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Identification of the neural component of torque during manually-applied spasticity assessments in children with cerebral palsy

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Highlights

1. Quantification of the neural torque component of ankle hypertonia
2. Comparison of the neural torque component between children with CP and control
3. Sensitivity of the neural torque component to treatment with Botulinum Toxin-A

Abstract

Clinical assessment of spasticity is compromised by the difficulty to distinguish neural from non-neural components of increased joint torque. Quantifying the contributions of each of these components is crucial to optimize the selection of anti-spasticity treatments such as Botulinum Toxin (BTX). The aim of this study was to compare different biomechanical parameters that quantify the neural contribution to ankle joint torque measured during manually-applied passive stretches to the

gastrocsoleus in children with spastic cerebral palsy (CP). The gastrocsoleus of 53 children with CP (10.9 ± 3.7 yrs; females $n=14$; bilateral/unilateral involvement $n=28/25$; Gross Motor Functional Classification Score I-IV) and 10 age-matched typically developing (TD) children were assessed using a manually-applied, instrumented spasticity assessment. Joint angle characteristics, root mean square electromyography and joint torque were simultaneously recorded during passive stretches at increasing velocities. From the CP cohort, 10 muscles were re-assessed for intra-rater reliability and 19 muscles were re-assessed 6 weeks post-BTX. A parameter related to mechanical work, containing both neural and non-neural components, was compared to newly developed parameters that were based on the modeling of passive stiffness and viscosity. The difference between modeled and measured response provided a quantification of the neural component. Both types of parameters were reliable ($ICC > 0.95$) and distinguished TD from spastic muscles ($p < 0.001$). However, only the newly developed parameters significantly decreased post-BTX ($p = 0.012$). Identifying the neural and non-neural contributions to increased joint torque allows for the development of individually tailored tone management.

1. Introduction

Common clinical assessment of spasticity in children with Cerebral Palsy (CP) is based on manipulation of the joint to feel the resistance in a passively stretched muscle. In 1954, Tardieu and colleagues emphasized the importance of differentiating between different causes of this increased resistance, or hypertonia [1]. According to the currently prevailing definition of spasticity, an increase in resistance during passive muscle stretch is termed spasticity when there is an accompanying velocity-dependent pathological stretch reflex activation resulting in muscle activity that resists or stops the motion[2]. In the absence of muscle activation, all other excessive increase in resistance during stretch is thought to be caused by passive stiffness and viscosity due to alterations of intra- and extracellular muscle, soft-tissue, and joint structures. Therefore, different components contribute to the feeling of increased resistance in passively stretched muscle: neural and non-neural components. Direct quantification of the different components in a clinical setting is highly relevant allowing for comprehensive tone assessment.

Tone-reducing medication, such as Botulinum Toxin-A (BTX) targets the neural component by blocking the release of acetylcholine at the cholinergic nerve terminals, which prevents the muscle from contracting. This treatment does not work when the increased resistance is of non-neural origin [3]. Methods to treat passive stiffness include casting, orthotic management, or when fixed contractures arise, orthopedic surgery. Therefore, to provide the appropriate treatment to children with CP, it is imperative to differentiate and quantify the components.

The clinical test proposed by Tardieu, and its modifications [4] attempt to differentiate components by comparing the range of motion (ROM) during a slow muscle stretch (R1 angle) to the catch angle during a fast stretch (R2). However, muscle activation during slow stretch has been reported in some spastic muscles [5,6]. Without verifying whether the muscle is inactive, the validity of R1 is uncertain. Additionally, inaccuracies when manually determining R2 have been reported [5] and its reliability is further compromised since the velocity of the fast stretch is not measured. Only an assessment that simultaneously collects electrophysiological and biomechanical signals during passive muscle stretch has the potential to differentiate the influence of different components in a valid and reliable way. This approach is used in research settings using motor-driven devices [7–9] that permit standardization of position displacements [7] or of the applied force [9]. For example, using a torque-motor that applied sinusoidal movements at a constant force, Lakie et al. used the peak resonance frequency as a measure of linear stiffness and viscosity in the wrist [9]. On the other hand, by controlling displacement position, De Vlugt et al. modeled the contribution of different non-linear components to

measured ankle torque[7]. However, to what extent 'clinically' assessed spasticity can be replicated by a motor-driven device is questionable. Rabita et al. [10] have shown that fewer stretch-reflexes are elicited when spastic muscles are stretched by a robot, than by an examiner.

A different group of evaluation techniques makes use of the straight forward clinical application combined with a quantitative approach, and are referred to as instrumented manual techniques [11,12]. These methods replicate a clinical spasticity test by having an examiner apply muscle stretches while simultaneously collecting synchronized electromyography (EMG), kinematics, and/or joint torque. By examining the change in signals with increasing muscle lengthening velocity, parameters that quantify spasticity have been developed and have been shown to be applicable and valid in clinical settings [6,11]. However, in these studies, the velocity-dependent effects from both neural and non-neural components are reflected in the parameters that quantify joint torque. To differentiate between the components, further muscle modeling is required.

The non-linear behavior of passive stiffness and viscosity have been well described in healthy and hemiplegic subjects [7,13]. However, to the best of our knowledge, these models have rarely been applied to data from an instrumented manual spasticity assessment [14]. The aim of this study was to quantify the amount of neural contribution to the joint torque measured during stretches of the gastrocnemius in children with spastic CP. To achieve this, we model the non-neural components of passive stiffness and viscosity on data collected during stretches at increasing velocities. We then assume that

the difference between modeled and measured response, represents the neural component. Specifically, we hypothesized that: (1) the neural component will have good between-session reliability; (2) all components will be higher in children with CP than in typically developing (TD) children; and (3) in comparison to a previously-described parameter [11], the neural component will be more sensitive to the effect of BTX treatment.

2. Method

2.1 Participants

Children with spastic CP aged 5-18 years were recruited from the University Hospital ***. Exclusion criteria were: presence of ataxia or dystonia; ankles with fixed varus or valgus deformities hindering pure sagittal plane passive ankle motion; cognitive problems that impeded assessment; BTX injections within 6 months prior to first testing; previous lower-limb orthopedic or neuro-surgery. An age-matched group of TD children acted as a control group. The hospitals' ethical committee approved the protocol (B32220072814) and all children's parents signed an informed consent.

To assess between-session reliability, a subgroup of children with CP underwent a repeated assessment (including replacement of all sensors) after a two hour rest interval in which no treatment was administered. As part of an individually-defined, multilevel treatment, a second subgroup of children with CP were additionally measured 4-8 weeks after intramuscular BTX injections (Allergan, UK) in the gastrocnemius under short

anesthesia. After injections, the children underwent lower-leg casting for ± 10 days, intensive rehabilitation, and orthotic management (day and night).

In children with unilateral CP, only the affected side was tested. In children with bilateral involvement, if time allowed, both sides were tested. If not, the most involved side was tested as defined by the clinical spasticity scales [4,15].

2.2 Experimental procedure

All assessments were performed by the same trained assessor as detailed in [11]. Joint motion was tracked using two inertial measurement units, joint forces and torques were measured using a 6 dof load-cell, and surface EMG (sEMG) was collected from the lateral gastrocnemius and tibialis anterior (Figure 1). The subjects were asked to remain relaxed throughout the measurement. The ankle joint was moved through the full ROM, at low velocity during 5s, at medium velocity (1s), and finally at high velocity, performed as fast as possible. At each velocity, four repetitions were carried out with an interval of seven seconds between.

2.3 Data analysis

2.3.1 Data processing

Data visualization and analyses were performed in MATLAB®. To estimate joint angles, a Kalman smoother [16] was applied on the inertial measurement unit data. Average maximum angular velocity (V_{MAX}) was calculated per velocity trial. Using measured segment-lengths and moment-arms, the net internal ankle joint torque was calculated from the measured external forces and moments as outlined in [11]. EMG

onset in the lateral gastrocnemius was defined according to [17] and used to confirm the presence or absence of muscle activation during stretches. Stretch repetitions were excluded when performed out-of-plane (see Supplement 1 in [11]), at inconsistent velocities between repetitions within a velocity trial (difference $>20^\circ/\text{s}$), and in case of poor quality sEMG (low signal-to-noise ratio or obvious artefacts). In children with CP, stretches were additionally excluded when there was no EMG onset detected during high velocity stretches.

2.3.2 Outcome parameters

The following model to describe healthy muscle passive stiffness and viscosity was approximated from de Vlugt et al.[7]:

$$T = \left(1 + b \frac{d\theta}{dt}\right) e^{k(\theta - \theta_0)} + T_0 \quad (1)$$

Where T is the total predicted internal joint torque; b , a viscosity coefficient; k , a passive stiffness coefficient; θ , angular position; θ_0 , angular position offset; and T_0 , offset torque. In contrast to the original model, the model is represented in angular positions and torques rather than muscle lengths and forces, i.e. assuming that effects of a changing lever arm are negligible. The model was fitted to a region starting at the time of V_{MAX} to the time at 90% ROM. Based on data visualization, in this region, only the agonist, rather than antagonist muscle was elongated, while the influence of end ROM discomfort was excluded. An optimal fit of the model to the measurement was computed using the Levenberg-Marquardt algorithm [18]. Figure 2 shows the measured and modeled torque during one low- and one high-velocity stretch in a CP and a TD child. However, rather than modeling individual stretches [7], data from multiple stretches at all

velocities were used to fit a model per assessed muscle providing more information on which to estimate the distinct model components (Figure 3).

To capture how the measured torque T_m deviated from the modeled torque T , the following two parameters were developed: average model deviation, was defined as the square root of the integral from the time at $V_{MAX}(t_{Vmax})$ to the time at 90% ROM ($t_{90\%ROM}$) of the squared deviation between T and T_m divided by the time interval between t_{Vmax} and $t_{90\%ROM}$:

$$\text{Average model deviation} = \sqrt{\frac{1}{t_{90\%ROM} - t_{Vmax}} \int_{t_{Vmax}}^{t_{90\%ROM}} (T - T_m)^2 dt} \quad (2)$$

Average work-deviation was defined as the integral from the angular position at $V_{MAX}(\theta_{Vmax})$ to the angular position at 90% ROM ($\theta_{90\%ROM}$) of the absolute deviation between T and T_m divided by the position interval between θ_{Vmax} and $\theta_{90\%ROM}$

$$\text{Average work deviation} = \frac{1}{\theta_{90\%ROM} - \theta_{Vmax}} \int_{\theta_{Vmax}}^{\theta_{90\%ROM}} |T - T_m| d\theta \quad (3)$$

This parameter corresponded to the amount of work exchanged between assessor and subject during the motion.

Additionally, work was calculated as the integral of T_m over angular position from θ_{Vmax} to $\theta_{90\%ROM}$ to compare the model parameters to previous literature [11]:

$$\text{Work} = \int_{\theta_{Vmax}}^{\theta_{90\%ROM}} T_m(\theta) d\theta \quad (4)$$

Average work over the four repetitions at both high and low velocity was calculated. The difference of these two was defined as 'work-change', see also [11].

2.5 Statistics

Model-deviation, work-deviation and work-change were calculated for each assessed muscle. Intra-class correlation coefficients (ICC_{1,1}) [19] were calculated and interpreted according to [20]. Standard error of measurement (SEM) values were derived from the square root of the mean square error from one-way ANOVA [21]. Parameters were compared using t-tests (CP vs. TD) or paired-sample t-tests (pre-vs. post-BTX). The average difference between groups and between pre- and post-BTX was evaluated in view of the minimal detectable change (MDC) calculated from SEM-values [22]. The relation between the developed parameters and subject age, diagnosis, clinical spasticity scores [4, 15], and the Gross Motor Functional Classification Scale were investigated using either Pearson correlation coefficients (continuous parameters), or ANOVA and post-hoc Tukey tests (categorical parameters). Analyses were performed using SPSS®. Significance was set at $p < 0.05$.

3. Results

Fifty-three children with CP and 10 TD children were included (Table 1). Three children with CP were assessed bilaterally, ten were re-assessed for between-session reliability, and 16 (19 muscles) underwent re-assessment on average 53.3 ± 11.6 days post-BTX (average dosage injected into the gastrocnemius was 4.52 ± 0.79 U/Kg).

Study results can be found in Table 2. During high velocity trials, average V_{MAX} was higher in the TD group than in the CP and in the CP group post-BTX than pre-BTX. ICC

values were high for all parameters except for V_{MAX} at medium velocity. The differences between the mean values for CP and TD children for work-change (1.78J), model-deviation (1.80Nm), and work-deviation (1.54J) were higher than their corresponding MDC values (0.82J, 0.84Nm, and 0.72J, respectively). Post-BTX, only model-deviation, and work-deviations significantly decreased. The mean pre-post decrease in model-deviation (0.93Nm) was larger than its MDC value (0.84Nm). Model-deviation, work-deviation, and work-change had fair and good correlations with age ($r=0.32$; $r=0.31$; $r=0.61$, $p<0.05$, respectively).

4. Discussion

The aim of this study was to compare different biomechanical parameters that estimate the amount of neural contribution to increased joint torque during manually-applied, passive ankle movements at different velocities. The developed parameters were assessed for their between-session reliability and validated by comparing children with CP to TD children and by the response of muscles with spasticity to BTX-treatment.

Muscle models have mostly been applied to data collected with motor-driven devices [7,13,23]. However, instrumented manual assessments have the advantage of being portable, easy to administer, and to tolerate. Their disadvantage is decreased control creating the risk that extracted data are influenced by measurement performance. Nevertheless, in the current study, a model approximated from [7], was successfully applied to data collected during manually-applied movements. The model accurately predicted the characteristic shape of the torque-position graph during

stretches at different velocities in healthy muscle. However, during high velocity stretches of muscle with spasticity, the model only fitted the data with a larger approximation error. This was not unexpected since the model did not incorporate neural components (reflex muscle activation). On the other hand, the parameters that quantified the amount of deviation between the measured and predicted torque during stretches were found to be reliable, discriminative between spastic and healthy muscles, and sensitive to the effect of BTX.

A major issue when estimating model parameters is the bias-variance trade-off [24]: a trade-off between model complexity (the number of parameters) and the accuracy of the estimated parameters. A model with many parameters fits the measured data very well (low bias), but the variables are not estimated accurately (high variance). Even though multiple stretches at different velocities were used for modeling, our motions still had a limited dynamic range. This made it even more difficult to estimate reliable model parameters. Therefore, a simple model describing healthy muscle was used. The amount of deviation between the model prediction and the measurements indicated the pathological neural activity. As such, the estimated model parameters themselves were not used, and the method relies on the assumption that the neural component cannot be fitted properly by the applied model. The current approach thus holds a middle between data-driven parameters (such as in [25]) and a model-driven approach, such as in [7].

Several experimental and modeling assumptions in the current study need to be recognized. Firstly, it was assumed that the ankle motion during stretch occurred in the

sagittal plane. However, as previously reported [11], small out-of-plane movements ($<10^\circ$) would cause only a $1-5^\circ$ error. Secondly, formula 2 is a further approximation, compared to the work of De Vlugt et al [7], since it describes passivemuscle behavior in function of torques and angles instead of muscle forces and lengths. However, as shown in Figures 2 and 3, the model could still effectively approximate the joint torque of TD subjects. Thirdly, for the reasons stated before with regards to over-fitting, we were unable to accurately and repeatedly quantify the stiffness and viscosity coefficients. However, this was not our primary aim. Fourthly, despite the gastrocnemius being bi-articular, the knee joint angle was not included in the model. Since the knee joint was fixed during ankle movements (see [11]), this was not necessary. Finally, average V_{MAX} during high velocity stretches was higher in the TD group than in CP, and higher post-BTX. This velocity difference caused an increase of viscous forces. However, our deviation parameters were robust against velocity variations since the model contained a viscosity parameter. Different velocities resulted in consistent deviation parameters.

The proposed modeling approach was validated by clinical results. All investigated parameters were higher in CP than in TD children. The average decrease post-BTX for model-deviation was larger than its MDC-value, indicating that it can be used as a measure of improvement. However, the heterogeneous results suggest that the measurement error is still too high to detect improvement in all subjects. Therefore, more effort is required to increase reliability and improve performance standardization.

The effects of BTX were not captured by work-change, which was not surprising as work-change was also influenced by stiffness and viscosity. This finding confirms that by

removing the non-neural components, the deviation parameters better captured the neural influence. This is in line with previous findings, that report little effect of BTX on passive myotendinous stiffness in the calf muscles of children with CP [3].

Muscle contractures already start developing at an early age [26] and can affect gait in children with CP [27]. This emphasizes the need for proper torque differentiation and more dedication in developing treatments that target passive stiffness. Casting, combined with BTX, has been found to be more effective than BTX alone in improving gait [28]. Despite the short casting period post-BTX, work-change in the current study, did not significantly decrease post-treatment. Recent results suggest that growth velocity, rather than spasticity, plays a crucial role in contracture development [29]. In line with these findings, muscle stiffness increases whereas spasticity decreases, with age [30]. In the current study, age had a better correlation to work-change than to the deviation parameters.

There was also a large response variability to BTX-treatment. This variation highlights the importance of searching for predictors of treatment response in order to better tailor individualized treatment. Apart from age, no other relations were found between the biomechanical parameters and subject characteristics, but larger studies are required. Future studies should investigate whether muscles with a low model-deviation value are poorer responders to BTX. Accordingly, the current method offers a way in which to fine-tune treatment to the individual muscles' underlying etiology. However, more explorations are required to understand the relation between spasticity as

assessed at rest in a non-weight bearing position and functional movements, such as gait.

In the current study, EMG was not analyzed and was only used to confirm the presence/absence of muscle activation. The amount of EMG was not used as it has previously been shown that the relative contribution of the lateral gastrocnemius to the total neural torque component in the ankle is only 3% [7]. A future study should collect EMG from more muscles acting on the ankle to validate the relation between the identified neural component and the amount and timing of pathological muscle activation.

In summary, the neural contribution to increased ankle torque during stretches of spastic gastrocnemius muscles was captured in two biomechanical parameters (model-deviation and work-deviation) that also decreased post-BTX. Work-change, that includes passive stiffness and viscosity, was higher in spastic than in TD muscles, but was not affected by BTX. Therefore, while there was a large response variability, treatment with BTX combined with casting, predominantly treated the neural component. This highlights the need to better fine-tune treatment modalities for the gastrocnemius in children with CP.

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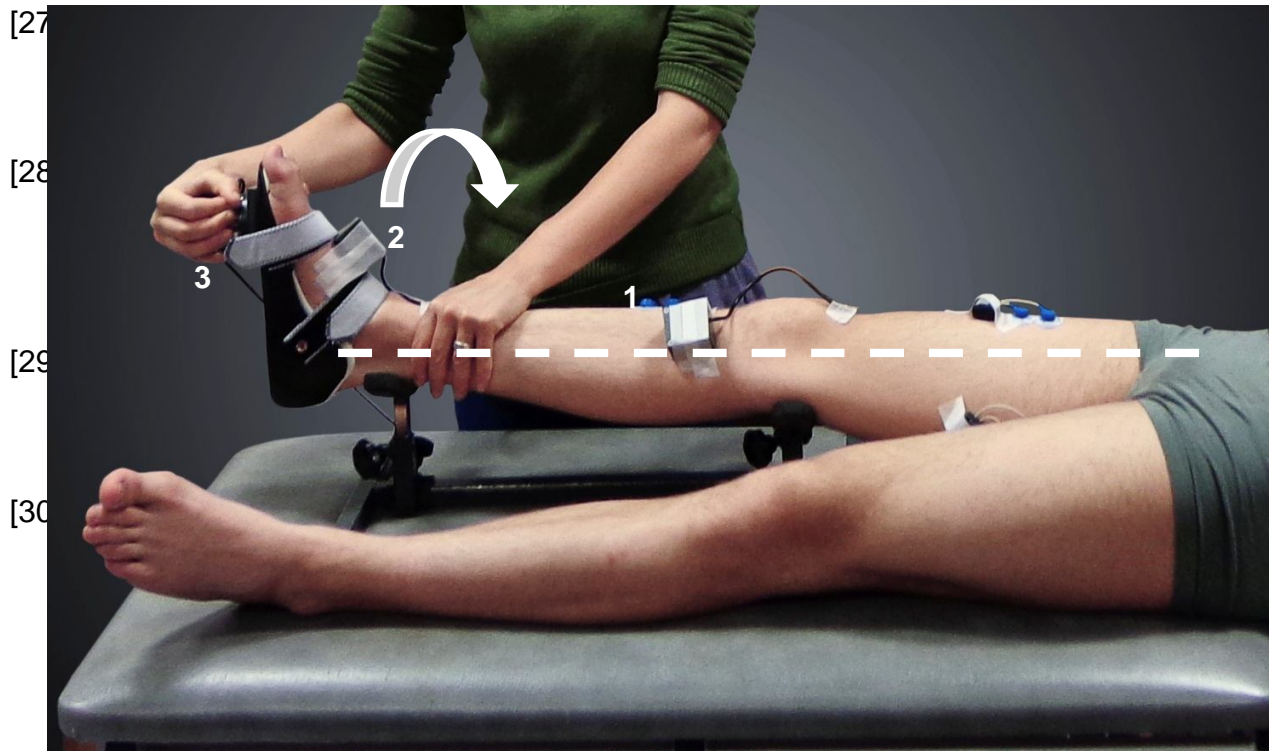


Fig. 1

Fig. 2

FF

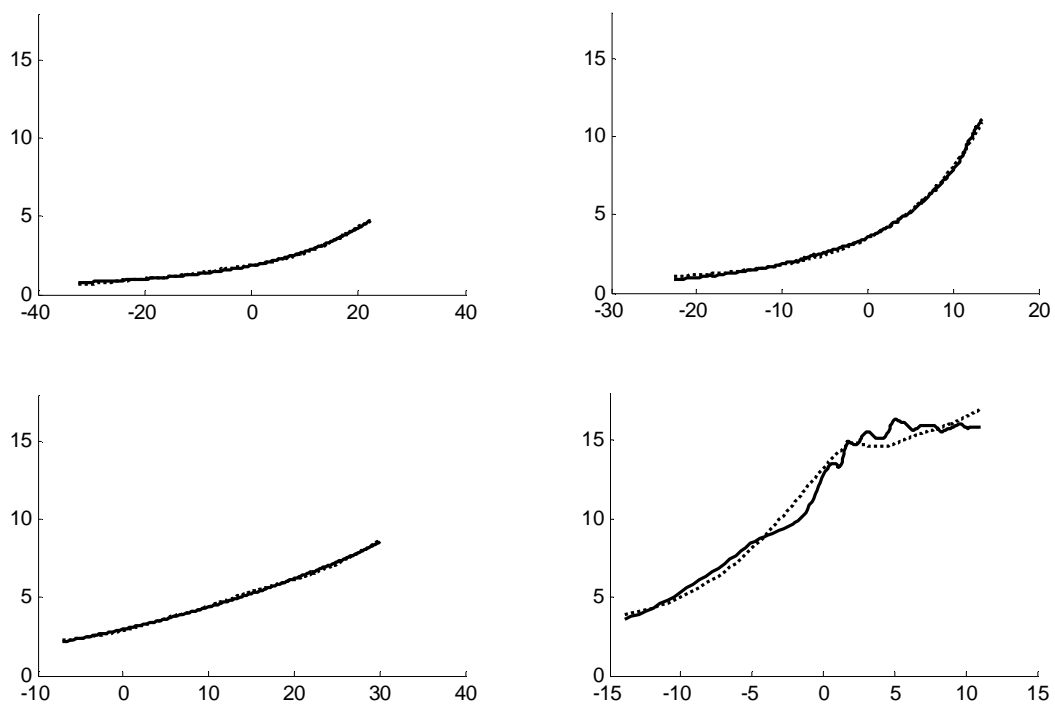
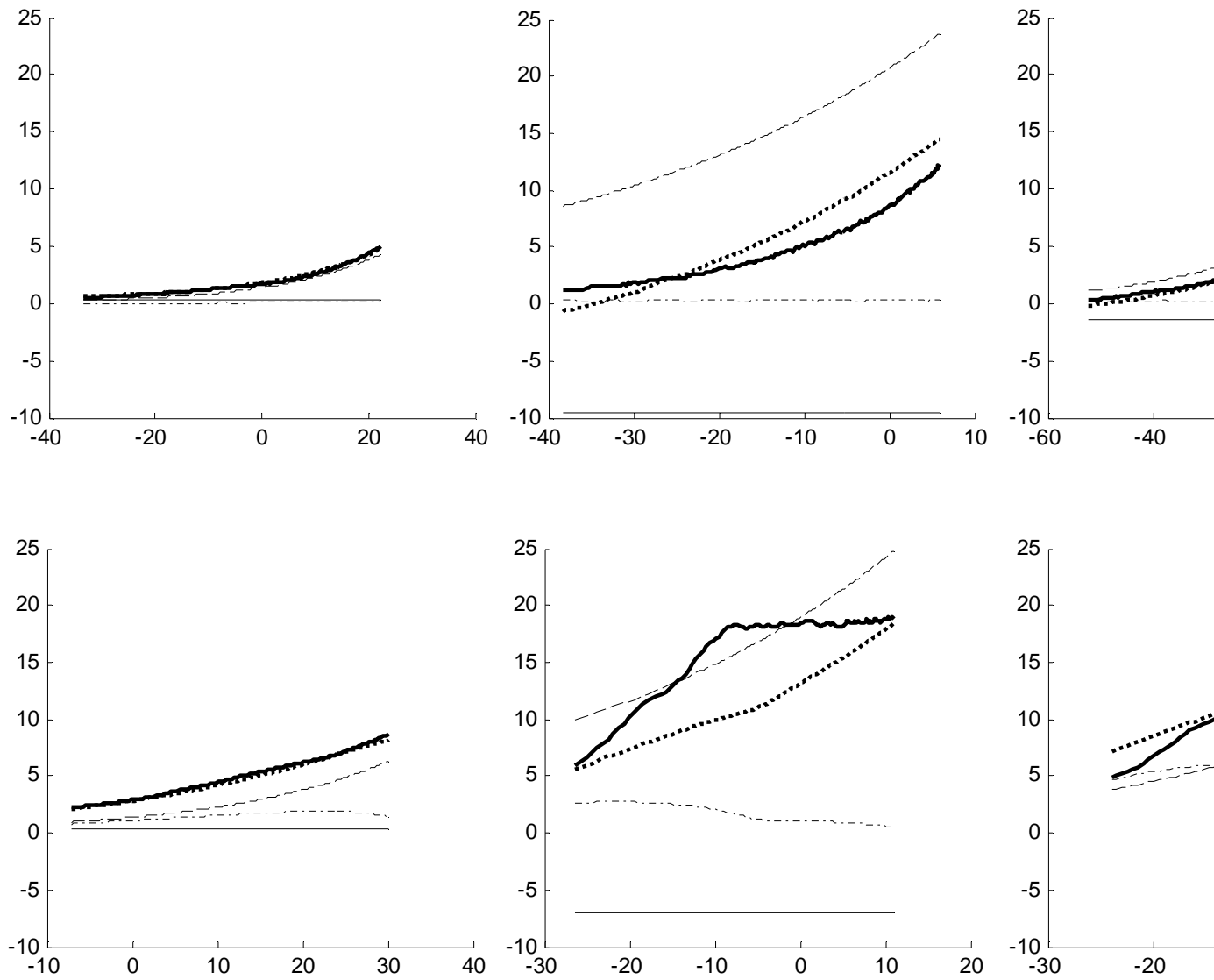


Fig. 2



Measured torque
 Model prediction
 Viscous component
 Stiffness component

Fig. 3

Table 1. Subject characteristics

Subjects	All children with CP (n=53, 56 muscles)	Subgroup of children with CP for reliability study (n=10)	Subgroup of children with CP for BTX study (n=16, 19 muscles)	TD children (n=10)
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Gender m/f	39/14	7/3	11/5	6/4
Mean age years (SD)	10.9 (3.7)	11.9 (3.8)	9.1 (2.7)	10.7 (3.4)
Diagnosis	Di: 26; LH: 11; RH: 14; Quad: 2	Di: 5; LH: 2; RH: 2; Quad: 1	Di: 7; LH: 3; RH: 6	NA
GMFCS score (I-IV)	I: 36; II:15; III:1; IV:1	I: 5; II: 4; IV: 1	I: 13; II:3	NA
MAS-score (I-V)	1: 4; 1+: 20; 2: 26; 3: 6	1+: 4 ;2: 4; 3: 2	1+: 4; 2: 13; 3: 2	NA
Average angle (SD)	MTS- -10.77° (9.1°)	-5.5° (10.9°)	-11.95° (6.67°)	NA

CP, cerebral palsy; BTX, Botulinum Toxin-A; Di, diplegia; LH, left hemiplegia; RH, right hemiplegia; Quad, quadriplegia; GMFCS, Gross Motor Function Classification Score; MAS, Modified Ashworth Scale for the gastrocnemius; MTS, Modified Tardieu Scale; TD, typically developing; NA, not applicable

Table 2. Comparison of stretch velocity and the biomechanical parameters in the three studies

Study	V _{MAX} low (°/s)	V _{MAX} med. (°/s)	V _{MAX} high (°/s)	Work-change (J)	Model-deviation (Nm)	Work-deviation (J)
Reliability (n=10 CP)						
Test mean (SD)	16.32 (5.67)	70.71 (24.20)	163.50 (30.97)	2.95 (1.40)	2.97 (1.35)	2.22 (1.05)
Retest mean (SD)	14.94 (7.74)	73.13 (23.14)	158.09 (18.62)	3.04 (1.35)	2.75 (1.39)	2.16 (1.10)
ICC	0.94	0.49	0.90	0.97	0.96	0.96
SEM	2.66	20.02	10.92	0.35	0.36	0.31
MDC	5.27	46.58	25.41	0.82	0.84	0.72
Construct validity (n=56 CP, n=10 TD)						
CP mean (SD)	19.29 (6.77)	85.52 (29.09)	168.62 (28.67)	2.99 (1.29)	2.70 (1.06)	2.07 (0.86)
TD mean (SD)	21.30 (4.38)	50.78 (23.18)	209.14 (34.87)	1.21 (0.55)	0.90 (0.63)	0.53 (0.33)
p-value	0.358	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
BTX study (n=19 CP)						
Pre-BTX mean (SD)	23.34 (9.07)	76.18 (28.66)	164.88 (24.49)	3.17 (1.46)	2.74 (1.01)	2.02 (0.86)
Post-BTX	22.01	81.86	177.55	2.67 (1.53)	1.80 (0.80)	1.31

mean (SD)	(7.01)	(31.09)	(25.52)			(0.50)
<i>p</i> -value	0.451	0.377	0.023*	0.183	0.006*	0.012*

CP: cerebral palsy; TD: typically developing; BTX: botulinum Toxin-A; V_{MAX} : maximum angular velocity; low: low velocity stretches; med.: medium velocity stretches; high: high velocity stretches; ICC: intra correlation coefficient; SEM: standard error of measurement; MDC: minimal detectable change. * $p < 0.05$

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