $r_s = 0.50$, respectively). Finally, also two negative moderate correlations were found, i.e., between damage to the lenticular nucleus and the AVS of scapular protraction/retraction ($r_s = -0.58$) and between damage to the caudate nucleus and the AVS of shoulder elevation plane ($r_s = -0.59$).

Multiple Regression

The LASSO regression revealed the ipsilesional temporal lobar score with lesion timing as interactor and the PLIC as the strongest predictors of the APS. Together, these variables explained 34% of the variance in APS, with damage to the temporal lobe combined with lesion timing as the strongest contributor (27%, $p = 0.002$; PLIC 7%, $p = 0.04$).

DISCUSSION

This study was the first to investigate differences in UL kinematics, quantified by means of an UL 3DMA between children with PWM and CDGM lesions and to explore the impact of lesion location and extent on UL kinematics within each lesion timing group. These insights are critical to identify the underlying neural mechanisms of UL movement pathology. We found significant differences in UL kinematics between both groups, whereby children with CDGM lesions exhibit more movement pathology, and further showed that lesion location and extent were more strongly related with UL kinematics in the CDGM group, except for proximal movement pathology. The PLIC was identified as the only important brain structure for UL movement pathology irrespective of lesion timing.

The results of this study demonstrated for the first time that lesion timing influences UL movement pathology in children with uCP. Children with CDGM lesions moved slower, reached their maximum velocity earlier and moved less smooth compared to children with PWM lesions. Additionally, the A-MAP showed that children with CDGM lesions have more deviant movement patterns than children with PWM lesions. Differences were significant for total movement pathology (APS) and movement deviations of wrist flexion/extension and shoulder elevation as well as a borderline significant difference for elbow pronation/supination. Inspection of the waveforms showed that the CDGM group executed the RGV task with more wrist flexion and elbow pronation and reached their maximal shoulder elevation earlier compared to the PWM group (Supplementary Material SF1). Current findings confirmed our hypothesis that UL kinematics are more deviant in children with later lesions. These findings are in line with previous studies reporting that children with CDGM lesions have a more impaired UL function, assessed with clinical outcomes, compared to children with PWM lesions (Feys et al., 2010; Holmström et al., 2010; Holmefur et al., 2013; Mackey et al., 2014).

Secondly, correlation analysis between UL kinematics and lesion location and extent clearly showed different results for each lesion timing group. In the CDGM group, moderate to high correlations were found between increasing brain damage and more deviating spatiotemporal parameters, while no correlations were found in the PWM group. Previously, only Van Der

TABLE 2 | Correlation coefficients between the spatiotemporal parameters and brain lesion scores in the CDGM group ($N = 15$).

	Duration (s)[a]	TimeVmax (%)[a]	Vmax (m/s)[a]	TS[a]
LESION LOCATION				
Lobes				
Frontal (0–3)	**0.65****	**−0.69****	–	**0.55***
Parietal (0–3)	**0.53***	**−0.57***	–	**0.55***
Temporal (0–3)	**0.55***	**−0.53***	–	**0.64***
Occipital (0–3)	**0.57***	**−0.64***	–	0.39
Layers				
PV (0–4)	**0.63***	**−0.68****	–	**0.62***
M (0–4)	**0.72****	**−0.78*****	–	**0.68****
CSC (0–4)	**0.60***	**−0.58***	−0.33	**0.54***
Subcortical structures				
Lenticular nc (0–1)	–	–	−0.32	–
Caudate nc (0–1)	0.35	–	–	0.35
PLIC (0–1)	0.45	**−0.57***	–	**0.58***
Thalamus (0–1)	0.45	**−0.57***	–	**0.58***
Brainstem (0–1)	0.45	**−0.57***	–	**0.58***
Corpus callosum (0–3)	–	–	**0.62***	–
LESION EXTENT (i.e., global and total scores)				
Hemispheric score (0–12)	**0.68****	**−0.72****	–	**0.64***
Subcortical score (0–5)	0.39	−0.38	–	**0.52***
Ipsilesional total (0–17)	**0.61***	**−0.64***	–	**0.63***
Contralesional total (0–17)	0.47	**−0.71****	–	0.33
Global score (0–40)	**0.90*****	**−0.82*****	–	**0.59***

[a]*biserial correlation coefficient; CDGM, cortical and deep gray matter; TimeVmax, timing to maximum velocity; Vmax, maximum velocity; TS, trajectory straightness; PV, periventricular; M, middle white matter; CSC, cortico-subcortical; nc, nucleus; PLIC, posterior limb of the internal capsule; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; –, no correlation ($r < 0.30$); 0.30–0.50, low correlation; 0.50–0.70, moderate correlation; 0.70–0.90, high correlation; moderate correlations are highlighted in bold.*

Heide et al. (2005) investigated the relation between brain lesion severity and trajectory straightness in 50 children with uCP during a reach-to-grasp task and reported only low correlations. However, these authors did not make a distinction depending on lesion timing, which might explain why they could not demonstrate a clear relationship. In addition, brain lesion severity was scored on a 3-point scale based on ultrasound images only, which is known to be less accurate to detect diffuse white matter injury compared to MRI (Inder et al., 2003).

Furthermore, more and stronger correlations between lesion location and extent and UL movement pathology were found in children with CDGM lesions compared to children with PWM lesions, however, only for the distal joints. In the CDGM group, involvement of the temporal lobe, cortico-subcortical layer, PLIC, thalamus, brainstem as well as higher ipsilesional hemispheric, ipsilesional subcortical, and ipsilesional total scores were correlated with increased movement pathology of wrist flexion/extension, elbow pronation/supination and elbow flexion/extension. Interestingly, despite moderate correlations between lesion location and extent and distal UL movement pathology, correlations between lesion location and extent and shoulder, scapula and trunk kinematics were scattered and low. Klingels et al. (2012) have previously reported that motor impairments, such as increased muscle tone and weakness were most prominent at the wrist and elbow, compared to the shoulder muscles. Hence, proximal UL movement pathology may not solely be affected by the impairments in those regions, but also by the posture of the child and the compensation strategies used to overcome the more pronounced distal deficits (Jaspers et al., 2011a; Simon-Martinez et al., 2017). This might also explain the few unexpected correlations implying a relation between increased brain damage and less proximal UL movement pathology. Overall, these findings suggest that structural brain damage impact less on shoulder, scapula and trunk kinematics compared to the wrist and elbow in children with CDGM lesions. In contrast, in the PWM group only a few and low correlations were found, mostly between damage to the PLIC and UL movement pathology. These findings correspond to a recent study of our research group, whereby lesion location and extent were more strongly related with clinical measures of UL function in children with CDGM lesions than children with PWM lesions (Mailleux et al., 2017b). There was an overlap of only five participant between both studies. It was hypothesized that in children with PWM lesions, other brain lesion characteristics, such as white matter microstructure and type of corticospinal tract (re)organization, might need to be considered next to lesion location and extent when investigating structure-function relationships in this group. Secondly, white matter damage in children with PWM lesions might allow a higher gray matter plasticity compared to children with CDGM lesions, which could also explain the lower correlations in the PWM group.

Diffusion-weighted MRI is found to be more sensitive in detecting subtle white matter abnormalities compared to a conventional MRI scan (Son et al., 2007) and is particularly well-suited to visualize white matter microstructure. Previous studies have already shown that white matter microstructural properties of both the corticospinal tract and thalamocortical tracts are associated with UL function in children with uCP (Holmström et al., 2011; Rose et al., 2011; Mackey et al., 2014; Tsao et al., 2014, 2015). Additionally, the type of corticospinal tract (re)organization (i.e., contralateral, ipsilateral or bilateral) has also been shown to play a role in defining UL function (Staudt et al., 2004; Holmström et al., 2010; Jaspers et al., 2016), which can be assessed using transcranial magnetic stimulation. Overall, children with an ipsilateral tract reorganization have a more impaired UL function compared to contralateral or bilateral tract reorganization. However, the efficacy of corticospinal tract reorganization largely depends on the timing of the lesion (Staudt et al., 2004). Due to the earlier onset of PWM lesions, these children have a higher efficacy of reorganizing to the contralesional hemisphere. Hence, future multimodal imaging studies might aid in unraveling the multifactorial interaction of these brain lesion characteristics on UL movement pathology in children with uCP, particularly in children with PWM lesions.

In the total group, regression analysis confirmed the importance of the PLIC for total UL movement pathology irrespective of lesion timing. Correspondingly, in both groups, damage to the PLIC was related with UL movement pathology.

TABLE 3 | Correlation coefficients between the APS and AVS and brain lesion scores in the PWM group ($N = 33$).

(A) APS and AVS of wrist and elbow

	APS[a]	WRIST[b]		ELBOW[b]	
		Fl Ext	Uln Rad Dev	Pro Sup	Fl Ext
LESION LOCATION					
Lobes					
Frontal (0–3)	–	–	–	–	–
Parietal (0–3)	–	–	–	–	–
Temporal (0–3)	–	–	–	–	–
Occipital (0–3)	–	–	–	–	–
Layers					
PV (0–4)	–	–	–	–	–
M (0–4)	–	–	–	–	–
CSC (0–4)	–	–	–	–	–
Subcortical structures					
Lenticular nc (0–1)	–	–	–	–	–
Caudate nc (0–1)	–	–	–	–	–
PLIC (0–1)	0.36*	–	0.31	–	0.35*
Thalamus (0–1)	–	–	–	–	–
Brainstem (0–1)	–	–	–	–	–
Corpus Callosum (0–3)	–	–	–	–	–
LESION EXTENT (i.e., global and total scores)					
HS (0–12)	–	–	–	–	–
SS (0–5)	–	–	–	–	0.40*
Ipsi total (0–17)	–	–	–	–	–
Contra total (0–17)	–	–	–	–	–
Global score (0–40)	–	–	–	–	–

(B) AVS of shoulder, scapula and trunk

	SHOULDER[c]			SCAPULA[c]			TRUNK[c]		
	Elev Plane	Elev	Rot	Pro/Retr	Med/Lat Rot	Tilt	Fl Ext	Lat Fl	Rot
LESION LOCATION									
Lobes									
Frontal (0–3)	–	–	–	–	–	–	–	–	–
Parietal (0–3)	–	–	–	–	–	0.33	–	–	–
Temporal (0–3)	–	–	–	–	–	–	–	–	–
Occipital (0–3)	–	–	–	–	–	–	–	–	0.30
Layers									
PV (0–4)	–	–	–	–	–	–	–	–	0.32
M (0–4)	–	–	–	–	–	–	–	–	–
CSC (0–4)	–	–	–	–	–	–	–	–	–
Subcortical structures									
Lenticular nc (0–1)	–	–	–	–	–	–	–	–	–
Caudate nc (0–1)	–	–	–	–	–	–	–	–	–
PLIC (0–1)	–	0.42*	–	–	–	–	–	–	0.38*
Thalamus (0–1)	–	–	–	–	–	–	–	–	0.44*
Brainstem (0–1)	–	0.32	–	–	–	–	−0.37*	–	–
CC (0–3)	–	–	–	−0.42*	0.32	–	–	−0.45*	–
LESION EXTENT (i.e., GLOBAL AND TOTAL SCORES)									
HS (0–12)	–	–	–	–	–	–	–	–	–
SS (0–5)	–	–	–	–	–	–	–	–	–
Ipsi total (0–17)	–	–	–	–	–	–	–	–	–
Contra total (0–17)	–	–	–	–	–	–	–	–	–
Global score (0–40)	–	–	–	–	0.39*	–	–	–	–

*[a]biserial correlation coefficient; [b]spearman correlation coefficient; APS, arm profile score; AVS, arm variable scores; Fl, flexion; Ext, extension; Uln, ulnar; Rad, radial; Dev, deviation; Pro, pronation; Sup, supination; PV, periventricular; M, middle white matter; CSC, cortico-subcortical; nc, nucleus; PLIC, posterior limb of the internal capsule; HS, hemispheric score; SS, subcortical score; ipsi, ipsilesional; contra, contralesional; *p < 0.05; –, no correlation (r < 0.30); 0.30–0.50, low correlation.*

*[c]spearman correlation coefficient; AVS, arm variable scores; Elev, elevation; Rot, rotation; Pro, protraction; Retr, retraction; Med, medial; Lat, lateral; Tilt, tilting; Fl, flexion; Ext, extension; PV, periventricular; M, middle white matter; CSC, cortico-subcortical; nc, nucleus; PLIC, posterior limb of the internal capsule; CC, corpus callosum; HS, hemispheric score; SS, subcortical score; ipsi, ipsilesional; contra, contralesional; *p < 0.05; –, no correlation (r < 0.30); 0.30–0.50, low correlation.*

TABLE 4 | Correlation coefficients between the APS and AVS and brain lesion scores in the CDGM group ($N = 15$).

(A) APS and AVS of wrist and elbow

	APS[a]	WRIST[b]		ELBOW[b]	
		Fl Ext	Uln Rad Dev	Pro Sup	Fl Ext
LESION LOCATION					
Lobes					
Frontal (0–3)	0.36	–	–	**0.51**	0.35
Parietal (0–3)	–	–	–	–	–
Temporal (0–3)	**0.63***	**0.64****	–	**0.65****	**0.55***
Occipital (0–3)	–	–	–	0.41	–
Layers					
PV (0–4)	0.43	0.39	–	0.48	–
M (0–4)	0.41	–	–	0.49	–
CSC (0–4)	**0.53***	**0.50**	–	**0.58***	**0.50**
Subcortical structures					
Lenticular nc (0–1)	–	0.42	–	–	–
Caudate nc (0–1)	**0.50**	0.43	**0.52***	0.39	0.40
PLIC (0–1)	0.46	**0.50**	–	0.41	**0.59***
Thalamus (0–1)	0.46	**0.50**	–	0.41	**0.59***
Brainstem (0–1)	0.46	**0.50**	–	0.41	**0.59***
Corpus Callosum (0–3)	–	–	–	–	–
LESION EXTENT (i.e., GLOBAL AND TOTAL SCORES)					
HS (0–12)	0.47	0.41	–	**0.54***	0.34
SS (0–5)	**0.52***	**0.62***	–	0.37	**0.51**
Ipsi total (0–17)	**0.51**	0.45	–	**0.50**	0.34
Contra total (0–17)	–	–	–	–	–
Global score (0–40)	–	–	–	0.35	–

(B) AVS of shoulder, scapula and trunk

	SHOULDER[c]			SCAPULA[c]			TRUNK[c]		
	Elev Plane	Elev	Rot	Pro/Retr	Med/Lat Rot	Tilt	Fl Ext	Lat Fl	Rot
LESION LOCATION									
Lobes									
Frontal (0–3)	–	–	–	–	–	–	–	–	–
Parietal (0–3)	–	–	–	0.33	–	–	–	0.32	–
Temporal (0–3)	–	0.36	–	–	–	–	–	–	–
Occipital (0–3)	–	0.38	–	–	–	–	–	–	–
Layers									
PV (0–4)	–	–	–	–	–	–	–	–	–
M (0–4)	–	–	–	0.38	–	–	–	–	–
CSC (0–4)	–	–	–	–	–	–	–	–	–
Subcortical structures									
Lenticular nc (0–1)	–	–	–	–	**−0.58***	–	–	–	–
Caudate nc (0–1)	–	**−0.59***	–	0.39	–	–	–	**0.59***	–
PLIC (0–1)	–	–	–	–	–	0.36	–	–	–
Thalamus (0–1)	–	–	–	–	–	0.36	–	–	–
Brainstem (0–1)	–	–	0.32	–	–	0.36	–	–	–
CC (0–3)	–	–	–	**0.53***	0.47	0.34	–	–	–
LESION EXTENT (i.e., global and total scores)									
HS (0–12)	–	–	–	–	–	–	–	–	–
SS (0–5)	–	–	–	–	–	–	0.31	–	–
Ipsi total (0–17)	–	–	–	–	–	–	–	–	–
Contra total (0–17)	–	0.46	–	–	–	–	–	–	–
Global score (0–40)	–	–	–	0.36	–	–	0.32	–	–

[a] *biserial correlation coefficient;* [b] *spearman correlation coefficient; APS, arm profile score; AVS, arm variable scores; Fl, flexion; Ext, extension; Uln, ulnar; Rad, radial; Dev, deviation; Pro, pronation; Sup, supination; PV, periventricular; M, middle white matter; CSC, cortico-subcortical; nc, nucleus; PLIC, posterior limb of the internal capsule; HS, hemispheric score; SS, subcortical score; ipsi, ipsilesional; contra, contralesional; *p < 0.05; –, no correlation (r < 0.30); 0.30–0.50, low correlation; 0.50–0.70, moderate correlation; moderate correlations are highlighted in bold.*

[c] *spearman correlation coefficient; AVS, arm variable scores; Elev, elevation; Rot, rotation; Pro, protraction; Retr, retraction; Med, medial; Lat, lateral; Tilt, tilting; Fl, flexion; Ext, extension; PV, periventricular; M, middle white matter; CSC, cortico-subcortical; nc, nucleus; PLIC, posterior limb of the internal capsule; CC, corpus callosum; HS, hemispheric score; SS, subcortical score; ipsi, ipsilesional; contra, contralesional; *p < 0.05; –, no correlation (r < 0.30); 0.30–0.50, low correlation; 0.50–0.70, moderate correlation; moderate correlations are highlighted in bold.*

This is not surprising since the main motor pathways for voluntary motor control, i.e., the corticospinal tract, pass through the PLIC in order to continue its path down to the spinal cord. Together, these results point to the importance of this brain structure for UL motor function, which is in line with previous work (Holmström et al., 2011; Mackey et al., 2014; Dinomais et al., 2015; Mailleux et al., 2017b). Nevertheless, regression analysis identified the ipsilesional temporal lobe as the strongest predictor to explain the variance in APS, but only when lesion timing was taken into account. Correlation analysis showed that damage to the temporal lobe was moderately related with the APS only in the CDGM group. Accordingly, two other studies also retained the temporal lobe as a significant contributor for UL function in children with CDGM lesions (Pagnozzi et al., 2016; Mailleux et al., 2017b). The temporal lobe is associated with action recognition, in case the action is related to the manipulation of a certain tool (Quandt and Chatterjee, 2015). Also, visual stimuli that confer information about the external world are processed in the temporal lobe (Quandt and Chatterjee, 2015). Such stimuli are needed in order to properly execute the task RGV. This task requires information about the distance to the object and the circumference of the object to be grasped in terms of anticipatory hand shaping. Hence, these functions of the temporal lobe might thus explain why this region is important for UL motor function.

In total, regression analysis revealed a substantial 34% of the variance in APS. Still, clearly other factors will play an additional role in determining UL movement pathology. For example, different neural mechanisms defining UL movement pathology or the influence of compensation strategies at the proximal joints on total movement pathology as mentioned previously. For future studies, it might be interesting to develop a distal and proximal APS to allow for a better distinction between distal and proximal UL movement pathology. Hence, we would expect that for the distal APS a larger part of the variance could be explained by structural brain damage compared to the proximal APS. Furthermore, this 3DMA protocol does not capture fine finger and thumb movements, which are indispensable for UL function. Taking into account these movements might allow a more in-depth analysis of the relation between structural brain damage and UL movement pathology.

Finally, we also explored the relation between contralesional brain damage and UL kinematics. Despite a diagnosis of uCP, bilateral lesions in these children are not a rare phenomenon. Previous studies reported frequencies of up to 50% (Feys et al., 2010; Holmström et al., 2010; Holmefur et al., 2013). In this study, bilateral lesions were seen in 33% of the children with PWM lesions ($N = 11$) as well as with CDGM lesions ($N = 5$). For the spatiotemporal parameters, one high correlation was found between contralesional brain damage and timing of maximum velocity in the CDGM group. However, no further correlations were found between contralesional brain damage (i.e., contralesional total score) and the summary indices, except for one low correlation with the AVS of shoulder elevation in the CDGM group. Hence, this might imply that contralesional brain damage does not affect movement pathology of the impaired UL. Correspondingly, previous studies have also shown no differences in bimanual performance between children with unilateral and bilateral lesions (Holmefur et al., 2013; Mailleux et al., 2017b).

Nevertheless, this study also has a few limitations to address. First, children with botulinum toxin-A injections were included in case these injections occurred at least 6 months prior to testing. However, even though the effect of botulinum injections is temporary, nothing is currently known on whether (repeated) botulinum toxin injections could permanently change UL movement patterns. Secondly, we decided to include only children with PWM and CDGM lesions as these types of lesions occur most often (50% and 20–30% respectively, Krägeloh-Mann and Horber, 2007; Feys et al., 2010). Consequently, current study results cannot be generalized to children with brain maldevelopments, which occur in 10–15% of the cases. We further must acknowledge that a correction for multiple testing was not applied, increasing the chance of a type 1 error. However, we decided not to apply a correction due to the explorative nature of the study and considered it clinically more meaningful to interpret correlations according to their strength. Although this study was applied on a large group of children with uCP ($N = 48$), classifying them according to lesion timing retained only 15 children in the CDGM group. Nevertheless, this study was the first to explore the relation between lesion location and extent and UL kinematics taking into account lesion timing, suggesting that the underlying neural mechanisms of UL movement pathology differ between children with PWM and CDGM lesions. Moreover, the current study findings emphasize the importance of taking into account brain lesion characteristics when interpreting the clinical picture of UL function in children with uCP, particularly in children with CDGM lesions and temporal lobe involvement. The higher amount of movement pathology in children with CDGM lesions compared to PWM lesions may be caused by the more severe underlying sensorimotor impairments in the CDGM group (Mailleux et al., 2017a; Simon-Martinez et al., 2017), which was also confirmed in our study (see Supplementary Material ST1). Thus, these children are more at risk of developing secondary musculoskeletal problems. In these children, therapy could focus on improving active range of motion and reducing muscle tone (e.g., botulinum toxin injections) in order to improve UL movement patterns. Hence, the findings of this study may aid in guiding patient selection for interventions and optimizing individualized intervention strategies. In addition, there is a need to further explore and validate the utility of brain lesion characterization using early imaging to predict motor outcome at an older age and thus, improve the prognostic information for patients and clinicians.

CONCLUSION

This study demonstrated that children with CDGM lesions have more deviant UL kinematics compared to children with PWM lesions. Secondly, more prominent relationships were shown between lesion location and extent and UL kinematics in the CDGM group compared to the PWM group. This finding might imply that the underlying neural mechanisms of UL movement pathology differ between children with different lesion timings. However, multimodal imaging studies are needed

to clarify whether white matter microstructure and type of corticospinal tract (re)organization can explain more of the variance in APS. The PLIC was the only significant predictor for UL movement pathology irrespective of lesion timing. Finally, it seemed that proximal UL movement pathology is less influenced by lesion location and extent compared to movement deviations at the wrist and elbow, particularly in children with CDGM lesions. Other factors, such as posture and compensation strategies might play a larger role in defining proximal UL movement pathology. Although this needs further investigation, the finding that structural brain damage mostly relates to distal UL movement pathology compared to proximal UL kinematics, clearly demonstrated the added value of using 3DMA to investigate structure-function relationships.

AUTHOR CONTRIBUTIONS

This study was designed by LM, KK, EO, and HF. LM, CS-M, and EJ were responsible for all data collection and analysis. EO scored all scans with the sqMRI scale. All authors contributed to the interpretation of the results and gave their critical views regarding the revision and editing of the manuscript written by LM. All authors approved the final version of the manuscript and agreed to be accountable for the content of the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2017.00607/full#supplementary-material

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Negative Influence of Motor Impairments on Upper Limb Movement Patterns in Children with Unilateral Cerebral Palsy. A Statistical Parametric Mapping Study

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Upper limb three-dimensional movement analysis (UL-3DMA) offers a reliable and valid tool to evaluate movement patterns in children with unilateral cerebral palsy (uCP). However, it remains unknown to what extent the underlying motor impairments explain deviant movement patterns. Such understanding is key to develop efficient rehabilitation programs. Although UL-3DMA has been shown to be a useful tool to assess movement patterns, it results in a multitude of data, challenging the clinical interpretation and consequently its implementation. UL-3DMA reports are often reduced to summary metrics, such as average or peak values per joint. However, these metrics do not take into account the continuous nature of the data or the interdependency between UL joints, and do not provide phase-specific information of the movement pattern. Moreover, summary metrics may not be sensitive enough to estimate the impact of motor impairments. Recently, Statistical Parametric Mapping (SPM) was proposed to overcome these problems. We collected UL-3DMA of 60 children with uCP and 60 typically developing children during eight functional tasks and evaluated the impact of spasticity and muscle weakness on UL movement patterns. SPM vector field analysis was used to analyze movement patterns at the level of five joints (wrist, elbow, shoulder, scapula, and trunk). Children with uCP showed deviant movement patterns in all joints during a large percentage of the movement cycle. Spasticity and muscle weakness negatively impacted on UL movement patterns during all tasks, which resulted in increased wrist flexion, elbow pronation and flexion, increased shoulder external rotation, decreased shoulder elevation with a preference for movement in the frontal plane and increased trunk internal rotation. Scapular position was altered during movement initiation, although scapular movements were not affected by muscle weakness or spasticity. In conclusion, we identified pathological movement patterns in children with uCP and additionally mapped the negative impact of spasticity and muscle weakness on these movement patterns,

providing useful insights that will contribute to treatment planning. Last, we also identified a subset of the most relevant tasks for studying UL movements in children with uCP, which will facilitate the interpretation of UL-3DMA data and undoubtedly contribute to its clinical implementation.

Keywords: cerebral palsy, motor impairments, spasticity, muscle weakness, motion analysis, upper limb, neurorehabilitation, Statistical Parametric Mapping

INTRODUCTION

An efficient use of the upper limb (UL) requires a fine-tuned coordination between head, trunk, arm and hand movements. This fine-tuned coordination is commonly impaired in children with unilateral cerebral palsy (uCP). They present with various motor and sensory impairments on one side of the body (Uvebrant, 1988), caused by a lesion in the developing brain (Bax et al., 2005). As a result, children with uCP often experience difficulties during various activities of daily life, ranging from simple reaching or grasping tasks to more complex movements such as object manipulation (Klingels et al., 2012). A vast body of literature has contributed to our understanding of the relation between motor and sensory impairments and UL activity limitations in children with uCP. For example, spasticity and muscle weakness at the level of the elbow and wrist have a negative impact on unimanual and bimanual task performance (Klingels et al., 2012; Brændvik et al., 2013). However, studies thus far mostly used clinical scales to assess UL function, which do not provide detailed quantitative information and, as such, lack the sensitivity to measure the fine-tuned coordination of UL function.

Apart from the clinical scales, three dimensional motion analysis (3DMA) offers a reliable and valid tool to examine UL movement patterns and coordination between the different joints (Jaspers et al., 2010). However, its output is complex due to the large amount of degrees of freedom involved in the UL, and the variety of tasks that can be measured. As a result, studies employing UL-3DMA mostly focus on temporal aspects of movement coordination during reaching (Chang et al., 2005; Butler and Rose, 2012), or report extracted metrics of joint angle kinematics such as maximum or minimum angle, range of motion, or end-point angles (Jaspers et al., 2011a). Based on these metrics, the negative impact of spasticity on trajectory straightness, peak velocity, or the number of movement units has already been demonstrated (Chang et al., 2005; van der Heide et al., 2005; Aboelnasr et al., 2017). Thus far, only two studies reported the negative relation between UL movement deviations, expressed as a summary index, and both muscle weakness and spasticity during various tasks (Jaspers et al., 2011c; Mailleux et al., 2017). Whilst these studies provide some first insights regarding the relation between motor deficits and UL movement pathology in uCP, results are based on an a-priori selection of extracted data points without a specific hypothesis, introducing bias in the results (Pataky, 2010, 2012; Pataky et al., 2016b).

Extracting specific data points, for example where the differences are maximum, leads to results that may exceed a certain α level that is uncorrected and unrepresentative for the actual number of data points in the dataset, which in turn increases the chances of committing a type I error (false positive). This "regional focus bias" questions the validity of currently used statistical inferences in 3DMA (Pataky et al., 2013). Recently, Statistical Parametric Mapping (SPM) has been proposed as a valid method to overcome the issues of multiple comparison, uncorrected threshold and interdependency between joint angles (vector components). SPM was originally developed for neuroimaging data, and has been transferred to the field of biomechanics to study bounded and continuous data. This analysis allows hypothesis testing over the entire waveform (Friston et al., 1991, 2007; Pataky, 2010) and reduces the chances of incorrectly rejecting the null hypothesis, since the number of statistical tests is lower (Pataky et al., 2013). However, the potential merit of SPM to investigate UL movement patterns has not yet been explored, which could offer valuable new insights that will help to further define a tailor-made UL treatment planning based on the individual needs of the child with uCP.

In this study, we used SPM for the first time to comprehensively assess UL movement patterns in children with uCP and in typically developing children (TDC). We first explored differences between both groups during eight tasks (reaching, reach-to-grasp, and gross motor tasks) and identified pronounced differences at all joint levels. Second, we investigated to what extent spasticity and muscle weakness at the level of the elbow and wrist impact on UL movement patterns in children with uCP, and found a negative influence of distal motor impairments at all joints except for the scapula. Finally, and based on these analyses, we aimed to identify the most discriminative and sensitive set of tasks to investigate UL movement patterns in children with uCP and proposed a selection of three tasks.

MATERIALS AND METHODS

Participants

This study included a cohort of 120 children, aged 5–15 years (60 spastic uCP, 60 TDC). Children with uCP were recruited via the CP care program of the University Hospital Leuven (Belgium) between 2010 and 2016. They were eligible to partake in the study if they were able to comprehend the test procedure and had sufficient UL function to actively open their hand. Children with uCP were excluded in case of previous UL surgery or botulinum neurotoxin-A injections 6 months prior to testing. TDC were recruited via schools and youth movements and were excluded in case of a history of any neurological or musculoskeletal disorder or previous UL surgery. This study was carried out in accordance with the recommendations of Ethical

Committee of the University Hospital Leuven with written informed consent from all subjects. All subjects gave their verbal assent to participate and parents gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethical Committee of the University Hospital Leuven (S55555; S56513).

Procedure

All children underwent an UL-3DMA at the Clinical Motion Analysis Laboratory of the University Hospital Leuven (Belgium). Children with uCP additionally received a clinical UL evaluation at body function level, including an assessment of muscle weakness and spasticity, evaluated with the Manual Muscle Testing (Hislop and Montgomery, 2007), and the Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987), respectively. The clinical evaluation of muscle tone and strength has been shown to be reliable in children with uCP (Klingels et al., 2010). Muscle weakness was evaluated for three muscle groups, i.e., elbow extensors, elbow supinators, and wrist extensors (total score: 0–15). Spasticity was assessed for three muscle groups, i.e., elbow flexors, elbow pronators, and wrist flexors (total score: 0–12). We opted for a composite score of these muscle groups based on a previous study (Klingels et al., 2012). All UL evaluations were conducted by four experienced physiotherapists (CSM, EJ, LM, CH).

UL-3DMA was conducted in a sitting position utilizing a custom-made chair that ensured foot and back-support. Seventeen reflective markers (14 mm diameter) were mounted on the trunk, acromion, upper and lower arm, and the hand, and several static calibration trials were performed to identify the anatomical landmarks of interest (Wu et al., 2005). The UL movement protocol consisted of eight tasks: three reaching tasks in different directions (forwards, RF; upwards, RU; sideways, RS), two reach-to-grasp tasks with different objects (grasp a sphere, RGS; or grasp a vertical cylinder, RGV), and three gross motor tasks simulating daily life activities (hand-to-head, HTH; hand-to-mouth, HTM; hand-to-shoulder, HTS). Reach and reach-to-grasp tasks were executed at shoulder height, except RU which was performed at eye height. All tasks were performed with the non-dominant/affected arm at self-selected speed. Children were instructed to repeat each task four times within one movement recording, two recordings were acquired per task, resulting in a total of eight movement repetitions per task. The starting position of every task was upright sitting with 90° of hip and knee flexion, hand on the ipsilateral knee. This protocol was shown to be reliable in both TDC and children with uCP (Jaspers et al., 2010, 2011b). For further details about the kinematic model, standardization and marker placement see Jaspers et al (Jaspers et al., 2010). Motion was recorded with 15 Vicon infrared cameras (Oxford Metrics, Oxford, UK) sampling at 100 Hz.

Data Processing

Data of 3D marker coordinates was processed offline using Vicon Nexus 1.8.5 software (Oxford Metrics, Oxford, UK). This data was filtered using a Woltring filtering routine with a predicted mean squared error of 10 mm^2 (Woltring, 1995). Movement cycles with marker occlusion exceeding 20% of movement duration were excluded. If marker occlusion was <20%, spline interpolation gap filling, implemented in Nexus, was applied to the marker 3D coordinate data. Start (hand on ipsilateral knee) and end of each movement cycle were identified. Task end-point was defined as follows: (1) touch a sphere with the palm of the hand (RF, RU, and RS), (2) grasp an object [sphere (RGS) or vertical cylinder (RGV)], and (3) touch different parts of the body [top of the head (HTH), mouth (HTM), or contralateral shoulder (HTS)]. The first and last repetitions of each recording were excluded to avoid start and stop strategies of the child, resulting in a total of four movement cycles per task. Movement cycles were time normalized (0–100%) and the root mean squared error (RMSE) of the kinematic signals of each cycle was computed and compared to the mean of the remaining three (per task). The three cycles with lowest RMSE were utilized for further statistical analysis, to maximize repeatability in performance. UL kinematic calculations were computed with ULEMA v1.1.9 (MATLAB-based open source software, available for download at https://github.com/u0078867/ulema-ul-analyzer). Extracted UL kinematics consisted of five joints with a total of 12 angles: trunk [three degrees of freedom (DoF): rotation, lateral flexion, and flexion-extension], scapula (three DoF: tilting, pro-retraction, and rotation), shoulder (three DoF: rotation, elevation plane, and elevation), elbow (two DoF: flexion-extension and pro-supination), and wrist (one DoF: flexion-extension). The interpretation of joint angle kinematics can be found in the open source documentation of the ULEMA software (page 14, https://github.com/u0078867/ulema-ul-analyzer/blob/master/AppendicesI-II.pdf).

Statistical Analysis

Descriptive statistics were used to report demographic and clinical data. The normal distribution of age was verified in both groups using the Kolmogorov–Smirnov test (TDC, $p = 0.20$; uCP, $p = 0.20$) and age differences between groups were tested using an unpaired Student's *t*-test. We used chi-square test to compare gender frequency between groups. For the ordinal scorings of muscle tone and strength, median and interquartile ranges (IQR) were reported, and non-parametric statistics were computed.

SPM1d version 0.4 (MATLAB-based open source software, available for download at http://www.spm1d.org/) was used to conduct vector field analysis (joint level) and corresponding *post-hoc* analysis of each vector component (joint DoF) (Pataky, 2012). SPM1d is identical to the conventional inferential statistics, with the following differences: (1) it takes into account the covariance among the vector components (joint DoF), (2) it considers field smoothness and size when calculating the critical threshold (test statistic), and (3) it utilizes random field theory to compute probability of cluster-based threshold crossings (*p*-values). For every task, UL movement patterns were compared between groups (TDC vs. uCP) using the Hotelling's T^2 test (SPM{T2}, analog to unpaired Student's *t*-test), with *post-hoc* scalar field *t*-tests for each vector component (SPM{t} per joint DoF). The relation between motor impairments and UL movement patterns in children with uCP was assessed using the non-parametrical Canonical Correlation analysis (SnPM{X2}, analog to linear regression), with *post-hoc* scalar field non-parametric linear regressions for each vector component (SnPM{t}, per joint DoF). Bonferroni correction was applied for *post-hoc* tests

taking into account the number of components (DoF) of each vector (e.g., three components for the scapula: tilting, rotation, pro-retraction; two components for the elbow: pro-supination and flexion-extension).

For each test, a statistical parametric map (SPM) was calculated by computing the conventional univariate statistic. Next, Random Field Theory was used to estimate (1) the critical threshold above which only 5% (i.e., $\alpha < 0.05$) of equally smoothed random data would be expected to cross, and (2) the probability that this would occur (i.e., *p*-value). If an SPM{t} crosses the critical threshold, this was identified as a statistically significant cluster at the vector field level. In case significance was reached in the vector field analysis, the correspondent *post-hoc* scalar field analysis was performed. When clusters were identified, information regarding the extent (percentage of the movement cycle), location (start and end points of the cluster), and a single *p*-value for each identified cluster was provided (see example in **Figure 1**).

RESULTS

Participants

Sixty children with uCP [mean age (SD) = 10 y 3 m (2 y 4 m), 25 girls, 29 left hand affected] and 60 TDC [mean age (SD) = 10 y 2 m (3 y 1 m), 24 girls, 53 right handed (left UL assessed)] participated in the study (**Table 1**). Age was not significantly different between groups ($p = 0.80$). Chi-square test showed no differences in gender frequency between groups ($p = 0.85$). According to the Manual Ability Classification System (MACS, Eliasson et al., 2006), 18 children with uCP were classified as level I, 28 as level II, and 14 as level III. Muscle weakness median score was 10.5 (IQR = 1.6), and spasticity median score was 3.5 (IQR = 2.0). Eight children showed no spasticity in any muscle, and the remaining 52 children presented with spasticity in at least one of the three muscles (sum score > 1). One child did not have any muscle weakness, whereas all other children presented with muscle weakness in at least one of the three muscles (sum score < 15).

UL Movement Patterns

In the following section, we will first report differences in UL movement patterns between children with uCP and TDC for each of the tasks. Next, we will describe the impact of muscle weakness and spasticity on UL movement patterns in children with uCP. Vector field analysis results are described with subsequent *post-hoc* analysis, if applicable. In general, results comprise a summary description of the identified clusters by SPM.

uCP vs. TDC

Results regarding the comparison between uCP and TDC for all UL joints can be found in **Table 2** (all tasks), **Figures 2–4** (RU, RGV, HTS) and Supplementary Material 1 (RF, RS, RGS, HTM, HTH).

At the level of the **wrist** (one DoF), *t*-test comparison showed *increased wrist flexion* in the uCP group during 100% of the movement (all tasks, $p < 0.001$), except during HTH (first 80% of the movement cycle, $p < 0.001$).

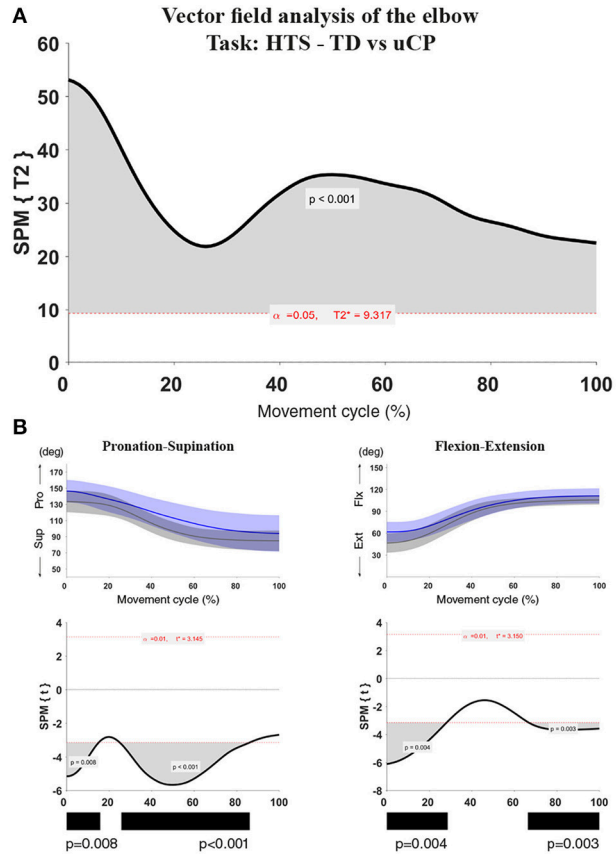

FIGURE 1 | Statistical Parametric Mapping output example for the comparison of elbow kinematics (two vector components) during the HTS task between children with uCP and TDC. **(A)** Hoteling's test output with one cluster over 100% of the movement cycle, the bold black line is the computed t-curve, the dashed red line indicates the random theory threshold calculated for this test (at 9.317 for $\alpha < 0.05$). Over 100% of the movement cycle, the vectors of the TDC and uCP group are significantly different; **(B)** Elbow vector decomposition (left: pro-supination; right: flexion-extension) with mean (bold line) and standard deviation (translucent area) of the TDC (gray) and uCP (blue) group. Below, the SPM{t} output correspondent to each of the vector components. Children with uCP show increased elbow flexion over 28 and 33% of the movement cycle in two different clusters (cluster 1: 0–28%, $p < 0.01$; cluster 2: 67–100%, $p < 0.01$) and increased pronation over 15 and 61% of the movement cycle in two different clusters (cluster 1: 0–15%, $p < 0.01$; cluster 2: 25–86%, $p < 0.01$). The black bars under each SPM{t} output correspond to the identified clusters. The SPM output will be represented in this summarized manner throughout the manuscript.

Vector field analysis at the **elbow** (two DoF) showed significant kinematic differences between the two groups during the entire movement cycle (all tasks, 100%, $p < 0.001$). *Post-hoc t*-tests showed significantly *increased pronation* (all tasks, at least 75% of movement cycle, $p < 0.01$) and *elbow flexion* (all tasks, approx. between 15 and 100% of the movement cycle, $p < 0.01$) in uCP compared to TDC.

At the **shoulder** level (three DoF), we found significant differences between both groups during 100% of the movement cycle (all tasks, $p < 0.001$). Overall, *post-hoc t*-tests identified that shoulder movement patterns of children with uCP were

TABLE 1 | Demographic and clinical characteristics of the study participants.

		uCP ($n = 60$)	TDC ($n = 60$)
Age	Mean, SD (range)	10y3m, 2y6m (5y2m–15y2m)	10y3m, 3y1m (5y–15y7m)
Gender	Boys [*n* (%)]	35 (58%)	36 (60%)
	Girls [*n* (%)]	25 (42%)	24 (40%)
Handedness (dominant or non-affected hand)	Right [*n* (%)]	29 (49%)	53 (88%)
	Left [*n* (%)]	31 (51%)	7 (12%)
MACS levels	I [*n* (%)]	18 (30%)	–
	II [*n* (%)]	28 (47%)	–
	III [*n* (%)]	14 (23%)	–
Muscle weakness*	Median (IQR)	10.5 (2.0)	–
Spasticity**	Median (IQR)	3.5 (2.0)	–

uCP, unilateral cerebral palsy; TDC, typically developing children; MACS, manual ability classification system; IQR, interquartile range.
Age was not significantly different between groups (unpaired t-test, p = 0.80).
**Muscle weakness for wrist and elbow extensors and elbow supinators (range 0–5 per muscle, total range 0–15).*
***Spasticity scores for wrist and elbow flexors and elbow pronators (range 0–4 per muscle, total range 0–12).*

characterized by increased *external rotation* (approx. between 30 and 100%, $p < 0.01$), increased *elevation in the frontal plane* (at least 40% of the movement cycle, $p < 0.01$) and *increased elevation* in movement initiation during the reach-to-grasp tasks (∼0–40%, $p < 0.01$) that significantly decreased toward the end of the movement cycle (approx. between 60 and 100%, $p < 0.01$).

For the **scapula** (three DoF), SPM vector field analysis showed significant kinematic differences RF, RGV, HTM, and HTS (100%, $p < 0.01$), and during a large extent of the movement cycle for RGS (cluster 1: 0–54%, $p < 0.02$; cluster 2: 58–100%, $p < 0.03$), RS (0–80%, $p = 0.01$), RU (0–60%, $p = 0.01$), and HTH (0–40%, $p = 0.02$). Scapular kinematics of children with uCP were characterized by *increased anterior tilting* (all tasks, 0–40%, $p < 0.01$), *medial rotation* (all tasks during movement initiation, $p < 0.01$) and *protraction* (different locations of the movement cycle, $p < 0.01$).

Trunk kinematics (three DoF) were significantly different between the two groups of RGV, HTM, and HTS (100%, $p < 0.003$). Smaller differences were found for RGS (48–54%, $p < 0.05$), RS (cluster 1: 1–15%, $p < 0.05$; cluster 2: 67–100%, $p = 0.03$), and HTH (33–100%, $p < 0.01$). *Post-hoc* analysis showed that trunk kinematics of children with uCP were characterized by *increased inwards rotation* for RGV, HTM, and HTS tasks ($p < 0.01$) and *increased outwards rotation* at the end of the movement cycle for RS ($p < 0.01$).

The Impact of Motor Impairments on UL Movement Patterns

Results regarding the impact of muscle weakness on UL movement patterns can be found in **Table 3** (all tasks), **Figures 5**–**7** (RU, RGV, HTS), and Supplementary Material 2 (RF, RS, RGS, HTM, HTH). Similarly, results related to the impact of spasticity are presented in **Table 4** (all tasks), **Figures 8**–**10** (RU, RGV, HTS), and Supplementary Material 3 (RF, RS, RGS, HTM, HTH).

Increased muscle weakness at the level of the **wrist** significantly increased wrist flexion for all tasks (100%, $p < 0.01$). Increased spasticity also negatively impacted on wrist flexion (all tasks, 100%, $p < 0.01$), except for RGV (cluster 1: 0–62%, $p < 0.01$; cluster 2: 76–100%, $p < 0.01$), and HTH (0–16%, $p < 0.01$).

SPM vector field analysis at the **elbow** (two DoF) showed that both muscle strength and spasticity scores significantly influenced elbow kinematics in the second half of the movement cycle for all tasks (muscle weakness $p = 0.01$; spasticity $p = 0.01$), except for RS, where neither motor impairment influenced the movement patterns ($p > 0.05$). *Post-hoc scalar field analysis for muscle weakness* showed that this impairment mainly contributed to increased elbow flexion in the reaching and reach-to-grasp tasks (44–100%, $p = 0.01$), whereas its contribution to increased pronation could be clearly observed in the gross motor tasks during a large extent of the movement cycle (∼30–100%, $p = 0.01$). RGV was the only task in which muscle weakness negatively influenced both elbow supination (19–100%, $p = 0.01$) and extension (44–100%, $p = 0.01$). *Post-hoc scalar field analysis for spasticity* showed that this factor mainly contributed to increased pronation in all tasks toward the end of the movement cycle (58–100%, $p = 0.01$), except in RS. The influence of spasticity on increased elbow flexion was visible in the last third of the movement cycle during reaching and reach-to-grasp (RF, RGS, and RGV: ∼75–100%, $p < 0.01$).

At the level of the **shoulder** (three DoF), both motor impairments had a negative impact on shoulder kinematics, ranging from at least 0–40% to up to 100% of the movement cycle in all tasks (muscle strength $p = 0.01$; spasticity $p < 0.02$). *Post-hoc scalar field analysis for muscle strength* showed that shoulder rotation and shoulder elevation were primarily responsible for the vector field results. Location of impact of muscle weakness on shoulder rotation varied among the tasks. Muscle weakness resulted in increased external rotation during RGS (cluster 1: 14–32%, cluster 2:76–100%, $p = 0.01$), RU (cluster 1: 0–28%, cluster 2: 52–100%, $p = 0.01$), RS (100%, $p = 0.01$), and HTH (18–26%, $p = 0.01$). Muscle weakness also explained the decreased shoulder elevation at the beginning of the movement cycle during reaching and HTH (0–50%, $p = 0.01$), and during HTM and HTS (28–100%, $p = 0.01$). The elevation plane was not significantly affected by muscle strength in any of the tasks. *Post-hoc scalar field analysis for spasticity* showed that shoulder elevation and elevation plane were mainly responsible for the significant vector field results. Spasticity resulted in less shoulder elevation in the middle part of the movement cycle (all tasks, approx. between 20 and 50%, $p = 0.01$) and increased elevation in the frontal plane second half of the movement cycle during reaching and reach-to-grasp (approx. between 52 and 100%, $p = 0.01$). Shoulder rotation was not significantly influenced by spasticity.

SPM vector field analysis for the **scapula** (three DoF) showed no significant influence of muscle weakness or spasticity on scapular kinematics.

For the **trunk** (three DoF), muscle weakness had a negative influence on trunk kinematics during reach-to-grasp and HTS toward the end of the movement cycle (approx. between 50 and 100%, $p < 0.02$). Increased spasticity also affected trunk movement patterns during RF, RS, both reach-to-grasp tasks

TABLE 2 | Statistical Parametric Mapping comparison of movement patters in children with uCP and TDC.

			RF	RU	RS	RGS	RGV	HTH	HTM	HTS
WRIST	Flexion Extension	*n* clusters	1	1	1	1	1	1	1	1
		(*p*-value)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
		% curve (range)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	80% (0–80)	100% (0–100)	100% (0–100)
ELBOW	VECTOR FIELD	*n* clusters	1	1	1	1	1	1	1	1
		(*p*-value)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
		% curve (range)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)
	Flexion Extension	*n* clusters	2	1	1	2	1	1	1	2
		(*p*-value)	(<0.01; <0.001)	(<0.001)	(<0.001)	(<0.01; <0.0001)	(<0.0001)	(<0.01)	(<0.01)	(<0.01; <0.01)
		% curve (range)	12% 52% (0–12) (48–100)	51% (49–100)	50% (50–100)	14% 64% (0–14) (36–100)	100% (0–100)	15% (0–15)	30% (0–30)	28% 33% (0–28) (67–100)
	Pro-supination	*n* clusters	1	1	1	1	1	1	1	2
		(*p*-value)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.01; <0.001)
		% curve (range)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	15% 61% (0–15) (25–86)
SHOULDER	VECTOR FIELD	*n* clusters	1	1	1	1	1	1	1	1
		(*p*-value)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
		% curve (range)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)
	Elevation	*n* clusters	1	1	–	2	2	1	1	–
		(*p*-value)	(<0.01)	(<0.01)		(<0.01; <0.01)	(<0.01; <0.01)	(<0.01)	(<0.01)	
		% curve (range)	19% (81–100)	31% (69–100)	–	28% 35% (17–45) (65–100)	18% 43% (22–40) (57–100)	24% (76–100)	5% (0–5)	–
	Rotation	*n* clusters	1	1	1	1	1	1	1	1
		(*p*-value)	(<0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.001)	(<0.01)	(<0.001)
		% curve (range)	50% (50–100)	55% (45–100)	77% (23–100)	59% (41–100)	66% (34–100)	74% (26–100)	67% (33–100)	72% (28–100)
	Elevation plane	*n* clusters	1	1	1	1	1	1	1	2
		(*p*-value)	(<0.0001)	(<0.0001)	(<0.01)	(<0.0001)	(<0.0001)	(<0.01)	(<0.01)	(<0.01; <0.01)
		% curve (range)	100% (0–100)	88% (0–88)	7% (0–7)	100% (0–100)	100% (0–100)	41% (0–41)	38% (0–38)	28% 28% (0–28) (72–100)
SCAPULA	VECTOR FIELD	*n* clusters	1	1	1	2	1	1	1	1
		(*p*-value)	(<0.001)	(<0.01)	(0.013)	(0.017; 0.026)	(<0.01)	(0.023)	(<0.001)	(<0.001)
		% curve (range)	100% (0–100)	63% (0–63)	62% (0–62)	54% 42% (0–54) (58–100)	100% (0–100)	41% (0–41)	100% (0–100)	100% (0–100)
	Tilting	*n* clusters	1	1	1	1	1	1	1	1
		(*p*-value)	(<0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.0001)
		% curve (range)	59% (0–59)	52% (0–52)	51% (0–51)	53% (0–53)	22% (0–22)	39% (0–39)	44% (0–44)	100% (0–100)

(Continued)

TABLE 2 | Continued

			RF	RU	RS	RGS	RGV	HTH	HTM	HTS
	Pro-retraction	*n* clusters	–	2	1	1	–	–	–	1
		(*p*-value)		(<0.01; <0.01)	(<0.01)	(<0.01)				(<0.01)
		% curve	–	6% 11%	47%	11%	–	–	–	79%
		(range)		(0–6) (15–26)	(12–59)	(0–11)				(21–100)
	Rotation	*n* clusters	2	1	1	1	2	1	1	1
		(*p*-value)	(<0.01; <0.01)	(<0.01)	(<0.01)	(<0.01)	(<0.01; <0.01)	(<0.01)	(<0.01)	(<0.01)
		% curve	49% 10%	48%	20%	20%	25% 48%	24%	77%	37%
		(range)	(0–49) (90–100)	(0–48)	(0–20)	(0–20)	(0–25) (52–100)	(0–24)	(0–77)	(0–37)
TRUNK	VECTOR FIELD	*n* clusters	0	0	2	1	1	1	1	1
		(*p*-value)			(0.046; 0.035)	(0.049)	(<0.001)	(<0.01)	(<0.01)	(<0.001)
		% curve	–	–	15% 33%	6%	100%	66%	100%	100%
		(range)			(1–15) (67–100)	(48–54)	(0–100)	(33–100)	(0–100)	(0–100)
	Axial Rotation	*n* clusters	–	–	1	–	1	1	1	1
		(*p*-value)			(<0.01)		(<0.001)	(<0.001)	(<0.0001)	(<0.0001)
		% curve	–	–	32%	–	78%	66%	100%	100%
		(range)			(68–100)		(22–100)	(34–100)	(0–100)	(0–100)

uCP, unilateral cerebral palsy; TDC, typically developing children; RF, reach forwards; RU, reach upwards; RS, reach sideways; RGS, reach-to-grasp a sphere; RGV, reach-to-grasp a vertical cylinder; HTH, hand-to-head; HTM, hand-to-mouth; HTS, hand-to-shoulder; n clusters, number of identified clusters; p-value, probability of the identified cluster: α < 0.05 vector field analysis, α < 0.017 (post-hoc with three components), α < 0.025 (post-hoc with two components); % curve, extent of the cluster over the waveform; range, start, and end point of the identified cluster.

and HTS (approx. between 57 and 100%, $p < 0.04$). *Post-hoc scalar field analysis* showed that axial rotation was the only responsible for the vector field results for both motor impairments. Muscle weakness resulted in increased trunk inward rotation toward the end of the movement cycle (reach-to-grasp tasks, HTS; approx. between 58 and 100%, $p = 0.01$). Increased trunk inward rotation toward the end of the movement was also seen in case of increased spasticity (RF, reach-to-grasp tasks; approx. between 64 and 100%, $p = 0.01$). In contrast, during RS, children with increased spasticity scores showed increased trunk outward rotation (41–100%, $p = 0.01$).

DISCUSSION

In this study, we used a statistical approach, i.e., vector field analysis based on SPM1D, (1) to examine differences in movement patterns between a large cohort of children with uCP and TDC during the execution of different UL tasks; and (2) to explore the relation between distal motor impairments and UL movement patterns in children with uCP.

The SPM vector field analysis identified pronounced differences between children with uCP and TDC, including increased wrist flexion, elbow flexion and pronation. These differences were present for most tasks and during a large extent of the movement cycle. Results are in line with previous studies reporting deviant distal kinematics in children with uCP, i.e., increased wrist or elbow flexion at the start or end of the movement, reduced elbow supination at the end of the movement and reduced elbow total range of motion (Kreulen et al., 2007; Jaspers et al., 2011a,c; Riad et al., 2011; Butler and Rose, 2012; Klotz et al., 2014). Proximally, children with uCP also showed deviant movement patterns compared to TDC during all UL tasks, mostly consisting of (1) increased shoulder external rotation, decreased shoulder elevation and a preference for movements in the frontal plane, (2) increased scapular anterior tilting, medial rotation and protraction, and (3) increased inwards trunk axial rotation. Interestingly, children with uCP showed most scapular deficits at rest and during movement initiation, whereas the second part of the movement was mostly characterized by deviant shoulder kinematics. For example, during HTS, children with uCP initiated the movement with large scapular deficits, which coincided with increased shoulder elevation in the frontal plane. Children only switched to the sagittal plane when approaching the contralateral shoulder (second half of the movement cycle), which was combined with increased external shoulder rotation. Such movement deviations can occur as a compensation for the lack of elbow supination. Previous literature, based on either extracted scalar metrics (end point angles, total range of motion) or summary indices, failed to identify differences in shoulder kinematics between uCP and TDC for most tasks (MacKey et al., 2006; Jaspers et al., 2011c). Lastly, movement deviations at the trunk consisted of increased inward rotation during all the tasks, except RS, where children with uCP showed an increased outward rotation. The increased trunk rotations could also be considered a compensation for

the distal deficits, which is in agreement with previous studies (Kreulen et al., 2007; Jaspers et al., 2011a). In general, it appears that for wrist, elbow and trunk kinematics, scalar metrics and summary indices might be sufficient to capture differences between children with uCP and TDC, although SPM1D was able to more specifically map the extent and the location of these differences over the movement cycle. Moreover, SPM1D analysis shows higher sensitivity to detect differences in kinematics at the shoulder and scapula compared to scalar metrics.

Current study results also showed that increased spasticity and muscle weakness explained the deviant wrist and elbow kinematics in the majority of tasks. Muscle weakness negatively influenced active elbow extension in the reaching and reach-to-grasp tasks, as well as active supination during the gross motor tasks. Spasticity also negatively influenced the supination deficit during reaching. The results at the level of the wrist and elbow are in agreement with previous literature (Jaspers et al., 2011c; Mailleux et al., 2017), which showed low to strong correlations between motor impairments and UL kinematics (either extracted parameters or summary indices). Remarkably, both muscle weakness and spasticity explained deviant shoulder kinematics, i.e., muscle weakness affected external rotation and elevation kinematics, whereas spasticity mostly influenced arm elevation and elevation plane kinematics. Also, both motor impairments were related to increased trunk deviations, with a stronger influence of spasticity on trunk rotation. This has recently been reported by Mailleux et al. who found low to moderate correlations with some extracted trunk kinematic parameters (Mailleux et al., 2017). The negative impact of distal motor impairments on proximal shoulder and trunk kinematics strongly supports the idea that these proximal movement patterns are compensations of the distal motor impairments. The lack of significant results at the level of the scapula in the present study suggests that scapula kinematics might be influenced by more proximal motor impairments. Efficient shoulder and scapula movements require an adequate stability and coordination of the scapulathoracic and glenohumeral joint and the surrounding muscle complex (Paine and Voight, 2013). The reported scapular deficits at rest could be caused by altered muscle length and muscle activation patterns of the scapulathoracic and glenohumeral muscles (McClure et al., 2001; Ludewig and Reynolds, 2009), as seen in stroke survivors (De Baets et al., 2016). Thus far, only the study of Mailleux et al. reported the relation between muscle weakness and kinematic deficits at each joint angle (Mailleux et al., 2017). The authors assessed scapula kinematics in three tasks and found no relation between UL muscle weakness and discrete parameters, except for a moderate correlation with the active range of motion of scapula rotation in one task. Their results implied that weaker children performed the task hand-to-mouth with increased lateral rotation, which is in contrast with our results. However, extracting specific scalars from a time-varying trajectory, i.e., kinematic waveform, has been suggested to increase the probability of false positive rate (Pataky et al., 2016b). The strength of SPM lies in decreasing the chances of incorrectly rejecting the null hypothesis by adjusting the threshold to the real number of comparisons. Therefore, we hypothesize that the moderate correlation found in the study of Mailleux et al may be due to the so called "regional focus bias" (Pataky et al., 2013). Nevertheless, firm conclusions based on our results cannot be drawn given the lack of an evaluation of proximal motor impairments. In summary, both studies by Jaspers et al and Mailleux et al previously reported a correlation between UL movement pathology and muscle weakness, although only Mailleux et al also found a correlation with spasticity (Jaspers et al., 2011c; Mailleux et al., 2017). However, both studies report deviations in UL movement patterns by extracting scalars or by computing summary indices of movement pathology (Jaspers et al., 2011c).

Overall, our results specifically highlight the importance of taking the entire movement cycle at the individual joint level into account to avoid an underestimation of the influence of underlying motor impairments on UL movement deviations. Interestingly, during the reaching tasks, muscle weakness mainly affected elbow extension, whereas during the gross motor tasks, muscle weakness mostly affected supination. We hypothesize that this is due to the muscle recruitment that each task requires. As we expected, for the RGV task, both muscle weakness and spasticity explained the elbow extension and supination deficits, given that this task simultaneously requires both motion components of elbow extension and supination, which are challenging for children with uCP. These results highlighted a task dependent influence of muscle weakness and spasticity and the relevance of choosing the right tasks for this population.

Current study results might have some interesting implications with respect to UL therapy planning in children with uCP. First, the fact that both spasticity and muscle weakness of the elbow and wrist have a negative impact on UL movement patterns, supports the use of interventions specifically targeting these impairments, such as Botulinum Neurotoxin-A (Park and Rha, 2006; Kreulen et al., 2007; Fitoussi et al., 2011) or functional strength training (Rameckers et al., 2008). SPM1D analysis would allow capturing the impact of these interventions at different levels of the UL kinematic chain. This might further aid in fine-tuning targeted interventions for the individual child with uCP. Second, the predominant distal impairments that are typically seen in children with uCP have thus far dominated UL rehabilitation programs such as Constraint-Induced Movement Therapy (Hoare et al., 2007; Eliasson et al., 2014), bimanual interventions (Gordon et al., 2007), or a combination of both (Gordon, 2011). Whilst it has been shown that treatment at the distal level may improve proximal movement patterns (shoulder and trunk; Kreulen et al., 2007; Fitoussi et al., 2011), our results suggest that these children might also benefit from scapulathoracic and glenohumeral stabilization training. These new insights in the relationship between motor impairments and movement patterns may provide a rationale for specific interventions targeting these motor impairments. However, further studies combining this information with clinical assessment scales are required to investigate the benefits of

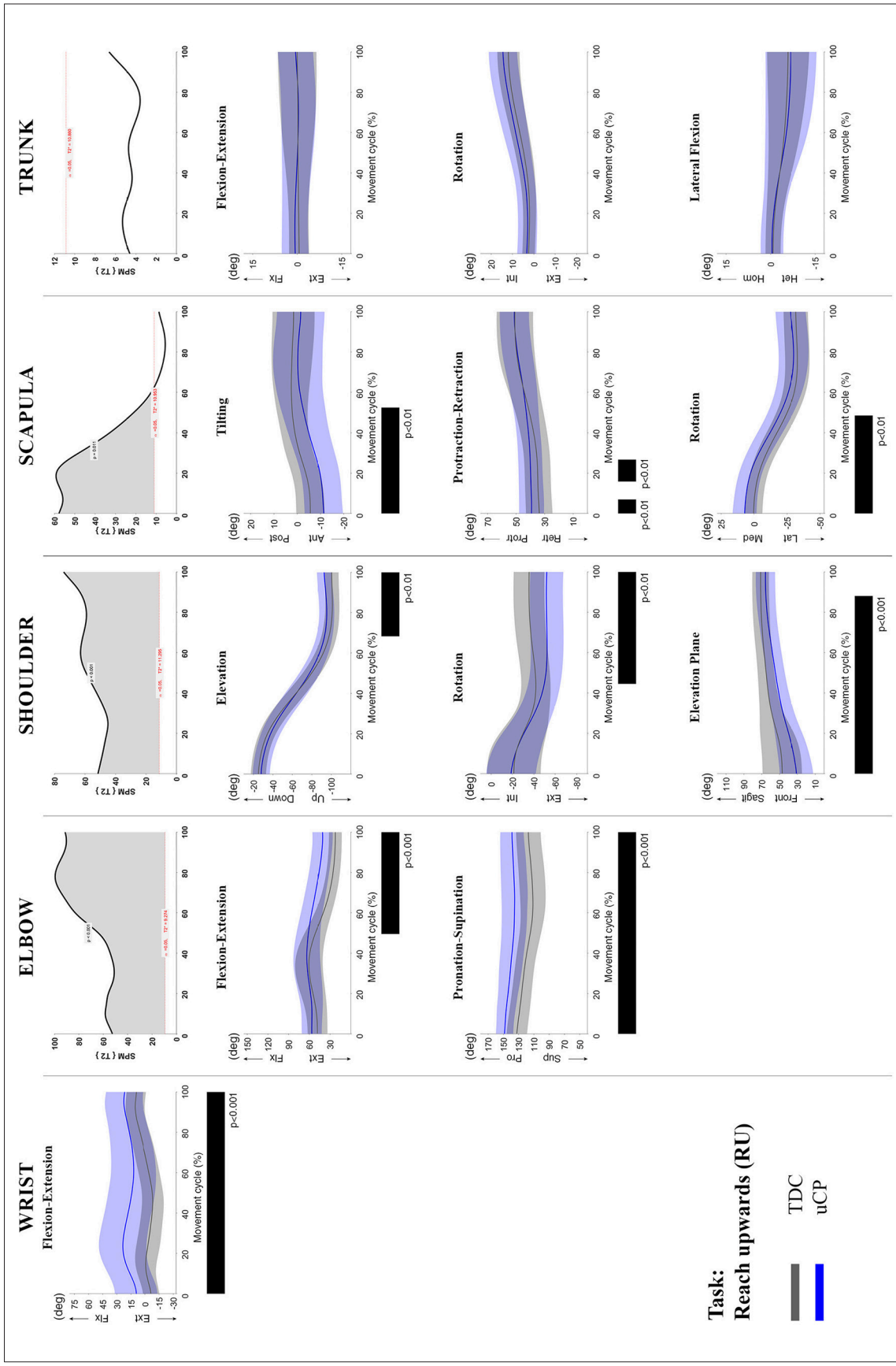

FIGURE 2 | Comparison between children with uCP and TDC during the RU task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, scapula, and trunk). The top image of each column is the SPM output of the vector field analysis (Hotelling's test, except for the wrist, where a *t*-test was computed). Below, mean (bold line) and standard deviation (translucent area) of the TDC (gray) and uCP (blue) of each vector component, and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant difference between groups.

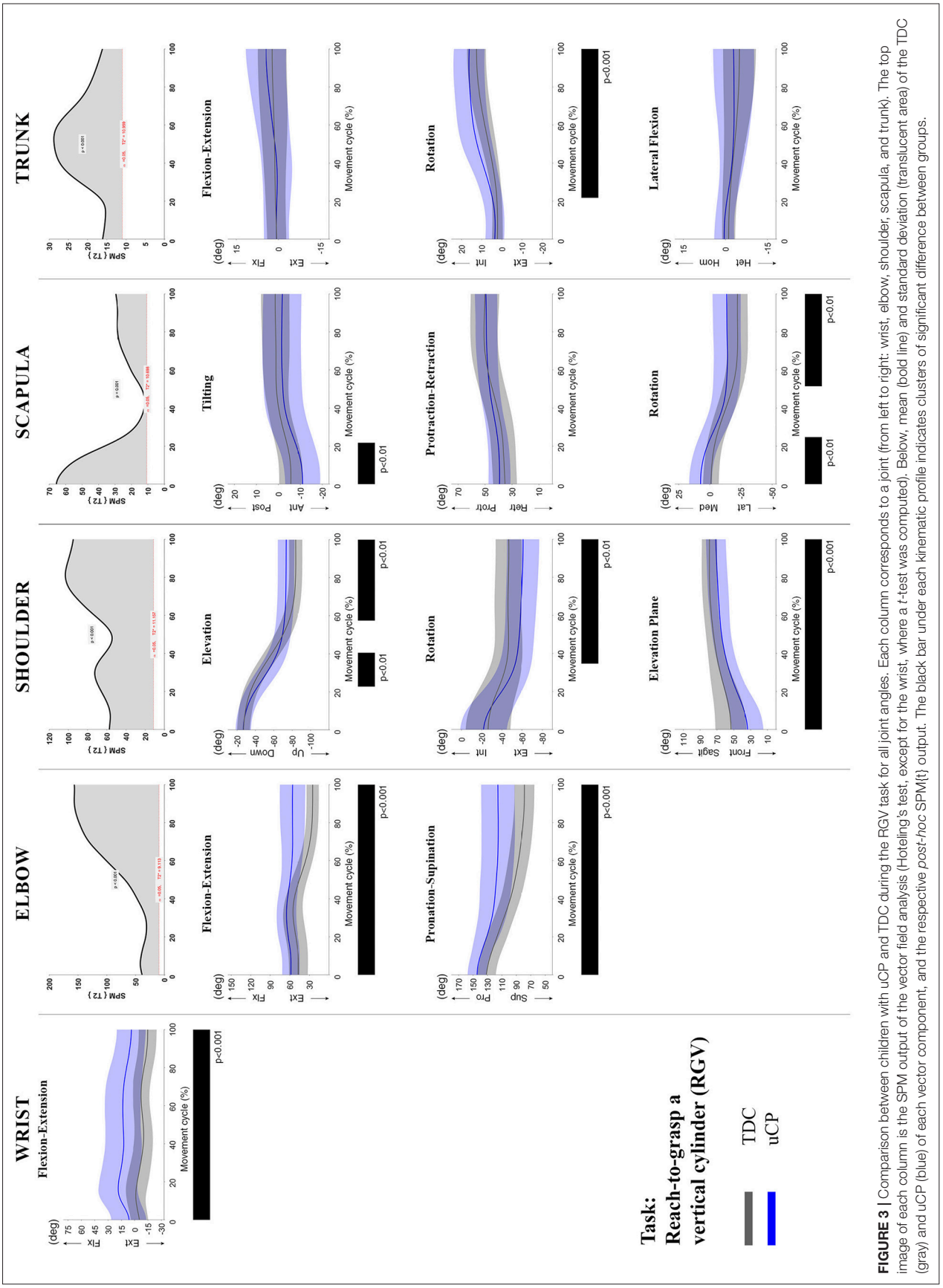

FIGURE 3 | Comparison between children with uCP and TDC during the RGV task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, scapula, and trunk). The top image of each column is the SPM output of the vector field analysis (Hoteling's test, except for the wrist, where a *t*-test was computed). Below, mean (bold line) and standard deviation (translucent area) of the TDC (gray) and uCP (blue) of each vector component, and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant difference between groups.

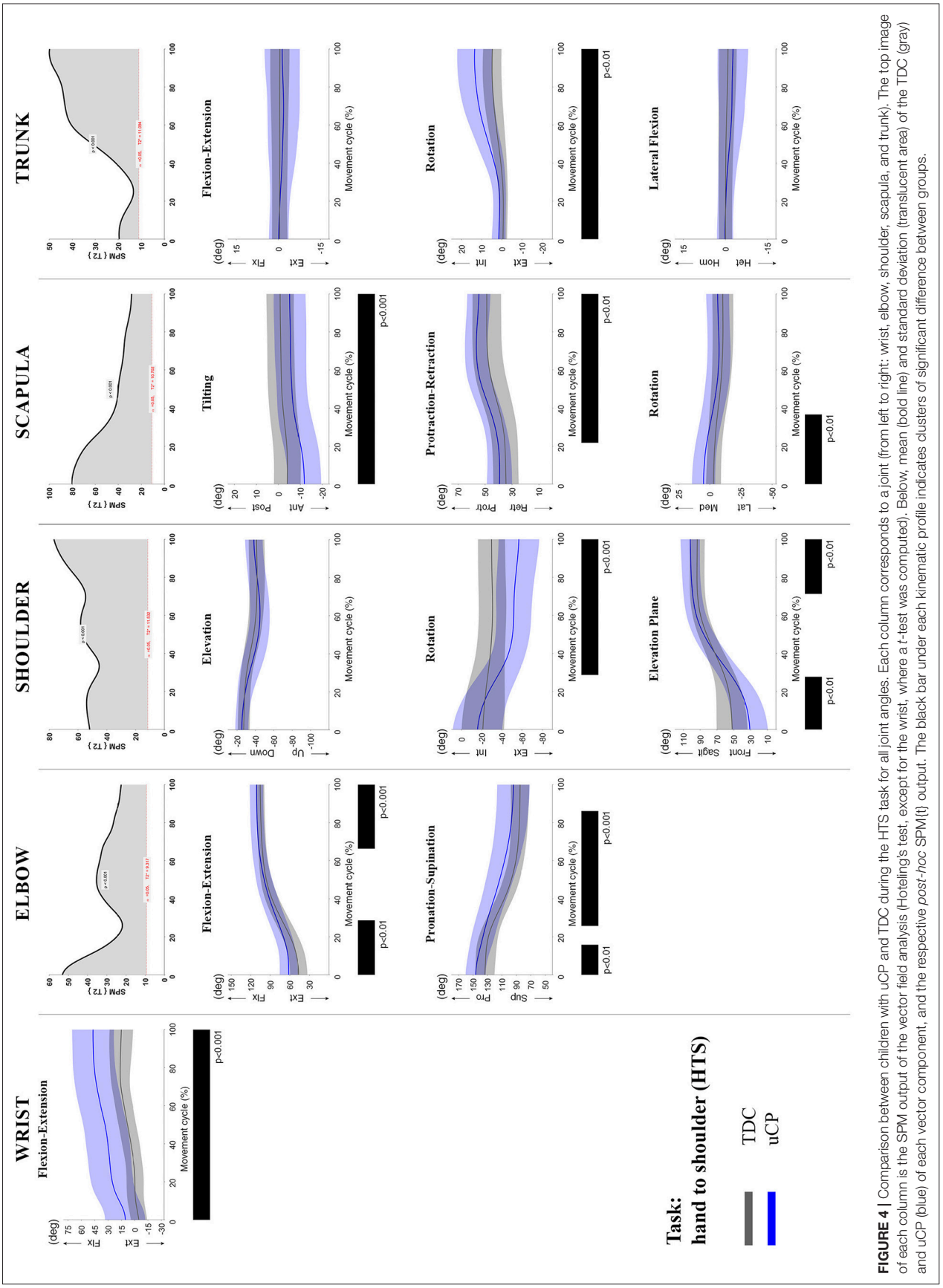

FIGURE 4 | Comparison between children with uCP and TDC during the HTS task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, scapula, and trunk). The top image of each column is the SPM output of the vector field analysis (Hoteling's test, except for the wrist, where a *t*-test was computed). Below, mean (bold line) and standard deviation (translucent area) of the TDC (gray) and uCP (blue) of each vector component, and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant difference between groups.

TABLE 3 | Impact of muscle weakness on UL movement patterns in children with uCP.

			RF	RU	RS	RGS	RGV	HTH	HTM	HTS
WRIST	Flexion Extension	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)
ELBOW	VECTOR FIELD	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	–	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	45% (55–100)	39% (61–100)		56% (44–100)	86% (14–100)	73% (27–100)	67% (33–100)	71% (29–100)
	Flexion Extension	*n* clusters (*p*-value)	1 (0.002)	1 (0.002)	–	1 (0.01)	1 (0.01)	–	–	–
		% curve (range)	40% (60–100)	38% (62–100)		49% (51–100)	56% (44–100)			
	Pro-supination	*n* clusters (*p*-value)	–	–	–	–	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)					81% (19–100)	70% (30–100)	71% (29–100)	66% (34–100)
SHOULDER	VECTOR FIELD	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	100% (0–100)	100% (0–100)	74% (0–74)	100% (0–100)	100% (0–100)	41% (0–41)	100% (0–100)	97% (3–100)
	Elevation	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	56% (0–56)	38% (9–47)	60% (5–65)	35% (14–49)	35% (9–44)	39% (11–50)	72% (28–100)	88% (12–100)
	Rotation	*n* clusters (*p*-value)	–	2 (0.01; 0.01)	1 (0.01)	2 (0.01; 0.01)	–	1 (0.01)	–	–
		% curve (range)		28% 48% (0–28) (52–100)	100% (0–100)	18% 24% (14–32) (76–100)		8% (18–26)		
TRUNK	VECTOR FIELD	*n* clusters (*p*-value)	0	0	0	1 (0.01)	1 (0.02)	0	0	1 (0.01)
		% curve (range)				71% (29–100)	50% (50–100)			72% (28–100)
	Axial Rotation	*n* clusters (*p*-value)	–	–	–	1 (0.01)	1 (0.01)	–	–	1 (0.01)
		% curve (range)				85% (15–100)	51% (49–100)			42% (58–100)

uCP, unilateral cerebral palsy; TDC, typically developing children; RF, reach forwards; RU, reach upwards; RS, reach sideways; RGS, reach-to-grasp a sphere; RGV, reach-to-grasp a vertical cylinder; HTH, hand-to-head; HTM, hand-to-mouth; HTS, hand-to-shoulder; n clusters, number of identified clusters; p-value, probability of the identified cluster: $\alpha < 0.05$ vector field analysis, $\alpha < 0.017$ (post post-hoc with three components), $\alpha < 0.025$ (post post-hoc with two components); % curve, extent of the cluster over the movement cycle; range, start, and end point of the identified cluster.

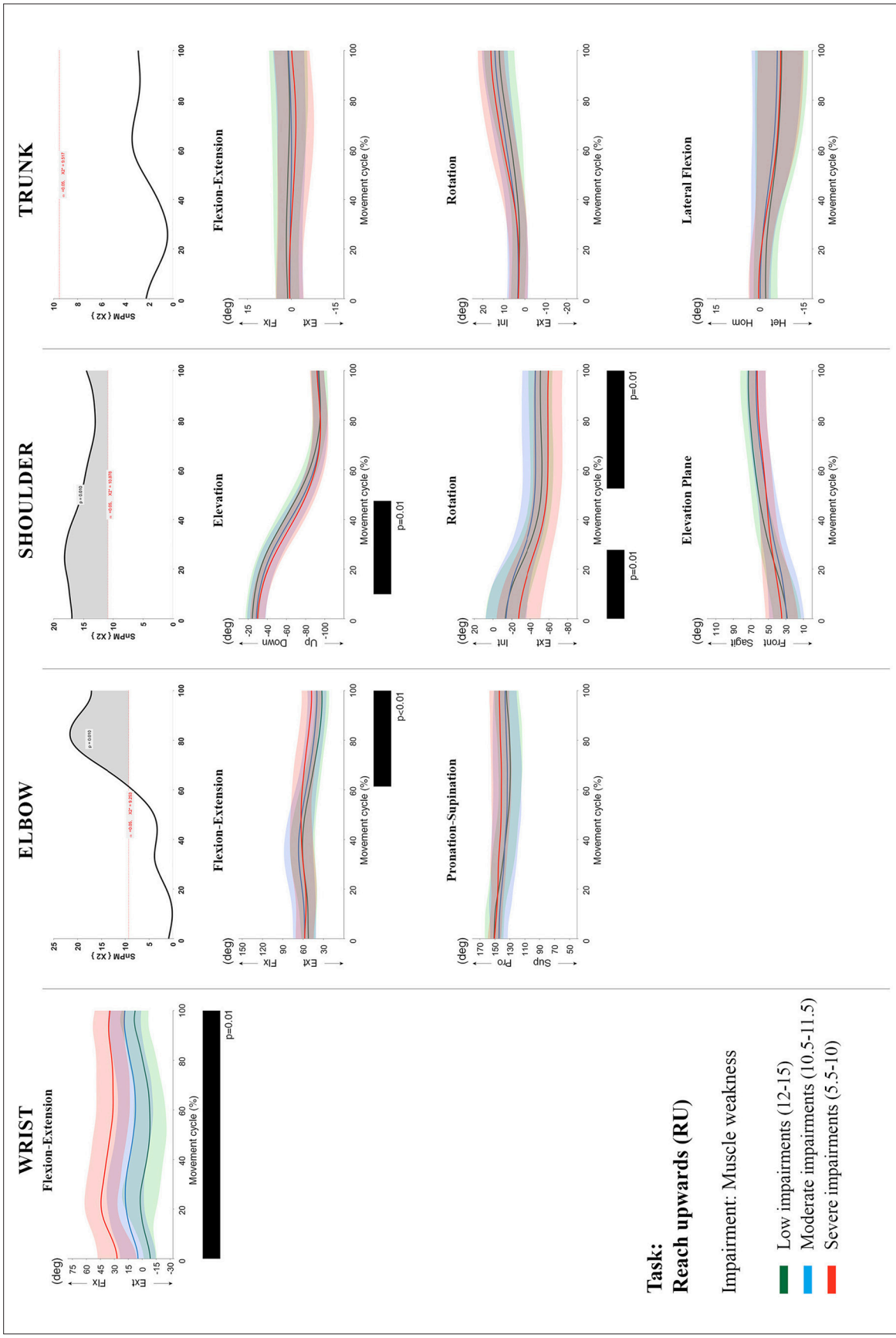

FIGURE 5 | Impact of muscle weakness on UL movement patterns in children with uCP during the RU task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, and trunk). The top image of each column is the SPM output of the vector field analysis (non-parametric Canonical Correlation Analysis test, except for the wrist, where a non-parametric linear regression was computed). For visualization purposes, kinematic data was grouped according to the level of motor impairments, i.e., muscle weakness total score: low impairments (score between 12 and 15, i.e., values above percentile 75), moderate impairments (score between 10.5 and 11.5, i.e., values between percentile 25 and 75), and severe impairments (score between 5.5 and 10, i.e., values below percentile 25). Below, mean (bold line) and standard deviation (translucent area) of the low impairments (green), moderate impairments (blue), and severe impairments (red) of each vector component and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant influence of the impairment level on the kinematic variable.

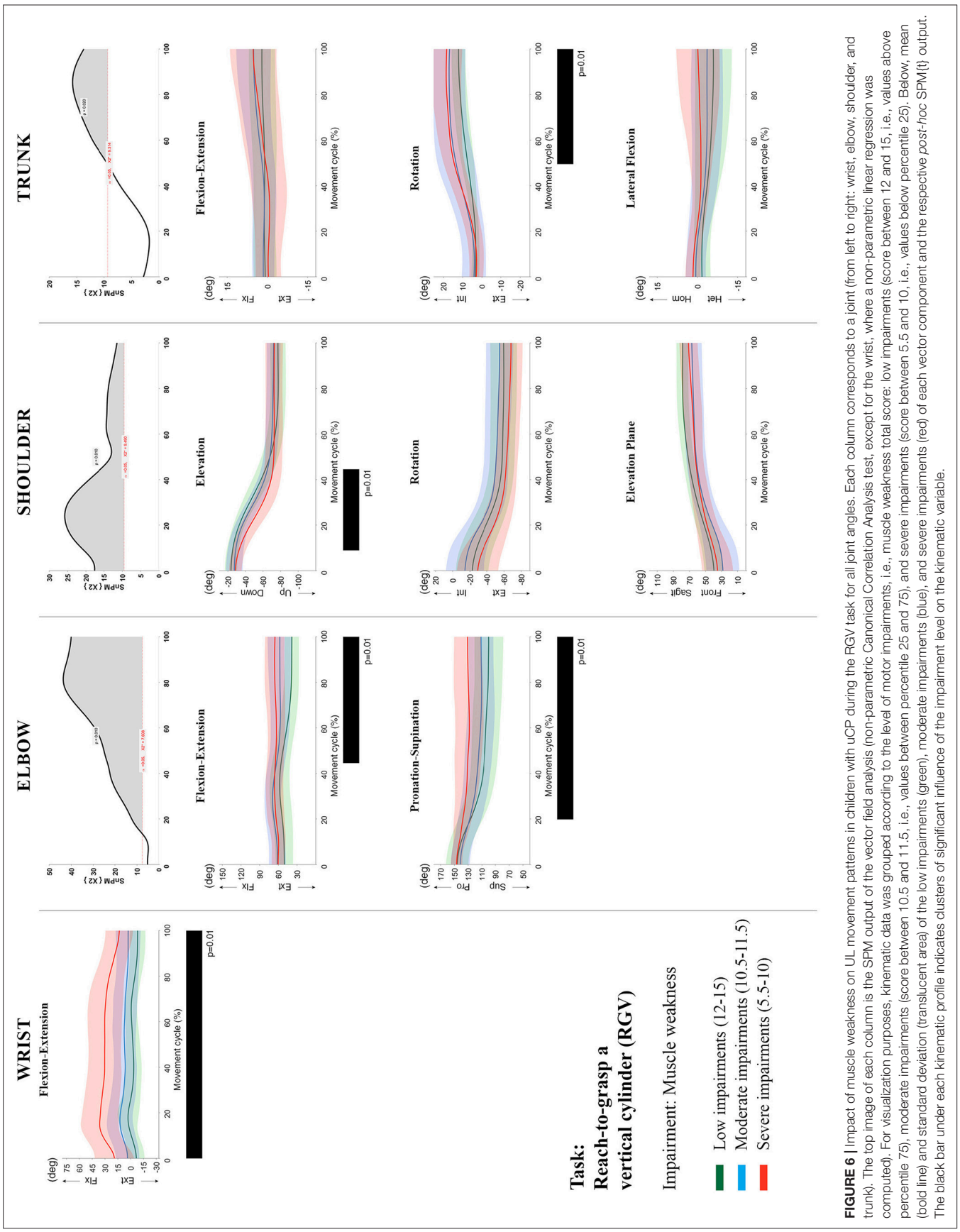

FIGURE 6 | Impact of muscle weakness on UL movement patterns in children with uCP during the RGV task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, and trunk). The top image of each column is the SPM output of the vector field analysis (non-parametric Canonical Correlation Analysis test, except for the wrist, where a non-parametric linear regression was computed). For visualization purposes, kinematic data was grouped according to the level of motor impairments, i.e., muscle weakness total score: low impairments (score between 12 and 15, i.e., values above percentile 75), moderate impairments (score between 10.5 and 11.5, i.e., values between percentile 25 and 75), and severe impairments (score between 5.5 and 10, i.e., values below percentile 25). Below, mean (bold line) and standard deviation (translucent area) of the low impairments (green), moderate impairments (blue), and severe impairments (red) of each vector component and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant influence of the impairment level on the kinematic variable.

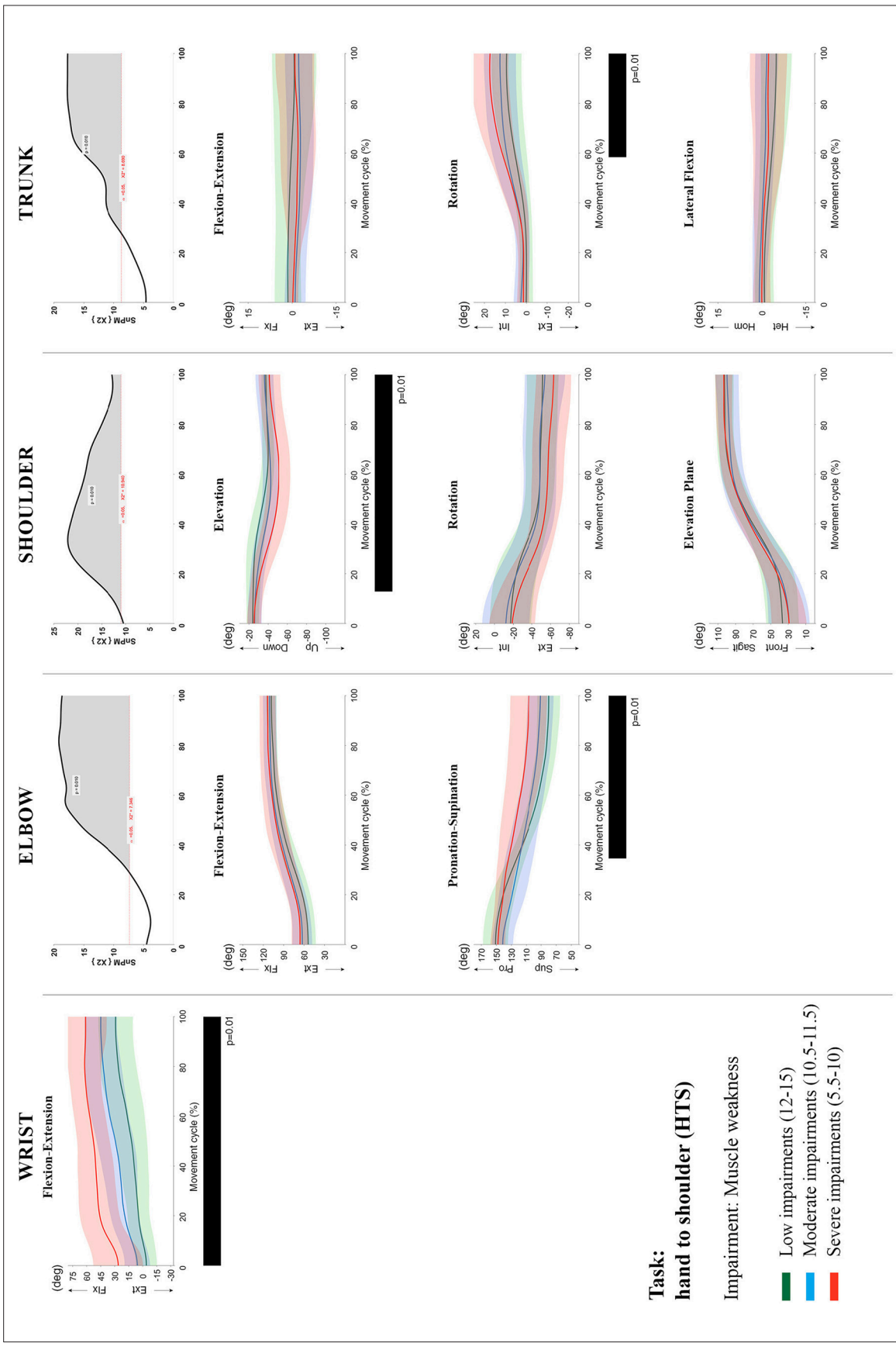

FIGURE 7 | Impact of muscle weakness on UL movement patterns in children with uCP during the HTS task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, and trunk). The top image of each column is the SPM output of the vector field analysis (non-parametric Canonical Correlation Analysis test, except for the wrist, where a non-parametric linear regression was computed). For visualization purposes, kinematic data was grouped according to the level of motor impairments, i.e., muscle weakness total score: low impairments (score between 12 and 15, i.e., values above percentile 75), moderate impairments (score between 10.5 and 11.5, i.e., values between percentile 25 and 75), and severe impairments (score between 5.5 and 10, i.e., values below percentile 25). Below, mean (bold line) and standard deviation (translucent area) of the low impairments (green), moderate impairments (blue), and severe impairments (red) of each vector component and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant influence of the impairment level on the kinematic variable.

TABLE 4 | Impact of spasticity on UL movement patterns in children with uCP.

			RF	RU	RS	RGS	RGV	HTH	HTM	HTS
WRIST	Flexion Extension	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.002)	2 (0.01; 0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	100% (0–100)	100% (0–100)	100% (0–100)	100% (0–100)	62% 24% (0–62) (76–100)	16% (0–16)	100% (0–100)	100% (0–100)
ELBOW	VECTOR FIELD	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	–	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	44% (56–100)	42% (58–100)		49% (51–100)	73% (27–100)	71% (29–100)	61% (39–100)	76% (24–100)
	Flexion Extension	*n* clusters (*p*-value)	1 (0.01)	–	–	1 (0.01)	1 (0.01)	–	–	1 (0.01)
		% curve (range)	14% (86–100)			33% (68–100)	26% (74–100)			15% (66–81)
	Pro-supination	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	–	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	71% (29–100)	33% (58–91)		71% (29–100)	79% (21–100)	75% (25–100)	51% (49–100)	7% (51–58)
SHOULDER	VECTOR FIELD	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	2 (0.01; 0.01)	1 (0.02)	1 (0.01)	1 (0.01)
		% curve (range)	100% (0–100)	95% (5–100)	61% (0–61)	87% (13–100)	50% 40% (0–50) (60–100)	33% (7–40)	84% (16–100)	44% (12–56)
	Elevation	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)	1 (0.01)
		% curve (range)	40% (10–50)	27% (18–45)	26% (24–50%)	37% (13–50)	27% (14–40)	21% (20–41)	72% (28–100)	35% (19–54)
	Elevation plane	*n* clusters (*p*-value)	1 (0.01)	1 (0.01)	–	1 (0.01)	1 (0.01)	–	–	–
		% curve (range)	42% (58–100)	48% (52–100)		60% (40–100)	34% (61–95)			
TRUNK	VECTOR FIELD	*n* clusters (*p*-value)	1 (0.01)	0	1 (0.01)	2 (0.04; 0.04)	1 (0.01)	0	0	1 (0.01)
		% curve (range)	35% (65–100)		54% (46–100)	12% 20% (0–12) (57–77)	63% (37–100)			42% (58–100)
	Axial Rotation	*n* clusters (*p*-value)	1 (0.01)	–	1 (0.01)	1 (0.01)	1 (0.01)	–	–	0
		% curve (range)	36% (64–100)		59% (41–100)	55% (45–100)	67% (33–100)			

uCP, unilateral cerebral palsy; TDC, typically developing children; RF, reach forwards; RU, reach upwards; RS, reach sideways; RGS, reach-to-grasp a sphere; RGV, reach-to-grasp a vertical cylinder; HTH, hand-to-head; HTM, hand-to-mouth; HTS, hand-to-shoulder; n clusters, number of identified clusters; p-value, probability of the identified cluster: $\alpha < 0.05$ vector field analysis, $\alpha < 0.017$ (post hoc with three components), $\alpha < 0.025$ (post post-hoc with two components); % curve, extent of the cluster over the movement cycle; range, start, and end point of the identified cluster.

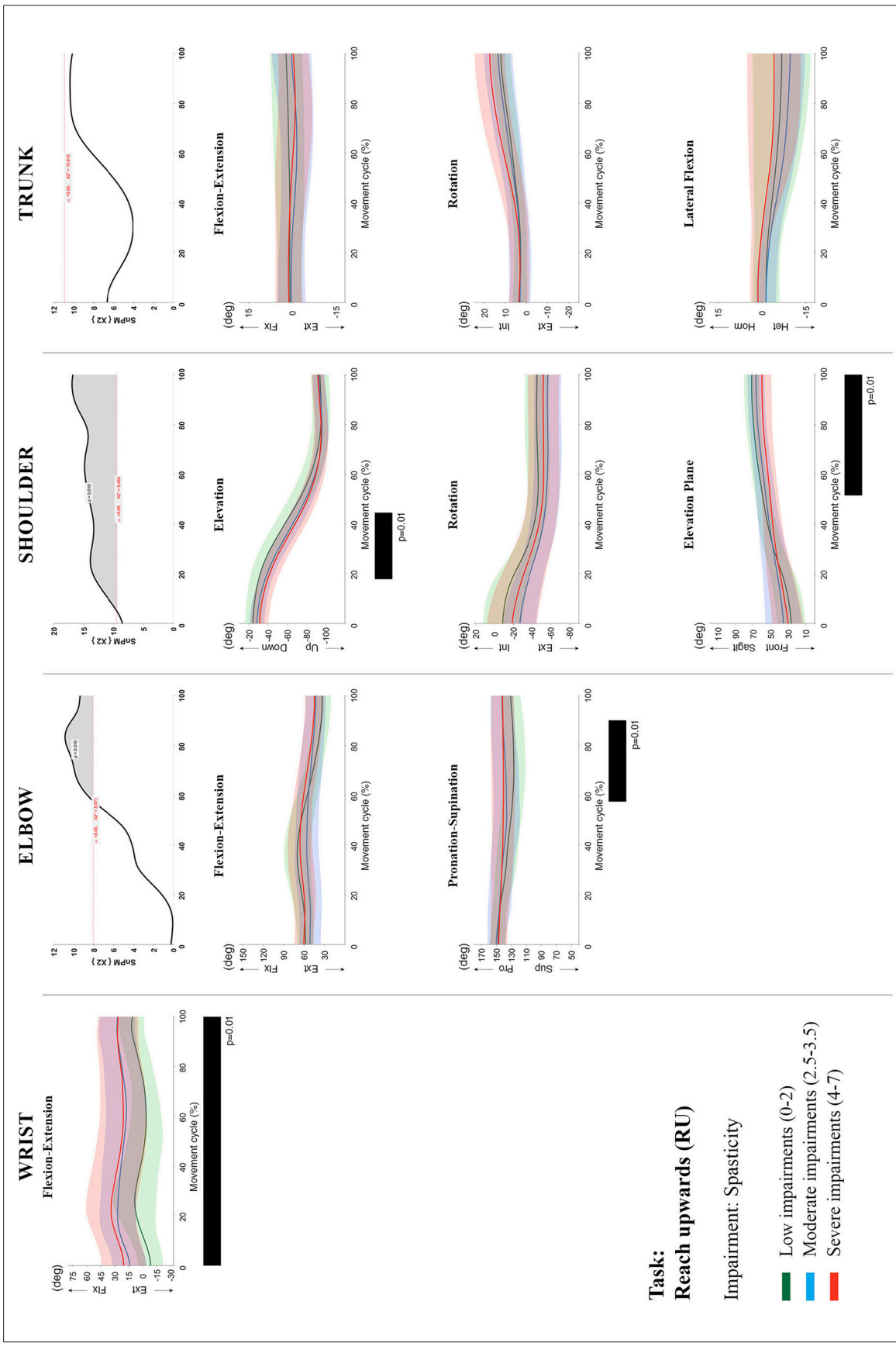

FIGURE 8 | Impact of spasticity on UL movement patterns in children with uCP during the RU task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, and trunk). The top image of each column is the SPM output of the vector field analysis (non-parametric Canonical Correlation Analysis test, except for the wrist, where a non-parametric linear regression was computed). For visualization purposes, kinematic data was grouped according to the level of motor impairments, i.e., spasticity total score: low impairments (score between 0 and 2, i.e., values above percentile 75), moderate impairments (score between 2.5 and 3.5, i.e., values between percentile 25 and 75), and severe impairments (score between 4 and 7, i.e., values below percentile 25). Below, mean (bold line) and standard deviation (translucent area) of the low impairments (green), moderate impairments (blue), and severe impairments (red) of each vector component and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant influence of the impairment level on the kinematic variable.

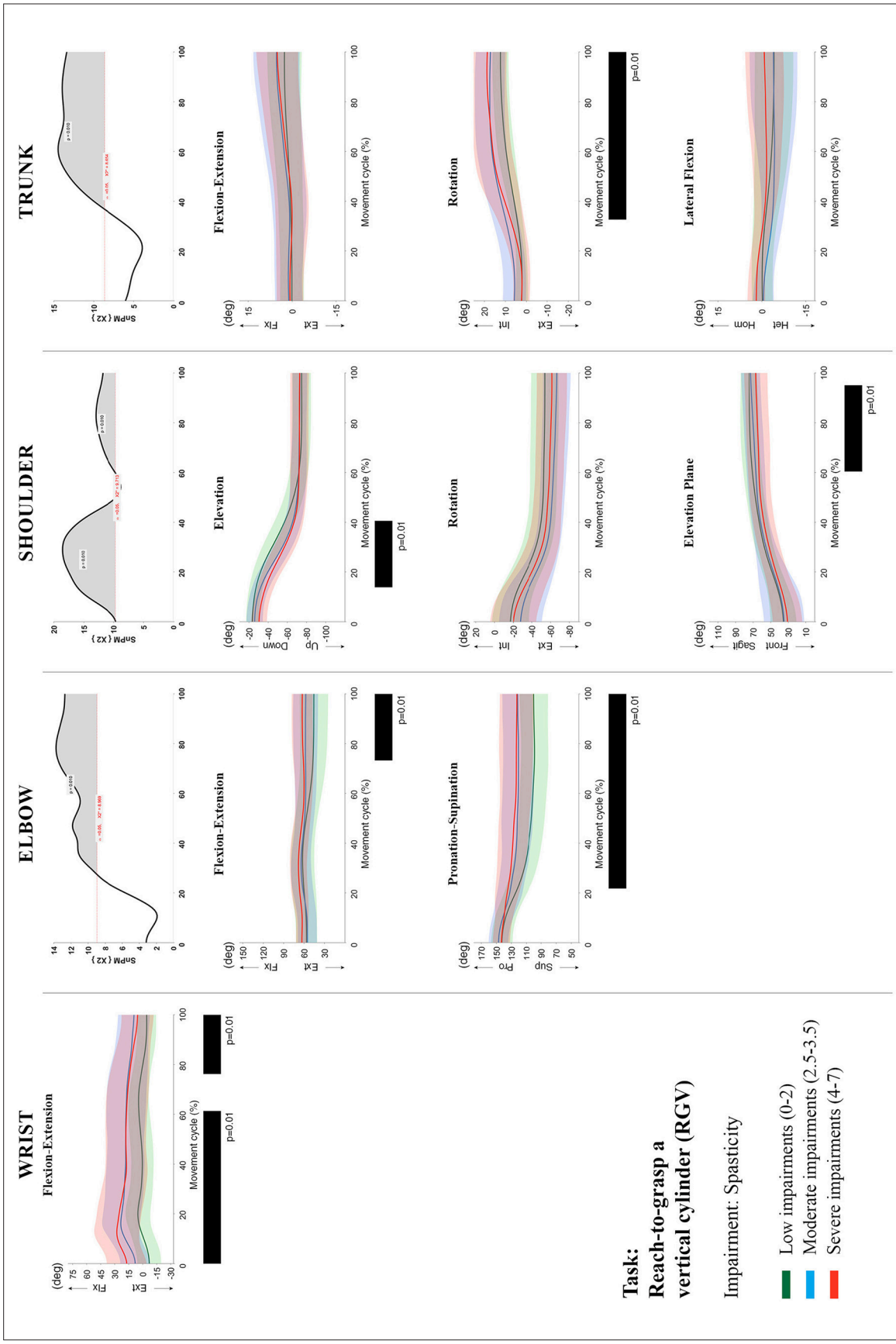

FIGURE 9 | Impact of spasticity on UL movement patterns in children with uCP during the RGV task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, and trunk). The top image of each column is the SPM output of the vector field analysis (non-parametric Canonical Correlation Analysis test, except for the wrist, where a non-parametric linear regression was computed). For visualization purposes, kinematic data was grouped according to the level of motor impairments, i.e., spasticity total score: low impairments (score between 0 and 2, i.e., values above percentile 75), moderate impairments (score between 2.5 and 3.5, i.e., values between percentile 25 and 75), and severe impairments (score between 4 and 7, i.e., values below percentile 25). Below, mean (bold line) and standard deviation (translucent area) of the low impairments (green), moderate impairments (blue), and severe impairments (red) of each vector component and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant influence of the impairment level on the kinematic variable.

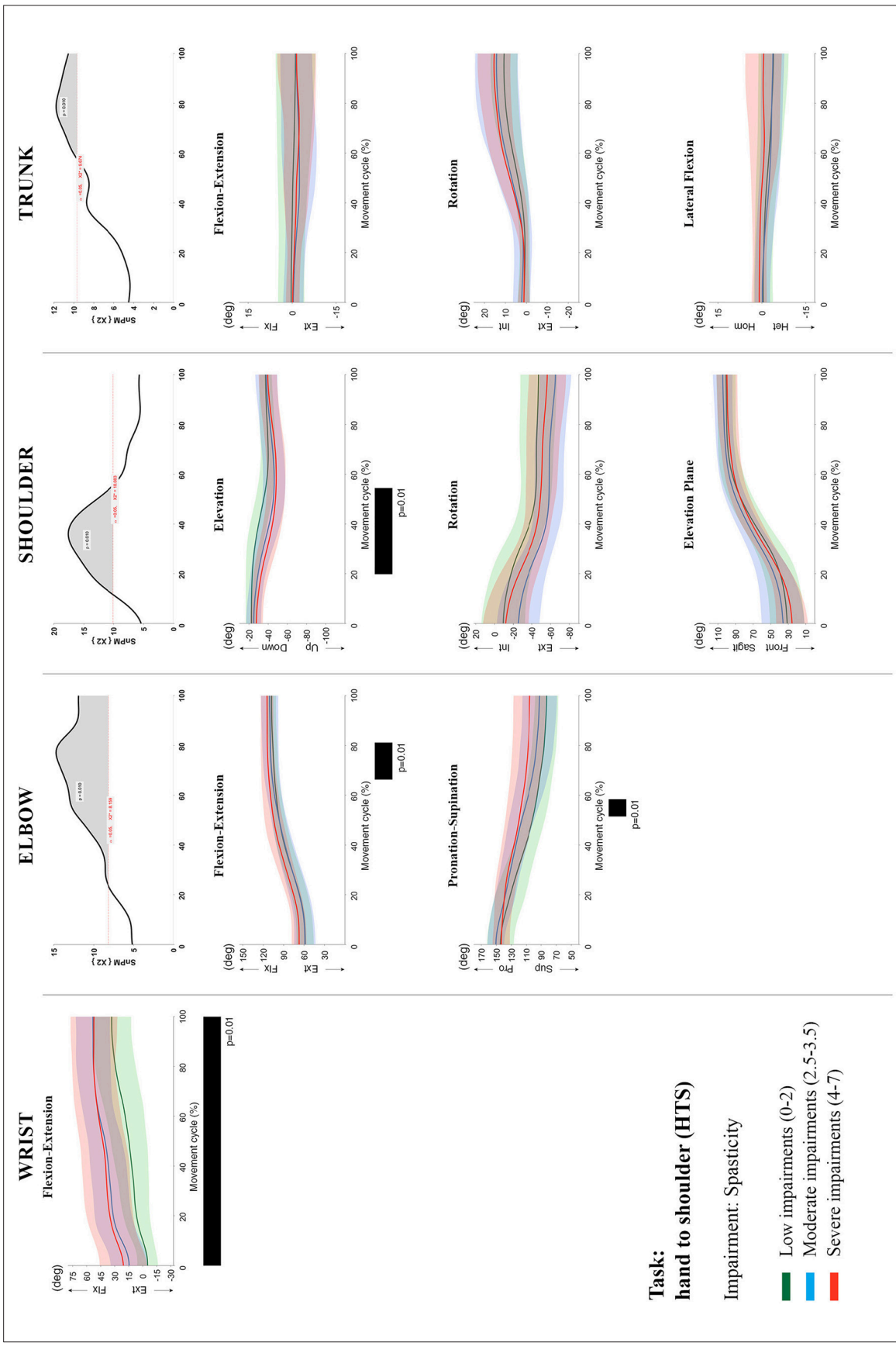

FIGURE 10 | Impact of spasticity on UL movement patterns in children with uCP during the HTS task for all joint angles. Each column corresponds to a joint (from left to right: wrist, elbow, shoulder, and trunk). The top image of each column is the SPM output of the vector field analysis (non-parametric Canonical Correlation Analysis test, except for the wrist, where a non-parametric linear regression was computed). For visualization purposes, kinematic data was grouped according to the level of motor impairments, i.e., spasticity total score: low impairments (score between 0 and 2, i.e., values above percentile 75), moderate impairments (score between 2.5 and 3.5, i.e., values between percentile 25 and 75), and severe impairments (score between 4 and 7, i.e., values below percentile 25). Below, mean (bold line) and standard deviation (translucent area) of the low impairments (green), moderate impairments (blue), and severe impairments (red) of each vector component and the respective *post-hoc* SPM{t} output. The black bar under each kinematic profile indicates clusters of significant influence of the impairment level on the kinematic variable.

an integrated approach with respect to targeted treatment planning.

Finally, whilst we did not directly compare UL movement patterns between the different tasks, we do believe that current study results allow formulating guidelines regarding task selection in children with uCP. First of all, a movement protocol should challenge UL motor performance in a variety of ways, depending on the individual child's functional potential. This requires the inclusion of a non-grasping task for those children with limited or no grasping capabilities. Our results showed most pronounced kinematic differences between children with uCP and TDC during the reaching upwards (RU) task, where UL movement deficits were strongly influenced by both spasticity and muscle weakness. Among the reach-to-grasp tasks, grasping a vertical cylinder (RGV) elicited most differences between children with uCP and TDC, and kinematics were also strongly negatively affected by both motor impairments. For the gross motor tasks, our results point toward the use of HTS, as this task additionally identified most differences at the level of the scapula. This set of tasks (RU, RGV, HTS) will ensure a complete evaluation of the UL and will provide sufficient and comprehensive information about the impact of motor impairments on UL movement patterns in children with uCP. Furthermore, our analysis identified specific deviant parts of the movement pattern, i.e., clusters, which may help establishing the basis for further studies. Combining these identified clusters (regions of interest, Pataky et al., 2016a), possibly together with spatiotemporal parameters and extracted scalars will permit further hypothesis driven research. Moreover, the implementation of dimensionality reduction tool [Principal Component Analysis (PCA), Independent Component Analysis (ICA), or kernel Principal Component Analysis (kPCA)] and/or machine learning tools [Artificial Neural Network (ANN), Support Vector Machines (SVM), or Self-Organizing Maps (SOM)] would be of interest to classify movement patterns. The potential merit of these approaches has already been demonstrated in the field of clinical biomechanics (Ferber et al., 2016) as well as to assess treatment response predictions after lower limb surgical interventions in children with CP (Reinbolt et al., 2009). Such progress is crucial to improve the interpretation of the vast amount of data this assessment offers and will thereby undoubtedly further contribute to the clinical implementation of UL-3DMA.

This study also warrants some critical reflections. First, spasticity and muscle weakness were measured with ordinal scales. Although the MAS is the most commonly used scale to measure spasticity in clinical practice and its reliability has been established (Bohannon and Smith, 1987; Klingels et al., 2010), some controversy regarding the value and accuracy of the MAS does exist (Pandyan et al., 2003; Fleuren et al., 2010). An instrumented spasticity assessment, similar to the one available for the lower limbs (Bar-On et al., 2014), would be a valuable addition in UL research. Secondly, spasticity and muscle weakness were only assessed distally (elbow and wrist). However, proximal motor deficits (at the level of the shoulder, scapula, or trunk) may also have a negative contribution to UL movement patterns. Given that the current study did not include a proximal evaluation of these motor deficits, we cannot fully discriminate the contribution of distal vs. proximal deficits to deviant UL movement patterns. It would be therefore valuable to investigate whether proximal impairments also play a role in proximal and distal movement patterns. This would allow the identification of other factors that could complement current treatment approaches. Third, spasticity and muscle weakness were measured in a static position, which may not reflect the dynamic factor of muscle (dys)function during motion (Crenna, 1998; van der Krogt et al., 2010). Including electromyography measures will contribute to a better understanding of the mechanisms of dynamic spasticity on UL movement patterns in children with uCP. Lastly, although we performed vector field analysis and took into account the covariance among the vector components, our *post-hoc* comparisons were computed with a *t*-test and linear regression. These latter tests do not account for vector component covariances and should thus be interpreted with caution. However, the development of SPM1D is still ongoing and more suitable *post-hoc* analysis will be offered in the near future.

To the best of our knowledge, this is the first study that used vector field analysis over the continuum of the movement cycle to investigate UL movement patterns in a large cohort of children with uCP and TDC. We found that children with uCP presented with deviant UL movement patterns compared to TDC at the level of the wrist, elbow, shoulder, scapula, and trunk. In general, results of the current study show the importance of investigating the entire movement cycle to better understand where the deficits are most pronounced during different UL movements. Moreover, UL kinematic deviations were also strongly negatively influenced by distal muscle weakness and spasticity for all joints, except for the scapula, where other factors such as scapulathoracic muscle activation might play a role. Finally, based on current study results, we would recommend three UL tasks, i.e., reaching upwards, reach-to-grasp a vertical cylinder and hand-to-shoulder, as a comprehensive assessment protocol that allows mapping deviant UL movement patterns in children with uCP. Such protocol reduction will facilitate the implementation of UL-3DMA in a clinical setting, which will lead to a better understanding of UL movement pathology and ensure a more detailed and individualized treatment planning in children with uCP, to ultimately warrant that the child reaches its full functional potential.

AUTHOR CONTRIBUTIONS

This study was designed by CS, KD, KK, EJ, and HF. CS, LM, and EJ were responsible for all data collection and processing. CS performed all data analysis with SPM1D. All authors contributed to the interpretation of the results and gave their critical views regarding the revision and editing of the manuscript, which was written by CS. All authors approved the final version of the manuscript and agreed to be accountable for the content of the study.

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SUPPLEMENTARY MATERIAL

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frontiers in Human Neuroscience

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Prevalence of Joint Gait Patterns Defined by a Delphi Consensus Study Is Related to Gross Motor Function, Topographical Classification, Weakness, and Spasticity, in Children with Cerebral Palsy

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During a Delphi consensus study, a new joint gait classification system was developed for children with cerebral palsy (CP). This system, whose reliability and content validity have previously been established, identified 49 distinct joint patterns. The present study aims to provide a first insight toward the construct validity and clinical relevance of this classification system. The retrospective sample of convenience consisted of 286 patients with spastic CP (3–18 years old, GMFCS levels I–III, 166 with bilateral CP). Kinematic and kinetic trials from three-dimensional gait analysis were classified according to the definitions of the Delphi study, and one classified trial was randomly selected for each included limb (n = 446). Muscle weakness and spasticity were assessed for different muscle groups acting around the hip, knee, and ankle. Subsequently, Pearson Chi square tests, Cramer's V, and adjusted standardized residuals were calculated to explore the strength and direction of the associations between the joint patterns, and the different patient-specific characteristics (i.e., age, GMFCS level, and topographical classification) or clinical symptoms (muscle weakness and spasticity). Patient-specific characteristics showed several significant associations with the patterns of different joints, but the strength of most identified associations was weak. Apart from the knee during stance phase and the pelvis in the sagittal plane, the results systematically showed that the patterns with "minor gait deviations" were the most frequently observed. These minor deviations were found significantly more often in limbs with a lower level of spasticity and good muscle strength. Several other pathological joint patterns were moderately associated with weakness or spasticity, including but not limited to "outtoeing" for weakness and "intoeing" for spasticity. For the joints in the sagittal plane, significantly stronger associations were found with muscle weakness and spasticity, possibly because most of the evaluated muscles in this study mainly perform sagittal plane motions.

Remarkably, the hip patterns in the coronal plane did not associate significantly with any of the investigated variables. Although further validation is warranted, this study contributes to the construct validity of the joint patterns of the Delphi consensus study, by demonstrating their ability to distinguish between clinically relevant subgroups in CP.

Keywords: cerebral palsy, gait, gait patterns, classification, prevalence, chi-square test

INTRODUCTION

Cerebral palsy (CP) is the result of a pre- or post-natal lesion in the developing brain of a fetus or child, primarily affecting motor behavior. The heterogenic clinical presentation of CP is emphasized, not only because of the numerous potential differences in timing, location, severity, and nature of brain lesions, but also because it is continuously altered by a maturing brain, musculoskeletal growth, and treatment (Bax et al., 2005). For epidemiological, treatment-related, and many other reasons, it is therefore important to identify relevant subgroups within the CP population. Several important categorizations of subgroups in CP have been reported before. For instance, the Gross Motor Function Classification System (GMFCS) and the Manual Ability Classification System are used to classify the severity of lower and upper limb motor function impairment (Palisano et al., 1997; Eliasson et al., 2006), while emphasizing on everyday performance (Palisano et al., 1997). Because of the complex interaction between primary and secondary motor symptoms in CP, for example between spasticity and muscle contractures, gait pathology varies a lot between patients. Hence, even though the GMFCS is a generally accepted functionality score for children with CP, it is not detailed enough to cover all gait-related deviations (Õunpuu et al., 2015).

In literature, several gait classifications have been defined based on three-dimensional gait analysis data (i.e., kinematics, kinetics, or muscle activation data) (Vaughan and O'Malley, 2005; Dobson et al., 2007; Toro et al., 2007; Ferrari et al., 2008; Carriero et al., 2009; Rozumalski and Schwartz, 2009; Bonnefoy-Mazure et al., 2013; Davids and Bagley, 2014). Gait classifications aim to define groups of gait deviations into distinct categories and may be built based on either qualitative or quantitative methods (Dobson et al., 2007). Recently, a new, qualitative overview of joint patterns during gait for all ambulatory children with spastic CP has been described, covering the wide range of gait deviations in the relevant lower limb joints across the three anatomical planes (Nieuwenhuys et al., 2016). Through a Delphi consensus study, an international expert panel defined 49 joint patterns during gait. Separate patterns were defined for the pelvis, hip, knee, ankle, and foot in the sagittal, coronal, and transverse planes. Recently, the content validity of this classification system (Nieuwenhuys et al., 2017a) was investigated on a cohort of 356 patients with CP and 56 typically developing (TD) children. Two experienced raters classified more than 1,700 kinematic and kinetic trials. Subsequently, the mean kinematic and kinetic waveforms for each pattern and the pattern of TD children were analyzed using statistical parametric mapping (SPM) (Pataky, 2010) to verify (1) whether the existence of the patterns and the subjective rules, which were defined during the consensus study, could be confirmed and (2) whether potential patterns and relevant information might have been missed. The results indicated that for each pattern, all key locations that were included in the pattern definitions, were also indicated as significant areas by the SPM analysis. A detailed definition of the different joint patterns is provided in Table S1 in the Supplementary Material. As the previously mentioned content validity study highlighted, the patterns that were originally labeled as "normal" may be misleading (Nieuwenhuys et al., 2017a). Hence, in Table S1, the original definitions of these joint patterns were modified to "minor gait deviations." Previous research has also showed that the created classification can be reliably used, even by inexperienced clinicians, displaying reliability levels that ranged between "substantial" to "almost perfect agreement" for all joints, except for the knee patterns during stance phase that showed moderate agreement (Nieuwenhuys et al., 2017b). However, the construct validity of this newly introduced joint gait classification system and its relevance for clinical and research practice has not yet been examined.

The construct validity can be assessed, by comparing the gait classification with a criterion classification (Zwick et al., 2004), or by assessing its relationships with scores of other instruments. Previous research has already shown the relevance of establishing the relation between specific gait features and other variables such as topographical classification, age, preceding treatments, and clinical measurements (Wren et al., 2005; Domagalska et al., 2013). Further, Rozumalski et al. (Rozumalski and Schwartz, 2009) investigated how different crouch gait patterns, which were determined via k-means cluster analysis, were characterized by range of motion, muscle strength, and spasticity. Dobson et al. (2011) reported on the construct validity of the Winters classification, by showing how the distribution of the patterns was associated with other validated classifications such as the Gross Motor Function Classification Scale (Palisano et al., 1997) (GMFCS) and Functional Mobility Scale (Graham et al., 2004). By providing evidence that the classification can make a distinction between relevant subgroups in CP, its usefulness and validity can be demonstrated.

The present study aims to provide a first insight toward the construct validity and clinical relevance of the aforementioned consensus-based joint patterns during gait in children with CP (Nieuwenhuys et al., 2016). The prevalence of the patterns and their association with other patient-specific characteristics and clinical symptoms, in particular muscle weakness and spasticity, is explored in an extended patient cohort. It is hypothesized that the prevalence of the patterns is associated with age, topographical classification, GMFCS level, and previous treatment. The study also examines how specific joint patterns

are characterized by weakness and spasticity. It is hypothesized that pelvis and hip patterns are associated in particular with the severity of weakness or spasticity in muscle groups that have a function around the pelvis and hip joint. Analogous to the previous hypothesis, knee and ankle patterns are expected to associate with the presence of weakness or spasticity in the muscles acting at the knee and ankle respectively.

MATERIALS AND METHODS

Patient Recruitment

This study was approved by the Medical Ethical Committee of University Hospitals Leuven (s56036). An extended retrospective convenience sample was available from the database of the hospital, comprising gait analysis sessions that were obtained for research or clinical purposes between November 2001 and August 2015. The sample contained a total of 459 sessions (from 356 children), which were all screened for the following inclusion criteria: (a) a diagnosis of unilateral or bilateral CP (b) predominantly spastic type of CP (c) 3–18 years of age, (d) GMFCS-level I–III, and (e) the availability of at least two good quality kinematic gait trials from three-dimensional gait analysis.

Instrumented Gait Analysis

Standardized three-dimensional gait analyses were performed using 10 to 15 VICON motion camera's (Vicon Motion Systems, Oxford, UK) and two AMTI force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA). Reflecting markers were placed on anatomical landmarks of the patient according to the Plug-In-Gait marker model and patients were instructed to walk barefoot and at a self-selected speed on a 10 m-walkway. Nexus software was used to define gait cycles and to estimate joint angles and joint moments in the three anatomical planes. For each kinematic and kinetic trial, one step per side (left and right) was identified. For patients with unilateral CP, only the affected body side was selected for all analyses. For patients with bilateral involvement, both sides were included in the analyses of side-specific variables (i.e., "previous surgery," spasticity, and weakness scores), while for all other comparisons, one side was randomly selected. All available steps were visually screened and steps with artifacts, signs of inaccurate marker placement, or steps that were not representative of a patient's gait (outliers), were excluded so that only trials of good quality remained. The remaining good quality steps, 1,719 in total, were then classified by a clinician who was experienced with the joint patterns (AN or EP). As a result, for each gait analysis session, one to seven steps per side per patient were classified. Subsequently, for each included session, one classified step was randomly selected per side, unless a pattern with a very low prevalence in the database was present (<10% of 1,719 trials), in which case that step was given priority. In a previous study, the reliability with which both raters could identify the joint patterns was assessed using a sample of 82 children with CP. Interrater agreement was shown to be almost perfect (overall percentage of agreement = 90%, kappa = 0.86, confidence interval = 078–0.94). **Table 1** shows the prevalence of the joint patterns in the recruited sample as well as a concise description of the patterns per joint.

TABLE 1 | Brief definition of all joint patterns during gait and their prevalence in the selected limbs (*N* = 446) from the patient population.

Sagittal plane	***N* (%)**
PELVIS	
PS0—Minor gait deviations	88 (19.7)
PS1—Increased range of motion	130 (29.1)
PS2—Increased anterior tilt on average	67 (15.0)
PS3—Increased anterior tilt and increased range of motion	157 (35.2)
PS4—Decreased anterior tilt (posterior tilt)	1 (0.2)
PS5—Decreased anterior tilt (posterior tilt) and increased range of motion	3 (0.7)
HIP	
HS0—Minor gait deviations	229 (51.3)
HS1—Hip extension deficit	136 (30.5)
HS2—Continuous excessive hip flexion	81 (18.2)
KNEE DURING STANCE	
KSTS0—Minor gait deviations	56 (12.6)
KSTS1—Increased knee flexion at initial contact	33 (7.4)
KSTS2—Increased knee flexion at initial contact and earlier knee extension movement	89 (20.0)
KSTS3—Knee hyperextension	38 (8.5)
KSTS4—Knee hyperextension and increased knee flexion at initial contact	53 (11.9)
KSTS5—Increased flexion in midstance and internal flexion moment present	100 (22.4)
KSTS6—Increased flexion in midstance and internal extension moment present	77 (17.3)
KNEE DURING SWING	
KSWS0—Minor gait deviations	140 (31.4)
KSWS1—Delayed peak knee flexion	103 (23.1)
KSWS2—Increased peak knee flexion	50 (11.2)
KSWS3—Increased and delayed peak knee flexion	42 (9.4)
KSWS4—Decreased peak knee flexion	53 (11.9)
KSWS5—Decreased and delayed peak knee flexion	58 (13.0)
ANKLE DURING STANCE	
ASTS0—Minor gait deviations	164 (36.8)
ASTS1—Horizontal second ankle rocker	133 (29.8)
ASTS2—Reversed second ankle rocker	53 (11.9)
ASTS3—Equinus gait	22 (4.9)
ASTS4—Calcaneus gait	74 (16.6)
ANKLE DURING SWING	
ASWS0—Minor gait deviations	165 (37.0)
ASWS1—Insufficient prepositioning in terminal swing	39 (8.7)
ASWS2—Continuous plantarflexion during swing (drop foot)	94 (21.1)
ASWS3—Excessive dorsiflexion during swing	148 (33.2)
Coronal plane	***N* (%)**
PELVIS	
PC0—Minor gait deviations	225 (50.4)
PC1—Increased pelvic range of motion	135 (30.3)
PC2—Continuous pelvic elevation	34 (7.6)
PC3—Continuous pelvic depression	52 (11.7)
HIP	
HC0—Minor gait deviations	278 (62.3)

(Continued)

TABLE 1 | Continued

Sagittal plane	*N* (%)
HC1—Excessive hip abduction in swing	87 (19.5)
HC2—Continuous excessive hip abduction	52 (11.7)
HC3—Continuous excessive hip adduction	29 (6.5)
Transverse plane	
PELVIS	
PT0—Minor gait deviations	204 (45.7)
PT1—Increased pelvic range of motion	136 (30.5)
PT2—Excessive pelvic external rotation during the gait cycle	66 (14.8)
PT3—Excessive pelvic internal rotation during the gait cycle	40 (9.0)
HIP	
HT0—Minor gait deviations	338 (75.8)
HT1—Excessive hip external rotation during the gait cycle	34 (7.6)
HT2—Excessive hip internal rotation during the gait cycle	74 (16.6)
FOOT PROGRESSION ANGLE	
FPA0—Minor gait deviations	279 (62.6)
FPA1—Outtoeing	73 (16.4)
FPA2—Intoeing	94 (21.1)

Definitions of the joint patterns are provided in Table S1 (Supplementary Material). Described deviations such as increased or excessive joint angles refer to deviations which are more than one standard deviation away from a reference database of typically developing children. A more detailed description of the patterns is available in Nieuwenhuys et al. (2016).

One gait analysis session was selected for each patient. Sessions were excluded if a patient had undergone Botulinum toxin type A treatment less than 180 days or surgery (i.e., single event multilevel surgery or selective dorsal rhizotomy) less than 365 days before the date of the gait analysis session. In case more than one session was still available for a patient, preference was given to the earliest pre-treatment session with the least amount of missing data from the clinical examination.

Clinical Examination of Weakness and Spasticity

Gait analysis sessions were preceded by a clinical examination during which muscle strength and muscle tone were evaluated. Isometric muscle strength was assessed by experienced physiotherapists using the manual muscle testing scale (MMT) (Daniels and Worthingham, 1986; Cuthbert and Goodheart, 2007). The MMT is scored on a six-point ordinal scale (scores range from 0 to 5) and it differentiates between a palpable contraction and a motion against gravity or against resistance. The maximum score of 5 indicates that a patient can move for the full range of motion against gravity and maximum resistance, whereas a score of 0 indicates that no contraction can be palpated. Isometric strength was assessed and scored for the following muscle groups: hip flexors, extensors, adductors, and abductors; knee flexors and extensors; ankle dorsi- and plantar flexors, and the muscle groups performing ankle inversion and eversion. In addition, muscle spasticity was evaluated using the Modified Ashworth Scale (MAS) (Mutlu et al., 2008), which is also a six-point ordinal scale (scores: 0, 1, 1+, 2, 3, 4), The MAS classifies the extent of increase in muscle tone felt by the assesor during the stretch of a passive muscle group through the full range of motion. The maximum score of 4 indicates that the evaluated muscle or muscle group is rigid and no motion is possible, whereas a score of 0 indicates a normal muscle tone. MAS scores were collected for the hip flexors, short adductors, and long adductors; for the hamstrings and rectus femoris muscles at the level of the knee; and for the gastrocnemius, soleus, and tibialis posterior muscles at the level of the ankle joint.

Because of the high number of muscles that were evaluated during the clinical examination and because of the explorative nature of the study, it was decided to group the muscles according to the joints around which they have their main function, such that the hip, knee, and ankle joint were characterized by one score for muscle weakness and one score for spasticity. For instance, the highest MAS score between the gastrocnemius, soleus, and tibialis posterior muscles was selected to represent the severity of spasticity around the ankle joint. The involved multidisciplinary team advised to select the most severe score for weakness (i.e., lowest score) and spasticity (i.e., highest score) at the level of each joint because of two reasons: on the one hand, the muscles most affected by weakness or spasticity were considered to have a larger influence on pathological gait deviations. On the other hand, the selection of the most severe score per joint, instead of averaged values or summation of muscle-specific scores, ensured that the impact of weakness or spasticity would not be filtered out (which might be expected if the average of the joint sub-scores was used). In addition, the clinical examination data was characterized by missing data as a result of the retrospective nature of the study. By selecting the most severe score per joint, the sample size of the study would not be reduced, which was expected to happen if the muscle-specific scores were summed. The influence of these missing data on the results was expected to be negligible, as the median percentage of missing data per MAS or MMT variable was 0.44% (range 0–5.6%). To illustrate the associations between the defined joint gait patterns and muscle weakness and spasticity, clinical case examples of the kinematic waveforms in combination with the respective scores of MAS or MMT, and supported by video fragments, are presented in Supplementary Material—Video 1.

Statistical Analysis

The first level of construct validity was evaluated by studying the association of the joint patterns with age, GMFCS level, previous orthopedic surgery and topographical classification (unilateral vs. bilateral CP). While the GMFCS cannot be considered detailed enough to report on specific gait-related deviations, it is a clinically accepted score of overall functionality of CP children. Therefore, it has been used to establish a relation between the severity of pathological function and the occurrence of each joint pattern. The next level of construct validity was evaluated by studying the association of the joint patterns with clinical examination scores (i.e., weakness of the muscles around the hip, knee, and ankle; spasticity of the muscles around the hip, knee, and ankle).

Descriptive statistics and cross-tables were used to describe the frequency distributions for all patterns, as well as for the patient-specific characteristics and clinical symptoms. Age was further categorized into three groups using the 25 and 75th percentile as cut-off values. These categories will further be referred to as the "youngest patients" (patients until 7.5 years old), "medium aged patients" (patients from 7.5 to 12.5 years old), and "oldest patients" (patients over 12.5 years old).

Pearson Chi-square tests (χ^2) were performed to investigate if the distribution of the patient-specific characteristics and clinical symptoms were significantly associated with the distribution of the patterns at the level of each joint ($\alpha = 0.05$). In χ^2, observed frequencies of individual counts are compared to expected frequencies which would be expected by chance. To allow for a valid interpretation of χ^2, a sufficiently large sample size is required for all the associations that were tested between the patient-specific characteristics or clinical symptoms (weakness and spasticity) and the joint patterns. Following the principles of χ^2 (Portney and Watkins, 2009), the expected frequency of cells should be at least $n = 1$ for every parameter and the expected frequencies below $n = 5$ can only be accepted in less than 20% of the cells of the cross-tables (Portney and Watkins, 2009). When this condition was not met and expected frequencies were less than $n = 5$ for a specific variable, two categories of a variable were combined, however only when merging those categories was clinically meaningful (e.g., Scores 4 and 5 of the MMT were often combined, both scores indicating that the patient could move against moderate to heavy resistance). In case of significant associations, the strength of the association was evaluated using Cramer's V, which is dependent on the degrees of freedom (DF). The DF was defined by the smallest value of the data (either rows or columns). For example, when examining the association between uni- or bilateral CP and the patterns of the hip in the sagittal plane, the DF were defined by the uni-/bilateral distribution and not by the hip patterns ($n = 2$ and $n = 3$ respectively). The strength of the association based on Cramer's V was thereby classified as weak, moderate or strong (Table S2) (Cohen, 1988). Subsequently, adjusted standardized residuals (ASR) were examined to explore the direction of significant associations. ASRs can identify significant combinations of specific categories of two variables that contributed stronger to the identified association than other combinations of categories. Because ASRs follow a normal distribution with mean "0" and standard deviation "1," ASR values larger than –2 or +2 indicate that the frequency count in a particular cell is respectively significantly smaller or higher than would be expected if the two variables were unrelated ($p < 0.05$).

RESULTS

Description of Experimental Patient Population

After the data selection process, the experimental sample consisted of 286 patients with spastic CP of which the majority had a diagnosis of bilateral CP ($n = 166$) and the median age was 10.2 years (**Table 2**). Gait analysis sessions of patients who had undergone previous orthopedic surgery were collected after a median of ∼2 years (interquartile range: 1 year and 3 months—5 years and 6 months). Because both sides could be included for the majority of the patients with bilateral CP, a total of 446 limbs were used for the statistical analyses of side-specific variables (i.e., "previous surgery," spasticity, and weakness scores).

TABLE 2 | Patient characteristics ($N = 286$).

	N (%)	
GENDER		
Male	165 (57.7)	
Female	121 (42.3)	
DIAGNOSIS		
Bilateral CP	166 (58.0)	
Unilateral CP	120 (42.0)	
GMFCS		
Level I	172 (60.1)	
Level II	89 (31.1)	
Level III	25 (8.7)	
PREVIOUS ORTHOPEDIC SURGERY		
Yes	55 (19.2)	($n = 100$ limbs)
No	231 (80.8)	($n = 346$ limbs)
NUMBER OF PREVIOUS BOTULINUM TOXIN TYPE A TREATMENTS		
None	111 (38.8)	($n = 159$ limbs)
One or two	104 (36.4)	($n = 155$ limbs)
Three or more	71 (24.8)	($n = 132$ limbs)
Weight [mean (*SD*), in kg]	34.3 (14.8)	
Height [mean (*SD*), in cm]	137.6 (19.7)	
Age at time of gait analysis [median (IQR), in years]	10.2 (7.5-12.5)	

SD, standard deviation; IQR, interquartile range.

Table 3 presents the frequency distribution of the spasticity and weakness scores around the hip, knee, and ankle joint, representing the sum of the most severe scores per joint (see section Clinical examination of weakness and spasticity). The muscles acting around the hip were least affected by spasticity, with 48.5% of all limbs classified as MAS 0 or 1. On the contrary, muscles around the ankle joint were most severely affected by spasticity, with 42.7% of all limbs classified as MAS 2, 3, or 4. The weakest muscle groups were also those with their main function around the ankle, with 16.3% of all limbs classified as MMT 0 or 1 as opposed to 1.6% and 0% for the same MMT scores at the hip and knee joint.

Table 1 presents the prevalence of the 49 patterns. Except for the knee during stance and the pelvis in the sagittal plane, the pattern with "minor gait deviations" was the most prevalent one in all other joints, indicating that patients mostly remained within one standard deviation from the mean of an age-matched group of typically developing children. Pathological patterns that were observed most frequently in the proximal joints were "increased pelvic anterior tilt and increased range of motion" (35.2%), "hip extension deficit" (30.5%), and "increased pelvic range of motion" in the sagittal (29.1%), coronal (30.3%), and transverse

TABLE 3 | Prevalence and distribution of MAS and MMT scores for the muscles around the hip, knee, and ankle joint in the selected limbs (*N* = 446) from the patient population.

	MAS score [*N* (%)]					
	0	**1**	**1+**	**2**	**3**	**4**
Hip	93 (20.9)	123 (27.6)	130 (29.1)	98 (22.0)	2 (0.4)	0 (0.0)
Knee	22 (4.9)	118 (26.5)	153 (34.3)	142 (31.8)	11 (2.5)	0 (0.0)
Ankle	9 (2.0)	46 (10.3)	196 (43.9)	164 (36.8)	26 (5.8)	5 (1.1)
	MMT score [*N* (%)]					
	0	**1**	**2**	**3**	**4**	**5**
Hip	0 (0.0)	7 (1.6)	33 (7.4)	231 (51.8)	162 (36.3)	13 (2.9)
Knee	0 (0.0)	0 (0.0)	14 (3.1)	191 (42.8)	221 (49.6)	20 (4.5)
Ankle	5 (1.1)	68 (15.2)	85 (19.1)	189 (42.4)	83 (18.6)	16 (3.6)

The muscles around the hip, knee, and ankle joint are summed following the approach described in section Clinical examination of weakness and spasticity. If less than 50 limbs were classified in a particular category of the MMT or MAS scale, the expected frequencies in the cross-tables were generally too low to allow a valid interpretation of χ^2, especially for analyses in combination with joints that have a high number of patterns [e.g., knee during stance (n = 7)]. Therefore, darker shaded categories were merged at the level of each joint, all indicating a lower level of spasticity or a higher level of muscle weakness. Lightly shaded areas were merged at the level of each joint, indicating a higher level of spasticity and a lower level of muscle weakness.

(30.5%) plane. For the distal joints, the patterns "excessive ankle dorsiflexion during swing" (33.2%), "horizontal second ankle rocker during stance" (29.8%), "delayed peak knee flexion during swing" (23.1%), and "excessive knee flexion and internal flexion moment during stance" (22.4%) were most frequently observed. Because the prevalence of "decreased pelvic anterior tilt" (0.2%) and "decreased pelvic anterior tilt and increased range of motion" (0.7%) was extremely low, both patterns needed to be excluded from further statistical analyses.

Tables 4, 5 report the results of all χ^2 analyses, which established the associations between the distribution of the joint patterns during gait and the patient-specific variables, previous surgery, spasticity, and weakness. Because many significant associations were identified, only the directions of significant moderate associations, where the ASR reached a value larger than 2, are discussed in detail (**Figures 1–6**). Detailed information on the direction of significant weak associations (ASRs) is available in Tables S3–S7 in the Supplementary Material.

Relations with Patient-Specific Characteristics (*n* = 286)

Topographical classification related moderately with the pelvic patterns in the transverse plane ($p < 0.0001$) and coronal plane ($p < 0.0001$) as well as with the knee patterns during swing ($p < 0.0001$) in the sagittal plane (**Figure 1**). Patients with unilateral CP were observed more often than expected with "excessive pelvic external rotation," "pelvic depression," and "minor gait deviations" in the knee during swing phase. In addition, patients with bilateral CP were classified more often with "increased pelvic range of motion" in the transverse plane, and "delayed peak knee flexion" during swing.

Age showed moderate associations with the knee patterns during swing ($p < 0.0001$) and ankle patterns during stance ($p < 0.001$) in the sagittal plane (**Figure 2**). A "horizontal" or "reversed second ankle rocker" was observed significantly more often in the youngest patients, whereas the oldest patients were more often classified as "calcaneus gait" or with "minor gait deviations." The youngest patients also showed more often a "delayed peak knee flexion" or a "delayed and increased peak knee flexion" during swing.

GMFCS level was moderately associated with the patterns of the pelvis ($p < 0.0001$) and hip ($p < 0.0001$) in the sagittal plane (**Figure 3**). Moderate associations were also found for the knee during stance and swing, as well as the ankle during stance. However, the results of these χ^2 analyses should be interpreted with caution due to the low number of patients classified as GMFCS level III in combination with pathological patterns that showed a low prevalence [e.g., equinus gait (4.9%)]. In general, patients with GMFCS level I were observed significantly more often in the patterns with "minor gait deviations" for the pelvis, hip, knee, and ankle joints in the sagittal plane. Patients with GMFCS levels II and III also displayed the patterns "hip extension deficit" and "increased pelvic anterior tilt" significantly more often than expected.

Relations with Side-Specific Variables and Clinical Symptoms (*n* = 446)

Previous surgery was moderately associated with the ankle patterns during swing ($p < 0.0001$; **Figure 4**). The categories that mainly contributed to this association were the higher frequency of "excessive dorsiflexion during swing" in combination with limbs that had undergone previous surgery.

The hip in the coronal plane was the only joint not associated with weakness or spasticity (**Table 5**). Further, only weak associations were identified for all joints in the coronal and transverse plane. Even though the associations were all weak, it was notable that the pattern "excessive hip internal rotation" was observed significantly more often in combination with higher levels of spasticity (MAS 2, 3, or 4) and weakness (MMT 0, 1, 2, or 3) for the muscles acting around the hip, knee, and ankle (Table S7).

In the sagittal plane, spasticity scores for muscles around the hip were moderately associated with the pelvis and hip patterns in the sagittal plane ($p < 0.0001$). Weakness at the level of the hip was moderately associated with the sagittal pelvis patterns ($p < 0.0001$), and weakly associated with the sagittal hip patterns ($p < 0.0001$; **Figure 5** and Video 1). The pattern with "minor gait deviations" in both the pelvis and hip joints was observed significantly more often in limbs with few signs of spasticity (MAS scores 0, 1) or weakness (MMT scores 4, 5). On the other hand, pathological patterns such as "increased pelvic anterior tilt and increased range of motion" or "continuous excessive hip flexion" were mainly observed in limbs that were markedly affected by spasticity (MAS 1+, 2, 3, 4) or weakness (MMT 0, 1, 2, 3).

Severity of spasticity around the knee joint was moderately associated with the knee patterns both during stance and swing

TABLE 4 | Pearson chi squared analyses (χ^2) and Cramer's V (*V*) identified significantly weak, moderate, and strong associations between the sagittal plane joint patterns and patient-specific characteristics, previous surgery, spasticity, and weakness.

	PS[b]		HS		KSTS		KSWS		ASTS		ASWS	
	χ^2	*V*	χ^2	*V*	χ^2	*V*	χ^2	*V*	χ^2	*V*	χ^2	*V*
***N* = 286 PATIENTS**												
Uni-/bilateral CP	7.77	0.17	8.84*	0.18	24.69**	0.29	27.46***	0.31	5.83	0.14	20.66**	0.27
Age	13.21*	0.15	11.03*	0.14	16.95	0.17	37.08***	0.26	28.02**	0.22	9.02	0.13
GMFCS	38.96***	0.26	30.49***	0.23	64.70[a]***	0.34	53.73[a]***	0.31	27.00[a]*	0.22	10.31	0.13
***N* = 446 LIMBS**												
Previous surgery	8.26*	0.14	8.83*	0.14	14.40*	0.18	1.05	0.05	18.70*	0.21	55.71***	0.35
MAS Hip joint	68.51***	0.23	41.95***	0.22	81.37***	0.25	149.48***	0.33	44.60***	0.18	14.16	0.10
MAS Knee joint	44.23***	0.22	27.41***	0.18	71.86***	0.28	91.68***	0.32	29.64**	0.18	18.47*	0.14
MAS Ankle joint	29.12***	0.26	4.07	0.10	39.30***	0.30	67.69***	0.39	42.28***	0.31	17.20*	0.20
MMT Hip joint	52.18***	0.34	30.25***	0.26	48.80***	0.33	51.31***	0.34	9.35	0.15	12.82*	0.17
MMT Knee joint	57.67***	0.36	35.44***	0.28	36.51***	0.29	72.23***	0.40	18.91*	0.21	10.33*	0.15
MMT Ankle joint	79.96***	0.25	38.31***	0.21	59.66***	0.21	78.05***	0.24	28.85*	0.15	33.43**	0.16

**p < 0.05; **p < 0.001; ***p < 0.0001; χ^2, Pearson chi squared; V, Cramer's V, indicating significantly weak (light gray), moderate (darker gray), and strong (dark gray) associations based on degrees of freedom (section Statistical analysis and Table S2); [a]Results should be interpreted with caution because >20% of cells had expected frequencies lower than n = 5; [b]N = 282 patients and N = 442 limbs due to exclusion of PS4 and PS5.*

TABLE 5 | Pearson chi squared analyses (χ^2) and Cramer's V (*V*) identified significantly weak and moderate associations between the coronal and transverse plane joint patterns and patient-specific characteristics, previous surgery, spasticity, and weakness.

	PC		HC		PT		HT		FT	
	χ^2	*V*	χ^2	*V*	χ^2	*V*	χ^2	*V*	χ^2	*V*
***N* = 286**										
Uni-/bilateral CP	24.92***	0.30	2.42	0.09	26.49***	0.30	3.10	0.10	14.56*	0.23
Age	13.63*	0.15	4.89	0.09	4.43	0.09	2.88	0.07	11.46*	0.14
GMFCS	10.02	0.13	17.28[a]*	0.17	19.42*	0.18	12.71[a]*	0.15	7.60	0.12
***N* = 446**										
Previous surgery	8.38*	0.14	2.29	0.07	2.71	0.08	10.25*	0.15	2.03	0.07
MAS Hip joint	23.84*	0.13	3.18	0.05	15.98	0.11	28.79***	0.18	21.75*	0.16
MAS Knee joint	19.51*	0.15	1.84	0.05	16.97*	0.14	15.31*	0.13	10.70*	0.11
MAS Ankle joint	6.32	0.12	5.24	0.11	5.07	0.11	8.94*	0.14	4.40	0.10
MMT Hip joint	12.64*	0.17	1.44	0.06	11.39*	0.16	9.31*	0.14	5.53	0.11
MMT Knee joint	9.26*	0.14	3.82	0.09	5.74	0.11	16.61**	0.19	7.42*	0.13
MMT Ankle joint	14.53	0.10	10.12	0.09	28.51*	0.15	23.61*	0.16	13.49*	0.12

**p < 0.05; **p < 0.001; ***p < 0.0001; χ^2, Pearson chi squared; V, Cramer's V, indicating weak (light gray) and moderate (darker gray) associations based on degrees of freedom (Statistical analysis and Table S2); [a]Results should be interpreted with caution because >20% of cells had expected frequencies lower than n = 5.*

($p < 0.0001$; **Figure 6** and Video 1). A moderate association was also identified between weakness scores at the level of the knee and the knee patterns during swing ($p < 0.0001$). For the knee patterns during swing, it was apparent that all patterns with the feature "delayed peak knee flexion" (KSWS1, KSWS3, KSWS5; **Figure 6** and Video 1) were observed significantly more often in combination with higher levels of spasticity (MAS 2, 3, 4) and weakness (MMT 0, 1, 2, 3). For the knee patterns during stance, "minor gait deviations" and "increased knee flexion at initial contact" were mainly observed in limbs with few signs of spasticity (MAS 0, 1) or weakness (MMT 4, 5). Limbs with higher levels of spasticity (MAS 2, 3, 4) or weakness (MMT 0, 1, 2, 3) were classified more often than expected as "increased knee flexion at initial contact and knee hyperextension" as well as "increased flexion during midstance and internal flexion moment present."

Spasticity at the level of the ankle was moderately associated with the ankle patterns during stance ($p < 0.0001$; **Figure 4** and Video 1), and weakly associated with the ankle patterns during swing ($p = 0.001$). The patterns "equinus gait" and "reversed second ankle rocker" were mainly observed in combination with marked signs of spasticity (MAS 2, 3, 4). Weakness at the level of the ankle was weakly associated with the ankle patterns both during stance and swing (both $p < 0.01$).

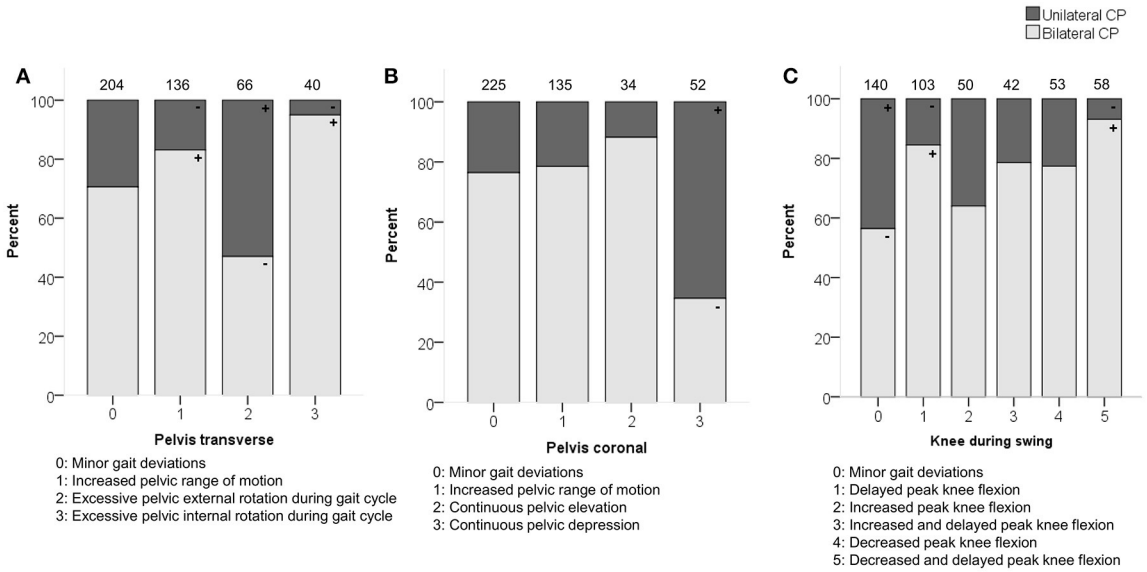

FIGURE 1 | Topographical classification associated moderately with (A) pelvis patterns in transverse plane (PT) **(B)** pelvis patterns in coronal plane (PC) and **(C)** knee patterns during swing (KSWS). The symbol "+" indicates that a pattern was observed significantly more frequently and "–" indicates that a pattern was observed significantly less frequently in children with unilateral or bilateral CP ($p < 0.05$). Specific ASRs are available in Tables S4, S6, S7. Numbers on top of each bar represent the number of patients that were classified into that pattern.

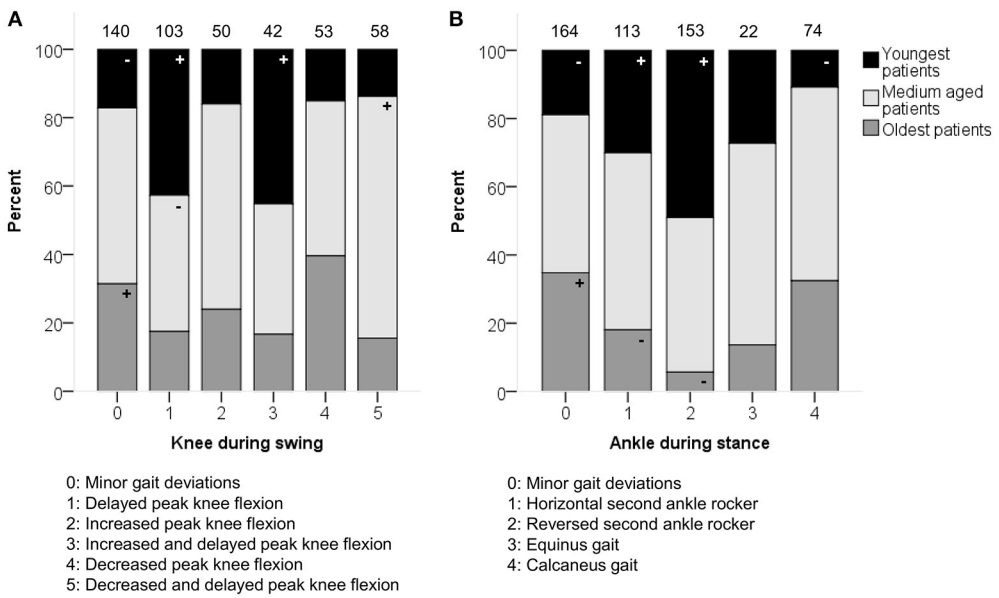

FIGURE 2 | Age associated moderately with the distribution of (A) knee patterns during swing (KSWS) and **(B)** ankle patterns during stance (ASTS). The symbol "+" indicates that a pattern was observed significantly more frequently and "–" indicates that a pattern was observed significantly less frequently in the youngest, medium aged, or oldest patients ($p < 0.05$). Specific ASRs are available in Tables S4, S5. Numbers on top of each bar represent the number of patients that were classified into that pattern.

DISCUSSION

In this exploratory study, the prevalence of joint patterns during gait in children with CP and their association to patient-specific characteristics, previous surgery, and clinical symptoms, was examined.

The pattern "minor gait deviations" was observed most frequently in all joints, apart from the knee during stance and the pelvis in the sagittal plane. The prevalence of "minor gait deviations" reached more than 50% for the hip across the three anatomical planes, the pelvis in the coronal plane, and the foot progression angle. The need to define a pattern

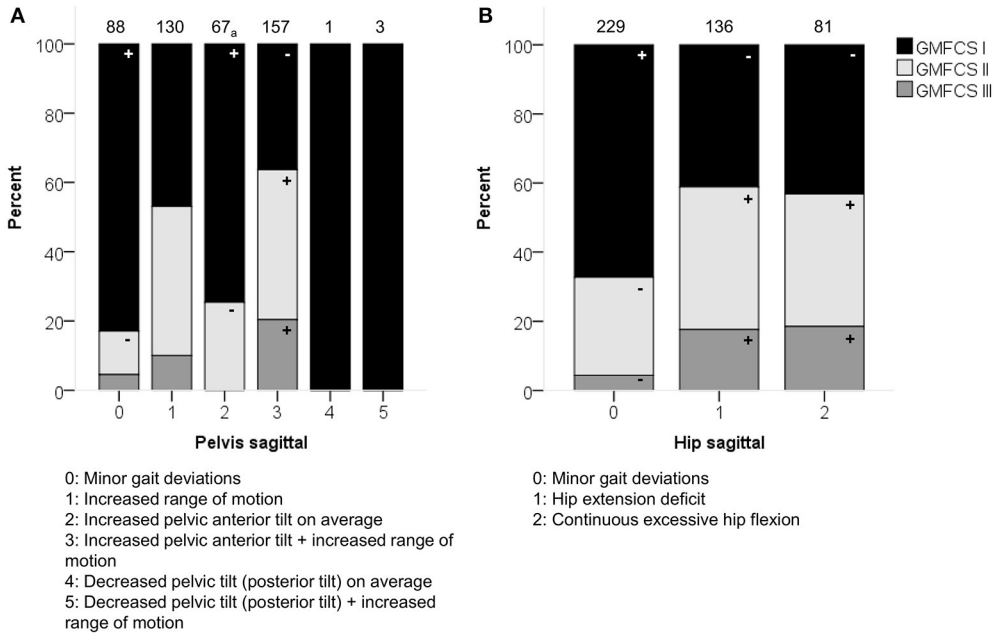

FIGURE 3 | GMFCS level associated moderately with the distribution of (A) pelvis patterns in sagittal plane (PS) and **(B)** hip patterns in sagittal plane (HS). The symbol "+" indicates that a pattern was observed significantly more frequently and "–" indicates that a pattern was observed significantly less frequently in patients with GMFCS level I, II, or III ($p < 0.05$). [a]Indicates that increased pelvic anterior tilt (PS2) was observed significantly less often in patients with GMFCS III. Specific ASRs are available in Table S3. Numbers on top of each bar represent the number of patients that were classified into that pattern.

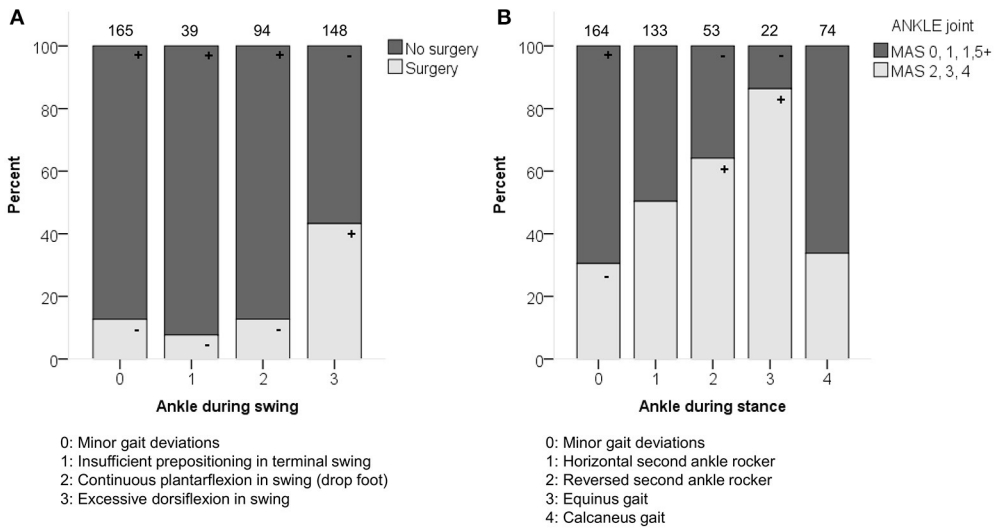

FIGURE 4 | (A) Previous surgery associated moderately with the distribution of the ankle patterns during swing (ASWS). **(B)** Spasticity of muscles acting around the ankle associated moderately with the distribution of the ankle patterns during stance (ASTS). The symbol "+" indicates that a pattern was observed significantly more frequently and "–" indicates that a pattern was observed significantly less frequently in limbs with or without surgery, or in limbs with lower (MAS 0, 1, 1+) vs. higher (MAS 2, 3, 4) levels of spasticity around the ankle ($p < 0.05$). Specific ASRs are available in Table S5 and video illustrations of some joint gait patterns are available in Video 1. Numbers on top of each bar represent the number of limbs that were classified into that pattern.

showing mild gait pathology has also been reported before, for example for the classifications of Winters et al. (1987) (hemiplegic patterns) and Rodda et al. (2004) (diplegic patterns) (Riad et al., 2007; McDowell et al., 2008; de Morais Filho et al., 2014). In both population- and hospital-based recruitment settings, the prevalence of these mild patterns has been reported to range between 12–43% (McDowell et al., 2008; de Morais Filho et al., 2014). The numbers in this study are generally higher, but this may be explained by the fact that the gait patterns in this study were evaluated at joint level, in contrast to the previous

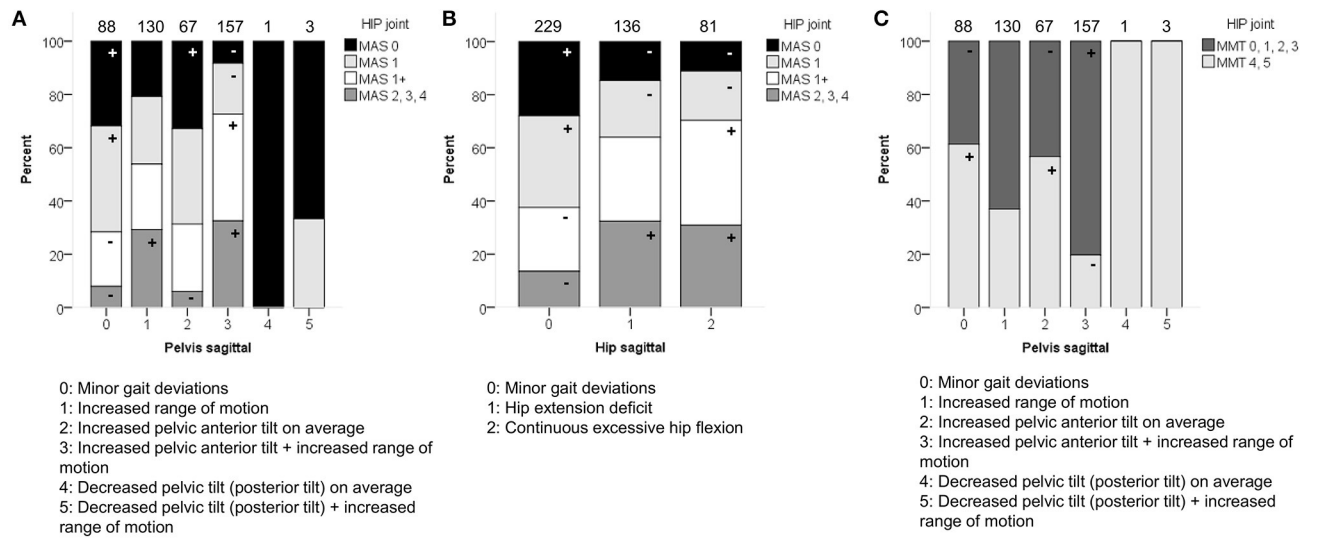

FIGURE 5 | Spasticity of muscles acting around the hip associated moderately with the distribution of (A) pelvis patterns in sagittal plane (PS), and **(B)** hip patterns in sagittal plane (HS). **(C)** Weakness of muscles acting around the hip associated moderately with PS. The symbol "+" indicates that a pattern was observed significantly more frequently and "–" indicates that a pattern was observed significantly less frequently in limbs with of a particular MAS score or in limbs with weaker (MMT 0, 1, 2, 3) or stronger (MMT 4, 5) muscles around the hip ($p < 0.05$). Specific ASRs are available in Table S3 and video illustrations of some joint gait patterns are available in Video 1. Numbers on top of each bar represent the number of limbs that were classified into that pattern.

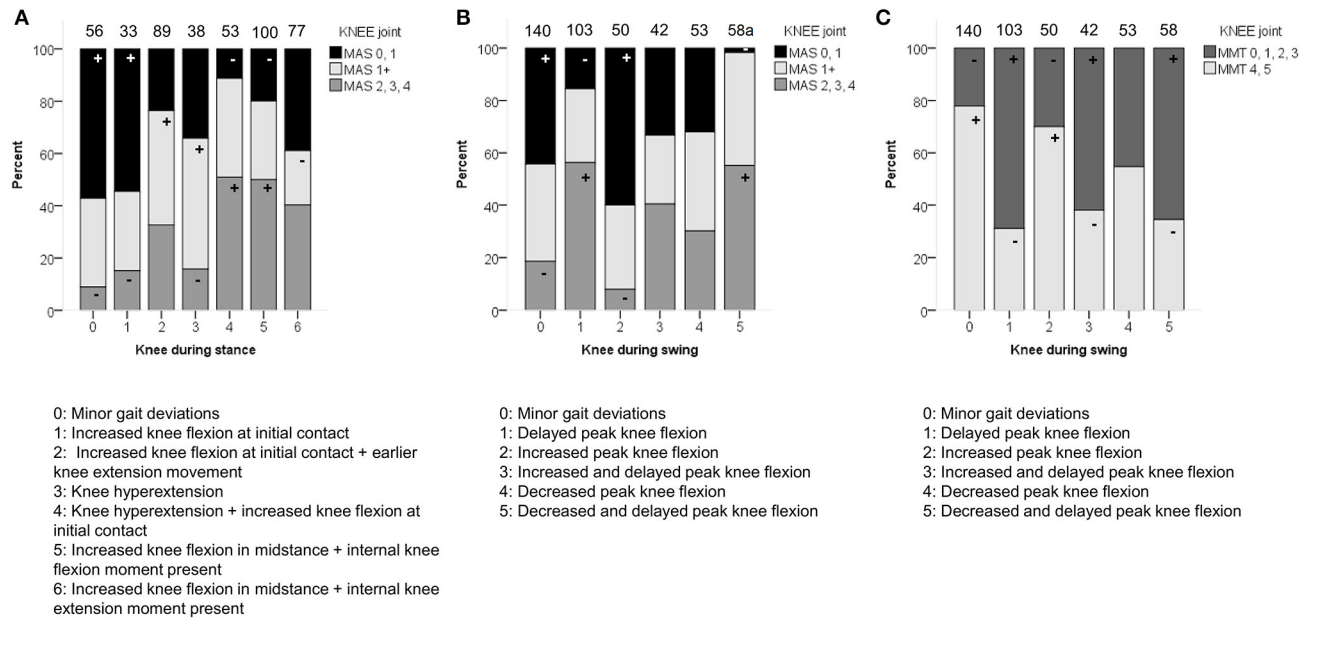

FIGURE 6 | Spasticity of muscles acting around the knee associated moderately with the distribution of (A) knee patterns during stance (KSTS), and **(B)** knee patterns during swing (KSWS). **(C)** Weakness of muscles acting around the knee associated moderately with KSWS. The symbol "+" indicates that a pattern was observed significantly more frequently and "−" indicates that a pattern was observed significantly less frequently in limbs with of a particular MAS score or in limbs with weaker (MMT 0, 1, 2, 3) or stronger (MMT 4, 5) muscles around the knee ($p < 0.05$). [a]Indicates that decreased and delayed peak knee flexion (KSWS5) was observed significantly less often with limbs classified as MAS 0 or 1. Specific ASRs are available in Table S4 and video illustrations of some joint gait patterns are available in Video 1. Numbers on top of each bar represent the number of limbs that were classified into that pattern.

studies where total gait patterns, including multiple joints, have been reported. In the present study, however, a high number of "minor gait deviations" in specific joints does not imply that most children with CP in this study walked closely to typical gait in general. Indeed, it was found that at patient level, only 6.7% of the included limbs were classified with "minor gait deviations" in at least eight joints (out of 11 joints spread over the three anatomical planes), indicating that gait is markedly pathological

in the majority of patients. So far, the way in which the various joint patterns across different planes combine in a total gait pattern is not yet fully understood.

Comparison of the prevalence of the pathological patterns to results from previous research is very challenging, as definitions of gait patterns as well as recruitment methods and inclusion criteria vary substantially across studies. For example, observed frequencies of excessive pelvic or hip rotation or in/outtoeing were markedly lower than the frequencies reported in previous studies (Wren et al., 2005; O'Sullivan et al., 2007; de Morais Filho et al., 2009; Simon et al., 2015). However, the definition of what constitutes excessive rotation across studies varies substantially. In the present study, a more strict definition was used by evaluating excessive rotation continuously over the entire gait cycle (or stance phase for FPA). This strict criterion is justified, taking into account the previously reported higher measurement errors for hip rotation and FPA (Schwartz et al., 2004). A notable finding of the current study was that both patterns showing "decreased pelvic anterior tilt" (or posterior tilt) with or without increased range of motion were observed only four times. Posterior pelvic tilt was previously included as a potential feature of the type IV gait pattern defined by Rodda et al. (2004), although it is unclear how often this feature is present in patients with type IV gait pattern (Rodda et al., 2004; Stott et al., 2005). The type IV pattern is mainly described for severely affected children. Following the assumption that posterior tilt will therefore be more prevalent in children with fewer functional abilities, the present study might have underestimated the prevalence of this pattern due to the relatively smaller sample size of children with GMFCS level III. Interestingly, the results of the previously mentioned study on the content validity of the Delphi gait classification (Nieuwenhuys et al., 2017a) indicated that all patterns, apart from PS4 and PS5, were statistically different from each other and from the patterns of TD children. With the low frequencies observed for the patterns PS4 and PS5 in the current study, and taking into consideration that the recent content validity study (Nieuwenhuys et al., 2017a) did not identify significant differences between these two joint patterns, the relevance of including both features as separate patterns in the classification should be re-examined in future research.

Relations with Patient-Specific Characteristics and Clinical Symptoms

It was hypothesized that the prevalence of the patterns would be associated with age, topographical classification, and GMFCS level. This hypothesis could be confirmed for some joints, but the strength of most identified associations was weak. The knee patterns during swing and the pelvis patterns in the frontal and transverse plane showed moderate associations with topographical classification. Hence, they can be considered as characterizing for children with unilateral or bilateral CP. The finding that children with unilateral CP have a relatively higher prevalence of pelvic depression and excessive pelvic external rotation compared to children with bilateral CP concurs with previous research investigating hemiplegic gait (Graham et al., 2005; O'Sullivan et al., 2007; Salazar-Torres et al., 2011). The results further showed that the prevalence of the ankle patterns during stance associated moderately with age, with the youngest patients showing a relatively higher frequency of a horizontal or reversed second ankle rocker. Wren et al. (2005) also noted decreased odds of equinus and increased odds of calcaneus gait with increasing age. The definition of equinus in their study (i.e., ankle plantarflexion >1 standard deviation below the mean for normal gait), would include the horizontal and reversed second ankle rocker, as well as the equinus pattern from the present study. These authors also reported an increased likelihood of presenting with internal hip rotation and/or outtoeing with increasing age (Wren et al., 2005). The present study also found that intoeing occurred significantly less often than expected in older subjects, but no significant association was identified between hip patterns in the transverse plane and age. Different definitions of excessive internal hip rotation between both studies might again be the main cause of the marked differences in the observed frequency of this pattern (ca. 40% in Wren et al., 2005, vs. 16.6% in this study). GMFCS levels are best characterized by the joint patterns in the sagittal plane. Although the results for the ankle and knee patterns should be interpreted with caution, a trend showed that patterns with minor gait deviations at the level of each joint were mainly observed in children with GMFCS I.

The study also examined how specific joint patterns during gait were characterized by weakness and spasticity. An obvious trend regarding all significant associations was that the patterns with minor gait deviations (PS0, HS0, KSTS0, KSWS0, ASTS0, ASWS0, PC0, PT0, HT0, FT0) were observed significantly more often in limbs with a low level of spasticity (MAS 0, 1, 1+) and good muscle strength (MMT 4 or 5), which appeared significantly less often than expected in other pathological patterns. The pathological patterns that were most characterized by both weakness (MMT 0, 1, 2, or 3) and spasticity were patterns related to pelvic anterior tilt (PS2 and PS3), patterns with increased knee flexion at initial contact (KSTS1 and KSTS4), patterns with abnormal knee flexion in swing (KSWS1, KSWS2, and KSWS5), ankle patterns characterized by excessive plantar flexion (ASTS3 and ASWS2), and "excessive hip internal rotation" (HT2). The patterns "increased and delayed peak knee flexion during swing" (KSWS3) and "outtoeing" (FPA1) were mainly characterized by weakness alone. On the other hand, "reversed second ankle rocker" (ASTS2) and "intoeing"' (FPA2) were mainly characterized by spasticity. It was also apparent that stronger associations with clinical symptoms were consistently found for the joints in the sagittal plane, possibly because most of the evaluated muscles in this study also perform sagittal plane motions as a main function (i.e., flexion and extension around the hip, knee, and ankle). Some of these associations are demonstrated in Video 1, where video fragments of patients' gait are provided as additional support to the kinematic waveforms and the respective joint gait patterns.

Remarkably, there were no significant associations identified with any of the investigated variables for the hip in the coronal plane. A recent study evaluated the level of clinician agreement with which these patterns could be identified and found that the hip in the coronal plane had the highest number of "unclassifiable" patients (Nieuwenhuys et al., 2017b). A future

point of attention could be to investigate whether deviations in the coronal plane are compensations for deviations in the sagittal or transverse plane, as suggested by Davids et al. (Davids and Bagley, 2014). Hence, the pattern definitions of the coronal plane patterns and their relevance or necessity in the classification could be re-examined.

Another hypothesis said that a specific joint would be associated in particular with the severity of weakness or spasticity in muscle groups that act around that joint. The results of this study confirmed that these associations were present, however, as **Tables 4, 5** demonstrate, joint patterns were also associated with weakness and spasticity scores of muscle groups acting around the other joints. For instance, for the knee patterns during swing, a significant association was found with the level of spasticity for the muscles around the knee, but also with the level of spasticity around the ankle and hip joint. The directions of these significant associations were the same for the spasticity scores at each level: with higher scores of spasticity, the patterns "delayed (and decreased)" peak knee flexion (KSWS1, KSWS5) were observed significantly more often; with lower scores of spasticity, the patterns "minor gait deviations" (KSWS0), and "increased peak knee flexion" (KSWS2) were more often observed. This finding can be extrapolated to all joint patterns: if joint patterns were associated with weakness or spasticity at more than one level (i.e., hip, knee, or ankle), the direction of the significant associations was similar for all levels (Tables S3–S7). This result suggests that specific gait deviations in one joint are not only caused by problems in the muscles surrounding that joint. They will rather be the result of a complex interplay of different muscles and movements at all lower limb joints.

LIMITATIONS

A few limitations of the study need to be addressed. The generalizability of the results of this study might be limited as the investigated study group was a sample of convenience, recruited from one hospital setting. Firstly, it was noted that there was an underrepresentation of patients with GMFCS III and an overrepresentation of patients with unilateral cerebral palsy in the studied sample compared to previously reported distributions of gross motor function and topographical classifications (Gorter et al., 2004; Rosenbaum, 2008). More clear trends with GMFCS level might be identified given a larger proportion of children with GMFCS III, especially for the knee patterns and for the ankle patterns during stance. Secondly, 70 of 356 patients were excluded, of which 14 patients (20%) were excluded due to missing data from the clinical examination. It was not possible to find out the precise reasons for these missing data (e.g., fatigue or age resulting in reduced collaboration of the child, oversight by clinician, etc.). As a result, a small bias toward the exclusion of weaker or more severely affected children in the studied sample cannot be excluded. Thirdly, because the study used retrospective data, a relatively large amount of patients had undergone previous Achilles tendon lengthening (29 out of 100 limbs that were operated upon). The generalizability of the results is therefore limited, as surgical strategies have evolved during the past 10 to 20 years and tendon lengthening procedures are performed much less frequently (Gage, 2003; Healy et al., 2011). It is therefore difficult to formulate strong conclusions regarding the influence of previous surgery on the distribution of the joint patterns. In the future, the effect of previous surgery should be investigated using more specific subgroups regarding previous surgical interventions, or alternatively, prospective longitudinal intervention studies should be carried out to test the responsiveness of the patterns to different treatment interventions. Another limitation of this study is that due to the sample size, a comparison between males and females, especially in the older patient group (>12 years old) could not be performed. In addition, in patients who were bilaterally involved, for side-specific variables both sides were included in the statistical analyses, whereas for the remaining comparisons, only one trial from one side was randomly selected. In this way, the possible effect of the contralateral leg in the observed gait patterns was not taken into consideration in the performed analyses. In this study, it was further decided to group muscles at the level of each joint depending on their main function, and to select the most severe MAS or MMT score to represent the severity of spasticity or weakness at that joint. This implicates that when weakness at the level of the ankle is associated with specific ankle patterns, some of the scores used for statistical analysis might have been the result of ankle dorsiflexor weakness, others might have been due to ankle plantarflexor weakness. It is obvious that different muscles such as ankle plantar- and dorsiflexors would affect gait differently and potentially stronger associations might be discovered if these analyses would be performed on a muscle-specific rather than joint-specific basis. However, detailed investigations of the muscle-specific MMT and MAS scores around each joint revealed that problems of spasticity or weakness were mostly present in more than one muscle group. Because several muscles are affected by weakness or spasticity to a similar extent, and because different categories of the MAS and MMT scale were merged, it can be assumed that muscle-specific analyses would not change the general interpretations of the currently presented results. Rather, they might point to specific muscles whose clinical characteristics are discriminating best between particular joint patterns during gait. Because different categories of the MAS and MMT scale were merged, the potential bias that could result from the missing clinical data in the analyzed patient sample, was also further reduced. Lastly, the classifications for each limb were based on a single representative trial, whereas CP children are known to have a certain amount of variability across trials. Future research may evaluate to what extent this variability affects the classifications and how consistently these patterns are assigned across multiple trials.

CONCLUSION

The usefulness of any classification essentially relies on its potential to make distinctions between clinically relevant subgroups in CP. This study provided first insights toward the construct validity and clinical relevance of joint gait patterns

in CP (Nieuwenhuys et al., 2016). Although further validation is warranted, the results of this study confirm that most joint patterns during gait are characterized by different patient-specific characteristics and that they are often associated with gross categories of muscle weakness and spasticity.

AUTHOR CONTRIBUTIONS

This study was designed by AN, EP, TD, and KD. AN and EP were responsible for all data acquisition and data analysis, SS created the Supplementary Material—Video 1. At each stage of the study, all authors have had complete access to the study data. Each author contributed to the interpretation of the results and was involved in the critical revision and editing of the manuscript that was written by AN and EP. All authors approve the final version of the manuscript and agree to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00185/full#supplementary-material

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REVIEW
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Neurologic Correlates of Gait Abnormalities in Cerebral Palsy: Implications for Treatment

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Cerebral palsy (CP) is the most common movement disorder in children. A diagnosis of CP is often made based on abnormal muscle tone or posture, a delay in reaching motor milestones, or the presence of gait abnormalities in young children. Neuroimaging of high-risk neonates and of children diagnosed with CP have identified patterns of neurologic injury associated with CP, however, the neural underpinnings of common gait abnormalities remain largely uncharacterized. Here, we review the nature of the brain injury in CP, as well as the neuromuscular deficits and subsequent gait abnormalities common among children with CP. We first discuss brain injury in terms of mechanism, pattern, and time of injury during the prenatal, perinatal, or postnatal period in preterm and term-born children. Second, we outline neuromuscular deficits of CP with a focus on spastic CP, characterized by muscle weakness, shortened muscle-tendon unit, spasticity, and impaired selective motor control, on both a microscopic and functional level. Third, we examine the influence of neuromuscular deficits on gait abnormalities in CP, while considering emerging information on neural correlates of gait abnormalities and the implications for strategic treatment. This review of the neural basis of gait abnormalities in CP discusses what is known about links between the location and extent of brain injury and the type and severity of CP, in relation to the associated neuromuscular deficits, and subsequent gait abnormalities. Targeted treatment opportunities are identified that may improve functional outcomes for children with CP. By providing this context on the neural basis of gait abnormalities in CP, we hope to highlight areas of further research that can reduce the long-term, debilitating effects of CP.

Keywords: cerebral palsy, brain injury, neuroimaging, neuromuscular deficits, gait

Abbreviations: ADC, apparent diffusion coefficient; ATP, adenosine triphosphate; BGTL, basal ganglia and/or thalamus lesions; BoNT-A, botulinum toxin-A; CP, cerebral palsy; CST, corticospinal tract; CT, computed tomography; DTI, diffusion tensor imaging; EMG, electromyography; GM, gray matter; GMFCS, Gross Motor Function Classification Scale; MRI, magnetic resonance imaging; MVC, maximal voluntary contraction; PVL, periventricular leukomalacia; SCALE, Selective Control Assessment of the Lower Extremity; SMC, selective motor control; TD, typically developing; VLBW, very low birthweight; WM, white matter.

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INTRODUCTION

Cerebral palsy is the most common movement disorder in children, with an overall prevalence worldwide of 2–3 per 1,000 live births, and a much higher prevalence of 60–150 per 1,000 among neonatal survivors weighing less than 1500 grams at birth (Oskoui et al., 2013). A diagnosis of CP is often made based on the observation of abnormal muscle tone or posture, delayed motor milestones, or the presence of gait abnormalities in young children, which range from mild, i.e., toe-walking, to severe, i.e., crouched, internally rotated gait (Wu et al., 2004). Gait begins to stabilize around age 3–4 years and matures by 7 years of age (Wu et al., 2015). Among children with CP who are not walking by age 2 years, only 10% walk independently by age 7 (Wu et al., 2004), underscoring the importance of early identification and intervention. In recent years, 3D gait analysis has become the gold standard for delineating gait abnormalities in children with CP (Gage and Novacheck, 2001). Furthermore, neuroimaging of high-risk neonates and of children diagnosed with CP have identified patterns of neurologic injury associated with CP. However, the link between neurologic injury, neuromuscular deficits, and specific gait abnormalities in CP is not well understood. This review of the neural basis of gait abnormalities in CP discusses what is known about links between the location and extent of brain injury and the type and severity of CP, in relation to the associated neuromuscular deficits, and subsequent gait abnormalities. We discuss current literature that addresses the nature of the brain injury in CP, as well as the neuromuscular deficits and subsequent gait abnormalities in CP on both a microscopic and functional level. Ultimately, we hope that this review clarifies some of the neurologic correlates of gait abnormalities and points to areas of further research that can improve functional outcomes for children with CP.

BRAIN INJURY IN CEREBRAL PALSY

Cerebral palsy describes "a group of permanent disorders affecting the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" (Rosenbaum et al., 2007). Although the initial brain injury is non-progressive, the musculoskeletal impairments and functional limitations associated with CP are indeed progressive (Bell et al., 2002; Sanger, 2015). A loss of oxygen to the developing brain, i.e., hypoxia-ischemia, is the primary mechanism by which brain injury occurs in CP. Other causes of brain injury include hemorrhage, infection, metabolic derangement, brain malformation, and bilirubin neurotoxicity. In contrast, birth asphyxia resulting in CP is relatively rare, accounting for <10% cases, (Paneth et al., 2006; Strijbis et al., 2006; Ellenberg and Nelson, 2013), and evidence of genetic influences on development of CP is newly emerging and thought to contribute to up to 30% of CP cases (Costeff, 2004; Moreno-De-Luca et al., 2012; MacLennan et al., 2015). The prevalence of CP increases with prematurity, ranging from 1.1 per 1000 infants born at 40 weeks' gestation to 90.7 per 1000 infants born at 26 weeks' gestation (Trønnes et al., 2014). The risk of CP decreases linearly with increasing gestational age: 8.5% for 23–27 weeks, 5.6% for 28–30 weeks, 2.0% for 31–33 weeks, 0.4% for 34–36 weeks, and 0.2% for 37+ weeks gestation. Male sex is also a general risk factor, as the rate of CP per 1000 male births exceeds that among females by about 30% (Jarvis et al., 2005).

There are three main types of CP: spastic, dyskinetic, and ataxic. Spastic CP is the most common, affecting approximately 87% of children with CP, while dyskinetic CP affects approximately 7.5%, and ataxic CP affects approximately 4% of children with CP (Sellier et al., 2016). There is evidence that different types of CP each have primary regions of brain damage linked to characteristic motor deficits, though different types of CP can co-exist. Emerging research indicates that spastic CP is associated with brain damage to cortical motor areas and underlying WM, dystonic CP is associated with damage to basal ganglia, and ataxic CP is associated with damage to cerebellar structures (**Figure 1**). In general, periventricular WM lesions are generally associated with mild and moderate motor impairments of spastic CP with fewer accompanying impairments, whereas brain maldevelopment and cortical/subcortical and basal ganglia lesions are associated with more severe and a greater number of accompanying impairments, such as cognitive and language deficits (Himmelmann and Uvebrant, 2011).

Spastic CP is often linked to damage to the periventricular WM due to hypoxia-ischemia, which may be caused by various maternal or prenatal factors. Spastic CP is further delineated by the distribution of affected limbs: hemiplegia, diplegia, and tetraplegia (also referred to as quadriplegia). Individuals with spastic CP present with varying degrees of weakness, short muscle-tendon unit, spasticity, and impaired SMC. In spastic CP, the severity of motor deficits, the distribution of affected limbs, and the extent to which the motor deficits involve distal to more proximal joints within a limb, are thought to be determined by the severity and extent of the brain injury (Serdaroglu et al., 2004), consistent with anatomical representation of the cortical homunculus and descending fibers (**Figure 1**). More medial brain injury, i.e., closer to the ventricles, results in more mild involvement of distal joints. More extensive injury that extends to lateral portion of periventricular WM results in more severe involvement of both distal and proximal joints. Accordingly, Staudt et al. (2000) found a strong correlation between the extent of the lateral lesion in the posterior semi-coronal plane on MRI and the lower limb motor impairment score ($r = 0.805$, $p = 0.001$). In addition, upper limb involvement is generally associated with a greater degree of lateral damage compared to lower limb involvement. Staudt et al. (2003) found that upper limb dysfunction was observed only in patients with a lateral lesion extent of 23 mm or more, whereas lower limb dysfunction was present with a lateral lesion extent of 20 mm.

Dyskinetic CP is the second most common type of CP, affecting approximately 7.5% of children with CP (Sellier et al., 2016). It is often linked to damage of the subcortical GM, i.e., basal ganglia and thalamus, due to hypoxia-ischemia, as well as hyperbilirubinemia and birth asphyxia (Himmelmann and Uvebrant, 2011). The definition of dyskinetic CP has evolved recently to include dystonic and choreoathetoid CP

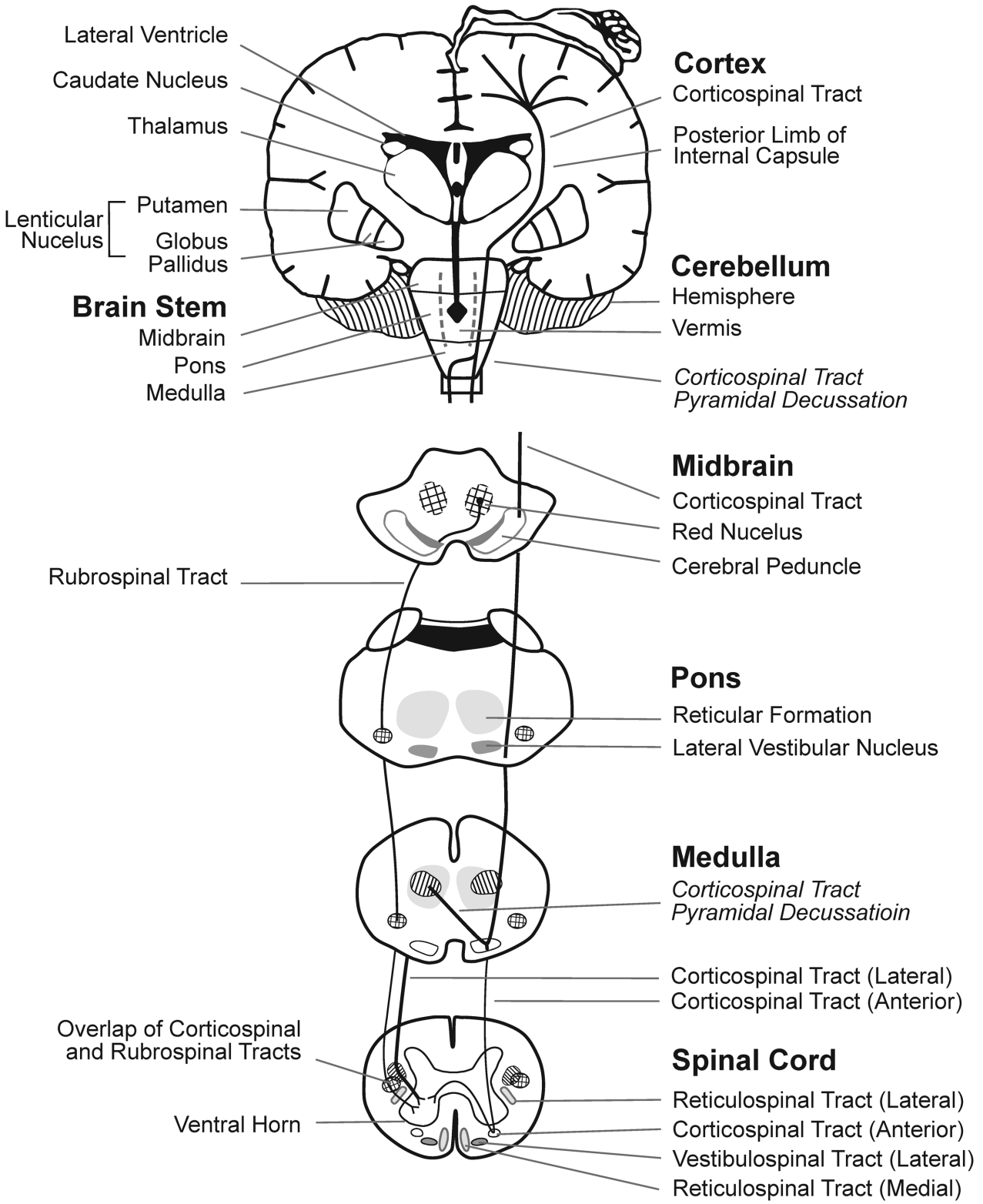

FIGURE 1 | Brain regions and WM motor tracts affected in spastic, dyskinetic, and ataxic CP. A portion of the motor homunculus is superimposed on the cortex. Representations of the lateral ventricles, subcortical nuclei, cerebellum, brain stem, and rubrospinal and CSTs are outlined. The vermis of the cerebellum (posterior to the brainstem) is represented by dotted lines. Regions where the reticulospinal and vestibulospinal tracts descend through each layer of the brainstem and the spinal cord are shaded.

(Aravamuthan and Waugh, 2016). As noted by Sanger (2006), symptoms of dyskinetic CP include both hyperkinetic and dystonic limb movements that impair function. Currently, it has not been determined whether these movements are random and variable or involve a small number of specific abnormal motor patterns (Sanger, 2006). The severity of motor impairment in dyskinetic CP has been found to be associated with lower volumes of the basal ganglia and thalamus (Laporta-Hoyos et al., 2014). In a study of 18 children with basal ganglia lesions and CP, 13 children had a diagnosis of dyskinetic CP, 12 had a diagnosis of dyskinetic CP with severe fine motor impairment and a GMFCS (Palisano et al., 2008) level of IV or V, representing severe CP with reduced or absent independent mobility (Himmelmann and Uvebrant, 2011).

Ataxic CP is the least common type of CP and is associated with cerebellar vermis injury, cerebellar malformations, and or genetic mutations; ataxic CP is characterized by impaired limb coordination during voluntary movements, as well as balance, stability, and speech impairments (Hughes and Newton, 1992; Schnekenberg et al., 2015; Graham et al., 2016). Few studies have examined the neurologic correlates of ataxic CP. Miller and Cala (1989) examined CT scans of 29 patients with ataxic CP born at term: 7 had simple ataxic CP and 10 had ataxic diplegia, which involves simple ataxia in addition to pyramidal signs of spastic diplegic CP. They identified brain abnormalities in only 18/29 children. Of the 7 children with simple ataxia, 5/7 had cerebral abnormalities and 4/7 had changes in the posterior fossa involving the vermis (Miller and Cala, 1989). Similarly, Bax et al. (2006) found that children with ataxic CP had the highest rate of normal MRI (8 out of 17), suggesting a need for further research utilizing higher resolution neuroimaging in ataxic CP.

Although early brain injury is the primary cause of CP, a recent study using exome sequencing reported that 14% of CP cases had causative single-gene mutations and up to 31% had clinically relevant copy number variations, suggesting a greater role of genetics in the development of brain injury and CP than previously recognized (MacLennan et al., 2015). Genes encoding processes related to catabolism of lipoprotein constituents, procoagulant factors, factors influencing central nervous system injury response, neuronal function (genes for potassium channels), cytoskeleton-interacting proteins, and adaptor proteins involved in intracellular trafficking are targets of further research as potential culprits of genetic causes for CP (Fahey et al., 2016). For the purposes of this review, we will focus primarily on the neurologic correlates of gait abnormalities in CP and the implications for treatment.

Currently, brain imaging using MRI is the gold standard for identifying neural injury in CP. Recently, Fiori et al. (2015) developed an MRI score that correlated with severity of CP. In a review of six studies, including 1065 MRI and CT images in children diagnosed with CP, the most common injuries were WM injury (19–45% of images), GM injury (14–22%), focal vascular insults (10%), malformations (11%), and miscellaneous abnormalities (4–23%) (Reid et al., 2014). WM injury was most common among all CP subtypes, though children with spastic diplegia had the highest rate of WM injury overall.

However, brain injuries in CP are not always visible on MRI; a review by Reid et al. (2014) revealed that abnormal MRI only accounts for about 86% of CP cases, i.e., 14% of children clinically diagnosed with CP show no signs of brain injury on MRI, particularly in children with ataxic CP, as noted above (Bax et al., 2006). These findings may be explained by the limitations of current imaging methodologies, such as insufficient spatial resolution, to reveal micro-lesions (Leonard et al., 2011; Benini et al., 2013). In fact, recent studies show that DTI can better predict motor function deficits from WM damage in the posterior limbs of the internal capsule than conventional MRI (Rose et al., 2007; Benini et al., 2013). Furthermore, a recent publication suggests that the combination of different MRI scans, including volumetric imaging and DTI, can help to identify potential relations between brain lesions and lower limb deficits or gait pathology in children with spastic CP (Meyns et al., 2016b).

Selective vulnerability of developing WM to injury during early phases of vascularization and WM myelination has been widely recognized (Inder and Volpe, 2000; Hoon et al., 2009). Regional differences in the trajectory of early WM development (Dubois et al., 2014; Rose et al., 2014) can influence vulnerability and thus the pattern of brain injury typically seen during the preterm, term, or postnatal periods (Volpe, 2003; Graham et al., 2016). That said, determining the time of onset of brain injury in CP can be difficult to pinpoint. Here, we discuss brain injury among infants based on a preterm (<37 weeks gestation) versus term birth and specify the time of injury when reported (**Table 1**).

Brain Injury in Preterm Infants

Incidence and Risk Factors in Preterm Infants

Preterm birth is associated with approximately one-third of all CP cases (Oskoui et al., 2013) and approximately 30% of dyskinetic CP (Himmelmann et al., 2009). Brain injury among preterm

TABLE 1 | Mechanisms and patterns of brain injuries commonly identified in pre-term and term infants that contribute to CP.

Preterm infants	Term infants
Mechanisms	**Mechanisms**
Intraventricular hemorrhage	Hypoxia-ischemia
Hypoxia-ischemia	Inflammation
Inflammation	Infection
Infection	
Postnatal sepsis	Postnatal sepsis
Postnatal brain injury	Postnatal brain injury
Postnatal bilirubin toxicity	
Patterns of injury	**Patterns of injury**
Periventricular white mater lesions	Border zone (watershed) white matter injury
Cystic periventricular leukomalacia	Combination deep gray matter and white matter injury
Non-cystic periventricular leukomalacia	Cystic encephalomalacia
Injury to thalamocortical sensory fibers	Focal infarcts
Cortical and deep gray matter lesions	Cerebellar injury
Reduction in brain volumes	Brain malformations
Cerebellar injury	
Brain malformations	

infants can occur in the prenatal, perinatal, or postnatal period. The timing of the injury and the developmental stage of the brain influences the type of deficit. For example, damage to the brain during the late second trimester, in which the vulnerable process of regional WM myelination of motor tracts occurs, results in lasting motor dysfunction. Preterm birth in instances of PVL was found by Serdaroglu et al. (2004) to correlate significantly with spasticity.

Preterm infants have an increased risk of prenatal hypoxia-ischemia, prenatal and postnatal intraventricular hemorrhage, and PVL, and thus, an increased risk for CP. Complications experienced by preterm infants such as sepsis and necrotizing enterocolitis also increase the risk of CP (Mallard et al., 2013). Indeed, VLBW preterm infants ($\leq$1500 g at birth, $\leq$32 weeks) who suffer relatively low levels of neonatal inflammation (based on serum levels of C-reactive protein) during the first 2 weeks of life, have a higher risk of neurodevelopmental impairment at 18–22 months (Rose et al., 2016), and neonatal infection has been shown to increase VLBW infants' risk for WM abnormalities that lead to neurodevelopmental impairment (Rose et al., 2014; Rand et al., 2016). Prenatal brain lesions or cerebral infarction can arise from thrombosis due to inflammation and low blood flow in the placenta, brain, or other organs (Nelson and Blair, 2015).

Pregnancy complications are common in preterm birth (42% of cases, $n = 92{,}320$) and often contribute to a diagnosis of CP. Such complications include chorioamnionitis (11.2% absolute risk of CP), cervical conization (9.3%), placental abruption (8.7%), placenta previa (8.3%), congenital malformation (8.3%), prolonged rupture of membranes (7.5%), intrauterine growth restriction (7.1%), unspecified bleeding (6.8%), multiple births (5.7%), and pre-eclampsia (3.7%) (Trønnes et al., 2014). Further, maternal infections during pregnancy (excluding the common cold, coughs, etc.) have been reported in 29.6% (118 of 400) of cases of CP (Bax et al., 2006). Specifically, 19.2% of the mothers reported a urinary tract infection during pregnancy and 15.5% of women reported taking antibiotics during pregnancy. Twins have a greater risk of CP compared with singletons, especially if the pair have growth discordance (Scher et al., 2002). In addition, the *in utero* death of one twin leaves the surviving infant at a tenfold increased risk for CP, as dispersed intravascular coagulation and emboli in the vascular anastomoses of the twin placenta likely contribute to prenatal cerebral injury in the surviving twin (Scher et al., 2002; Nelson and Blair, 2015). Marked fetal growth restriction with presence of major birth defects is also associated with an increased risk of CP (Decouflé et al., 2001; Blair and Nelson, 2015). In addition, sex differences in neurodevelopment have been identified: the incidence of moderate-to-severe CP was found by Hintz et al. (2015) to be 50% higher in males (10.7%) than in females (7.3%) in extremely low-birthweight ($<$1000 g) preterm infants. They found no measurable risk factors or events, including a diagnosis of intraventricular hemorrhage on ultrasound, that explained the sex differences in neurodevelopmental outcomes. Findings indicate a distinct disadvantage in male infants for developing CP that is exacerbated in the preterm population.

Mechanisms of Injury in Preterm Infants

The regions of the brain adjacent to the lateral ventricles are especially susceptible to hypoxia-ischemia, i.e., insufficient blood flow combined with reduced concentration of oxygen in arterial blood, during prenatal development. In the preterm brain, the intrinsic architecture of the arterial border culminates in end zones that lie within the WM. This physiologic propensity to develop ischemia is further perturbed by impaired regulation of cerebral blood flow and metabolic needs during development (Khwaja and Volpe, 2008). Oligodendrocytes in the periventricular WM actively proliferate and myelinate during the third trimester (27–40 weeks gestation), and their high metabolic demand renders them vulnerable in preterm infants (Raybaud, 1983; Talos et al., 2006).

The increased risk for infection/inflammation (including ischemia-induced inflammation) during fetal development also contributes to the mechanism of injury in PVL. Upregulation of pro-inflammatory cytokines and activation of microglia within immature WM results in damage to the vulnerable premyelinating oligodendrocytes. This cell-specific damage results in WM hypo-myelination, and necrotic microscopic lesions lead to proliferation of glial cells in response to injury, a common finding in non-cystic PVL and among preterm children with CP (Graham et al., 2016). Mallard et al. (2013) suggested that the inflammation-induced opening of connexin hemichannels plays a pivotal role in initiating a cycle of excessive ATP release, over-activation of purinergic receptors on microglia and astrocytes, and subsequent brain damage.

After initial injury by hypoxia-ischemia and infection/inflammation, excitotoxicity and free radical attack by reactive oxygen and nitrogen species are the main downstream mechanisms of injury in PVL. Current evidence supports that oligodendroglial development is susceptible to oxidative attack within a maturation-dependent window of vulnerability. This window of vulnerability is due mainly to delayed development of antioxidant enzymes and the acquisition of iron for oligodendrocyte differentiation. Human brain studies have shown a delay in the development of superoxide dismutase (antioxidant) enzymes, e.g., manganese superoxide dismutase, copper/zinc superoxide dismutase, and catalase (Folkerth et al., 2004). Further, observations show that developing WM uses iron both for oligodendrocyte differentiation (Connor and Menzies, 1996) and to convert hydrogen peroxide to its hydroxyl radical, thereby resulting in the increased free iron levels in the cerebrospinal fluid of children with posthemorrhagic ventricular dilation (Savman et al., 2001). Excitotoxicity likely leads to injury to premyelinating oligodendrocytes by promoting Ca^{2+} influx and generation of reactive oxygen and nitrogen species. Glutamate is capable of inducing maturation-dependent death of premyelinating oligodendrocytes by receptor-mediated mechanisms *in vivo* (Khwaja and Volpe, 2008). Premyelinating oligodendrocytes contain glutamate receptors that, when excessively activated, lead to cell injury. The excess glutamate comes from oligodendrocytes that express AMPA/kainate-type glutamate receptors and NMDA receptors, the over-activation of which results in cell death (Káradóttir and Attwell, 2007; Khwaja and Volpe, 2008). In addition, the AMPA/ kainate receptors have

been found to be upregulated in premyelinating oligodendrocytes rather than in mature oligodendrocytes (Rosenberg et al., 2003; Jensen, 2005).

Patterns of Injury in Preterm Infants

Patterns of brain injury on MRI among preterm children with CP who suffered hypoxia-ischemia revealed 51/104 (49%) had signs of PVL or signal abnormalities in the periventricular WM (Sie et al., 2000). Indeed, periventricular WM lesions are the most common injury among preterm children, followed by cortical and deep GM lesions (Hoon et al., 2009). **Figure 2** highlights the brain regions and WM tracts commonly affected in CP.

The WM tracts essential for motor function descend near the periventricular region through the posterior limbs of the internal capsule; therefore, periventricular WM injury may result in impaired motor function and a diagnosis of CP (**Figure 2**). The CST is the major WM tract responsible for voluntary movement. About 40% of its fibers originate from the primary motor cortex in the precentral gyrus; the other 60% originate in the supplementary motor area, the premotor cortex, the somatic sensory cortex, the parietal lobe, and the cingulate gyrus. These fibers descend through the corona radiata and posterior limb of the internal capsule to reach the brainstem, where 80% of the fibers decussate at the spinomedullary junction and continue their descent contralaterally as the lateral CST (Mtui et al., 2016, p. 169–178). Damage to developing WM in the CST is considered a major mechanism for motor dysfunction in preterm children with spastic CP (Roelants-van Rijn et al., 2001; Rose et al., 2007).

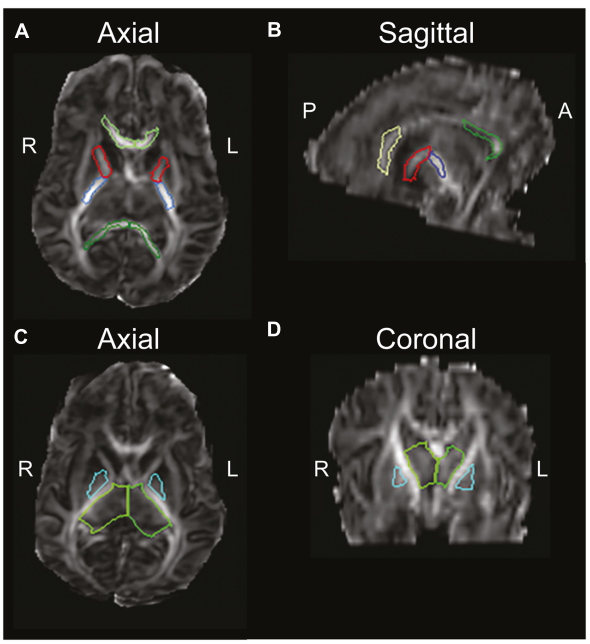

FIGURE 2 | Diffusion-weighted image of an infant, highlighting brain regions of interest commonly affected in CP, using the semi-automated JHU neonatal atlas (http://cmrm.med.jhmi.edu/cmrm/Data_neonate_atlas/atlas_neonate.htm). Axial view **(A)** and sagittal view **(B)** of the genu (light-green) and splenium (dark-green) of the corpus callosum, and anterior (red) and posterior (blue) limbs of the internal capsule. An axial view **(C)** and coronal view **(D)** highlight the thalamus (green) and globus pallidus (cyan). A, anterior; P, posterior; R, right; L, left. Figure reprinted with permission from Rose et al. (2015) Pediatric Research. http://www.nature.com/pr/journal/v78/n6/fig_tab/pr2015157f2.html

A growing body of evidence from DTI and tractography studies suggests that thalamocortical sensory fibers are also particularly vulnerable during the preterm period. The thalamocortical sensory fibers extend from the thalamus to the primary and secondary somatosensory areas, terminating in cortical layers of the lateral postcentral gyrus. Injury to these WM fibers can impair motor and somatosensory function in children with CP (Hoon et al., 2002, 2009; Rose et al., 2011; Tsao et al., 2015). Hoon et al. (2002, 2009) found that the severity of injury in the thalamocortical sensory pathways correlated to the severity of deficits in sensorimotor function in children with CP born preterm. Similarly, abnormalities assessed using DTI in preterm infants were seen in both CST and thalamocortical projections to the somatosensory cortex, and both tracts were associated with underlying pathology on conventional MRI (Lennartsson et al., 2015).

Cortical GM and BGTL may occur in preterm children as a result of hypoxia-ischemia. Injury to the GM has been linked most frequently to spastic quadriplegic CP and dyskinetic CP (Reid et al., 2014).

Preterm children may also have long-term reductions in regional brain volumes of the sensorimotor cortex, which are associated with poorer cognitive and visuomotor outcomes (Peterson et al., 2000).

Postnatal Brain Injury in Preterm Infants

Preterm children may be more susceptible to brain injury or insult during the postnatal period. Postnatal sepsis has been associated with non-cystic PVL in preterm children who later develop CP (Volpe, 2008). Male infants under 1 year of age, who were born weighing less than 1500 g, are at the greatest risk for developing CP following postnatal sepsis (Blair and Stanley, 1982). Other causes of postnatal brain injury resulting in CP include cerebrovascular accidents, head trauma, and epilepsy (Arens and Molteno, 1989; Australian Cerebral Palsy Register Report [ACP], 2013). Postnatal intraventricular hemorrhage among preterm children with CP can also result in cerebellar injury, which may contribute to diminished walking and verbal abilities, a higher incidence of epilepsy, and visual impairment (Kitai et al., 2015). Postnatal bilirubin toxicity is a complication among preterm infants that may be related to GM injury. The exposure to even moderate levels of unconjugated bilirubin may cause damage to the developing central nervous system, specifically the basal ganglia and cerebellum. Brain lesions identified on MRI following extreme hyperbilirubinemia have been linked to dyskinetic CP, though this is rare in developed countries (Rose et al., 2014) as a result of effective monitoring and treatment for hyperbilirubinemia in preterm infants.

Brain Injury in Term-Born Infants

Incidence and Risk Factors in Term-Born Infants

The majority of CP cases (60%) are acquired in the term-born population during the perinatal period (Australian Cerebral Palsy

Register Report [ACP], 2013). Approximately 70% of dyskinetic CP cases are linked to insults acquired in the term-born infant (Himmelmann et al., 2009). The risk factors for CP among term-born infants in developed countries include: placental abnormalities, birth defects, low birthweight for gestational age, meconium aspiration, instrumental/emergency Cesarean delivery, neonatal seizures, respiratory distress syndrome, hypoglycemia, and neonatal infection (Review: McIntyre et al., 2013). Neonatal infections include chorioamnionitis (which has been associated with WM damage), neurotropic virus infection, cytomegalovirus infection, and maternal urinary tract infection (Ahlin et al., 2013). Infection-related factors have been shown to be independent risk factors for spastic hemiplegic CP, but not for spastic diplegia, tetraplegia, or dyskinetic CP in term-born infants (Ahlin et al., 2013). A recent review of 23 studies on perinatal risk factors of CP refutes birth asphyxia as a primary cause of CP (Ellenberg and Nelson, 2013).

Although perinatal ischemic stroke accounts for less than 5% of all term-born CP cases (Wu et al., 2011), it accounts for 30% of hemiplegic CP cases (Wu et al., 2006). Embolization from the placenta near the time of delivery, a period characterized by hypercoagulability, has been suggested as a cause of perinatal stroke. Larger vessels are more frequently involved, especially the left middle cerebral artery (Nelson and Blair, 2015) resulting in left-sided brain lesions, which correspond to right-sided motor deficits.

Mechanisms of Injury in Term-Born Infants

Neonatal encephalopathy due to presumed hypoxia-ischemia remains an important clinical problem in term-born infants, with placental pathology providing insight to the underlying mechanisms. Among term-born infants, an elevated nucleated red blood cell count in the placenta was significantly related to watershed (border zone) WM brain injury (Frank et al., 2016). A watershed (border zone) injury arises from prolonged, partial ischemia of the WM between two major arteries, commonly the anterior–middle and posterior–middle cerebral arteries. Further, infants with small infarcts or an elevated nucleated red blood cell count on placental pathology were less likely to develop BGTL injury following perinatal hypoxia-ischemia, and were more likely to have a favorable neurodevelopmental outcome. Frank et al. (2016) have posited that both small infarcts and elevated nucleated red blood cell counts, which reflect adverse intrauterine conditions, might be involved in a pathway to preconditioning resistance against acute brain injury, i.e., neuroprotective factors. The mechanisms linking infection and cerebral ischemia are still largely undetermined, but inflammation is thought to exacerbate the natural prothrombotic state present during normal pregnancy, and stimulates coagulation (Grau et al., 1995; Ahlin et al., 2013).

Patterns of Injury in Term-Born Infants

In a study of 173 term-born infants with neonatal encephalopathy, the pattern of brain injury on MRI revealed 45% of newborns had predominantly a watershed (border zone) pattern of WM injury, 25% had BGTL injury and 30% had normal MRI (Miller et al., 2005). The predominant region of injury was often accompanied by lesser damage to other regions. For example, 31% of newborns with the watershed (border zone) predominant pattern had some BGTL injury, and 45% of newborns with the BGTL predominant pattern had total brain injury. The BGTL predominant pattern was significantly associated with severe neonatal signs, encephalopathy, seizures, and severe motor and cognitive outcome at 30 months. Among term-born children with CP, Sie et al. (2000) found that nearly 20% had bilateral BGTL injury involving the putamen and thalamus. Among these children, one-third had additional globus pallidus lesions and about half had additional hippocampal lesions and WM abnormalities. These WM abnormalities were unique from that of PVL and varied from ventricular dilatation to diffuse and patchy mild WM signal changes. Brain malformations, such as congenital microcephaly, and GM lesions are more often seen in term-born children than preterm children with CP (Miller et al., 2005; Krägeloh-Mann and Horber, 2007).

Another pattern of injury present among term-born children with CP and hypoxic-ischemic injury is multicystic encephalopathy, which involves multiple large cystic cavities in the WM separated from each other by membranes and is associated with periventricular, subcortical, and cortical damage (Sie et al., 2000).

Focal vascular insults are seen predominantly in term-born children with hemiplegic CP, whereas malformations tend to be associated with ataxic, quadriplegic, and diplegic CP (Reid et al., 2014). Of these malformations, schizencephaly occurs more often in patients with spastic hemiplegia than in any other CP subtype (Kulak et al., 2011).

Postnatal Brain Injury in Term-Born Infants

Among 3135 individuals with CP born from 1993–2006, 5.6% of individuals acquired a brain injury due to a recognized event more than 28 days after birth, with the predominant cause listed as cerebrovascular accident (34.2%) (Australian Cerebral Palsy Register Report [ACP], 2013). The cerebrovascular accident was either spontaneous, associated with surgery, or due to complications of cardiac defects. Other causes of postnatal brain injury in term-born infants leading to CP include head trauma, cerebral infections, prolonged seizures, and respiratory arrest or anoxia (Blair and Stanley, 1982; Arens and Molteno, 1989). Approximately 7% of dyskinetic CP cases are linked to brain injuries incurred during the postnatal period (Kyllerman, 1982).

NEUROMUSCULAR DEFICITS OF CEREBRAL PALSY

Neuromuscular deficits differ among spastic, dyskinetic, and ataxic CP and involve abnormal motor drive, muscle tone, motor patterns, and coordination caused by the original brain injury. In addition, subsequent sensorimotor and musculoskeletal changes result from chronic abnormal muscle activation, biomechanical imbalance around joints, neglect, and/or disuse. These factors, combined with rapid limb growth and increasing body weight

in children, contribute to gait abnormalities in CP (Meyns et al., 2016a).

Neuromuscular Deficits of Spastic CP

In spastic CP, neurological injury to the CST results in four interrelated neuromuscular deficits: muscle weakness, shortened muscle-tendon unit, spastic and passive resistance to stretch, and impaired SMC. These deficits arise from brain injury and subsequent changes in the motor unit, muscle growth, and muscle fiber composition. Further involvement of sensory-motor regions can impair proprioception and motor function (Hoon et al., 2009). Together, these neuromuscular deficits result in the gait abnormalities commonly seen in children with spastic CP.

The motor unit is the functional unit of the motor system, consisting of a single motor neuron, the neuromuscular junction, and the muscle fibers innervated by the motor neuron. In the gastrocnemius, for example, a motor unit consists of a single motor neuron with approximately 2000 associated muscle fibers, whereas smaller muscles in the hand that are responsible for fine motor control have a much smaller muscle fiber-to-motor neuron ratio. Rose and McGill (2005) found reduced neuromuscular activation and motor-unit firing rates in the medial gastrocnemius and tibialis anterior in spastic CP. The altered neural input to muscle has been associated with altered muscle growth, fiber type and size variability, sarcomere length, as well as altered collagen, fat, and extracellular matrix composition. These changes in skeletal muscle morphology contribute to functional changes in muscle strength, the length of the muscle-tendon unit, and the reflexive and passive resistance to stretch.

Muscle fiber development and growth rely on a number of neuronal, nutritional, and hormonal factors, as well as initial and repeating patterns of muscle use (Kimball and Jefferson, 2010; Braun and Gautel, 2011; Gundersen, 2011). Muscle growth increases rapidly during the prenatal and neonatal periods. For example, the sartorius muscle fibers double in diameter between mid-gestation and term (Moore et al., 1971), and accelerated growth in overall muscle fiber diameter has been noted between 35 weeks of gestation and term (Schloon et al., 1979). Thus, preterm delivery may interfere with early muscle growth, and compromised nutritional status in the preterm infant likely contributes to poor skeletal muscle growth (Thorn et al., 2009). It has been shown that muscle size is reduced in spastic CP (Barber et al., 2011), and muscle volume is especially reduced in the gastrocnemius and semitendinosus, both of which are critical for gait (Smith et al., 2011). Recent work by Dayanidhi and Lieber (2014) suggests that satellite cells also play an important role in muscle growth. Muscle biopsies from children with CP had 60–70% fewer satellite cells when compared to that of age-matched, TD children, which may contribute to muscle contracture in CP.

Muscle biopsy reveals an increased proportion of type-1 muscle fibers and an increased variability in muscle fiber diameter in the muscles affected by spastic CP, likely as a result of prolonged low-frequency motor unit firing rates (Rose et al., 1994). Complex changes occur at both the level of the fiber and the gross muscle, including an altered transcriptional profile, increased sarcomere length, stiffer extracellular matrix, and reduced overall muscle length, all of which contribute to muscle contracture (Smith et al., 2011). Other changes in spastic muscle in CP include increased collagen (Booth et al., 2001) and fat content (Johnson et al., 2009). Although spastic muscle contains a larger amount of extracellular matrix material compared with normal muscle, the quality of the extracellular matrix is much lower, contributing to the overall increased stiffness (Lieber et al., 2003).

Weakness in Spastic CP

Children with spastic CP suffer from significant weakness that contributes to abnormal posture and movement (Brown et al., 1991; Damiano et al., 1995; Rose and McGill, 2005; Barber et al., 2012; Noble et al., 2014). Studies suggest that the loss of excitatory motor signals descending in the CST results in reduced muscle activation and reduced muscle size, which is aggravated further by pathological changes in the elasticity of the muscle (Brown et al., 1991; Wiley and Damiano, 1998; Engsberg et al., 2000). MVC of the quadriceps, plantar flexors, and dorsiflexors are significantly reduced in CP (Damiano et al., 2002; Elder et al., 2003; Rose and McGill, 2005; Stackhouse et al., 2005; Barber et al., 2012). Barber et al. (2012) found a 33% lower ankle plantarflexion torque in children with spastic CP compared to their TD peers. This reduced ankle plantarflexion torque was partially explained by 37% smaller medial gastrocnemius muscle and 4% greater antagonistic co-contraction.

It has been posited that individuals with spastic CP do not develop sufficient tension frequently enough to encourage normal muscular growth (Noble et al., 2014). Noble et al. (2014) found that the medial and lateral gastrocnemius, soleus, tibialis anterior, rectus femoris, semimembranosus, and semitendinosus of patients with CP had reduced volumes compared to TD children, even when adjusted for body mass. This lack of growth may be mediated through reduced muscle and neurotrophic factors that are released in response to neuronal activation, acetylcholine release, and contraction (Gough and Shortland, 2012), further contributing to weakness. Affected muscles in spastic CP have substantially reduced neuromuscular activation and strength (Damiano et al., 2001; Rose and McGill, 2005; Stackhouse et al., 2005) and an inability to sufficiently recruit and drive motor-units at higher firing rates (Rose and McGill, 2005). Further, musculoskeletal manifestations progress as skeletal growth out-paces muscle growth, leading to reduced muscle volumes associated with weakness (Noble et al., 2014). Muscle endurance is also reduced in CP compared to TD individuals; specifically, adolescents with CP have a reduced capacity to endure activities at similar relative loads compared with TD adolescents (Eken et al., 2014).

Common surgical procedures for CP negatively affect muscle strength. For example, selective dorsal rhizotomy reduces antigravity support that may have been provided by spasticity (Giuliani, 1991), surgical muscle-lengthening or tendon transfer decrease muscle force production, intrathecal baclofen directly weakens the muscle to reduce spasticity (Hallett, 2000), and orthoses or serial casting may exacerbate weakness due to immobilization. Similarly, BoNT-A weakens the injected muscles

in order to reduce spasticity (Hallett, 2000). However, a more recent study on the effects of BoNT-A suggests no decrease in long-term muscle strength at 6 weeks or 6 months after a one-time injection of BoNT-A in children with CP (Eek and Himmelmann, 2016).

While the neural correlates of muscle weakness are not well studied, Meyns et al. (2016b) recently found a correlation between asymmetry in strength and asymmetry in the CST ADC calculated from DTI ($r = 0.639$, $p < 0.034$) of the segment of the CST that runs through the posterior limb of the internal capsule (CST_{PLIC}). Thus, greater asymmetry in strength was associated with a greater ADC asymmetry of the CST_{PLIC}. Further research is needed to clarify the brain structure-function relations underlying weakness in spastic CP to develop effective treatments.

Short Muscle-Tendon Unit in Spastic CP

Impaired muscle growth and muscle fiber changes result in a shortened muscle-tendon unit in the muscles affected by spastic CP. The failure of muscle growth to keep pace with bone growth is most evident in the bi-articular muscles, e.g., the gastrocnemius, hamstrings, and rectus femoris, and contributes to joint contractures and gait abnormalities such as toe-walking and flexed-knee gait.

Among TD children ages 5–12 years, the medial gastrocnemius has been shown to demonstrate 20% longitudinal growth compared to 80% cross-sectional growth of muscle fibers (Benard et al., 2011). In the CP population, while muscles on the affected side of children with hemiplegic CP were smaller compared to the unaffected side, the altered morphology was not due to a decrease in fascicle length, i.e., longitudinal growth, but rather a lack of cross-sectional growth (Barrett and Lichtwark, 2010). Similarly, Shortland et al. (2001) concluded that a smaller medial gastrocnemius in ambulatory children with spastic diplegia was not due to reduced muscle fiber length, but rather to shortened aponeuroses of the pennate muscle via reduced muscle fiber cross-sectional diameter. Shortened muscle tendon units in spastic CP result in part from reduced muscle growth. Barber et al. (2016) found that normalized medial gastrocnemius muscle growth rate was significantly less in children with unilateral CP compared to children with bilateral CP and TD children. Treatment with muscle growth factors has not been studied to date, however, it has potential to increase muscle size and length and warrants investigation as a treatment for CP. Smith et al. (2009) assessed the transcriptional profile in biopsies of spastic muscle in six children with CP and compared it with that of two typically developing children. They noted competing upregulation of both insulin-like growth factor 1 and myostatin, as well as an aberrant regulation of excitation-contraction coupling genes. More research is needed to better characterize the adaptations occurring at a molecular level, but these studies point to growth factors as an avenue of research for novel therapies.

The short muscle-tendon unit also likely contributes to weakness. The active force generated by muscle is a function of the number of cross-bridges formed, which depends on the extent of myofilamentary overlap. Muscle force is maximal at intermediate muscle lengths with optimal myofilament overlap and declines at shorter and longer relative lengths (Gordon et al., 1966). Thus, short muscles with lengthened sarcomeres, as has been found in spastic muscle in CP (Lieber et al., 2004), may result in an inefficient overlap of myofilaments, thereby contributing to weakness. Research on the neural correlates of short muscle-tendon unit is needed, considering the impact of reduced descending excitatory signals on muscle growth, muscle-to-bone growth rate discrepancy, and muscle fiber diameter.

Spasticity in Spastic CP

Resistance to muscle stretch in children with spastic CP is primarily due to two factors: neural-mediated reflex stiffness (muscle spasticity) and passive muscle stiffness. Spasticity and passive resistance to muscle stretch particularly influence bi-articular muscles, such as the rectus femoris, hamstrings, and gastrocnemius, which require greater excursion across two joints.

Spasticity has been defined as "a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex" (Mayer, 1997). Loss of descending inhibition of the stretch reflex pathway to affected muscles in spastic CP may result in increased sensitivity to stretch (Rose and McGill, 1998).

In addition to the velocity-dependent sensitivity to stretch (Sanger et al., 2003), spasticity may also be position-dependent. Wu et al. (2010) found that evaluating patients at different velocities and positions helped to distinguish passive stiffness from spasticity. The delayed catch angle at higher velocities may be due to position change, as the joint is moved into a stiffer position.

Although muscle spasticity is a primary symptom of spastic CP, objective quantification has been challenging (Bar-On et al., 2014b). Recent data on the profile of imposed muscle accelerations, including the muscle length–velocity relationship, hold promise for quantifying spasticity. Bar-On et al. (2014c) quantified integrated biomechanical (joint position and torque) and electrophysiological (surface EMG) signals of manually performed passive stretches on the medial hamstrings and gastrocnemius and found that measurement reliability was moderately high for both muscles, and spasticity parameters were significantly higher in children with spastic CP than in TD children. Similarly, biomechanical parameters quantifying the neural and non-neural contributions to ankle joint torque were measured during manually applied passive stretches to the gastroc-soleus in children with spastic CP, and the parameters based on modeling of passive muscle stiffness and viscosity were able to detect a significant decrease in spasticity ($p = 0.012$) following BoNT-A in 53 children with spastic CP (Bar-On et al., 2014a). This type of musculoskeletal modeling combined with spasticity measurement may allow for individually tailored spasticity treatments. Further, investigation of fast and slow passive rotations imposed during manual and motorized assessments may yield greater insights into the development of movement profiles to better mimic spasticity imposed during functional tasks such as walking (Sloot et al., 2016).

Increased passive muscle stiffness has been demonstrated in spastic CP. Lee et al. (2016) used shear wave elastography to measure muscle stiffness in eight children with hemiplegic CP and found that the more-affected limb had greater muscle stiffness than the less-affected limb. The increased passive mechanical stiffness accounted for nearly all of the measurable increase in joint stiffness (Lieber et al., 2004), suggesting that spastic muscles have an altered resting sarcomere length and altered cellular elastic modulus. Smith et al. (2011) also found that the increased stiffness of hamstring contractures in children with spastic CP compared to age-matched, TD children was likely due to increased stiffness of the extracellular matrix and increased *in vivo* sarcomere length.

Neural correlates of spasticity are emerging. Serdaroglu et al. (2004) found PVL to be associated with spasticity. Specifically, spasticity was found in 54 of 69 participants with body PVL and in 7 of 20 without body PVL. Body PVL was defined as PVL injury in the WM adjacent to the middle region of the lateral ventricle. In addition, lower volume of the total corpus callosum as well as lower volume in the posterior aspect of the central corpus callosum correlated to increased incidence of spasticity (Serdaroglu et al., 2004). Meyns et al. (2016b) recently found a correlation between asymmetry in spasticity and asymmetry in the CST ADC calculated from DTI ($r = 0.608$, $p < 0.048$). Further study will clarify neural correlates and the mechanism underlying spastic and passive resistance in muscle stretch and guide more effective treatment.

Impaired Selective Motor Control in Spastic CP

Impaired SMC is defined as an "impaired ability to isolate the activation of muscles in a selected pattern in response to demands of a voluntary posture or movement" (Sanger et al., 2006). Impaired SMC occurs when flexor or extensor synergies interfere with isolated joint movements, resulting in impaired functional movements, such as gait (Rose, 2009; Cahill-Rowley and Rose, 2014). Children with mild to severe spastic CP consistently demonstrate co-activation of the quadriceps and gastrocnemius on EMG, distinguishing spastic CP from idiopathic toe walking (Rose et al., 1999; Policy et al., 2001). Individuals with CP demonstrate reduced complexity of neuromuscular control during gait compared with unimpaired individuals, as determined by the calculation of the muscle synergies during gait (Steele et al., 2015).

Recent studies suggest that spared "extrapyramidal" motor tracts, such as the rubrospinal and reticulospinal tracts, may provide imperfect compensation in recovering motor function. The rubrospinal tract originates in the red nucleus, crosses to the other side of the midbrain, and enters the spinal cord adjacent to the lateral CST. It is thought to mediate flexion and extension movements (Mtui et al., 2016, p. 324–337) and is more developed in infants than TD children and adults. However, rubrospinal tract WM development assessed using DTI was reported to be increased in acute and chronic stroke, yielding characteristic impaired SMC movement patterns post-CST injury (Yeo and Jang, 2010; Rüber et al., 2012). Cortical mapping with DTI in stroke patients suggests that a loss of SMC is also associated with increased overlap of joint representation in the sensorimotor cortices (Yao et al., 2009). The reticulospinal tract originates in the reticular formation in the midbrain and descends to act on the motor neurons supplying the trunk and proximal limb flexors and extensors (Mtui et al., 2016, p. 324–337). It is also thought to modulate pain and influence muscle tone. Current research suggests that infants rely on both the reticulospinal tract and CST for movements, while adults rely primarily on the CST (Forssberg, 1985; Yamaguchi and Goto, 2006). Loss of efferent motor signals descending in the CST provides both excitatory and inhibitory input to subcortical nuclei. Therefore, disruption of these signals may reduce normal inhibition that contributes to SMC. Further studies are needed to characterize development and function of the rubrospinal and reticulospinal tracts, as well as their response to CST injury in spastic CP and their potential for plasticity for compensatory signal transduction and motor function.

Impaired SMC has been assessed using the SCALE, an observation-based measure for children with spastic CP (Fowler et al., 2009). The SCALE has been proven to reliably and systematically quantify the SMC of various joints involved in children with CP. In addition, SCALE scores for children with spastic CP correlate with the GMFCS (Fowler et al., 2009). Further study will clarify neural correlates and the mechanism underlying impaired SMC in spastic CP and guide more effective treatment (Rose, 2009).

Neuromuscular Deficits in Dyskinetic CP

Dyskinetic CP is characterized by involuntary hyperkinetic or repetitive dystonic limb movements that impair function (Sanger, 2006). More specifically, these movements are dystonic or choreoathetotic in nature: involuntary, uncontrolled, recurring, and occasionally stereotyped, in which the primitive reflex patterns predominate and muscle tone fluctuates (Sankar and Mundkur, 2005; Aravamuthan and Waugh, 2016). Dystonia is a movement disorder in which involuntary sustained or intermittent muscle contractions causes twisting and repetitive movements, abnormal postures, or both (Sanger et al., 2003), and choreoathetosis presents as a mix of chorea and athetosis. Chorea is defined as an ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments, while athetosis is a slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture (Sanger et al., 2010).

Sanger (2006) found that children with dyskinetic CP had a significantly reduced signal-to-noise ratio compared with TD children, indicating increased movement variability. This finding is consistent with the hypothesis that inadequate removal of noisy signals causes the movement disorder in dyskinetic CP (Sanger, 2006). Most measures of dyskinetic CP have focused solely on dystonia, ignoring choreoathetotic movements. However, Monbaliu et al. (2016) created a scale to measure both dystonia and choreoathetosis in dyskinetic CP, the "Dyskinetic Impairment Scale." The Dyskinetic Impairment Scale can assess separate movement subscores and has been shown to have high inter-rater reliability (Monbaliu et al., 2016). Further study of neuromuscular deficits in dyskinetic CP will clarify their impact on gait and guide more effective treatment.

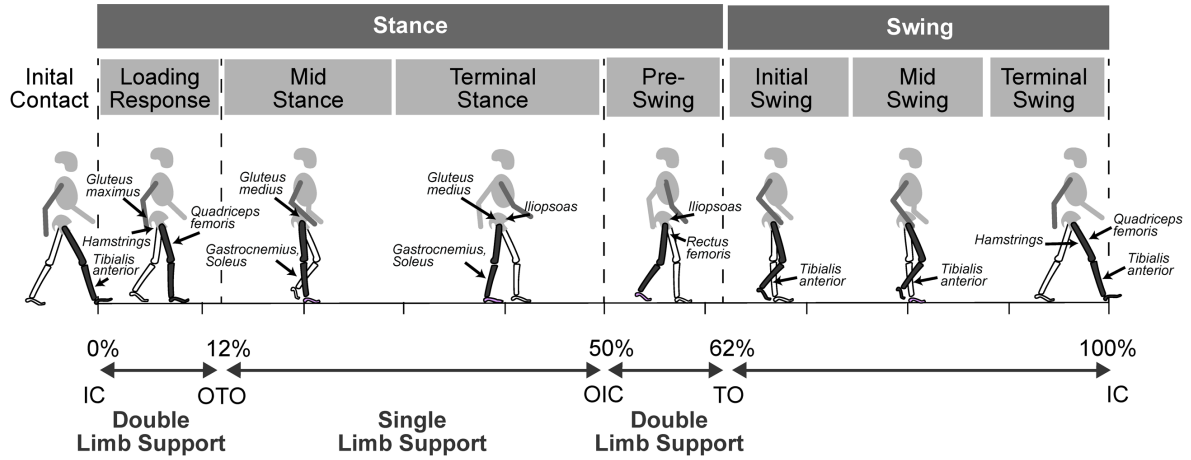

FIGURE 3 | The gait cycle showing muscles that are influenced by neuromuscular deficits and contribute to gait abnormalities in spastic CP, in relation to phases of the gait cycle. IC, initial contact; OTO, opposite toe-off; OIC, opposite foot initial contact; TO, toe-off.

Neuromuscular Deficits in Ataxic CP

Ataxic CP is characterized by hypotonia, impaired limb coordination, balance, and stability (Hughes and Newton, 1992; Schnekenberg et al., 2015; Graham et al., 2016). Impaired balance is well recognized in ataxic CP, however, the scope of other neuromuscular deficits is not well studied. Postural balance deficits assessed on center-of-pressure force plate measures were identified in 8/23 children diagnosed with spastic diplegic CP and gait abnormalities (Rose et al., 2002), suggesting mixed forms of CP. However, the degree to which primary cerebellar balance deficits versus biomechanical factors, such as foot contact area and base of support impair balance in children with CP is not well studied. The vermis of the cerebellum (**Figure 1**) is thought to mediate posture and balance, and it is in this region that the "extrapyramidal" vestibulospinal tract originates. The vestibulospinal tract is comprised of the medial and lateral vestibulospinal tracts. The lateral vestibulospinal tract innervates paravertebral extensors and proximal limb extensors which function to counteract the force of gravity and control posture and balance (Mtui et al., 2016 p. 324–337). Recent studies of treatment to improve balance in children with spastic and ataxic CP are promising and include the application of cerebellar transcranial direct current stimulation, in combination with treadmill training (Lazzari et al., 2016).

INFLUENCE OF NEUROMUSCULAR DEFICITS ON GAIT IN CEREBRAL PALSY: TREATMENT IMPLICATIONS

Neuromuscular deficits of spastic, dyskinetic, and ataxic CP differ and therefore influence gait in different ways. Neuromuscular deficits include abnormal motor drive, muscle tone, motor patterns, coordination, and sensorimotor impairments caused by the original brain injury. Subsequent sensorimotor and musculoskeletal changes also contribute to gait abnormalities in children with CP.

The Influence of Neuromuscular Deficits in Spastic CP

The neuromuscular deficits of spastic CP, including muscle weakness, short muscle-tendon length, spasticity, and impaired SMC influence gait in different but predictable ways and contribute to common gait abnormalities such as plantar-flexed gait, flexed-knee gait, or a stiff-knee gait. Plantar-flexed gait includes both 'drop-foot' gait where weakness of the tibialis anterior prevents adequate dorsiflexion in swing phase, as well as equinus gait which arises from short and/or spastic plantar-flexors and impacts both stance and swing phases of the gait (**Figure 3** and **Table 2**). In both cases there is typically forefoot initial contact and disruption of the normal heel-toe progression of gait. The plantarflexed position of the ankle causes an early and 'double bump' plantarflexion moment that reduces forward momentum. Additionally, the plantarflexed position results in reduced foot contact area in stance that can impair balance.

Flexed-knee gait can arise from short and spastic hip and knee flexors, as well as from weak hip extensors and ankle plantar flexors. Impaired SMC also contributes to flexed-knee gait and results in diminished knee extension during the terminal-swing phase of gait (Rha et al., 2016) (**Figure 3** and **Table 2**). Flexed-knee gait causes abnormal mechanical loads and muscle forces across the hip and knee during stance. In young children, that can result in bone deformities and a permanently flexed, rotated gait later in life (Bell et al., 2002; Steele et al., 2012). In the absence of full hip extension during early gait, the immature 30 degree femoral neck anteversion does not reduce to the normal 15 degrees of anteversion seen in TD children, resulting in internal hip rotation in children with CP (Shefelbine and Carter, 2004).

TABLE 2 | Neuromuscular deficits and their contributions to different gait abnormalities in spastic cerebral palsy, in terms of the muscles affected and the timing during the gait cycle.

Neuromuscular deficit	Muscle groups	Gait cycle event	Gait abnormality
Weakness	Ankle Dorsiflexors: *tibialis anterior*	IC, Swing	Foot-slap, Drop-foot
	Ankle Plantar flexors: *gastrocnemius, soleus*	Single limb support	Uncontrolled forward tibial rotation → increased hip and knee flexion
			Poor push-off mechanics→ reduced knee flexion in swing
	Knee Extensors: *quadriceps femoris*	IC – Midstance	Increased knee flexion
	Hip Extensors: *gluteus maximus, hamstrings*	IC – Midstance	Increased hip flexion
	Hip Flexors: *iliopsoas*	Preswing	Reduced peak knee flexion in swing
	Hip Abductors: *gluteus medius*	Single limb stance	Contralateral pelvic drop and ipsilateral trunk lean
Short Muscle-tendon	Ankle: *gastrocnemius, soleus*	Throughout gait cycle	Increased ankle plantar flexion
	posterior tibialis	Throughout gait cycle	Ankle equinovarus
	Knee: *hamstrings*	Stance, Terminal swing	Increased knee flexion
	Hip: *iliopsoas*	Stance	Increased hip flexion
	adductors	Throughout gait cycle	Adducted, scissoring gait
	gluteus medius	Throughout gait cycle	Internally rotated hip and foot progression angle
Spasticity	Ankle: *gastrocnemius, soleus*	Stance, Terminal swing	Increased ankle plantar flexion
	posterior tibialis	Throughout gait cycle	Ankle equinovarus
	Knee: *hamstrings*	Single limb support	Increased knee flexion
	Hip: *iliopsoas*	Pre-swing	Reduced hip extension
	rectus femoris	Terminal stance, Pre-Initial swing	Reduced hip extension, Reduced knee flexion in swing
	adductors	Throughout gait cycle	Adducted, scissoring gait
	gluteus medius	Throughout gait cycle	Internally rotated hip and foot progression angle
Impaired SMC	Ankle: *plantar flexor coupling with knee extensors*	IC, Terminal swing	Forefoot IC
	Ankle: *plantar flexor coupling with hip and knee extensors*	Midstance	Plantar flexed equinus gait → knee hyperextension in stance
	Knee: *knee flexor coupling with hip flexors*	Terminal swing	Flexed knee at IC
	Hip: *slow transition from terminal stance hip and knee extension to hip and knee flexion in initial swing*	Terminal stance – Midswing	Reduced hip and knee flexion in early swing → reduced foot clearance

IC, initial contact.

Further compounding the problem, the internal rotation moment arms of hip muscles, such as the anterior gluteus medius, increase with flexed knee gait (Delp et al., 1999).

Stiff-knee gait arises from spastic knee extensors which impair pre-swing mechanics that limit knee flexion in early swing. In addition, hip flexor weakness impairs hip and knee flexion in early swing, and impaired SMC slows the transition from the stance phase hip and knee extension to the swing phase hip and knee flexion. The neuromuscular deficits contributing to stiff-knee gait primarily impact pre-swing through mid-swing phases of gait in spastic CP (**Figure 3** and **Table 2**). Here, we explore the influence of neuromuscular deficits on gait in the three types of CP with a focus on spastic CP.

The Influence of Weakness on Gait in Spastic CP: Treatment Considerations

The impact of weakness in spastic CP most notably affects ankle dorsiflexion in swing phase and hip and knee extension in stance phase. Thus, weakness affects all phases of the gait cycle (**Figure 3** and **Table 2**). Weak ankle dorsiflexors result in excessive ankle plantar flexion in swing and poor foot clearance with compensatory motion such as hip circumduction to clear the foot. Weak ankle dorsiflexors also cause excessive plantar flexion at initial contact, disrupting the normal heel-toe progression of gait. Weak plantar flexors fail to restrain tibial forward rotation over the foot in mid stance, increasing hip and knee flexion in stance. Furthermore, failure to stabilize the ankle during heel rise reduces the normal ankle plantar-flexion

moment in terminal stance and can decrease peak knee flexion in swing. Weak hip and knee extensors contribute to flexed hip and knee postures during the stance phase of gait. Weak hip flexors can contribute to reduced peak knee flexion in swing. Weak hip abductors cause contralateral pelvic drop and increase ipsilateral trunk sway, shifting the body's center of mass closer to the hips' axis of rotation and thereby reducing the muscular demand on the hip abductors.

Steele et al. (2012) found children walking in flexed hip and knee gait had less passive skeletal support of body weight and utilize substantially higher muscle forces to walk than unimpaired individuals. Flexed hip and knee gait relied on the same muscles as unimpaired gait to accelerate the mass center upward, including the soleus, vasti, gastrocnemius, gluteus medius, rectus femoris, and gluteus maximus. However, these muscles were active throughout single-limb stance during flexed-knee gait in order to resist gravity, in contrast to the modulation of muscle forces seen during single-limb stance of unimpaired gait (Steele et al., 2012). Further, muscle weakness has been shown to have a negative effect on the Gait Profile Score, a measure of overall gait function (Schweizer et al., 2014).

Treatment with strength training targeting weak muscles has been found to be effective at improving gait, although further studies of targeted intensive strength training are needed. Evidence is accumulating around strength training as a means of improving mobility in CP without adverse effects (Dodd et al., 2002; Scholtes et al., 2012). To elucidate interventions that improve and maintain strength, i.e., force-generating capacity, and endurance, Fowler et al. (2010) studied 62 ambulatory children with spastic diplegic CP who underwent 30 intensive stationary cycling episodes over 12 weeks. They saw improvements in locomotor endurance, gross motor function, and some measures of strength in the cycling group but not the control group (Fowler et al., 2010). A review by Steele et al. (2012) found that individuals without hamstring spasticity had greater improvement in knee extension after strength training. In a study conducted by Scholtes et al. (2012), there was an improvement in muscle strength, but not mobility or spasticity, directly after training among 51 children with spastic CP who received 12 weeks of functional training; however, a detraining effect was observed 6 weeks after training ended. Jung et al. (2013) found that ankle plantarflexor strengthening improved strength and spatiotemporal gait parameters of six children with spastic CP. These subjects performed a heel raise exercise, which included progressive resistance ankle plantar flexor training for 6 weeks. In patients for whom weakness is a major contributor to gait deficits, strength training (as measured by force-generating capacity) in the extensor muscle groups may improve walking function and alignment, though further studies are needed to confirm kinematic and functional improvements (Damiano et al., 2010). Repetitive functional electrical stimulation to induce muscle strengthening has shown evidence of use-dependent muscle growth in children with CP with foot drop, though lasting improvements in voluntary ankle control have not been demonstrated (Damiano et al., 2013). More research is needed to develop the most effective treatment strategies for lasting improvements in strength that translate to improved gait function.

The Influence of Short Muscle-Tendon Units on Gait in Spastic CP: Treatment Considerations

Short muscle-tendon units of the hip and knee flexors and ankle plantar-flexors, particularly the bi-articular muscles, contribute to joint contracture and abnormal joint mechanics, and represent a primary cause of gait abnormalities in spastic CP (**Figure 3** and **Table 2**). Short plantar flexor muscle-tendon unit contributes to excessive ankle plantarflexion in stance and swing, leading to toe-walking or 'equinus' gait which limits foot clearance in swing. Equinus may co-exist with ankle dorsiflexor weakness, further impairing normal ankle dorsiflexion in swing phase. Limited foot clearance in swing causes compensatory movements such as hip circumduction in swing to clear the foot. A shortened posterior tibialis can contribute to equinovarus gait, which includes plantarflexion, inversion, and adduction of the foot. In cases of moderate to severe spastic CP where there is both distal and proximal limb involvement, flexed-knee gait is a common debilitating gait abnormality that creates abnormal mechanics across the hip, knee, and ankle that can result in bone deformity and increased fatigue while walking. Short semitendinosus contributes to two-thirds of all cases of flexed-knee gait (Arnold et al., 2006) at both initial contact and during the single limb support phase of the gait cycle. Musculoskeletal models of hamstring length and lengthening velocity just prior to initial contact quantify the contribution of short hamstrings to flexed knee gait (Arnold et al., 2006) and guide treatment decisions. Rha et al. (2016) found that a short medial gastrocnemius correlated with increased knee flexion at initial contact, whereas a short semitendinosus correlated with increased knee flexion at both initial contact and single limb support. In more severe cases, proximal involvement of hip flexors, adductors, and internal rotators contribute to flexed, adducted, and internally rotated gait. Recently, Kalsi et al. (2016) found an increased lengthening of the medial gastrocnemius during stance phase of gait in children with unilateral spastic CP compared to TD subjects, suggesting greater muscle excursion demands during gait.

Treatments for shortened muscle-tendon units in spastic CP include tendon lengthening and serial casting, however, both contribute to muscle weakness. In contrast, treatments that promote strength and increase muscle fiber diameter may also increase muscle length given the pennate angle of muscle fascicles (Shortland et al., 2001; Gough and Shortland, 2012). Treatment with muscle growth factors has not been well studied to date, however, it has potential to increase muscle size and length and warrants investigation as a treatment for CP. Work by Smith et al. (2009) and Barber et al. (2016) point to the importance of characterizing the nature of shortened muscle-tendon units and investigating growth factors as a potential therapy. While the impact of shortened

muscle on gait has been fairly well studied, an optimal solution that preserves strength has not been developed. Further research can elucidate the links between WM brain injury, loss of normal neuromuscular activation to affected muscles, impaired musculoskeletal growth, short muscle-tendon unit, and the resulting gait abnormalities may lead to more effective treatments.

The Influence of Spasticity on Gait in Spastic CP: Treatment Considerations

Spasticity contributes to gait abnormalities by further compounding abnormal joint postures and by restraining normal rapid flexion or extension during gait. Spasticity contributes to excessive ankle plantarflexion, knee flexion, and hip flexion, adduction, and/or rotation (**Figure 3** and **Table 2**). Plantarflexor spasticity increases the equinus deformity of the ankle contributing to toe-walking and forefoot only contact in stance and poor foot clearance in swing. Spasticity of the posterior tibialis increases the equinovarus deformity of the foot, which includes ankle plantarflexion, inversion, and adduction. Hamstrings spasticity can limit knee extension in terminal swing and lead to increased knee flexion at initial contact. Indeed, Steele et al. (2012) found that hamstring spasticity was associated with an undesirable increase in knee flexion during walking. Stiff-knee gait can result from increased spasticity and passive resistance to stretch in the rectus femoris, thereby restricting the normal rapid knee flexion in early swing and limiting peak knee flexion. Hip adductor spasticity can lead to an adducted, scissoring gait, contributing to tripping. Spasticity of the hip internal or external hip rotators will contribute to an internally or externally rotated hip, respectively.

Treatments for spasticity include BoNT-A injections, oral or intrathecal baclofen, and dorsal rhizotomy. However, treatments that promote strength may also be effective. A study conducted by Williams et al. (2013) found that simultaneous use of BoNT-A and strength training was successful in spasticity reduction, improving strength, and achieving functional goals, over and above treatment with BoNT-A alone in 15 children (aged 5–12 years) with spastic diplegic CP. Further research is needed to assess the efficacy of treatments that promote strength, such as intensive strength training and functional electrical stimulation, for reducing spasticity and improving overall gait function.

The Influence of Impaired Selective Motor Control on Gait in Spastic CP: Treatment Considerations

Impaired SMC results in obligatory muscle co-activation of flexor or extensor muscle synergies during gait. For example, at least three gait events are impacted by impaired SMC (**Figure 3** and **Table 2**). Ankle plantarflexion in terminal swing may increase when the knee is extending as part of an extensor synergy, leading to a forefoot initial contact. Increased ankle plantarflexion may also occur in stance when the knee is normally extended as part of an extensor synergy, leading to equinus gait and knee hyperextension. Knee extension in terminal swing may be limited when the hip is normally flexed as part of a flexor synergy, leading to a flexed-knee posture at initial contact. Rha et al. (2016) showed that while a short semitendinosus correlated with increased knee flexion at both initial contact and single limb support, impaired SMC assessed using the SCALE proved to be a stronger correlate of knee flexion at initial contact than semitendinosus length. In addition, a slow transition from hip and knee extension in terminal stance to hip and knee flexion in initial swing leads reduced foot clearance in swing due to reduced hip and knee flexion. Chruscikowski et al. (2017) studied 194 patients with bilateral CP and found a significant, negative correlation between SMC measured using SCALE and gait impairment, as measured by Gait Profile Score, suggesting that impaired SMC negatively affects gait function.

Recently, Shuman et al. (2016) examined EMG patterns of muscle activation during gait in CP and found increased patterns of muscle synergies. They developed an EMG analysis to quantify synergy patterns during gait and found that prolonged antigravity muscle activation is necessary to prevent collapse in flexed-knee gait. However, prolonged and simultaneous antigravity muscle activation may be a compensatory symptom, separate from impaired SMC and therefore requires further delineation.

Treatments utilizing intensive exercise patterns outside of synergy patterns, such as knee extension combined with ankle dorsiflexion, may prove beneficial and warrant further investigation. Research is needed to determine the efficacy of intensive exercise on improving SMC using exercise patterns that combine flexion and extension of adjacent joints. Further work is needed to determine if improvements in SMC translates to improved gait patterns.

The Influence of Neuromuscular Deficits on Gait in Dyskinetic CP

Dyskinetic CP is characterized by involuntary hyperkinetic or repetitive dystonic limb movements that impair motor function (Sanger, 2006). Primitive reflexes are more prominent and persist for a longer time in dyskinetic CP and may interfere with gait (Sankar and Mundkur, 2005). The influence of neuromuscular deficits in dyskinetic CP is not well studied. However, the increased movement variability and involuntary muscle contractions in children with dyskinetic CP (Sanger, 2006; Sanger et al., 2010) undoubtedly impact gait. Further, children with dystonia are at risk of developing fixed musculoskeletal deformities, which progress faster with worsening GMFCS level and among children with both dystonia and spasticity (Lumsden et al., 2016). Determining whether dyskinetic movements are random and variable or involve a small number of specific abnormal motor patterns (Sanger, 2006) will clarify the influence on gait and guide more effective treatment.

Deep brain stimulation to the globus pallidus internus may be an effective treatment option for children with dyskinetic CP (Review: Koy et al., 2013). It has been shown that response to pallidal deep brain stimulation in the treatment of dystonia yields better outcomes if administered earlier in life (<7 years of age) (Lumsden et al., 2013), highlighting a need for early intervention.

The Influence of Neuromuscular Deficits on Gait in Ataxic CP

Ataxic CP is characterized by impaired limb coordination, balance, and stability (Hughes and Newton, 1992; Schnekenberg et al., 2015; Graham et al., 2016). These neuromuscular deficits impose instability and result in a compensatory wider base of support and elevated, outreaching arm postures to improve balance during gait. In addition, a more circuitous or less direct gait path may be observed. Little work has been done to specifically characterize the neuromuscular deficits in ataxic CP and their influence on gait. Better characterization of the deficits can help develop more effective treatment methods.

Neural Correlates of Gait Abnormalities in CP

To date, few studies have examined the neural correlates of motor deficits and gait abnormalities. Staudt et al. (2003) found correlations ($r = 0.8$; $p < 0.01$) between lower limb motor dysfunction assessed with the Movement ABC and extent of contralateral PVL, as assessed on semi-coronal reconstructions from 3D-MRI in 13 adolescents with CP. In addition, Rademaker et al. (2004) found an inverse association between motor function assessed on Movement ABC scores and corpus callosum area assessed on MRI in 204 preterm children with VLBW. The association existed in frontal, middle, and posterior corpus callosum areas but increased in the direction of the posterior part. Lee et al. (2011) found a strong relationship between motor dysfunction assessed with GMFCS and fractional anisotropy values assessed on DTI within the bilateral CST and posterior body of the corpus callosum ($p < 0.03$); Cortical volume of the pre- and post-central gyri, and the paracentral lobule was negatively associated with GMFCS levels ($p < 0.005$).

Meyns et al. (2016b) found that the severity of gait abnormality assessed using the Gait Profile Score correlated to total corpus callosum ($r = -0.441$; $p < 0.040$) and subpart 1 ($r = -0.437$; $p < 0.042$) volumes in children with CP (Witelson, 1989). Furthermore, Rose et al. (2007) found evidence to support early prognosis of gait abnormalities in VLBW preterm children. They found that neonatal WM microstructure of the posterior limbs of the internal capsule assessed with DTI fractional anisotropy correlated to severity of gait abnormalities at 4 years of age, measured using 3D kinematics ($r = 0.89$, $p < 0.0$) and to GMFCS ($r = 0.65$, $p < 0.04$). In a separate cohort of VLBW preterm children, gait velocity at 18–22 months of age correlated ($r = -0.374$, $p < 0.007$) with near term brain microstructure in the genu of the corpus callosum assessed on DTI mean diffusivity (Rose and McGill, 1998).

CONCLUSION

Emerging evidence suggest that important links exist between neurologic injury, neuromuscular deficits, and specific gait abnormalities in CP. A better understanding of these relationships can elucidate underlying mechanisms of gait impairments and lead to more strategic treatments. Here, we have reviewed the nature of brain injuries in CP, the associated neuromuscular deficits, and the subsequent gait abnormalities on both a microscopic and functional level.

Our understanding of brain abnormalities in CP have been informed by rapidly evolving neuroimaging techniques. However, inconsistent methodology and reporting of data limit interpretation. These discrepancies have been identified as "(1) inappropriate assignment of etiology to morphologic findings, (2) inconsistent descriptions of radiologic findings, (3) uncertain relationship of pathologic findings to brain insult timing estimates, and (4) study designs that are not based on generalizable samples" (Korzeniewski et al., 2008). In addition, consistent, standardized language across studies would help compare findings in context of the existing body of knowledge. Neuroimaging findings are rarely reported with anatomical descriptions sufficient for direct comparison between studies. For example, the localization of atrophy of GM or WM, the location of cavities, and the nature of anomalies found on imaging are not specified in a consistent manner. However, the National Institute of Neurological Disorders and Stroke (NINDS), in conjunction with the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) have recently developed a set of Common Data Elements for use in CP research, including neuroimaging diagnostics, which promises to standardize clinical language and improve data collection consistency for future research on CP (Odenkirchen et al., 2016).

The criteria for estimating the time of injury are also not well described; thus, exactly how prenatal and perinatal insults are differentiated is unclear, and there is a need to develop accurate, standardized techniques. Automated analysis of MRI is an exciting new field that can facilitate precise identification of brain abnormalities and improve consistency in the interpretation of MRI scans. Automated brain lesion segmentation using the Least Absolute Shrinkage and Selection Operator (LASSO) on both WM and GM from T1-weighted MRI sequences was recently validated against manual expert classifications of lesions (Pagnozzi et al., 2016). The prognostic ability of MRI to determine mild motor impairment and exactly which motor functions will be compromised is still limited. Thus, further work on developing a quantitative relationship between lesion burden and functional outcome will help increase the utility of structural MRI in predicting individual prognoses and planning targeted therapeutic interventions.

Precision in identifying microstructural brain abnormalities on DTI will also advance our understanding of brain abnormalities in CP. Current DTI techniques are limited by spatial resolution, intravoxel averaging of anisotropy by adjacent tracts, partial volume effects, and image artifacts. DTI imaging of the reticulospinal and rubrospinal tracts will improve our understanding of the contribution of these tracts to gait abnormalities in children with CP. Developments to the diffusion tensor model, which uses optimized acquisition schemes, such as high angular resolution diffusion imaging (HARDI)

(Tuch et al., 2002) and higher-order modeling of diffusion anisotropy, will improve the resolution of crossing fibers within each voxel. With better resolution, more accurate estimations of tract injury or plasticity within corticomotor networks can be made (Rose et al., 2011). Multi-modal imaging such as functional neuroimaging (functional MRI or magnetoencephalography) guided DTI holds promise for correlating structure-function relations in children with CP (Reid et al., 2016). Improved techniques to precisely quantify neuromuscular deficits in CP are also needed to clarify these important structure-function relations.

By discussing the neurologic correlates of gait abnormalities within this context, we hope to encourage the reader to recognize specific mechanisms of gait abnormalities in CP and discover targeted treatment opportunities that can substantially improve functional outcomes for children with CP.

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JZ, EB, and JR synthesized literature and wrote the paper. All authors discussed and commented on the manuscript.

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The Differential Effect of Arm Movements during Gait on the Forward Acceleration of the Centre of Mass in Children with Cerebral Palsy and Typically Developing Children

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Background: We aimed to study the contribution of upper limb movements to propulsion during walking in typically developing (TD) children ($n = 5$) and children with hemiplegic and diplegic cerebral palsy (CP; $n = 5$ and $n = 4$, respectively).

Methods: Using integrated three-dimensional motion capture data and a scaled generic musculoskeletal model that included upper limbs, we generated torque driven simulations of gait in OpenSim. Induced acceleration analyses were then used to determine the contributions of the individual actuators located at the relevant degrees of freedoms of the upper and lower limb joints to the forward acceleration of the COM at each time point of the gait simulation. The mean values of the contribution of the actuators of upper limbs, lower limbs, and gravity in different phases of the gait cycle were compared between the three groups.

Findings: The results indicated a limited contribution of the upper limb actuators to COM forward acceleration compared to the contribution of lower limbs and gravity, in the three groups. In diplegic CP, the contribution of the upper limbs seemed larger compared to TD during the preswing and swing phases of gait. In hemiplegic CP, the unaffected arm seemed to contribute more to COM deceleration during (pre)swing, while the affected side contributed to COM acceleration.

Interpretation : These findings suggest that in the presence of lower limb dysfunction, the contribution of the upper limbs to forward propulsion is altered, although they remain negligible compared to the lower limbs and gravity.

Keywords: cerebral Palsy, upper limbs, walking, induced acceleration, propulsion

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INTRODUCTION

Arm swinging during walking has been proposed to have several benefits in healthy adults (Meyns et al., 2013), including optimization of energy consumption (Collins et al., 2009) and reduction of instability (Ortega et al., 2008). Given the positive effect of arm swing in healthy subjects, a significant assistive effect is to be expected in patient populations. In previous studies, we found

that children with diplegic (DiCP) and hemiplegic (HeCP) Cerebral Palsy (CP) adopt specific arm postures related to their gait instability (Meyns et al., 2012a). Additionally, HeCP are known to walk with a decreased arm swing on the hemiplegic side due to the altered tone of the muscles in their hemiplegic arm (Meyns et al., 2011). Contrarily, their arm swing on the non-hemiplegic side is significantly increased, which was found to counteract an increased angular momentum produced by the legs. As such, the non-hemiplegic arm aims to control total body angular momentum (Bruijn et al., 2011). Furthermore, it is suggested that DiCP are able to increase walking speed more than HeCP (despite the two affected lower limbs in DiCP) due to more adequate compensations of both (unaffected) upper limbs (Meyns et al., 2011).

Although the arms were found not to make a significant contribution to the forward acceleration of the center of mass (COM) in healthy subjects (Hamner et al., 2010; Hamner and Delp, 2013), it can be questioned whether in CP patients the arm movements contribute more to gait propulsion. This is particularly relevant as arm movements play a more important role for locomotion in CP compared to typically developing (TD) children. Therefore, we expected that the arms' contribution to propulsion was different between HeCP, DiCP, and TD. Specifically, we hypothesized that the contribution to propulsion of the COM was increased for both arms in DiCP and for the unaffected arm in HeCP compared to TD.

MATERIALS AND METHODS

Five TD and nine CP children (five HeCP and four DiCP) participated (see **Table 1**).

CP children were recruited from the Clinical Movement Analysis Laboratory at UZ Pellenberg (UZ Leuven). They were ambulant (without walking aids), were diagnosed with the predominantly spastic type of CP, and had sufficient cooperation to follow verbal instructions. They did not receive lower limb surgery or did not undergo Botulinum Toxin treatment within the past 6 months.

The local ethical committee (Commissie Medische Ethiek KU Leuven) approved the experiments (approval number S51498). In accordance with the Declaration of Helsinki, written informed consent was obtained of the participants' parents.

The total-body PlugInGait marker set was used to collect three-dimensional kinematic data with an eight camera Vicon system (Oxford Metrics, Oxford, UK) at 100 Hz (see also Meyns et al., 2011). Marker coordinates were filtered and smoothed using Woltring's quintic spline routine. Workstation (5.2beta 20, Oxford Metrics) was used to define gait cycles and label individual marker trajectories. Ground reaction forces were measured using two force plates (AMTI, Watertown, MA) embedded in the 10 m walkway. Kinematic and kinetic data is publicly available on the SimTK website for other researchers to evaluate and use for future research (https://simtk.org/projects/cp-child-gait). All participants walked barefoot at self-selected walking speeds. Since in HeCP, one side of the body is significantly more affected, both sides were investigated separately: The most affected side was defined as the side which showed the highest median spasticity score on the Modified Ashworth Scale. In DiCP and TD data on both sides of the body were averaged.

TABLE 1 | Patient characteristics.

	TD	DiCP	HeCP
N	5	4	5
Trials	8	6	7
Gender (M/F)	2/3	3/1	5/0
GMFCS (I/II)	–	3/1	4/1
Age (years)	8.40 ± 1.50	10.50 ±1.66	9.00 ± 2.28
Weight (kg)	32.54 ± 8.37	32.98 ± 6.26	28.70 ±7.09
Height (cm)	136.96 ± 10.36	142.93 ± 12.83	132.46 ± 9.90

Table 1 *presents characteristics of the three groups (Typically Developing children [TD], children with diplegic cerebral palsy [DiCP], and children with hemiplegic cerebral palsy [HeCP]).*
Note that age, weight and height are presented as follows: Mean ± standard deviation. N, number of subjects; M/F, male/female; GMFCS, Gross Motor Function Classification System.

Based on the integrated 3D motion capture data, dynamic torque-driven simulations of gait were created in OpenSim (Delp et al., 2007), using a model with 14 segments and 21 degrees of freedom (including three shoulder motion DOFs and one elbow motion DOF). This model was scaled to the anthropometry of the individual based on the marker positions measured during a static trial and body weight. Inverse kinematics were used to compute joint angles for the model that best reproduce the participant's motion. Tracking errors for the different DOFs were below 1°. Using inverse dynamics, the joint moments were calculated for each participant. The residual reduction algorithm (RRA), which slightly adjusts the joint kinematics, trunk COM location and model mass properties, was then used to optimize the simulation's dynamic consistency. Using the adjusted model and kinematics determined from RRA, the computed muscle control algorithm (CMC) was used to generate a set of excitations of the torque actuators at the individual DOF (Thelen et al., 2003; Thelen and Anderson, 2006). These excitations produce a coordinated torque-driven simulation that accurately tracks the participant's movement. Induced acceleration analysis was then used to compute the contributions of individual actuators to the forward acceleration of the body COM at each time point of the participant's gait simulation, more specific the acceleration of the COM was evaluated for an instantaneous increase of the torque actuator with 1 Nm (**Figure 1**) (Zajac and Gordon, 1989; Riley and Kerrigan, 1999; Anderson and Pandy, 2003). For each actuator of the right and left limbs, we calculated the mean induced acceleration produced during loading response, single stance, preswing and swing separately. Likewise, the contribution of gravity was calculated. To test simulation accuracy, superposition was verified and the error was on average 0.22 m/s^2 for horizontal acceleration varying between 2.37 and -2.43 m/s^2. Maximal errors up to 0.78 m/s^2 were reported, mainly at the instant of initial contact, a finding reported by others previously (Liu et al., 2006). Total induced acceleration was calculated for the

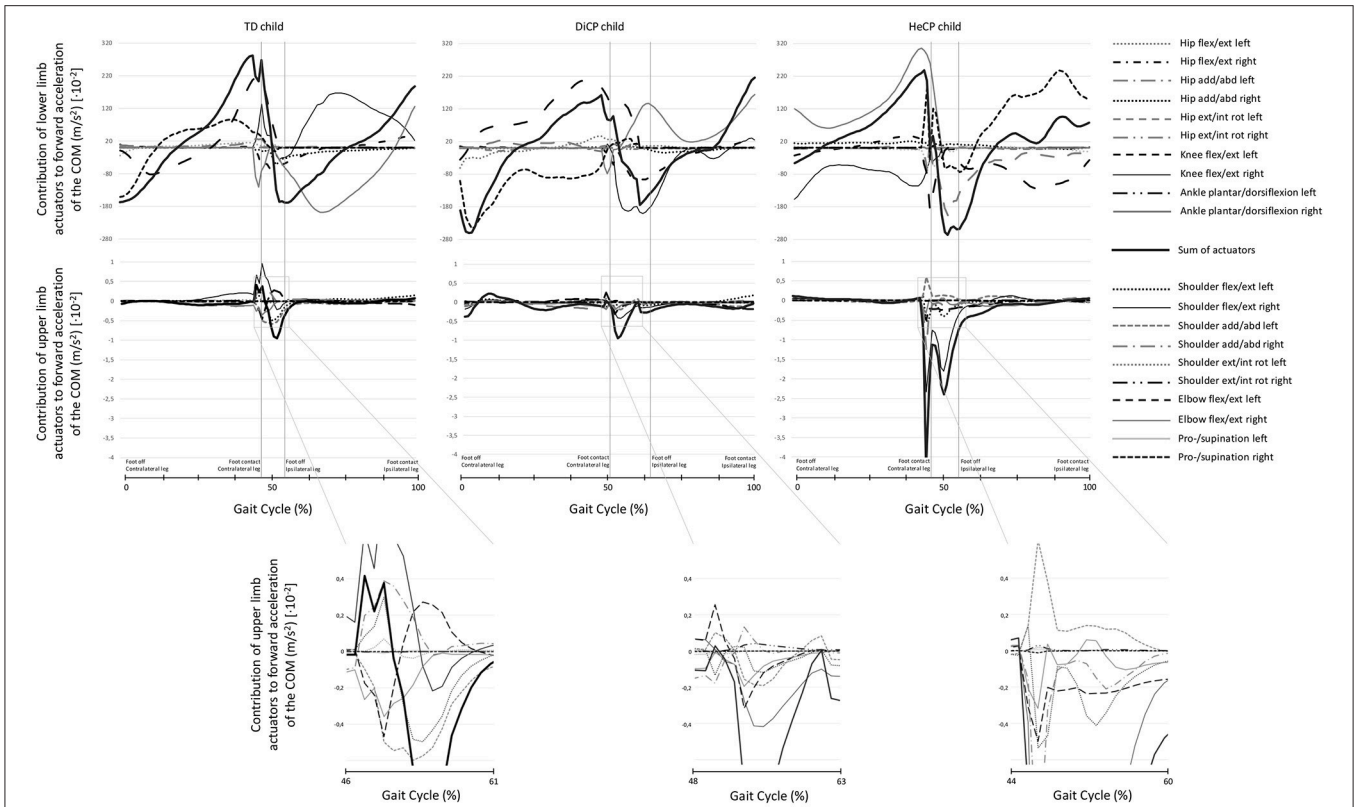

FIGURE 1 | Examples of individual data of the induced acceleration analysis representative for the group. The contribution to forward acceleration/deceleration of the COM in three individuals (a Typically Developing child [TD; left column], a child with diplegic cerebral palsy [DiCP; middle column], and a child with hemiplegic cerebral palsy [HeCP; right column]) for the lower limbs (upper row) and upper limbs (lower row) are presented over the gait cycle. The sum of the contribution of the different actuators (thin lines) of the lower limbs is presented as a thick black line (upper row). The actuators of the lower limbs included (left and right); hip extension/flexion, hip abduction/adduction, hip external/internal rotation, knee flexion/extension, ankle dorsiflexion/plantarflexion. Similarly, the sum of the contribution of the different actuators (thin lines) of the upper limbs is presented as a thick black line (lower row). The actuators of the upper limbs included (left and right); shoulder extension/flexion, shoulder abduction/adduction, shoulder external/internal rotation, elbow flexion/extension, pronation/supination. To increase readability of the graphs, for the actuators of the upper limbs a part of the graph is enlarged close to preswing. As such, the contribution of the different upper limb actuators to forward acceleration of the COM can be better distinguished for each participant. Vertical lines indicate foot contact and foot off gait events.

actuators of the right and left upper and lower limbs separately. Finally, the percentage contribution of the actuators of the different segments (upper limbs, lower limbs) and gravity was expressed with respect to the combined total contribution of the segments and gravity. For HeCP, averages for affected and unaffected side were calculated separately. For TD and DiCP, values of right and left side were averaged for the respective gait phases.

Given the small sample size, individual data points, and descriptive statistics (mean and standard deviation) were used to describe the differences between the groups.

RESULTS

For the three groups, the torque actuators of the lower limbs contributed the most to the forward acceleration of the body COM, while the torque actuators of the upper limbs contributed minimally (less than 1%; **Figure 2**, **Table 2**). The magnitude of the contribution of the lower limbs and gravity were similar between the groups (**Figure 2**, **Table 2**). However, the contribution of the upper limbs was less consistent (**Figure 2**): In CP, the torque actuators of the upper limbs contributed more to forward acceleration of the COM during different phases in the gait cycle. In DiCP, the upper limbs seemed to contribute more to COM forward acceleration during preswing and swing. Similar results were found for the affected upper limb in HeCP. However, the unaffected arm in HeCP seemed to contribute more to COM forward acceleration during single stance.

Timing between the Upper and Lower Limbs' Contributions

In TD the contribution of the lower limb actuators and upper limb actuators are synchronous during the loading response, single stance and swing phases of gait (**Figure 2**, **Table 2**). At these instances, both the upper and lower limb actuators decelerate the COM. Only

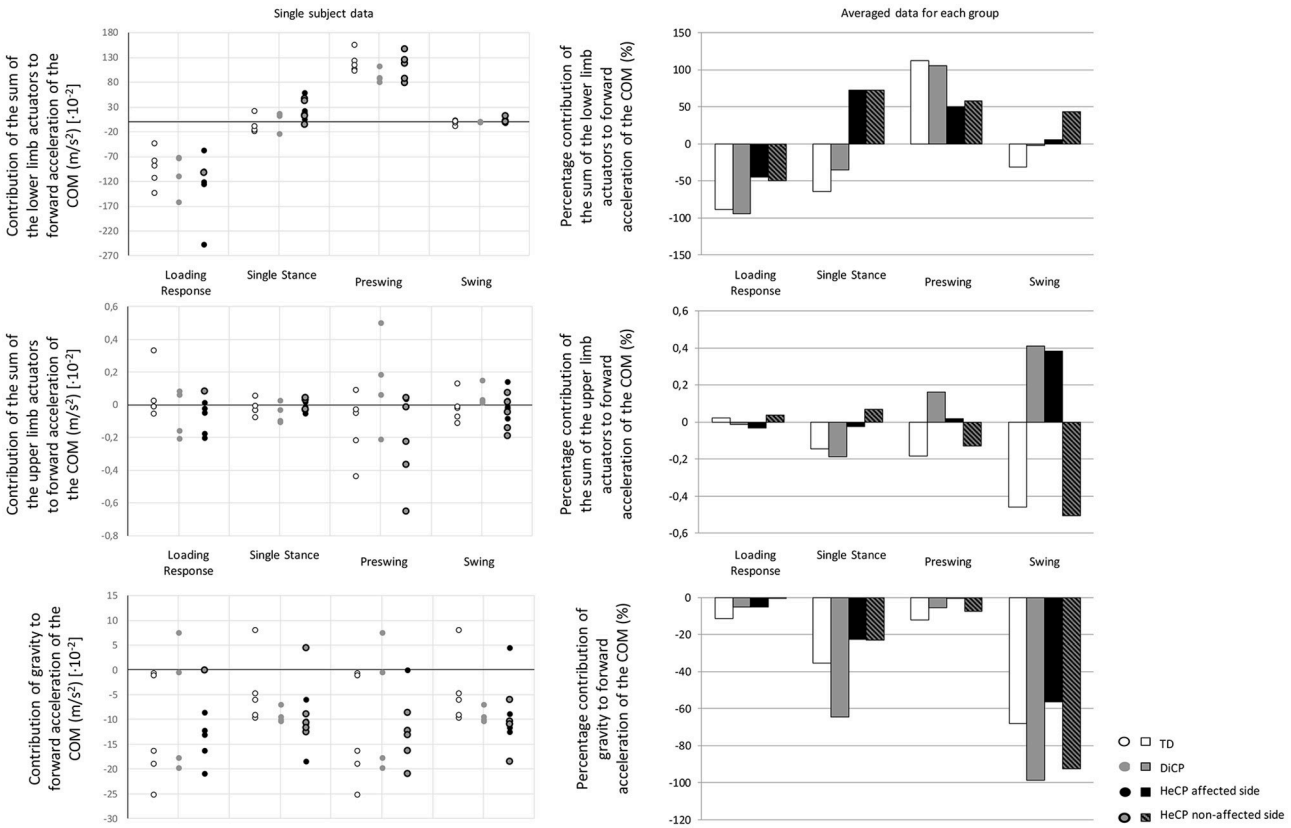

FIGURE 2 | Single subject data (left) and the averaged data for the three groups of the percentage contribution (right) to forward acceleration/deceleration of the COM (Typically Developing children [TD], children with diplegic cerebral palsy [DiCP], and children with hemiplegic cerebral palsy [HeCP]) for the lower limbs (upper graph), upper limbs (middle graph), and gravity (lower graph) at the different phases of the gait cycle (loading response, single stance, preswing, and swing). The percentage contribution of the sum of the actuators of the upper limbs, lower limbs or gravity is expressed with respect to the combined total contribution of the segments and gravity.

TABLE 2 | Absolute average (*SD*) contribution to COM forward acceleration [·10^{-2}]

	Loading response	Single stance	Preswing	Swing
LOWER LIMBS				
TD (m/s^2)	–98.256 (43.334)	–10.624 (18.300)	117.708 (52.238)	–2.699 (10.482)
DiCP (m/s^2)	–93.903 (36.685)	–5.241 (23.533)	98.874 (17.102)	–0.153 (1.037)
HeCP affected side (m/s^2)	–127.231 (55.926)	31.077 (5.889)	81.462 (36.408)	–0.612 (1.679)
HeCP unaffected side (m/s^2)	–102.566 (19.307)	18.109 (23.501)	112.312 (34.079)	–4.541 (6.809)
UPPER LIMBS				
TD (m/s^2)	0.026 (0.178)	–0.024 (0.045)	–0.192 (0.292)	–0.039 (0.101)
DiCP (m/s^2)	–0.011 (0.137)	–0.028 (0.062)	0.151 (0.235)	0.040 (0.058)
HeCP affected side (m/s^2)	–0.088 (0.116)	–0.011 (0.062)	0.032 (0.123)	0.039 (0.099)
HeCP unaffected side (m/s^2)	0.080 (0.116)	0.017 (0.088)	–0.253 (0.334)	–0.053 (0.097)
GRAVITY				
TD (m/s^2)	–12.681 (11.713)	–5.849 (6.592)	–12.681 (11.713)	–5.8491 (6.592)
DiCP (m/s^2)	–5.298 (11.479)	–9.565 (1.397)	–5.298 (11.479)	–9.565 (1.397)
HeCP affected side (m/s^2)	–14.767 (4.699)	–9.742 (2.056)	–0.150 (0.874)	–5.720 (5.123)
HeCP unaffected side (m/s^2)	–0.150 (0.874)	–5.720 (5.123)	–14.767 (4.699)	–9.742 (2.056)

Table 2 *presents the mean (SD) of the absolute values of the contribution to the forward Centre of Mass (COM) acceleration of the Lower Limbs, Upper Limbs and Gravity during Loading Response, Single Stance, Preswing, and Swing in the three groups (Typically Developing children [TD], children with diplegic cerebral palsy [DiCP], and children with hemiplegic cerebral palsy [HeCP]).*

during preswing, the lower limb actuators accelerate the COM while the upper limbs appear to decelerate the COM.

Contrarily, in DiCP the contribution of the lower limb and upper limb actuators are synchronous in all phases of gait (**Figure 2**, **Table 2**). All actuators decelerate the COM during the loading response and single stance, while they accelerate the COM during swing and preswing.

In HeCP, on the other hand, there is an asynchronous contribution of the upper and lower limb actuators during swing and preswing (**Figure 2**, **Table 2**). Similar as in TD, during preswing, the lower limb actuators accelerate while the upper limbs actuators decelerate the COM. During swing, the lower limb actuators in HeCP accelerate the COM while the upper limb actuators of the non-affected side decelerate the COM."

DISCUSSION

The aim of the current study was to investigate whether upper limb movements influence forward acceleration of the COM during walking, in particular in hemiplegic and diplegic CP. The current results confirmed our hypothesis that there was minimal contribution of the upper limb muscles to propulsion of the COM in TD children. Even though the current findings seemed to confirm our hypothesis that the contribution to COM propulsion of the arms in DiCP and HeCP was altered compared to TD, the contribution of the upper limbs to the propulsion of the COM was also minimal in both CP groups compared to the contribution of the lower limbs.

Nevertheless, from the descriptive statistics it appeared that in DiCP, the upper limb contribution to the COM acceleration was increased during preswing and swing compared to TD, indicating that children with DiCP rely more on additional acceleration of the COM through arm swing during phases where propulsion is important.

In HeCP, strikingly, both the affected and unaffected upper limbs appear to compensate for the reduced contribution of the lower limbs; i.e., the unaffected side showed an increased contribution to COM acceleration during single stance, while the affected side contributes more to acceleration during preswing and swing.

Furthermore, it appeared that the timing between the contribution of the upper and lower limbs to the forward acceleration/deceleration is different compared to TD. In TD the contribution of the lower limb and upper limb actuators are synchronous during the loading response, single stance and swing phases of gait, and asynchronous during preswing. From the current results, it appeared that in DiCP, the contribution of the upper and lower limbs was synchronous in all phases of gait. In HeCP, however, we found that during swing, the lower limb actuators contribute to the forward acceleration of the COM while the upper limb actuators of the non-affected side contribute to the deceleration of the COM.

Even though the contribution of the arms to COM propulsion in DiCP and HeCP seemed altered compared to TD, their contribution to forward COM acceleration remains negligible compared to that of the lower limbs and gravity (similarly as in TD). Additionally, the timing of the contribution between the upper and lower limb actuators differ between TD and both CP groups. Combined this might suggest that the altered contribution of the upper limb movements to COM propulsion may be related to their coordination deficits (Meyns et al., 2012b), rather than a compensation strategy to increase forward acceleration of the COM. Hence, the clinical implication of the current study is that the arm movements do not need to be incorporated in the gait rehabilitation of children with CP to increase the propulsion of the COM. On the other hand, from the current results, it appears that the natural arm movements in children with CP should also not necessarily be discouraged, even though they are altered, as there does not appear to be a negative effect (i.e., increased deceleration) on the COM. On the other hand, the natural arm movements in children with CP have been related to gait stability (Meyns et al., 2012a, 2016). When the arms are not allowed to move during walking, children with CP show a decreased gait stability, especially in bilaterally affected children (Delabastita et al., 2016). Hence, from this point of view the natural arm movements in children with CP should not be discouraged or unlearned in gait rehabilitation. A next step in research could be to investigate the contribution of the upper limbs to medio-lateral acceleration of the COM as a measure of gait stability. Furthermore, future research could focus on the effect of balance training on gait stability in children with CP and whether this will induce changes in arm movements during walking in these children. Additionally, it is of interest to determine the effect of botulinum toxin treatment of spastic upper limb muscles on the arm movements during gait in children with CP and whether this will have an effect on their gait stability.

When interpreting the results of the current study, one should take into account some limitations. The sample size of the study is too small to perform statistical comparisons. Hence, this study provides inconclusive results concerning the differences on the effect of the upper and lower limb actuators on the forward COM acceleration between children with hemiplegia, diplegia and typically developing children. Nevertheless, from the descriptive results it is safe to state that the arms do not contribute significantly to linear accelerations of the COM in CP and typical gait. There are some limitations concerning the use of simulation techniques. The models used in this study were scaled from adult models and it is possible that they cannot account for the possible bone deformities or altered muscle physiology of the included children with cerebral palsy. The included participants did not show significant bone deformities. The use of such a simplified model could have affected the results to some degree. On the other hand, the difference in contribution between the lower limb actuators and upper limb actuators for each group was of such an extent that using another model will only show negligible changes.

ETHICS STATEMENT

The local ethical committee (Commissie Medische Ethiek KU Leuven [Medical Ethics Committee UZ KU Leuven/Research]) approved the experiments. In accordance with the Declaration of Helsinki, written informed consent was obtained of the participants' parents prior to the experiment. The participants parents supervised the measurement session.

AUTHOR CONTRIBUTIONS

PM, GM, JD, and IJ conceived and designed the experiment. PM performed the experiments. PM and GM performed patient recruitment. PM and IJ analyzed the data. PM wrote the paper. The writing process and the data analysis were supervised by GM, JD, and IJ.

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Part 2: Adaptation of Gait Kinematics in Unilateral Cerebral Palsy Demonstrates Preserved Independent Neural Control of Each Limb

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Motor adaptation, or alteration of neural control in response to a perturbation, is a potential mechanism to facilitate motor learning for rehabilitation. Central nervous system deficits are known to affect locomotor adaptation; yet we demonstrated that similar to adults following stroke, children with unilateral brain injuries can adapt step length in response to unilateral leg weighting. Here, we extend our analysis to explore kinematic strategies underlying step length adaptation and utilize dynamical systems approaches to elucidate how neural control may differ in those with hemiplegic CP across legs and compared to typically developing controls. Ten participants with hemiplegic CP and ten age-matched controls participated in this study. Knee and hip joint kinematics were analyzed during unilateral weighting of each leg in treadmill walking to assess adaptation and presence and persistence of after-effects. Peak joint angle displacement was used to represent changes in joint angles during walking. We examined baseline and task-specific variability and local dynamic stability to evaluate neuromuscular control across groups and legs. In contrast to controls, children with unilateral CP had asymmetries in joint angle variability and local dynamic stability at baseline, showing increased variability and reduced stability in the dominant limb. Kinematic variability increased and local stability decreased during weighting of ipsilateral and contralateral limbs in both groups compared to baseline. After weight removal both measures returned to baseline. Analogous to the temporal-spatial results, children with unilateral CP demonstrated similar capability as controls to adapt kinematics to unilateral leg weighting, however, the group with CP differed across sides after weight removal with dominant limb after-effects fading more quickly than in controls. The change in kinematics did not completely return to baseline in the non-dominant limb of the CP group, producing a transient improvement in joint angle symmetry. Recent studies demonstrate that neural control of gait is multi-layered with distinct circuits for different types of walking and for each leg. Remarkably, our results demonstrate that children with unilateral brain injury retain these separate circuits for each leg during walking and, importantly, that those networks can be adapted independently from one another to improve symmetry in the short term.

Keywords: neural circuits, after-effects, brain injury, knee angle, local dynamic stability, neurorehabilitation

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INTRODUCTION

Motor adaptation is defined as a gradual, trial-by-trial modification of a previously learned movement in response to a specifically applied perturbation that is retained, at least briefly, as an after-effect following its removal (Martin et al., 1996; Bastian, 2008). The distinguishing feature of motor adaptation is the after-effect, which has been postulated as evidence that the perturbation altered the internal dynamical model used by the central nervous system to control movement (Shadmehr and Mussa-Ivaldi, 1994). The possibility of altering neural control makes adaptation to a perturbation an attractive potential mechanism for motor learning strategies to enhance skill level during training and rehabilitation.

Because of its importance for independence and daily living, the ability to modify locomotor strategies via motor adaptation has been studied extensively. Split belt treadmill based paradigms, in which one belt is sped up while the other is slowed down for a pre-determined time interval and then returned to the same speed, are commonly used to study adaptation during locomotion; for a review see Torres-Oviedo et al. (2011). In healthy adults, split belt paradigms have consistently shown that interlimb parameters which involve both legs, such as double support time, swing time, and stride length, show adaptation with strong after-effects (Dietz et al., 1994; Reisman et al., 2005), while intralimb parameters, such as limb excursion and timing of joint kinematics, showed either an immediate or no change with no after-effect, suggesting no adaptation occurred (Reisman et al., 2005). Others have examined weighting of a single limb in healthy adults during walking, which showed immediate changes in bilateral kinematics followed by slow adaptation back toward baseline levels (Noble and Prentice, 2006; Savin et al., 2010). After removal of the weight, kinematics showed an overshoot following by a quick return to baseline levels, i.e., an after-effect. The same effect on lower extremity joint kinematics has also been demonstrated using a velocity-dependent force field paradigm in a robotic gait trainer (Cajigas et al., 2010).

Deficits in the central nervous system are known to affect locomotor adaptation capability. In particular, cerebellar damage has been shown to affect interlimb adaptation in a split belt paradigm while immediate non-adaptive intralimb changes were unaffected (Morton and Bastian, 2006). Changes in adaptation capability may be related to injury severity as those with mild cerebellar ataxia some show similar adaptation as healthy controls (Hoogkamer et al., 2015). Interestingly, in a separate study, those with cerebellar damage showed more variability in intralimb coordination in response to limb weighting compared to healthy controls (Ilg et al., 2008), suggesting adaption strategy and the structures involved may be perturbation specific. The ability of those with unilateral stroke to adapt step symmetry and other interlimb parameters to a split-belt treadmill suggests that the cerebellum, not cerebral structures, is primarily responsible for motor adaptation (Reisman et al., 2010; Malone and Bastian, 2014).

Brain development may also play a role in the capacity for adaptation. A split belt treadmill study of children less than 3 years of age found that adaptation was inconsistently observed within the group, with 23/26 children showing adaptation of double support time with after-effects, while only 12/27 showed adaptation in step length (Musselman et al., 2011). These results agree with another study showing that children younger than 6 years did not adapt spatiotemporal parameters in a split belt paradigm while children as old as 11 took longer to adapt and for after-effects to disappear than healthy adults (Vasudevan et al., 2011).

Repeated adaptation and de-adaptation may result in motor learning, or the formation of a new motor pattern through long-term practice (Bastian, 2008). Such motor learning could be effective for rehabilitation, though that remains an open question. Preliminary evidence suggests that beneficial effects of short-term adaptation on step symmetry in those with stroke may be extended by repetitive training (Reisman et al., 2013), although the effect was only seen in roughly half of the participants and may have been related to baseline characteristics. Similarly, weighting of both the paretic (Lam et al., 2009) and non-paretic (Regnaux et al., 2008) leg appears to have training benefits on functional ability after weight removal.

In our analysis of the temporal-spatial results from the same cohort as reported here, we demonstrated that children with hemiplegic cerebral palsy (CP) have the same capability as age-matched controls to adapt step length in response to unilateral limb weighting (Damiano et al., 2017). These results from our cohort which had 9/10 individuals with focal, unilateral lesions are similar to those from adult onset stroke described above, and provide further evidence that cerebral damage may not be as detrimental to impaired adaptation as damage to the cerebellum.

Yet, much is still unknown about the underlying control of gait and the process of error-based motor learning as it pertains to walking. One difficulty is the multi-layered neural architecture subserving locomotion, which constitutes a hierarchical system that must coordinate between circuits spanning multiple anatomical levels from the spinal cord to the cortex to achieve functional walking. For instance, differences in adaptation of interlimb parameters (e.g., step length) and intralimb parameters (e.g., joint kinematics) to the same perturbation suggests multiple levels of control. Previous studies of healthy individuals have indicated the existence of distinct control networks for different types of walking and for each leg (Choi and Bastian, 2007). Furthermore, variability in the level of conscious attention paid to the perturbation affects spatial and temporal elements of walking differently (Malone and Bastian, 2010) providing additional evidence of multiple, distinct neural circuits underlying control of walking.

Recent models and experimental results demonstrate that short-term motor learning involves a combination of processes operating at both fast- and slow-time scales (Smith et al., 2006), the former of which may be based on recalibration of internal models while the latter may focus on reinforcement of these changes (Huang et al., 2011). Reinforcement theory also suggests that in reward-based motor learning, in which error signals are omitted but feedback is provided based on successful task execution, motor exploration via enhanced movement variability plays a critical role (Izawa and Shadmehr, 2011). Interestingly, recent studies have demonstrated that motor

variability is also advantageous for error-based (i.e., perturbation-based) adaptation capability as individuals with higher task-oriented variability at baseline showed faster learning rates (Wu et al., 2014). The same study also demonstrated that, when trained in environments specific to single perturbation type, expedient learners reorganized their output motor variability in line with the perturbation. Thus, motor variability, rather than necessarily reflecting noise in the system output, also appears to play a key role in one's ability to adapt previously refined motor skills in response to perturbations.

In an interesting parallel, stride-to-stride kinematic variability during walking was traditionally assumed to arise primarily from noise in the motor output of the system, with low deviations interpreted as indicators of a well learned pattern (Winter, 1984). As such, typical gait analysis comparing healthy and pathological walking is based on averaging of data across strides (Winter, 1989). While revealing important quantitative and descriptive measures of activity patterns underlying gait, this approach ignores the overall dynamical nature of walking that may be contained in the variability. Techniques used to study non-linear dynamical systems, such as local dynamical stability, provide further insights into the underlying neuromuscular control of walking (Hurmuzlu and Basdogan, 1994). Local dynamic stability quantifies the system sensitivity to small perturbations such as the natural stride-to-stride variability in joint angles. This approach has been previously deployed to demonstrate that individuals with neuropathic pain reduce gait speed to enhance stability while simultaneously increasing stride-to-stride kinematic variability (Dingwell and Cusumano, 2000), and that motor control strategies optimizing stability during gait are altered in those with unilateral trans-tibial amputations (Wurdeman et al., 2013). Examination of stride-to-stride variability, particularly in the context of local dynamic stability, may provide further insights into underlying shifts in neuromuscular control during adaptation and persistence of aftereffects.

Neuromuscular control differs in children with CP compared to those with typical development (TD). Children with CP exhibit reduced activation during maximum voluntary contraction along with reduced ability to modulate firing rates of some motor units (Rose and McGill, 2005). In submaximal isometric contractions, children with CP have increased variability, especially at more distal joints (Arpin et al., 2013). During walking, children with CP show elevated co-contraction and different activation timing compared to TD (Unnithan et al., 1996). Fewer muscle synergies are required to describe variations in muscle activity during walking in some individuals with CP compared to TD and this reduction has been correlated with clinical measures of function (Steele et al., 2015), suggesting that those with CP utilize less complex control strategies. However, the neuromuscular control complexity during walking in those with CP is still an open research question, and adaptation paradigms offer one method for its study.

The goal of this study was to extend our analyses of temporal spatial data by examining adaptation of intralimb kinematics in response to unilateral leg weighting in children with hemiplegia from CP and age-matched controls. Based on our first study that showed children with CP can adapt step length in response to limb weighting (Damiano et al., 2017), we hypothesized that at the group level children with unilateral CP would show asymmetries between dominant and non-dominant limbs in both kinematic variability and local dynamic stability while typically developing controls would not. We also hypothesized that similar to controls, the group with CP would adapt the kinematics of each limb when weighted. Finally, we expected the adaptation and after-effects to be asymmetric in the CP group demonstrating that similar to healthy individuals, children with unilateral brain injury maintain distinct neural circuitry for controlling each limb.

MATERIALS AND METHODS

Participants

Ten participants with CP (mean age: 14.8 ± 3.8 years, GMFCS range: I–II) were recruited to participate in the study, and 10 participants without CP (mean age: 11.4 ± 3.6 years) were selected from a recruitment database in order to match gender and age to the group with CP. Further details on subject demographics are available in Damiano et al. (2017). All participants met the following inclusion criteria: at least 5 years of age, no surgery within the previous year, no leg injury that may affect their ability to walk, and weight less than 150 lbs. We pre-determined that maximal ankle weight should not exceed 12 lbs., so we further limited participants to 150 lbs. to ensure that the load would remain between 8 and 10% of the participants' body weight.

This study was approved by the institutional review board (Protocol #90-CC-0168). Written informed consent was obtained from participants 18 years and older. Written consent was obtained from a parent or legal guardian as well as written assent of the participant if they were less than 18 years of age.

Procedures

Reflective markers were placed on the pelvis and lower extremities, and 3D motion was tracked by a 10-camera MX motion capture system and collected in Nexus (Vicon Motion Systems; Denver, CO, USA). Kinematic data were processed in Visual3D (C-Motion; Germantown, MD, USA) and MATLAB (MathWorks; Natick, MA, USA).

Prior to walking on the treadmill (Bertec; Columbus, OH, USA), each participant walked overground at their self-selected pace. Walking velocity was estimated from the pelvis velocity of three trials. Each participant then walked on the treadmill at this speed for 2–5 min until they felt comfortable with the task, and the speed was adjusted (usually decreased) for some subjects per their request. Participants were instructed not to use the handrails, and they wore a harness attached to the ZeroG system (Aretech; Ashburn, VA, USA) for safety.

An ankle weight of approximately 10% of body weight up to a maximum of 12 lbs. was attached unilaterally to induce an adaptation to gait. Preliminary testing showed that 10% was adequate to cause changes without causing the participant to stop walking or trip. Details regarding treadmill speed and weight applied for each group are provided in Part 1 of this study (Damiano et al., 2017).

Data collection consisted of five treadmill trials: a 2 min baseline, 6 min with the ankle weight on the non-dominant leg, 2 min post-weight, 6 min with the ankle weight on the dominant leg, and 2 min post-weight. Leg dominance was determined in the CP cohort as the less affected limb, while in the TD group leg dominance was appropriated from self-reported hand dominance. Each participant took a short standing rest in the middle of each 6 min trial to reduce fatigue. Each of the five trials began standing at rest on the treadmill followed by 0.3 m/s^2 acceleration to the chosen self-selected speed. The ankle weight was attached and removed between trials while the participant stood still. They were instructed to keep their feet flat on the ground before and after the weighted trials to prevent acclimatization the new condition.

Data Analyses

Hip and knee angles were used to quantify changes in kinematics during different walking conditions. The kinematics for each stride (heel strike to heel strike) were time normalized to 101 samples (0–100% of gait cycle) using cubic spline interpolation. We examined the peak joint angle and total range of motion during each stride at both the hip and knee joint. A general linear mixed model was used to evaluate group difference in hip and knee joint kinematics with leg (dominant, non-dominant) as the within subjects factor and group (TD, CP) as the between subjects factor and *post hoc* tests as indicated. Statistical analysis was performed in Matlab software (The Mathworks, Natick, MA, USA). To quantify the gait variability we computed the standard deviation of each joint (hip and knee) angle at each normalized time point across all strides of each trial, and then averaged over the normalized stride to compute a single measure of variability for each subject and condition. Variability was examined for statistical differences with a mixed model with leg, joint, and condition (baseline, non-dominant weighted, post non-dominant weighted, dominant weighted, and post dominant weighted) as within subject factors and group as a between subject factor. *Post hoc* tests using Welch's t-test to account for unequal variances were performed to assess differences in group means. We report effect size as the ratio of the sum of squares explained to the total sum of squares (η^2) for ANOVA and as the ratio of difference in means to the pooled standard deviation (Cohen's *d*) for t-tests.

Phase plots of hip angle vs. knee angle were examined for each leg (dominant/unaffected and non-dominant/affected) of every subject during each walking condition. Trajectory shifts in the phase space were used to quantify the adaptation in response to the perturbation and the after effects (i.e., unlearning or washout) following removal of the perturbation. We computed the limit cycle as the mean phase plot over the final 95% of the baseline trial. We utilized the displacement from the limit cycle at the point of maximum knee angle (Δ_{Knee}) and minimum hip angle (Δ_{Hip}) to quantify the phase shift between each walking condition and the baseline trial (**Figure 1**).

The question of whether kinematics across conditions differ by group is difficult to answer precisely because each condition (adaptation and post-adaptation) contains within it a transient period in which the kinematics of walking are changing, thus a general model testing for differences in group means may not be the best approach. One way of handling this, which has been applied in previous literature, is to split the adaptation and after-effects trials into early (e.g., first x strides) and late (e.g., last x strides) periods for purposes of comparison. However, setting the same early and late periods (i.e., the value of x) for each participant does not capture the underlying dynamics of the shifts in control in response to the perturbation, which was the goal here.

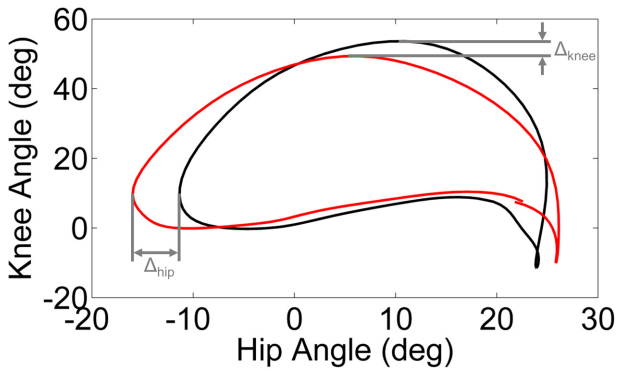

FIGURE 1 | Schematic illustration of Δ_{Knee} and Δ_{Hip} computed from the limit cycle (black line) and typical gait cycle phase (red line). The limit cycle was computed as the mean phase of the final 95% of strides of the baseline walking trial.

Instead, we performed a group analysis of Δ_{Knee} and Δ_{Hip} by plotting the group mean for each stride and fitting time constants to characterize convergence for each condition and group, as described below. Due to variation in the total number of strides across the group under each condition, the time course for this analysis was truncated to the minimum number for each cohort. The minimum number of gait cycles used to fit time constants was 67 and 88 for TD and CP groups, respectively, which required trimming a maximum of 42 and 48 gait cycles from each cohort. When plotted versus time, as measured by the stride number, these values provide a curve that quantifies convergence to the limit cycle. To parameterize this convergence, we fit an exponential function of the following form to each convergence curve:

$$D(t) = K_o e^{\frac{t}{\tau}}$$

where $D(t)$ represents the distance from the limit cycle as a function of time t measured in strides, K_o represents the initial distance from the limit cycle, and τ is the time constant that describes how quickly the walking converges. Note that τ can have a positive or negative sign, depending on the direction of the perturbation. The coefficients of the exponential function were estimated using iterative non-linear regression in Matlab. The regression procedure is moderately sensitive to the initial guess of parameter values. We used a t-statistic to evaluate the fit of the regression, and we adjusted the initial guess if $p < 0.05$ for any of the coefficients. For each condition and leg, we computed the time constant for group average convergence to baseline as

a measure of adaptation. If we were unable to successfully fit a model to the group convergence after 100 repetitions, we did not report a time constant. The time constants fit to the unweighted trials immediately following the weighted trials were used to parameterize adaptation via the group after-effect.

Finally, we applied non-linear dynamical systems analysis to examine the effects of perturbation and adaptation on kinematics. Previous work has demonstrated that walking kinematics, when quantified using appropriate state variables, oscillate in a rhythmic but not strictly periodic manner, and thus, their closed loop trajectories constitute an attractor or limit cycle (Dingwell and Cusumano, 2000). We constructed multi-dimensional state spaces for each kinematic variable (left hip, right hip, left knee, and right knee) using a time embedding approach (Dingwell and Cusumano, 2000; Dingwell et al., 2001)

$$S(t) = [\theta(t),\ \theta(t + \Delta t),\ \theta(t + 2\Delta t),\ ...,\ \theta(t + (d_e - 1)\Delta t)]$$

where $S(t)$ is the d_e dimensional state vector, $\theta(t)$ is the original kinematic time series, Δt is the time delay, and d_e is the embedding dimension. Similar to previous studies (Dingwell et al., 2001) Δt was chosen to minimize correlation between components of the reconstructed vectors while d_e was identified using a false nearest neighbors analysis. For our analysis $\Delta t = 10$ samples ($f_s = 120$ Hz) and $d_e = 5$, though it should be noted that dynamical system analyses have been shown to be insensitive to moderate changes in these parameters (Dingwell et al., 2007).

Local dynamic stability, a method for quantifying the effect of small perturbations during walking, was examined by fitting the average rates of divergence of initially neighboring trajectories as they evolved over each walking bout. In a similar manner as previous studies (Dingwell et al., 2001), we estimated local divergence exponents (λ) from the slope of a linear fit of the exponential divergence curve:

$$y(i) = f_s * \{\ln[d_j(i)]\}_\mu$$

where $y(i)$ is the linear fit of the curve, f_s is the sampling frequency, $d_j(i)$ is the Euclidean distance between the jth pair of initially nearest neighbors after i samples, and $\{\}_\mu$ denotes the average over all j pairs. Short-term exponents (λ_s) were calculated as the slope of the divergence between 0 and 1 stride, normalized by the average stride frequency. A larger value for λ_s indicates decreased stability.

RESULTS

Kinematics

When examining kinematics at baseline, there was a noticeable asymmetry between the dominant and non-dominant legs in the group with CP (**Figure 2**). There was a significant interaction of group and leg on peak hip flexion during baseline ($\eta^2 = 0.10$; $p = 0.036$), with *post hoc* tests indicating a significant effect for leg only in the CP group ($d = 1.14$; $p = 0.020$) with the dominant leg having a mean peak hip flexion of $35.8 \pm 7.5°$ compared to $25.5 \pm 10.3°$ for the non-dominant leg. There was a similar interaction at the knee ($\eta^2 = 0.14$; $p = 0.009$), with no significant effect for leg dominance in TD but a significant effect in CP ($d = 1.35$; $p = 0.008$) with a mean peak knee flexion of $56.6 \pm 12.4°$ in the dominant leg compared to $40.1 \pm 12.0°$ in the non-dominant leg. For total hip excursion, analysis revealed no main or interaction effects for group or leg. At the knee, there was only a main effect for group ($\eta^2 = 0.43$; $p < 0.001$) with the typically developing group having a mean of $65.1 \pm 3.7°$ while the CP group had a mean of $50.9 \pm 11.2°$.

There were significant main effects on variability for joint ($\eta^2 = 0.26$; $p < 0.001$) and condition ($\eta^2 = 0.06$; $p < 0.001$). As expected, the knee joint kinematics showed significantly greater variability (mean 3.2°) than the hip joint (mean 2.2°). Likewise, variability was greater during the weighted trials than during baseline walking for the non-dominant ($d = 0.60$; $p < 0.001$) and dominant ($d = 0.70$; $p < 0.001$) limbs while variability in the two post-weight trials was not significantly different from baseline. There was a significant interaction effect on variability for group and leg ($\eta^2 = 0.03$; $p < 0.001$). *Post hoc* tests showed a significant effect only in the CP group ($d = 0.62$; $p < 0.001$) with the dominant leg showing more variability than the non-dominant.

Adaptation and After-effects

Stark differences were seen during adaptation to weighting in the knee and hip joints of the non-dominant leg between the CP and TD groups (**Figure 3**). The CP cohort showed more variability in peak knee (Δ_{Knee}) and hip (Δ_{Hip}) measures during walking than the TD cohort (**Table 1**). The largest variability was observed in the non-dominant leg of the CP group during the 2 min post-weight trial showing after-effects. At the knee, both groups showed an immediate knee flexion decrease in response to weighting the non-dominant limb, with the decrease initially larger in the CP group, but then slowly returning to baseline during the trial, while the TD remained roughly constant so that by the end of the weighted trials, the TD and CP groups had similar Δ_{Knee} values. In the group with CP, decreased knee flexion of the non-dominant leg during its weighting was accompanied by increased flexion of ipsilateral hip, a response not seen in the TD group. Interestingly, the contralateral (dominant) hip and knee flexion also increased immediately but transiently during that trial for both CP and TD groups. The non-dominant knee showed after-effects in both CP and TD, indicating that motor adaptation occurred in both groups. The TD group showed a relatively quick loss of the after effect while it persisted in the CP group as we were unable to fit a time constant (**Table 2**). However, the non-dominant hip showed an after-effect that disappeared in both groups, although the time constant was significantly slower in the CP group compared to TD. Interestingly, in the dominant leg, both TD and CP showed no after-effect in Δ_{Knee} and similar after-effect magnitudes and time constants for Δ_{Hip} during the unweighted period following the non-dominant weighting period, suggesting similar motor learning capability on the dominant side.

Additionally, both TD and CP showed similar motor adaptation capability in the dominant limb in response to its weighting (**Figure 3**). At the knee an opposite pattern from the non-dominant side was observed across groups whereby the weight resulted in greater knee flexion reduction in TD than

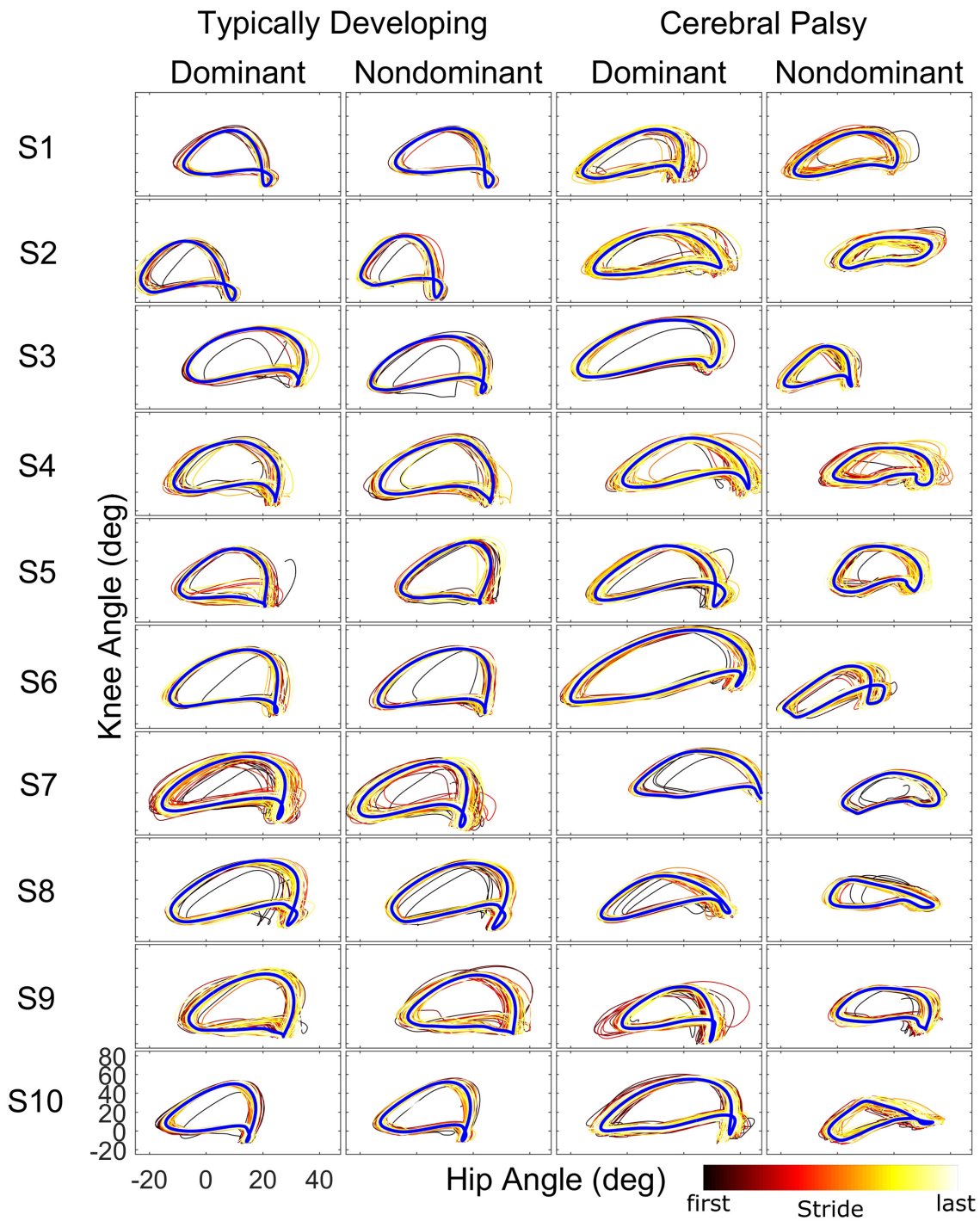

FIGURE 2 | Phase plots (hip angle vs. knee angle) during the baseline walking trial for the ten subjects of each cohort. For each leg and subject, each stride of the baseline trial is depicted starting from the first stride (black) to the final stride (white) as indicated by the color bar. The blue line represents the limit cycle.

CP initially, a difference that slowly diminished such that Δ_{Knee} was similar across groups by the end of the weighted period. Remarkably, after-effects in the dominant knee disappeared more quickly in the CP group (**Table 2**), suggesting less adaptation in response to weighting. Response of the dominant hip to ipsilateral weighting was similar across groups; little after-effect was observed and a time constant was unable to be fit. As in the dominant leg, the non-dominant hip in both TD and CP

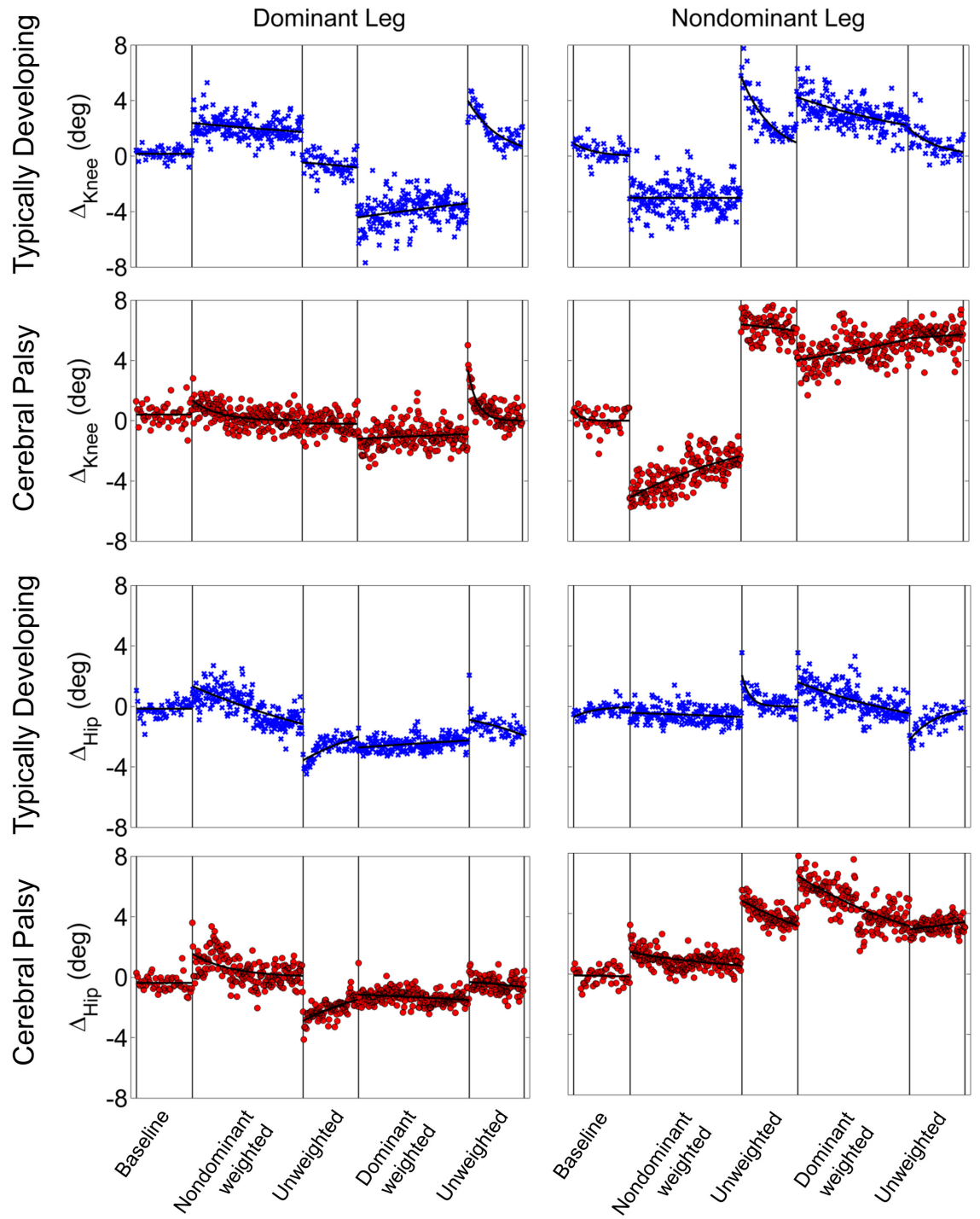

FIGURE 3 | Group mean changes in peak knee (Δ_{Knee}) and peak hip (Δ_{Hip}) across the experimental conditions for participants with cerebral palsy (red circle) and typical development (blue x). Vertical lines indicate the transition between experimental conditions.

showed immediately increased flexion in response to weighting the contralateral limb before returning toward baseline. However, in the CP group Δ_{Hip} returned only to the value reached at the end of the washout following the non-dominant weighted walking, and no after-effect nor time constant was observed while in TD Δ_{Hip} showed an after-effect that returned to baseline (**Table 2**). No after-effects for Δ_{Knee} were observed in the non-dominant leg following dominant weighting for either TD or CP.

TABLE 1 | Average standard deviation of peak knee (Δ_{Knee}) and hip (Δ_{Hip}) measures.

Condition	Δ_{Hip} (°)		Δ_{Knee} (°)	
	TD	CP	TD	CP
Baseline	1.23	3.78	1.75	4.83
Non-dominant weighted	1.86	3.83	3.18	4.13
Non-dominant unweighted	2.00	5.71	3.54	6.55
Dominant weighted	2.69	3.95	3.74	3.91
Dominant unweighted	2.99	3.99	2.91	3.96

TABLE 2 | Time constants following unweighting.

		Ipsilateral		Contralateral	
		Δ_{Knee}	Δ_{Hip}	Δ_{Knee}	Δ_{Hip}
Typically developing	Dominant	57.7	–	–	172.1
	Non-dominant	56.2	13.7	51.7	47.5
Cerebral palsy	Dominant	16.6	–	–	147.8
	Non-dominant	–	239.1	–	–

Time constants are reported in strides. Variables for which a model could not be accurately fit (as judged by t-statistic) are indicated by dash.

However, increased knee flexion was maintained in the CP group while knee flexion steadily returned toward baseline in the TD group.

Stability

Similar to joint excursion and variability, there was a pronounced baseline asymmetry in local stability in the group with CP which was not present in TD (**Figure 4**). At the hip, there was a significant main effect for condition ($\eta^2 = 0.16$, $p < 0.001$), with both the non-dominant weighted ($d = 1.12$; $p < 0.001$; mean $\lambda_s = 2.31 \pm 0.14$) and dominant weighted ($d = 1.07$; $p < 0.001$; mean $\lambda_s = 2.30 \pm 0.15$) conditions showing reduced stability compared to baseline (mean $\lambda_s = 2.11 \pm 0.21$). There were no significant differences between baseline and the trials after the weight was removed at the hip. There was an interaction between group and leg ($\eta^2 = 0.06$; $p < 0.001$) with *post hoc* tests showing lower λ_s ($d = 1.36$; $p < 0.001$) in the non-dominant (2.24 ± 0.14) versus dominant hip (2.41 ± 0.14) in the CP group, indicating greater stability, while there were no differences between dominant and non-dominant legs in the TD group. Similar results were observed at the knee, with a significant main effect for condition ($\eta^2 = 0.16$; $p < 0.001$) showing greater instability in the non-dominant ($d = 1.14$; $p < 0.001$; $\lambda_s = 2.29 \pm 0.11$) and dominant ($d = 1.04$; $p < 0.001$; $\lambda_s = 2.28 \pm 0.11$) weighted trials than baseline with no significant differences between baseline and unweighted. There was also a significant interaction between group and leg for the knee ($\eta^2 = 0.04$; $p < 0.001$), with post-hoc tests showing significantly ($d = 1.20$; $p < 0.001$) less stability in the dominant leg ($\lambda_s = 2.34 \pm 0.13$) compared to non-dominant leg ($\lambda_s = 2.21 \pm 0.13$) for the group with CP and no significant differences across legs in controls. The increase in λ_s in the dominant leg accounted for the significant reduction in stability in those with CP compared to TD at the both the hip ($d = 1.21$; $p < 0.001$) and knee ($d = 0.74$; $p < 0.001$).

DISCUSSION

Our analysis showed that both children with hemiplegia from CP and typically developing children were able to adapt their intralimb kinematics in response to unilateral weighting. In the dominant limb, application of ∼10% body weight to the ankle resulted in similar adaptation and after-effect patterns in both groups, although children with CP displayed a washout period that was approximately three times faster than TD as judged by the time constant, a result that some may interpret as evidence that children with CP take longer to adapt walking patterns than TD. Another possible interpretation for this result is that children with CP have delayed motor development, given previous work showing that typically developing children younger than those in the age range of this study also take longer to adapt (Vasudevan et al., 2011). Yet, our analysis revealed asymmetry in the CP group with significantly greater peak knee flexion at baseline on the dominant side. The dominant side in this group also showed increased stride-to-stride knee angle variability in response to weighting compared to TD. Additionally, dominant knee and hip local dynamic stability was significantly reduced in CP compared to TD. While variability and local dynamic stability quantify fundamentally different aspects of locomotor behavior (Dingwell et al., 2001), the differences in each across groups suggest that the dominant leg is controlled differently in CP. Thus, it is not surprising that application of the same perturbation (by % body weight) may have a reduced effect on intralimb parameters such as knee angle in the stronger dominant leg. Given evidence that children with CP do adapt and show after-effects in the dominant leg (**Figure 2**), it may be possible that this perceived reduction in motor learning capacity (e.g., faster washout of after-effects) not be an indictment on the motor learning capability of those with CP, but instead may be attributed to a greater resistance to adapt due to the elevated functional role of the dominant limb in locomotion which makes it less susceptible to the perturbation. This possibility is further supported by the reduced effect of the weight on local stability in the dominant limb in CP compared to TD (**Figure 3**) and the fact that the ability of children with CP to adapt interlimb parameters, such as step lengths, was not different from TD (Damiano et al., 2017). Future studies utilizing a larger perturbation on the dominant limb could confirm this hypothesis.

In contrast to the dominant limb, we observed significant differences between CP and TD groups in the adaptation behavior, specifically the after-effects, of the non-dominant limb. In the TD group, non-dominant limb adaptation and after-effects of hip and knee kinematics in response to weighting were similar to their dominant limb. However, in CP the non-dominant leg showed a persistent after-effect which was not present in the dominant side or in the TD group, indicating that the CP group partly retained the adaptation on this

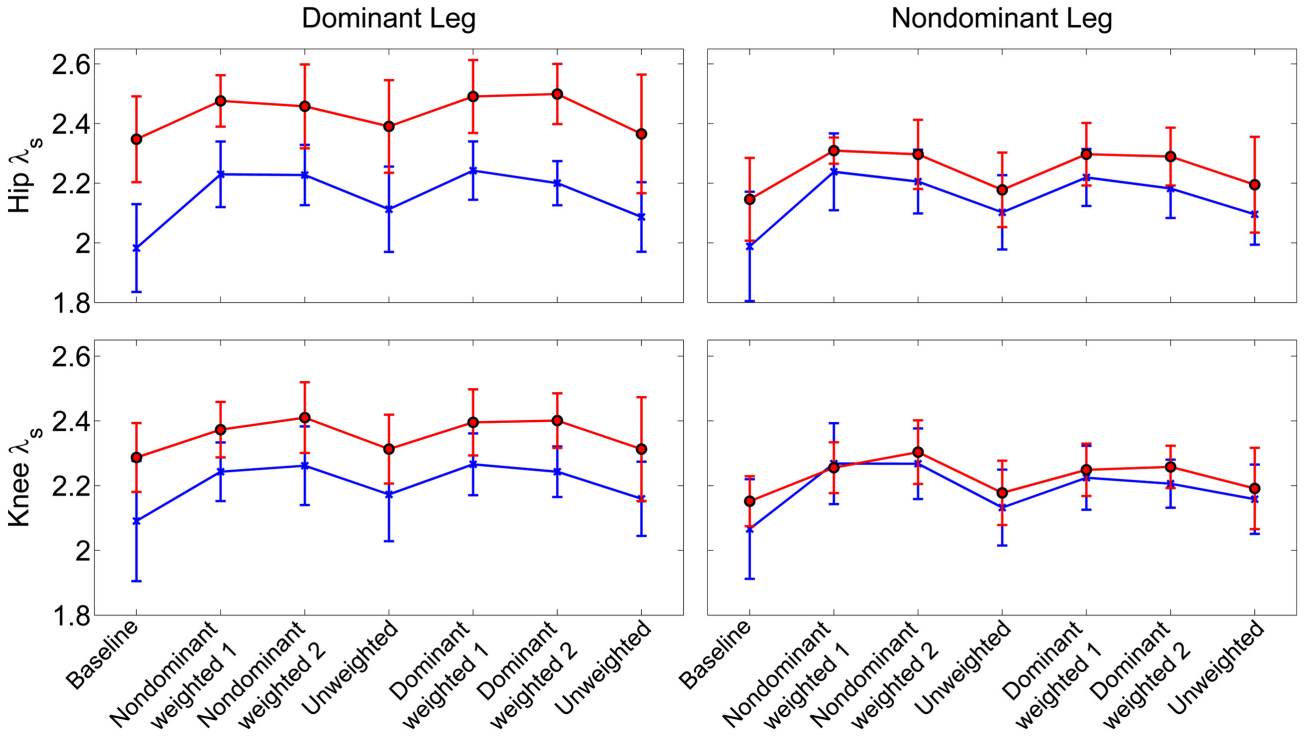

FIGURE 4 | Local stability as assessed by short term exponents across the experimental conditions at the knee and hip joints. Exponents are plotted as group mean ± 1 standard deviation for each walking trial. Participants with cerebral palsy are shown in red, those with typical development are shown in blue. *Post hoc* testing showed significantly ($p < 0.05$) reduced stability in the hip and knee joint of the dominant limb of those with CP compared to TD.

side. Importantly, this result provides evidence that similar to healthy adults (Choi and Bastian, 2007), children with unilateral brain injury retain separate control circuits for each leg which can be adapted independently. Gait asymmetry in children with CP elucidated these distinct circuits which were not apparent in the symmetric TD group. Furthermore, we observed changes in the contralateral limb during unilateral weighting in both groups. Thus, coordination of neural control across legs, which has been previously demonstrated in healthy individuals (Ting et al., 2000; Verschueren et al., 2002) appears to be preserved in children with unilateral brain injury as well.

The persistence of adaptation after-effects in the non-dominant leg of the CP group may reveal an opportunity for potential therapeutic benefit. Similar to previous studies in adults with hemiplegia following stroke (Regnaux et al., 2008; Reisman et al., 2013) our results indicate that loading the more affected limb has beneficial effects. More specifically, when weighting the more affected (non-dominant) limb in the CP group, knee flexion – as judged by Δ_{Knee} – was significantly reduced followed by the after-effect of increased knee flexion by approximately 6° after weight removal. Given the initial 16° asymmetry in peak knee flexion at baseline, our results demonstrate that temporarily accentuating the error at the knee by unilateral weighting actually reduced the asymmetry when the perturbation was removed, at least during the short-term.

A similar effect is seen in individuals with hemispatial neglect following stroke, in which an optical deviation imposed via prism in the direction of the error results in a larger compensation than healthy controls (Rossetti et al., 1998). The resultant improvement in asymmetry was also found to be perturbation specific, as those with neglect did not adapt to a prismatic deviation in the direction opposite the functional error. Individuals with cerebellar damage have a reduced motor adaptation in response to similar prism perturbations (Martin et al., 1996), although it is not clear if adaptation is completely absent or proceeds more slowly. Interestingly, some individuals with cerebellar ataxia have diminished adaptation but a similar after-effect as controls (Fernandez-Ruiz et al., 2007). Conversely studies of individuals with basal ganglia disorders such as Huntington's or Parkinson's disease show similar capacity for adaptation to prisms but the after-effect is reduced (Fernandez-Ruiz et al., 2003). Taken together, these results demonstrate that visuomotor adaptation is a confluence of multiple neuronal processes that are differentially affected by neuropathology.

Similarly, motor adaptation in response to force perturbation is a result of multiple neural processes that adjust to the error and retain that information at different, i.e., slow and fast, rates (Smith et al., 2006). This hierarchy accounts for the observation in healthy individuals that the rate at which adaptation fades after removal of the perturbation is often faster than the initial

adaptation. Our results show the same effect in both limbs of the TD group, but only on the dominant limb of the CP group. A complete return to baseline after weighting was non-existent, or at the very least much slower than the rate of adaptation in the more affected limb in those with CP. Retention of motor adaptation is more dependent on the slow component (i.e., 100s of trials) than the fast component (<10 trials) in healthy individuals (Joiner and Smith, 2008). In this study, both groups and both limbs experienced the perturbation for roughly the same time period (minimum of 198 gait cycles). Given the disparity in rate of de-adaptation, our results suggest that the sensitivity of this slow component is altered in the circuitry controlling the affected limb in children with unilateral brain injury. Indeed, neuroimaging studies have identified distinct neural circuitry activated during adaptation and de-adaptation to prisms (Chapman et al., 2010)and during slow and fast motor adaptation (Krakauer et al., 2004), supporting the possibility of this unilateral affect in response to a focal lesion. A limitation of this study was that our data were collected in a single session, and thus we are unable to assess whether this beneficial effect on the more affected limb was retained in the medium or long term; future studies will examine this possibility.

While stroke typically occurs in adulthood after walking has presumably become a refined motor skill, injury in CP happens during early development. On the one hand, this means that children with CP may not have an established motor repertoire to lean on post injury, yet on the other the potential for plasticity is reportedly greater in the developing central nervous system (Eyre, 2007), providing the opportunity for improved effectiveness of rehabilitation. This enhanced plasticity has been one pillar of hypotheses that robotic assisted training, which provides the opportunity for mass, task oriented practice under guidance of a controlled perturbation (i.e., robotic force), may expedite gait training outcomes (Dobkin and Duncan, 2012). While randomized controlled trials comparing robotic gait training to equal intensity therapies have not been performed in children with CP, studies in stroke survivors have shown no advantage (Hidler et al., 2009). Rather than using a robot to guide the user's legs toward a specified gait pattern, adaptation via introduction of a perturbation may provide an improved training strategy. Recently, Wu et al. (2014), demonstrated that in healthy individuals, the motor control system restructures movement variability in such a way to promote learning in the perturbed environment. That is, following training with a specific perturbation, the motor system increases variability related to the perturbation, a process hypothesized to increase exploration in the task space, thereby potentiating skill learning. Here, we examined variability in hip and knee joint angle during walking, and found that variability increased during the weighted (training) trials in both TD and CP groups. *Post hoc* testing of the weighted trials showed no difference between limbs (dominant vs. non-dominant) in the TD group while variability increased more in the dominant limb compared to non-dominant during weighting in the CP group. This result suggests that elevated variability in response to weighting may actually expedite exploration of the task space, thus providing a potential mechanism to enable adaptation. Yet, the multi-rate models of motor adaptation described above suggest that extended exposure to the perturbation may be a more critical metric for retention of the adaptation (i.e., motor learning) than the amount of adaptation observed during the training session. Future studies should examine each of these factors to identify viable methods for training in this population.

In summary, this study demonstrated that children with hemiplegic CP are able to adapt intralimb kinematics in response to unilateral leg weighting during treadmill walking. The adaptation in the CP group was different than the healthy age-matched controls. The observed adaptation after-effects differed between the dominant and non-dominant sides in those with CP, suggesting that independent neural control of each limb is preserved in this population. Unilateral weighting of the more affected leg also resulted in a transient increase in symmetry, providing impetus to study this approach as a potential strategy for rehabilitation in these children.

AUTHOR CONTRIBUTIONS

TB, CS, and DD had substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be submitted for publication. All further agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Motor Learning Abilities Are Similar in Hemiplegic Cerebral Palsy Compared to Controls as Assessed by Adaptation to Unilateral Leg-Weighting during Gait: Part I

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Introduction: Individuals with cerebral palsy (CP) demonstrate high response variability to motor training insufficiently accounted for by age or severity. We propose here that differences in the inherent ability to learn new motor tasks may explain some of this variability. Damage to motor pathways involving the cerebellum, which may be a direct or indirect effect of the brain injury for many with CP, has been shown to adversely affect the ability to learn new motor tasks and may be a potential explanation. Classic adaptation paradigms that evaluate cerebellar integrity have been utilized to assess adaptation to gait perturbations in adults with stroke, traumatic brain injury and other neurological injuries but not in children with CP.

Materials and Methods: A case-control study of 10 participants with and 10 without hemiplegic CP within the age range of 5–20 years was conducted. Mean age of participants in the CP group was slightly but not significantly higher than controls. Step length and swing time adaptation, defined as gradual accommodation to a perturbation, and aftereffects, or maintenance of the accommodation upon removal of the perturbation, to unilateral leg weighing during treadmill gait were quantified to assess group differences in learning.

Results: Adaptation and aftereffects were demonstrated in step length across groups with no main effect for group. In CP, the dominant leg had a greater response when either leg was weighted. Swing time accommodated immediately (no adaptation) in the weighted leg only, with the non-dominant leg instead showing a more pronounced response in CP.

Discussion: This group of participants with unilateral CP did not demonstrate poorer learning or retention similar to reported results in adult stroke. Deficits, while not found here, may become evident in those with other etiologies or greater severity of CP. Our data further corroborate an observation from the stroke literature that repeated practice of exaggerating the asymmetry (error augmentation), in this case by

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weighting the more involved or shorter step leg, vs. minimizing it by weighting the less involved or longer step leg (error reduction) may be a useful training strategy to improve step symmetry in unilateral CP.

Keywords: asymmetry, aftereffects, cerebellar deficits, brain injury, children

INTRODUCTION

Human gait is a highly versatile process with continual adjustments to ever-changing external environments. These adjustments may be anticipatory (e.g., see an object up ahead) or reactive (e.g., surface is unexpectedly slippery) and may occur immediately or through an iterative process of error recognition and correction. Some particularly novel or challenging, as well as persistent, perturbations may lead to motor adaptation during functional tasks such as gait or reaching, which is the modification of a well-learned motor behavior through a process of adjustment to an altered task demand (Martin et al., 1996). Adaptation requires a period of practice with gradual accommodation, or incremental error reduction, to a new demand such that when it is removed, the new behavior will persist for a brief period. This transient persistence is referred to as an *aftereffect* and is evidence that the central nervous system has stored the adaptation at least temporarily (Martin et al., 1996; Bastian, 2008).

Studies have shown healthy adults (Savin et al., 2010) and even very young children (Musselman et al., 2011) can adapt to and temporarily store novel motor patterns within a single session. Most clinical studies have evaluated adaptation in adults with cerebellar damage (Ilg et al., 2008) who frequently present with motor learning deficits or those with unilateral brain injuries due to stroke (Reisman et al., 2010; Malone and Bastian, 2014). Split-belt treadmill paradigms have been utilized frequently to assess gait adaption and aftereffects within a single session (Reisman et al., 2007) and more recently as a repetitive training strategy to reduce step length asymmetry in adults post-stroke (Reisman et al., 2013). Investigators have been able to differentiate parameters that "adapted" or showed gradual accommodation such as step length, from those that had a more immediate response to the split-belt perturbation such as stance and swing times. The interpretation was that the latter did not require learning and consequently also did not demonstrate aftereffects (Reisman et al., 2005).

Investigators have hypothesized that with repetition (training), temporary learning during a single adaptation session could be reinforced and made to persist far longer. In one such training study, 12 subjects were post-stroke trained for 12 sessions over a 4-week period using the split-belt paradigm (Reisman et al., 2013). Counter-intuitively, subjects practiced walking with the belt speed slower on the side with the initially longer step length thus exaggerating the asymmetry. Slightly more than half (7/13) were deemed "responders" in that step symmetry post training that improved more than the individual difference between the two baseline sessions. However, nearly half did not improve suggesting that training using alternate strategies such as increasing, rather than slowing, the belt speed on the longer side, should also be investigated.

Responses to adaptation paradigms may vary not only due to brain pathology but also to maturation of brain pathways during normal development. Musselman et al. (2011) studied adaptation in very young children 3 years of age or less who were able to walk continuously on a treadmill using a split-belt paradigm to examine normal development of this phenomenon. Adaptation in step length was seen in 12 of 26 children. Authors postulated that inter-individual differences in the degree or rate of myelination of cerebellar tracts may explain developmental variations in adaptation.

Less commonly, other types of perturbations besides split treadmill belts have been utilized in adaptation paradigms with similar effects. These include unilateral leg weighting during treadmill walking which demonstrated both gradual accommodation in lower limb kinematics and a pronounced aftereffect (Noble and Prentice, 2006) or podokinetic stimulation (rotating treadmill) which produced consistent after-rotation during stationary stepping in healthy subjects that was shown to be disrupted in cerebellar patients (Earhart et al., 2002).

Cerebral palsy (CP), the focus of this study, encompasses a group of brain disorders occurring early in life with a resultant motor disability as the hallmark feature. Cerebellar abnormalities have recently been documented in unilateral CP and related to arm function (Fiori et al., 2015). The ability to adapt to a novel task demand and retain it may be predictive of the ability to learn or improve motor skill through training and therefore may prove to be an important source of the variance in response to training paradigms observed in this population. To our knowledge, no classic adaptation studies, in which subjects adjust to a new perturbation during a learned task such as reaching or gait and its subsequent removal, have been conducted in children with CP. The objective of this study was to compare how children with unilateral CP and without CP are able to accommodate to a novel gait perturbation and how well individuals with CP can temporarily retain new motor behaviors compared to those within the same age range but without CP. We hypothesized that, on a group level, children with unilateral CP would have poorer adaptation to the weighting of each leg compared to controls. We further hypothesized that they would have less pronounced aftereffects on weight removal, also indicating diminished learning capabilities. Gait adaptation paradigms that involve being subjected to two different treadmill belt speeds, or unilateral weighting, as done here, or bilateral weighting of the lower extremities (Vashista et al., 2013) while walking may also provide novel therapeutic approaches for improving step length or kinematic asymmetry in those with unilateral CP similar to studies in stroke, as well as

addressing other types of gait deviations in those with bilateral involvement.

MATERIALS AND METHODS

Participants

The recruitment goal was to obtain complete data sets on 10 participants less than 21 years of age with unilateral CP and 10 without CP of similar age to serve as a control, based on the sample size in a similar unilateral weighting paradigm in nondisabled adults (Savin et al., 2010) and in a second study examining adaptation in a children with unilateral brain injuries (Choi et al., 2009). All participants had to be at least 5 years of age to be able to comply well with instructions, and have had no surgery within the previous year and no leg injury besides CP that would affect their ability to walk. All were recruited and completed the study within a 2 year period. Participants with hemiplegia were self-referred or referred by local physicians or therapists, and controls were selected from a recruitment database based on similarity in gender and age to the clinical group. We further restricted the weight of all participants to 150 lbs maximum so that the percent of load (which we set at an absolute maximum of 12 lbs based on pilot testing) would not go below 8% of body weight. The study was approved by the institutional review board (Protocol #90-CC-0168). Written informed consent was obtained from participants 18 years and older. For those younger than 18, written consent was obtained from a parent or legal guardian as well as written assent of the participant. The setting was a motion analysis laboratory in a large research hospital.

Participants ranged from 5 to 20 years of age and included 10 with unilateral CP, mean age 14.8 ± 3.8 years and 10 controls without CP, mean age of 11.4 ± 3.6 years, with relevant group characteristics summarized in **Table 1**. Two additional participants with CP were enrolled in, but did not complete, the study. One needed to hold onto treadmill side rails when walking and the other was unable to lift the weighted leg well enough to sustain a consistent pace on the treadmill. These two participants were replaced to meet the recruitment goal. The rest of the participants completed the study with no reports or evidence of fatigue. Mean age and weight were slightly but not significantly higher in the group with CP.

All with CP had a diagnosis of hemiplegia predominantly due to unilateral stroke (n = 7) with others due a bleed secondary to an arterial-venous malformation (1) tumor resection (1) and asymmetric periventricular leukomalacia (1) all of which occurred early in life. The actual ankle weights used were on average 8.72% and 8.89% of body weight for CP and control groups, respectively, due to a fixed limit to the maximum amount of weight (12 lbs). **Figure 1** depicts the weight as placed on one of the subjects.

TABLE 1 | Summary of demographic, physical and study-specific characteristics of participants.

	Unilateral CP (n = 10)	Control group (n = 10)
Gender	6 M, 4 F	6 M, 4 F
Age (years)	14.8 ± 3.8	11.4 ± 3.6
Body mass (lb.)	115.8 ± 26.6	103.9 ± 34.5
GMFCS Level	I (3), II (7)	N/A
Side dominance	Right (3), Left (7)	Right (8), Left (2)
Treadmill speed (m/s)	0.93 ± 0.13	1.05 ± 0.13
Ankle weight (% BW)	8.72%	8.89%

FIGURE 1 | Participant shown standing on the treadmill with the unilateral ankle weight attached.

Procedures

Prior to data collection, reflective markers were placed at specific locations to record lower extremity kinematics and temporal spatial data during the walking trials using a 3D motion capture system. Data were collected with Nexus (Vicon Motion Systems, Denver, CO, USA) and processed with Visual3D (C-Motion; Germantown, MD, USA) and Matlab (Mathworks, Natick, MA, USA). Only temporal-spatial data are reported here.

Each participant completed a single test session lasting less than 2 h which consisted of multiple treadmill walking trials (Bertec, Columbus, OH, USA) at self-selected speed as estimated from three trials of over ground walking. For all treadmill trials, participants wore a harness without weight support (Zero-G; Aretech, Ashburn, VA, USA) to ensure safety since they were instructed not to use the handrails. The gait adaptation paradigm consisted of a unilateral ankle weight of approximately 10% of body weight up to a maximum of 12 lbs which was deemed sufficient through preliminary testing to induce changes in the walking pattern without making it too difficult to walk. The weight was secured firmly onto the lower calf with Velcro with care not to place it so low as to interfere with ankle motion.

Each child performed five walking trials: a 2-min baseline, a 6-min trial with the weight on the non-dominant leg, a 2-min post-weight trial, a second 6-min trial with the weight on the dominant leg, and a final 2-min post-weight trial. A brief rest was provided at the midpoint of each 6-min weighted trial to reduce leg fatigue. Each trial began with the subject standing

on the treadmill, then the belt accelerated at 0.3 m/s^2 up to the self-selected speed. The weight was attached and removed between trials while the participant stood still on the treadmill. Participants were instructed not to move their feet before the post-weight trials. Motion capture data were collected for the duration of each trial condition. We focused on two parameters commonly reported in other gait adaptation studies, step length and swing time. Since standardized procedures were utilized across groups and the primary outcomes were from gait analyses, sources of biases during testing or data analyses were well-controlled.

Data Analyses

Mean values for step length and swing time were computed within groups for each leg during the baseline, weighted and post-weight trials. To evaluate changes across conditions, groups and legs, a generalized linear mixed model was used with leg (dominant and non-dominant) and condition (baseline, non-dominant leg weighted, post non-dominant weight, dominant leg weighted, post dominant leg weight) as within subject factors and group (control and CP) as the between subject factor, with *post hoc* tests performed as indicated and *p*-values adjusted for the number of comparisons.

To better evaluate changes over time during the weighted conditions, we separated the data in the first and second half of that trial for the *post hoc* analyses. Since adaptation is a gradual process of adjustment to the perturbation, we expected to see a greater change in the second half vs. the first half of the weighted trial. In contrast, if the adjustment to the weight was immediate as indicated by a greater change between baseline and the first half of the weighted trial, this would mean that there was not progressive error reduction or adaptation. Similarly, aftereffects are a transient persistence of a learned behavior, so if these were present, we would not necessarily expect to see a difference between the second half of the weighted trial and the post-weight trial, but there should be a difference from the baseline trial.

Step length asymmetry is a consistent finding in those with unilateral CP, so we were also interested in how unilateral weighting of each leg would affect symmetry while the weight was on and after it was removed. The main goal here was to assess the effect of the perturbation, weighting one leg, before and after adaptation to it occurred and also at the end of the session to determine whether a return to baseline was seen. For this, we averaged step lengths over the first and last 5 steps of each condition. A symmetry index (SI) was computed as the ratio of dominant over non-dominant step lengths and compared across the two weighted and post weight conditions and groups. To evaluate changes in SI, a general linear mixed model was used with the condition as the within subject factor and group as the between subject factor.

RESULTS

Step Length and Swing Time

Figure 2A shows time series data for the averaged step length of each step per leg separated by group during the two unilateral weighted (dominant, non-dominant) and three unweighted conditions (baseline and two post-weight trials). **Figure 2B** shows similar data for swing time. Since the number of steps across subjects was not equal, the number of steps from the participant with the lowest number in each condition determined the number of steps included for averaging, with extra steps excluded always from the end of the each condition. Statistical results for mean differences across conditions by group, leg and parameter are shown in **Table 2**.

For step length, analyses showed a main effect for condition but no main effect for group or leg. The weighted conditions clearly altered behavior in both legs; however, the pattern of significant changes differed between the weighted and non-weighted leg as shown by the *post hoc* analyses for condition in **Table 3** with results shown for each leg in the entire sample and also by group (with p values adjusted to <0.0031 for multiple [16] comparisons). In the unweighted legs, step length increased

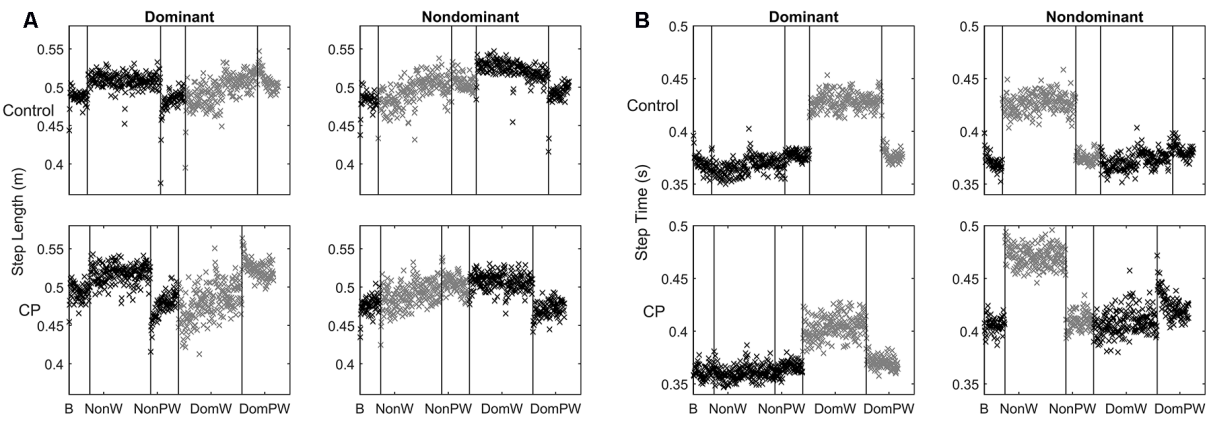

FIGURE 2 | (A,B) Time series data for: **(A)** step length shown here as the mean value for each step across each condition separated by group and leg with the weighted leg and its subsequent post-weight period shown in gray; and **(B)** swing time shown here as the value for each step across each condition separated by group and leg with the weighted leg and its subsequent post-weight period shown in gray.

TABLE 2 | General linear mixed model results for step length, swing time and symmetry index with all *p*-values listed and those <0.05 indicated in bold.

	Condition	Leg	Group	C × L	C × G	L × G	C × L × G
Step length	**<0.001**	0.68	0.89	**<0.001**	0.10	0.38	**0.04**
Swing time	**<0.001**	**<0.001**	0.16	**<0.001**	0.35	**<0.001**	0.10
Symmetry index	**<0.001**	–	0.38	–	**0.04**	–	–

C, condition; L, leg; G, group.

immediately as indicated by a significant increase from baseline to the first half of the weighted trials that was maintained but did not increase further in the second half of the weighted trials. Values also returned to those at baseline in the post-weight trials. In the weighted legs, the baseline condition did not differ significantly from the first half of either the weighted trials, but step length instead gradually increased during weighting. This lead to a significant difference from the first to the second half of the weighted period in the non-dominant weight condition that did not reach significance in the dominant weight condition even though the mean step length showed a similarly increasing trend. Step lengths failed to return to baseline and were significantly less than those of the post-weight trials for both weighted legs. These results indicate that only the weighted legs showed adaptation (i.e., more gradual increase) and persistence of after effects (i.e., no return to baseline). Since the perturbation was unilateral, it is not surprising that leg behavior varied depending on whether it was weighted or not; hence these results also explain why a significant interaction between condition and leg was found.

The absence of a main effect for group indicates that children with CP had similar capabilities to children without CP in adapting their step lengths to a leg perturbation and in retention of the adaptation. As seen in **Figure 2A**, the sample with CP had greater variability in step lengths, as seen visually by more dispersion in the data points, than controls especially in the leg that was weighted, but their step length patterns were remarkably similar across groups. Aftereffects were also visually apparent in both post-weight conditions in both groups and were of similar magnitudes.

The lack of a main effect for leg seemed surprising at first since it is visually apparent that the legs behaved differently in CP vs. controls. However, this difference was revealed instead by a triple interaction between condition, leg and group. This can be explained by the tendency for children with unilateral CP to make greater adjustments with their dominant relative to their non-dominant leg regardless of which leg was weighted, which was not the case in the controls. *Post hoc* analyses for conditions within groups separated by leg, show this more clearly (**Table 3**). When the non-dominant leg was weighted, only the dominant leg in CP demonstrated a significant mean change from baseline to weighting and from weighting to weight removal. Differential group responses were also seen in the dominant weight condition. The control group showed a significant change from baseline to the first half of the dominant weight condition for the non-dominant leg that was not seen in CP, although both groups showed significant changes in the non-dominant leg from the second the half of the weighting trial to the post-weight condition. While not conclusive, these results further support the observed greater reliance on the dominant leg in the CP group.

For swing time, analyses revealed significant main effects for condition and leg, and leg by group and leg by condition interactions. No main effects for group were found. The main effect for leg is related to the immediate and persistent response on the weighted leg of decreased swing time. The leg by group interaction can be explained by asymmetry in the response magnitude across legs only in the CP group, with the non-dominant leg showing a more pronounced response to weighting in this case than the dominant leg. This contrasts the more similar response to weighting across legs in controls and is opposite to step length results in CP where the dominant leg made relatively greater adjustments.

The pattern for swing time while clearly distinct from that for step length, was again remarkably similar across groups. The weighted leg had a more apparent adjustment to the weight and it was immediate and consistent over the time period the weight was on (i.e., no adaptation). The post-weight response was a similarly strong and immediate return to baseline, rather than a brief persistence of the learned behavior (i.e., no after effects). The *post hoc* analyses supported this, revealing a significant

TABLE 3 | *Post hoc* comparisons for step length for each condition, separated by leg, in the entire sample and within groups with statistically significant changes indicated in BOLD (*p* value set at <0.0031 to account for multiple comparisons).

Comparisons	*p* value (all)	*p* value (Control)	*P* value (CP)
NONDOM leg weighted			
Base-W1 NONDOM	0.970	0.926	0.966
W1-W2 NONDOM	**0.001**	**0.003**	0.123
W2-PW NONDOM	0.563	0.682	0.309
Base-PW NONDOM	**<0.001**	0.019	**0.002**
Base-W1 DOM	**0.001**	0.023	**<0.001**
W1-W2 DOM	0.287	0.635	0.367
W2-PW DOM	**<0.001**	0.006	**<0.001**
Base-PW DOM	0.509	0.423	0.116
DOM leg weighted			
Base-W1 NONDOM	**<0.001**	**0.001**	0.009
W1-W2 NONDOM	0.131	0.072	0.822
W2-PW NONDOM	**<0.001**	**0.002**	**0.003**
Base-PW NONDOM	0.680	0.321	0.282
Base-W1 DOM	0.355	0.878	0.219
W1-W2 DOM	**0.001**	0.022	0.009
W2-PW DOM	0.066	0.629	0.026
Base-PW DOM	**<0.001**	0.022	**<0.001**

NONDOM, non-dominant leg; DOM, dominant leg; CP, cerebral palsy; Base, baseline; W1, first half of the weighting period; W2, second half of the weighting period; PW, period after weight removal.

mean change from the baseline to the weighted condition and from that to the post-weight condition for the weighted leg in both groups with no difference between the baseline and post-weight condition. Additionally, in the control group only, there was a significant mean change from the weighted to the post-weight trial in the leg opposite the one that was weighted.

Results for the SI for step length showed a main effect for condition. Basically when examining the group as a whole, with initial weighting the unweighted leg took longer steps lengths significantly increasing the asymmetry from baseline. Upon weight removal, there was a significant "rebound" effect in the opposite direction. Each of these reverted back towards baseline over time. No main effect for group was identified; however, a significant interaction effect between group and condition was found which likely reflected the asymmetry in the responses to weighting seen across legs in CP. Of the ten participants with CP, six had an initial SI more than one standard deviation greater than that in controls indicating a longer step length on the dominant side and three had a SI more than one standard deviation less than controls with one within the normal range. The pattern of change in SI for the control group compared to the entire group with CP and the two sub-groups with CP (those with greater or lesser asymmetry than normal) are shown in **Figures 3A,B**, respectively. **Figure 3A** illustrates the greater tendency in CP to rely on the dominant leg as seen by the upper shift in nearly all comparable data points. **Figure 3B** shows that in both subgroups with CP, error augmentation or weighting the leg with the shorter step length in CP, regardless of whether that leg is the dominant or non-dominant one, results in a greater limb symmetry at the end of the session.

DISCUSSION

Contrary to our hypothesis, those with unilateral CP did not differ from controls in ability to adapt their step lengths to a unilateral perturbation and to retain this adaptation. Masia et al. (2011) noted that children may have a less well-calibrated sensorimotor system than adults due to less motor experience and continual readjustments in response to rapid growth which makes learning less efficient for them. Children with CP may have even greater motor "noise" as seen here by their more variable responses to weighting than those without CP; however, it is interesting to note that their learning abilities were not found to differ from controls.

Similar findings of no differences in adaptation have interestingly been reported in adults post-stroke and with Parkinson Disease and authors attributed these results to little if any involvement of the cerebellum in those patient groups (Reisman et al., 2010). In contrast, patients with clear cerebellar involvement (Ilg et al., 2008) and even those with more diffuse brain injuries such as traumatic brain injury (Vasudevan et al., 2014) did demonstrate impaired adaptation. In our sample, most had focal unilateral lesions (9 of 10), with seven of those having stroke as the primary etiology so it is perhaps not surprising that their response was similar to that in adult-onset stroke. A previous study comparing balance in children with and without CP, showed that the relative difference in performance between eyes open and closed balance conditions was similar across groups indicating no evidence of significant cerebellar involvement (Damiano et al., 2013). Children with CP in that study also had mild motor deficits and could stand independently although they had poorer balance than

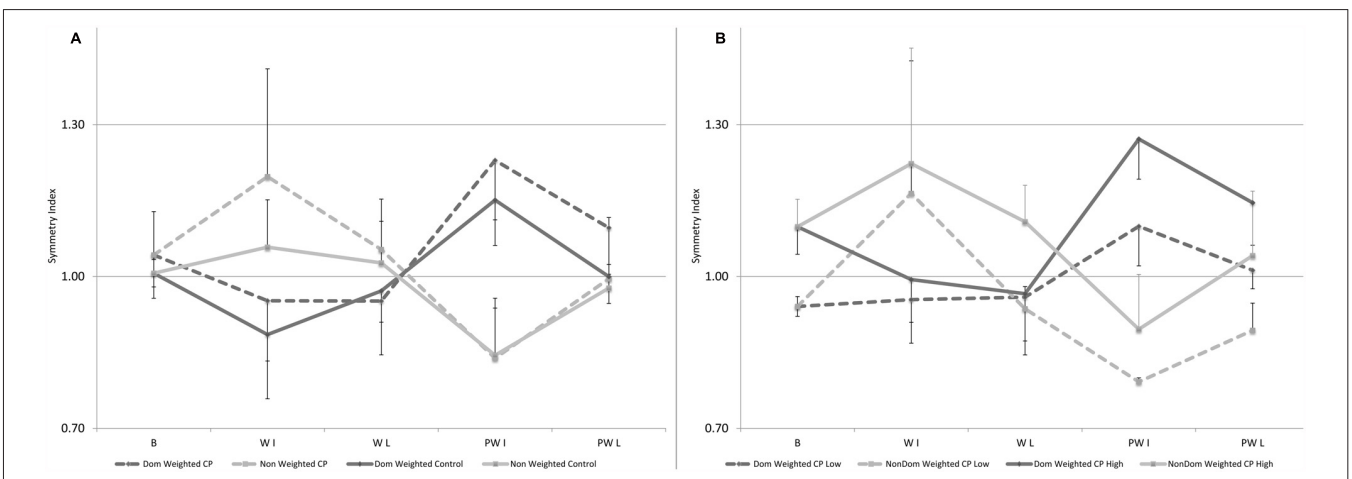

FIGURE 3 | (A,B) Mean data for Symmetry Index (SI), defined as the ratio of dominant over non-dominant step length, shown here for baseline, and for the first and last five steps in the weighted and post-weight periods in: **(A)** the control group and the group with CP with the dominant leg weighted condition in black (or black-dotted) and the non-dominant weighted condition in gray (or gray-dotted). Errors bars are shown in one direction to avoid overlap and are directed up for the non-dominant leg and down for the dominant leg; and **(B)** the two subgroups with CP with the one having SI greater than normal (n = 6) shown by solid lines and the one having SI lower than normal (n = 3) in the dotted lines, with dominant leg weighted conditions in black for the subgroup with the high SI or black-dotted for the subgroup with the low SI and the non-dominant weighted condition in gray for the subgroup with the high SI or gray-dotted for the subgroup with the low SI. Error bars are shown in one direction only, this time by sub-group, with those for the solid lines pointing up and those with the dotted lines pointing down. Some error bars were too small to be visible beyond the data point.

controls in the static eyes open position. Many with CP, especially those with bilateral brain injuries, tend to have more diffuse white matter (periventricular leukomalacia) or gray matter (anoxic) brain injuries, so they may be more likely to have direct or indirect involvement of the cerebellar pathways and therefore a greater likelihood of demonstrating deficits in motor learning than the children with unilateral CP who were studied here.

As seen in adults with stroke, children with unilateral brain injuries also demonstrate gait asymmetry that could perhaps be targeted using adaptation-based training approaches. Regnaux et al. (2008) had subjects with stroke undergo a single session where their unaffected leg was "constrained" using a unilateral weight on that side. Immediately after weighting and up to 20 min post, they observed a significant mean increase in loading on the affected side and increased gait speed. Individual step lengths were not reported but mean step length was 0.07 meters longer on the paretic side at onset. Both legs increased mean step lengths by the same amount immediately after training although only the change on the paretic side reached significance. After 20 min both increased again but the degree of step asymmetry remained virtually the same (mean paretic step length was 0.07 and 0.06 m longer immediately and after 20 min, respectively). Reisman et al. (2013) employed a similar strategy although the stated rationale was different: to exaggerate the asymmetry rather than constraining the better limb. Using a split-belt paradigm, they slowed belt speed on the side with the initially shorter step length which was the non-paretic side in 11/12 subjects and trained them this way for 12 sessions. Their subjects were categorized as either "responders" ($n = 7$) whose step asymmetry was reduced though bilateral increases in step length that were more pronounced on the initially shorter side, and "non-responders" ($n = 5$) whose step asymmetry did not change. Stance time asymmetry, although clearly manipulated here, did not change significantly in either subgroup.

While not reported, it is very possible that the mean results for their entire sample (responders plus non-responders; Reisman et al., 2013) failed to show a significant change in asymmetry from training, similar to the mean results from the previous single training bout study (Reisman et al., 2007); however, their study points to the importance of going beyond mean results and examining individual or sub-group responses to training to identify and ultimately characterize those that might benefit from a specific strategy (Damiano, 2014). In our study, the effects of loading *both* legs were examined so we could compare changes in asymmetry in response to each. As seen in **Figure 3A**, the control group showed a very symmetrical pattern across legs with a clear asymmetry in the response across legs in CP (note: only performance of the weighted leg is shown in this figure). Although sub-groups were too small for statistical analyses, in **Figure 3B**, we show the SI data separately for the participants with CP who have a longer step length on the dominant side (solid lines indicate SI is greater than 1; $n = 6$) vs. on the non-dominant side (dotted lines indicate SI less than 1; $n = 3$), with the one participant whose step asymmetry was within 1 standard deviation excluded. Our data indicate, similar to the conclusions from the two stroke studies, that loading (or speeding up in the split belt treadmill studies) the leg with the initially shorter step length leads to greater step symmetry in the retention phase, both immediately upon weight removal and at the end of the 2 min post-weight trial, and this principle holds for both sub-groups; whereas the opposite strategy on both sides failed to reduce and in some cases worsened the degree of asymmetry. Thus this study provides additional evidence that error augmentation may be more effective than reduction for improving step asymmetry.

Vaswani and Shadmehr (2013) further explored the important role of error in adaptation-induced change showing that as errors were artificially eliminated, the motor changes (learning) started to decay. They also postulated that adaptation involves two types of memories, one that disengages when the brain detects a change in the task and one that persists despite the change which they referred to as a trace of the motor memory. This may help explain why even after single session paradigm where the behavior rapidly shifts towards baseline on removal of the perturbation, there also appears to be some residual short term effect, as seen here in the improvement in symmetry. These findings have clinical relevance for therapists who have long recognized that they could perturb the system to facilitate a change in behavior within a treatment session. However, we now know that for these changes in behavior to persist, extensive practice is required. Also relevant to practice, therapists often try to incrementally improve or shape motor skill through practice, as seen for example in constraint-induced movement therapy approaches. However, stimuli that produce adaptation are typically fairly dramatic manipulations and may be an effective alternative strategy to shift motor behaviors that warrants further investigation.

Another interesting result here was that the leg asymmetry differed in the two parameters with the weighted non-dominant leg showing the greater relative change in swing time and the dominant leg showing slightly larger and more variable responses in step length when either leg was weighted. It could perhaps be concluded that individuals with CP rely more on the dominant leg to adjust to challenging perturbations simply because it has greater motor capabilities because cortical areas subserving them were not damaged. Studies in stroke have demonstrated greater connectivity in the unaffected vs. affected hemisphere and its dominant role particularly earlier in recovery (Bajaj et al., 2015). The change in swing time appears to be a more automatic or already well-learned response to the perturbation that does not involve further learning and may be stronger on the non-dominant side because the dominant side is more engaged in learning to accommodate step length to the perturbation. In the Musselman et al. (2011) study on infants and adults using the split-belt paradigm, they also showed immediate changes in stance time in all infants, regardless of their response to step length, suggesting that these had different neural mechanisms. Interestingly, they also showed that infants had slower rates of learning than adults, similar to the findings by Masia et al. (2011) in older children, and that the larger

the error they experienced to the perturbation, the slower the learning.

One limitation of this study was the decision to weight the dominant leg first which we presumed would be easier and then proceed to the harder task of weighting the non-dominant leg instead of counterbalancing to avoid the possibility of order effects. However, we do not think that this had a significant effect on the results because the main comparison was between groups, each of which followed the same order and the response to unweighing was similar across legs in the control group. Another potential limitation was the possibility of fatigue especially in the children with CP. However, the values for step length and swing time in the final post-weight trials were either greater than or equal to the baseline values in both groups, indicating that fatigue was unlikely an issue here. Also, while the mean age across groups was not statistically different, the control group was several years younger than the group with CP. Since adaptation seems to increase with age, it is possible that older children with CP, while similar in adaptation ability to younger children without CP, may not be as capable as children of the exact same age.

In conclusion, in this first gait adaption study in CP, participants with unilateral CP did not differ in adaptation or retention from age-matched controls, suggesting similar abilities to learn new motor skills. Further examination of individual participants in this study or of children with different types of CP may be warranted to help explore as yet unexplained variability in responses to motor training that have been reported in CP. Weighting the side with shorter step length side, but not the converse, lead to improvements in step symmetry in CP as has been shown in stroke, suggesting that error augmentation may be an effective training strategy.

AUTHOR CONTRIBUTIONS

DLD, CJS, TCB and HSP had substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content and final approval of the version to be submitted for publication. All (DLD, CJS, TCB, HSP) further agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Children with Spastic Cerebral Palsy Experience Difficulties Adjusting Their Gait Pattern to Weight Added to the Waist, While Typically Developing Children Do Not

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The prevalence of childhood overweight and obesity is increasing in the last decades, also in children with Cerebral Palsy (CP). Even though it has been established that an increase in weight can have important negative effects on gait in healthy adults and children, it has not been investigated what the effect is of an increase in body weight on the characteristics of gait in children with CP. In CP, pre and post three-dimensional gait analyses are performed to assess the effectiveness of an intervention. As a considerable amount of time can elapse between these measurements, and the effect of an alteration in the body weight is not taken into consideration, this effect of increased body weight is of specific importance. Thirty children with the predominantly spastic type of CP and 15 typically developing (TD) children were enrolled (age 3–15 years). All children underwent three-dimensional gait analysis with weight-free (baseline) and weighted (10% of the body weight added around their waist) trials. Numerous gait parameters showed a different response to the added weight for TD and CP children. TD children increased walking velocity, step- and stride length, and decreased double support duration with a slightly earlier timing of foot-off, while the opposite was found in CP. Similarly, increased ranges of motion at the pelvis (coronal plane) and hip (all planes), higher joint angular velocities at the hip and ankle, as well as increased moments and powers at the hip, knee and ankle were observed for TD children, while CP children did not change or even showed decreases in the respective measures in response to walking with added weight. Further, while TD children increased their gastrocnemius EMG amplitude during weighted walking, CP children slightly decreased their gastrocnemius EMG amplitude. As such, an increase in weight has a significant effect on the gait pattern in CP children. Clinical gait analysts should therefore take into account the negative effects of increased weight during pre–post measurements to avoid misinterpretation of treatment results. Overweight and obesity in CP should be counteracted or prevented as the increased weight has detrimental effects on the gait pattern.

Keywords: Cerebral Palsy, gait, weight, body mass, EMG, muscle weakness

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INTRODUCTION

According to the World Health Organization (WHO), in 2014 more than 1.9 billion adults were overweight. Of these over 600 million were obese (World Health Organization, 2016b). Furthermore, the worldwide prevalence of obesity has more than doubled between 1980 and 2013 (Finucane et al., 2011; Ng et al., 2014).

Obesity has an important impact on reduced quality of life (Taylor et al., 2013) and public health (Visscher and Seidell, 2001), as it is related to the development of several non-communicable diseases such as cardiovascular disease, type 2 diabetes mellitus, and osteoarthritis (World Health Organization, 2016b).

Similarly, in children an increase in overweight and obesity has been observed over the last decades (de Onis et al., 2010). This is not only the case in typically developing children (TDc), but also in children that already present with a pathology; e.g., children with Cerebral Palsy (CPc) (Rogozinski et al., 2007; Park et al., 2011).

Cerebral Palsy is the most common developmental cause of physical disability in the world (Aisen et al., 2011), with a prevalence of 2–3 in 1000 live births (Odding et al., 2006). It originates from non-progressive impairments to the brain before, during or shortly after birth (Bax et al., 2005), resulting in persistent (primary) motor and sensory impairments such as abnormal motor control, muscle strength, and/or muscle tone. As a result of abnormal muscle activity or loading of the bones, secondary impairments can develop over time, such as shortened muscles which will restrict the joint range of motion. These primary and secondary impairments result in a pathological gait pattern in CPc.

Many treatment modalities in CP are aimed at improving the gait pattern, by focusing on the primary and secondary impairments. Orthoses, for instance, are often used to control the position and movement of the ankle (Novacheck et al., 2009). Neurosurgery, on the other hand, can reduce the patient's spasticity by means of selective dorsal rhizotomy or intrathecal baclofen, while orthopedic surgery can address bone deformities and muscle contractures (Novacheck and Gage, 2007). Gait analysis has a crucial role in the treatment of gait impairments in CPc, as it allows (1) the identification of the specific deficits of each patient, and (2) the evaluation of the outcome of treatment interventions specifically selected to target those deficits (Schwartz et al., 2004; Novacheck and Gage, 2007).

Interventions in CPc are often assessed via pre–post treatment three-dimensional gait analysis. Until now though, the effect of an alteration in the body weight is usually not taken into consideration when interpreting pre–post data, even though a considerable amount of time can elapse between the two measurements.

However, literature in other populations provides indications that changes in body weight result in alterations in the gait pattern. In children with overweight and obesity for example, it has been reported that additional body mass leads to higher foot loading, with a disproportional impact on the midfoot area (Cousins et al., 2013; Mueller et al., 2016). Both adults and children with obesity have been found to walk with increased peak knee adduction moments (which may result in excessive joint loading) (Gushue et al., 2005; Browning and Kram, 2007). Adults with obesity also have been reported to walk with increased external knee flexion moments, and decreased knee rotation moments compared to non-overweight adults (Harding et al., 2012).

Furthermore, some researchers have indicated changes in EMG activations due to obesity in children and adults as well. Blakemore et al. (2013), showed that during fast walking, overweight children had longer gastrocnemius activity during stance, but shorter gastrocnemius activity during swing (Blakemore et al., 2013). A study by Amiri et al. (2015) indicated that adults with obesity walked with significantly prolonged gastrocnemius and quadriceps EMG activity during the stance phase (Amiri et al., 2015). In adults, walking while carrying load resulted in increased EMG activations of the vastus lateralis and gastrocnemius, as well as increased durations of biceps femoris, gastrocnemius, vastus lateralis, and semimembranosus activity (Ghori and Luckwill, 1985; Simpson et al., 2011).

As such it appears that increased weight has a significant effect on several aspects of the gait pattern, including kinematics, kinetics and EMG.

To the best of our knowledge, the effect of increasing the body weight on the characteristics of gait in CPc has not yet been investigated. To examine this experimentally, one could either gradually increase the weight of CPc over several weeks, or investigate the effect of an immediate increase in weight. One could argue that the gait adaptations to an immediate increase of weight will not necessarily resemble those that happen during the slow increase in body weight as is the case for obesity. In the latter case, the gait pattern can slowly adapt to very small increments in weight. However, body weight can increase more rapidly during daily life as well, i.e., during the growth spurt. During the grow spurt, ambulatory CPc typically show fast increases in body weight, similarly as TDc (Day et al., 2007). In the current study we have opted for the latter, as this is the first step to take to provide further insights into the possible adaptations in CPc to added weight. Thus, the experimental paradigm used in the current study, more closely resembles this phenomenon rather than a slow increase in body weight. As CPc often undergo treatment interventions at an age before or close to the growth spurt, it is of interest to investigate the influence of an immediate increase in weight on the gait parameters in CPc.

The current study examined whether experimentally increasing the body weight influences the spatio-temporal gait characteristics, three-dimensional gait kinematics, kinetics, and EMG activations in CPc. We hypothesize that CPc will experience difficulties in adjusting their gait pattern to the added weights; i.e., they will present with more negative changes in their gait due to the increase of body weight compared to TDc (e.g., decrease walking speed, smaller step lengths and ranges of joint motion). Additionally, we hypothesize that more negative changes in the gait pattern will appear in CPc with relatively weaker lower limb muscles compared to children with relatively strong lower limb muscles as they will experience more difficulties negotiating the increased load imposed on their musculoskeletal system.

TABLE 1 | Participant characteristics.

	CP group		TD group
	Adequate muscle strength group (*n* = 17)	**Moderate muscle strength group (*n* = 13)**	**Typical: typical muscle strength group (*n* = 15)**
Average age (SD)	9 y 6 m (±1 y 3 m)	6 y 5 m (±2 y 3 m)	8 y 6 m (±1 y 3 m)
Average weight (SD)	31.8 kg (±10.7 kg)	24.3 kg (±9.3 kg)	29.8 kg (±7.6 kg)
Median (IQR) range of motion (degrees)			
Hip extension	0° (0–0°)	0° (−5–0°)	Nr
Knee extension	0° (0–0°)	0° (0–5°)	Nr
Ankle dorsiflexion	0° (0–10°)	5° (0–10°)	Nr
Selectivity (range 0–2)			
Knee flexors	2 (2–2)	1.5 (1.5–2)	Nr
Knee extensors	2 (2–2)	2 (1.5–2)	Nr
Ankle plantarflexors	1.5 (1.25–2)	1.5 (1–1.5)	Nr
Diagnosis	CP	CP	TD
Unilateral	9	3	Na
Bilateral	8	10	Na
GMFCS			
I	13	4	Na
II	4	9	Na

SD, standard deviation; y, years; m, months; IQR, interquartile range; range of motion, maximal joint angle achieved passively; Nr, normal; CP, cerebral palsy; TD, typically developing; Na, not applicable; GMFCS, Gross Motor Functional Classification Score.

MATERIALS AND METHODS

Patients

For this study, a group of CPc meeting specific inclusion criteria (*CP group*) was compared to a control group of TDc. The characteristics of both groups are discussed below and summarized in **Table 1**. A schematic overview of the study design can be found in **Figure 1**.

For the *CP group*, CPc were recruited at the Laboratory of Clinical Motion Analysis of the University Hospital Leuven (UZ Pellenberg), when they met the following inclusion criteria: (a) predominantly spastic type of CP, (b) age between 3 and 15 years, (c) ability to walk (with or without walking aids), (d) sufficient cooperation to follow verbal instructions, (e) no history of lower limb surgery, (f) no lower limb Botulinum Toxin-A treatment within 6 months prior to the 3DGA, and (g) adequate or moderate lower limb muscle strength. The latter was defined as a MMT-score of at least >2.5 on a 9-point scale (Supplementary Table A) based on the MMT scale developed by Daniels and Worthingham's scale for manual muscle testing (Daniels and Worthingham, 1986; Cuthbert and Goodheart, 2007). Strength was assessed for the knee flexors, knee extensors, and plantarflexors, as these muscles are assumed to be the main actuators for handling the additional load during the weighted walking (weighted walking task is described below). Based on the median MMT-score for these three muscle groups, the CPc were subdivided into two muscle strength groups: children whose median MMT $\geq$ 4 were classified into the *adequate* lower limb muscle strength group, while children with a median MMT-score between 2.5 and 4 were classified into the *moderate* lower limb muscle strength group. This cut-off value was selected based on the results of initial pilot tests where it was observed that children with a MMT score > 2.5 were still able to accurately execute the weighted walking task for the full testing procedure. In addition to strength, the selectivity of the three lower limb muscles was assessed using a five-point scale as described by Trost (2009) (Supplementary Table A).

Thirty CPc were enrolled in the *CP group*. Their average age was 8 years 5 months (±2 years 3 months). Twelve children were classified as unilaterally involved while 18 were bilaterally involved. Seventeen children were classified as GMFCS level I and 13 as level II. Seventeen children had *adequate* lower limb muscle strength, while 13 showed *moderate* lower limb muscle strength. Specific lower limb ranges of motion and levels of selective motor control are summarized in **Table 1**.

The TD control group consisted of 15 children with an average age of 8 years 6 months (±1 year 3 months) without a history of orthopedic or neurological pathology. Comparison of the gait adaptations in response to the weighted walking task in the *CP group* to those observed in the TD group enabled the identification of 'non-typical responses' (gait adaptations that were not observed in the TD group). Non-typical responses unmask 3D gait parameters that alter due to the addition of weight which are specific to the *CP group*.

To avoid the inclusion of correlated data we studied one of the lower limbs in each participant. Therefore, in CPc with unilateral involvement only the involved lower limb side was considered, while in children with bilateral involvement the most involved side was selected. When both sides were equally involved, the left or right lower limb was randomly selected. For TDc, only the right lower limb was investigated.

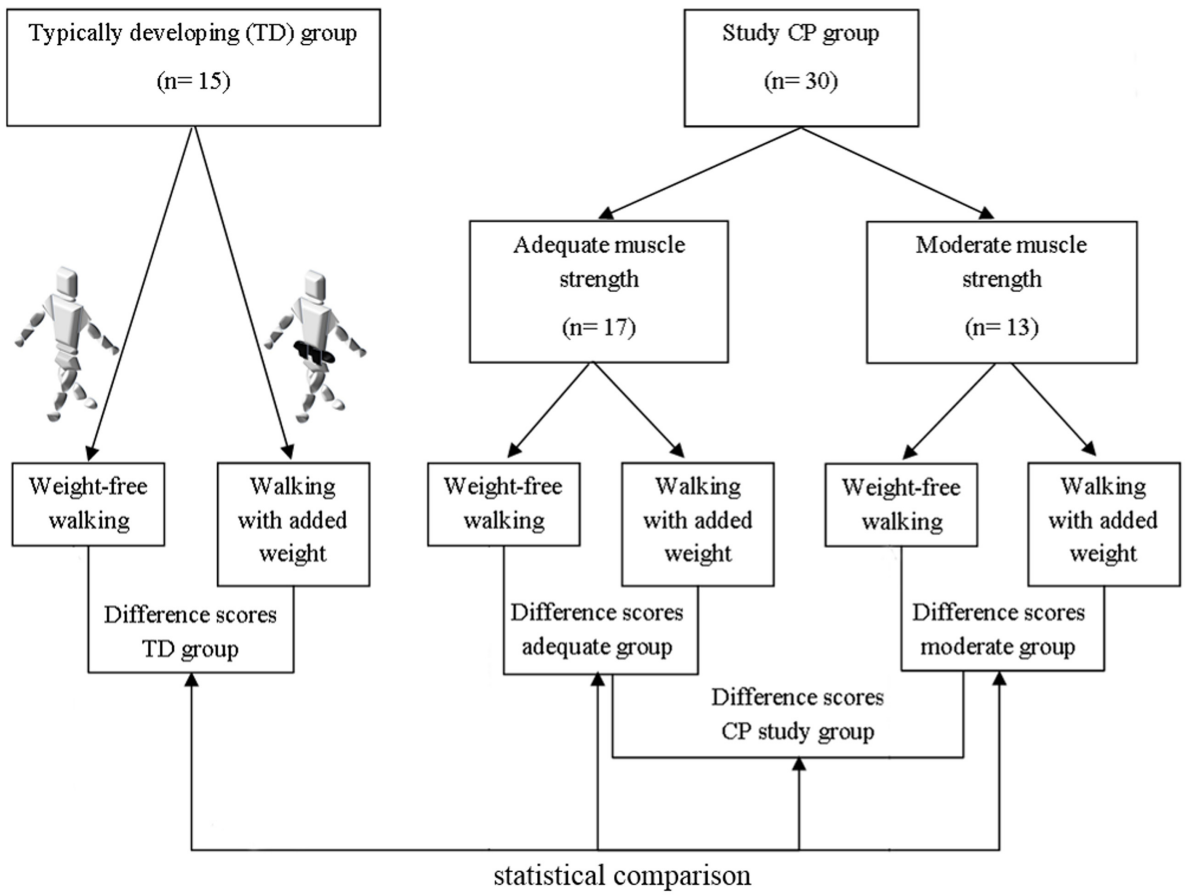

FIGURE 1 | Schematic overview of the set-up of the study. The difference scores (walking with added weights vs. weight-free walking) of typically developing (TD) children, all Cerebral Palsy (CP) children from the CP study group, CP children with adequate strength, and CP children with moderate strength are compared in the current study. In the weighted walking task, 10% of the body weight was added evenly around the waist by means of a black belt. The belt was positioned close to the location of S2 to avoid challenging the equilibrium and ensuring full visibility of the markers of the lower limb Plug-in-Gait marker set.

All experiments were approved by the local ethical committee and informed, written consent was obtained from the study subjects' parents.

3D Gait Analysis and Weighted Walking Task

Gait was evaluated through 3D gait analysis (3DGA). Prior to the 3DGA, lower limb dimensions, body height, and weight were measured to enable an estimation of joint center locations and segmental inertia parameters. Patients walked on a 10-meter walkway at a self-selected speed. Spatiotemporal and kinematic measurements were collected using an eight-camera VICON system (612 data capturing system measuring at 100 Hz; VICON, Oxford Metrics, Oxford, UK), with the lower limb Plug-In-Gait marker set (Kadaba et al., 1990). Two force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) were embedded in the walkway for force registration enabling calculation of kinetics. Surface EMG data were collected from the medial hamstrings, rectus femoris, and lateral gastrocnemius muscles using a 16 channel EMG system (K-lab, Biometrics, The Netherlands; or Zerowire, Aurion, Italy), synchronized with the motion capture system. EMG data was collected with a sampling rate of 1500 Hz and filtered with a zero-phase 6th order butterworth filter with a passband ranging from 20 to 500 Hz. Nexus software (Oxford Metrics, Oxford, UK) was used to define the gait cycles, to calculate the spatiotemporal parameters, and to estimate the joint angles and internal moments and powers normalized to body mass. Seventy-one discrete parameters were extracted from the continuous kinematic and kinetic waveforms based on a study of the literature (Inman et al., 1981; Winter, 1987; Perry, 1992; Schutte et al., 2000; Goldberg et al., 2006; Wolf et al., 2006) and the routine gait analysis protocol used for children with CP at the Clinical Movement Analysis Laboratory of the University Hospital Leuven (Pellenberg).

All children walked barefoot (baseline/weight-free walking). In addition, all children executed the weighted walking task consisting of barefoot walking with 10% of the body weight added around the waist. This percentage of body weight was selected based on initial pilot tests ($n = 9$). In these tests, it was observed that adding 10% of the body weight resulted in an increased load

TABLE 2 | Overview of the spatiotemporal, kinematic and kinetic 3DGA parameters that responded significantly different to walking with added weight between typically developing (TD) children and children from the full CP group, CP children with adequate strength (aCP), and CP children with moderate strength (mCP).

	TD		CP		aCP		mCP	
3DGA parameter	**Weight-free (±SE)**	**Weighted (±SE)**	**Weight-free (±SE)**	**Weighted (±SE)**	**Weight-free (±SE)**	**Weighted (±SE)**	**Weight-free (±SE)**	**Weighted (±SE)**
Step length (m)	0.54 (0.02)	0.57 (0.03)	0.46 (0.02)	0.44 (0.02)	0.49 (0.02)	0.48 (0.02)	0.42 (0.02)	0.39 (0.03)
Walking velocity (m/s)	1.17 (0.03)	1.28 (0.06)	1.03 (0.04)	0.94 (0.04)	1.09 (0.04)	1.02 (0.05)	0.94 (0.06)	0.83 (0.06)
Stride length (m)	1.07 (0.03)	1.14 (0.05)	0.95 (0.03)	0.89 (0.04)	1.03 (0.04)	0.96 (0.04)	0.84 (0.04)	0.78 (0.05)
Duration of double support (s)	0.18 (0.01)	0.16 (0.01)	0.18 (0.01)	0.22 (0.01)	0.18 (0.02)	0.21 (0.01)	0.17 (0.02)	0.24 (0.03)
Timing of foot-off (% GC)	59.4 (0.5)	58.9 (0.4)	57.9 (0.7)	60.6 (0.7)	58.48 (0.95)	60.35 (0.89)	57.18 (1.07)	60.96 (1.09)
Pelvic rom, cor (°)	7.3 (0.4)	8.0 (0.4)	11.6 (0.7)	9.2 (0.6)	11.57 (1.05)	9.29 (0.89)	11.52 (0.92)	8.97 (0.88)
Max hip fl swing (°)	35.3 (1.1)	39.1 (1.2)	44.6 (1.6)	44.9 (1.6)	44.15 (2.37)	45.41 (2.24)	45.16 (1.90)	44.28 (2.16)
Hip rom, sag (°)	45.3 (1.1)	50.1 (1.3)	46.9 (1.5)	48.1 (1.8)	47.22 (2.50)	47.26 (2.58)	46.54 (1.37)	49.17 (2.52)
Hip rom, cor (°)	12.6 (0.7)	14.1 (0.6)	14.4 (0.7)	13.6 (0.9)	14.68 (1.12)	13.22 (1.15)	13.98 (0.83)	14.09 (1.34)
Hip rom, trans (°)	21.3 (1.0)	25.6 (1.6)	21.7 (1.1)	20.1 (1.0)	23.47 (1.10)	21.63 (0.85)	19.40 (1.91)	18.03 (1.99)
Max hip fl vel in swing (°/s)	220.5 (6.6)	251.5 (10.0)	223.6 (9.1)	229.8 (11.2)	226.1 (14.2)	229.3 (16.8)	220.5 (10.5)	230.5 (14.6)
Max plfl vel at toe-off (°/s)	161.9 (12.8)	200.9 (10.2)	127.0 (7.8)	121.2 (9.8)	128.4 (10.4)	116.0 (10.5)	125.1 (12.2)	128.1 (18.3)
Max hip ext moment in stance (Nm)	0.50 (0.08)	0.98 (0.07)	0.99 (0.07)	0.80 (0.07)	1.11 (0.09)	0.90 (0.09)	0.79 (0.09)	0.62 (0.10)
Max hip power gen in stance (W)	0.49 (0.09)	0.76 (0.07)	1.36 (0.16)	1.07 (0.14)	1.42 (0.22)	1.18 (0.20)	1.25 (0.21)	0.88 (0.15)
Max hip power abs in stance (W)	−0.69 (0.05)	−0.97 (0.08)	−0.97 (0.09)	−0.94 (0.09)	−0.99 (0.11)	−1.01 (0.12)	−0.92 (0.16)	−0.82 (0.14)
Max hip power gen at toe-off (W)	1.30 (0.09)	1.65 (0.16)	1.15 (0.11)	1.08 (0.14)	1.32 (0.14)	1.33 (0.19)	0.85 (0.16)	0.63 (0.10)
Max knee power gen in stance (W)	0.54 (0.06)	0.99 (0.13)	0.89 (0.14)	0.89 (0.16)	1.00 (0.20)	1.01 (0.23)	0.69 (0.13)	0.67 (0.11)
Max ankle power abs at loading response (W)	−0.63 (0.08)	−0.73 (0.08)	−0.96 (0.09)	−0.82 (0.08)	−0.95 (0.12)	−0.83 (0.10)	−0.97 (0.15)	−0.81 (0.14)

The values of these parameters for both baseline (weight-free) walking trials and weighted walking trials are presented.
TD, typically developing; CP, cerebral palsy; 3DGA, 3D gait analysis; SE, standard error; rom, range of motion; cor, coronal plane; sag, sagittal plane; trans, transversal plane; max, maximal; fl, flexion; plfl, plantarflexion; ext, extension; vel, velocity; gen, generation; abs, absorption.

on the lower limbs without overloading, assuring the ability to walk across the gait lab for the full test procedure. The results from these pilot tests indicated that adding more than 10% of the body weight limited some patients to perform the walking trials. Hence, 10% of the body weight was chosen. The weight was applied evenly around the waist by means of a belt. The belt was positioned close to the level of S2 (approximate location of the center of gravity) to avoid challenging the equilibrium of the children, and above the marker of the pelvis to ensure full visibility of the lower limb Plug-In-Gait marker set. For both conditions, the children walked at a self-selected speed until three trials with full kinematics, kinetics and EMG were recorded. Internal moments and powers for the weighted walking trials were normalized to the child's body weight plus the additional weight.

Statistical Analysis

For this study, a subset of 71 gait parameters was selected from the output of the 3DGA for both walking conditions (baseline and weighted walking). Spatiotemporal parameters, discrete values of joint angles, moments and powers at specific points in the gait cycle, and the mean EMG frequency over one full gait cycle were automatically extracted from the gait waveforms by means of custom-made software implemented in MATLAB (Mathworks). All parameters were averaged per walking condition over the three registered walking trials. Additionally, the percentage increase/decrease in mean EMG amplitude (raw signal) in response to the added weight was calculated. All EMG parameters were investigated for the medial hamstrings, rectus femoris, and lateral gastrocnemius muscles.

The difference scores between baseline walking and weighted walking were calculated for all the 3DGA parameters of the *CP group* and the TD group. These scores illustrate how the children responded to an increase in body weight. A Kruskal–Wallis test with *post hoc* Mann–Whitney *U* tests [with False Discovery Rate (FDR) correction for multiple testing] compared the responses of the TD children to the responses of (1) all CPc in the *CP group*, (2) CPc with adequate strength, and (3) CPc with moderate strength. A non-parametric method was applied as not all outcome parameters were characterized by a normal or

TABLE 3 | Statistically significant 3DGA parameters and their level of significance per statistical comparison.

	Mann–Whitney *U*-values, *P*-values and Effect Sizes of comparisons based on difference scores (between baseline walking and weighted walking)			
3DGA parameter	**TD vs. CP**	**TD vs. aCP**	**TD vs. mCP**	**aCP vs. mCP**
Step length (m)	89 (0.03)/−0.45	ns	ns	ns
Walking velocity (m/s)	81 (0.02)/−0.49	ns	ns	ns
Stride length (m)	86 (0.02)/−0.47	ns	ns	ns
Duration of double support (s)	74 (0.02)/−0.49	ns	ns	ns
Timing of foot-off (% GC)	56 (<0.01)/−0.59	40 (<0.01)/−0.57	16 (<0.01)/−0.68	ns
Pelvic rom, cor (°)	55 (<0.01)/−0.61	23 (<0.001)/−0.70	32 (<0.01)/−0.57	ns
Max hip fl swing (°)	64 (<0.01)/−0.58	53 (<0.01)/−0.50	11 (0.001)/−0.75	ns
Hip rom, sag (°)	113 (0.03)/−0.40	ns	ns	ns
Hip rom, cor (°)	108 (0.03)/−0.42	ns	ns	ns
Hip rom, trans (°)	92 (0.02)/−0.48	ns	ns	ns
Max hip fl vel in swing (°/s)	108 (0.03)/−0.42	ns	ns	ns
Max plfl vel at toe-off (°/s)	91 (0.02)/−0.48	ns	ns	ns
Max hip ext moment in stance (Nm)	28 (<0.001)/−0.70	15 (<0.001)/−0.75	13 (<0.01)/−0.66	ns
Max hip power gen in stance (W)	82 (0.02)/−0.47	ns	ns	ns
Max hip power abs in stance (W)	89 (0.03)/−0.44	ns	ns	ns
Max hip power gen at toe-off (W)	88 (0.03)/−0.44	ns	ns	ns
Max knee power gen in stance (W)	89 (0.03)/−0.40	ns	ns	ns
Max ankle power abs at loading response (W)	96 (0.04)/−0.42	ns	ns	ns
Mean EMG ampl gastroc increase/decrease (%)	108 (0.03)/−0.42	ns	ns	ns

*Comparisons were based on the difference scores between baseline walking and walking with added weights (for the data, see **Table 2**).*
Data is presented as follows; U-value (p-value)/Effect size. 3DGA, 3D gait analysis; TD, typically developing; CP, cerebral palsy study group; aCP, adequate strength CP group; mCP, moderate strength CP group; ns, not significant; na, not applicable; rom, range of motion; cor, coronal plane; sag, sagittal plane; trans, transversal plane; max, maximal; fl, flexion; plfl, plantarflexion; ext, extension; vel, velocity; gen, generation; abs, absorption; ampl, amplitude; gastroc, gastrocnemius muscle.

Gaussian distribution. All statistical procedures were performed with the SAS system (SAS Institute Inc, SAS Campus, Dr. Cary, NC 27513). Level of significance was set at $P < 0.05$.

RESULTS

When children walked with added weight, changes in the gait pattern were observed for both TDc and CPc. However, for several 3DGA parameters, CPc responded significantly different to the added weight when compared to TDc. **Tables 2** and **3** provide detailed results.

Overall, the TDc appeared to increase their walking velocity, step- and stride length, and decreased their duration of double support while the timing of foot-off decreased slightly, while the opposite pattern was found in CPc (**Figure 2**; **Table 2**).

Increased ranges of motion at the pelvis (coronal plane) and hip (all planes), as well as higher joint angular velocities at the hip and ankle appeared for TDc, while CPc did not seem to change or even decreased the respective ranges of motion and joint angular velocities in response to walking with added weight (**Figure 2**). Furthermore, several moments and powers at the hip, knee, and ankle appeared to increase in TDc, while CPc mainly seemed to decrease their moments and powers during weighted walking (**Tables 2** and **3**).

Finally, a significantly different response in EMG amplitude could be observed in the gastrocnemius. In general, TDc increased their gastrocnemius EMG amplitude when they walked with added weight, while CPc slightly decreased their gastrocnemius EMG amplitude (**Figure 3**).

When the TD group was compared to the subgroups representing the adequately and moderately strong CP children separately, the response of four 3DGA parameters (timing of foot-off, pelvic range of motion in the coronal plane, maximal hip flexion in swing and maximal hip extension moment in stance) was found to differ significantly confirming the above described results (**Tables 2** and **3**). No differences in gait parameters due to the increased weight were found between the two CP groups (the adequately and moderately strong CPc).

DISCUSSION

Walking with extra weight applied around the waist resulted in multiple changes in the gait pattern of both TDc and CPc. For several 3DGA parameters, these changes were significantly different between the TDc and the *CP group*.

The current results are of clinical importance as, due to the increase in prevalence of overweight and obesity in CPc over the last decades (Rogozinski et al., 2007; Park et al., 2011), the gait pattern in CPc to date can be negatively influenced. Consequently, when interpreting 3D gait analysis data, weight should also be considered as a potential factor influencing the gait parameters.

While TDc seemed to be able to successfully handle the extra weight, CPc experienced difficulties to walk with the

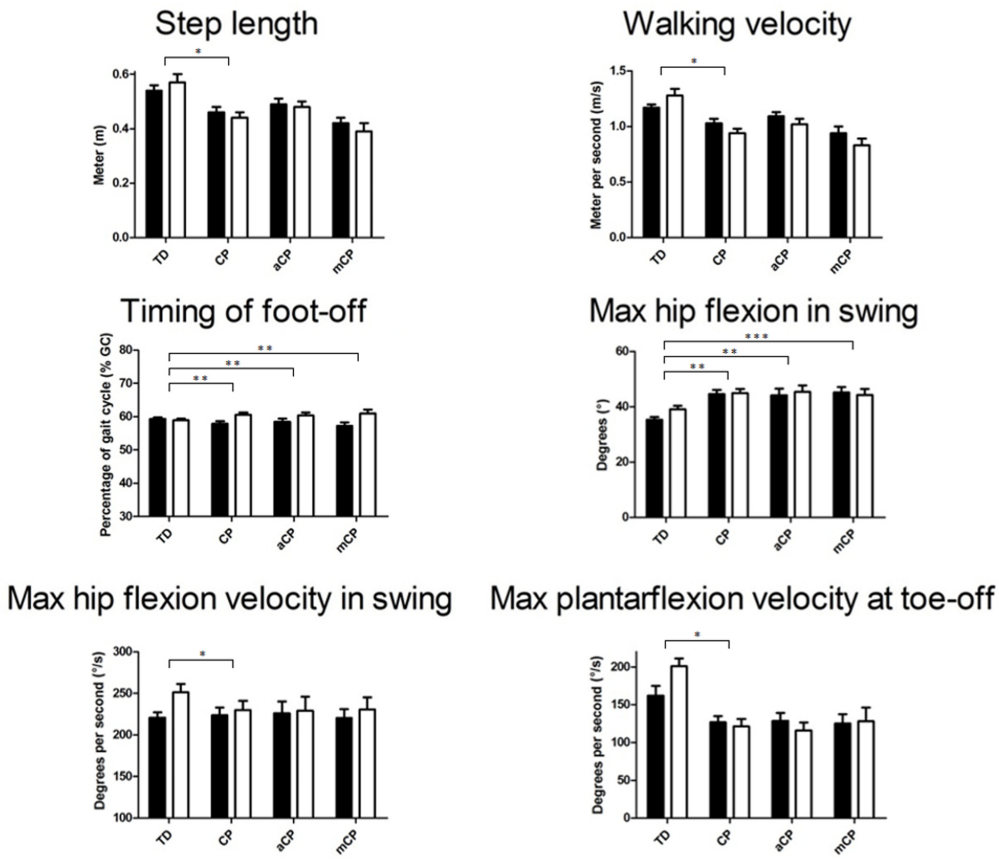

FIGURE 2 | Mean (+SE) 3D gait analysis parameters that significantly differed in response to walking with added weight between TD children and children with CP and/or between TD, CP children with adequate strength (aCP) and CP children with moderate strength (mCP). Black bars represent the weight-free trials, white bars represent the weighted walking trials. See **Tables 2** and **3** for specific significance values. m, meter; % GC, percentage of gait cycle; m/s, meter per second; Gas, gastrocnemius muscle; ampl, amplitude. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

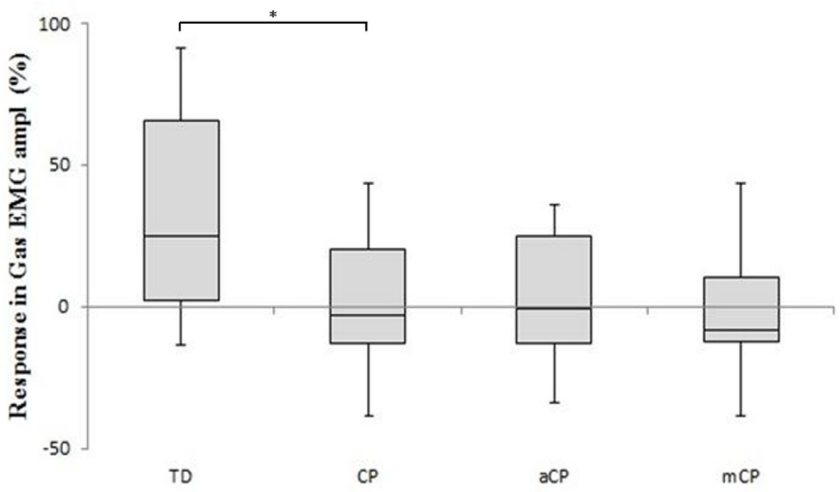

FIGURE 3 | The EMG amplitude difference scores [mean (+SE)] of the gastrocnemius muscle for the TD children and the children with CP in response to walking with added weights. Comparisons are made to the full CP study group and separately to the two muscle strength CP sub-groups: aCP, adequate lower limb strength; mCP, moderate lower limb strength. Difference scores are expressed as percentage increase/decrease. *$p \leq 0.05$.

increased demand. TDc walked with larger ranges of joint motion, and higher moments and powers in response to the added weight (**Table 2**; **Figure 2**). In fact, it appeared that TDc even overcompensated for the extra weight as their resulting gait was faster and more dynamic (reflected in increased kinetics). In contrast, CPc walked slower, with smaller step lengths and ranges of joint motion, and decreased moments and powers. Furthermore, while in TDc the EMG amplitude of the gastrocnemius muscle increased as a result of the added weight, in CPc the EMG amplitude slightly decreased (**Figure 3**). To increase its force output, a muscle can apply two strategies (or a combination of both). Either more motor units are recruited, or the activity of already recruited motor units is synchronized. The first strategy will increase both the EMG frequency and amplitude, while the latter decreases the EMG frequency whilst increasing the amplitude (Lauer et al., 2008). As the EMG amplitude slightly decreased in CPc, it appears that in CP the muscles failed to successfully increase their force output during weighted walking. This finding is supported by the conclusions in the study of Dallmeijer et al. (2011) who found that the lower limb muscles of CPc are characterized by a small muscle reserve during walking (Dallmeijer et al., 2011).

When the CP group was further subdivided into children with adequate and moderate lower limb muscle strength, no significant differences in 3DGA parameters were found due to the added weight in the two subgroups. As such, it appears that the difference in muscle strength between the two CP strength subgroups did not lead to a significantly different response to the added weight. Nevertheless, both CP subgroups presented with difficulties to walk as a result of an increase in weight.

Previous research already provided an indication that weight could have a negative impact on the gait pattern in CPc. Specifically, the sudden increase in body weight during the pubertal growth spurt has been previously related to a more rapid development of the crouch gait pattern in children with diplegic CP (Gage, 2004). This rapid development was suggested to be related to increased body mass with an unfavorable mass-to-strength ratio; i.e., weak muscles can no longer support the toe walking pattern due to the sudden increase in weight (Kedem and Scher, 2016).

The finding that an increase in body weight has significant negative consequences on several gait parameters in CPc that are frequently used in clinical gait analysis (and the overall gait pattern) is of high clinical importance. Given the fact that interventions in CPc are often evaluated via pre- and post 3D-gait analyses, clinical gait analysts should take into account the increase in weight of the patient, definitely if the assessments take place during or close to the growth spurt. If not, unfavorable (or less favorable than expected) gait outcomes could be related to the treatment rather than to the increase in body weight.

These findings underscore the importance of initiatives such as that of the European Union and the World Health Organization to attempt to cease the rise in overweight and obesity in children (European Union, 2014; World Health Organization, 2016a). These initiatives are of vital importance as they can halt the related health problems associated to overweight, but also stop the negative influence of overweight on the gait pattern in CPc.

When interpreting the results of the current study, one should consider some possible limitations.

It could be argued that similar changes in spatiotemporal parameters of gait have been previously reported as specific markers of balance problems (Liao et al., 1997). However, the weighted walking task of the current study was specifically designed to increase the body weight without challenging the equilibrium by adding the weight evenly around the waist and close to the center of gravity. Nevertheless, it cannot be ruled out that there was no effect on balance. Further research could focus on further elucidating the individual role of balance on (spatiotemporal) gait parameters during weighted walking.

The decrease in EMG amplitude in CPc could also be partly related to muscle fatigue. It has been described in healthy adults that muscle fatigue influences the EMG signal and, e.g., reduces its frequency (Rogers and MacIsaac, 2011). Fatigue could have played a part in the setup of the current study, as the muscle endurance during submaximal tasks in CPc is reduced compared to TDc (Eken et al., 2014). Hence, the combination of the different walking trials with and without weights, and the reduced capacity of CPc to endure activities could have induced muscle fatigue. Combined with the fact that CPc have been shown to have a small muscle reserve during walking (Dallmeijer et al., 2011), this means that the EMG amplitude could not be increased in CPc. Further research examining the mean EMG frequencies and amplitudes of lower limb muscles during gait for several consecutive steps of a large group of CP children might further elucidate this problem.

In the current study, the participants' response was investigated when the weight of the body was experimentally/artificially increased. This allowed us to investigate fundamental changes in the gait pattern in TDc and CPc as a response to a sudden increase in body weight. It could, however, be argued that an increase in body weight in daily life (as happens with overweight and obesity) occurs over a long period of time in which the gait pattern can slowly adapt. Even though the participants in the current study received some practice trials with the weights (until they indicated to feel comfortable with the weights), it is possible that a longer period of adaption could have an impact on the gait pattern changes. Nevertheless, results from previous studies in people with overweight and obesity support our findings (e.g., increase in EMG activations, and knee power generation in TDc). Furthermore, our experimental setup could be specifically interesting in the case of a more rapid increase in body weight which occurs during the growth spurt (Day et al., 2007). In this case, however, one should consider that the current setup does not take into account the combination of the lengthening of the body combined with the increase in body weight. Hence, the weight increase during the growth spurt is spread over the body rather than focused on the trunk.

CONCLUSION

The results of the current paper indicate that a multitude of gait parameters (including spatiotemporal measures, kinematics, kinetics, and EMG) are significantly influenced by adding 10% body weight during walking in TDc and CPc. Furthermore, many of these gait parameters differed significantly between TDc and CPc in response to the added weight. Given the rapid increase in body weight during the growth spurt in CPc, specialists in clinical gait analysis should take into account the negative effect of the increased body weight during pre–post measurements to avoid misinterpretation of the treatment results. Overweight and obesity in CPc should be counteracted or prevented as the increased weight has a detrimental effect on their gait pattern (and other health issues).

AUTHOR CONTRIBUTIONS

LVG and KD conceived and designed the experiment. GM, PDC, EO, and LVG performed patient recruitment. PM and LVG tested the participants. PM, LVG, and LB-O performed statistical analyses and interpreted the data. HW, EA, and HB created the software for the data extraction of the three dimensional gait analyses. LVG, MG, HW, and EA performed data quality checks. PM, LVG, and KD wrote the paper. MG performed the lay-out and edited the paper. The writing process and data analysis were supervised by KD.

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SUPPLEMENTARY MATERIAL

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No Decrease in Muscle Strength after Botulinum Neurotoxin-A Injection in Children with Cerebral Palsy

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Spasticity and muscle weakness is common in children with cerebral palsy (CP). Spasticity can be treated with botulinum neurotoxin-A (BoNT-A), but this drug has also been reported to induce muscle weakness. Our purpose was to describe the effect on muscle strength in the lower extremities after BoNT-A injections in children with CP. A secondary aim was to relate the effect of BoNT-A to gait pattern and range of motion. Twenty children with spastic CP were included in the study, 8 girls and 12 boys (mean age 7.7 years). All were able to walk without support, but with increased muscle tone interfering with motor function and gait pattern. Sixteen children had unilateral spastic CP and four bilateral spastic CP. Twenty-four legs received injections with BoNT-A in the plantar flexor muscles. The children were tested before treatment, around 6 weeks after at the peak effect of BoNT-A, and at 6 months after treatment, with measurement of muscle strength, gait analysis, and range of motion. There were no differences in muscle strength in plantar flexors of treated legs at peak effect compared to baseline. Six months after treatment, there was still no change in untreated plantar flexor muscles, but an increasing trend in plantar flexor strength in legs treated with BoNT-A. Parents reported positive effects in all children, graded as: small in three children, moderate in eight, and large in nine children. The gait analysis showed a small improvement in knee extension at initial contact, and there was a small increase in passive range of motion for ankle dorsiflexion. Two children had a period with transient weakness and pain. We found that voluntary force production in plantar flexor muscles did not decrease after BoNT-A, instead there was a trend to increased muscle strength at follow-up. The increase may be explained as an effect of the blocking of involuntary nerve impulses, leading to an opportunity to using and training the muscles with voluntary control. Adequate muscle strength is important for maintaining the ability to walk and knowledge of how a treatment affects muscle strength is useful when selecting interventions.

Keywords: cerebral palsy, spasticity, botulinum toxin, muscle strength, children

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INTRODUCTION

Spasticity is a common problem in children with cerebral palsy (CP) (SCPE, 2002; Himmelmann et al., 2007), which may have an adverse effect on motor development (Gormley, 2001). About 80% of CP is classified as spastic. Spasticity can be defined as a velocity-dependent increase in resistance to passive movement (Sanger et al., 2003), which may prevent voluntary movement and cause muscle shortening (contracture), which in turn can also affect skeletal development.

It has been possible since the 1990s to treat spasticity with botulinum neurotoxin A (BoNT-A). BoNT-A is injected directly into the muscle and inhibits the release of neurotransmitter at the neuromuscular junction, thus blocking nerve impulses to the muscle (Simpson et al., 2008). The effect will increase gradually over a few weeks and maximum effect is usually seen after four to 6 weeks, when the muscle becomes more flexible. The effect is reversible. Improving gait in children who can walk but in whom spasticity is an obstacle is one indication.

The muscle is theoretically weakened by blocking nerve impulses to the muscle fibers, and muscle weakness has been reported in experiments with rabbits and cats (Yaraskavitch et al., 2008; Fortuna et al., 2011). In studies of BoNT-A treatment in children with CP, muscle weakness also has been reported, although only often as comments (Naumann et al., 2006; O'Flaherty et al., 2011). Before the start of the present study we found only one study that actually measured muscle strength (Bjornson et al., 2007). Bjornson et al. compared BoNT-A to a control group receiving saline injections and found that muscle strength had increased 24 weeks after treatment in the BoNT-A group but not in the group receiving saline injections. Thus the reports are conflicting and it is not fully known how BoNT-A affects voluntary muscle strength.

Muscle weakness is common in children with CP and has been described as being more pronounced distally and with an imbalance across joints (Wiley and Damiano, 1998; Ross and Engsberg, 2002). It has been shown to correlate with walking ability, where more than 50% of the predicted normal strength was associated with the ability to walk without aids (Eek and Beckung, 2008). A relationship between muscle strength and gait has been demonstrated in terms of velocity, stride length, gait kinematics, and the gross motor function measure (GMFM; Damiano et al., 2000; Desloovere et al., 2006; Ross and Engsberg, 2007). Gage described five prerequisites for a normal gait pattern (Gage, 2004); stability in stance, foot clearance in swing, pre-positioning of the foot for initial contact, adequate step length, and energy conservation, all of which may be compromised by muscle weakness. The plantar flexor muscles are of special interest as they are the major force generators for forward progression (Kepple et al., 1997; Sadeghi et al., 2001).

Weakness often co-exists with spasticity. This is almost always the case in the gastrocnemius muscle in children with CP. However, muscle strength and selective motor control have a higher correlation with gait parameters than spasticity and joint mobility (Ross and Engsberg, 2002; Ostensjo et al., 2004; Desloovere et al., 2006). With this in mind, it is important not to make weak muscles even weaker with treatment, with a risk of compromising gait pattern and walking ability.

The plantar flexor muscle group is difficult to measure in typically developing children above the age of nine because of the short lever arm, leading to high forces and difficulties in stabilizing with a hand held device (Eek et al., 2006). However, as children with CP often exhibit weakness in the plantar flexors, this makes it possible to measure muscle strength among children over 9 years of age as well.

The primary aim of the study was to describe the effect on muscle strength in the lower extremities after BoNT-A injections in children with CP by means of measurement of torque. A secondary aim was to relate the effect of BoNT-A to gait pattern and joint range of motion.

MATERIALS AND METHODS

Participants

Children with spastic CP were recruited consecutively from the spasticity clinic at the Regional Rehabilitation Centre in Gothenburg, Sweden. Inclusion criteria were increased muscle tone interfering with motor function/gait pattern and ability to walk without support. Twenty-three children were recruited; three were lost to follow-up (due to not returning for follow-up), resulting in a total of 20 children, 8 girls and 12 boys with a mean age of 7 years 8 months at injection (*SD* 2:9). Sixteen children had unilateral spastic CP and four bilateral spastic CP, according to the CP classification by Surveillance of Cerebral Palsy in Europe (SCPE, 2000). Nineteen children were classified at level I, according to the gross motor function classification system (GMFCS) and one with bilateral spastic CP at level II (Palisano et al., 2006). Their mean weight was 27.3 kg (*SD* 11.7) and mean height 125.5 (*SD* 17.4).

Procedure

The children were tested three times: at baseline before treatment with BoNT-A, at peak effect around 6 weeks after, and at a follow-up when the effect leveled off around 24 weeks after injection.

BoNT-A injections (Botox®; Allergan or Dysport®, Ipsen) were made during sedation with ketamine and midazolam in combination (rectal administration), or with nitrous oxide sedation, after local anesthetic EMLA® cream was applied to injection sites. Injections were guided with neuromuscular electric stimulation; using Teflon-coated Botox needles (37 mm, 27 gage) diluted to100 Units (U)/mL. Doses were calculated according to size of the muscle, body weight, and degree of spasticity (Love et al., 2010).

Measurements of muscle strength were made in four muscle groups (knee: extensors and flexors, ankle: dorsi- and plantar flexors) with a handheld device (Chatillon, AMETEK Test & Calibration Instruments, USA) using the "make" technique and standardized positions. The positions used in this study were similar to a normative study (Eek et al., 2006). Three attempts were made after instruction and familiarization with the procedure, and the maximum recording was used for data analysis. The lever arm for each muscle group was measured with a tape measure, and torque was calculated and normalized to body weight (Nm/kg). Muscle strength in children with CP can be measured with good reliability with a handheld electronic myometer (Berry et al., 2004; Taylor et al., 2004).

A two-dimensional gait analysis was performed in all legs with BoNT-A injections in the gastrocnemius muscle, with registration of spatiotemporal data and joint kinematics. For

data acquisition, we used a motion capture camera with a sampling rate of 50 Hz (Oqus, Qualisys AB, Göteborg, Sweden), placed at a distance of 3 m from the subject. Four markers (Ø 16 mm) were attached with double-sided adhesive tape to the skin at bony landmarks (trochanter major, lateral knee joint, lateral malleolus, and head of metatarsale V). Data was processed with the QTM software (Qualisys AB, Göteborg, Sweden) and exported to an excel worksheet for calculation of gait velocity, stride length, and joint angles in the knee and ankle, using the coordinates of the reflective markers. The same examiner, who has 15 years of experience with the method, placed the markers. Children walked barefoot, and measurements where parents confirmed that the gait pattern was relaxed and typical for the child were chosen for analysis. Values for joint angles at initial contact, as well as peak values for knee extension and dorsiflexion in stance were used for statistical testing.

Passive range of motion (ROM) was measured with a plastic goniometer. Spasticity was graded according to a modified Ashworth scale (Bohannon and Smith, 1987) with the children lying supine in a relaxed position with head in midline.

The children received physiotherapy during 2–3 months post injection with their regular therapist, with individual programs focusing on active movements and selective control around the ankle, as well as activities including gait and balance.

One month after injection, parents were interviewed or asked to fill in a questionnaire about the effect of the treatment. This was reported as a positive and/or negative effect and graded as: no effect, small effect, moderate effect or large effect.

This study was approved by the Regional Ethics Review Board, University of Gothenburg, with written informed consent from parents of all subjects.

Statistical Analysis

According to a previous study on muscle strength training in children with CP, a sample size of 17 was sufficient to analyze change in muscle strength with a power of 0.8 (Eek et al., 2008).

Muscle strength in the plantar flexor group was analyzed in children given injections in the gastrocnemius muscles, and knee flexor strength was analyzed for injections in the hamstring muscles. Muscle strength in the corresponding muscle groups in untreated legs served as controls. Muscle strength in the antagonists (ankle dorsiflexors and knee extensors) was also used for comparison.

Data were tested for normality with the Shapiro–Wilks test. It was found that all variables were not normally distributed, and non-parametric methods were thus used for analysis. Data were analyzed with the Mann–Whitney *U*-test for comparison between treated and control legs at baseline. Repeated measures ANOVA was used for comparison before and after treatment, and with a post hoc test with Bonferroni correction for multiple comparisons, for variables showing a statistically significant difference in the ANOVA test. When assumption of sphericity was violated, the Greenhouse–Geisser correction was used. The software packages Statview and SPSS were used for the analyses. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Both legs were treated in children with bilateral involvement; in total the gastrocnemius muscles of 24 legs/20 children received injections with BoNT-A. In addition the soleus muscles were treated in 9 legs/9 children and m. tibialis posterior in 10 legs/8 children. Eight legs/six children had injections in hamstring muscles. Mean dose/kg bodyweight injected into gastrocnemius was (Botox®) 3.2 Allergan units/kg, or (Dysport®) 6 units/kg; mean dose in hamstrings (Botox®) 1.5 Allergan units/kg, or (Dysport®) 2.5 units/kg.

Three children wore lower limb casts after the injection; one child wore a cast for 2 weeks and two children for 2+2 weeks. The casts were put on 2 weeks after treatment to allow time for muscle relaxation before the children were given the casts. Measurements of muscle strength for these children were made at least 2 weeks after the casts were removed.

Tests at peak effect were made at a mean of 5 weeks and 5 days (*SD* 1 week 3 days) after injection and were followed up at 5 months and 3 weeks (*SD* 1 month) after.

Muscle Strength

Data on muscle strength are presented in **Table 1** and **Figures 1** and **2**. At baseline, plantar flexor muscles subjected to BoNT-A were weaker than control muscles ($p = 0.005$, confidence interval (CI) 0.10; 0.44). There was no difference in plantar flexor strength at peak toxin effect as compared to baseline. At follow-up 6 months after treatment, repeated measures ANOVA showed no difference in control muscles, but a difference in plantar flexor muscles with BoNT-A injection [$F(2,46) = 4.44$, $p = 0.017$], showing a trend to increased plantar flexor strength (CI −0.25; −0.01). The opposite pattern was found in the knee flexor group, with no change in knee flexors treated with BoNT-A but an increase in control muscles [$F(1.7,52.3) = 4.60$, $p = 0.019$] (CI −0.14; −0.02). In the antagonistic muscle groups, there was no change of strength in dorsiflexors, but increased muscle strength in knee extensors [$F(2,78) = 8.38$, $p = 0.001$] (CI −0.31; −0.07).

Gait

There was no difference in gait velocity or stride length after treatment.

Kinematic gait data from all three occasions were available in 23 legs/20 children with BoNT-A treatment in the gastrocnemius. At peak effect, the 2D gait analysis showed a small improvement in knee extension at initial contact [$F(2,44) = 3.78$, $p = 0.031$] (CI 1.1; 6.5). At baseline the ankle was in plantar flexion at initial contact in all but two legs subject to BoNT-A treatment. There were no differences regarding ankle angle in gait after treatment.

Muscle Tone and Passive ROM

Spasticity grading of the gastrocnemius muscle at baseline was available in 35 legs (23 with BoNT-A and 12 controls). Muscle tone at baseline was increased in legs planned for treatment (grade 1 in 13, grade 1+ in 6, and grade 2 in 4) and in five control legs (grade 1). Grading of spasticity after treatment was available in 14 of the legs treated with BoNT-A. There was a decrease in muscle tone in 7 legs and no change in the rest.

TABLE 1 | Muscle strength, gait data and range of motion at baseline, peak effect and follow-up, presented as median (interquartile range).

			Baseline	Peak effect	Follow up	*ANOVA*	*diff 1-2*	*diff 1-3*
Muscle strength Nm/kg		***n***						***p***
Plantar flexors	BoNT-A	24	0.94 (0.38)†	0.88 (0.38)	1.02 (0.43)	***0.017***	*1.000*	*0.069*
	control	14	1.20 (0.25)†	1.25 (0.25)	1.20 (0.39)	*0.660*		
Knee flexors	BoNT-A	8	0.91 (0.33)	0.89 (0.43)	0.89 (0.35)	*0.445*		
	control	32	0.90 (0.29)	1.04 (0.29)	1.00 (0.34)	***0.019***	***0.036***	***0.008***
Dorsiflexors		40	0.31 (0.15)	0.32 (0.17)	0.34 (0.20)	*0.916*		
Knee extensors		40	1.37 (0.52)	1.52 (0.69)	1.48 (0.75)	***0.001***	*0.180*	***0.001***
Gait data for legs with gastrocnemius injections								
Velocity m/sec		20	1.06 (0.18)	1.06 (0.18)	1.11 (0.19)	*0.159*		
Stride length		20	0.98 (0.24)	0.98 (0.18)	1.04 (0.27)	*0.060*		
Knee angle at initial contact (°)		22	19.8 (14.9)	17.7 (9.6)	20.7 (14.4)	***0.031***	***0.035***	*0.469*
Knee extension in stance (°)		23	11.8 (11.8)	11.4 (9.9)	10.2 (9.6)	*0.100*		
Ankle angle at initial contact (°)		23	−7.0 (13.9)	−7.9 12.4)	−8.3 (9.9)	*0.414*		
Dorsiflexion in stance (°)		23	8.2 (7.4)	9.5 (8.5)	6.6 (4.4)	*0.619*		
Range of motion								
Passive dorsiflexion with extended knee (°)		15	15.0 (8.8)	15.0 (9.5)	18.0 (11.0)	***0.048***	*0.058*	*0.114*

p-values (in italic) for ANOVA and at peak effect and follow up compared to measurement at baseline for variables with a statistically significant ANOVA test. Statistically significant differences indicated in bold figures. †Statistically significant difference between muscles treated with botulinum neurotoxin-A (BoNT-A) and control muscles at baseline p = 0.004.

Data on passive dorsiflexion in the ankle at baseline were available in 31 legs (19 BoNT-A and 12 controls). There was a statistically significant difference ($p < 0.001$, CI 7.8; 18.1) between muscles planned for injection (median 15.0°, interquartile range (IQR) 8.8) compared to controls (median 22.5°, IQR 11.0). Data from all three occasions were available in 15 legs treated with BoNT-A in the gastrocnemius (**Table 1**). There was a small increase in passive dorsiflexion [$F(2,28) = 3.40$, $p = 0.048$].

Parent Reports

The parent reports all indicated positive effects graded as: small (three children), moderate (eight children), and large (nine children). Some parents specifically mentioned that their child was not walking on toe and could more easily make heel contact. One child had pain for a couple of weeks after the casts, and one child felt insecure/weak in the first weeks after injection.

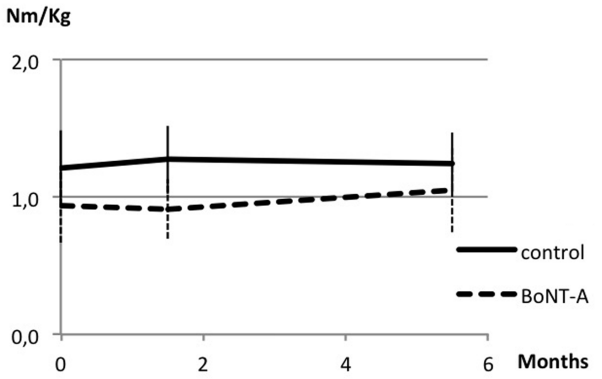

FIGURE 1 | Muscle strength in plantar flexor muscles at baseline, peak effect and follow-up after botulinum neurotoxin-A (BoNT-A) treatment. Data in torque normalized to body weight (Nm/kg), presented as mean and with SD error bars.

DISCUSSION

The primary aim of the study was to see whether voluntary muscle strength is affected by BoNT-A, with a focus on plantar flexor muscles, as being important for walking. We found no sign of decreased torque in plantar flexor muscles at the point at which the toxin effect was at its peak. There was instead an increasing trend in strength at follow-up in muscles treated with BoNT-A. No increase was seen in the untreated plantar flexors that acted as controls during the study period. This finding is similar to that in a study by Bjornson et al. (2007) who found increased muscle strength 6 months after treatment compared to saline injections. Williams et al. (2013b) found no difference in strength 5 weeks after injections in the gastrocnemius, while Barber et al. (2013) found an increased muscle volume after BoNT-A treatment, suggesting increased muscle strength. In reports of adverse effects, weakness is mentioned as occurring over short transient periods during the first weeks after injection (Naumann et al., 2006; O'Flaherty et al., 2011). The parents of one child in our study reported a transient period of muscle weakness in the first days/first week after injection.

It has been demonstrated that the concurrent treatment of BoNT-A and strength training can achieve positive outcomes in terms of strength, spasticity and for the achievement of functional goals (Williams et al., 2013a). Physiotherapy after injection in our study focused on voluntary control in the ankle, and exercises in standing balance and gait. Many of these activities, as well as everyday life, include using both legs, and both legs thus

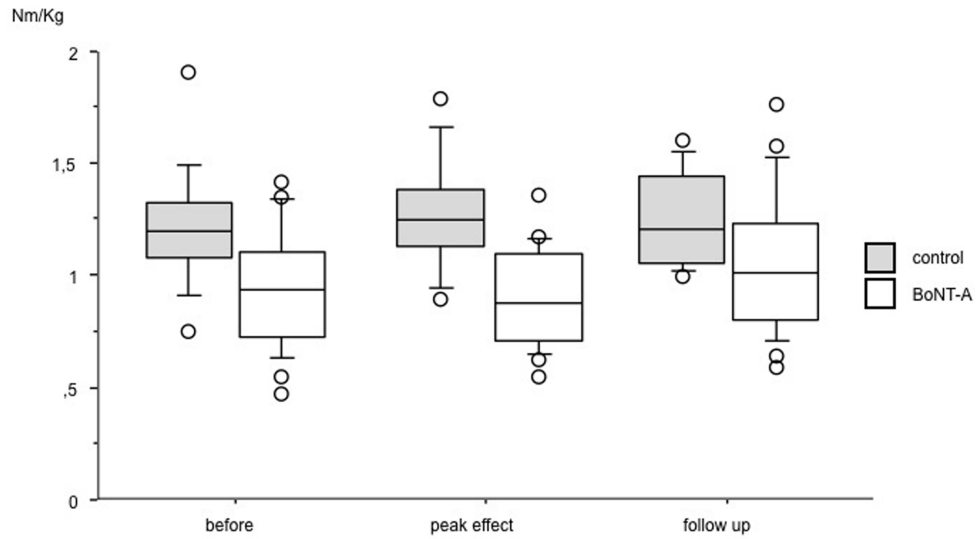

FIGURE 2 | Muscle strength in plantar flexor muscles at baseline, peak effect and follow-up after BoNT-A treatment. Data in torque normalized to body weight (Nm/kg), presented as boxes indicating 25–75 percentile, a line indicating median and circles showing observations outside 10 or 90 percentile.

receiving about the same amount of muscle activity. In our study, most of the children had injections in only one leg, and in this way muscle strength development in not injected muscles in the other leg could serve as control to injected muscles. Spasticity, muscle weakness, and poor voluntary control often co-exist in children with CP (Gormley, 2001). The increasing trend in muscle strength in plantar flexors after BoNT-A can be explained as an effect of the blocking of involuntary nerve impulses leading to an opportunity to take better voluntary control, and the increasing trend in muscle strength as an effect of training and using the muscle with voluntary control. As standing and gait involves muscle activity in the whole leg it may not be surprising that there was also increased muscle strength in knee extensors and knee flexors. Contrary to this we found no change in ankle dorsiflexors. In growing children, 6 months may be sufficient time for a natural increase in muscle strength and here the not injected muscles also can serve as controls. According to a previous study of muscle strength in children with CP, 5-15 years of age (Eek, 2009), there is an increase in torque with age for knee extensors and knee flexors, but not for ankle plantar and dorsiflexors. The findings in the present study can therefore be interpreted as an expected development for knee extensors, knee flexors and ankle dorsiflexors.

Gait pattern improved regarding knee extension at initial contact in legs with BoNT-A treatment in the gastrocnemius, but there were no changes in ankle angle in the gait analysis. This is different from previously reported findings of improved peak ankle dorsiflexion in stance after BoNT-A (Sutherland et al., 1999). Interestingly, parents reported improvement in heel strike and foot contact, which is similar to a study with video analysis, who found improvement in initial foot contact following BoNT-A (Ubhi et al., 2000). However, an improved position in the knee at initial contact and during the stance phase facilitates the possibility to make heel contact (which is easy to see with the eye) while the exact angle in the knee and ankle is difficult to see without instrumented measurement. In contrast to the lack of improved dorsiflexion in gait, there was increased passive ROM in the ankle which was small but statistically significant. Even small differences can be clinically relevant if the increase in dorsiflexion is close to the neutral position of the ankle, and letting the ankle dorsiflex a few degrees can be what is needed for a better gait pattern. The lack of change in ankle angle in the gait pattern may be explained by weakness in dorsiflexors, and also the fact that as a bi-articular muscle the improved range of motion in gastrocnemius was gained at the proximal end, thus facilitating knee extension.

The children in the study did not have very severe spasticity, most of them with a grade 1–1+ according to the Ashworth scale, with a resistance to quick stretch at the end or in the second half of the movement. There was decreased spasticity in only half of the treated legs after treatment. This may depend on the Ashworth scale as a subjective way of testing and also that muscle tone may vary with the situation, and if the child is excited. Testing was, however, performed in a standardized way with the child in rest, lying supine with the head in midline. This position does not always reflect what is happening in activity and at baseline assessment it was visible that there was an increase in muscle tone in activity, affecting movement patterns. There is yet no way (that we know of) of measuring muscle tone in activity in a clinical setting.

Limitations

There are some limitations that need to be acknowledged in this study. There was a variety in location of injections; some children were also given injections in soleus, tibialis posterior, and hamstring muscles in addition to gastrocnemius. This makes

the sample heterogeneous but they were considered too few to be possible to analyze as subgroups in this study. Three children were immobilized in the ankle by casts for 2 weeks after BoNT-A, to increase stretch. This immobilization can induce weakness and for that reason measurement of muscle strength was performed at least 2 weeks after removal of the casts, to let them regain some muscle strength.

However, the primary aim and focus of the study was to measure whether muscle strength deteriorated, and we found that this was not the case. There was instead an increasing trend in muscle strength at follow-up.

Clinical Implications

Voluntary force production in plantar flexor muscles was not decreased by BoNT-A. Muscle strength instead showed an increasing trend at follow-up. Gait pattern improved in terms of better knee extension in stance.

Adequate muscle strength is important for maintaining the ability to walk. Knowledge of how a treatment affects muscle strength is necessary when selecting interventions in order not to make muscles weaker with treatment.

AUTHOR CONTRIBUTIONS

ME and KH made substantial contributions to the design, acquisition, analysis, and interpretation of data for the work, as well as drafting and final approval of the version to be published. And agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Spared Primary Motor Cortex and The Presence of MEP in Cerebral Palsy Dictate the Responsiveness to tDCS during Gait Training

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The current priority of investigations involving transcranial direct current stimulation (tDCS) and neurorehabilitation is to identify biomarkers associated with the positive results of the interventions such that respondent and non-respondent patients can be identified in the early phases of treatment. The aims were to determine whether: (1) present motor evoked potential (MEP); and (2) injuries involving the primary motor cortex, are associated with tDCS-enhancement in functional outcome following gait training in children with cerebral palsy (CP). We reviewed the data from our parallel, randomized, sham-controlled, double-blind studies. Fifty-six children with spastic CP received gait training (either treadmill training or virtual reality training) and tDCS (active or sham). Univariate and multivariate logistic regression analyses were employed to identify clinical, neurophysiologic and neuroanatomic predictors associated with the responsiveness to treatment with tDCS. MEP presence during the initial evaluation and the subcortical injury were associated with positive effects in the functional results. The logistic regression revealed that present MEP was a significant predictor for the six-minute walk test (6MWT; $p = 0.003$) and gait speed ($p = 0.028$), whereas the subcortical injury was a significant predictor of gait kinematics ($p = 0.013$) and gross motor function ($p = 0.021$). In this preliminary study involving children with CP, two important prediction factors of good responses to anodal tDCS combined with gait training were identified. Apparently, MEP (integrity of the corticospinal tract) and subcortical location of the brain injury exerted different influences on aspects related to gait, such as velocity and kinematics.

Keywords: cerebral palsy, neuromodulation, non-invasive brain stimulation, gait training, motor evoked potential

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Abbreviations: EEG, electroencephalogram; IRB, Institutional Review Board; GMFM, gross motor function measure; GMFCS, gross motor function classification system; MRI, magnetic ressonance image; MEP, motor evoked potential; RMS, root mean square; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; 6MWT, six-minute walk test.

INTRODUCTION

The neuromodulatory effects of transcranial direct current stimulation (tDCS) on cortical excitability can optimize motor learning and functional improvements in patients with neurological injuries (Lefebvre et al., 2015), which is a promising therapeutic technique for gait rehabilitation (Jayaram and Stinear, 2009; Tahtis et al., 2014). Previous studies involving children with cerebral palsy (CP) have found that anodal tDCS over the primary motor cortex combined with gait training resulted in positive effects in comparison to sham stimulation (Duarte et al., 2014; Grecco et al., 2014, 2015). However, a detailed analysis (group vs. individual effects) of the our data revealed varied effects.

Although the effect of tDCS has been well-documented and seems to be a promising therapeutic tool for this neurological disorder, there are as-yet no clear predictors of responsiveness. Based on the experience of our research group, some children achieved excellent results following anodal tDCS, whereas others demonstrated no effect. Based on the heterogeneity of our discoveries, we believe that tDCS would be effective for patients in which the brain injury spared the motor cortex (cortical vs. subcortical lesions) under the stimulating electrode. We also believe that children with a corticospinal pathway responsive to transcranial magnetic stimulation (TMS), as indicated by the presence of the motor-evoked potential (MEP) in the quadriceps muscle, would have a better response to tDCS. This suggests the potential of the susceptibility of areas of corticospinal system responsible for the motor control of the lower limbs, specifically the quadriceps muscle, to activation by local electrical fields.

There is no complete understanding of how neuroimaging and TMS findings are related to motor function or whether a given patient will respond well when noninvasive brain stimulation is combined with physical therapy, thereby benefiting the motor rehabilitation process. Identifying respondent and non-respondent patients is a major focus of studies involving brain stimulation intervention. Knowledge of neurophysiologic and neuroanatomic predictors of the responsiveness to tDCS is critical in the context of clinical research and it is especially important in guiding the choice of an effective intervention (Brunoni et al., 2015) for a given child.

In the present study, we investigated clinical and neurophysiologic variables to test whether age, gross motor function, laterality of motor impairment (hemiparesis or diparesis), injury location (cortical or subcortical) and MEP (present or absent) are predictors of the responsiveness to tDCS over the primary cortex associated with gait training for children with CP. The secondary aim was to compare the effects of the MEP and injury location, considering active and sham tDCS intervention in the six-minute walk test (6MWT), gait speed, kinematic gait profile and gross motor function in children with CP. Our hypothesis was that children with cortical injuries would respond less to tDCS intervention than those with a subcortical injury. We also predicted that the presence of MEP would favor responsiveness to tDCS, as it demonstrates local susceptibility to electric fields.We further explored the data for an interaction among neurophysiologic and neuroanatomic variables during tDCS and the effects on gait function.

MATERIALS AND METHODS

In the present study, we evaluated data from our three previous trials to analyze response predictors of anodal tDCS regarding gait performance (Duarte et al., 2014; Grecco et al., 2014, 2015). These studies received approval from the Human Research Ethics Committee of Universidade Nove de Julho, Brazil, under process number 69803/2012 and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Each study was parallel, randomized, sham-controlled and double-blinded. The eligibility criteria of our previous studies were a diagnosis of spastic hemiparetic or diparetic CP, children with cortical or subcortical lesions, classification on levels I, II or III of the gross motor function classification (Palisano et al., 1997), independent gait for at least 12 months, age between 5 and 10 years, and degree of comprehension compatible with the execution of the procedures. The exclusion criteria were a history of surgery or neurolytic block in the previous 12 months, orthopedic deformities, epilepsy, metal implants in the skull, the use of hearing aids, anticonvulsant or muscle relaxing drugs. In these protocols, children were randomly allocated to two treatment groups: (1) treadmill training combined with anodal or sham tDCS (Grecco et al., 2014); and (2) virtual reality training combined with anodal or sham tDCS (Grecco et al., 2015).

These trials lasted 7 weeks, comprising a baseline assessment (1 week prior to the intervention), 2 weeks of intervention (5 sessions per week), a post-intervention assessment (1 week after intervention) and a follow-up assessment (4 weeks after the end of the intervention). The gait training and tDCS started simultaneously and lasted 20 min. Treadmill training was performed on the Inbramed treadmill (Millenium ATL, Brazil) without body weight support. Training speed was 80% of the maximum speed reached during the baseline exercise test. The training speed was gradually increased after the first 2 min and slowly decreased in the last 2 min of treadmill training. Gait training with virtual reality was performed using the Kinect program (Xbox 360, Microsoft, WA, USA). The activity selected (your shape: fitness evolved 2012 run the world) consisted of walking for 20 min in virtual environments, simulating tourist destinations around the world. This game included speed targets—the participants were required to walk with slow and fast paces in random periods determined by the game. Visual and audio feedback was provided when the activity was not performed properly in the virtual reality environment (for further details see Grecco et al., 2014, 2015). It is important to report that treadmill training achieved better results than the virtual reality training on the 6MWT, walking velocity and the gait profile score in

both the active and sham tDCS groups ($p < 0.05$ for all analyses).

The tDCS montage was as follows: anodal electrode positioned over the primary motor cortex (between Cz and C3 or C4 positions, following the 10–20 International Electroencephalogram (EEG) System; Homan et al., 1987); and cathode over the supraorbital region on the contralateral side. In children with diparetic CP, the anodal electrode was positioned over the primary motor cortex contralateral to the lower limb with greater motor impairment. For the patients with hemiparetic CP, stimulation was standardized over the affected hemisphere. In the active groups, stimulation at a current intensity of 1 mA was applied for 20 min simultaneously to gait training. For the sham intervention, the device was switched on for 30 s, giving the children the initial sensation of the stimulation, but no current was delivered during the rest of the time.

Motor Outcomes

All motor outcomes were measured 1 week before the beginning of the intervention (pre-intervention), 1 week after the end of the intervention (post-intervention) and 1 month after the end of the intervention (follow-up). The outcome parameters were absolute changes having occurred during the intervention, considering the post-intervention effect (post minus pre-intervention values) and follow-up effect (follow-up minus pre-intervention values). The following four motor parameters were employed:

- The 6MWT quantifies functional mobility based on the distance in meters covered in 6 min (Borg, 1982). The 6MWT was chosen as primary outcome, since this is a validated test for children with CP and an important quantitative variable of functional gait (Maher et al., 2008).
- Dimension E of the gross motor function measure (GMFM-88) allows a quantitative assessment of walking, running and jumping activities (Russell et al., 2000).
- Gait speed (mean velocity of progression, m/s) was documented using a three-dimensional gait analysis test.
- The gait profile score is based on gait analysis output data. This index was calculated according to the procedure implemented by Baker et al. (2009). It represents the root mean square (RMS) difference between a particular gait trial and averaged data from individuals with no gait pathology. This parameter summarizes the global deviation in the kinematic gait data relative to normative data. The overall gait profile score is based upon gait variable scores that are clinically important kinematic parameters (pelvic anterior/posterior, pelvic up/down obliquity, left-side rotation, hip flexion, abduction, internal rotation, knee flexion, dorsiflexion and foot progression for the left and right sides). In the analysis, a gait profile score was determined for each side based on all nine gait variable scores. A higher gait profile score value denotes a less physiological gait pattern. In the literature, the gait profile score has been used to quantify gait alterations in different adverse health conditions in children and adults (Baker et al., 2009; Cimolin and Galli, 2014).

Since there is no accepted standardization regarding a clinically relevant improvement in the motor outcomes used in the present study (distance traveled on the 6MWT, score on dimension E of the GMFM and gait profile score) for children with spastic CP, a minimum increase of 30% was considered for these variables in the post-intervention and follow-up evaluations (Bartels et al., 2013).

Neurophysiologic and Neuroanatomic Outcomes

Responses to stimuli applied to the motor cortices were recorded in the quadriceps muscle contralateral to the stimulated side, with two electrodes placed midway between the iliac crest and the lateral joint line of the knee to record vastus lateralis activity (the ground electrode was placed on the contralateral patella). We chose to use the MEP in the quadriceps muscle as this is a gait training study. These measures were performed for the right and left motor cortex. The resting motor threshold (rMT) was evaluated with muscles at rest and measured in each region assessed using five transcranial magnetic pulses for each 2% increment of stimulator output intensity. The children were seated and instructed to remain relaxed without performing muscle contractions of the lower limbs. The vertex was identified and TMS pulses were made 1 cm anterior to 3 cm posterior to the vertex as well as 2 cm over the left and right motor cortices. The MT was defined as the minimum intensity that generates an MEP of at least 100 μV of amplitude in three of five stimuli. TMS was set to an intensity of 110% of the rMT. MEP responses were filtered and amplified using surface electromyography (1000× gain, band-pass filter 20–400 Hz). The signals were processed through offline analysis of the MEP amplitudes. Ten individual MEP measures were recorded and the mean was used for the statistical analysis. The MEP evaluations were performed before and after the interventions as well as during the follow-up evaluation. The MEP was considered absent when there was no response at a stimulator output of 100%.

The children were classified into two groups according to clinical radiological parameters. The cortical group had injuries involving primary motor cortex that could extend to the underlying white matter; and subcortical group had deeper injuries of the internal capsule (excluding the cerebral cortex, brainstem and cerebellum). Radiological classification involved structural magnetic ressonance image (MRI) performed up to 1 year before the onset of the intervention.

The present study was approved by the Human Research Ethics Committee of Nove de Julho University, Brazil (Institutional Review Board (IRB) number: 69803/2012) and it was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians.

STATISTICAL ANALYSIS

The aim of this exploratory study was to identify the clinical and neurophysiologic characteristics associated with a greater

effect of active tDCS in children with CP. Thus, logistic regression models were performed using the responsiveness to the intervention (yes/no) as the outcome (dependent variable). Four outcomes were considered: 6MWT, gait velocity, gait profile score and GMFM. Thus, separate models were run. Responsiveness was defined as a 30% increase in the child's performance in these outcomes in comparison to baseline. The predictor (independent) variables were age (years), sex (male/female), level of gross motor function (GMFCS levels), topography of the motor impairment (hemiparesis/diparesis), MEP presence, MEP amplitude at baseline evaluation and location of the injury (cortical/subcortical). Univariate logistic regressions were performed for each variable. Based on these initial analyses, predictors associated with outcome at a *p*-value less than or equal to 0.05 were used in the multivariate model.

In addition, we performed analyses of variance (ANOVA) with the Bonferroni *post hoc* test to compare the effects of MEP (present or absent) and injuried area (cortical or subcortical) on the main outcome variables. Correction for multiple comparisons was employed for each variable, resulting in alpha level of 0.0125.

RESULTS

Fifty-six cases presented the necessary demographic and clinical data to be included in the analysis. All children had motor impairment secondary to injuries of the pyramidal system, with non-progressive lesions having occurred prior to 2 years of age. Thirty-three cases received active tDCS intervention (23 with treadmill training and 10 with virtual reality training) and 23 subjects received sham tDCS intervention (13 with treadmill training and 10 with virtual reality training). Five children had spastic hemiparesis and 51 had spastic diparesis. Mean age at baseline was 8.2 ($\pm$1.6) years. There was a significant difference between children with presence or absence of MEP ($p = 0.04$) and cortical or subcortical (sham tDCS groups; $p = 0.03$) regarding gait speed. There were no other significant differences between cortical and subcortical groups or the presence/absence of MEP for other clinical and demographic variables at the baseline assessment (**Table 1**).

The regression models were performed considering all clinical, functional, neurophysiologic and neuroanatomic results. The analyses demonstrated no significant interaction between clinically relevant improvements in the outcomes (minimum increase of 30% on the 6MWT, gait speed, gait profile score and dimension E of the GMFM) and clinical or demographic variables such as age, sex, motor function level (levels I, II or III of the GMFCS) or type of motor impairment (hemiparesis or diparesis).

The univariate logistic analysis considering only the children who received active tDCS combined with gait training revealed two predictors significantly associated with the responsiveness

TABLE 1 | Clinical and demographic variables according to injured area (cortical and subcortical) and presence or absence of motor evoked potential (MEP) at baseline assessment.

	Injury location			Motor evoked potential		
	Cortical	**Subcortical**	***p***	**Present**	**Absent**	***p***
N	23	33	–	29	27	–
Age (years)*	8.1 (1.7)	7.5 (1.9)	0.48	8.0 (2.0)	7.8 (2.1)	0.71
Active tDCS	7.3 (1.6)	7.1 (1.1)	0.23	7.6 (1.6)	7.9 (1.9)	0.75
Sham tDCS	7.5 (1.8)	7.8 (1.1)	0.76	8.1 (1.3)	7.6 (2.2)	0.81
GMFCS (I/II/III)**	1/10/12	4/13/16	0.51	3/14/12	2/9/16	0.46
Active tDCS	0/5/5	3/10/10	0.48	1//10/8	1/4/9	0.47
Sham tDCS	1/5/7	1/3/6	0.91	2/4/4	1/5/7	0.94
Hemiparetic/Diparetic**	2/21	3/30	0.92	4/25	1/26	0.80
Active tDCS	1/9	2/21	0.40	3/16	1/13	0.41
Sham tDCS	1/12	1/9	0.84	1/9	0/13	0.37
6MWT (m)*	252.4 (62.7)	241.4 (70.2)	0.54	261.3 (98.4)	249.9 (80.2)	0.45
Active tDCS	242.3 (25.1)	250.5 (57.8)	0.98	261.2 (20.6)	242.3 (25.1)	0.30
Sham tDCS	227.9 (40.8)	251.0 (49.9)	0.06	249.4 (43.3)	227.7 (40.8)	0.25
Gait speed (m/s)*	0.58 (0.17)	0.55 (0.12)	1.0	0.61 (0.13)	0.54 (0.12)	0.04
Active tDCS	0.54 (0.07)	0.57 (0.05)	0.53	0.55 (0.06)	0.54 (0.007)	0.05
Sham tDCS	0.51 (0.16)	0.48 (0.11)	0.03	0.48 (0.07)	0.48 (0.06)	0.08
Gait profile score (°)*	11.3 (2.1)	12.1 (2.9)	0.23	11.9 (3.1)	11.2 (1.7)	0.30
Active tDCS	11.8 (0.6)	11.5 (1.0)	0.06	11.2 (0.5)	11.2 (0.6)	0.28
Sham tDCS	11.3 (0.6)	11.3 (1.0)	0.61	10.9 (0.6)	10.9 (0.7)	0.33
MEP (mV)*	1.5 (0.5)	1.6 (0.4)	0.42	1.6 (0.7)	–	–
Active tDCS	0.9 (0.6)	0.8 (0.7)	0.78	1.3 (0.2)	–	–
Sham tDCS	0.7 (0.4)	0.7 (0.6)	0.93	1.2 (0.3)	–	–
Active tDCS (%)	10 (43.7%)	23 (69.6%)		19 (65.5%)	14 (51.8%)	

*Legend: GMFCS, gross motor function classification system; tDCS, transcranial direct current stimulation; 6MWT (m), six-minute walk test; MEP, motor evoked potential. *Data expressed as mean and standard deviation. Analyses performed with unpaired t-test. **Numbers indicate frequency (n) of children in each group. Analyses performed with Chi-square.*

TABLE 2 | Results of linear logistic regressions in the active and sham tDCS groups.

Variables	Active tDCS				Sham tDCS			
	Respondent (Yes/No)	B (SE)	Exp (B)	*p*	Respondent (Yes/No)	B (SE)	Exp (B)	*p*
6MWT								
MEP present	19/0	2.5 (0.86)	8.9	0.003	5/4	0.9 (0.76)	0.4	0.400
Subcortical injury	18/5	2.6 (0.93)	8.0	0.004	6/4	0.8 (0.38)	0.6	0.664
Gait velocity								
MEP present	16/3	1.6 (0.77)	4.8	0.028	3/6	0.8 (0.90)	2.4	0.331
Subcortical injury	10/13	1.1 (0.80)	1.8	0.170	6/4	0.8 (0.76)	0.4	0.384
Gait profile score								
MEP present	10/9	1.0 (0.74)	1.9	0.168	4/5	1.7 (1.30)	0.1	0.172
Subcortical injury	17/6	2.1 (0.85)	6.1	0.013	4/6	1.2 (1.12)	0.3	0.281
GMFM dimension E								
MEP present	11/8	1.0 (0.73)	2.1	0.147	3/6	2.0 (1.30)	0.1	0.120
Subcortical injury	15/8	1.9 (0.84)	5.3	0.021	7/3	1.2 (0.73)	0.4	0.479

*Respondent (Yes/No) shows the frequency of children considered responders to intervention with MEP present (active tDCS: 19 and sham tDCS: 9 children) and subcortical injury (active tDCS: 23 and sham tDCS: 10 children). Legend: SD, standard deviation; B, B coefficient; SE, standard error of B coefficient; Exp (B), measurement of likelihood ratio of association between predictor variable and outcome. *p < 0.05.*

to the intervention: MEP present during the initial evaluation and location of the injury (**Table 2**). The presence of MEP was significantly associated with responsiveness, based on the 6MWT ($p = 0.003$) and gait speed ($p = 0.028$). Considering the results of the follow-up evaluation (1 month after the end of the intervention), a significant association was only found between the presence of MEP and the 6MWT ($p = 0.010$). The analysis also showed that the subcortical injury was a significant predictor of improvements in 6MWT ($p = 0.004$), gait profile score ($p = 0.013$) and gross motor function ($p = 0.021$). **Table 3** displays the functional findings considering the presence/absence of MEP and location of the injury (cortical or subcortical).

To determine whether there may have been a confounding effect between the presence of MEP and injury location, both variables were incorporated simultaneously in the logistic regression model. The results of this analysis demonstrated that the presence of MEP remained significantly associated with the results of the 6MWT ($p = 0.007$) and gait speed ($p = 0.011$), and that the subcortical injury remained significantly associated

TABLE 3 | Mean and SD of results in children with presence and absence of MEP, and subcortical and cortical lesions considering active and sham tDCS.

	MEP present		MEP absent		Subcortical injury		Cortical injury	
	Active	Sham	Active	Sham	Active	Sham	Active	Sham
6MWT (m)								
Pre-intervention	261.2 (20.6)	249.4 (43.3)	242.3 (25.1)	227.7 (40.8)	250.5 (57.8)	251.0 (49.9)	241.5 (28.3)	212.1 (43.9)
Post-intervention	418.2 (60.8)*	310.1 (11.8)	366.9 (41.3)	331.1 (47.1)	393.9 (62.4)#	339.0 (54.4)	345.3 (40.5)	317.6 (79.5)
Follow-up	393.8 (58.2)	286.8 (92.2)	356.9 (47.9)	305.3 (50.3)	354.2 (62.1)	322.2 (42.9)	338.4 (53.8)	287.4 (56.3)
Gait speed (m/s)								
Pre-intervention	0.55 (0.06)	0.48 (0.07)	0.54 (0.07)	0.48 (0.06)	0.54 (0.11)	0.51 (0.16)	0.57 (0.05)	0.48 (0.11)
Post-intervention	0.82 (0.16)*	0.56 (0.12)	0.59 (0.08)	0.56 (0.12)	0.77 (0.18)#	0.62 (0.19)	0.68 (0.11)	0.57 (0.10)
Follow-up	0.71 (0.13)	0.58 (0.06)	0.56 (0.05)	0.58 (0.06)	0.70 (0.13)	0.58 (0.24)	0.63 (0.06)	0.54 (0.14)
Gait profile score (%)								
Pre-intervention	11.2 (0.5)	10.9 (0.6)	11.2 (0.6)	10.9 (0.7)	11.8 (0.6)	11.3 (0.6)	11.5 (1.0)	11.3 (1.0)
Post-intervention	8.8 (0.9)*	9.2 (0.8)	9.1 (1.1)	9.1 (0.5)	8.5 (1.2)#	9.9 (0.6)	10.4 (1.0)	9.8 (1.4)
Follow-up	9.8 (0.9)	9.7 (1.0)	9.7 (0.2)	9.7 (0.8)	9.4 (1.6)#	10.0 (1.1)	10.8 (1.1)	10.3 (1.3)
GMFM-88 (dimension E)								
Pre-intervention	53.9 (13.0)	56.7 (8.6)	52.1 (11.2)	48.8 (12.4)	52.0 (11.3)	53.4 (19.9)	51.6 (10.9)	49.8 (13.8)
Post-intervention	69.4 (14.4)	76.3 (11.6)	69.3 (9.7)	62.8 (12.6)	68.8 (13.7)#	66.4 (10.5)	63.7 (14.3)	61.6 (16.8)
Follow-up	66.2 (15.7)	68.9 (10.6)	64.1 (9.8)	61.1 (14.4)	63.8 (14.1)	63.6 (8.2)	57.1 (12.1)	59.4 (15.9)
MEP (mV)								
Pre-intervention	1.3 (0.2)	1.2 (0.3)	–	–	0.9 (0.6)	0.7 (0.4)	0.8 (0.7)	0.7 (0.6)
Post-intervention	2.3 (0.3)	1.5 (0.4)	–	–	1.5 (1.0)	1.0 (0.9)	1.4 (1.3)	0.9 (0.8)
Follow-up	1.6 (0.4)	1.2 (0.5)	–	–	1.0 (0.8)	0.8 (0.5)	1.0 (0.9)	0.7 (0.6)
Resting motor threshold (rMT, %)	57.9 (11.1)	60.1 (13.2)	–	–	52.6 (12.6)	54.3 (13.5)	58.8 (11.8)	57.6 (12.5)

*Legend: GMFM, gross motor function measure. Analyses performed using analysis of variance (ANOVA) followed by Bonferroni post hoc test. *p < 0.05: analysis considering the groups: MEP present and active tDCS, MEP present and sham tDCS, MEP absente and active tDCS, MEP absent and sham tDCS. #p < 0.05: analysis considering the groups: subcortical injury and active tDCS, subcortical injury and sham tDCS, cortical injury and active tDCS, cortical injury and sham tDCS.*

with the gait profile score ($p = 0.038$) and gross motor function ($p = 0.046$).

We also incorporated the type of gait training (treadmill training and virtual reality training) into the regression model to adjust the analysis to the type of training, but no significant changes in the results were found. Then, we tested whether there was an interaction between these two variables and found that the type of formation virtually exerted no alteration in the interaction of these variables. The presence of MEP continued to demonstrate a significant association with 6MWT ($p = 0.006$) and gait speed ($p = 0.039$), and subcortical injury demonstrated a significant association with the gait profile score ($p = 0.008$). However, the association between subcortical injury and gross motor function was not maintained in this analysis ($p = 0.095$).

Multivariate regression analysis was performed with the incorporation of the variable MEP * injury location to determine a possible interaction with the functional outcomes. The analysis demonstrated that a significant interaction was only found with the 6MWT ($p = 0.001$), whereas no significant associations were found with regard to gait speed ($p = 0.519$), gait profile score ($p = 0.358$) or gross motor function ($p = 0.103$).

As the primary objective of the present study was to identify factors predictive of the response to active tDCS, the analyses and discussion focused only on the results obtained through the regression models that incorporated the participants who have received active tDCS. To clarify the findings, however, it should be stressed that the linear regression analyses were performed considering the group of children who received sham tDCS and measures considered possible response factors. There were no significant interactions between MEP and injury location with regard to the variables (**Table 2**).

We compared the effects on the variables analyzed considering the presence or absence of MEP (MEP present and active tDCS; MEP present and sham tDCS; MEP absent and active tDCS; MEP absent and sham tDCS) and the location of the injury (cortical lesion and active tDCS; cortical lesion and sham tDCS; subcortical lesion and active tDCS; subcortical lesion and sham tDCS). The variance analysis performed considering the four subgroups refering to the MEP demonstrated significant differences in 6MWT ($F_{(11,1)} = 22.1$, $p < 0.001$), gait velocity ($F_{(11,1)} = 13.0$, $p < 0.001$) and gait profile score ($F_{11,1} = 13.8$, $p < 0.001$). The *post hoc* test showed that the subgroup "MEP present and active tDCS" achieved better results than the other groups regarding the 6MWT ($p < 0.001$), gait velocity ($p < 0.001$) and gait profile score ($p < 0.001$) during the post-intervention evaluation (**Figure 1**). In the analysis considering the four subgroups related to location of the lesion, different effects were found regarding 6MWT ($F_{(11,1)} = 15.3$, $p < 0.001$), gait velocity ($F_{(11,1)} = 5.6$, $p < 0.001$), gait profile score ($F_{(11,1)} = 5.0$, $p < 0.001$) and dimension E of GMFM ($F_{(11,1)} = 3.4$, $p = 0.003$). The *post hoc* test showed that the subgroup "subcortical injury and active tDCS" achieved better results than the other subgroups analyzed regarding 6MWT ($p < 0.001$), gait velocity ($p = 0.007$), gait profile score ($p = 0.024$) and dimension E of GMFM ($p = 0.002$; **Figure 2**).

DISCUSSION

Although the effects of tDCS are encouraging, divergent results are often encountered. The clinical predictors of responsiveness to this method are not currently known. Therefore, the major challenge in clinical investigations on noninvasive brain stimulation is to identify biomarkers associated with positive responses. Levels of BDNF in patients with depressive disorders (Fidalgo et al., 2014) and levels of ipsilesional GABA in stroke survivors are biomarkers commonly cited in the literature (O'shea et al., 2014).

Since the primary motor cortex is the most commonly employed electrode montage and considering the modulation of the MEP amplitude, we had predicted that: (1) the benefits of tDCS would be related to the preservation of the underlying primary motor cortex (not affected by the injury); and (2) the presence of MEP, demonstrating the integrity of the corticospinal tract, could also be related to the beneficial effects of anodal tDCS. We hypothesized that tDCS would have a greater effect on children with CP with an intact primary motor cortex to receive anodal tDCS and when an MEP could be produced, as such children would have anatomic and physiologic evidence of their potential to responsiveness to such treatment. The findings demonstrated that the presence of a pre-intervention MEP was significantly associated with children with CP, who responded satisfactorily to gait training combined with anodal tDCS in terms of the distance traveled on 6MWT and gait speed, whereas the subcortical location of the injury demonstrated a significant association with the kinematic gait pattern and gross motor function.

Different neurophysiologic mechanisms are involved in the physiopathology of CP. Spastic CP is secondary to a pyramidal injury, compromising voluntary motor control with a reduction in cortical activity in motor areas, leading to a reduction in up-down muscle control (Burton et al., 2009; Kurz and Wilson, 2011; Pitcher et al., 2012). To evaluate the MEP in previous studies by our research group, we quantified electromyographic activity in the quadriceps muscles, which is important to the prognosis of standing and walking. Therefore, it is more appropriate to analyze a muscle directly related to the trained motor activity. We recognize that the cortical representation of the quadriceps muscle is more complex due to its location in comparison to an upper limb muscle. However, we believe that the use of the MEP of an upper limb muscle would not adequately represent this study goals. The presence of MEP can be understood as the integrity of the corticospinal tract to generate muscle activity or control muscle movement, therefore being considered a reliable predictor of clinical responsiveness. Thus, the use of anodal tDCS over the primary motor cortex likely facilitated the activity of this cortical area during gait training and consequently optimized the progress of motor training.

The literature suggests that an absent MEP may be associated with a poor prognosis in adult stroke survivors with hemiparesis (Van Kuijk et al., 2009; Lai et al., 2015). Although no studies

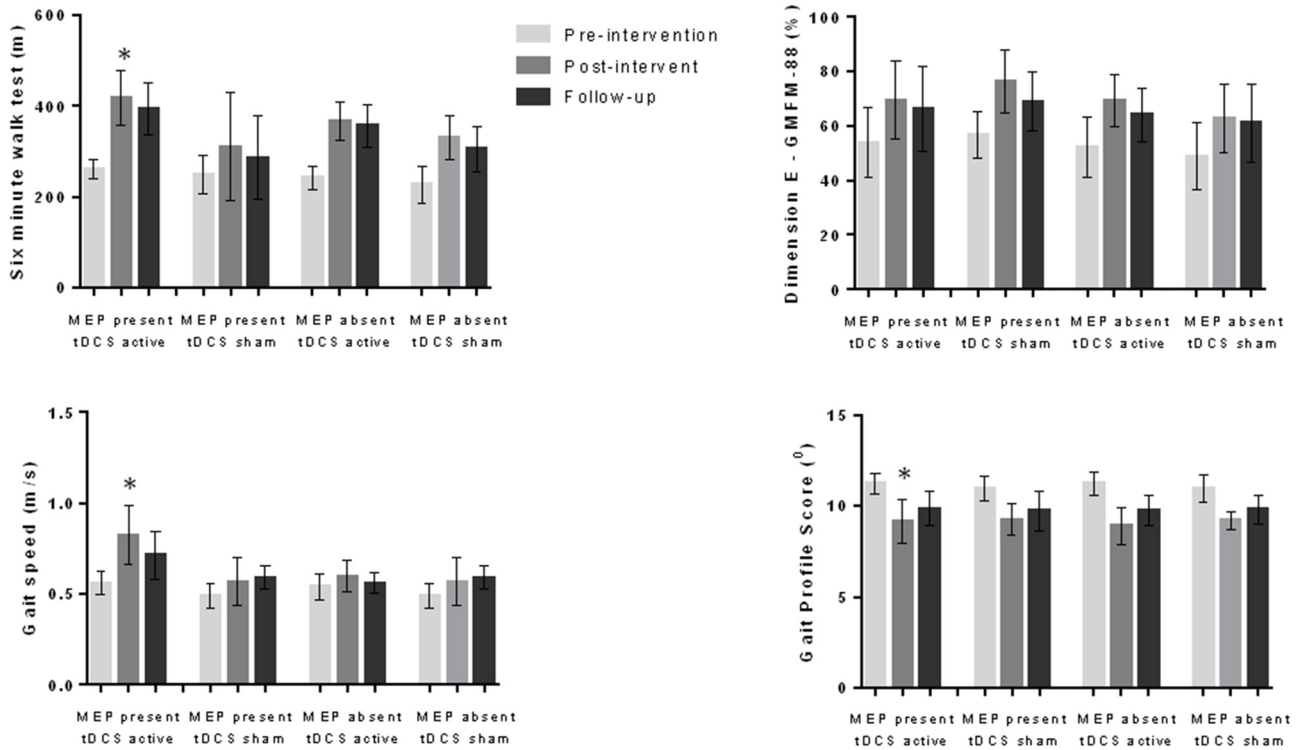

FIGURE 1 | Data for six-minute walk test (6MWT), gait speed, gait profile score and dimension E of the gross motor function measure (GMFM-88) during pre-intervention, post-intervention and follow-up evaluations considering motor evoked potential (MEP) present and absent as well as active and sham transcranial direct current stimulation (tDCS; 56 children). Children with MEP present at pre-intervention evaluation and who received active tDCS demonstrated better results at the post-intervention evaluation in comparison to other groups for 6MWT, gait speed and gait profile score. *$p < 0.05$ analysis of variance (ANOVA) followed by Bonferroni *post hoc* test.

were encountered on this aspect in children with CP, we found that the children responded to motor rehabilitation equally well with or without MEP. It should be stressed that children who received either active or sham stimulation responded to gait training, as described in previous studies. However, those who received active stimulation demonstrated greater effects in comparison to those who underwent sham stimulation. Thus, one may suggest that a single-pulse TMS can be used to identify subjects who will be respondent to tDCS by the presence or absence of a MEP, but not those who will be responsive to motor training. This finding indicates the specificity of tDCS affecting the corticospinal system to exert a supplementary benefit.

We believe that this result may be related to the adaptation process following a brain injury. Previous studies have demonstrated that a significant number of children with hemiparetic CP have cortical motor representations ipsilateral to movement (Mackey et al., 2014; Pihko et al., 2014). In cases of diparesis, the information is not yet fully clarified and there may be ipsilateral representations or even bilateral representations of movement (Kesar et al., 2012). Neurophysiologic studies have demonstrated that ipsilateral representations are strongly associated with greater motor impairment and there is no specific information on the relationship between cortical representations and the responsiveness to motor rehabilitation (Holmström et al., 2010; Van de Winckel et al., 2013; Mackey et al., 2014).

The present study did not include an evaluation of the area referring to the cortical motor representation (ipsilateral or contralateral to movement). We evaluated the amplitude of the MEP of the primary motor cortex. As all children exhibited active movement of quadriceps muscle (knee extension movement with sufficient force to overcome gravity), some area of the brain was apparently responsible for the control of this movement. Thus, this aspect may be considered a limitation of the present study. Administering anodal stimulation over most affected primary motor cortex without being sure that the area was responsible for the motor control of the most affected lower limb (especially in children with hemiparesis, since the unaffected brain hemisphere may be responsible for the control of both hemibodies), we assume the risk of tDCS not generating the desired modulatory effects and not optimizing the benefits of gait training. However, it should be emphasized that our previous randomized controlled studies, from which the data for the present investigation were extracted, demonstrated significant improvements in the groups that received active tDCS combined with gait training, even when tDCS was administered over the more affected primary cortex and with

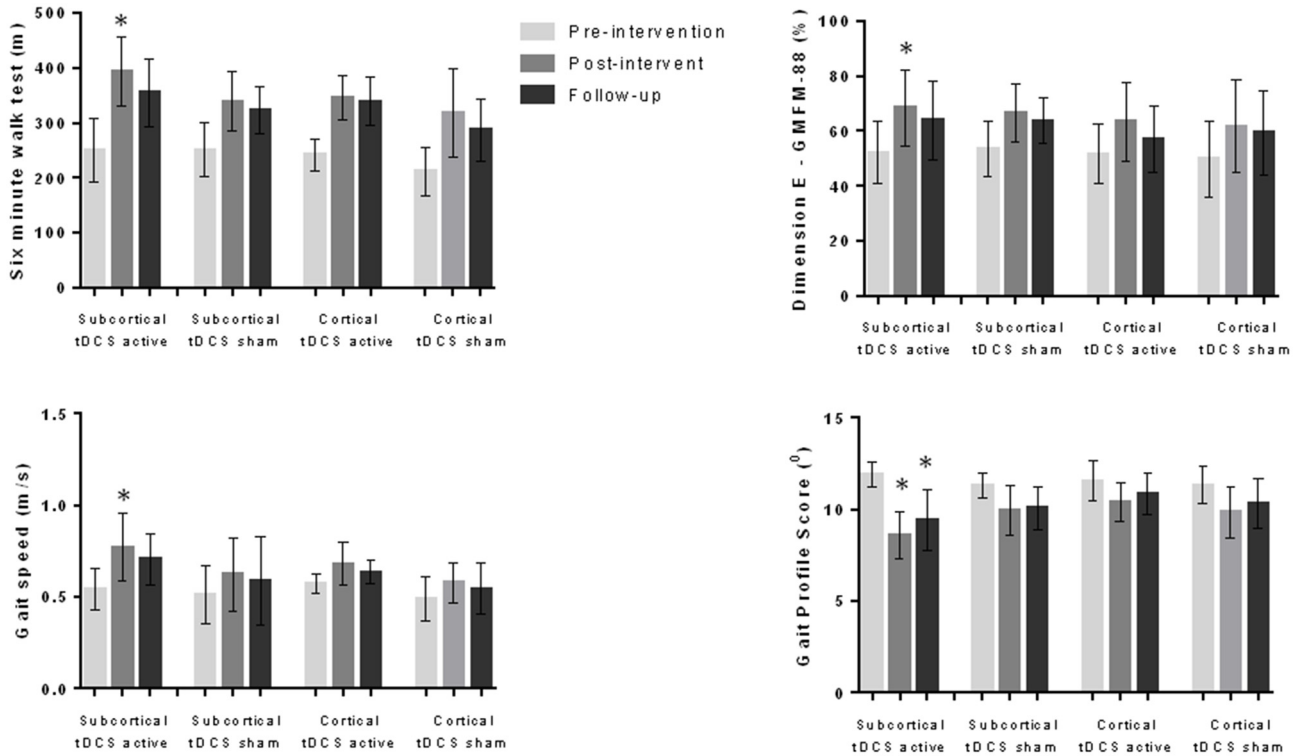

FIGURE 2 | Data for 6MWT, gait speed, gait profile score and dimension E of the GMFM-88 during pre-intervention, post-intervention and follow-up evaluations considering subcortical and cortical injuries as well as active and sham tDCS groups (56 children). Children with subcortical injury and who received active tDCS presented better results at the post-intervention evaluation in comparison to other groups for all variables. This group also had better results regarding gait profile score at follow-up evaluation. *$p < 0.05$ ANOVA followed by Bonferroni *post hoc* test.

anode positioned between Cz and C3 or C4. This suggests that the montage was beneficial to optimizing motor gains and contributed to the maintenance of the results 1 month following the end of the interventions. A hypothesis for this finding is based on modeling studies indicating that the current and effects are distributed between the anode and cathode rather than merely beneath the anode. Thus, the area responsible for the lower limbs may have been involved in the present investigation.

We believe that the evaluation of the complete motor map, with the administration of TMS pulses in the motor cortex bilaterally during bilateral electromyographic readings could clarify the influence of cortical representation and the presence of the MEP on the effect of the intervention in children with CP. The motor cortical map enables identification of the brain area responsible for controlling movements (that motor training could improve) and a more precise analysis of the corticospinal tract integrity. Thus, it could be possible to determine the target area for noninvasive brain stimulation more precisely, thereby increasing the efficiency of this technique. If this procedure were performed prior to or following the motor intervention process, the results could assist in clarifying cerebral motor adaptations in CP as well as provide information on the adaptation process of the brain during physical rehabilitation.

The effect of active tDCS on 6MWT was significantly greater among children with CP with a present MEP in comparison to those without the presence of this physiological aspect during the pre-intervention evaluation. This finding, together with the results of the regression analyses demonstrating a significant interaction between MEP and 6MWT, suggests that MEP may be a prerequisite for complementary treatment with tDCS. The results of the statistical analyses make sense and lend support to our hypotheses. To obtain the clinical effects of tDCS, it is important to have connectivity between the stimulated cortical area and structures of the neural motor system responsible for execution of the motor activity. Therefore, careful selection of target areas for noninvasive brain stimulation is of extreme importance. Apparently, the determination of such area based exclusively on the location of the injury and merely by the aim of either facilitating or inhibiting a given area is insufficient for adequate therapeutic planning. Moreover, the 10–20 EEG system commonly employed in clinical trials may not be the best option for locating the target area for stimulation in children with CP. However, these suppositions need to be tested in future studies.

Previous randomized controlled studies conducted by our research group, from which the data for the present investigation were extracted, demonstrated significant improvements in groups that received active tDCS combined with gait training,

even when tDCS was administered over the more affected primary motor cortex. Thus, one could infer that this montage is beneficial to optimizing motor gains and contributes to the maintenance of such gains 1 month after the end of the intervention.

The motor prognosis of children with CP is generally based on different aspects related to the injury such as its location and extent. For a long time, the size of injury was considered the main factor associated with the development of satisfactory or unsatisfactory motor development. Currently, studies have demonstrated that injury size is not necessarily the major aspect governing the magnitude of motor impairment. Neurophysiologic adaptations secondary to the injury may exert an important influence on the functional prognosis. The literature offers no further information on the impact of cortical-subcortical injuries in comparison to injuries that exclusively affect cortical areas regarding neurophysiologic adaptations in this population.

The classification of the injury (cortical and subcortical) has proven to be extremely important in the field of noninvasive brain stimulation. During tDCS, there is significant dispersal of current and only a small amount reaches out cortical areas. The subcortical effects of tDCS are secondary to alterations in the cortical excitability generated by the current that reaches the cortex. Children with subcortical injuries who received active tDCS achieved better results on gait profile score and gross motor function than those with cortical injuries who received active stimulation. However, acquisition of motor functions following an injury to the cortex is possible. As shown in our previous studies, children with CP demonstrate improvement of the variables studied after gait training, but this study showed that the effects of gait training were optimized with active tDCS, especially in children with subcortical lesions.

Physiotherapists observe important motor gain in their patients every day. Motor acquisitions are often achieved through numerous postural compensations in the medium and long terms, which can lead to additional problems for the patient. Adequate motor control during the execution of a movement requires the precise activation of superior neurological systems. Although the present findings may have been influenced by other factors and it is not possible to perform an exclusive analysis on the role of the subcortical injury regarding movement quality, we believe that future studies with the aim of more adequately clarifying the impact of cortical and subcortical injuries on movement quality in children with CP are of extreme importance to the field. The present study was unable to prove the hypothesis that cortical damage compromises movement quality more than subcortical damage, but could be used for the development of future studies addressing this issue (Rahman et al., 2015).

Adults with hemiparesis following a cortical injury demonstrate poor results with regard to noninvasive brain stimulation in comparison to those with subcortical injuries (Reynolds et al., 2014). The present results demonstrate that the MEP * injury location interaction is a predictor of the responsiveness to the intervention regarding the 6MWT assessment. It is likely that the heterogeneity in the results of the group with cortical injuries is related to the amount of preserved nerve tissue over the area to which tDCS was administered. Thus, further studies should be developed that include the specific quantification of damage to the corticospinal tract with the use of tractography, for example. The results obtained with this method could clarify the relationship between the extent of the motor tract injury and the cortical effects of tDCS.

The present investigation is an exploratory study that presents a critical discussion regarding the importance of understanding the influence of neurophysiologic and neuroanatomic biomarkers on the results obtained with the combination of tDCS and motor training in children with CP. The findings demonstrate that the presence of MEP is associated with functional measures such as 6MWT and gait speed, whereas the subcortical injury is associated with more specific variables (e.g., gait kinematics). There is a need for further studies performing a more in-depth exploration through controlled clinical trials on the influence of MEP, the cortical representation of movement and the location of injury regarding the responsiveness to the use of tDCS; and also seeking to understand the influence of these measures on the motor prognosis of children with CP, and jump thick in activities such as walking, running, movement (cinada to gait training for the 6MWT).

The main limitation of the present study was the use of a secondary analysis of previous trials data. Therefore, no specific sample size calculation was performed. Regarding the primary outcome (6MWT) in the analysis comparing children with cortical or subcortical injuries, 74 subjects per group would be necessary to possibly demonstrate an effective influence of injury location on gait training. However, this is an innovative, pioneering study that assessed the influence of neurophysiologic and anatomic parameters on the effects of gait training combined with tDCS. Additional investigations may provide specific information to clarify the interaction between these aspects and neural motor recovery in patients with CP. Other possible predictive factors should be investigated in future trials such as specific location and extent of injury (including an analysis of periventricular lesions), and motor cortical adaptation (motor cortical representation—unilateral, bilateral or contralateral and pattern of cortical activation during movement through functional magnetic resonance imaging (fMRI) and tractography). Studies on the effects of tDCS and its parameters for use in children with CP are still in early stages and many questions need to be clarified before the technique can be considered effective at optimizing the physical rehabilitation of these children.

AUTHOR CONTRIBUTIONS

LACG, DJE and FF designed research; LACG, NdACD, CC, NZ and CSO performed research; LACG, MG, DJE and FF analyzed data; LACG, DJE and FF wrote the article.

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ORIGINAL RESEARCH
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Restricted Arm Swing Affects Gait Stability and Increased Walking Speed Alters Trunk Movements in Children with Cerebral Palsy

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Observational research suggests that in children with cerebral palsy, the altered arm swing is linked to instability during walking. Therefore, the current study investigates whether children with cerebral palsy use their arms more than typically developing children, to enhance gait stability. Evidence also suggests an influence of walking speed on gait stability. Moreover, previous research highlighted a link between walking speed and arm swing. Hence, the experiment aimed to explore differences between typically developing children and children with cerebral palsy taking into account the combined influence of restricting arm swing and increasing walking speed on gait stability. Spatiotemporal gait characteristics, trunk movement parameters and margins of stability were obtained using three dimensional gait analysis to assess gait stability of 26 children with cerebral palsy and 24 typically developing children. Four walking conditions were evaluated: (i) free arm swing and preferred walking speed; (ii) restricted arm swing and preferred walking speed; (iii) free arm swing and high walking speed; and (iv) restricted arm swing and high walking speed. Double support time and trunk acceleration variability increased more when arm swing was restricted in children with bilateral cerebral palsy compared to typically developing children and children with unilateral cerebral palsy. Trunk sway velocity increased more when walking speed was increased in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy and typically developing children and in children with bilateral cerebral palsy compared to typically developing children. Trunk sway velocity increased more when both arm swing was restricted and walking speed was increased in children with bilateral cerebral palsy compared to typically developing children. It is proposed that facilitating arm swing during gait rehabilitation can improve gait stability and decrease trunk movements in children with cerebral palsy. The current results thereby partly support the suggestion that facilitating arm swing in specific situations possibly enhances safety and reduces the risk of falling in children with cerebral palsy.

Keywords: cerebral palsy, gait, stability, walking speed, trunk movements, arm swing

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INTRODUCTION

The forelimbs have a clear locomotor function in quadrupedal walking. In human walking, this function most likely changed as the upper limbs do not make contact to the ground during upright walking. Irrespective of its quadrupedal neural base (Jackson, 1983; Dietz and Michel, 2009; Dominici et al., 2011), research indicates that arm swing facilitates balance recovery following a perturbation (Bruijn et al., 2010; Pijnappels et al., 2010). Moreover, the typical anti-phase arm swing pattern is suggested to reduce the energetic cost of human walking (Collins et al., 2009; Yizhar et al., 2009; Meyns et al., 2014).

In pathological populations, the arm swing pattern can be affected or altered during gait, which could result in changes in the function of the arm swing. Altered arm swing patterns have been reported in children with cerebral palsy. Cerebral palsy is a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occur in the developing fetal or infant brain (Rosenbaum et al., 2007). Previous research found that arm swing amplitude was decreased on the hemiplegic side compared to the non-hemiplegic side in children with unilateral cerebral palsy (Meyns et al., 2011). Furthermore, children with bilateral cerebral palsy showed increased shoulder abduction and both children with unilateral as well as bilateral cerebral palsy walked with more elbow flexion compared to typically developing children (Romkes et al., 2007; Galli et al., 2014; Meyns et al., 2014). Moreover, the altered arm swing amplitude and arm posture changed inter-limb coordination in children with cerebral palsy (Meyns et al., 2012b). Children with cerebral palsy showed less stable coordination patterns and altered arm-leg movement frequency ratios compared to typically developing children (Meyns et al., 2012b).

While several changes of arm swing patterns have been reported in children with cerebral palsy, experimental evidence investigating the cause for these findings is still lacking. Nevertheless, such evidence should facilitate a more targeted therapeutic approach. For instance, previous correlational research suggested that altered arm swing in children with cerebral palsy plays an increased role in maintaining gait stability compared to typically developing children (Meyns et al., 2012a). As such, facilitating arm swing during gait rehabilitation could enhance safety, reduce the risk of falling and complement balance training in children with cerebral palsy. Therefore, the current experimental study aimed to examine the influence of restricting arm swing on gait stability in typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. It is hypothesized that gait stability would decrease more in children with cerebral palsy compared to typically developing children when arm swing is restricted. Moreover, children with bilateral cerebral palsy are expected to present more gait instability because of bilateral involvement. Indeed, research previously suggested that children with bilateral cerebral palsy have more problems to generate situation-specific neuromuscular responses to maintain postural stability compared to children with unilateral cerebral palsy (Woollacott and Shumway-Cook, 2005). Therefore, it is hypothesized that gait stability would decrease more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy when arm swing is restricted.

Additionally, other authors previously suggested a possible influence of walking speed on gait stability. However, the exact relationship remains unclear (Dingwell and Marin, 2006; England and Granata, 2007; Bruijn et al., 2009, 2013b), especially in children with cerebral palsy. Therefore, current study aimed to examine the influence of increasing walking speed on gait stability in typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. It is hypothesized that gait stability would decrease more in children with cerebral palsy compared to typically developing children when walking speed is increased. Furthermore, it is hypothesized that gait stability would decrease more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy when walking speed is increased.

Finally, a strong reciprocal influence between arm swing and walking speed was previously reported in children with cerebral palsy (Meyns et al., 2011). Therefore, the current study aimed to examine the influence of restricting arm swing combined with increasing walking speed influences on gait stability in typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. It is expected that gait stability would decrease more in children with cerebral palsy compared to typically developing children when both arm swing is restricted and walking speed is increased. Moreover, it is hypothesized that gait stability would decrease more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy when both arm swing is restricted and walking speed is increased. Additionally, it is hypothesized that the influence of restricting arm swing combined with increasing walking speed is larger compared to the isolated influence of these tasks.

MATERIALS AND METHODS

Participants

Twenty-six children with cerebral palsy (age range 4–12 years) and 24 typically developing children (age range 5–12 years) were included in the study. The cerebral palsy group consisted of 11 children with unilateral cerebral palsy and 15 children with bilateral cerebral palsy, recruited from the Clinical Motion Analysis Laboratory of the U.Z. Leuven (Pellenberg). The children with cerebral palsy were only included in the study if they were diagnosed with the predominantly spastic type of cerebral palsy. Diagnosis and type of cerebral palsy were determined by a multidisciplinary team of neuropediatricians, pediatric orthopedicians, and rehabilitation physicians after neurological examination (including magnetic resonance imaging). The participants had to be able to walk without assistive devices and were only allowed to participate if they showed enough cooperation to follow the instructions concerning the walking trials. The children were excluded if they underwent Botulinum Toxin A treatment within the past 6 months or if they previously underwent lower limb surgery.

The local ethical committee (Commissie Medische Ethiek KU Leuven) approved all experiments (approval number S51498). In accordance with the Declaration of Helsinki, written informed consent was obtained of the participants' parents.

Protocol

Three-dimensional total-body kinematic data (100 Hz) were captured by an eight camera Vicon system (Oxford Metrics, Oxford, UK) to detect the reflective markers placed on the participant's skin. Similarly to Romkes et al. (2007), 34 reflective markers were used (Romkes et al., 2007). All children were first asked to walk at a self-selected speed along the 10 m walkway on a straight line with no restricted arm swing ("free arm swing and preferred walking speed") or with the arms crossed in front of the body to restrict arm swing ("restricted arm swing and preferred walking speed"). Subsequently, the children were asked to walk as fast as possible with normal arm swing ("free arm swing and high walking speed") and restricted arm swing ("restricted arm swing and high walking speed"). Three successful trials were recorded in each condition. A trial was considered successful when at least four consecutive foot strikes with full-marker-visibility were recorded. A trial was not retained if the participant made excessive movements of the head, arms or trunk unrelated to walking. Before recording the data, each participant completed some practice trials.

Data Processing

The marker coordinates were filtered and smoothed using Woltring's quintic spline routine with a predicted mean-squared error of 15. Further processing in Workstation (Vicon Workstation 5.2 beta 20, Oxford Metrics, Oxford, UK) and Polygon (version 3.1, Oxford Metrics, Oxford, UK) consisted of defining gait cycles and calculating spatiotemporal gait parameters. In children with cerebral palsy, the most affected side was defined as the side on which the highest median spasticity score (Modified Ashworth Scale) was obtained in the lower limb. In typically developing children, the least affected side was defined as their dominant side.

Various outcome measures were assessed to determine the children's stability during walking. In accordance with recent literature concerning stability measures in experimental situations, several spatiotemporal parameters were calculated (Bruijn et al., 2013a). Double support time was defined as the time of the gait cycle where both feet were in contact with the ground. Step length was calculated as the distance along the line of progression from the opposite foot contact to the current foot contact. Equivalently, step width was described as the distance normal to the line of progression, from the toe marker on one foot to the toe marker on the opposite foot when initial foot contact occurs. Last, stride length is the distance along the line of progression from current foot contact to the next foot contact. Double support time was normalized to total stride time. Step width, as well as step length and stride length, were normalized to the participant's height. Only values of the most affected side were retained for further analysis.

Furthermore, maximal amplitude, maximum velocity and maximum acceleration values for trunk sway and trunk rotation were calculated for all trials. The maximal amplitude was defined as the angle between the maximal value of trunk excursion on the most affected side and the maximal value of trunk excursion on the least affected side in one trial. Trunk sway was quantified in the frontal plane by calculating the angle between the axis through the C7 marker and the sacrum marker and the vertical axis. Similarly, the angle between the axis through the shoulder markers and the axis through the pelvic markers in the coronal plane was determined to evaluate trunk rotations.

In addition to the spatiotemporal parameters and the kinematic trunk data, the margin of stability was used as a measure of gait stability. The margin of stability is specifically developed as a measure of dynamic stability (Pai and Patton, 1997; Hof et al., 2005). Recently, this measure has often been used to predict gait stability in different subject groups (Denommé et al., 2014; Lin et al., 2015; Matsubara et al., 2015; Nagano et al., 2015; Simon et al., 2015) including children with cerebral palsy (Dixon et al., 2016). It is calculated as the shortest distance from the extrapolated center of mass to the borders of the base of support (Pai and Patton, 1997; Hof et al., 2005; Hof, 2008). With regard to the inverted pendulum model, a condition is considered to be stable when the vertical projection of the body center of mass is kept within the boundaries of the base of support in general static situations. However, the extrapolated center of mass encompasses both the current position and velocity of the center of mass. Therefore, the margin of stability extends the inverted pendulum model of stability in static situations to dynamic situations. It provides a model of gait stability with a strong biomechanical base (Bruijn et al., 2013a). Following the approach described by Hak et al. (2013), the extrapolated center of mass was calculated by adding the velocity and a factor $\sqrt{(l/g)}$ to the position of the subject's center of mass. The center of mass was computed from the position and the relative weight from the segments of the PlugInGait-model. This method was found to be reliable (Gard et al., 2004). The parameter l represents the maximal height of the subject's calculated center of mass and g represents the gravitational acceleration. A schematic illustration of the margin of stability as a measure of gait stability is depicted in **Figure 1**. The margin of stability was assessed in the frontal plane by subtracting the maximum absolute extrapolated center of mass-value from the current lateral ankle position during foot contact (Hak et al., 2013).

All outcome measures were calculated for three successfully recorded trials in each condition of the experiment. Both the mean values and standard deviations over these trials were retained for further analysis. To avoid misinterpretations, "variability" will be used to refer to the magnitude of the standard deviations of the parameters.

Statistical Analysis

A one-way ANOVA was used to compare age, height and weight of typically developing children, children with unilateral and children with bilateral cerebral palsy. A general linear model was used to compare walking speed between subject groups in different walking speed conditions. Herein, subject group was included as a factor (between-subjects) and both arm swing condition (free arm swing or restricted arm swing) and walking

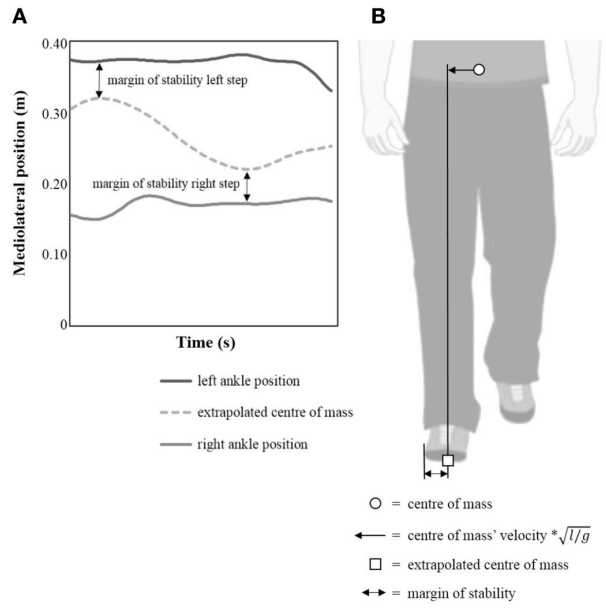

FIGURE 1 | Comprehensive illustration of the margin of stability as a measure of dynamic gait stability. (A) schematic representation of the "extrapolated center of mass"-position and the position of the lateral ankle markers. **(B)** illustration of center of mass' position, "extrapolated center of mass"-vector and margin of stability-calculations.

speed condition (preferred walking speed or walking "as fast as possible") were included as repeated measures factors (within-subjects). Moreover, a Mann-Whitney U Test was used to compare children with unilateral cerebral palsy and children with bilateral cerebral palsy for differences regarding the Gross Motor Function Classification Scale-levels and the Modified Ashworth Scale-grades (on the most affected side).

A general linear model was performed to determine the influence of restricting arm swing and increasing walking speed on the outcome parameters, i.e., mean values and the variability of the previously described (1) spatiotemporal parameters; (2) kinematic parameters of trunk movement; (3) margin of stability. The general linear model included subject group as a factor (between-subjects) and arm swing condition (free arm swing or restricted arm swing) and walking speed condition (preferred walking speed or walking "as fast as possible") as repeated measures factors (within-subjects). To explore group differences regarding the influence of restricting arm swing on gait stability, the arm swing condition * subject group interactions of the performed general linear models were analyzed. Walking speed condition * subject group interactions were analyzed to explore group differences regarding the influence of increasing walking speed on gait stability. Similarly, arm swing condition * walking speed condition * subject group interactions were analyzed to explore group differences regarding the combined influence of restricting arm swing and increasing walking speed on gait stability. Following the general linear model, Tukey's Honestly Significant Difference-tests were used to perform pairwise comparisons. Moreover, Partial Eta Squared-tests were performed to compute effect sizes for all interactions revealed by the general linear models. Cohen's D-test were performed to compute effect sizes for the pairwise comparisons revealed by the Tukey's Honestly Significant Difference-test.

Statistical analyses were performed using Statistica 8.0 (StatSoft, Inc., USA). The level of significance was set at 0.05 for all tests.

RESULTS

Characteristics of Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Group comparisons revealed no differences regarding age and weight (**Table 1**). However, group differences were found regarding height ($F = 3.690$, $p = 0.032$). Children with unilateral cerebral palsy were significantly smaller than typically developing children ($p = 0.025$). No differences between children with bilateral cerebral palsy and children with unilateral cerebral palsy were found regarding Gross Motor Function Classification System-levels. Children with bilateral cerebral palsy had higher overall median Modified Ashworth Scale-grades on the most affected side compared to children with unilateral cerebral palsy ($Z = 2.011$, $p = 0.044$).

Walking Speed in Different Experimental Conditions of Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Statistical analysis revealed a significant walking speed condition * subject group interaction for walking speed ($F = 9.901$, $p < 0.001$, partial eta-squared = 0.301; **Table 2**). Walking speed increased more in typically developing children compared to both children with bilateral cerebral palsy and children with unilateral cerebral palsy. This resulted from increased walking speed in typically developing children compared to children with bilateral cerebral palsy at both preferred walking speed ($p = 0.003$, Cohen's $d = 6.633$) and at high walking speed ($p < 0.001$, Cohen's $d = 9.352$). Furthermore, walking speed increased more in typically developing children compared to children with unilateral cerebral palsy. This resulted from increased walking speed in typically developing children compared to children with unilateral cerebral palsy at high walking speed ($p = 0.004$, Cohen's $d = 4.736$), while walking speed was similar at preferred walking speed. This is confirmed by the analysis of the effect sizes: the effect size regarding the increase from the preferred walking speed conditions to the high walking speed conditions is higher for typically developing children ($p < 0.001$, Cohen's $d = 15.794$) compared to both children with bilateral cerebral palsy ($p < 0.001$, Cohen's $d = 8.042$) and children with unilateral cerebral palsy ($p < 0.001$, Cohen's $d = 8.173$).

TABLE 1 | Subject characteristics.

	Typically developing children	Children with bilateral cerebral palsy	Children with unilateral cerebral palsy
N	24	15	11
Gender (M/F)	12/12	11/4	8/3
GMFCS (I/II/III)	–	8/6/1[a]	7/4/0
Modified ashworth scale			
Hip flexors		1 (0 – 2); 1 (0 – 2)	0 (0 – 1); 1 (0 – 1+)
Bi-articular hip adductors		1 (0 – 2); 1+ (0 – 2)	0 (0 – 1); 1 (0 – 1+)
Mono-articular hip adductors		1 (0 – 2); 1+ (0 – 2)	0 (0 – 1); 0 (0 – 1.5)
Hamstrings		1+ (0 – 3); 1+ (0 – 3)	1 (0 – 1+); 1+ (1 – 2)
Ankle plantarflexors (measured at 0° knee flexion)		1+ (1 – 2); 2 (0 – 3)	0 (0 – 1+); 2 (0 – 3)
Ankle plantarflexors (measured at 90° knee flexion)		1+ (0 – 2); 1+ (0 – 2)	0 (0 – 1+); 1+ (0 – 2)
Overall median		1+ (0 – 3); 1+ (0 – 3)	0 (0 – 1+); 1 (0 – 3)
Age (y: years, m: months)	9y 5m ± 2y 2m	9y 11m ± 2y 6m	7y 10m ± 3y 0m
Weight (kg)	31.72 ± 8.64	31.54 ± 13.36	23.87 ± 7.57
Height (m)	1.38 ± 0.14	1.34 ± 0.19	1.22 ± 0.15

Age, weight, and height are presented as follows: mean ± standard deviation. Modified Ashworth Scale values are presented as follows: least affected side median value (least affected side minimum value – least affected side maximum value); most affected side median value (most affected side minimum value – most affected side maximum value).
N, number of subjects; M/F, male/female; GMFCS, Gross Motor Function Classification System.
[a]*One subject with GMFCS-level 3 was included because this subject was able to complete the walking trials of the experiment without walking aids.*

TABLE 2 | Walking speed in different experimental conditions.

Experimental condition		Typically developing children ($n = 24$)	Children with bilateral cerebral palsy ($n = 15$)	Children with unilateral cerebral palsy ($n = 11$)
"Free arm swing and preferred walking speed"	(m/s)	1.19 ± 0.16	0.94 ± 0.24	1.10 ± 0.13
"Restricted arm swing and preferred walking speed"	(m/s)	1.18 ± 0.16	0.83 ± 0.35	1.01 ± 0.13
"Free arm swing and high walking speed"	(m/s)	1.93 ± 0.26	1.41 ± 0.41	1.67 ± 0.18
"Restricted arm swing and high walking speed"	(m/s)	1.98 ± 0.16	1.35 ± 0.47	1.61 ± 0.16

Walking speeds are presented as follows: mean ± standard deviation.

The Influence of Restricting Arm Swing on Gait Stability in Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Spatiotemporal Parameters

Statistical analysis revealed a significant arm swing * subject group interaction for double support time ($F = 6.164$, $p = 0.004$, partial eta-squared = 0.211; **Table 3**). Double support time increased more in children with bilateral cerebral palsy compared to typically developing children and children with unilateral cerebral palsy. This resulted from a significant increase in double support time in children with bilateral cerebral palsy when arm swing was restricted ($p = 0.031$, Cohen's $d = 2.517$; **Figure 2A**). Moreover, double support time was higher in children with bilateral cerebral palsy compared to typically developing children ($p < 0.001$, Cohen's $d = 6.560$; **Figure 2A**) and children with unilateral cerebral palsy walking ($p = 0.018$, Cohen's $d = 4.845$; **Figure 2A**) when subjects walked with restricted arm swing.

Trunk Parameters

A significant arm swing * subject group interaction was found regarding trunk sway acceleration variability ($F = 4.824$, $p = 0.013$, partial eta-squared = 0.173; **Table 4**). Trunk sway acceleration variability increased more in children with bilateral cerebral palsy compared to typically developing children and children with unilateral cerebral palsy. This resulted from higher trunk sway acceleration variability in children with bilateral cerebral palsy walking with restricted arm swing compared to walking with free arm swing ($p = 0.045$, Cohen's $d = 2.326$; **Figure 2B**).

Margin of Stability

No statistically significant group differences were revealed regarding the influence of restricting arm swing on the margin of stability (**Tables 3**, **4**).

The Influence of Increasing Walking Speed on Gait Stability in Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Spatiotemporal Parameters

A significant walking speed condition * subject group interaction was found for step length ($F = 5.279$, $p = 0.009$, partial eta-squared = 0.187; **Table 5**). Step length increased more in typically developing children compared to children with bilateral

TABLE 3 | Influence of restricting arm swing on different spatiotemporal parameters, kinematic trunk parameters, and margin of stability.

	Typically developing children ($n = 24$)		Children with bilateral cerebral palsy ($n = 15$)		Children with unilateral cerebral palsy ($n = 11$)		GLM
	Free	Restricted	Free	Restricted	Free	Restricted	
Double support time (%)	0.169 ± 0.011	0.154 ± 0.011	0.199 ± 0.014	0.233 ± 0.013	0.158 ± 0.016	0.165 ± 0.015	*
Step length (%)	0.448 ± 0.009	0.448 ± 0.011	0.364 ± 0.011	0.354 ± 0.013	0.422 ± 0.013	0.403 ± 0.016	
Step width (%)	0.084 ± 0.008	0.081 ± 0.012	0.102 ± 0.010	0.119 ± 0.015	0.080 ± 0.011	0.090 ± 0.017	
Stride length (%)	0.904 ± 0.018	0.898 ± 0.022	0.714 ± 0.023	0.667 ± 0.028	0.854 ± 0.026	0.834 ± 0.032	
Trunk sway amplitude (°)	5.662 ± 0.905	5.852 ± 0.869	13.717 ± 1.121	13.234 ± 1.076	7.880 ± 1.309	7.320 ± 1.256	
Trunk sway velocity (°/s)	0.354 ± 0.055	0.334 ± 0.045	0.761 ± 0.068	0.700 ± 0.056	0.563 ± 0.080	0.534 ± 0.066	
Trunk sway acceleration (°/s^2)	0.119 ± 0.031	0.061 ± 0.041	0.130 ± 0.039	0.179 ± 0.051	0.148 ± 0.045	0.208 ± 0.060	*
Trunk rotation amplitude (°)	22.192 ± 1.652	22.329 ± 1.915	27.199 ± 2.046	26.226 ± 2.371	26.771 ± 2.389	25.280 ± 2.769	
Trunk rotation velocity (°/s)	1.298 ± 0.115	1.251 ± 0.100	1.649 ± 0.142	1.564 ± 0.124	1.746 ± 0.166	1.708 ± 0.144	
Trunk rotation acceleration (°/s^2)	0.433 ± 0.125	0.220 ± 0.065	0.575 ± 0.155	0.402 ± 0.080	0.562 ± 0.181	0.609 ± 0.094	
Margin of stability (m)	0.051 ± 0.007	0.053 ± 0.007	0.074 ± 0.008	0.077 ± 0.009	0.064 ± 0.008	0.057 ± 0.009	

*Descriptive statistics are presented as mean ± standard deviation for all subjects groups in the free arm swing and the restricted arm swing conditions for all outcome parameters. A general linear model with subject group as a factor and both arm swing condition and walking speed condition as repeated measures factors was performed. An asterisk represents a significant ($p < 0.05$) subject group * arm swing interaction effect for the indicated outcome parameter.*
Free, free arm swing conditions; Restricted, restricted arm swing conditions; GLM, general linear model.

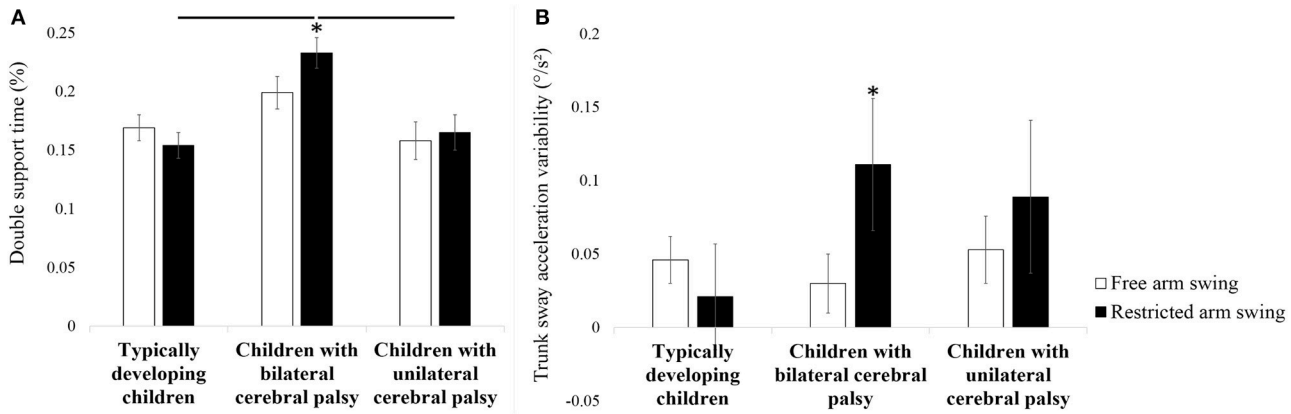

FIGURE 2 | Influence of restricting arm swing on double support time (A) and trunk sway acceleration variability (B). Bars and error bars represent, correspondingly, mean values and standard deviations of the presented outcome parameter for typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. White (gray) bars represent the values for the free arm swing conditions, black (gray) bars represent the values for the restricted arm swing conditions. An asterisk indicates a significant within subject group difference ($p < 0.05$) in the restricted arm swing conditions compared to the free arm swing conditions (Tukey's pairwise comparisons). A horizontal lines indicates a significant between subject group difference ($p < 0.05$) for the indicated subject groups in the indicated experimental conditions (Tukey's pairwise comparisons).

cerebral palsy. This resulted from larger step lengths in typically developing children compared to children with bilateral cerebral palsy at both preferred walking speed ($p = 0.001$, Cohen's $d = 6.337$; **Figure 3A**) and at high walking speed ($p < 0.001$, Cohen's $d = 9.135$; **Figure 3A**). Also, step length increased more in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy. This resulted from larger step lengths in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy at high walking speed ($p = 0.001$, Cohen's $d = 2.120$; **Figure 3A**) while step lengths were similar at preferred walking speed.

A significant walking speed condition * subject group interaction was found for stride length ($F = 5.950$, $p = 0.005$, partial eta-squared = 0.206; **Table 5**). Stride length increased more in typically developing children compared to children with bilateral cerebral palsy. This resulted from larger stride lengths in typically developing children compared to children with bilateral cerebral palsy at both preferred walking speed ($p < 0.001$, Cohen's $d = 7.509$) and at high walking speed ($p < 0.001$, Cohen's $d = 10.151$). Furthermore, stride length increased more in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy. This resulted from larger stride lengths in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy at both preferred walking speed ($p = 0.013$, Cohen's $d = 5.034$) and at high walking speed ($p = 0.002$, Cohen's $d = 5.641$).

TABLE 4 | Influence of restricting arm swing on the variability of different spatiotemporal parameters, kinematic trunk parameters, and margin of stability.

	Typically developing children ($n = 24$)		Children with bilateral cerebral palsy ($n = 15$)		Children with unilateral cerebral palsy ($n = 11$)		GLM
	Free	Restricted	Free	Restricted	Free	Restricted	
Double support time (%)	0.035 ± 0.009	0.020 ± 0.007	0.029 ± 0.011	0.045 ± 0.008	0.028 ± 0.012	0.024 ± 0.010	
Step length (%)	0.023 ± 0.002	0.019 ± 0.002	0.028 ± 0.003	0.025 ± 0.003	0.027 ± 0.004	0.026 ± 0.003	
Step width (%)	0.016 ± 0.002	0.015 ± 0.002	0.019 ± 0.003	0.017 ± 0.002	0.017 ± 0.003	0.022 ± 0.003	
Stride length (%)	0.042 ± 0.005	0.035 ± 0.004	0.040 ± 0.006	0.039 ± 0.005	0.038 ± 0.008	0.045 ± 0.006	
Trunk sway amplitude (°)	1.500 ± 0.178	1.535 ± 0.144	2.370 ± 0.220	2.555 ± 0.179	1.705 ± 0.237	1.654 ± 0.209	
Trunk sway velocity (°/s)	0.083 ± 0.013	0.071 ± 0.012	0.123 ± 0.016	0.146 ± 0.015	0.122 ± 0.019	0.106 ± 0.017	
Trunk sway acceleration (°/s^2)	0.046 ± 0.016	0.021 ± 0.036	0.030 ± 0.020	0.111 ± 0.045	0.053 ± 0.023	0.089 ± 0.052	*
Trunk rotation amplitude (°)	4.145 ± 0.534	4.317 ± 0.577	4.429 ± 0.661	4.964 ± 0.714	4.427 ± 0.772	5.860 ± 0.834	
Trunk rotation velocity (°/s)	0.260 ± 0.070	0.251 ± 0.058	0.462 ± 0.087	0.379 ± 0.072	0.441 ± 0.101	0.506 ± 0.084	
Trunk rotation acceleration (°/s^2)	0.158 ± 0.122	0.071 ± 0.056	0.426 ± 0.152	0.193 ± 0.069	0.276 ± 0.177	0.353 ± 0.081	
Margin of stability (m)	0.019 ± 0.005	0.017 ± 0.004	0.016 ± 0.005	0.018 ± 0.004	0.022 ± 0.005	0.024 ± 0.005	

*Descriptive statistics are presented as mean ± standard deviation for all subjects groups in the free arm swing and the restricted arm swing conditions for the variability of all outcome parameters. A general linear model with subject group as a factor and both arm swing condition and walking speed condition as repeated measures factors was performed. An asterisk represents a significant ($p < 0.05$) subject group * walking speed interaction effect for the variability of the corresponding outcome parameter.*
Free, free arm swing conditions; Restricted, restricted arm swing conditions; GLM, general linear model.

TABLE 5 | Influence of increasing walking speed on different spatiotemporal parameters, kinematic trunk parameters, and margin of stability.

	Typically developing children ($n = 24$)		Children with bilateral cerebral palsy ($n = 15$)		Children with unilateral cerebral palsy ($n = 11$)		GLM
	Preferred	High	Preferred	High	Preferred	High	
Double support time (%)	0.197 ± 0.011	0.127 ± 0.010	0.248 ± 0.014	0.185 ± 0.013	0.193 ± 0.016	0.129 ± 0.015	
Step length (%)	0.405 ± 0.010	0.492 ± 0.011	0.335 ± 0.012	0.382 ± 0.013	0.380 ± 0.014	0.445 ± 0.015	*
Step width (%)	0.082 ± 0.013	0.083 ± 0.007	0.123 ± 0.016	0.098 ± 0.009	0.089 ± 0.018	0.081 ± 0.011	
Stride length (%)	0.811 ± 0.020	0.991 ± 0.022	0.641 ± 0.025	0.741 ± 0.027	0.780 ± 0.030	0.908 ± 0.032	*
Trunk sway amplitude (°)	4.870 ± 0.858	6.644 ± 0.943	12.233 ± 1.062	14.718 ± 1.168	6.223 ± 1.240	8.977 ± 1.364	
Trunk sway velocity (°/s)	0.258 ± 0.044	0.430 ± 0.058	0.574 ± 0.055	0.843 ± 0.072	0.375 ± 0.064	0.723 ± 0.084	*
Trunk sway acceleration (°/s^2)	0.102 ± 0.032	0.078 ± 0.040	0.117 ± 0.039	0.192 ± 0.050	0.127 ± 0.046	0.229 ± 0.058	*
Trunk rotation amplitude (°)	15.790 ± 1.507	28.730 ± 1.984	21.889 ± 1.866	31.535 ± 2.457	20.279 ± 2.179	31.772 ± 2.869	
Trunk rotation velocity (°/s)	0.883 ± 0.093	1.666 ± 0.124	1.193 ± 0.115	2.019 ± 0.154	1.249 ± 0.134	2.205 ± 0.180	
Trunk rotation acceleration (°/s^2)	0.384 ± 0.092	0.268 ± 0.102	0.362 ± 0.113	0.615 ± 0.126	0.466 ± 0.132	0.705 ± 0.147	*
Margin of stability (m)	0.046 ± 0.006	0.058 ± 0.008	0.067 ± 0.007	0.084 ± 0.010	0.058 ± 0.007	0.062 ± 0.010	

*Descriptive statistics are presented as mean ± standard deviation for all subjects groups in the free arm swing and the restricted arm swing conditions for all outcome parameters. A general linear model with subject group as a factor and both arm swing condition and walking speed condition as repeated measures factors was performed. An asterisk represents a significant ($p < 0.05$) subject group * walking speed interaction effect for the indicated outcome parameter.*
Preferred, preferred walking speed conditions; high, high walking speed conditions; GLM, general linear model.

Trunk Parameters

A significant walking speed condition * subject group interaction was found for trunk sway velocity ($F = 5.083$, $p = 0.010$, partial eta-squared = 0.181; **Table 5**). Children with bilateral cerebral palsy increased trunk sway velocity more compared to typically developing children when walking speed was increased. This resulted from higher trunk sway velocity in children with bilateral cerebral palsy compared to typically developing children at both preferred walking speed ($p = 0.004$, Cohen's $d = 6.345$; **Figure 3B**) and high walking speed ($p < 0.001$, Cohen's $d = 6.317$; **Figure 3B**). Furthermore, children with unilateral cerebral palsy increased trunk sway velocity more compared to typically developing children when walking speed was increased. This resulted from higher trunk sway velocity at high walking speed in children with unilateral cerebral palsy compared to typically developing children ($p = 0.025$, Cohen's $d = 4.059$; **Figure 3B**), while trunk sway velocity was similar at preferred walking speed. Moreover, children with unilateral cerebral palsy increased trunk sway velocity more compared to children with bilateral cerebral palsy when walking speed was increased. At high walking speed, trunk sway velocity in children with bilateral cerebral palsy and children with unilateral cerebral palsy was similar. At preferred walking speed, trunk sway velocity was higher in children with bilateral cerebral but similar in children with unilateral cerebral palsy compared to typically developing children. This is confirmed by the analysis of the effect sizes: the

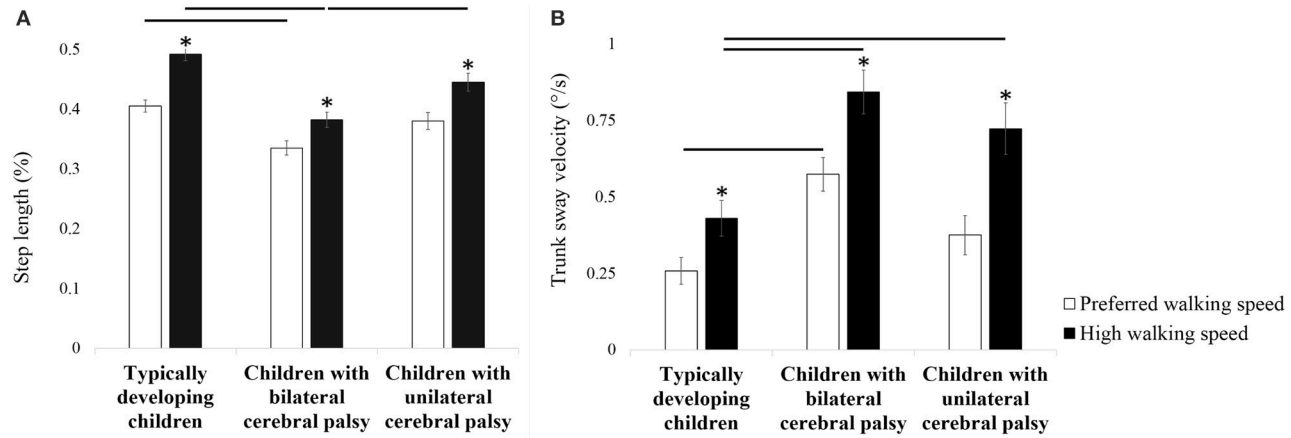

FIGURE 3 | Influence of increasing walking speed on step length (A) and trunk sway velocity (B). Bars and error bars represent, correspondingly, mean values and standard deviations for of the presented outcome parameter for typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. White bars represent the values for the preferred walking speed conditions, black bars represent the values for the high walking speed conditions. An asterisk indicates a significant within subject group difference ($p < 0.05$) in the high walking speed conditions compared to the preferred walking speed conditions (Tukey's pairwise comparisons). A horizontal line indicates a significant between subject group difference ($p < 0.05$) for the indicated subject groups in the indicated experimental conditions (Tukey's pairwise comparisons).

TABLE 6 | Influence of increasing walking speed on the variability of different spatiotemporal parameters, kinematic trunk parameters, and margin of stability.

	Typically developing children ($n = 24$)		Children with bilateral cerebral palsy ($n = 15$)		Children with unilateral cerebral palsy ($n = 11$)		GLM
	Preferred	High	Preferred	High	Preferred	High	
Double support time (%)	0.022 ± 0.002	0.033 ± 0.011	0.028 ± 0.003	0.046 ± 0.013	0.023 ± 0.004	0.029 ± 0.015	
Step length (%)	0.021 ± 0.003	0.021 ± 0.002	0.026 ± 0.003	0.026 ± 0.003	0.031 ± 0.004	0.022 ± 0.003	
Step width (%)	0.015 ± 0.002	0.016 ± 0.002	0.018 ± 0.003	0.018 ± 0.003	0.018 ± 0.003	0.021 ± 0.003	
Stride length (%)	0.036 ± 0.005	0.041 ± 0.005	0.035 ± 0.006	0.043 ± 0.006	0.051 ± 0.007	0.031 ± 0.008	*
Trunk sway amplitude (°)	1.166 ± 0.123	1.869 ± 0.188	2.179 ± 0.152	2.747 ± 0.233	1.382 ± 0.177	1.978 ± 0.272	
Trunk sway velocity (°/s)	0.071 ± 0.013	0.083 ± 0.012	0.118 ± 0.016	0.151 ± 0.015	0.091 ± 0.018	0.137 ± 0.018	
Trunk sway acceleration (°/s^2)	0.045 ± 0.022	0.023 ± 0.030	0.069 ± 0.028	0.071 ± 0.037	0.053 ± 0.032	0.089 ± 0.043	
Trunk rotation amplitude (°)	3.164 ± 0.440	5.298 ± 0.664	3.999 ± 0.545	5.394 ± 0.822	4.259 ± 0.636	6.028 ± 0.960	
Trunk rotation velocity (°/s)	0.225 ± 0.066	0.286 ± 0.054	0.370 ± 0.082	0.470 ± 0.067	0.439 ± 0.096	0.508 ± 0.078	
Trunk rotation acceleration (°/s^2)	0.155 ± 0.067	0.074 ± 0.109	0.232 ± 0.083	0.387 ± 0.135	0.273 ± 0.097	0.356 ± 0.158	
Margin of stability (m)	0.012 ± 0.004	0.023 ± 0.006	0.015 ± 0.004	0.019 ± 0.006	0.020 ± 0.004	0.025 ± 0.006	

*Descriptive statistics are presented as mean ± standard deviation for all subjects groups in the free arm swing and the restricted arm swing conditions for the variability of all outcome parameters. A general linear model with subject group as a factor and both arm swing condition and walking speed condition as repeated measures factors was performed. An asterisk represents a significant ($p < 0.05$) subject group * walking speed interaction effect for the variability of the indicated outcome parameter.*
Pref, preferred walking speed conditions; high, high walking speed conditions; GLM, general linear model.

effect size regarding the significant increase from the preferred walking speed conditions to the high walking speed conditions is higher for children with unilateral cerebral palsy ($p < 0.001$, Cohen's $d = 4.660$) compared to children with bilateral cerebral palsy ($p < 0.001$, Cohen's $d = 4.199$).

Margin of Stability

No significant group differences were revealed regarding the influence of increasing walking speed on the margin of stability (**Tables 5**, **6**).

The Influence of Restricting Arm Swing Combined with Increasing Walking Speed on Gait Stability in Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Spatiotemporal Parameters

No significant group differences were found regarding the spatiotemporal parameters.

Trunk Parameters

A significant arm swing condition * walking speed condition * subject group interaction was observed for trunk sway velocity ($F = 9.320$, $p < 0.001$, partial eta-squared = 0.288; **Table 7**). Children with bilateral cerebral palsy increased trunk sway velocity more compared to typically developing children from "restricted arm swing and preferred walking speed" to "restricted arm swing and high walking speed." This resulted from higher trunk sway velocity in "restricted arm swing and high walking speed" in children with bilateral cerebral palsy compared to typically developing children ($p = 0.033$, Cohen's $d = 6.326$; **Figure 4**), while trunk sway velocity was similar in "restricted arm swing and preferred walking speed." Besides these different interactions, another interesting difference was observed. Trunk sway velocity was lower in "restricted arm swing and preferred walking speed" compared to "free arm swing and preferred walking speed" for typically developing children ($p = 0.010$, Cohen's $d = 2.391$; **Figure 4**).

Statistical analysis also revealed a significant arm swing condition * walking speed condition * subject group interaction for trunk rotation velocity ($F = 6.976$, $p = 0.002$, partial eta-squared = 0.233; **Table 7**). Typically developing children increased trunk rotation velocity more from "restricted arm swing and preferred walking speed" to "restricted arm swing and high walking speed" compared to children with bilateral cerebral palsy and unilateral cerebral palsy. This resulted from lower trunk rotation velocity in "restricted arm swing and preferred walking speed" compared to "free arm swing and preferred walking speed" in typically developing children ($p = 0.018$, Cohen's $d = 4.634$; **Figure 5**). Trunk rotation velocity was similar in "free arm swing and preferred walking speed" and in "restricted arm swing and high walking speed" for all three subject groups.

Margin of Stability

Analysis of the arm swing * walking speed * group interactions of the margin of stability revealed no significant differences (**Table 7**). Moreover, no significant differences were found for the arm swing * walking speed * group interactions of the variability of the margins of stability (**Table 8**).

DISCUSSION

In the current study, the influence of restricting arm swing and increasing walking speed in typically developing children and children with both unilateral and bilateral cerebral palsy was compared to gain insight on the stabilizing role of arm swing during walking. First, it was hypothesized that gait stability would decrease more in children with cerebral palsy compared to typically developing children when arm swing is restricted. It was also expected that gait stability would decrease more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy when arm swing is restricted. Second, it was hypothesized that gait stability would decrease more in children with cerebral palsy compared to typically developing children when walking speed is increased. It was also expected that gait stability would decrease more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy when walking speed is increased. Finally, it was hypothesized that gait stability would decrease more in children with cerebral palsy compared to typically developing children when both arm swing is restricted and walking speed is increased. It was also expected that gait stability would decrease more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy when both arm swing is restricted and walking speed is increased. Additionally, it was expected that the influence of restricting arm swing combined with increasing walking speed would be larger compared to the isolated influence of these tasks.

The Influence of Restricting Arm Swing on Gait Stability in Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Previous research suggested that altered arm postures in children with cerebral palsy were related to gait instability (Meyns et al., 2012a). The current results partly support these observational findings.

Double support time increased more in children with bilateral cerebral palsy compared to typically developing children and children with unilateral cerebral palsy when arm swing was restricted. Children with bilateral cerebral palsy may have tried to enhance stability of walking by minimizing the impact of an instable single support phase (Kim and Son, 2014). Therefore, the larger increase in double support time in the children with cerebral palsy (when they are not allowed to freely swing their arms) is considered as an indication for the stabilizing role of arm swing in children with bilateral cerebral palsy.

The larger increase in trunk sway acceleration variability in children with bilateral cerebral palsy also suggests an increase in gait instability when arm swing is restricted. Measures of kinematic variability have been extensively used to quantify gait stability (Bruijn et al., 2013a). For instance, measures of trunk acceleration variability reliably estimated the risk of falls in elderly (Doi et al., 2013). Higher trunk acceleration variability could decrease gait stability through the disturbance of optic flow and vestibular signals (Holt et al., 1999; Iosa et al., 2014). Therefore, the larger increase in trunk acceleration variability in children with bilateral cerebral palsy when arm swing was restricted is also considered as an indication for the stabilizing role of arm swing in children with bilateral cerebral palsy.

Increased trunk sway acceleration variability in children with bilateral cerebral palsy could also be explained by trunk control deficits in children with cerebral palsy (Heyrman et al., 2011, 2014; Attias et al., 2015). Trunk control deficits have been shown to be strongly correlated to the level of impairment (Attias et al., 2015) and to increased range of motion of trunk movements in children with cerebral palsy (Heyrman et al., 2013, 2014). However, the children with cerebral palsy included in the study were only mildly impaired. Therefore, trunk control deficits in the current population can be expected to be mild. Furthermore, no differences were observed regarding trunk sway and trunk rotational range of motion. Although the adopted computational methods may differ, the values reported in literature (Heyrman

TABLE 7 | Combined influence of restricting arm swing and increasing walking speed on different spatiotemporal parameters, kinematic trunk parameters and margin of stability.

	Typically developing children ($n = 24$)				Children with bilateral cerebral palsy ($n = 15$)				Children with unilateral cerebral palsy ($n = 11$)				GLM
	Free Pref.	Restr. Pref.	Free High	Restr. High	Free Pref.	Restr. Pref.	Free High	Restr. High	Free Pref.	Restr. Pref.	Free High	Restr. High	
Double support time (%)	0.207 ± 0.010	0.186 ± 0.013	0.131 ± 0.014	0.123 ± 0.012	0.231 ± 0.013	0.264 ± 0.016	0.167 ± 0.017	0.202 ± 0.014	0.190 ± 0.015	0.195 ± 0.019	0.125 ± 0.020	0.134 ± 0.017	
Step length (%)	0.404 ± 0.009	0.406 ± 0.012	0.493 ± 0.011	0.491 ± 0.011	0.341 ± 0.011	0.328 ± 0.015	0.386 ± 0.013	0.379 ± 0.014	0.388 ± 0.013	0.372 ± 0.018	0.455 ± 0.015	0.434 ± 0.014	
Step width (%)	0.083 ± 0.006	0.081 ± 0.013	0.084 ± 0.005	0.081 ± 0.006	0.107 ± 0.008	0.138 ± 0.017	0.098 ± 0.007	0.099 ± 0.007	0.088 ± 0.009	0.090 ± 0.020	0.073 ± 0.008	0.089 ± 0.008	
Stride length (%)	0.810 ± 0.018	0.812 ± 0.025	0.999 ± 0.022	0.984 ± 0.023	0.678 ± 0.022	0.604 ± 0.031	0.750 ± 0.027	0.731 ± 0.028	0.795 ± 0.026	0.765 ± 0.036	0.913 ± 0.032	0.903 ± 0.033	*
Trunk sway amplitude (°)	5.108 ± 0.939	4.632 ± 0.811	6.216 ± 0.957	7.072 ± 0.999	12.818 ± 1.162	11.649 ± 1.005	14.615 ± 1.186	14.820 ± 1.237	6.366 ± 1.357	6.080 ± 1.173	9.394 ± 1.384	8.560 ± 1.445	
Trunk sway velocity (°/s)	0.306 ± 0.053	0.209 ± 0.039	0.402 ± 0.063	0.459 ± 0.056	0.607 ± 0.066	0.540 ± 0.048	0.825 ± 0.078	0.860 ± 0.070	0.363 ± 0.077	0.386 ± 0.056	0.763 ± 0.091	0.682 ± 0.082	*
Trunk sway acceleration (°/s^2)	0.171 ± 0.030	0.033 ± 0.025	0.067 ± 0.024	0.089 ± 0.036	0.092 ± 0.037	0.143 ± 0.031	0.168 ± 0.030	0.216 ± 0.044	0.079 ± 0.043	0.175 ± 0.037	0.218 ± 0.034	0.240 ± 0.052	*
Trunk rotation amplitude (°)	17.464 ± 1.167	14.116 ± 1.137	26.919 ± 1.451	30.541 ± 1.949	23.761 ± 1.445	20.017 ± 1.408	30.637 ± 1.797	32.434 ± 2.413	21.968 ± 1.687	18.591 ± 1.645	31.574 ± 2.098	31.970 ± 2.818	
Trunk rotation velocity (°/s)	1.134 ± 0.124	0.631 ± 0.090	1.461 ± 0.133	1.871 ± 0.150	1.237 ± 0.153	1.150 ± 0.112	2.061 ± 0.165	1.978 ± 0.186	1.244 ± 0.179	1.255 ± 0.131	2.249 ± 0.193	2.161 ± 0.217	*
Trunk rotation acceleration (°/s^2)	0.658 ± 0.131	0.111 ± 0.082	0.207 ± 0.155	0.329 ± 0.069	0.371 ± 0.162	0.353 ± 0.102	0.779 ± 0.192	0.451 ± 0.086	0.373 ± 0.189	0.558 ± 0.119	0.750 ± 0.224	0.660 ± 0.100	*
Margin of stability (m)	0.045 ± 0.004	0.047 ± 0.005	0.057 ± 0.006	0.058 ± 0.007	0.064 ± 0.005	0.069 ± 0.006	0.083 ± 0.008	0.085 ± 0.008	0.062 ± 0.005	0.055 ± 0.006	0.066 ± 0.008	0.059 ± 0.008	

*Descriptive statistics are presented as mean ± standard deviation for all subjects groups in all experimental conditions for all outcome parameters. A general linear model with subject group as a factor and both arm swing condition and walking speed condition as repeated measures factors was performed. An asterisk represents a significant ($p < 0.05$) subject group * arm swing condition * walking speed interaction effect for the variability of the indicated outcome parameter.*

Free, free arm swing condition; Restr, restricted arm swing condition; Pref, preferred walking speed condition; High, high walking speed condition; GLM, general linear model.

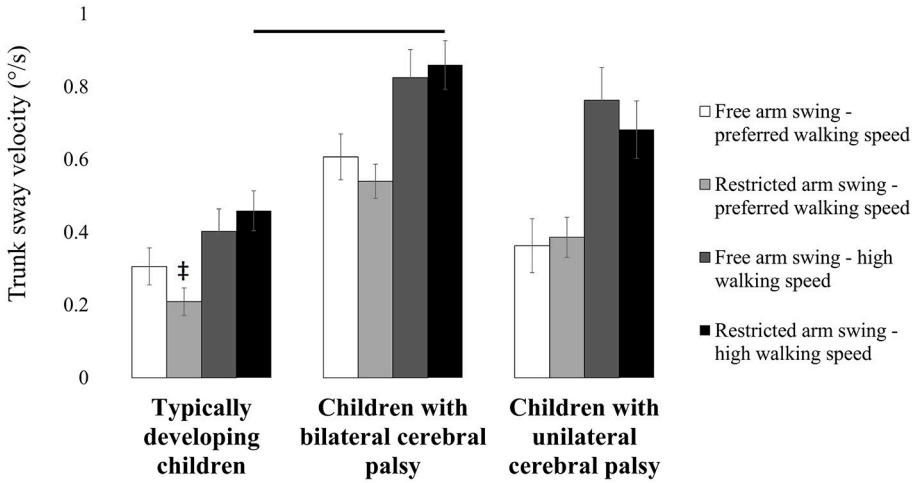

FIGURE 4 | Influence of restricting arm swing combined with increasing walking speed on trunk sway velocity. Bars and error bars represent, correspondingly, mean values and standard deviations for trunk sway velocity of typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. White bars represent the values for "free arm swing and preferred walking speed." Light gray bars represent the values for "restricted arm swing and preferred walking speed." Dark gray bars represent the values for "free arm swing and high walking speed." Black bars represent the values for "restricted arm swing and high walking speed." A double dagger indicates a significant between subject group difference ($p < 0.05$) in "restricted arm swing and preferred walking speed" compared to "free arm swing and preferred walking speed" (Tukey's pairwise comparisons). A horizontal line indicates a significant between subject group difference ($p < 0.05$) for the indicated subject groups in the indicated experimental conditions (Tukey's pairwise comparisons).

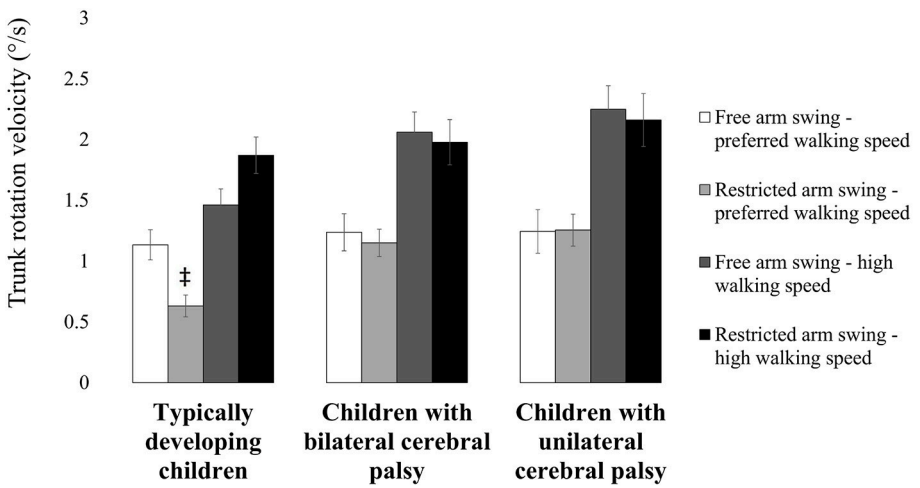

FIGURE 5 | Influence of restricting arm swing combined with increasing walking speed on trunk rotation velocity. Bars and error bars represent, correspondingly, mean values and standard deviations for trunk rotation velocity of typically developing children, children with bilateral cerebral palsy and children with unilateral cerebral palsy. White bars represent the values for "free arm swing and preferred walking speed." Light gray bars represent the values for "restricted arm swing and preferred walking speed." Dark gray bars represent the values for "free arm swing and high walking speed." Black bars represent the values for "restricted arm swing and high walking speed." A double dagger indicates a significant between subject group difference ($p < 0.05$) in "restricted arm swing and preferred walking speed" compared to "free arm swing and preferred walking speed" (Tukey's pairwise comparisons).

et al., 2013; Attias et al., 2015) are similar to the values reported in the current study. Therefore, it is assumed that, in the mildly impaired subjects included in the current study, trunk control deficits did not primarily cause the group differences in trunk sway acceleration variability when arm swing was restricted.

Next to possible trunk control deficits, altered angular momentum in children with cerebral palsy could also partly explain the observed group differences regarding trunk kinematics. Previous research indicated that arm swing movements compensated for the angular momentum (around a vertical axis) disruptions during walking by the involved leg in children with unilateral cerebral palsy (Bruijn et al., 2011). Possibly, restricting arm swing forces the trunk to take over the role of the arms in compensating angular momentum

TABLE 8 | Combined influence of restricting arm swing and increasing walking speed on the variability of different spatiotemporal parameters, kinematic trunk parameters, and margin of stability.

	Typically developing children ($n = 24$)				Children with bilateral cerebral palsy ($n = 15$)				Children with unilateral cerebral palsy ($n = 11$)				GLM
	Free Pref.	**Restr. Pref.**	**Free High**	**Restr. High**	**Free Pref.**	**Restr. Pref.**	**Free High**	**Restr. High**	**Free Pref.**	**Restr. Pref.**	**Free High**	**Restr. High**	
Double support time (%)	0.022 ± 0.002	0.022 ± 0.003	0.049 ± 0.017	0.018 ± 0.014	0.026 ± 0.003	0.030 ± 0.004	0.031 ± 0.021	0.060 ± 0.017	0.022 ± 0.004	0.023 ± 0.005	0.033 ± 0.024	0.024 ± 0.020	
Step length (%)	0.022 ± 0.004	0.020 ± 0.003	0.024 ± 0.003	0.019 ± 0.003	0.028 ± 0.005	0.025 ± 0.004	0.028 ± 0.004	0.024 ± 0.003	0.035 ± 0.005	0.027 ± 0.005	0.020 ± 0.005	0.025 ± 0.004	
Step width (%)	0.014 ± 0.002	0.016 ± 0.002	0.018 ± 0.002	0.014 ± 0.002	0.019 ± 0.002	0.017 ± 0.003	0.019 ± 0.003	0.016 ± 0.002	0.012 ± 0.003	0.024 ± 0.003	0.022 ± 0.003	0.020 ± 0.003	
Stride length (%)	0.036 ± 0.005	0.036 ± 0.004	0.048 ± 0.006	0.034 ± 0.005	0.036 ± 0.006	0.035 ± 0.006	0.043 ± 0.007	0.043 ± 0.006	0.049 ± 0.007	0.054 ± 0.006	0.026 ± 0.008	0.037 ± 0.007	
Trunk sway amplitude (°)	1.123 ± 0.167	1.209 ± 0.150	1.877 ± 0.251	1.862 ± 0.240	2.015 ± 0.207	2.342 ± 0.186	2.726 ± 0.310	2.768 ± 0.297	1.428 ± 0.242	1.336 ± 0.217	1.982 ± 0.362	1.973 ± 0.346	
Trunk sway velocity (°/s)	0.080 ± 0.015	0.062 ± 0.016	0.086 ± 0.017	0.080 ± 0.015	0.101 ± 0.018	0.136 ± 0.020	0.146 ± 0.021	0.156 ± 0.019	0.092 ± 0.021	0.091 ± 0.024	0.151 ± 0.024	0.122 ± 0.022	
Trunk sway acceleration (°/s^2)	0.070 ± 0.014	0.019 ± 0.026	0.022 ± 0.014	0.024 ± 0.032	0.022 ± 0.018	0.116 ± 0.032	0.037 ± 0.017	0.105 ± 0.040	0.022 ± 0.021	0.084 ± 0.037	0.083 ± 0.020	0.095 ± 0.046	
Trunk rotation amplitude (°)	3.178 ± 0.338	3.150 ± 0.454	5.112 ± 0.602	5.484 ± 0.610	3.524 ± 0.418	4.473 ± 0.562	5.334 ± 0.746	5.455 ± 0.755	3.599 ± 0.489	4.919 ± 0.656	5.254 ± 0.871	6.801 ± 0.882	
Trunk rotation velocity (°/s)	0.278 ± 0.082	0.172 ± 0.096	0.241 ± 0.089	0.330 ± 0.046	0.349 ± 0.102	0.392 ± 0.119	0.576 ± 0.110	0.365 ± 0.057	0.385 ± 0.119	0.493 ± 0.139	0.496 ± 0.129	0.519 ± 0.067	
Trunk rotation acceleration (°/s^2)	0.257 ± 0.082	0.052 ± 0.081	0.058 ± 0.183	0.089 ± 0.054	0.247 ± 0.102	0.218 ± 0.100	0.605 ± 0.226	0.168 ± 0.067	0.143 ± 0.119	0.402 ± 0.117	0.409 ± 0.264	0.303 ± 0.078	
Margin of stability (m)	0.012 ± 0.003	0.013 ± 0.004	0.026 ± 0.006	0.021 ± 0.004	0.015 ± 0.003	0.016 ± 0.004	0.018 ± 0.006	0.020 ± 0.004	0.020 ± 0.003	0.021 ± 0.005	0.023 ± 0.007	0.026 ± 0.005	

*Descriptive statistics are presented as mean ± standard deviation for all subjects groups in all experimental conditions for all outcome parameters. A general linear model with subject group as a factor and both arm swing condition and walking speed condition as repeated measures factors was performed. No significant ($p < 0.05$) subject group * arm swing condition * walking speed interaction effects were found for the variability of the presented outcome parameters. Free, free arm swing condition; Restr, restricted arm swing condition; Pref, preferred walking speed condition; High, high walking speed condition; GLM, general linear model.*

disruptions. However, other research found that angular momentum around the vertical axis was similar for children with bilateral cerebral palsy and typically developing children during walking (Russell et al., 2011). Therefore, it is assumed that, when arm swing was restricted, trunk compensation for angular momentum disruptions around the vertical axis did not primarily cause the group differences regarding increased trunk sway acceleration variability.

It is remarkable that no differences were detected regarding the influence of restricting arm swing on gait stability for children with unilateral cerebral palsy compared to typically developing children. It seems that restricting arm swing did not sufficiently challenge children with unilateral cerebral palsy to increase gait instability more compared to typically developing children. Therefore, it is assumed that the role of arm swing in gait stability is smaller in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy.

Furthermore, no changes in margins of stability and step width were found when arm swing was restricted (nor when walking speed was increased; see below). This possibly suggests that gait stability is very mildly affected. On the other hand, it is possible that restricting arm swing affects gait stability in a specific direction. Previous research indicated that children with unilateral cerebral palsy show gait instability in both the medio-lateral and the antero-posterior direction (Bruijn et al., 2013b). Since restricting arm swing did not affect the margins of stability nor step width, it seems reasonable to suggest that restricting arm swing does not specifically affect medio-lateral gait stability.

In conclusion, children with bilateral cerebral palsy showed larger increases in double support time and trunk sway acceleration variability compared to typically developing children and children with unilateral cerebral palsy. As hypothesized, these findings suggest that arm swing has a stabilizing role during gait in children with bilateral cerebral palsy. Trunk control deficits and trunk compensations for disrupted angular momentum are also suggested to influence gait instability in children with bilateral cerebral palsy (although to a smaller degree). Furthermore, the hypothesis that restricting arm swing would decrease gait stability more in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy seems to be confirmed.

The Influence of Increasing Walking Speed on Gait Stability in Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

Since we aimed to evaluate the combined effect of increasing walking speed and restricting arm swing, the isolated influence of walking speed on the measures of stability is described first.

Typically developing children increased step length and stride length more compared to children with bilateral cerebral palsy when walking speed was increased. Children with cerebral palsy face muscle shortening, muscle contractures and/or spasticity. Since spasticity is dependent of muscle lengthening velocity, this could influence step length more when increasing walking speed. Children with unilateral cerebral palsy increased step length more compared to children with bilateral cerebral palsy when walking speed was increased. This difference is likely to be explained by the lower spasticity values in children with unilateral cerebral palsy and bilateral involvement in children with bilateral cerebral palsy (in contrast to unilateral involvement in children with unilateral cerebral palsy).

The reported group differences regarding the increase in trunk sway velocity when walking speed was increased could also be explained by compensations for differences regarding the increase in step length and stride length. However, step (stride) length increased more in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy. If step (stride) length primarily caused the reported group differences regarding trunk sway velocity, one would expect a smaller increase in trunk sway velocity in children with bilateral cerebral palsy compared to children with unilateral cerebral palsy. Clearly, this is not supported by the results. Moreover, previous research indicated that altered trunk movements in children with cerebral palsy are not likely to be compensations due to lower limb impairments (Heyrman et al., 2014). Therefore, it is assumed that trunk compensation for muscle spasticity in the legs did not primarily cause the group differences regarding increased trunk sway velocity when walking speed was increased.

Furthermore, increased trunk sway acceleration variability in children with bilateral cerebral palsy could also be explained by trunk control deficits in children with cerebral palsy (Heyrman et al., 2011, 2014; Attias et al., 2015). However, it is assumed that, in the mildly impaired subjects included in the current study, trunk control deficits did not primarily cause the group differences in trunk sway acceleration variability when arm swing was restricted. A profound elaboration can be found in the previous section.

Additionally, the reported group differences regarding the increase in trunk sway velocity when walking speed was increased could be explained by differences regarding the angular momentum around the vertical axis. Both children with bilateral cerebral palsy and children with unilateral cerebral palsy increased trunk sway velocity more when walking speed was increased. Previous research already indicated that the angular momentum around the vertical of the unaffected arm and leg in children with unilateral cerebral palsy were higher compared to typically developing children (Bruijn et al., 2011). Furthermore, upper body angular momentum around the vertical axis was higher in children with bilateral cerebral palsy compared to typically developing children (Russell et al., 2011). Moreover, previous research indicates that the angular momentum of body segments around a vertical axis increases with walking speed (Bruijn et al., 2008). As such, the larger increase in trunk sway velocity could be explained by the larger increase in walking speed in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy. Therefore, the group differences regarding the increase in trunk sway velocity when walking speed was increased are considered as an indication for trunk compensational movements for angular momentum disruptions.

In conclusion, children with cerebral palsy showed larger increases regarding trunk sway velocity when walking speed was increased compared to typically developing children. Furthermore, children with unilateral cerebral palsy increased trunk sway velocity more compared to children with bilateral cerebral palsy when walking speed was increased. It is proposed that the group differences regarding the increase in trunk sway velocity when walking speed was increased may be considered as an indication for trunk compensational movements for angular momentum disruptions. Trunk control deficits, trunk compensations for muscle spasticity and impaired step length are also suggested to influence trunk sway velocity in children with bilateral cerebral palsy (although to a smaller degree). In contrast to the research hypothesis, gait stability did not decrease more in children with cerebral palsy compared to typically developing children when walking speed was increased.

The Influence of Restricting Arm Swing Combined with Increasing Walking Speed on Gait Stability in Typically Developing Children, Children with Bilateral Cerebral Palsy, and Children with Unilateral Cerebral Palsy

An important group difference regarding the combined influence of restricting arm swing and increasing walking speed was found (similar to the isolated influence of increasing walking speed). A stronger increase in trunk sway velocity has been observed in children with bilateral cerebral palsy compared to typically developing children when subjects walking with restricted arm swing were asked to increase walking speed. This possibly suggests that increasing walking speed combined with restricting arm swing decreases gait stability more in children with bilateral cerebral palsy compared to typically developing children. However, these findings should certainly be interpreted with care because other factors (trunk control deficits, altered angular momentum and compensations for lower limb impairments) may interfere with the combined influence of arm swing and walking speed on gait stability (as mentioned above).

Furthermore, typically developing children showed a specific reaction when arm swing was restricted at preferred walking speed (and not at increased walking speed). Both trunk sway and trunk rotation decreased compared to walking with the arms free at the preferred walking speed. This "en bloc" strategy was not found in either group of children with cerebral palsy. Therefore, it is assumed that the trunk is required to move in children with cerebral palsy when arm swing is restricted.

In conclusion, children with bilateral cerebral palsy increased trunk sway velocity more compared to typically developing children when subjects walking with restricted arm swing were asked to increase walking speed. Overall, evidence is insufficient to conclude that restricting arm swing combined with increasing walking speed induced larger group differences regarding gait stability compared to their isolated effects. Thereby, the experimental data could not confirm the postulated research hypotheses regarding the influence of both restricted arm swing and increased walking speed on gait stability. However, the results showed that children with cerebral palsy adopted different responses to arm swing restriction compared to typically developing children regarding trunk kinematics.

Limitations to the Current Research

When interpreting the results of the current study, certain methodological issues should be taken into account. It is possible that the study sample consisting of 24 typically developing children and 26 children with cerebral palsy was too small and/or heterogeneous. This could have caused some marginally non-significant changes that were reported. Additionally, more children with bilateral cerebral palsy had a GMFCS level II than children with unilateral cerebral palsy. These differences certainly need to be taken into account when comparing these two groups. Most of the subjects included in the group of children with cerebral palsy had a GMFCS level I. This mildly involved population could have caused an underestimation of the actual differences between typically developing children and children with cerebral palsy.

Second, Bruijn et al. (2013a) reported a vast amount of possible parameters to assess stability of gait. Since gait stability is a multifactorial concept, not all parameters measure the same part of this concept and different parameters of gait stability possibly reflect different and contrasting viewpoints. For instance, previous research did not find a correlation between a measure of local dynamic stability and step length variability (Kurz et al., 2012). Therefore, further research to validate and to frame these measures in the global concept of gait stability needs to be conducted (Bruijn et al., 2013a). Research for measures of gait stability with proven validity and reliability in children with cerebral palsy specifically and across different population groups is still needed.

Finally, trunk movements were not described using joint angles. However, elevation angles were used (i.e., the angle between segments projected in one plane). As such, a simplified kinematic method was used. In previous research, this approach was found to be adequate to detect meaningful changes in the kinematics during walking in this population, in agreement with literature using joint angles (Meyns et al., 2011, 2012a,b).

CONCLUSION

In conclusion, restricting arm swing influenced gait stability more in children with bilateral cerebral palsy compared to both typically developing children and children with unilateral cerebral palsy. As such, the current study is the first to support experimentally that arm swing compensates (at least partly) for affected stability in children with bilateral cerebral palsy. Results were less clear for children with unilateral cerebral palsy. In contrast to the research hypotheses, increasing walking speed did not affect gait stability more in children with cerebral palsy compared to typically developing children (nor in children with bilateral cerebral palsy compared to children with unilateral

cerebral palsy). However, the current results indicate that increasing walking speed increased trunk compensations for altered angular momentum around a vertical axis more in children with cerebral palsy compared to typically developing children. The effects were larger in children with unilateral cerebral palsy compared to children with bilateral cerebral palsy because more trunk movements were already observed in children with bilateral cerebral palsy at preferred walking speed. In contrast to the research hypotheses, restricting arm swing combined with increasing walking speed did not induce larger group differences regarding gait stability compared to their isolated effects. Overall, it is proposed that facilitating arm swing during gait rehabilitation can improve gait stability and decrease trunk movements in children with cerebral palsy. The current results partly support the suggestion that facilitating arm swing in specific situations possibly enhances safety and reduce the risk of falling in children with cerebral palsy. Other authors already suggested a similar approach for other pathologies (e.g., stroke and spinal cord injury) in previous research (Stephenson et al., 2010; Tester et al., 2011). Moreover, previous research of our research group in a cerebral palsy population supports this conclusion (Meyns et al., 2011).

AUTHOR CONTRIBUTIONS

PM and KD conceived and designed the experiment. PM performed the experiments. PM and TD together analyzed the data. Furthermore, TD, PM, and KD wrote the paper. The writing process and the data analysis were supervised by PM and KD.

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