Failure of normal development of central drive to ankle dorsiflexors relates to gait deficits in children with cerebral palsy

Tue Hvass Petersen,1,2 Simon F. Farmer,3,4 Mette Kliim-Due,2 and Jens Bo Nielsen1,2

1Department of Exercise and Sport Sciences & Department of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, Denmark; 2Helene Elsass Center, Charlottenlund, Denmark; 3Sobell Department of Motor Neuroscience & Movement Disorders, Institute of Neurology, University College London, London, United Kingdom; and 4Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery, London, United Kingdom

Submitted 12 March 2012; accepted in final form 1 November 2012


Neurophysiological markers of the central control of gait in children with cerebral palsy (CP) are used to assess developmental response to therapy. We measured the central common drive to a leg muscle in children with CP. We recorded electromyograms (EMGs) from the tibialis anterior (TA) muscle of 40 children with hemiplegic CP and 42 typically developing age-matched controls during static dorsiflexion of the ankle and during the swing phase of treadmill walking. The common drive to TA motoneurons was identified through time- and frequency-domain cross-correlation methods. In control subjects, the common drive consists of frequencies between 1 and 60 Hz with peaks at beta (15–25 Hz) and gamma (30–45 Hz) frequencies known to be caused by activity within sensorimotor cortex networks: this drive to motoneurons strengthens during childhood. Similar to this drive in control subjects, this drive to the least affected TA in the CP children tended to strengthen with age, although compared with that in the control subjects, it was slightly weaker. For CP subjects of all ages, the most affected TA muscle common drive was markedly reduced compared with that of their least affected muscle as well as that of controls. These differences between the least and most affected TA muscles were unrelated to differences in the magnitude of EMG in the two muscles but positively correlated with ankle dorsiflexion velocity and joint angle during gait. Time- and frequency-domain analysis of ongoing EMG recruited during behaviorally relevant lower limb tasks provides a noninvasive and important measure of the central drive to motoneurons in subjects with CP.

can the developmental outcome of children with prenatal brain lesions causing cerebral palsy (CP) be improved, and if so, what would be the neurophysiological correlates of such an improvement (Blauw-Hospers et al. 2007)? In individuals diagnosed with hemiplegic CP, the ability to walk is impaired and loss of locomotor capability may greatly affect these subjects’ ability to participate in everyday activities such as education and fitness activities (Lepage et al. 1998). Maintaining or even improving mobility throughout development in these children is a therapy goal of great importance. However, attempts at optimizing gait training, for example, are hampered by our lack of knowledge of the neural mechanisms involved in the control of gait, how they change during motor development, and the effect of early brain lesion on these changes. Normal human lower limb muscle activation and walking involves activity in multiple neural networks that are hierarchically organized (Hultborn and Nielsen 2007; Rossignol 2006). In studies of healthy and neurologically impaired subjects, the strong corticospinal drive to tibialis anterior (TA) muscle during gait has received particular attention because loss of TA activation is a universal feature of the lower limb upper motoneuron syndrome (see Nielsen 2003 for review).

The CP syndrome emerges as the result of developmental adaptations to early brain lesions that involve central motor pathways, and as such, the activity within the neural networks that provide drive to spinal motoneurons is of crucial importance in understanding the pathophysiology of CP. A neurophysiological measure of the central drive to spinal motoneurons involved in lower limb muscle activation and gait is required, and changes in the central drive in children developing with CP need to be understood.

Through time- and frequency-domain analysis of pairs of electromyography (EMG) signals, the common drive to motoneurons can be detected without experimental perturbation (Farmer 1998). Common drive is detected over a broad frequency range between 1 and 60 Hz (De Luca et al. 1993; Farmer et al. 1993a; Halliday et al. 1995). Beta (15–25 Hz) and gamma (30–45 Hz) frequencies, which are in excess of the mean motor unit firing rate, are of particular interest, since they are strongly related to oscillatory corticospinal drive from the sensorimotor cortex (Brown et al. 1998; Conway et al. 1995; Kilner et al. 2000; Mima and Hallett 1999). Recently, the oscillatory central common drive to spinal motoneurons during tonic leg muscle activation (Perez et al. 2006; Ushiyama et al. 2011) and during walking has been measured in adults using EMG-EMG (Halliday et al. 2003) and electroencephalography (EEG)-EMG coherence analysis (Petersen et al. 2012). In adult subjects common drive to motoneurons is reduced by lesions of the corticospinal pathways projecting to upper (Farmer et al. 1993b; Smith et al. 1999) and lower limb muscles (Hansen et al. 2005; Nielsen et al. 2008). Furthermore, in a recent study of subjects with spinal cord lesions, reduction in common drive to the TA muscle during walking was linked to the degree of foot drop (Barthelemy et al. 2010).

The common drive to upper limb human motoneurons undergoes a developmental increase both during static and dynamic muscle activation (Deutsch et al. 2011; Farmer et al. 2007; James et al. 2008). Recently, it was shown that the common drive to motoneurons controlling the TA muscle in
the beta (15–25 Hz) and gamma (30–45 Hz) frequency bands increases with age in healthy children during static dorsiflexion of the TA muscle and during the dynamic swing phase of walking during which TA is active (Petersen et al. 2010). It was suggested that this age-related increase in common drive reflects the functional maturation of the central neural networks responsible for control of the ankle joint during walking.

In the present study we build on these findings and ask what effect early acquired brain lesions causing hemiplegic CP have on the central drive to spinal motoneurons pools and its emergence over the course of childhood and early adolescence. We hypothesize that children with hemiplegic CP will show loss and failure of developmental emergence of central common drive to their TA motoneurons during static muscle activation and during walking. We expect that this will be most evident for their most affected muscle and that this loss of drive will correlate with deficits in the control of the ankle joint during walking.

METHODS

Subjects. Forty children with CP (26 male and 14 female; mean age 10 yr; age range 4–15 yr) participated in the study. All children were diagnosed with congenital spastic hemiplegia (19 subjects with right hemiplegia and 21 subjects with left hemiplegia) and classified according to the Gross Motor Function Classification System (GMFCS), which is validated for use in CP subjects and describes five levels of impairment (Palisano et al. 1997). Classification was performed by a pediatric neurophysiotherapist (M. Kliim-Due). In this study only children with mild-to-moderate hemiplegia at GMFCS levels I and II were included (level I, n = 36; level II, n = 4). The study was approved by the local ethics committee (H-B-2009-017), and all procedures were conducted within the standards of the Helsinki declaration. Before all experiments, all parents received written and verbal information, and consent for participation was obtained from the parents and the child. Two subjects were excluded from further analysis due to cross talk in the EMG measurements (see below). Six subjects had undergone lengthening of the Achilles tendon a minimum of 1 year before the study. An analysis was performed excluding these subjects, but since this did not change any conclusions, data from all subjects are presented. Subjects who had received botulinum toxin injections into the most affected calf muscle were included providing no injections had been given within 6 mo of the recordings. No subjects had received botox injections into the TA muscle. Twenty-one children had been treated with a botulinum toxin between 6 mo and 7 years before the study (median, 12 mo). Two subjects were taking baclofen at the time of the study, one subject was taking levitiracetam to prevent epileptic seizures, one subject was taking a luteinizing hormone-releasing hormone antagonist (Procren), and one was taking sertraline as treatment for attention deficit hyperactivity disorder.

Data from static muscle activation (n = 36, 21 male and 15 female; mean age 9.4 yr, age range 4–15 yr) and walking (n = 42, 24 male and 18 female; mean age 9.5 yr; age range 4–15 yr) in typically developing subjects was used to compare with the CP subjects. The common drive developmental profile of this group has previously been published (Petersen et al. 2010). For the purpose of further analysis, all children (CP and controls) were split into three different age groups: 4–7, 8–11, and 12–15 yr.

Experimental procedures. Two sets of experiments were performed in all subjects. First, we examined static muscle activation of the TA muscle. The children were asked to sit comfortably on a plastic box that could be adjusted according to height. With the left or right foot in front of them, keeping an angle of 100 deg in both the knee and the ankle joint, they were asked to produce a nonfatiguing weak static contraction of the TA muscle for 1 min against the hand of the experimenter who opposed the movement. The experimenter monitored the EMG signal online. Two to three minutes of rest were allowed before another trial was initiated. The hemiplegic subjects were able to produce EMG activity in both legs (see for example Fig. 1). However, it should also be noted that the CP subjects reported that it took more effort to complete the task with the most affected leg, and the root mean square (RMS) EMG values were lower (see RESULTS). The second part of the experiments consisted of 5 min of treadmill walking. The children were asked to choose their own walking speed. Details of this can be found in Table 1. After 5–10 min of familiarization, EMG measurements and three-dimensional (3-D) kinematic data were collected. All children had previous experience of treadmill walking and did not experience any difficulties regarding this task; however, most held on to the handlebar in front of the treadmill with one or both hands for safety.

EMG recordings. Bipolar EMG recordings were obtained from two sets of nonpolarizable Ag-AgCl electrodes (Blue Sensor; AMBU, Ballerup, Denmark) placed at the proximal and distal end of the TA muscle, respectively. In the control children we recorded only from the left leg TA muscle, whereas recordings in the hemiplegic subjects were obtained from both left and right TA muscles and were designated with respect to the side of the hemiplegia as the most affected (MA) and least affected (LA) muscles, respectively. In all cases the interelectrode pair distances were 2 cm. Details on the distance (influenced by limb size) between the two sets of electrode pairs can be found in Table 1. The signal was amplified (gain = 1,000) and bandpass filtered (10 Hz to 1 kHz) with a wireless EMG system (Zerowire EMG, Aurion, Italy), sampled at 2 kHz (using a micro 1401 analog-to-digital converter and Spike 2 software; Cambridge Electronic Design, Cambridge, UK), and stored on a personal computer for further analysis. A pressure-resistive sensor placed under the heel of both feet was used to monitor the time of heel contact in the case of treadmill walking. In three hemiplegic subjects the sensor was placed under the medial part of the forefoot since these subjects failed to make heel contact during walking. It was ensured in all cases that the heel trigger was activated with the first contact between the foot and the ground with each step. The heel contact data were used as triggers for the EMG epochs used in the frequency-domain analysis. In the static muscle activation experiment we included 60 s of EMG data. For the experiment on treadmill walking we used a total of 300 steps for each leg (EMG epochs) for each subject. Each epoch consisted of 500–600 ms of data corresponding to the EMG activity observed before heel strike. We avoided the use of EMG from the time of heel strike and onward to exclude heel strike artifacts from the analysis. Cross talk between the bipolar EMG recordings was recognized through visual inspection of the EMG and through calculation of time- and frequency-domain analysis. Cross-talk contamination is easily identified in the cumulant density function from the presence of very narrow peaks (<2 ms) and in the coherence estimates from the presence of coherence at all frequencies represented in the data (see Fig. 1 in Hansen et al. 2005). All recordings with central peaks in the cumulant density function lasting <5 ms or with coherence over the interval 0–150 Hz were consequently omitted from further analysis. It should be noted that the risk of cross talk increases with reduced muscle size, and hence shorter interelectrode differences, and with increased motor unit size. This issue was addressed by measuring interelectrode

| Table 1. Summary of data from the three different age groups |
|----------------|----------------|----------------|
|                | 4–7 yr         | 8–11 yr        | 12–15 yr       |
| Electrode distance MA, cm | 7.0 ± 0.7       | 10.6 ± 0.6     | 12.5 ± 1.0     |
| Electrode distance LA, cm  | 7.4 ± 0.4       | 10.8 ± 0.5     | 12.5 ± 0.9     |
| Walking speed, km/h        | 1.9 ± 0.4       | 2.5 ± 0.2      | 2.8 ± 0.2      |

Values are means ± 95% confidence intervals (CI) from each of the 3 age groups: 4–7 (n = 7), 8–11 (n = 17), and 12–15 yr (n = 14) for interelectrode distance between the proximal and distal electrode pair placed above the least (LA) and most affected (MA) muscle and for treadmill walking speed.

J Neurophysiol • doi:10.1152/jn.00218.2012 • www.jn.org
distances (see Table 1). The results of the present study show opposite effects to those expected from EMG cross talk: there is lack of coherence in the youngest (i.e., those with the smallest interelectrode distance) and in the MA TA muscle (expected to have the largest motor units).

Kinematic recordings and analysis. Six infrared Qgos cameras (Qualisys, Göteborg, Sweden) were used for kinematic recordings. Markers were placed on both legs on 1) the caput fibulae, 2) the lateral malleolus, and 3) the lateral side of the 5th metatarsophalangeal joint. The data were collected at a rate of 200 Hz on a personal computer and stored for further analysis. On the basis of 30 randomly selected steps, we calculated the mean amount of ankle dorsiflexion performed during the early swing phase, $\mu \Delta \theta$, the standard deviation (SD) of this value, and the mean time, $\Delta t$, this movement took. From these parameters we calculated the mean velocity of the dorsiflexion movement, $\mu \Delta \theta / \Delta t$, and the coefficient of variation (CV) of the dorsiflexion movement, SD/$\mu \Delta \theta$.

Frequency-domain and statistical analysis. Frequency-domain analysis of the data was undertaken using the methods set out in detail by Halliday et al. (1995). Briefly, the practice of full wave rectification of surface EMG signals was adopted. This approach has been shown to maximize the information regarding timing of motor unit action potentials (MUAP) while suppressing information regarding MUAP waveform shape (Boonstra and Breakspear 2012; Halliday and Farmer 2010; Myers et al. 2003). As a precursor to undertaking waveform shape (Boonstra and Breakspear 2012; Halliday and Farmer 2010; Myers et al. 2003). As a precursor to undertaking waveform shape, a two-way factorial ANOVA general linear model was calculated using SigmaPlot 11, with age range (4 – 7, 8 – 11, and 12 – 15 yr) as one factor and muscle (MA, LA, and control) as the other factor.

For the comparison of MA/LA ratios of beta and gamma coherence, RMS EMG amplitude and kinematic measures across the three age groups, a one-way ANOVA was calculated. Multiple pairwise comparisons were performed using Tukey’s t-test. All values are given as means ± 95% confidence intervals. For correlation analysis we used Pearson’s product-moment correlations. Multiple linear regression analysis was used to account for the effect of age or RMS EMG amplitude on the correlations between peak coherences and kinematic parameters.

RESULTS

Static muscle activation. During static activation all CP subjects were able to produce EMG in the MA and LA TA muscles. A typical example is shown in Fig. 1, A and B, in which EMGs from the LA and MA TA muscles were recorded in a 12-yr-old subject during static ankle dorsiflexion. The corresponding power spectra and output from the time/frequency analysis are displayed in Fig. 1. The $\chi^2$ difference of coherence measure (Fig. 1L) calculated for the two muscles emphasizes that the main differences in the common drive between the LA and MA TA muscles are at 10, 16–22, and 24–40 Hz, with the highest coherence values obtained from
the LA TA muscle. The corresponding time domain measures of synchrony show a central peak at time 0 with broad side lobes indicative of broad-peak synchrony in the MA TA muscle (Fig. 1A). The LA muscle (Fig. 1M) shows a narrower central peak with a peak value double that of the MA muscle. From the phase plots (Fig. 1, H and J) it can be seen that the two EMGs were in phase over the frequency range up to 50 Hz for the LA TA (Fig. 1J), whereas this was only the case for frequencies up to 10 Hz for the LA TA (Fig. 1H).

By using the technique of pooled coherence and $\chi^2$ comparisons, the common drive to the muscles during static activation was quantified for the MA and LA sides in all subjects (Fig. 2). The subjects were divided into three age groups: 4–7 (n = 7; Fig. 2, A and B), 8–11 (n = 17; Fig. 2, D and E), and 12–15 yr (n = 14; Fig. 2, G and H). In keeping with the results illustrated for the individual subject there were marked MA vs. LA differences in pooled coherence (Fig. 2, C, F, and J). The $\chi^2$ difference of coherence between MA and LA muscles for the older age groups (8–11 and 12–15 yr) showed marked differences in the range 10–50 Hz ($\chi^2$: 75–125). The comparison for the younger age group (4–7 yr) showed a less impressive MA and LA difference ($\chi^2$: 20 in range 10–50 Hz and 50 at 5 Hz). The interaction between age and the effects of the central nervous system (CNS) lesion was further explored through $\chi^2$ comparisons and through calculation of the correlation between age and peak coherence (see Fig. 3).

Figure 3 shows $\chi^2$ differences for within-side MA vs. LA comparisons across age groups. The three age groups were compared against one another: 4–7 vs. 8–11 yr (Fig. 3, A and B); 4–7 vs. 12–15 yr (Fig. 3, C and D), and 8–11 vs. 12–15 yr (Fig. 3, E and F). For the MA muscle coherence there was an increase in common drive for the youngest (4–7 years) compared with the oldest (12–15 yr) age group ($\chi^2$: 40–50 in frequency range 15–40 Hz). Some small changes in common drive were observed when the MA coherence was compared between the 4–7 and 8–11 yr age groups and also between the 8–11 and 12–15 yr age group ($\chi^2$: 10–20 for frequency range 15–40 Hz). The $\chi^2$ differences were overall much smaller than those observed in the same subjects when the LA muscle coherence strength was compared between the different age groups. For the LA muscle there was a marked increase in common drive in the range 15–50 Hz when the youngest age group was compared with the two older groups ($\chi^2$: 40–125 for frequency range 15–40 Hz). The largest difference between the coherence values was observed for age ranges 4–7 vs. 12–15 yr. These results demonstrated that it was between the ages 4–7 and 8–11 yr that there was a maximal increase in the development of the common drive to the LA muscle.
Figure 3, G and H, displays peak coherence (mean ± 95% confidence intervals) for the three age groups in the beta (15–25 Hz) and gamma frequency bands (30–45 Hz) for the MA and LA TA muscle compared with that of the TA muscle in typically developing children (control group).Peak values are given in Table 2.

A significant effect of age group \( F(2,103) = 7.9, P < 0.001 \) and muscle \( F(2,103) = 39.6, P < 0.001 \) was found for peak beta coherence, with no interaction between the two parameters \( F(4,103) = 1.1, P = 0.34 \). For peak gamma coherence an effect of age group \( F(2,103) = 15.6, P < 0.001 \) and muscle \( F(2,103) = 15.59, P < 0.001 \) was found, with no significant interaction between the two parameters \( F(4,103) = 1.0, P = 0.39 \).

Pairwise comparisons across age ranges showed significantly lower levels of peak beta coherence in the 4–7 yr age group compared with the 8–11 \( (P = 0.005) \) and the 12–15 yr age groups \( (P < 0.001) \), respectively. No significant difference was observed between the 8–11 and the 12–15 yr age groups \( (P = 0.68) \).

Pairwise comparisons across muscle showed significantly lower levels of peak beta coherence in the MA TA muscle compared with the LA \( (P < 0.001) \) and the control TA muscle \( (P < 0.001) \), respectively. No significant difference was observed between the MA and the control TA muscle \( (P = 0.68) \).

Pairwise comparisons across age ranges showed significantly lower levels of peak gamma coherence in the 4–7 yr age group compared with the 8–11 \( (P < 0.001) \) and the 12–15 yr age groups \( (P < 0.001) \), respectively. No significant difference was observed between the 8–11 and the 12–15 yr age groups \( (P = 0.63) \).

Pairwise comparisons across muscle showed significantly lower levels of peak gamma coherence in the MA TA muscle compared with the LA \( (P < 0.001) \) and the control TA muscle \( (P < 0.001) \), respectively. Significantly lower levels of gamma coherence were observed between the LA and the control TA muscle \( (P = 0.08) \).

Figure 3, G and H, displays peak coherence (mean ± 95% confidence intervals) for the three age groups in the beta (15–25 Hz) and gamma frequency bands (30–45 Hz) for the MA and LA TA muscle compared with that of the TA muscle in typically developing children (control group). Peak values are given in Table 2.

A significant effect of age group \( F(2,103) = 7.9, P < 0.001 \) and muscle \( F(2,103) = 39.6, P < 0.001 \) was found for peak beta coherence, with no interaction between the two parameters \( F(4,103) = 1.1, P = 0.34 \). For peak gamma coherence an effect of age group \( F(2,103) = 15.6, P < 0.001 \) and muscle \( F(2,103) = 15.59, P < 0.001 \) was found, with no significant interaction between the two parameters \( F(4,103) = 1.0, P = 0.39 \).

Pairwise comparisons across age ranges showed significantly lower levels of peak beta coherence in the 4–7 yr age group compared with the 8–11 \( (P = 0.005) \) and the 12–15 yr age groups \( (P < 0.001) \), respectively. No significant difference was observed between the 8–11 and the 12–15 yr age groups \( (P = 0.68) \).

Pairwise comparisons across muscle showed significantly lower levels of peak beta coherence in the MA TA muscle compared with the LA \( (P < 0.001) \) and the control TA muscle \( (P < 0.001) \), respectively. No significant difference was observed between the MA and the control TA muscle \( (P = 0.68) \).

Pairwise comparisons across age ranges showed significantly lower levels of peak gamma coherence in the 4–7 yr age group compared with the 8–11 \( (P < 0.001) \) and the 12–15 yr age groups \( (P < 0.001) \), respectively. No significant difference was observed between the 8–11 and the 12–15 yr age groups \( (P = 0.63) \).

Pairwise comparisons across muscle showed significantly lower levels of peak gamma coherence in the MA TA muscle compared with the LA \( (P < 0.001) \) and the control TA muscle \( (P < 0.001) \), respectively. Significantly lower levels of gamma coherence were observed between the LA and the control TA muscle \( (P = 0.08) \).

Higher amplitudes of RMS EMG were found for the LA side compared with the MA side \( (P < 0.001, \) for ratio MA/LA see Fig. 3I). In the CP subjects, for both the coherence and RMS EMG, the ratio for the MA and LA muscles (MA/MA/LA) was calculated for each subject. The results are presented for each of the three age groups in Fig. 3I. The ratio MA/LA for the beta-band coherence decreased with increasing age group \( F(2,35) = 3.6, P = 0.04 \). The gamma coherence ratio MA/LA did not change significantly with increasing age group \( F(2,35) = 1.3, P = 0.29 \). The ratio MA/LA for the RMS EMG increased with increasing age group \( F(2,35) = 6.4, P = 0.004 \). When the ratio MA/LA was examined for individual subjects, the tendency for RMS EMG to increase with age was confirmed \( (r = 0.46, P = 0.004) \). The coherence MA/LA ratios for individual subjects showed an effect of reduction with increasing age for beta frequencies \( (r = -0.40, P = 0.01) \) and a tendency in this direction for gamma frequencies \( (r = -0.25, P = 0.13) \). Thus, although the RMS EMG values for the MA muscle approach those of the LA muscle with increasing age, the relative modulation of the EMG due to common drive either does not increase for gamma frequencies or decreases for beta frequencies. To summarize, during static TA muscle activation there are differences in beta- and gamma-band coherence between the MA muscle and the LA muscle with a reduction of age-related increases in coherence in the MA muscle.

Muscle activation during walking. Figure 4 illustrates for a single subject (same subject as Fig. 1) the common drive to the TA muscle during gait. Rectified and averaged EMG from the MA and LA TA muscles during the swing phase of gait is shown (Fig. 4, A and B). The heel strike occurred at 0 ms. Both MA and LA TA muscles showed modulation of the EMG activity throughout the swing phase. We focused on the EMG activity before the heel strike, indicated by shaded areas that correspond to the first peak of EMG activity, where the forefoot is lifted to clear the toes above the ground during the swing phase. Power spectra recorded from the two electrodes
on the left and right sides, as well as coherence and phase plots for the EMG-EMG correlation, are shown in Fig. 4, C–J. For the MA muscle there is coherence at low frequencies with little coherence at frequencies in excess of 10 Hz. For the LA muscle there is significant coherence at all frequencies between 1 and 45 Hz. The difference in common drive (higher magnitude coherence in the LA muscle) between MA and LA muscles is quantified by the $\chi^2$ difference plot (Fig. 4 L) in which the primary differences between the two muscles during gait are at low coherence frequencies (<5 Hz and at 10 Hz) and in the range 17–27 Hz. Figure 4, K and M, shows the corresponding MA and LA cumulant densities for this subject, and from these it can be seen that the overall level of EMG-EMG synchrony in the MA TA muscle is less than 50% of that of the LA TA muscle. Note the longer duration of the central peak of synchronization during gait compared with static contraction. This is explained by the synchronizing effect of the EMG envelope during gait (cf. Hansen et al. 2005; Nielsen et al. 2008).

The pooled coherence data for all CP subjects during walking are shown in Fig. 5. As for the static contractions, the data are presented for the MA and LA TA muscle across three age groups: 4–7 ($n = 7$; Fig. 5, A and B), 8–11 ($n = 17$; Fig. 5, D and E), and 12–15 yr ($n = 14$; Fig. 5, G and H). Compared with the MA muscle, the values of coherence in the LA muscle across a broad frequency range (1–50 Hz) at each age were greater, and this is shown clearly in the $\chi^2$ comparisons (Fig. 5, C, F, and I). The $\chi^2$ coherence difference was least marked for the MA vs. LA comparison in the 4–7 yr age group ($\chi^2$: 150 at 3 Hz and 10–50 for range 10–40 Hz). The most marked
Table 2. Summary of peak coherence values for the MA, LA, and control TA muscle across the three different age groups

<table>
<thead>
<tr>
<th>Coherence Estimates</th>
<th>Static Contraction</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP MA side</td>
<td>CP LA side</td>
</tr>
<tr>
<td>Peak beta band</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–7 yr</td>
<td>0.05 ± 0.02</td>
<td>0.11 ± 0.06</td>
</tr>
<tr>
<td>8–11 yr</td>
<td>0.07 ± 0.02</td>
<td>0.18 ± 0.04</td>
</tr>
<tr>
<td>12–15 yr</td>
<td>0.07 ± 0.03</td>
<td>0.24 ± 0.07</td>
</tr>
<tr>
<td>Peak gamma band</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–7 yr</td>
<td>0.04 ± 0.01</td>
<td>0.07 ± 0.04</td>
</tr>
<tr>
<td>8–11 yr</td>
<td>0.08 ± 0.03</td>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td>12–15 yr</td>
<td>0.11 ± 0.07</td>
<td>0.21 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± 95% CI from MA, LA, and control tibialis anterior (TA) muscle for peak coherence in the beta (15–25 Hz) and gamma (30–45 Hz) frequency bands during static muscle activation and walking in cerebral palsy (CP) subjects. Refer to text for detailed statistics.

differences between the MA and LA muscles were identified for the older age groups, 8–11 and 12–15 yr, with particularly marked differences for the 4–7 vs. 8–11 yr age group comparison at low (<10 Hz) frequencies (χ²: −200) as well as frequencies between 10 and 50 Hz (χ²: 50–150).

The effect of age was explored further through χ² comparisons and through calculation of the correlation between age and peak coherence (Fig. 6). As with static contraction for the MA muscle of CP subjects, there was a similar effect of age to that observed in typically developing subjects performing the same task (see Petersen et al. 2010). The youngest age group (4–7 yr) showed less gamma band (~40 Hz) common drive compared with the 8–11 and 12–15 yr age groups (Fig. 6, B and D; χ²: 25 for range 25–50 Hz). In the gamma frequency range there was little difference in common drive between the two older age groups (Fig. 6F). With the use of χ² analysis, no evidence of a clear age-related increase in the beta frequency band was observed for gait. Interestingly, the χ² comparison detected differences for the MA TA muscle in favor of the oldest group compared with the two younger groups (see Fig. 6, C and E; χ²: 20–50 at 35 Hz), suggesting that weak gamma common drive during gait developed late for the MA muscle.

Figure 6, G and H, show peak coherence (mean ± 95% confidence intervals) for the three age groups in the beta (15–25 Hz) and gamma frequency bands (30–45 Hz) for the MA and LA TA muscle in CP subjects and for the TA muscle of typically developing children. Peak values are given in Table 2. No significant effect of age range [F(2,109) = 2.3, P = 0.11] but a significant effect of muscle [F(2,109) = 24.4, P < 0.001] was found for peak beta coherence, with no interaction between the two parameters [F(4,109) = 0.39, P = 0.82].

For peak gamma coherence a significant effect of both age range (F = 10.2, P < 0.001) and muscle (F = 36.0, P < 0.001) was found, with no significant interaction between the two parameters [F(4,109) = 1.0, P = 0.46].

Pairwise comparisons across muscle showed significantly lower levels of peak beta coherence in the MA TA muscle compared with the LA (P < 0.001) and the control TA muscle (P < 0.001), respectively. No significant difference was observed between the LA and the control TA muscle (P = 0.97).

Pairwise comparisons across age ranges showed significantly lower levels of peak gamma coherence in the 4–7 yr age group compared with the 8–11 (P = 0.02) and the 12–15 yr age groups (P < 0.001), respectively. No significant difference was observed between the 8–11 and the 12–15 yr age groups (P = 0.13).

Pairwise comparisons across muscle showed significantly lower levels of peak gamma coherence in the MA TA muscle compared with the LA (P < 0.001) and the control TA muscle (P < 0.001), respectively. No significant difference was observed between the LA and the control TA muscle (P = 0.63).

In the CP subjects the ratio of the coherence and RMS EMG between the MA and LA muscles during walking was calculated for each subject. The results are presented for each of the three age groups in Fig. 6I. The ratio MA/LA for the beta- and gamma-band coherence ranges showed a tendency to decrease with increasing age (see Fig. 6I), but these did not reach statistical significance [F(2,35) = 0.75, P = 0.48 and F(2,35) = 1.0, P = 0.39]. The ratio MA/LA for the RMS EMG showed a tendency to increase between the youngest and oldest age groups, but this did not reach statistical significance [F(2,35) = 1.1, P = 0.33]. When the ratio MA/LA was examined for individual subjects, the tendency for RMS EMG to increase with age was confirmed (r = 0.18, P = 0.28). The coherence MA/LA ratios for individual subjects showed little effect of subject age (r = −0.03, P = 0.85 for beta and r = −0.22, P = 0.19 for gamma). Thus there was a weaker tendency for MA/LA to increase for RMS EMGs and decrease for coherence with increasing age during walking compared with static muscle activation. To summarize, during walking differences were found between the MA and the LA muscles in beta- and gamma-band coherence with a loss of age-related increases in coherence in the MA.

EMG-EMG synchronization during static muscle activation and walking. Figure 7 shows pooled cumulant density plots obtained during static activation for the MA, LA, and control TA muscle across all three age groups: 4–7 (Fig. 7, A–C), 8–11 (Fig. 7, D–F), and 12–15 yr (Fig. 7, G–I). Peak cumulant magnitudes and peak cumulant durations are given in Table 3. The peak size showed an overall effect of age group [F(2,109) = 15.8, P < 0.001] and muscle [F(2,109) = 23.2, P < 0.001], with no significant interaction between the two parameters [F(4,109) = 0.8, P = 0.53].

Pairwise comparisons showed significantly smaller peaks for the 4–7 yr age group compared with the 8–11 (P = 0.02) and the 12–15 yr age groups (P < 0.001), respectively. No significant difference was observed between the 8–11 and the 12–15 yr age groups (P = 0.34).

Pairwise comparisons across muscle showed significantly smaller peaks in the MA TA muscle compared with the LA...
Pairwise comparisons showed significantly longer peak duration for the MA TA muscle compared with the LA (P = 0.002) and the control TA muscle (P = 0.02), respectively. No significant difference was observed between the LA and the control TA muscle (P = 0.99).

Pairwise comparisons across muscle showed significantly longer peak duration for the MA TA muscle compared with the LA (P = 0.002) and the control TA muscle (P = 0.02), respectively. No significant difference was observed between the LA and the control TA muscle (P = 0.61).

Figure 7 also shows pooled cumulant density plots obtained during walking for the MA, LA, and control TA muscle across all three age ranges: 4–7 (Fig. 7, J–L), 8–11 (Fig. 7, M–O), and 12–15 yr (Fig. 7, P–R). Peak sizes and durations are given in Table 3. The peak size showed no significant effect of age group [F(2,109) = 0.002, P = 0.99], but an overall effect of muscle [F(2,109) = 42.8, P < 0.001] with no significant interaction between the two parameters [F(4,109) = 0.69, P = 0.60] was observed.
Pairwise comparisons across muscle showed significantly smaller peaks in the MA TA muscle compared with the LA (P < 0.001) and the control TA muscle (P < 0.001), respectively. No significant difference was observed between the LA and the control TA muscle (P = 0.75).

No differences (P > 0.05) were observed for the peak duration, and the effect of gait modulation on the peak duration renders it meaningless.

Kinematic recordings. There was a significant effect of age group [F(2,109) = 3.6, P = 0.03] and leg [F(2,109) = 19.1, P < 0.001] when the ankle joint dorsiflexion movement ranges were compared (Fig. 8A). A significant higher movement range was found for the LA and control ankle joint compared with the MA leg for the two oldest age groups (8–11 yr, P < 0.001 and P = 0.011, respectively; 12–15 yr, P < 0.001 and P = 0.01, respectively).

There was not a significant effect of age group [F(2,109) = 2.3, P = 0.11] but a significant effect of leg [F(2,109) = 34.4, P < 0.001] when the ankle joint dorsiflexion movement velocities were compared (Fig. 8B). A significantly higher movement velocity was found for the LA and control ankle joint compared with the MA leg for all three age groups (4–7 yr, P = 0.013 and P = 0.004, respectively; 8–11 yr, P > 0.001 and P < 0.001, respectively; 12–15 yr, P < 0.001 and P < 0.001, respectively).

The CV of the dorsiflexion movement decreased with age for the LA side (r = 0.56, P < 0.001) but not for the MA side (r = 0.28, P = 0.085), showing a similar effect for the LA side as for that of the controls (Petersen et al. 2010). No significant relationship between MA or LA CV of the dorsiflexion movement and peak MA or LA beta and gamma coherence was observed (P > 0.05), and the MA/TA beta or gamma coherence ratio was not correlated with the MA/LA CV ratio (P > 0.05).

The functional significance of the difference in coherence between the LA and MA TA muscle was further explored. Because of intersubject differences and the effects on coherence of age, we calculated the ratio peak coherence magnitude for beta and gamma frequency ranges (see Figs. 3I and 6I) and compared this with the ratio of ankle joint movement range and the ratio of ankle joint velocity. Comparison between the beta coherence ratio and the ankle dorsiflexion angle ratio and movement velocity ratio (Fig. 8, C and D) revealed positive relationships independent of the effects of age and RMS EMG (r = 0.57, P < 0.001 and r = 0.61, P < 0.001, respectively). No relationship was observed between either the MA/LA gamma coherence ratio (r = 0.08, P = 0.64 and r = 0.11, P = 0.5, respectively) or the MA/LA RMS EMG ratio (r = 0.17, P = 0.32 and r = 0.24, P = 0.15, respectively) and the MA/LA ratios for range and velocity of joint movement (Fig. 8, E–H). No significant (P > 0.05) relationships were observed between the MA/LA coherence ratios obtained during static contraction and kinematic parameters.

DISCUSSION

We have shown that the common drive to the most affected TA muscle during static dorsiflexion and walking in children with CP is reduced compared with the least affected TA muscle and typically developing control subjects. The reduction of common drive during gait in the CP children was related to deficits in their ability to lift the foot in the swing phase of gait.

Methodological considerations. Cross talk between recording electrodes will always be a concern for analysis of coherence between EMG recordings from adjacent muscles or, as in the present study, from the same muscle. To minimize the influence of cross talk, we ensured that the distance between recording electrodes was as large as possible. In previous studies we have ensured a distance of more than 10 cm between electrodes, which exceeds the length of individual muscle fibers in the adult TA muscle. It was not possible to separate the electrodes by as long a distance, especially in the smaller children participating in this study (Table 1). We do not know the exact length of TA muscle fibers in the different age groups, but if there is a relatively proportionate scaling to body size, the distance between electrodes was considerably...
longer than the fiber length even in the youngest (smallest) children. It may also be argued that the youngest children had the shortest distance between electrodes but the least coupling between the recordings in both the time and frequency domains. Cross talk due to sampling of activity from too closely located electrodes would have been expected to produce the opposite result. To further minimize any influence from cross talk, all data showing either very narrow peaks in the cumulant density function (<2 ms) or equal and significant coherence at all frequencies were deemed to be influenced by cross talk and therefore omitted from further analysis. All recordings that were used for the analysis thus showed coherence for only restricted frequency band and central peaks of synchrony in the time domain with a similar duration as observed for surface EMG recordings in the present study have been observed in wire and needle recordings of the activity of individual motor units (Farmer et al. 1993b; Hansen et al. 2005).

Central motor pathways underlying common drive in CP. On the basis of studies of patients with CNS lesions, primate physiology, and magnetoencephalography (MEG)/EEG-EMG coherence, it is recognized that motor unit synchronization and beta and gamma rhythm common drive to upper (Baker et al. 1997; Brown et al. 1998; Conway et al. 1995; Datta et al. 1991; Farmer et al. 1993a, 1993b; Halliday et al. 1998; Mima and Hallett 1999; Salenius et al. 1997) and lower limb motoneurons (Gross et al. 2000; Hansen and Nielsen 2004; Hansen et al. 2002) are the result of oscillatory activity in cortical networks. Other peripheral feedback mechanisms may play a supportive but not essential role in maintaining EMG-EMG and EEG-EMG coherence (Farmer et al. 1993a; Hansen et al. 2002; Kilner et al. 2004; Pohja and Salenius 2003). In healthy adults the duration of single TA motor unit synchrony during static muscle activation is ~13 ms between TA motor units (Datta et al. 1991). In subjects who have suffered stroke damage to central motor pathways or spinal cord damage, short-term synchrony is lost and may be replaced by longer duration (~29 ms). The beta and gamma rhythm common drive in CP are shown across the age groups in panels A–H.

![Fig. 6. Statistical comparisons of pooled coherence obtained during walking using the extended χ² test for difference of coherence. Comparisons are shown for 4–7 vs. 8–11 yr for the MA muscle (A) and LA muscle (B), 4–7 vs. 12–15 yr for the MA muscle (C) and LA muscle (D), and 8–11 vs. 12–15 yr for the MA side (E) and LA side (F). Comparisons of peak beta-band coherence (G) and peak gamma-band coherence (H) from MA muscle, LA muscle, and control group (data from Petersen et al. 2010) are shown across the 3 different age groups. Error bars denote 95% confidence intervals. Ratios (MA/LA) for peak beta coherence, peak gamma coherence, and RMS EMG amplitude are shown across the 3 different age groups (I). Refer to text for detailed statistics.](http://jn.physiology.org/abstracts/JN-00218-2012.pdf)
broad-peak synchrony (Datta et al. 1991). In the CP subjects the central cumulant peak size was smaller for the MA TA muscle during both static muscle activation and walking, supporting the results of Rose and McGill (2005) showing that CP subjects during static contraction had reduced short-term synchronization compared with controls. Spinal cord lesions in cat produce a loss of short-term synchrony with the emergence of broad-peak synchrony, which results from lesion-induced increased drive to the motoneuron pool from synchronized polysynaptic inputs (Kirkwood et al. 1982). In CP subjects the combined results of the loss of higher frequencies of coherence coupled with smaller central cumulant peaks of longer duration during static muscle activation suggest that for the MA muscle, motoneuron activation is achieved through polysynaptic pathways rather than from directly projecting corticospinal pathways. The RMS EMG amplitude was larger for all age groups in the LA TA muscle compared with the MA TA muscle. However, taking into account individual differences in the CP subjects through calculation of the ratio MA/LA for coherence and RMS EMG amplitude, we were able to show that for static muscle activation with increasing age, in contrast to the coherence values, the RMS EMG ratio between the MA and LA muscle normalized. We suggest therefore that RMS EMG levels during static muscle activation cannot explain the developmental pathophysiology of CP without taking into account the failure of the modulatory effects on motoneuron activity of common drive to develop.

Fig. 7. Pooled cumulant density plots are shown for the LA, MA, and control TA muscle for the 3 age groups: 4–7 (A–C and J–L), 8–11 (D–F and M–O), and 12–15 yr (G–I and P–R), for static muscle activation (A–I) and walking (J–R), respectively. Peak magnitudes and peak durations are given in Table 3. Refer to text for detailed statistics.
Conclusion. We conclude that children with CP show reduced oscillatory beta and gamma common drive to spinal motoneurons that innervate the MA TA muscle during static contraction and gait. The relationship between the MA/LA ratio of beta coherence and the range and velocity of dorsiflexion in the swing phase of walking. The MA/LA ratio gives a measure of the difference in function between the two legs within each individual and thus greatly reduces intersubject variability. The significant correlation of beta coherence with the functional kinematic parameters, corrected for age and EMG magnitude, suggests that this measure of central drive to TA motoneurons is of functional significance for the gait ability of the children. Furthermore, the MA/LA ratios of beta and gamma coherence for static muscle activation did not correlate with the functional kinematic parameters. Static muscle activation is used widely in the measurement of motor unit synchrony; however, our finding signifies that the common drive should also be measured during functionally relevant conditions.

We do not as yet have data showing increases in EEG-EMG coherence during static TA activation and during walking across childhood or in subjects with CP. However, for upper limb muscles the increases in EMG-EMG synchrony and coherence seen in childhood are mirrored by an increase in beta and gamma EEG-EMG coherence during childhood (Graziadio et al. 2010; James et al. 2008). We have suggested therefore that the developmental increases in TA EMG-EMG synchrony and coherence in static activation and walking across childhood reflect that the TA muscle receives increased oscillatory drive from motor cortex networks. We now suggest that the failure of the MA TA muscle to show increases in beta- and gamma-range coherence across childhood is evidence that in CP there is a failure of development of oscillatory motor cortex networks and a failure to integrate TA EMG activity through the mechanism of oscillatory synchrony with these cortical networks.

We conclude that children with CP show reduced oscillatory beta and gamma common drive to spinal motoneurons that innervate the MA TA muscle during static contraction and gait. The relationship between the MA/LA ratio of

Table 3. Summary of cumulant density estimates for the MA, LA, and control TA muscle across the three different age groups

<table>
<thead>
<tr>
<th>Cumulant Estimates</th>
<th>Static Contraction</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP MA side</td>
<td>CP LA side</td>
</tr>
<tr>
<td>Peak size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–7 yr</td>
<td>0.047 ± 0.014</td>
<td>0.083 ± 0.043</td>
</tr>
<tr>
<td>8–11 yr</td>
<td>0.066 ± 0.015</td>
<td>0.110 ± 0.016</td>
</tr>
<tr>
<td>12–15 yr</td>
<td>0.072 ± 0.020</td>
<td>0.144 ± 0.042</td>
</tr>
<tr>
<td>Peak width, ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–7 yr</td>
<td>42 ± 20</td>
<td>26 ± 12</td>
</tr>
<tr>
<td>8–11 yr</td>
<td>31 ± 7</td>
<td>22 ± 3</td>
</tr>
<tr>
<td>12–15 yr</td>
<td>23 ± 6</td>
<td>18 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± 95% CI from MA, LA, and control TA muscle for peak sizes and peak durations (width) for static muscle activation and walking in CP subjects. Refer to text for detailed statistics.

Relationship between common drive and TA muscle activation during walking. Tibialis anterior is the prime dorsiflexor of the ankle, and its activation is essential in allowing the toes to clear the ground during the swing phase of gait. The importance of central drive for normal TA muscle function is evident clinically and in neurophysiological studies (Barthelmy et al. 2010; Halliday et al. 2003; Hansen et al. 2005; Nielsen et al. 2008; Petersen et al. 2001). It has recently been shown that during the swing phase of gait the EEG is coherent with TA muscle EMG at frequencies in the range 24–40 Hz (high beta-gamma range) and at 10 Hz (Petersen et al. 2012). These results show that during the swing phase of gait the TA muscle EMG synchronizes with EEG over the leg area of sensorimotor cortex, indicating that during this period of gait TA EMG is also integrated (synchronized) within a cortical oscillatory network. Taken together, these findings support the view that, as for static TA activation during walking, the beta and gamma drives to the muscle are the result of oscillatory synchrony within cortical circuits that include the leg area of the primary motor cortex.

Impaired central drive to TA results in a dropped foot and a gait pattern characterized by toe rather than heel strike. Interestingly, common drive of 24–40 Hz to thigh muscles has been shown to increase following treadmill training and improvement of locomotion skills (Norton and Gorassini 2006). During normal gait the common drive is present in the early and late part of the swing phase with a maximum right before the foot is placed on the ground in very late swing phase (Halliday et al. 2003). Therefore, measurement of common drive provides important information about the corticospinal involvement in the control of the TA muscle at a time when precise control of the ankle joint is required during human walking. Gamma range common drive (~35–55 Hz) has been described in strongly contracting hand muscles (Brown et al. 1998; McAuley et al. 1997) and is coherent with cortical rhythms (Brown et al. 1998). Our previous study and the results of the present study support those of Omlor et al. (2007), which showed a switch from beta- to gamma-band drive during dynamic force output for upper limb muscles. Omlor et al. (2007) suggested that gamma-range EEG-EMG coherence underpins binding of the attentional, visual, and somatosensory information necessary for control of dynamic force output as opposed to static force output. We suggest that such integrated dynamic force control of the ankle joint during gait is essential for co-ordinated walking and that failure of development of gamma-range common drive to TA muscle during walking may be a pathophysiological underpinning of the increased clumsiness and excess falls seen in CP children. In our recent study on normally developing children we found an increase in gamma-band coherence with age that was associated with a reduction in the step-to-step variability (CV) (Petersen et al. 2010). In the present study a similar relationship was not found for CP children for either the most or least affected leg, although CV decreased with age for the LA side but not for the MA side. This lack of correlation is in all likelihood explained by low values and large interindividual variability of common gamma drive levels in the CP subjects. We did find, however, a significant relation between the MA/LA ratio of beta coherence and the range and velocity of dorsiflexion in the swing phase of walking. The MA/LA ratio gives a measure of the difference in function between the two legs within each individual and thus greatly reduces intersubject variability. The significant correlation of beta coherence with the functional kinematic parameters, corrected for age and EMG magnitude, suggests that this measure of central drive to TA motoneurons is of functional significance for the gait ability of the children. Furthermore, the MA/LA ratios of beta and gamma coherence for static muscle activation did not correlate with the functional kinematic parameters. Static muscle activation is used widely in the measurement of motor unit synchrony; however, our finding signifies that the common drive should also be measured during functionally relevant conditions.

J Neurophysiol • doi:10.1152/jn.00218.2012 • www.jn.org
beta and gamma coherence during gait and the kinematics of gait suggests that the time- and frequency-domain analyses of EMGs may in the future provide pathophysiologically meaningful and functionally relevant measures of the effect of gait training and other therapeutic interventions on the cortical drive to spinal motoneurons during gait in children with CP. The ease with which these techniques may be applied makes them ideal for longitudinal studies of training interventions in which mechanistic understanding of neuroplastic changes in central networks is required.

**ACKNOWLEDGMENTS**

We acknowledge Camilla Voigt for participation in some of the experiments. We acknowledge Dr. Lucinda Carr for constructive feedback on the manuscript. We acknowledge David Halliday for providing the MATLAB routines used for analysis. We also acknowledge the Helene Elsass Center for the use of laboratory facilities.

**GRANTS**

This work was supported by a grant from the Ludvig and Sara Elsass Foundation. S. F. Farmer is supported by the University College London
Hospitals National Health Service Foundation Trust/University College London Comprehensive Biomedical Research Centre.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.H.P., S.F.F., and J.B.N. conception and design of research; T.H.P. and M.K.-D. performed experiments; T.H.P. and S.F.F. analyzed data; T.H.P., S.F.F., and J.B.N. interpreted results of experiments; T.H.P. prepared figures; T.H.P., S.F.F., and J.B.N. drafted manuscript; T.H.P., S.F.F., M.K.-D., and J.B.N. edited and revised manuscript; T.H.P., S.F.F., M.K.-D., and J.B.N. approved final version of manuscript.

REFERENCES


J Neurophysiol • doi:10.1152/jn.00218.2012 • www.jn.org


