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Maturation of feedforward toe walking motor program is impaired in children with cerebral palsy

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Voluntary toe walking in adults is characterized by feedforward control of ankle muscles in order to ensure optimal stability of the ankle joint at ground impact. Toe walking is frequently observed in children with cerebral palsy, but the mechanisms involved have not been clarified. Here, we investigated maturation of voluntary toe walking in typically-developing children and typically-developed adults and compared it to involuntary toe walking in children with cerebral palsy. Twenty-eight children with cerebral palsy (age 3–14 years), 24 typically-developing children (age 2–14 years) and 15 adults (mean age 30.7 years) participated in the study. EMG activity was measured from the tibialis anterior and soleus muscles together with knee and ankle joint position during treadmill walking. In typically-developed adults, low step-to-step variability of the drop of the heel after ground impact was correlated with low tibialis anterior and high soleus EMG with no significant coupling between the antagonist muscle EMGs. Typically-developing children showed a significant age-related decline in EMG amplitude reaching an adult level at 10–12 years of age. The youngest typically-developing children showed a broad peak EMG-EMG synchronization (>100 ms) associated with large 5–15 Hz coherence between antagonist muscle activities. EMG coherence declined with age and at the age of 10–12 years no correlation was observed similar to adults. This reduction in coherence was closely related to improved step-to-step stability of the ankle joint position. Children with cerebral palsy generally showed lower EMG levels than typically-developing children and larger step-to-step variability in ankle joint position. In contrast to typically-developing children, children with cerebral palsy showed no age-related decline in tibialis anterior EMG amplitude. Motor unit synchronization and 5–15 Hz coherence between antagonist EMGs was observed more frequently in children with cerebral palsy when compared to typically-developing children and in contrast to typically-developing participants there was no age-related decline. We conclude that typically-developing children develop mature feedforward control of ankle muscle activity as they age, such that at age 10–12 years there is little agonist–antagonist muscle co-contraction around the time of foot-ground contact during toe walking. Children with cerebral palsy, in contrast, continue to co-contract agonist and antagonist ankle muscles when toe walking. We speculate that children with cerebral palsy maintain a co-contraction activation pattern when toe walking due to weak muscles and insufficient motor and sensory signalling necessary for optimization of feedforward motor programs. These findings are important for understanding of the pathophysiology and treatment of toe walking.

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Introduction

Toe walking has been estimated to occur in >50% of children with spastic cerebral palsy and it is the most frequent reason for surgery and botulinum toxin treatment in this patient population (Rethlefsen *et al.*, 2017). Reducing the plantar flexed foot posture is a therapeutic goal for paediatric neurologists, physiotherapists and orthopaedic surgeons, since it is a general concern that long-term toe walking may lead to pain, arthritis and other musculotendon-joint problems. Therapies to reduce plantar flexion at the ankle during gait include stretching, casting, gait training, botulinum toxin injections and tendon lengthening surgery, but there is no general agreement on the efficacy of these therapies (Blackmore *et al.*, 2007; Koog and Min, 2010; Franki *et al.*, 2012; Sees and Miller, 2013; Valentin-Gudiol *et al.*, 2013; Galey *et al.*, 2017). To devise a rational approach to therapy it is important to develop a clear understanding of the physiological and pathophysiological mechanisms that underlie toe walking within a neuro-developmental context (Cappellini *et al.*, 2016).

Toe walking has been linked to premature activation of the ankle plantar flexors in the swing phase of walking and co-contraction of antagonist ankle muscles during gait and its presence is often used to estimate the extent of pathological motor control in children with cerebral palsy (Tardieu *et al.*, 1989; Hesse *et al.*, 2000; Farmer, 2003; Syczewska and Swiecicka, 2016). Toe walking is typically thought of as a clinical feature of spasticity involving hyperexcitable reflexes in the ankle plantar flexors (Brown *et al.*, 1991; Buffenoir *et al.*, 2004; Lampe and Mitternacht, 2011). However, reflex measurements during walking in children with cerebral palsy have failed to find evidence of exaggerated sensory input to ankle plantar flexors in the swing phase of walking (Willerslev-Olsen *et al.*, 2014). Furthermore, several independent lines of research support the view that toe walking may be primarily related to impaired muscle growth (Smith *et al.*, 2011; Gough and Shortland, 2012; Barber and Boyd, 2016; Herskind *et al.*, 2016). Due to lack of neural activation and reduced daily physical activity levels, muscle growth in children with cerebral palsy is impaired. The shortened muscles therefore have an altered length-force relationship (Barber *et al.*, 2011, 2017; Gough and Shortland, 2012; Herskind *et al.*, 2016). Therefore, to obtain efficient forward propulsion during walking, children with cerebral palsy may have to plantar flex the ankle to a greater degree in order to make optimal use of the force-length relation of the shortened muscles (Gough and Shortland, 2012). This suggests that toe walking in children with cerebral palsy should be conceptualized as part of an adaptation process, where the nervous system attempts to solve the mechanical constraints induced by muscles that are too short. Recent theories in computational motor neuroscience postulate that movements are generated in a feedforward manner, where sensory feedback is predicted more or less precisely (Shadmehr *et al.*, 2010; Wolpert *et al.*, 2011; Wolpert and Flanagan, 2016) and with repetition the movement is optimized through a reduction in the difference between the predicted and actual sensory feedback (Wolpert and Flanagan, 2016). It has been recently demonstrated that when adults walk on their toes they use a feedforward motor program, which involves activation of plantar flexor muscles 50–100 ms prior to ground contact (Lorentzen *et al.*, 2018). Lorentzen *et al.* (2018) found that the muscle activity around ground contact was unchanged when sensory feedback from the ankle was blocked by ischaemia or when the ground was suddenly removed as evidence of the feedforward nature of the muscle activity. It is likely that this feedforward motor program requires several years of practice during childhood to be as efficient and precise as in adults. We hypothesize that in cerebral palsy the combination of disrupted central control of movement and abnormal muscle properties rather than spinal hyper-reflexia leads to poor development of feedforward motor control, such that the physiology of toe walking in cerebral palsy participants will show clear differences to that of voluntary toe walking in typically-developed children and typically-developed adults. In the present study we investigated whether maturation of feedforward control of toe walking towards an adult pattern is observed in typically-developed children and we investigate the extent to which a similar maturation pattern is observed in children with cerebral palsy.

Materials and methods

Participants

Twenty-four typically-developed children (age range: 2–14 years), 15 able-bodied adult volunteers [mean ± standard error of the mean (SEM) age 30.7 ± 3 years] and 28 children with cerebral palsy (age range: 3–14 years) participated in the study. The mean age and the age distribution in the typically developed and children with cerebral palsy populations were similar (Table 1). The local ethics committee, Region H, granted approval of the study (H-1–2014–006), and all parents and adult volunteers provided written consent prior to participation. Experimental procedures conformed with the Declaration of Helsinki. All children with cerebral palsy had been diagnosed as spastic and as toe walkers by a trained

Table 1 Population characteristics

	TD heel $n = 24$	TD toes $n = 24$	CP $n = 28$	Adult heels $n = 15$	Adults toes $n = 15$
Age, years	6.5 (0.6)	6.5 (0.6)	7.0 (0.9)	30.7 (3.0)	30.7 (3.0)
Gait speed, km/h	1.5 (0.5)	1.5 (0.5)	1.1 (0.3)*	3	3
Stride length, cm	47.1 (2.5)	43.1 (2.3)	39.1 (2.6)	55 (1.0)	54 (1.5)
Cycle duration, s	1.2 (0.3)	1.1 (0.2)	1.6 (0.4)*	1.2 (0.1)	1.1 (0.2)
Angle at ground, degrees	106.5 (2.4)	126.5 (2.8)*	120.3 (2.8)*	107.7 (3.2)	125.3 (2.8)*
Movement range, degrees	20.0 (3.7)	16.4 (5.7)*	14.6 (7.4)*	25.1 (4.3)	15.5 (4.5)*

Values are presented as mean (SEM). *Significant difference from typically-developing (TD) heel walking. CP = cerebral palsy.

senior neuropaediatrician upon recruitment. The children with cerebral palsy were evaluated (by J.L.O. and J.B.N.) as part of a neurological examination prior to the experiments. None of the children had reduced passive range of movement which prevented them from walking on their heels. All children were able to walk with at least a speed of 0.4 km/h on a treadmill. The majority of children were independent walkers, but six children with cerebral palsy had not yet developed independent ambulation. Fifteen were classified as Gross Motor Function Classification Scale (GMFCS) I, 8 as GMFCS II, and 5 as GMFCS III. Twelve children were classified as diplegic and 16 children were classified as hemiplegic. One child was classified as quadriplegic.

Experimental design

Gait

All children walked on a treadmill at their preferred speed. The child was gently requested to walk faster if a parent indicated that the child was normally able to walk faster than the speed initially chosen by the child. The children were allowed some minutes to get accustomed to walking on a treadmill before measurements were started. All participants were asked to hold on to the rails on the treadmill in front of them to allow maximum stability of walking. Where necessary, one of the parents was allowed to sit in front of the treadmill to encourage the child during measurements. The children were asked to walk as they normally would, which for typically-developed children involved making ground contact with the heel first; whereas children with cerebral palsy made contact with the forefoot first. In addition to normal walking, typically-developed children were asked also to walk on toes. Each measurement period lasted 2 min during which the child was asked to walk as steadily on the treadmill as possible. The typically-developed children walked with an average speed of 1.5 ± 0.5 km/h and the children with cerebral palsy walked with an average speed of 1.1 ± 0.3 km/h. Similar to typically-developed children, adults were asked to walk normally with heel strike as well as on toes. They were requested to walk at a speed of 3.0 km/h in both cases (Table 1).

Stride length was similar in the two populations of children, but cycle duration was significantly longer in the children with cerebral palsy than in typically-developed children (Table 1; $P < 0.05$). Children with cerebral palsy made contact with the ground at a significantly more plantar flexed position of the ankle joint than the typically-developed children when walking normally (Table 1; $P < 0.05$). This is consistent with the fact that all children with cerebral palsy had been diagnosed as toe walkers. When typically-developed children were asked to walk voluntarily on toes they replicated the position of the ankle joint at ground contact seen in children with cerebral palsy (Table 1; $P = 0.1$). The mean movement range in the ankle joint during the gait cycle was lower in children with cerebral palsy than in typically-developed children when walking normally ($P < 0.05$), but similar to the movement range in typically-developed children when walking on heels (Table 1). For comparison data from adults during both normal walking with heel strike and toe walking are also shown in Table 1.

Motion analysis

A motion analysis system (Qualisys) consisting of six infrared source cameras (Oqus120) was used to collect the 3D position of 14 mm reflective markers placed bilaterally on the base of the little toe, the lateral malleolus, caput fibula and crista illiaca. Sampling rate was 200 Hz. These data were used to calculate joint angles at the knee and ankle joint, cycle duration, step length and gait speed. Drop of the heel following ground contact was calculated as the difference in ankle joint position at ground contact and the most dorsiflexed ankle joint position within the initial 150 ms after ground contact (*cf.* Lorentzen *et al.*, 2018). Step-to-step variability in the drop was expressed as the standard deviation of this calculation.

EMG recording

EMG activity was recorded from both legs using four sets of custom-made bipolar electrodes with small recording areas (9 mm^2) and a short bipolar inter-electrode distance (0.5 cm). Two of the electrodes were placed bilaterally on the skin over the belly of the tibialis anterior muscle, whereas the other two electrodes were placed bilaterally over the soleus muscle distal to the insertion of the gastrocnemius muscles. The skin was prepared by first brushing the skin softly with sandpaper (3 M red dot). Electrode impedance was kept below 5 kΩ. Data were sampled at 2000 Hz, filtered (band-pass, 1–1000 Hz), and stored on a PC for off-line analysis.

Offline analysis

Signal processing and analysis were performed off line. All data were imported into MATLAB (Mathworks, Massachusetts, USA) for further analysis. Periods with no EMG activity or significant artefacts or noise were removed

before analysis of EMG magnitude, muscle co-contraction and EMG-EMG synchronization and coherence was performed.

Calculation of co-contraction between antagonist muscles

To calculate the amount of co-contraction between tibialis anterior and soleus muscle activities, the time of ground contact for each leg in each individual step was identified first. This was done by identifying the time point where movement of the markers on that leg changed direction from forward to backward. This way of identifying ground contact was chosen because children made ground contact with different parts of the foot, which made triggering on a force sensitive resistance difficult and unreliable. The time of ground contact was used to divide the step cycle into a swing phase, which lasted from ground contact for the opposite leg to ground contact for the investigated leg, and a stance phase, which covered the remaining time in the step cycle. Co-contraction between the two antagonist muscles was calculated separately for the swing and stance phase. For the swing phase, the calculation was made for a period from 200 ms to 0 ms prior to ground contact for the investigated leg. For the stance phase a period from 0 ms to 200 ms after ground contact was used. For this calculation we include both the period immediately after ground contact where tibialis anterior rather than soleus is active during normal gait with heel strike as well as the later part of the stance phase where soleus muscle is dominantly active.

Several different indices of muscle co-contraction were investigated according to Rosa *et al.* (2014). As we did not find any major differences in the findings whether we used one or the other index, we decided to report the simplest of the indices. We used root mean square EMG magnitude (RMS) to calculate the amount of soleus and tibialis anterior EMG activity within the 200-ms time periods during the swing and stance phases, respectively. We then expressed the amount of co-contraction as the ratio between soleus and tibialis anterior RMS EMG activity in the swing phase and the ratio between tibialis anterior and soleus EMG activity in the stance phase.

Calculation of coherence and cumulant density estimates

Frequency domain analysis of the data was undertaken using the methods set out in detail by (Halliday *et al.*, 1995). The practice of band-pass filtering (3 Hz high pass and 100 Hz low pass) and 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) whilst suppressing information regarding MUAP waveform shape (Myers *et al.*, 2003; Halliday and Farmer, 2010; Boonstra and Breakspear 2012; Ward *et al.*, 2013). As a precursor to undertaking coherence and synchronization analysis of the data, the EMG signals were normalized to have unit variance (Halliday and Rosenberg, 2000). The rectified normalized EMG signals are assumed to be realizations of stationary zero mean time series denoted by x and y. Segments of EMG activity lasting 200 ms before and after ground contact were used for the analysis. The results of analysis of individual records generated estimates of the auto-spectra of the two EMG signals $fxx(\lambda)$, $fyy(\lambda)$, and their cross-spectra $fxy(\lambda)$. We then estimated three functions that characterize the signals' correlation structure: coherence, $|R_{xy}(\lambda)|^2$; phase, $\varphi_{xy}(\lambda)$; and cumulant density, $q_{xy}(u)$. Coherence estimates are bounded measures of frequency association between the signals and are defined over the range [0, 1]. The time domain cumulant density estimate of synchrony between the signals is not bounded. The phase between the signals is defined over the range $[-\pi, +\pi]$. For the present data, coherence estimates provide a measure of the fraction of the activity in one signal at any given frequency that can be predicted by the activity in the second signal. In this way, coherence estimates quantify the strength and range of frequencies of common oscillations that are shared between two EMGs. The timing relations between two EMG signals are estimated from the phase. The cumulant density, calculated from the inverse Fourier transform of the cross-spectrum, provides an unbounded time-domain representation of the EMG-EMG correlation structure analogous to the cross-correlogram and thus captures both correlation and timing information between signals (Halliday *et al.*, 1995). The cumulated sum of the logarithmic values of EMG–EMG coherence in the 5–15 Hz, 15–35 Hz and 35–60 Hz frequency range were calculated to quantify the amount of coherence in individual children. This is similar to previous studies in which coherence has been quantified (Kristeva *et al.*, 2007; Willerslev-Olsen *et al.*, 2015).

Statistical analysis

Population averages were compared using unpaired two-tailed *t*-test. Pearson product moment correlation was used to test for age-related changes in measurements as well as significant correlations between measurements obtained from individual participants. ANCOVA was used to determine whether age-dependent changes of measurements differed between typically-developed and children with cerebral palsy. Chi-square test was used to identify differences in prevalence of specific features of coherence and cumulant density functions in typically-developed and children with cerebral palsy.

All values are given as mean ± SEM. All analyses were performed with Sigmaplot 12.5 (SYSTAT Software, San Jose, CA, USA) for Windows except ANCOVA test which was performed in SPSS (v.24, IBM, USA).

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Figure 1 shows examples of ankle joint position, soleus and tibialis anterior EMG activity during heel and toe walking in a healthy adult (Fig. 1A), a 6-year-old typically-developed child (Fig. 1B) and a 6-year-old child with cerebral palsy (Fig. 1C). The adult participants (Fig. 1A) shows the characteristic features of controlled toe walking, which have already been reported in adults (Lorentzen *et al.*, 2018): (i) initiation of soleus EMG activity 50–100 ms prior to ground contact; (ii) a quick dorsiflexion

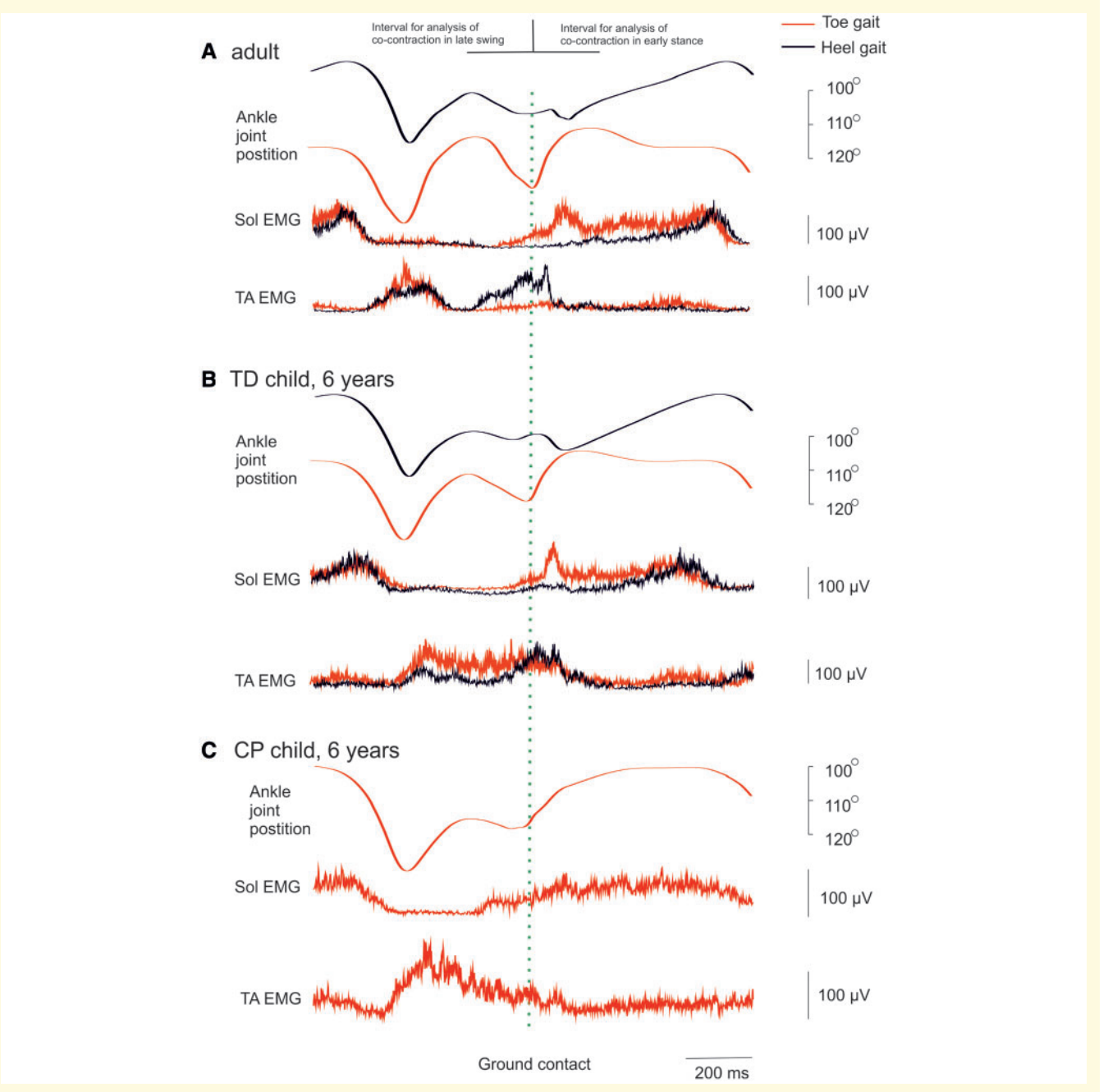

Figure 1 Ankle joint position and muscle EMG activity. Ankle joint position and soleus and tibialis anterior EMG activity during heel (black) and toe (red) walking in an adult (**A**), typically-developed child (**B**) and child with cerebral palsy (**C**). The ankle joint position is given in degrees and the EMG activities in microvolts. *X*- and *y*-scales are indicated as horizontal and vertical bars to the right of the graphs. Time of ground contact is indicated by a green, dotted vertical line. The time windows in which the soleus and tibialis anterior EMG activity were quantified in relation to ground contact are indicated above the upper most graph. All traces are the average of 50 steps. CP = cerebral palsy; Sol = soleus muscle; TA = tibialis anterior muscle; TD = typically-developing.

movement of the ankle joint at ground contact; (iii) pronounced soleus EMG activity in early stance with a clear burst of EMG activity 50–100 ms after ground contact; and (iv) absence of tibialis anterior EMG activity during the stance phase. The first three features may also be observed in the typically-developed child voluntarily toe walking (Fig. 1B), but note that, in contrast to the adult participants, in the child, significant tibialis anterior EMG activity was observed continuously throughout the swing phase and 200 ms into stance. The child with cerebral palsy toe walking showed smaller maximal EMG activity in both tibialis anterior and soleus muscles during the gait cycle when compared to the typically-developed child and the adult, but otherwise the EMG spatio-temporal 'pattern' was similar to that observed in the typically-developed child (Fig. 1C).

Age-dependent changes in EMG activity during toe and heel walking

To quantify differences in the ankle joint muscle activation pattern across the different age groups, we measured the amount of soleus EMG activity in the last 200 ms prior to ground contact and the amount of tibialis anterior EMG activity in the initial 200 ms after ground contact. In adults, the amount of soleus EMG activity prior to ground contact was small as compared to children and showed little variability during both heel and toe walking (Fig. 2A and B). In typically-developed children during toe walking, the soleus EMG activity decreased significantly with age reaching a similar level to adults in 10–12-year-old children (Fig. 2A and B; $r^2 = 0.15$; $P < 0.02$). Typically-developed children walking normally (heel strike first) showed no age-related difference in tibialis anterior EMG activity during early stance (Fig. 2D), consistent with earlier reports that toe lift and heel strike, which are associated to the burst of EMG activity before and after heel strike are already fully developed in 1–2-year-old children (Forssberg, 1992). In contrast, during toe walking in typically-developed children tibialis anterior EMG activity declined very significantly with age (Fig. 2E; $r^2 = 0.62$; $P < 0.001$) reaching adult low values at ages 10–12 years. In children with cerebral palsy, soleus and tibialis anterior EMG values as low as in adults were observed already at 2–3 years of age and no age-related differences were observed ($P < 0.2$).

Age-dependent changes in the amount of co-contraction between antagonist ankle muscle

When the magnitude of soleus EMG activity was related to the magnitude of tibialis anterior EMG activity in late swing phase, a significant age-dependent relationship was observed for both heel (Fig. 3A; $r^2 = 0.49$; $P < 0.01$) and toe walking (Fig. 3B; $r^2 = 0.54$; $P < 0.01$). The level of co-contraction in early stance also decreased significantly with age during toe walking (Fig. 3E; $r^2 = 0.48$; $P < 0.01$), but not during heel walking (Fig. 3D; $r^2 = 0.05$; $P = 0.81$). The level of co-contraction showed no significant age-dependent relation in either the swing (Fig. 3C; $r^2 = 0.17$; $P = 0.36$) or stance phase (Fig. 3F; $r^2 = 0.35$; $P = 0.07$) in children with cerebral palsy.

Age-dependent changes in control of ankle joint position at ground contact

Following ground contact when toe walking a much larger drop of the heel was observed in adults and the oldest

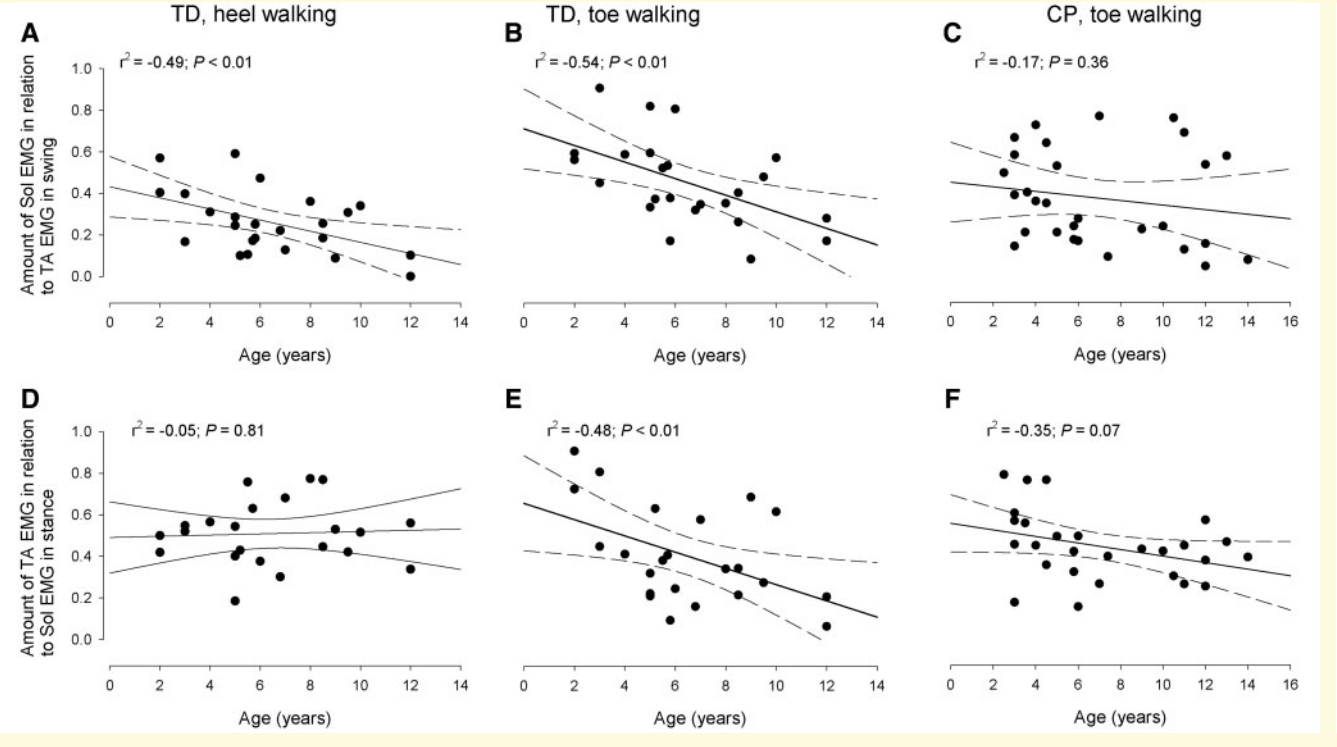

Figure 2 Muscle EMG in toe walking. Amount of soleus EMG in swing (**A**–**C**) and tibialis anterior EMG in stance (**D**–**F**) during heel (**A** and **D**) and toe walking in typically-developed children (**B** and **E**) and during toe walking in children with cerebral palsy (**C** and **F**) as a function of age (in years). Each symbol illustrates data from a single child. Full lines indicate regression lines. Dashed lines indicate 95% confidence intervals. Average EMG levels in the population of 15 typically-developed adults have been marked in **A**, **B**, **D** and **E** as horizontal dashed lines and open circles with vertical bars indicating standard deviation. CP = cerebral palsy; Sol = soleus muscle; TA = tibialis anterior muscle; TD = typically-developing.

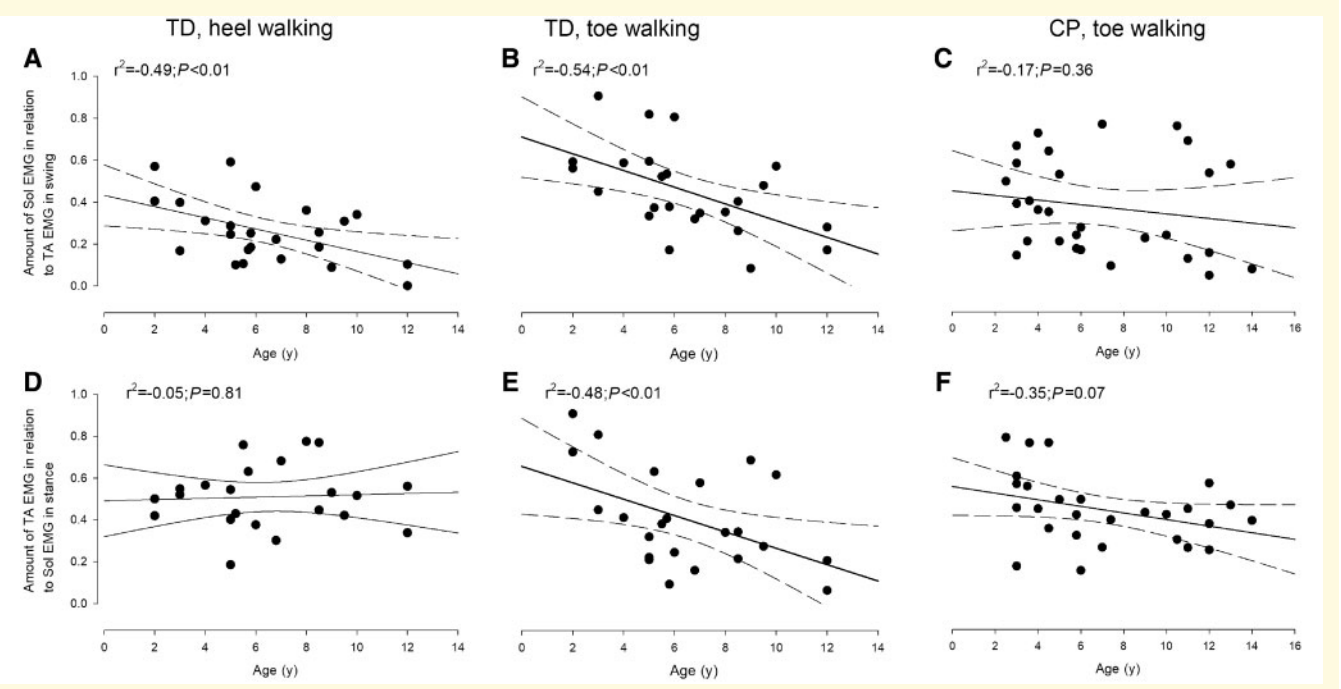

Figure 3 Age-related changes in co-contraction during heel and toe walking. Age-related changes in co-contraction across the ankle joint in late swing (**A**–**C**) and early stance (**D**–**F**) in typically-developed children during heel (**A** and **D**) and Toe walking (**B** and **E**) and in cerebral palsy children (**C** and **F**). Each symbol indicates data from one child. Full lines indicate regression lines calculated for the populations of children. Dashed lines indicate 95% confidence intervals. Correlation coefficients and level of statistical significance are given in the upper left corner of each graph. CP = cerebral palsy; Sol = soleus muscle; TA = tibialis anterior muscle; TD = typically-developing.

typically-developed children when compared to younger typically-developed children (Fig. 4A). The amount of heel drop following ground contact thus increased with age in typically-developed children when toe walking (Fig. 4A and B; $r^2 = 0.27$; $P < 0.01$). A similar trend was also observed in children with cerebral palsy, but it did not reach statistical significance (Fig. 4B; $r^2 = 0.14$; $P = 0.06$). Since co-contraction of antagonist muscles is an efficient way of stabilizing the ankle joint position, we calculated the total amount of EMG activity in the tibialis anterior and soleus muscles in the 200-ms period after ground contact to determine if the stability of the joint position after ground contact was related to tibialis anterior and soleus muscle co-contraction. As can be seen in Fig. 4C this was the case: children who co-activated the ankle muscles showed significantly less drop of the heel following ground contact compared to children and adults who showed less muscle co-activation (Fig. 4C; $r^2 = 0.39$; $P < 0.0001$). A similar relation was not observed for children with cerebral palsy (Fig. 4D; $r^2 = 0.0001$; $P = 0.95$). This indicates that the youngest children walked with a stiffer ankle joint with less movement induced by ground contact due to greater co-activation of antagonist muscles, whereas older children and adults allowed greater movement of the joint after ground contact.

Despite the larger ankle joint movement following ground contact, the oldest children and the adults showed little step-to-step variability in the size of the movement (Fig. 4E). The step-to-step variability in the heel drop following ground contact thus decreased significantly with age and was lowest in adults (Fig. 4E; $r^2 = 0.057$; $P < 0.001$). A similar relationship was not observed in children with cerebral palsy (Fig. 4F; $r^2 = 0.00001$; $P = 0.98$). Interestingly, the step-to-step variability in heel drop was unrelated to the total amount of EMG activity in the tibialis anterior and soleus muscles after ground contact. Co-contraction as such thus did not seem to relate to the step-to-step variability in the ankle joint position at ground contact (Fig. 4G; $r^2 = 0.07$; $P = 0.2$). This was also the case in children with cerebral palsy (Fig. 4H; $r^2 = 0.04$; $P = 0.3$).

Cumulant density and coherence analysis of coupling between antagonistic ankle muscles

We calculated the cumulant density and coherence functions between simultaneous tibialis anterior and soleus EMG activities within the 200-ms period after ground contact to investigate whether the common drive to agonist and antagonist muscle motor neuron pools during co-contraction was related to developmental reduction of step-to-step variability in heel drop. Figure 5 shows examples of the different observed patterns of coherence and cumulant density. In adults, there was no evidence for tibialis anterior-soleus motor unit synchronization in the cumulant

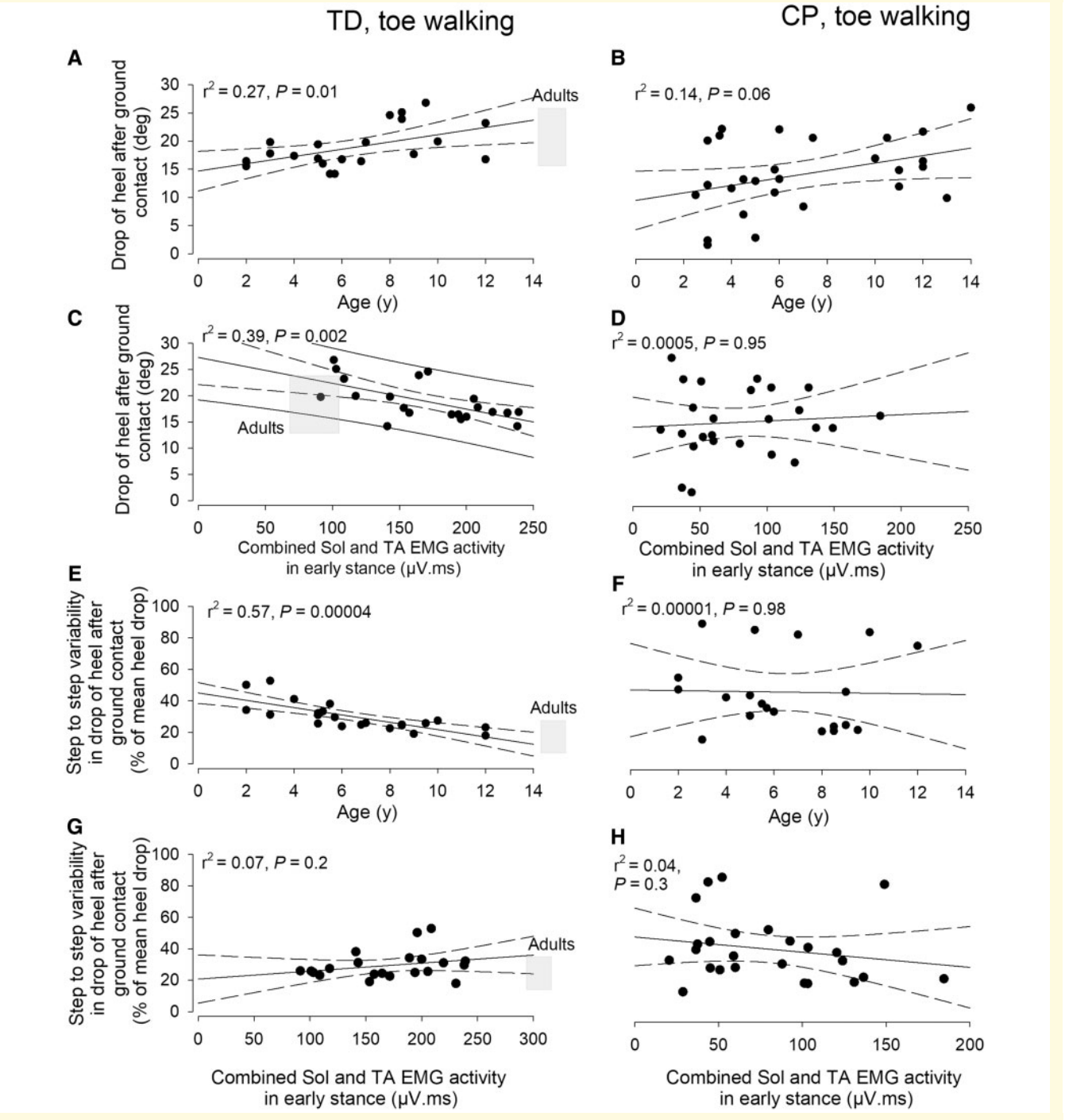

Figure 4 Age-related changes in ankle joint control at ground contact in typically-developed children (A, C, E and G) and children with cerebral palsy (B, D, F and H). Each symbol indicates data from one child. Full lines indicate regression lines calculated for the populations of children. Dashed lines indicate 95% confidence intervals. Correlation coefficients and level of statistical significance are given in the upper left corner of each graph. The range of measurements from adults is indicated as a grey rectangle in the graphs. CP = cerebral palsy; Sol = soleus muscle; TA = tibialis anterior muscle; TD = typically-developing.

density function and only weak coherence was observed in the frequency range 5–15 Hz, as illustrated for the participant in Fig. 5A. In comparison to adults, younger typically-developed children and children with cerebral palsy showed stronger EMG-EMG coherence (Fig. 6). Three patterns of EMG-EMG coupling were identified. The first pattern was detected in two typically-developed and three children with cerebral palsy (illustrated by the 3-year-old typically-developed child in Fig. 5B). In these children coherence at frequencies below 20 Hz was observed and in the

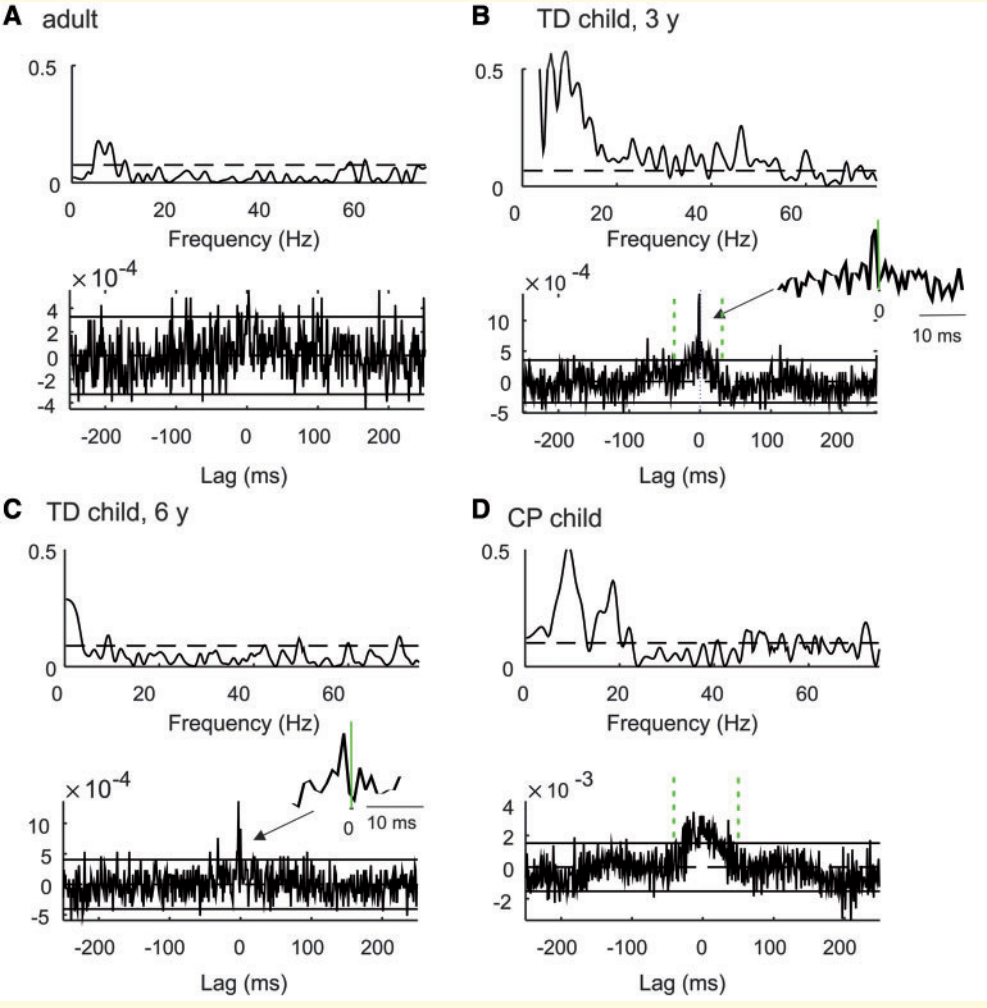

Figure 5 Coherence and cumulant density function. Examples of coherence (*upper graphs*) and cumulant density function (*lower graphs*) calculated for an adult (**A**), a 3-year-old typically-developed child (**B**), a 6-year-old typically-developed child (**C**) and a 6-year-old child with cerebral palsy (**D**). For the coherence graphs the abscissa is the frequency in Hz, whereas for the cumulant density graphs the abscissa is the lag either side of time zero in milliseconds. In **B** and **C,** the cumulant density function is also shown as an inset with expanded time scale to illustrate that the central peak was not at time zero (indicated by full green line). This demonstrates that cross-talk was not responsible for the narrow synchronization peak. In **B** and **D** dashed, vertical green lines indicate the duration of broad peak synchronization. CP = cerebral palsy; Sol = soleus muscle; TA = tibialis anterior muscle; TD = typically-developing.

associated EMG-EMG cumulant density function there was a narrow central peak of synchronization (peak duration < 10 ms) situated on top of a peak of broader EMG-EMG synchronization (> 100 ms duration; indicated by vertical dashed lines). The second pattern was detected in seven typically-developed and two children with cerebral palsy (represented by the 6-year-old typically-developed child in Fig 5C). This was characterized by narrow peak of EMG-EMG synchronization in the cumulant density function without broader peak synchronization and with minimal coherence between the two muscles except at low frequencies (< 5 Hz). Finally, in three typically-developed and nine children with cerebral palsy (represented by the 6-year-old child with cerebral palsy in Fig. 5D) no narrow central peak was observed in the cumulant density function, but a broad peak of synchronization was detected (marked by vertical dashed lines in Fig. 5D). This was associated with coherence below 20 Hz. Coherence at higher frequencies was only observed rarely. Table 2 summarizes the presence of key features in the cumulant density function for typically-developed and children with cerebral palsy < 6 years, 6–10 years, > 10 years and typically-developed adults. Importantly, EMG-EMG synchronization indicated by a peak in the cumulant density function was only a feature in typically-developed children < 10 years of age. In a significant number of children with cerebral palsy motor unit synchronization between the agonist and antagonist muscles persisted. Chi-square analysis showed a significant difference in the distribution of features between typically-developed and cerebral palsy as well as between the different typically-developed age groups ($P < 0.01$).

Coherence and synchronization between the antagonist muscle EMGs were related to the age of the participant and step-to-step variability in the heel drop after ground contact (Fig. 6). The different symbols in the graphs indicate observation of different features in the cumulant density function for each individual participant: black circles indicate no peak of synchronization, red symbols indicate short lasting central synchronization and open circles indicate broad peak synchronization (in some cases with short lasting synchronization on top of a broad peak). As can be seen coherence decreased significantly with age in typically-developed children to reach adult values in 10–12-year-old children (Fig. 6A; $r^2 = 0.35$; $P = 0.003$). A similar decline in coherence was not observed in children with cerebral palsy (Fig. 6B; $r^2 = 0.07$; $P = 0.2$). Broad peak synchronization was seen in the youngest children with cerebral palsy and the typically-developed children. With maturity the EMG-EMG synchronization was lost in typically-developed children, but not in some of the children with cerebral palsy. No age-related changes in coherence in the 15–35 Hz and 35–60 Hz frequency bands were found (not shown).

Step to step variability of the heel drop following ground contact was positively correlated with the amount of coherence in the typically-developed children (Fig. 6C; $r^2 = 0.3$; $P = 0.007$) as well as in the children with cerebral palsy (Fig. 6D; $r^2 = 0.24$; $P = 0.01$). Thus, improved control of heel movement at heel strike was associated with decreased agonist-antagonist coherence.

Table 2 Distribution of short-term and broad peak (long-duration) synchronization in the cumulant density function from children and adults

	Short term, %	Broad, %	None, %
Typically developing			
<6 years	50	37.5	12.5
6–10 years	31	15	54
>10 years	0	0	100
Adults	0	0	100
Cerebral palsy			
<6 years	18	54	27
6–10 years	0	75	25
>10 years	20	20	60

Observations from typically-developing individuals are given in the upper part of the table and observations from children with cerebral palsy are given in the lower part. All observations are given as a percentage of all individuals in the respective age groups.

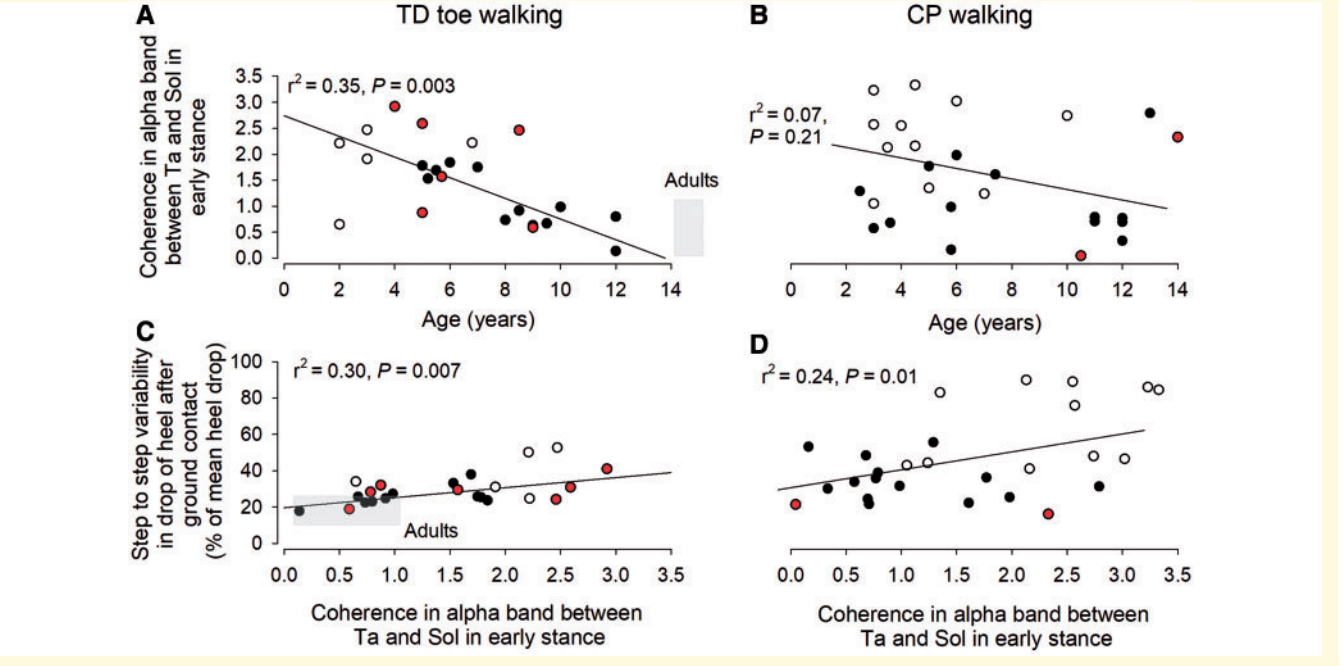

Figure 6 Age related differences in alpha band coherence. Age related differences in alpha band coherence (cumulative sum of log coherence) between antagonist muscles (**A** and **B**) and the relation between step to step variability of heel drop and alpha band coherence (**C** and **D**) in typically-developed children (**A** and **C**) and children with cerebral palsy (**B** and **D**). White circles = no EMG-EMG synchronization; black triangles = broad peak synchronization; red circles = short-term synchronization; red triangles = short-term synchronization + broad peak synchronization. Each symbol indicates data from one child. Full lines indicate regression lines calculated for the populations of children (including all data in the plots regardless of specific feature in the cumulant density function). Correlation coefficients and level of statistical significance are given in the upper left corner of each graph. The grey rectangles indicate the range of coherence in adults (**A**) and the level of step to step variability (*y*-axis) as well as the level of alpha band coherence (*x*-axis) in adults. CP = cerebral palsy; Sol = soleus muscle; TA = tibialis anterior muscle; TD = typically-developing.

Discussion

In adults, toe walking is controlled by a feedforward motor program, which involves prediction of the mechanical consequences of ground impact and ensures constant step-to-step control of the ankle joint position (Lorentzen *et al.*, 2018). This feedforward program is characterized by selective and well-timed activation of plantar flexors just prior to ground contact and large plantar flexor activity after ground contact with no or little simultaneous ankle dorsi flexor activity. In the present study, we confirm the differences in EMG patterns between heel and toe strike walking in adults and show that in typically-developed children an adult pattern of heel strike and toe strike EMGs is achieved by age 10 years. We next focused on the normal and impaired maturation of the EMG patterns associated with the toe walking program in typically-developed children and children with cerebral palsy and assessed if—and when—the adult EMG pattern associated with feedforward motor control of toe walking was achieved.

Biomechanical considerations of differences in toe gait in children and adults

When walking on toes, the weight of the body has to be supported by contraction of muscles around the ankle joint to maintain a stable position of the joint at the impact with the ground. As shown in the study by Lorentzen *et al.* (2018) and further explored here, adults achieve this by making an anticipatory contraction of ankle plantar flexor muscles prior to ground contact and they maintain a high activation of plantar flexor muscle EMG throughout the early part of the stance phase of gait. In doing this, adult participants minimize co-activation of antagonists (tibialis anterior is silent throughout late swing and early stance) and as a result it can accommodate a relatively large descent of the heel with each step, with interestingly a remarkably low step-to-step variability in the size of the descent. As shown by Lorentzen *et al.* (2018) during toe walking, at this point in the step cycle muscle activation is dependent on feedforward central drive and is not influenced by afferent feedback: there is no change in muscle activation when sensory afferents are blocked by ischaemia or when the ground is unexpectedly removed (Gorassini *et al.*, 1994). Thus, in adults during toe walking there is a prediction of the sensory consequences of the impact with the ground (including the resulting stretch of the plantar flexor musculo-tendinous complex) to exert a precise feedforward control of the ankle joint position with each step (Lorentzen *et al.*, 2018).

Typically-developed children below 10–12 years, in contrast to typically-developed adults, use co-contraction around the ankle joint as a control strategy during toe walking throughout most of the gait cycle including the point leading up to and just after ground contact. Co-contraction between antagonists is an efficient way of stabilizing the position of a joint, since it increases the stiffness of the joint considerably and diminishes the degrees of freedom of movement (Smith, 1981; Nielsen, 1998; Osu *et al.*, 2009). Antagonist-agonist muscle co-contraction is observed in the early stages of motor learning (for example, during pistol shooting or learning to throw a dart; Smith, 1981). In the lower limbs co-contraction assists motor learning during ski training (Hong and Newell, 2006), when balancing on a beam (Llewellyn *et al.*, 1990; Nielsen, 1998) or when walking over a slippery surface (Chambers and Cham, 2007). Muscle co-contraction has been demonstrated to be the most optimal strategy when accommodating to an external perturbation applied in an unpredictable manner during a reaching task (Burdet *et al.*, 2001). We suggest that the age-related decline in co-contraction and its close relation to reduced step-to-step variability in ankle joint position, reflects developmental and motor learning processes in which the timing of the sensory consequences of ground impact are improved. As a consequence, the degrees of freedom can be relaxed through age-related reduction of co-contraction, culminating in an adult pattern of control of toe gait between the ages of 10 and 12 years. This maturational process closely resembles the reduction in co-contraction observed in relation to sensorimotor learning of a novel complex task and we speculate that Bayesian learning processes involving predictive coding of the sensory consequences of movement are similarly involved (Burdet *et al.*, 2001; Franklin *et al.*, 2003, 2007; Shadmehr *et al.*, 2010; Wolpert *et al.*, 2011; Wolpert, 2014; Wolpert and Flanagan, 2016). This reduction of muscle co-contraction with increasing age is impaired in children with cerebral palsy.

Central common drive to antagonists during toe walking in typically-developed children

We used frequency- and time-domain synchronization analysis to characterize the nature of the central drive underlying the co-activation of the antagonist muscles in the children during toe walking. We found no or little activity in the 15–35 Hz and 35–60 Hz frequency bands, which have been associated to central drive to individual muscles during gait, posture and isometric upper limb tasks and agonist muscle pairs in adults (Farmer, 1998; Halliday *et al.*, 2003; Petersen *et al.*, 2012). Instead, 5–15 Hz (alpha rhythm) oscillatory common drive to antagonists around ground impact was observed.

Oscillations in movement and EMG motor signals observed during movement have since long been related to physiological (or essential) tremor and are known to be increased by muscle fatigue (Furness *et al.*, 1977; Loscher *et al.*, 1996; McAuley *et al.*, 1997; Hansen *et al.*, 2002). Oscillations have been particularly well studied during slow finger movements, which occur in a ratchet

like fashion with intermittent bursts of agonist and antagonist activity united by ~8–10 Hz rhythmicity (Wessberg and Vallbo, 1995, 1996). Coherence at this frequency in contrast, to beta and gamma rhythms, spreads over large anatomical distances and across body segments, for example, between left and right leg muscles and between eye tracking and finger tracking movements (McAuley *et al.*, 1997, 1999). The exact mechanism of generation of 8–10 Hz oscillations is unknown, but there is evidence that they reflect 8–10 Hz intermittency in cerebellar output pathways (Timmermann *et al.*, 2004; Pedrosa *et al.*, 2014) and that they may be enhanced—at least for lower limb muscles—by sensory input (Cresswell and Loscher, 2000; Hansen and Nielsen, 2004). If our interpretation that children under 10–12 years of age have not yet incorporated precise prediction of the sensory consequences of ground impact during toe walking in an optimal feedforward motor program is correct, it is possible that the sensory input related to ground contact, such as stretch of the plantarflexor musculo-tendinous complex, is responsible for the larger 5–15 Hz oscillations in the younger children. The reduction of 5–15 Hz oscillations as the children grow older is then explained by a gradual reduction of the central effects of the sensory input at ground contact, which would be consistent with an improved prediction of the sensory consequences of the movement.

The association of 5–15 Hz oscillations with long-duration EMG-EMG synchronization in several of the younger children, and the persistence of agonist-antagonist synchronization in a number of the mature children with cerebral palsy, is of interest. Long-duration (broad-peak) EMG-EMG synchronization has been suggested from previous work in human and animals to be related to presynaptic synchronization of activity in a large group of different last-order neurons—in all likelihood at spinal level (Kirkwood and Sears, 1978; Kirkwood *et al.*, 1982; Datta *et al.*, 1991; Kirkwood, 2016). It is probable that co-activation of antagonist ankle muscles after ground impact in children younger than 10–12 years is generated through a group of spinal interneurons, which receive significant 5–15 Hz common drive from cerebellar output pathways (e.g. via vestibulospinal or other descending pathways), which is enhanced by sensory input at ground impact. Whilst we are not able to determine the precise origin of the 5–15 Hz common drive to the agonist and antagonist muscles, the above considerations indicate that it is unlikely to be cortical in origin. We note also that during development rhythm-generation interneuronal networks responsible for the basic locomotor rhythm become more efficiently controlled by supraspinal centres and are less influenced by sensory input as children grow older and improve their gait ability (Kiehn, 2016). This may also explain the reduction of EMG-EMG coherence with age.

Short-term EMG synchronization, which is an indication of presynaptic drive to the motor neurons from common last-order neurons (Kirkwood and Sears, 1978; Datta and Stephens, 1990; Kirkwood, 2016), was also observed in some typically-developed children and children with cerebral palsy, but in none of the typically-developed adults. These narrow central peaks did not appear to be related to cross-talk, since they did not show features that are normally associated to cross-talk (peak had a small lag in relation to zero; also coherence between muscle recordings was not observed or only in distinct frequency bands; Petersen *et al.*, 2010; Willerslev-Olsen *et al.*, 2015). Similar short-term synchronization of antagonist ankle motor units has been reported previously in adults during static co-contraction tasks (Nielsen and Kagamihara, 1994; Hansen *et al.*, 2002) and there is also evidence from primate studies of descending pathways with collaterals to antagonist motor pools (Smith, 1981; Fetz and Cheney, 1987). Such collaterals may represent persistent connections that have not been removed during the period of development where superfluous connections are normally removed or 'pruned' and they may be redundant and without functional relevance (Gottlieb *et al.*, 1982; Myklebust *et al.*, 1982; O'Sullivan *et al.*, 1998; Gibbs *et al.*, 1999; Martin *et al.*, 2007). In the present context, it is difficult to reach any firm conclusions regarding their significance. The lack of significant common drive in the time and frequency domain in adults and mature children is consistent with restriction of this drive to motor neurons belonging to the same muscle or close synergists (Halliday *et al.*, 2003; Nielsen *et al.*, 2005; Norton and Gorassini, 2006).

Maturation of motor and sensory pathways

The age-related development of an adult-like toe walking ability in typically-developed children resembles the age-related development of corticospinal control of normal heel gait, which has been documented in other studies and has also been related to a reduction in the step-to-step variability of the ankle joint position (Petersen *et al.*, 2010, 2013). It is of note that an age-related reduction in spinal reflex transmission during gait has also been documented in children between 6 and 12 years of age; this is likely to be related to increased presynaptic inhibition of sensory afferents (Hodapp *et al.*, 2007*a*, *b*; Willerslev-Olsen *et al.*, 2014). It is probable that the findings presented here reflect similar age-related mechanisms that result in an adult gait pattern around the age of 10–12 years. Gating of sensory input (reafference) has been linked to optimization of movements where the prediction of the sensory consequences of movement becomes increasingly precise and the expected sensory information therefore increasingly irrelevant (Blakemore *et al.*, 1998; Wolpert and Flanagan, 2010; Wolpert *et al.*, 2011). Increased presynaptic inhibition with age maybe related to the learning process leading to improved gait performance observed here.

Clinical significance: findings in children with cerebral palsy

Children with cerebral palsy below 10 years of age showed a similar extent of co-activation around ground contact as young typically-developed children and they also showed a similar amount of 5–15 Hz coherence between antagonists which was correlated with larger step-to-step variability in heel drop after ground contact. Previous studies have shown also that the agonist-antagonist muscle co-contraction pattern of cerebral palsy and typically-developed children during toe walking cannot be differentiated (Davids *et al.*, 1999; Romkes and Brunner, 2007). Likewise, our data do not support the idea that excessive agonist-antagonist co-contraction *per se* is the cause of toe walking in children with cerebral palsy. Although our data cannot determine whether muscle shortening in children with cerebral palsy forces them to toe walk (Smith *et al.*, 2011; Gough and Shortland, 2012; Barber and Boyd, 2016; Herskind *et al.*, 2016), it does suggest that the co-contraction pattern is part of an age-dependent control strategy for toe walking in both typically-developed and cerebral palsy below the age of 10–12 years. Importantly, the co-contraction pattern persists in the children with cerebral palsy and a mature pattern of toe walking gait is not achieved.

In contrast to typically-developed children, the amount of co-contraction of the antagonist muscles, the 5–15 Hz coherence and the step-to-step variability of heel drop at ground contact did not decrease with age in the children with cerebral palsy. In the children with cerebral palsy there was also no clear decline with age in broad peak EMG-EMG synchronization and the broad peak synchronization pattern was present in ~40% of the older children with cerebral palsy i.e. an adult pattern of zero EMG-EMG synchronization was never reached. This suggests that the normal maturation of an adult feedforward motor program for toe walking is arrested in children with cerebral palsy and that there is a pathological persistence of a central drive that is common to the agonist and antagonist motor neurons. Previous studies have similarly demonstrated an arrested maturation of transmission in sensory and motor pathways in children with cerebral palsy in the same age range as studied here (i.e. 6–14 years; Hodapp *et al.*, 2007*a*, *b*; Petersen *et al.*, 2013; Willerslev-Olsen *et al.*, 2014).

One interpretation of these observations is that children with cerebral palsy may have more difficulty when compared to typically-developed children in acquiring the appropriate adult feedforward control of toe walking due to the effect of the brain lesion on motor and/or sensory signalling. We speculate that CNS lesions resulting in cerebral palsy may lower the signal to noise ratios in both motor and sensory systems. This in turn will interfere with the optimization of an internal model of the walking based on comparison between predicted and actual sensory consequences of movement (Shadmehr *et al.*, 2010; Wolpert *et al.*, 2011; Wolpert and Flanagan, 2016). We note that simulation studies have indicated that in situations where signal to noise ratios are low, Bayesian models of motor learning will converge on a solution where movements are slow and stiff; i.e. they will involve co-contraction of antagonists similar to that observed in cerebral palsy (Kording and Wolpert, 2004; Osu *et al.*, 2009).

Co-contraction is a reasonable strategy to adopt when muscles are weak, which is the case for ankle muscles in the majority of children with cerebral palsy, including older children (Wiley and Damiano, 1998; Damiano *et al.*, 2001; Damiano, 2006; Schweizer *et al.*, 2013). Co-contraction of the ankle antagonists around ground contact may continue to be a simple necessity for the children with cerebral palsy in order to maintain stability around the joint in the absence of sufficient plantar flexor muscle power (Schweizer *et al.*, 2013). It should also be noted that we had insufficient age-matched data to allow for an investigation of possible differences between children with hemiplegia and diplegia, or a possible relation to the severity of cerebral palsy or gait speed. Such issues will require further studies.

The idea that toe walking in children with cerebral palsy may be an adaptive neural computational solution to the problems associated to reduced sensory and motor signal-to-noise ratios and weak muscles, opens a window for a new approach to physical therapy in children with cerebral palsy guided by these principals. We suggest that rather than aiming to diminish presumed excessive muscle activity through anti-spasticity medication, there should be greater focus on assisting a child's learning of the most efficient gait patterns taking the biomechanical constraints into account. This may be a question of providing clearer sensory feedback signals or longer lasting gait training to ensure learning despite of impaired central mechanisms.

Conclusion

We conclude that typically-developed children during toe walking develop a mature feedforward control of ankle muscle activity which involves little co-contraction during toe walking by the age of 10–12 years. Children with cerebral palsy, in contrast, maintain a co-contraction activation pattern when toe walking which is associated with pathological common drive to antagonist-agonist motoneurone pools. These findings are important for our understanding of the pathophysiology and treatment of toe walking.

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Competing interests

The authors report no competing interests.

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