Contributors to excess antagonist activity during movement in children with secondary dystonia due to cerebral palsy

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Abstract

Children with secondary dystonia due to cerebral palsy exhibit abnormal upper extremity postures and slow voluntary movement. However, the interaction between abnormal postures and abnormal movement in dystonia is still unclear. Some mechanisms by which postures are maintained in dystonia include stretch reflexes, overflow of muscle activation to other muscles, and direct coactivation of antagonist muscles. This study explores the independent contributions of each of these postural mechanisms to abnormal biceps brachii (antagonist) activity during elbow extension, which slows movement. A linear model of biceps activation as a function of velocity-dependent reflexes, triceps-dependent overflow and direct drive to the biceps was fitted to experimental data from eleven children and young adults with secondary dystonia due to cerebral palsy and eleven age-matched control subjects. Subjects performed elbow extension movements against each of four levels of resistance without perturbations or in each of two perturbation conditions. Results show that biceps activity in children with dystonia consists of significant contributions of reflex activation, overflow from triceps and direct muscular drive. Additionally, stretch reflexes during movement are shown to be elevated at three latencies after stretch. These findings suggest that there are postural mechanisms involved in stabilizing the elbow along its slow trajectory during movement and provide a quantitative basis for the selection of treatments targeting specific impairments in children with secondary dystonia due to CP.
Introduction

Abnormal postures are characteristic of childhood secondary dystonia due to cerebral palsy (CP) (Sanger et al. 2003). Another key feature is abnormal movement. Movements in CP often have decreased speed and range of motion (Lebiedowska et al. 2004), increased variability (Sanger 2006) and increased overflow of muscle activation to unintended muscles (Gordon et al. 2006).

Although abnormalities in posture and movement co-associate in this disorder, it is not clear to what extent one affects the other. The link between posture and movement in healthy subjects has been extensively explored in single-joint arm and neck movements suggesting that certain types of movement result from commands that shift between different postures. These postures are described by stable equilibrium points, which are maintained by coactivation of antagonist muscle pairs or by stabilizing reflexes (for example: Asatryan and Feldman 1965; Feldman 1974a,b; Bizzi et al. 1976, 1984; Polit and Bizzi 1979; Kelso and Holt 1980). In this study we begin to explore the possibility that specific abnormalities of postural mechanisms could play a significant role in impeding movement in secondary dystonia due to CP. In particular, we investigate whether inappropriate activation of the biceps brachii (biceps, antagonist) muscle occurs during voluntary attempts at elbow extension. We also study whether inappropriate activation of the biceps is due to elevated stretch reflex responses, overflow of muscle activity from the triceps brachii (triceps, agonist), or coactivation due to abnormal direct drive to both triceps and biceps muscles.
Normal postural control is accomplished through both feedforward central motor commands and the feedback response to disturbances. Central motor commands can individually control activation of single muscles or sets of muscles, including coactivation of antagonist muscle groups. In dystonia, there may be a spread of these central commands to other muscles, or overflow, which can lead to specific abnormal postures (Berardelli et al. 1998, Gordon et al. 2006). When active, through direct activation or overflow, muscles naturally resist perturbation due to their inherent spring-like properties (Hogan 1985).

Postural responses to unexpected disturbances are also mediated by stretch reflexes, which can be distinguished by differing reflex delays hypothesized to result from different reflex pathways. “Short latency” stretch reflexes in the human arm occur as fast as 20 ms after stretch (Sherrington 1906; Hammond 1955; Hammond et al. 1956) and “long latency” stretch reflexes occur between 50 ms and 100 ms after stretch (Matthews 1984; Corden et al. 2000; Capaday et al. 1991). Anticipatory postural adjustments are also an important component of postural control and these are present for expected disturbances (Cordo and Nashner 1982). Abnormalities in any of these components can affect postural control and we test whether some of these components are abnormal during movement in children with dystonia due to CP.

Reports in the literature of stretch reflexes and coactivation in childhood dystonia are inconsistent. One study showed normal tendon reflexes in the knee (Lebiedowska et al. 2004), however another study showed an association of the
disorder with position- and velocity-dependent reflexes in the elbow (van Doornik et al. 2009). In one study, coactivation was shown to be increased from normal (Lebiedowska et al. 2004), and in another, coactivation was not necessarily present during movement (Malfait and Sanger, 2007). In addition to relating components of postural control to movement, this study aims to clarify the nature of stretch reflexes and coactivation in dystonia due to CP.

Since slow reaching is observed in children with CP and since antagonist muscle activation counteracts and can potentially slow intended movements, we focus our study on the activity in the biceps muscle (antagonist) during voluntary elbow extension. Figure 1 provides a simple diagram of how postural mechanisms may affect muscle activity in the biceps during elbow extension. We test the hypothesis that postural mechanisms, including stretch reflexes, overflow, and direct drive, contribute to abnormal muscle activation in dystonia and we propose to determine specific contributions of each using the biceps activation model shown in Figure 1. We further test the hypothesis that the stretch reflex responses during movement are exaggerated from normal at different latencies in dystonia. Results indicate that stretch reflexes, overflow and direct activation all contribute significantly to biceps activity during elbow extension. Furthermore, postural reflexes in dystonia are elevated at three latencies after stretch (20–50 ms, 50–80 ms, and 80–100 ms). One consequence is that an assisting stretch in the direction of the target (extension) results in the arm pulling back away from the target. These results highlight the role of postural mechanisms, including
stretch reflexes and coactivation, in stabilizing the elbow along its abnormally slow trajectory during movement. The results may provide a quantitative basis for the selection of treatments targeting specific impairments in children with secondary dystonia due to CP.

Materials and Methods

Participants

Eleven children and young adults (ages 8-24 years) with dystonic hypertonia due to CP (Dystonia group) and 11 age-matched individuals (ages 9-25 years) without dystonia, CP or other neurological movement disorders (Control group) were recruited to participate in this study. The subject groups are further described in Table 1. All subjects were required to voluntarily extend their tested elbow. If the subjects in the Dystonia group had voluntary control over both elbows, the more severely impaired side was chosen for testing. The dominant arm was tested in the Control group. Children with a spastic catch, clonus, elevated tendon reflexes, pyramidal distribution weakness or other signs of spasticity in the tested arm were excluded from the study. Three subjects with dystonic hypertonia (indicated by * in Table 1) were on baclofen, an anti-spasticity medication without which they may have shown signs of spasticity. Children with dystonia were rated on the upper extremity component of the Barry Albright Dystonia (BAD) scale, an ordinal severity scale from 0 (no dystonia) to 4 (severe dystonia) (Barry et al. 1999). The Stanford University Institutional Review Board approved this protocol. A parent or guardian of each participant
gave written informed consent for testing and authorization for use of protected health information, and all children indicated assent. The study was registered with clinicaltrials.gov (NCT00285870).

**Experimental Apparatus**

Participants were seated comfortably in a supportive chair or their own wheelchair. Lap belts and chest straps were used when necessary to provide support and maintain a consistent posture throughout testing. The arm was positioned horizontally at shoulder level (90 degree shoulder flexion with a varying degree of abduction between subjects based on the size of their wheelchair) in a jointed elbow brace that could be belt-driven by a strong motor (D063M-23-1310, Kollmorgen DDR, peak torque = 90 Nm, and S620-NA, Kollmorgen SERVOSTAR drive). An optical position encoder in the motor provided a measurement of elbow angle and velocity. The motor was controlled (SpiiPlus PCI motion controller, ACS Motion Control) to stop or extend the elbow through custom-written software (ACSPL+). The device was equipped with safety switches in hardware and software. A two-channel Bagnoli™ Handheld EMG System (Delsys Inc., 1000 ± 1% amplification) was used to obtain recordings of muscle activity through single differential surface EMG electrodes (DE-2.1 active bipolar electrodes, Delsys Inc., bandpass 20-450 Hz) over the belly of the biceps brachii (biceps) and triceps brachii (triceps) muscles. Electrode positioning was determined by palpation of the muscles. Biceps and
triceps EMG, joint angle and velocity were sampled and digitized at 1000 Hz for analysis (Power 1401, Cambridge Electronic Design Ltd.).

**Experimental Protocol**

Participants rested their arm at an angle of 90 degrees flexion in the elbow device. To provide a measurement of the maximum voluntary isometric contraction (MVIC), participants were asked to maximally contract their biceps and triceps muscles alternately for approximately 4 s each. Sufficient rest was provided between trials to avoid muscle fatigue. The maximum peak rectified EMG over three separate MVIC trials was used to normalize all subsequent EMG measurements after visual inspection to confirm the MVIC values were not spurious values. During the MVIC trials, participants were given feedback of their EMG activity on a computer screen and given verbal encouragement to activate their muscle as strongly as possible.

To test elbow extension, subjects were asked to start with their elbow at an angle of 120 degrees and extend their elbow voluntarily to a target placed at least 10 degrees short of their full extension (0 degrees represents a fully extended elbow). The actual end position differed between subject groups (Control: 23.30 ± 8.4 degrees, Dystonia: 32.67 ± 10.6 degrees) since full voluntary extension was not always possible for individuals in the Dystonia group. Since the difference in end position between subject groups is a small fraction of the total range of movement, it is unlikely to confound results of the study. Mechanical
stops were placed at the starting location and at the maximum extension angle for safety.

Upon hearing the command “Reach”, subjects were instructed to extend their elbow at their preferred speed. After a pause of approximately 3 s and upon hearing the command “Return”, subjects were instructed to flex their arm slowly back to the starting position. The “Reach” and “Return” phases of the movement were cued individually to prevent cyclic movements. Prior to testing, subjects were given sufficient time to become comfortable extending their elbow in the device, stopping voluntarily at their target position and flexing their elbow back to the start position. To assist some of the more severely impaired subjects in the Dystonia group with completion of the task and prevent fatigue, the experimenter passively flexed the elbow to the starting position (“Return”) after each extension movement. This did not interfere with the subject’s own voluntary elbow extension movement (“Reach”).

Subjects were asked to perform four sets of 36 extension movements each, totaling 144 movements. Each set of movements was against one of four different levels of a constant background opposing torque (0.71 Nm, 1.42 Nm, 2.13 Nm, 2.84 Nm). The first six trials of each set were unperturbed and allowed the study of group differences in natural movement. In the following 30 trials, 10 trials were unperturbed (“Free”), 10 trials included an externally imposed extension stretch during movement (“Stretch”), and 10 trials included a brief
externally imposed stop during movement ("Stop") in the same pseudorandom order for each subject. The "Free", "Stretch" and "Stop" conditions caused variations in the speed of movement independent of the subject's own voluntary velocity in order to fit the $a_1$ (reflex activation of biceps) parameter in the biceps activation model (Figure 1). By moving against the four background levels of resistance at the same speed, different levels of triceps activation could be elicited in order to fit the $a_2$ parameter (overflow from triceps) in the biceps activation model (Figure 1). The remaining variance not explained by reflex activity ($a_1$) or overflow ($a_2$) is attributed to direct activation of the biceps ($a_3$).

The "Stretch" and "Stop" perturbations occurred at a joint angle of 75, 85 or 95 degrees in the same pseudorandom order for all subjects to prevent the prediction of perturbation onset. Figure 2 shows an example of the elbow position and velocity during one movement in each condition in a subject from the Control group. The "Stretch" condition extended the elbow toward the target at a speed higher than the voluntary movement velocity of the subject. The stretch was applied at approximately 350 degrees/s for 100 ms, after which time subjects were free to move on their own. Usually, the elbow was extended past the target stop point by the end of the 100-ms stretch. The exact velocity during the "Stretch" trials varied based on the participant’s own voluntary movement speed. The "Stop" perturbation forced movement velocity to stop (0 degrees/s) for 200 ms, after which time subjects were able to continue their elbow extension movement. (The motor exhibited a brief flexion transient at the onset of the
stretch perturbation, which could potentially have contributed to a stretch reflex response in the triceps muscle and reciprocal inactivation of the biceps muscle. However, decreased biceps activity was not observed.)

Measurements and Analysis

Due to the fact that the EMG data were not normally distributed, the mean and rectified biceps EMG and triceps EMG were log transformed (natural log) before analysis.

1. Unperturbed movement

The first six unperturbed trials in each set of movements at the lowest resistance level (0.71 Nm) were studied to assess differences between groups on natural movement at each subject’s own preferred velocity. The mean velocity was computed over the first 400 ms of each movement, which incorporated the period of acceleration. This period of time was chosen for analysis because abnormalities during movement acceleration can decrease movement speed, and movements in dystonia are known to be abnormally slow. Due to the abnormal multiphasic nature of movement velocity and EMG in the Dystonia group, the analysis period could not be defined by kinematic parameters or muscle burst characteristics.

A subset of eleven trials from each subject group in which the mean velocity was between 94 and 106 degrees/s was selected to test for group differences on
biceps and triceps EMG. Age-matching of subject groups was preserved in this subset of trials (Control: 13.9 ± 4 yrs, Dystonia: mean 13.7 ± 4 yrs). Trials were selected based on velocity because faster movements are expected to correlate with increased triceps activation, and therefore differences between groups on movement speed could confound the analysis of EMG. Mean biceps EMG and mean triceps EMG in the velocity-matched trials were computed over the first 400 ms of each movement in both groups.

Group differences in mean velocity, mean triceps EMG and mean biceps EMG were tested using separate linear mixed effects models. All mixed effects models accounted for repeated measures within each subject and the same identifier was used for each pair of age-matched subjects. Subject age was included as an additional regressor in order to assess changes during development in addition to differences between subject groups. In the cases where age was not a significant factor, it was removed from the model. Since the range of severity of dystonia did not span the full range of the Barry Albright Dystonia scale, severity was not used as a regressor in this or other statistical tests. A significance level of 0.05 was used for all statistical tests.

2. Perturbed movement – Biceps activation model
Testing with the three perturbation conditions and the four levels of resistance provided data to fit the biceps activation model. Mean biceps EMG, mean velocity and mean triceps EMG were computed in each trial during the reflex
period, 20 – 100 ms after perturbation. In the “Free” trials, where there was no
perturbation, data were averaged over the 20 – 100 ms period following the time
when the elbow angle first exceeded 95 degrees. A post hoc analysis (linear
mixed effects model) of the “Free” trials showed no difference in mean biceps
EMG 20 – 100 ms after an elbow angle of 75, 85, or 95 degrees (Control: p =
0.9341, Dystonia: p = 0.9468). Therefore, for simplicity, the analysis period in all
“Free” trials was in reference to an elbow angle of 95 degrees.

The biceps activation model (Figure 1) was fitted to the mean biceps EMG, mean
velocity and mean triceps EMG data for each subject group individually. To
account for repeated measurements within each subject, a subject identifier was
added as an additional factor in the linear model. The Type II sum of squares
was computed for each factor and the residual in the linear regression model.
The adjusted total sum of squares was calculated by subtracting the sum of
squares for the subject identifier from the total sum of squares, since we are not
concerned with subject-specific effects within each group. The fraction of the
adjusted total sum of squares for each remaining factor (velocity and triceps
EMG) and the residuals (a3 constant that accounts for direct activation drive to
biceps) was then computed. This fraction provides a description of the amount of
variance in biceps EMG explained by each factor/residual. In this way the
contributions of stretch reflexes (velocity), overflow (triceps EMG) and direct drive
to the biceps could be determined.
3. Perturbed movement – Reflexes during movement

Mean biceps EMG responses were then computed at three response latencies after “Stretch” (M1: 20-50 ms, M2: 50-80 ms and M3: 80-100 ms, as in Yamamoto and Ohtsuki 1989). Mean biceps EMG in each of these time windows was compared between subject groups (Control vs. Dystonia) using a linear mixed effects model, including subject age as an additional regressor. In the cases where age was not a significant factor, it was removed from the model. When comparing reflex response amplitudes between groups at three different latencies, the Bonferroni correction was applied to minimize the likelihood of significance of multiple tests due to chance. Reported p-values from all other tests do not include the Bonferroni correction since these tests evaluated distinct hypotheses.

Results

All subjects were able to perform between one and three sets of 36 elbow extension movements (20 of which included perturbations), each set with a different level of background resistance to movement. Muscle fatigue and the length of testing prevented the collection of four sets of data, against all four levels of resistance, from each subject. Over all subjects in each group, 28 sets of movements were collected in the Control group and 23 sets were collected in the Dystonia group.
Figure 3 presents an example of the mean EMG response over ten trials to each of the three perturbation conditions (“Free”, “Stretch” and “Stop”) in a representative from the Control group (a) and the Dystonia group (b). The top row displays the joint angle trajectory and the bottom three rows display EMG activity. In both figures, biceps EMG is presented on the positive axis and triceps EMG is on the negative axis. As expected in all traces for both groups, the triceps is active throughout the elbow extension movement, however triceps activity is greater in the subject from the Dystonia group than the Control group. Similarly, between the two examples, biceps activity is also greater in the Dystonia example, as indicated by the dotted arrows in Figure 3. There is increased biceps activity in the reflex period (gray region) of the “Stretch” trials in the Dystonia subject compared with the Control subject as indicated by the solid arrows in Figure 3. In both subject groups, the absence of clear bursts of agonist (triceps) activity to accelerate the arm and antagonist (biceps) activity to decelerate the arm in the “Free” condition, typically seen in ballistic movements, is likely due to the relatively low movement velocity (Brown and Gilleard 1991).

**Slow elbow extension and overactive biceps in dystonia**

The elbow extension velocity in the Dystonia group was significantly slower than the Control group (mean ± sd: Control = 114.63 ± 24.5 degrees/s, Dystonia = 76.18 ± 32.2 degrees/s, p < 0.0001; peak ± sd: Control = 205.42 ± 77.8 degrees/s, Dystonia = 145.39 ± 57.1 degrees/s, p = 0.0145). In a subset of trials from each group where mean movement velocity was the same (between 94 and
106 degrees/s), there was excess muscle activation in the Dystonia group compared to the Control group in biceps (Control: 0.476 ± 0.415% MVC, Dystonia: 2.16 ± 1.85% MVC, p < 0.0001) and triceps (Control: 1.97 ± 1.51% MVC, Dystonia: 9.20 ± 3.51% MVC, p < 0.0001). The increased triceps activity shows that slow movement in dystonia is not due to insufficient activation of the triceps (agonist), but rather must be due to excessive activation of the elbow flexors (antagonist).

Contributors to excess biceps activity during movement in dystonia

The biceps activation model (Figure 1) was fitted to the experimental data from each subject group separately to determine the contribution of velocity-dependent reflexes, triceps-dependent overflow, and direct coactivation drive to biceps EMG during elbow extension (Control: $R^2 = 0.829$, Dystonia: $R^2 = 0.657$, including subject-specific effects within each group). There was little correlation between velocity and triceps EMG in the Control group (Pearson’s product-moment correlation coefficient, $r = -0.00839$) and the Dystonia group ($r = -0.118$) since velocity and triceps activity were controlled independently in the experiment. This allowed analysis of the specific contributions of the independent factors. Figure 4a shows the contributions of these mechanisms to biceps EMG in both subject groups, computed using Type II sum of squares as described above in the Methods. The heights of the bars in Figure 4a represent the difference between mean biceps EMG during unperturbed movement and the portion of that amount due to subject-specific effects for each group.
Contributions of reflexes, overflow and direct coactivation are all greater (14.4, 24.3 and 11.7 times, respectively) in the Dystonia group than the Control group.

The biceps activation models for both groups yielded statistically significant positive coefficients for both velocity (reflex coefficient $a_1$, $p < 0.0001$ for both groups) and triceps EMG (overflow coefficient $a_2$, $p < 0.0001$ for both groups), indicating an increase in biceps EMG with both velocity and triceps EMG (Figure 4b). The reflex ($a_1$), overflow ($a_2$) and direct drive ($a_3$) coefficients were larger in the Dystonia group than the Control group and outside the 95% confidence intervals of the same coefficients in the Control group indicating a stronger dependence of biceps EMG on reflexes, overflow and direct drive in dystonia.

When the biceps activation model was fit to each subject individually, the majority of subjects (Control: 9/11, Dystonia: 8/11) had statistically significant positive coefficients on velocity and triceps EMG indicating that the group statistics were not spurious.

Elevated short and long latency stretch reflexes during movement in dystonia

Figure 5 provides an example of biceps and triceps EMG in the reflex period after biceps stretch during movement of one representative subject from the Control group (a) and the Dystonia group (b). Biceps EMG is plotted on the positive y-axis and triceps EMG is plotted on the negative y-axis. Both subjects exhibited EMG activity in the biceps during all three phases of the reflex period (M1, M2 and M3), however reflex activation was greater in the Dystonia subject. The
relatively small biceps response to stretch in the Control subject is exaggerated by the y-axis scale in Figure 5a, which was chosen to match the axis of the data from the Dystonia subject for comparison. The non-zero triceps EMG in both subjects reflects triceps activation to achieve elbow extension. Comparing subject groups over all subjects, biceps EMG amplitudes were significantly elevated in the Dystonia group at M1 (p < 0.0003), M2 (p < 0.0003) and M3 (p < 0.0003) (see Figure 6). Of the three time periods, the M3 response was the most pronounced in the Dystonia group.

Effect of normalization on measurements

To reduce the effect of variation in electrode placement and skin impedance, stretch reflex responses from each electrode are normalized by each subject’s own MVIC for that electrode. Although this is a standard method, there is a potential confound if there is an error in measurement of the MVIC. A previous study demonstrated that the ability of children to recruit all the motor units of a muscle during voluntary contraction is diminished in spasticity due to CP (Rose and McGill 2005). However, the same is not yet known in children with dystonia due to CP. To address the potential confound of reduced voluntary recruitment of motor units in dystonia, reflex responses to stretch of the biceps during movement were also analyzed without MVIC normalization. The results remain unchanged; biceps EMG amplitudes were significantly elevated in the Dystonia group compared to the Control group at M1 (p < 0.0003), M2 (p < 0.0003), and M3 (p < 0.0003). This indicates that it is unlikely that the exaggerated reflexes in
the Dystonia group observed in this study were due to a systematic error in estimating the MVIC.

Effect of age on measurements
There was no effect of age on biceps EMG activity or velocity during unperturbed movement. There was also no effect of age on the M1 and M2 biceps stretch reflex responses. On the other hand, there was an increase in triceps EMG activity with increasing age during unperturbed movement (p < 0.0001) and an increase in the M3 biceps stretch reflex response with increasing age (p = 0.0075). In other words, older children were able to activate their triceps more strongly relative to their MVIC during elbow extension and exhibited larger long latency biceps stretch reflex responses than younger children.

Discussion
Slow reaching movements in secondary dystonia due to CP can be attributed to excess antagonist activation that is due to a combination of (1) elevated reflexes during three time periods after an unexpected stretch, (2) overflow activity related to the activity of the agonist, and (3) coactivation of antagonistic muscle pairs due to direct activation of the antagonist independent of the agonist. We observe these results in children and young adults across a range of ages and severity of disability, suggesting that these contributors to excess biceps activity are common features of many individuals with secondary dystonia due to CP.
Several assumptions and choices were made that could have influenced our results. The analysis was based on a linear model of the multiple contributors to biceps activity, and therefore nonlinear effects may not have been detected. However, the relatively good fit of the linear model suggests that nonlinear effects are not likely to be major contributors. All subjects moved at their preferred speed rather than their maximal speed. This was done because we were concerned that attempts at maximal effort in dystonia would lead to overflow that might not be present during more natural movements. By performing the analysis with speed-matched trials we believe that we have reduced the likelihood of bias due to differences in maximal speed. Slow movement in patients with dystonia may be due to a compensatory strategy to improve reach accuracy or muscle weakness. These two potential contributors to slow movement cannot be distinguished using this experiment and would be reflected in the “direct drive” component of muscle activity. Four of the subjects were taking oral baclofen at the time of the study. Baclofen could change the electrophysiological results through multiple mechanisms. However, because these subjects continued to manifest clinical dystonia and because baclofen is a commonly used medication in this subject group, we believe that the measurements reflect the electrophysiology of dystonia in a realistic clinical population.

Preactivation of a muscle is known to increase the stretch reflex response in a muscle (Marsden et al 1976, Matthews 1986). Elevated stretch reflexes in
dystonia were associated with increased preactivation of the stretched muscle
during movement in this study (linear regression, M1: $R^2 = 0.7903$, $p < 0.0001$;
M2: $R^2 = 0.5889$, $p < 0.0001$; M3: $R^2 = 0.493$, $p < 0.0001$). However, it is not
clear whether elevated stretch reflexes and preactivation are caused by the same
mechanism, different mechanisms or whether one causes the other in dystonia.
Irrespective of the factors that may contribute to the elevated stretch reflexes,
they present the potential for interference during movement in dystonia. Future
studies are required to address the origin of the elevated stretch reflexes in
dystonia as well as the specific contributions of stretch reflexes to functional
abnormalities in reaching.

**Abnormal posture during movement**

Antagonist muscle activation during movement in dystonia due to CP slows
movement and is characterized by increased stretch reflexes that oppose the
direction of movement and oppose assistive perturbations that would otherwise
facilitate reaching the target. This tendency for the arm to resist perturbations
during movement is similar to the behavior predicted by the equilibrium point
hypothesis, in which movement is said to result from the shift of stable postures
determined by the length-tension properties of antagonistic muscles toward the
final goal position (Asatryan and Feldman 1965; Feldman 1974a,b; Bizzi et al.
1976, 1984; Polit and Bizzi 1979). The exaggerated biceps stretch reflex
response during slow voluntary elbow extension suggests that in dystonia, a
sequence of stable postures occurring during movement is maintained against
perturbation and thus form a stable but abnormally slow equilibrium point trajectory. Therefore abnormal movement could result from the same pathophysiological mechanism that causes abnormal posture in childhood dystonia (Sanger et al. 2003).

The conjecture that postural control mechanisms lie at the root of the movement disorder in dystonia due to CP is consistent with a recent hypothesis (Blood 2008). This hypothesis suggests that all forms of dystonia (not restricted to childhood dystonia due to CP) reflect increased activity of postural mechanisms. The proposition that postural stabilization is implemented by coactivation of antagonistic muscles is supported by our data. In addition to direct coactivation, we have also shown postural stabilization by elevated stretch reflexes in children with dystonia due to CP.

**Spinal contributions to abnormal movement**

Spinal stretch reflex responses in healthy individuals are known to increase the stability of joint postures (Solomonow et al. 1987; Solomonow and Krogsgaard 2001). There is also evidence that stretch reflex activity is modulated during movement (Gottlieb et al. 1970; Bennett 1993) and can play an important role in coordinating joints during movement (Nichols 2002; Yakovenko et al. 2004). Additionally, the alteration of spinal stretch reflexes through operant conditioning can lead to significant functional improvements in locomotion in spinal cord
injured rats (Chen et al. 2006). Therefore abnormal spinal activity or modulation of spinal activity could be a contributor to dystonic postures.

Since reciprocal inhibition, carried out by spinal interneuronal circuits, acts to inhibit the antagonist muscle during movement, reduced inhibition can lead to overflow of muscle activity from the agonist to the antagonist at the spinal level. Reduced reciprocal inhibition is observed in patients with dystonia of different etiologies (Berardelli et al. 1998; Chen et al. 1995). If reciprocal inhibition is also reduced in children with dystonia due to CP, it may lead to the observed overflow in this study. Additionally, if the pathways involved in reciprocal inhibition are not suppressing the biceps during elbow extension in dystonia, reflexes may also not be suppressed. In this case, the exaggerated stretch reflexes in dystonia would be amplified from normal, as observed in this study.

Supraspinal contributions to abnormal movement

The biceps activation model proposed in this study provides a means to assess contributions of supraspinal coactivation drive to the biceps, which is otherwise difficult to probe non-invasively in children. The component of biceps EMG due to direct coactivation drive was the largest of the three, and suggests that understanding supraspinal involvement in movement abnormalities is critical to the correct characterization of childhood dystonia. Since motor cortex is known to play a role in normal postural tasks (Kurtzer et al. 2005; Jacobs et al. 2007), and postural mechanisms are abnormal during movement in CP, we conjecture
that motor cortex may be involved in the pathophysiology of childhood dystonia due to CP.

Long latency stretch reflexes, which are hypothesized to involve transcortical loops (Capaday et al. 1991), were found to be elevated in dystonia due to CP. It is therefore possible that motor cortex facilitates the stretch reflex responses observed. In addition, there are known supraspinal modulatory effects on stretch reflexes of all latencies (Houk 1979), further suggesting that some abnormalities in antagonist muscle activation in dystonia due to CP have a central origin.

Direct biceps activation during voluntary triceps activation was elevated in children with dystonia due to CP, as expected from similar reports in dystonia from various etiologies (Marsden 1984; Berardelli et al. 1998; Sanger et al. 2003). Coactivation of antagonist muscles during normal movement can be modulated centrally in relation to many factors, including movement speed (Suzuki et al. 2001) and movement accuracy (Gribble et al. 2003). The excessive direct coactivation observed in children with secondary dystonia during movement may thus be due to supraspinal abnormalities and contribute to the apparent deficits in movement speed and variability (Berardelli et al., 1996; Sanger 2006).

**Implications for treatment of secondary dystonia due to CP**

The treatment of secondary dystonia due to CP is difficult because children have
unpredictable responses to medication and surgery. This study provides a quantitative basis to determine the relative contribution of stretch reflexes, overflow and direct coactivation to abnormalities in muscle activation patterns, which can be useful to predict which of the available therapies may be beneficial for a specific child. For instance, in addition to the effect of botulinum toxin in reducing activity in $\alpha$-motoneurons that activate the force-generating fibers of muscle (Molgó and Thesleff 1984), there is also evidence for its effect on $\gamma$-motoneurons that activate the stretch-sensing muscle fibers involved in stretch reflexes (Filippi et al. 1993). Therefore, use of botulinum toxin injections may be of greatest benefit to children who have a relatively large component of biceps activation due to stretch reflex activity. Correspondingly, improvements in reaching due to botulinum toxin injections in the biceps were observed in children with dystonia due to CP (Sanger et al. 2007). In addition, specially designed EMG biofeedback protocols have been shown to alter central motor commands to scapular muscles (Holtermann et al. 2009). Similar biofeedback protocols may also be applied to individuate control of the upper arm muscles in children with elevated central coactivation to improve reaching. Knowledge of the contributors to abnormal muscle activation in dystonia may thus inform treatment decisions that could greatly benefit children with secondary dystonia due to CP.
Acknowledgements

This work was supported by the Cerebral Palsy International Research Foundation. We thank Rosemary Workman and Erin Umberg for their efforts in subject recruitment and management.
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Figure legends

Figure 1: Biceps activation model. EMG activity in the biceps muscle during elbow extension is modeled as a linear combination of velocity-dependent stretch reflexes, triceps-dependent overflow and direct coactivation.

Figure 2: Kinematics of perturbations in single trials from a subject in the Control group. The perturbations were used to introduce variations in velocity (independent of voluntary movement velocity) to test effects of velocity on biceps EMG during elbow extension. The stretch perturbation created a higher than normal velocity and the stop perturbation created a lower than normal velocity. There was no perturbation in the free trial.

Figure 3: EMG activity during unperturbed and perturbed movement. The mean EMG response over 10 trials is presented for one subject from the Control group (a) and the Dystonia group (b). Biceps EMG activity is plotted on the positive y-axis and triceps EMG on the negative y-axis. Comparison of data indicated by dotted arrows demonstrates excess biceps activation during unperturbed elbow extension in dystonia. Comparison of data indicated by solid arrows demonstrates an increased biceps stretch response in the reflex period during movement in dystonia.

Figure 4: Biceps activation model estimates of contributors to biceps activity during elbow extension (a) and model coefficients (b). Contributions of reflexes,
overflow and direct drive to biceps EMG are 14.4, 24.3 and 11.7 times greater in
the Dystonia group than the Control group, respectively (a). All coefficients are
larger in the Dystonia group than the Control group and exceed the 95%
confidence limits (horizontal gray bar) of the same coefficients in the Control
group (b).

Figure 5: Individual biceps stretch reflexes during movement in a subject from the
Control group (a) and the Dystonia group (b). Rectified biceps EMG is plotted on
the positive y-axis and rectified triceps EMG is plotted on the negative y-axis.
The stretch responses at M1, M2 and M3 during movement exceed baseline
activation before stretch in both subjects. Biceps EMG amplitudes are greater in
the Dystonia subject than the Control subject at all latencies. The non-zero
triceps EMG reflects activation of triceps required for elbow extension in both
groups.

Figure 6: Biceps stretch reflex amplitude at different latencies during elbow
extension. Reflex response amplitude is increased in the Dystonia group at all
latencies after stretch. Bars represent mean values plus one standard deviation
over all movements. ** p < 0.0003.
Table Legends

Table 1: All subjects in the Dystonia group had dystonia in the tested elbow and no spasticity in that joint on clinical examination. Subjects with an asterisk (*) were on baclofen (anti-spasticity medicine) at the time of the study. BAD refers to the upper extremity assessment only (4 = maximum severity).
**Table 1: Subject characteristics**

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supraspinal motor centers

spinal interactions

\[ \text{overflow} \ (a_2) \]

\[ \text{direct drive} \ (a_3) \]

\[ \text{reflex} \ (a_1) \]

\[ \text{biceps EMG} = \text{reflex} + \text{overflow} + \text{direct drive} \]

\[ \log(\text{EMG}_b) = a_1 \times \text{Velocity} + a_2 \times \log(\text{EMG}_t) + a_3 \]