RESEARCH ARTICLE

Contribution of corticospinal drive to ankle plantar flexor muscle activation during gait in adults with cerebral palsy

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Abstract

Impaired plantar flexor muscle activation during push-off in late stance contributes importantly to reduced gait ability in adults with cerebral palsy (CP). Here we used low-intensity transcranial magnetic stimulation (TMS) to suppress soleus EMG activity during push-off as an estimate of corticospinal drive in CP adults and neurologically intact (NI) adults. Ten CP adults (age 34 years, SD 14.6, GMFCS I–II) and ten NI adults (age 33 years, SD 9.8) walked on a treadmill at their preferred walking speed. TMS of the leg motor cortex was elicited just prior to push-off during gait at intensities below threshold for motor-evoked potentials. Soleus EMG from steps with and without TMS were averaged and compared. Control experiments were performed while standing and in NI adults during gait at slow speed. TMS induced a suppression at a latency of about 40 ms. This suppression was similar in the two populations when differences in control EMG and gait speed were taken into account (CP 18%, NI 16%). The threshold of the suppression was higher in CP adults. The findings suggest that corticospinal drive to ankle plantar flexors at push-off is comparable in CP and NI adults. The higher threshold of the suppression in CP adults may reflect downregulation of cortical inhibition to facilitate corticospinal drive. Interventions aiming to facilitate excitability in cortical networks may contribute to maintain or even improve efficient gait in CP adults.

Keywords Cerebral palsy · Corticospinal drive · Plantar flexor muscles · Push-off

Introduction

Cerebral palsy (CP) is caused by a non-progressive lesion of the developing brain primarily characterized by disordered movement and posture (Graham et al. 2016). Gait impairment has a crucial impact on physical independence, social participation and quality of life in adults with CP (Andersson and Mattsson 2001; Jahnsen et al. 2004; Morgan and McGinley 2014; Verschuren et al. 2018).

Common gait characteristics in persons with CP are reduced gait speed, reduced and asymmetrical step length with increased energy expenditure (Winters et al. 1987; Roche et al. 2014; Morgan et al. 2016). Weak plantar flexor muscles have been found to be associated with impaired

propulsive force and reduced gait speed in both children (Olney et al. 1990; Barber et al. 2017) and adults with CP (Riad et al. 2012; Roche et al. 2014). Propulsion is generated during the push-off phase in late stance of the gait cycle, where force generated by plantar flexor muscles is transferred to the ground propelling the body upward and forward (Winters et al. 1987; Neptune et al. 2001; Honeine et al. 2014). The neural drive to the plantar flexors is the result of integration of the input to spinal motor neurons from a number of different sources all of which may potentially be affected in CP. Transmission in specific spinal pathways contributes to the coordination of muscle activity during movement, including gait, and have been shown to be impaired in adults with CP (Achache et al. 2010). Sensory feedback mechanisms, which contribute to the activation of the motor neurons during gait, have also been found to be impaired in persons with CP (Willerslev-Olsen et al. 2014; Frisk et al. 2017). This likely reflects that sensory feedback is not sufficiently integrated with central motor commands to generate an efficient muscle activation at push-off (Nielsen 2002, 2003). Among the descending pathways, the corticospinal tract has received the most interest because of its

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dominant importance for voluntary movements in humans, including gait (Petersen et al. 2003, 2012). Damage to the corticospinal tract is a characteristic of spastic CP and in line with this, previous studies using coherence analysis of muscular activity have implied that corticospinal drive to ankle dorsiflexors during the swing phase of gait is impaired in children with CP (Petersen et al. 2013; Willerslev-Olsen et al. 2015). Investigating how the corticospinal drive contributes to plantar flexor muscle activation at the time of push-off may provide information about abnormal activation of plantar flexor muscles, which is likely to be involved in inefficient propulsion and thus reduced gait speed in individuals with CP.

Transcranial magnetic stimulation (TMS) provides one way of studying the corticospinal pathway in human subjects. Several studies have measured motor-evoked potentials (MEPs) at rest or during static contraction to obtain a measure of the integrity of the corticospinal pathways, which has then been related to gait ability in people with lesions of the central nervous system (Palmer et al. 2016, 2017; Barthelemy et al. 2010, 2013). It is a general finding from these studies that reduced amplitude and prolonged latency of MEPs in ankle muscles are weakly to moderately correlated to gait speed, indicating that impaired transmission in the corticospinal pathways contributes to reduced gait function in these subjects (Palmer et al. 2016). However, there are at least two main problems in the interpretation of these studies. First, measurements performed at rest or during static contraction may have little relevance for the functional transmission in the corticospinal tract during gait. Second, MEPs do not only reflect excitability of the corticospinal neurons in the motor cortex as is often wrongly stated, but also the excitability of the spinal motor neurons and the excitability of other subcortical neurons, including spinal interneurons, in indirect corticospinal pathways (see Petersen et al. 2003 for discussion). The first of these problems may be addressed by measuring MEPs during gait. This has been done in neurologically intact (NI) subjects showing that MEPs in ankle muscles are modulated with the gait cycle as a possible indication of changes in transmission in the corticospinal pathways (Schubert et al. 1997; Petersen et al. 1998, 2001; Capaday et al. 1999). To our knowledge, MEPs have not been measured during gait following lesions of the central nervous system. One possible way of addressing the second problem in MEP measurements is to evaluate the suppression of the EMG activity elicited by subthreshold TMS (Davey et al. 1994; Petersen et al. 2001; Barthelemy et al. 2010). This technique was introduced by Davey et al. (1994) for the upper limb during static contraction and takes advantage of a lower threshold to TMS stimulation for cortical inhibitory interneurons than for the corticospinal projection neurons. It has been shown that low-intensity TMS do not produce descending volleys in the corticospinal tract

by recordings from epidural space in the spinal cord (Di Lazzaro et al. 1998b). This indicates that the suppression is caused by activation of cortical inhibitory interneurons, which project to corticospinal neurons and reduce their firing activity, so that their contribution to the EMG activity is reduced (Davey et al. 1994; Nielsen and Petersen 1995; Di Lazzaro et al. 1998a, b). At TMS intensities below MEP threshold it is possible to elicit a short-lasting suppression of voluntary EMG activity, which reflects a temporary reduction of corticospinal drive to the muscle due to the inhibitory effect elicited by TMS (Davey et al. 1994; Di Lazzaro et al. 1998b; Petersen et al. 2001; Zuur 2013). Davey et al. (1998) used this method during isometric muscle contractions of the thenar muscle in patients with spinal cord injury (SCI). This study found reduced EMG suppression which was suggested to be due to impaired corticospinal drive (Davey et al. 1998). Additionally, the authors also found that higher TMS intensities were required to elicit EMG suppression suggesting reduced conduction of the corticospinal drive after SCI (Davey et al. 1998). Petersen et al. (2001) introduced the technique for the lower limb during gait and demonstrated that it is possible to demonstrate a suppression of ankle muscle EMG activity in NI individuals during gait as an indication of a corticospinal contribution to the activation of the muscles (Petersen et al. 2001). To our knowledge this TMS technique has not been used to investigate corticospinal transmission during gait following central nervous lesions. In the present study we consequently investigated the corticospinal drive to the soleus EMG activity at the time of push-off in adults with CP and NI adults using low-intensity TMS to induce suppression of the ongoing soleus EMG.

We hypothesized that the contribution of the corticospinal drive to the plantar flexor muscle activation during push-off would be reduced in adults with CP with respect to NI adults as a consequence of their brain injury.

Method

Participants

Ten adults with CP (age 34 years, range 19–58) participated in the study. Since the experiments required some gait ability, only individuals with GFMCS I and II were included. Exclusion criteria were surgery and/or botulinum toxin treatment in the ankle joint or in surrounded muscles within 6 months before the experiments. Eleven NI adults (age 33 years, range 22–55) participated as a control group. All descriptive information about the enrolled participants can be seen in Table 1.

The local ethics committee of the greater area of Copenhagen approved the study (H-16028528). The experiments were performed in accordance with the Helsinki Declaration.

Table 1 Descriptive information about enrolled participants

	n	Sex (men:women)	Age (years)	Weight (kg)	Height (cm)	Paresis (diplegic:hemiplegic)	Most affected side (left:right)	GMFCS (I:II)
CP	10	7:3	34 (14.6)	67 (4.7)	174 (7.7)	3:7	5:5	5:5
NI	11	6:6	33 (9.8)	70 (15.2)	175 (10)	–	–	–

Data are reported as mean values with standard deviations in the parenthesis

CP group of participants with cerebral palsy, *NI* group of neurological intact participants, *GMFCS* Gross Motor Function Classification System

All participants received written and verbal information and written consent was obtained before the experiments.

The experiment

Evaluation of the contribution of the corticospinal drive to the soleus muscle was done by eliciting low-intensity TMS (subthreshold to MEP) to induce EMG suppression as previously done (Davey et al. 1998; Petersen et al. 2001; Barthelemy and Nielsen 2010).

The EMG suppression, which we have studied, has similarities to the so-called paired pulse short-latency intracortical inhibition (SICI) where a subthreshold TMS pulse is used to inhibit MEPs by a subsequent TMS pulse above threshold and the two may share common mechanisms. SICI is accepted to provide valuable information of intracortical inhibitory mechanisms and is generally found to be reduced in people with central motor lesions such as stroke (Bütefisch et al. 2003; Perez and Cohen 2009; Huynh et al. 2016) and CP (Berweck et al. 2008; Zewdie et al. 2017). We chose to investigate the EMG suppression rather than SICI in the present study for three main reasons. First, SICI requires that one pulse is above MEP threshold, which requires very high intensities in people with CP (Berweck et al. 2008; Vry et al. 2008). These high intensities may be uncomfortable for the participant and may disturb the gait pattern significantly. Second, the corticospinal neurons activated in the MEP may not be corticospinal neurons that are active and contribute to the muscle activity during voluntary movements. SICI therefore provides no information of the descending drive to the spinal motor neurons. Third, the use of two stimuli of the same cortical structure in close succession opens the possibility that some of the effects are related to excitability changes in axons following the first stimulus (Chan et al. 2002; Fisher et al. 2002).

Further, it is important not to confuse EMG suppression with the silent period following the MEP. In contrast to the EMG suppression, which we have studied here, the silent period is by definition caused by TMS sufficiently strong to activate both corticospinal neurons and spinal motor neurons and it is therefore in all likelihood influenced to a very large extent by spinal mechanisms, such as after hyperpolarization of the spinal motor neurons, recurrent inhibition and other inhibitory mechanisms at subcortical level (Renshaw 1941; Lloyd 1951). Determining a possible contribution of cortical inhibitory mechanisms to the silent period is therefore problematic, although such attempts have been made in children with CP (Vry et al. 2008; Parvin et al. 2017).

Experimental procedures

In the present experiment the participants walked on a treadmill with no inclination (Fig. 1a). The CP participants walked at a self-selected walking speed and NI participants walked at 3.5 km/h reflecting their preferred gait speed. To ensure that gait speed did not affect the amount of the soleus EMG suppression an additional gait trial was recorded with the NI group walking at 1.5 km/h.

The effects of TMS were recorded from the soleus and tibialis anterior (TA) muscle by electromyographic (EMG) activity using surface bipolar electrodes (Ambu Blue Sensor NF-00-S/12, Ambu, Ballerup, Denmark; recording area 0.5 cm², inter-electrode distance 2 cm). The electrodes were placed over the muscle belly of the soleus muscle and on the proximal part of TA. EMG signals were Bandpass filtered 10–1000 Hz, amplified 1000X and stored on a PC for offline analysis. The EMG signals were digitally filtered (zero-lag Butterworth fourth order filter; bandpass 10–450 Hz) before rectification. Initial foot contact was registered by a pressure-sensitive footswitch placed under the shoe and was used to initiate EMG recordings. Soleus EMG activity 50 ms prior to and 200 ms after the magnetic stimulations were chosen for the analysis.

Transcranial magnetic stimulation (TMS)

Single pulses of TMS were applied through a figure-of-eight batwing coil (loop diameter, 9 cm) over the leg area of the motor cortex using a rapid magnetic stimulator (Magstim Rapid 2 stimulator; Magstim Company Ltd, Dyfed, UK). Prior to the experiments the coil was positioned with great care slightly lateral (approximal 1.5–2 cm) to the vertex (Di Lazzaro et al. 2001). Vertex was measured as the midway between Glabella and the external occipital protuberance (sagittal orientation) and the midway between helix crus of the ears (frontal orientation). The coil was positioned

Fig. 1 a, b Illustrates different effects of TMS intensity on the soleus EMG activity: **a** shows a relative high stimulation of 63% of maximal stimulator output (MSO) inducing EMG facilitation and **b** shows a slightly lower intensity of 60% of MSO inducing EMG suppression. **c, d** Shows examples of 100 ms time windows around the time TMS was applied during push-off which induced soleus EMG suppression in a NI (**c**) and CP (**d**) participant, respectively. **e, f** Shows EMG suppression during isometric contraction of the plantar flexor muscles while standing in a NI (**e**) and CP (**f**) participant, respectively. Black arrows indicate the time of stimulation and grey-shaded areas indicate time of soleus EMG suppression. Black lines represent averaged steps with TMS and grey lines represent averaged control steps without TMS
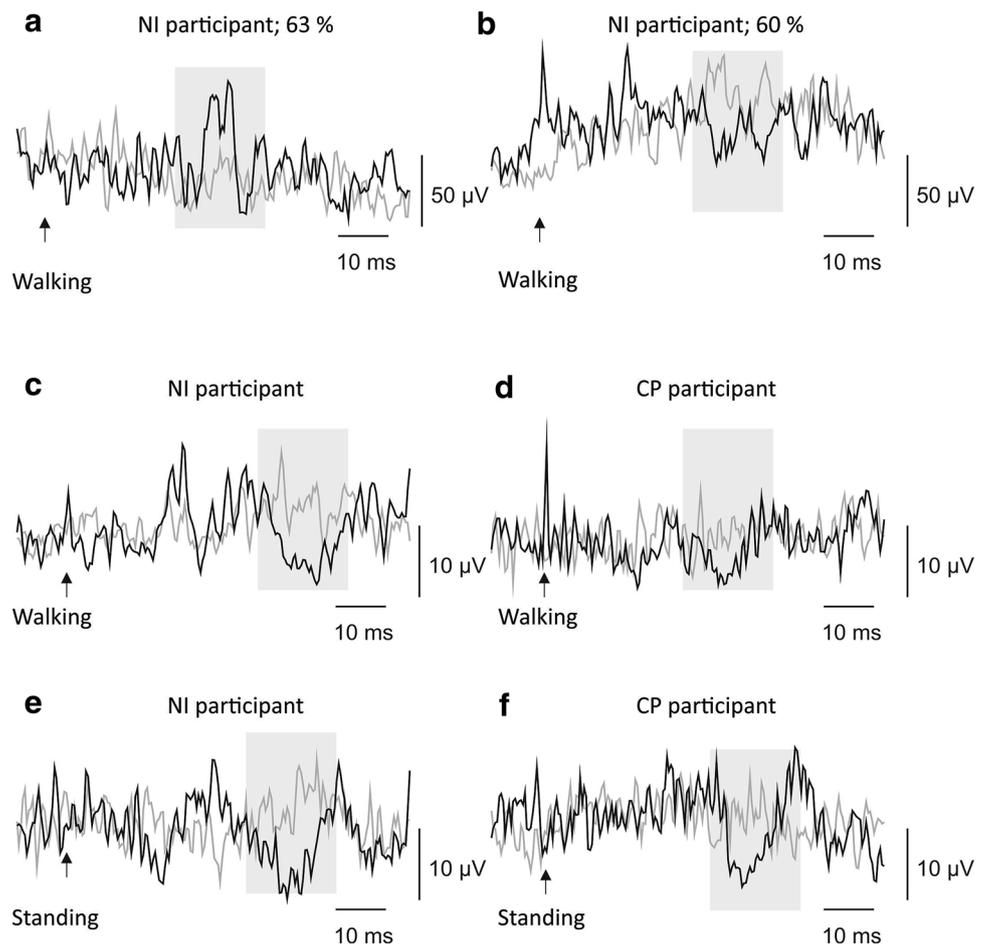
contralateral to the side of investigation with the current of the magnetic field running in a posterior–anterior direction. During the experiments, the coil was fixed very tightly with respect to the head by a harness (modified from Balgrist Tec, Zurich; Switzerland) (Schubert et al. 1997; Petersen et al. 1998) which prevented the coil from moving during the experiment. The coil position was inspected regularly during the experiments in relation to markers drawn on the scalp or a fixed hut. Additionally, at the end of the trials we ensured that it was possible to evoke an EMG facilitation using similar TMS intensities as prior to the trials. The cable attached to the coil was carried by elastic bands attached to the ceiling to reduce the weight on the participants' head and neck.

The timing of the TMS stimuli was adjusted for each participant in relation to the trigger signal at initial ground contact. It was ensured that the trigger signal was activated immediately at ground contact in each participant to ensure that stimuli were given at a constant time in relation to the gait cycle. In some of the participants with CP it was difficult to identify a clear heel strike. In such cases the foot switch was moved slightly forward on the foot. In all participants the TMS stimuli were timed with respect to the trigger to elicit a response (facilitation or suppression) just

prior to push-off during late stance phase. At this time of stance, soleus EMG had reached a peak plateau and had not yet started to decrease. Several trials were performed initially prior to the actual recordings to find this delay. In the individual participants it varied between 450 and 600 ms depending on the stride length of the participant. This procedure is similar to previous work from our laboratory when evaluating the contribution of sensory feedback to soleus EMG activity at the time of push-off (Frisk et al. 2017).

The TMS intensity was determined during walking at the time of push-off as described above. It has previously been shown that TMS at higher intensities elicit facilitation in the EMG activity of the soleus muscle around 30–35 ms after the stimulation and that the suppression occurs shortly, around 40–45 ms after the stimulation (Petersen et al. 2001). Since a facilitation has a duration around 10–15 ms, this response is likely to mask the onset and amount of the following suppression of the EMG activity. Therefore, several intensities were used to determine the optimal intensity to suppress the soleus EMG activity. Initially, relatively high stimulation intensities were used to elicit a clear facilitation in the soleus EMG activity (Fig. 1a), where the onset latency was registered. The TMS intensity was subsequently reduced

until a clear suppression of the soleus EMG occurred without an appearance of EMG facilitation prior to the suppression (Fig. 1b). During this process, timing of the EMG facilitation was used as guidance to determine the onset of the EMG suppression. The onset of the EMG suppression was determined in accordance with Petersen et al. (2001) as the first time within 40–50 ms after the stimulus where the STIM EMG was lower than the CTRL EMG for at least five consecutive milliseconds. EMG suppression did occur according to what we expected around 40–50 ms after the stimulation corresponding to approximately 10 ms after the registered time for the EMG facilitation. Average soleus EMG activity during steps with (STIM) and without TMS (CTRL) was superimposed for each participant. Suppression of the soleus EMG activity at the time of push-off is shown in Fig. 1c for a NI participant and Fig. 1d for a participant with CP. The onset of the suppression was marked with a cursor and an additional cursor marked when the STIM EMG returned to CTRL EMG. Stimulations were delivered randomly on average once every 3 steps and minimum 70 steps were recorded while applying TMS. The suppression was quantified as the area under the curve (AUC) and calculated as the difference in the rectified EMG between CTRL and STIM steps and as the percentage suppression in soleus EMG activity in respect to CTRL EMG as previously done (Petersen et al. 2001; Barthelemy and Nielsen 2010). This procedure ensured the comparability of the soleus EMG suppression between the groups in case of differences in the amount CTRL EMG.

Additionally, TMS was also applied during an isometric contraction of the plantar flexor muscles while standing as a control situation characterized as non-rhythmical voluntary contraction of the calf muscles. The participants were instructed to push both feet against the floor by plantar flexing the ankle joint, whereby the participants stood with slightly plantar-flexed ankle joint on the front foot/toes as stable in the same position as possible. The isometric contraction was ensured by visual inspection of the soleus EMG activity. Suppression of the soleus EMG during standing is shown in the Fig. 1e for a NI participant and in Fig. 1f for a participant with CP.

Data processing and statistics

Normal distribution of the obtained data was ensured using histograms, QQ plots, and Shapiro–Wilk tests.

The soleus EMG suppression evoked by TMS was used as primary outcome to describe the corticospinal contribution to the soleus muscle at the time of push-off.

Several secondary outcomes were obtained to characterize when TMS was elicited during the stance phase of walking and to describe the effect of TMS on the soleus EMG. These exploratory ad hoc analyses consisted of unpaired t tests of secondary outcomes to ensure that potential differences in the timing for eliciting TMS and gait parameters did not affect the primary outcome measure (contribution of the corticospinal drive to the soleus EMG activity). Tests regarding gait parameters and primary and secondary outcomes were corrected using the Benjamin–Hochberg method to reduce the risk of type I errors. Timing of TMS, onset, and duration of the EMG facilitation and suppression and peak EMG were normalized to the duration of the stance phase. This normalization allowed comparison between the two groups in case of differences in gait parameters.

Separate non-paired t tests were used to compare both primary and secondary measures between the NI and the CP group during walking and standing, respectively. To ensure that gait speed did not affect the amount of the EMG suppression a paired t-test was performed between walking speed at 3.5 km/h and 1.5 km/h in the NI group and a non-paired t-test between the CP group and the NI group walking at 1.5 km/h.

Additionally, correlation analysis was performed to ensure that TMS intensity and the amount of CTRL EMG did not affect the EMG suppression and whether amount of CTRL EMG and body mass were related. Furthermore, it may be speculated that larger body mass will increase the amount of CTRL EMG activity. Therefore, to ensure that the amount of CTRL EMG was not influenced by body mass, an additional correlation analysis was performed.

Results are presented as mean values with standard deviations (SD) and 95% confidence intervals (CI). The level of significance was $p = 0.05$. The statistical tests were carried out in SAS Enterprise Guide 7.1. Illustrations of the EMG activity were made in Signal 5.02 and other figures in SigmaPlot 13.0.

Results

The participants with CP walked slower than the NI group (CP: 2.2 km/h, SD 0.5, CI 1.9–2.6, NI: 3.5 km/h, SD 0, $p = 0.0005$) and had a longer duration of the stance phase at their preferred gait speed (CP: 805 ms, SD 121, CI 718–891, NI: 693 ms, SD 55.28, CI 656–730, $p = 0.025$). Area of CTRL EMG used to estimate the EMG suppression was not statistically different between the two groups (CP: 0.84 µV s, SD 0.57, CI 0.57–11.1, NI: 1.06 µV s, SD 0.58, CI 0.67–14.6, $p = 0.37$). The CP group showed significantly smaller peak soleus EMG at the time of push-off than the NI group (CP: 61 µV, SD 22, CI 45–77, NI: 126 µV, SD 54, CI 90–162, $p = 0.005$), which occurred on average 79.5 ms later in relation to heel strike (CP: 587 ms, SD 70, CI 536–637, NI: 507 ms, SD 65, CI 463–551, $p = 0.025$). Later peak soleus EMG is likely due to a longer duration of the stance phase as no difference appeared after normalizing the time

of peak soleus EMG in respect to duration of the stance phase (CP: 73% into the stance phase, SD 7, CI 69–78, NI: 73%, SD 7, CI 68–78, $p = 0.94$). Additionally, no correlation was found in either of the two groups between body mass and area of CTRL EMG (CP: corr. 0.03, $p = 0.93$, NI: corr. 0.02, $p = 0.95$).

EMG suppression during walking

During preferred gait speed the suppression of the rectified soleus EMG was slightly larger in the NI group but was not statistically significant (CP: 0.15 µV s, SD 0.06, CI 0.1–0.19, NI: 0.19 µV s, SD 0.18, CI 0.07–0.31, $p = 0.72$). Expressing the EMG suppression relative to CTRL EMG showed no difference between the two groups (CP: 18%, SD 6, CI 14–23, NI: 16%, SD 7, CI 12–21, $p = 0.80$, Fig. 2). The average onset latency defined as the time from stimulation to the onset of the soleus EMG suppression was similar for the two groups (CP: 41 ms, SD 6, CI 36–45, NI: 40 ms, SD 8, CI 35–46, $p = 0.95$). Further, no differences appeared between the groups regarding onset latency after normalization to stand phase duration (CP: 70% of stance phase duration, SD 8, CI 64–75, NI: 71%, SD 6, CI 67–75, $p = 0.89$). The duration of the soleus EMG suppression was longer in the CP group, but this was not statistically significant (CP: 16 ms, SD 5, CI 12–20, NI: 10 ms, SD 5, CI 7–13, $p = 0.16$). This was also the case after normalization to the stance phase duration (CP: 2% of stance phase duration, SD 0.5, 1.7–2.3, NI: 1.5, SD 0.8, CI 1–2, $p = 0.23$).
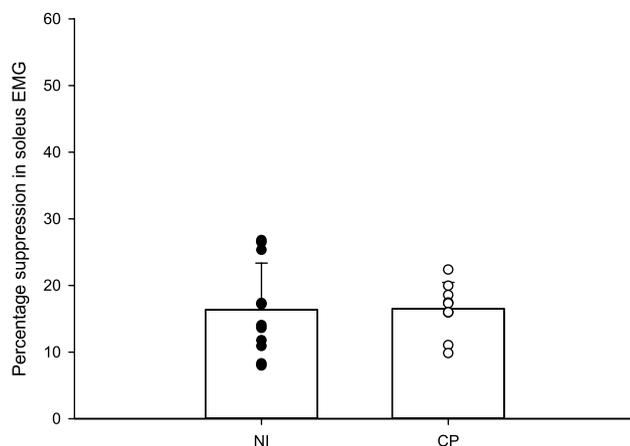

Fig. 2 Suppression of the ongoing soleus EMG activity at the time of push-off during walking, expressed as percentage suppression in respect to control EMG. The suppression was induced by eliciting subthreshold TMS over the leg area of the motor cortex contralateral to the muscles investigated. Bar charts represent group averages and error bars indicate the standard deviations. Black circles represent individual datapoints from neurological intact (NI) adults and white circles represent individual datapoints from adults with cerebral palsy (CP). A non-paired t test revealed no difference between the groups. The level of significance was < 0.05

TMS intensity

The TMS intensity required to elicit the smallest detectable EMG facilitation was slightly larger in the CP group but this did not reach statistical significance (CP: 58% of maximal stimulator output (MSO), SD 5.6, CI 54–62, NI: 51%, SD 9.8, CI 44–57, $p = 0.19$). The TMS intensity used to suppress the soleus EMG activity was also larger in the CP group than in the NI group but did not reach statistical significance (CP: 56% MSO, SD 5.5, CI 52–60, NI: 48%, SD 9.5, CI 42–54, $p = 0.19$). This was also the case when the intensity was expressed as a percentage of the TMS intensity for evoking EMG facilitation (CP: 0.86 of facilitation threshold, SD 0.3, CI 0.65–1, NI: 0.96, SD 0.01, CI 0.94–0.95, $p = 0.42$). The additional correlation analysis showed no relation between TMS intensity and the amount of EMG suppression (CP: $r = -0.1$, $p = 0.73$, NI: $r = 0.35$, $p = 0.23$, Fig. 3a), indicating that the difference in TMS intensity did not affect the results. TMS was elicited 65 ms later (from heel strike) in the CP group than in the NI group, although this was not statistically significant (CP: 495 ms after heel strike, SD 78, CI 439–551, NI: 430 ms, SD 56, CI 393–467, $p = 0.18$). Timing for eliciting TMS did not differ between the groups in respect to the duration of the stance phase (CP: 62% into the stance phase, SD 7, CI 57–67, NI: 62%, SD 6, CI 58–66, $p = 0.95$). Timing of TMS did also not differ between the two groups in relation to peak soleus EMG (CP: 86% of peak EMG, SD 8.2, CI 80–92, NI: 86%, SD 7.9, CI 81–91, $p = 0.95$), and in respect to the time distance from peak soleus EMG (CP: 92 ms, SD 41, CI 62–121, NI: 77 ms, SD 25, CI 60–94, $p = 0.60$). Further, the correlation analysis revealed no relationship between CTRL EMG and the EMG suppression in the NI group ($r = -1.13$, $p = 0.7$) or in the CP group ($r = -0.03$, $p = 0.9$) (Fig. 3b).

Effect of gait speed

To investigate whether the fast-walking speed of the NI group could explain the lack of difference in the suppression between the two groups, the NI group was asked to walk at a slower speed (1.5 km/h) in a control experiment. Here, the area of the rectified EMG suppression decreased compared with preferred gait speed, although this was not statistically significant (NI 1.5 km/h: 0.14 µV s, SD 0.08, CI 0.09–0.19, NI 3.5 km/h: 0.19 µV s, SD 0.18, CI 0.07–0.31, $p = 0.95$). Contrary, when the EMG suppression was expressed relative to the CTRL EMG the EMG suppression tended to increase while walking in slow speed, although this was not statistically significant (NI 1.5 km/h: 23%, SD 8.5, CI 17–29, NI 3.5 km/h: 16%, SD 7, CI 12–21, $p = 0.19$). Comparing the NI group while walking 1.5 km/h with the CP group, no differences appeared concerning the area of the EMG suppression (CP: 0.15 µV s, SD 0.06, CI 0.1–0.19, NI 1.5 km/h:
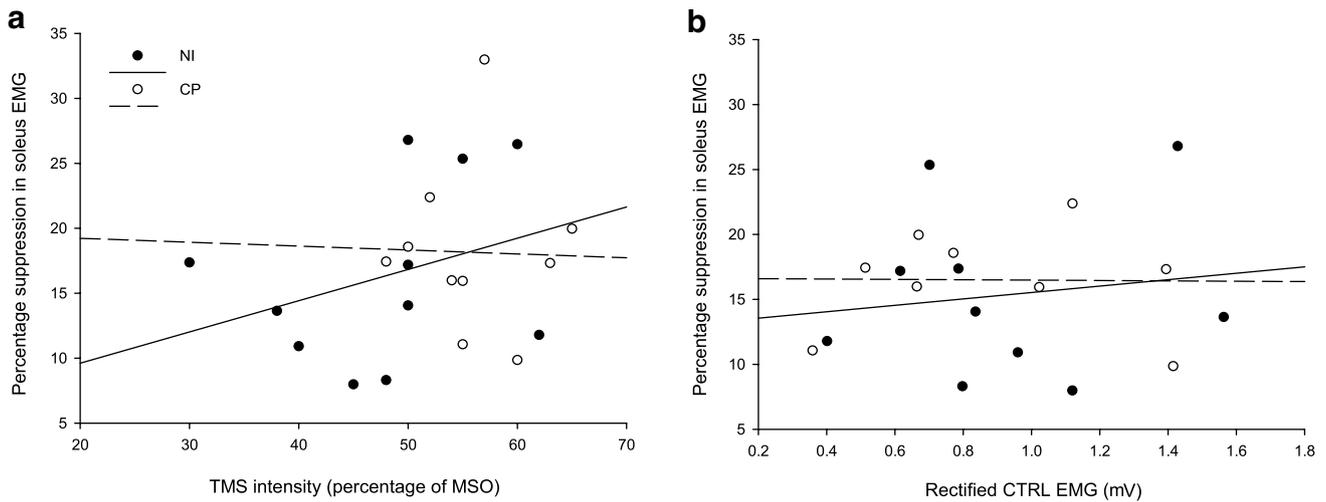
Fig. 3 Illustration of post hoc correlation analysis to ensure that the amount of soleus EMG suppression was not influenced by **a** TMS intensity and **b** the amount of CTRL EMG. No correlations appeared in either groups. The analysis was based on EMG data collected while the NI group worked at 3.5 km/h and the CP group on average 2.2 km/h. *MSO* maximal stimulator output, *CTRL EMG* control EMG from steps without TMS

14 µV s, SD 0.08, CI 0.09–0.19, $p = 0.95$). When expressed in relation to CTRL EMG the EMG suppression tended to be smaller in the CP group but this was also not statistically significant (CP: 18%, SD 6, CI 14–23, NI 1.5 km/h: 23%, SD 8, CI 17–29, $p = 0.34$). Additionally, no difference appeared between the CP group and the NI group when walking at 1.5 km/h concerning peak soleus EMG (CP: 61.2 µV, SD 21.9, CI 45–77, NI: 70.2 µV, SD 56.4, CI 56–84, $p = 0.61$).

EMG suppression while standing

TMS was also elicited during isometric contraction of the plantar flexor muscles while standing on the front foot/ toes. Here, no difference appeared between the NI and CP group in either rectified EMG (CP: 0.19 µV s, SD 0.29, CI 0.03–0.41, NI: 0.13 µV s, SD 0.08, CI 0.07–0.19, $p = 0.98$) or relative to CTRL EMG (CP: 23%, SD 13, CI 13–33, NI: 25%, SD 6, CI 20–29, $p = 0.98$) (Fig. 4). As can been seen in the CP group one participant has a very large suppression. However, excluding this outlier did not affect the estimate significantly (CP: 20%, SD 8, CI 13–16, $p = 0.14$). No difference was observed in onset latency (CP: 39 ms, SD 4, CI 36–42, NI: 39 ms, SD 9, CI 32–46, $p = 0.98$) or in duration of the soleus EMG suppression between the groups (CP: 14 ms, SD 6, CI 9–18, NI: 13 ms, SD 6, CI 9–18, $p = 0.98$). The TMS intensity used to suppress the soleus EMG activity while standing was also not different between the groups (CP: 51% of maximal stimulator output (MSO), SD 4, CI 48–54, NI: 49% MSO, SD 11, CI 41–58, $p = 0.98$). Further, no statistical difference was observed on area of CTRL EMG between the groups (CP: 0.62 µV s, SD 0.53, CI 0.21–1.03, NI: 0.50 µV s, SD 0.21, CI 0.33–0.66, $p = 0.98$).
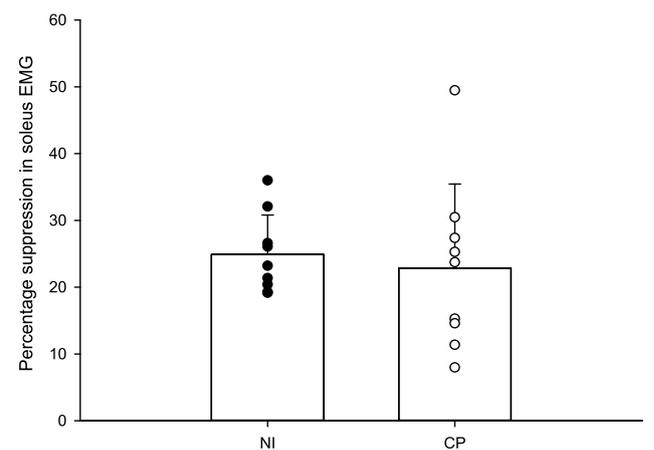

Fig. 4 Suppression of the soleus EMG activity during isometric contraction of the plantar flexor muscles while standing on the front foot/ toes. The suppression is expressed as the percentage suppression in respect to control EMG. The suppression was induced by eliciting subthreshold TMS over the leg area of the motor cortex contralateral to the muscles investigated. Bar charts represent group averages and error bars indicate the standard deviations. Black circles represent individual datapoints from neurological intact (NI) adults and white circles represent individual datapoints from adults with cerebral palsy (CP). A non-paired t-test revealed no difference between the groups. The level of significance was < 0.05. Excluded the outlier in the CP group did not affect the estimate

Discussion

The main finding of this study is that the amount of suppression of soleus EMG elicited by TMS in late stance just prior to push-off was similar in adults with CP and NI

adults when taking differences in CTRL EMG and walking speed into account. These findings suggest that corticospinal drive to ankle plantar flexors at push-off is comparable between the two populations.

Is corticospinal drive to ankle plantar flexors during push-off altered in adults with CP?

The EMG suppression was slightly smaller in the rectified soleus EMG in adults with CP than in NI adults when the two populations walked at their respective preferred walking speed, although this was not statistically different. When the larger EMG activity in NI adults was taken into account by expressing the EMG suppression relative to CTRL EMG or when NI individuals walked at slow gait speed where the CTRL EMG was comparable to that of the CP population, no difference in the suppression was observed. This indicates that there were no major differences in the corticospinal drive to plantar flexors in the two populations. This is in contrast to Davey et al. (1998) who found reduced EMG suppression in individuals with SCI. However, at least three factors should be considered to interpret our findings. Firstly, it must be assumed that the adults with CP walked at a speed closer to their maximal gait speed than the NI adults who could easily walk much faster than they did and even run if necessary. It may therefore be assumed that the NI adults would be able also to increase corticospinal drive significantly more than what was the case during the experiments, whereas this may not be the case for the CP population. A difference between the two populations might therefore have been demonstrated if a more demanding task for the NI adults had been used for comparison.

A second factor that needs to be considered is that higher intensities of TMS were required to reach threshold for EMG facilitation and the EMG suppression in the CP group than in NI group. This should be interpreted with caution since this was not a statistically significant observation ($p = 0.19$). However, the observation is similar to previous studies in individuals with CP (Berweck et al. 2008; Vry et al. 2008; Parvin et al. 2017) poststroke (Bütefisch et al. 2003; Huynh et al. 2016; Palmer et al. 2016, 2017) and SCI (Davey et al. 1998) for eliciting MEPs and SICI. The higher intensity of TMS required to elicit the suppression may indicate that the cortical inhibitory interneurons have a lower excitability in adults with CP than in NI adults. If so, the similar size of the suppression may conceal a difference in the corticospinal drive in the two populations.

Thirdly, it should be considered that observations in relation to TMS do not necessarily apply to normal physiological conditions. It is reasonable to assume that adults with CP have to use more mental effort to activate the neural circuits in the motor cortex than NI adults at a given gait speed. This would not show up as a difference in the EMG suppression

(or corticospinal drive), but may be one reason why fatigue is often reported among adults with CP as a contributing factor to limitation of ambulation (Morgan et al. 2016; Benner et al. 2017; Lundh et al. 2018).

Methodological consideration

The interpretation of the amount of the EMG suppression must also be taken into consideration. While there is good evidence to support that the EMG suppression provides a measure of corticospinal drive, it is far less certain that larger or smaller EMG suppression when comparing different tasks or different populations (as we have done in the present study) simply reflect larger or smaller corticospinal drive. The amount of the EMG suppression does not only depend on how much of the EMG is generated by corticospinal drive, but also how easily the cortical inhibitory interneurons, which suppress the activity of the corticospinal neurons, are activated by TMS. If the excitability of the interneurons is smaller in one population than in another, it may be more difficult to elicit a suppression of the EMG in this population and the corticospinal drive may therefore wrongly be interpreted as being smaller. SICI estimated using paired pulse TMS has been shown to be reduced in children and young adults with CP (Berweck et al. 2008; Zewdie et al. 2017), which would suggest that the EMG suppression would be smaller in the CP adults—not because of lower corticospinal drive, but because of reduced efficiency of cortical inhibition. We may therefore speculate that the corticospinal drive in the CP population is in reality larger than what the EMG suppression (in rectified EMG or relative to CTRL EMG) would suggest. This may also be the case for the NI group when walking at slow gait speed where larger EMG suppression relative to CTRL EMG was observed. Larger EMG suppression during slower gait speed may indicate a decreased demand for activating the muscle as more inhibitory interneurons are activated by TMS, which suppress the corticospinal drive to larger extent than when walking at faster gait speed. Another related speculation is that the composition of the corticospinal neurons contributing to the corticospinal drive to a given muscle, such as the soleus muscle in the present study, may also influence the amount of the EMG suppression importantly. It is a possibility that fewer corticospinal neurons contribute to the corticospinal drive in adults with CP due to their brain lesion. To achieve a given corticospinal drive (i.e., eventually a given amount of EMG activity) these neurons would need to be more active than in NI adults who have more corticospinal neurons that may contribute to the corticospinal drive. The susceptibility of the corticospinal neurons to inhibition from cortical inhibitory interneurons may be very different in these two populations because of this difference in composition of the corticospinal drive. This also needs to be taken into account when comparing the EMG suppression in the two populations.

Our findings also showed larger EMG suppression during the isometric contraction of the plantar flexor muscles while standing. As discussed above, this may reflect excitability changes of intracortical inhibitory interneurons rather than increased corticospinal drive. Thus, increased excitability during standing may result in activation of more intracortical interneurons by TMS, which would cause a larger inhibition of the corticospinal neurons (Barthelemy and Nielsen 2010). Accordingly, the suppression of the soleus EMG may thus only be used to confirm the contribution of the corticospinal pathway, but not to determine amount, the significance or how it changes between different motor tasks (Barthelemy and Nielsen 2010).

The findings of our study may be influenced by the low sample size included in the study. However, Davey et al. (1998) used similar sample size as in our study and found lower EMG suppression in individuals with SCI. Additionally, in the present study the variation within the two groups is almost similar which may point to that a larger sample size would not change our finding concerning the amount of EMG suppression.

Implications for neurorehabilitation

The finding that corticospinal drive appears to contribute to plantar flexor muscle activation at push-off during gait in adults with CP emphasizes that rehabilitation of gait function in persons with brain and spinal cord injuries should not be directed only at facilitating the rhythmicity of the spinal locomotor network (Dietz and Harkema 2004; Lunenburger et al. 2004; Darekar et al. 2015; Belmonti et al. 2016), but should also involve ways of strengthening and integrating descending drive from the motor cortex in the activation of muscles during gait. In view of the specific role of the motor cortex in adaptation and modification of gait in response to visual information (Drew et al. 1996, 2002; Schubert et al. 1999; Jensen et al. 2018) one possibility would be to ensure that gait training involves visual guidance and stimuli, which the trained individual has to use actively to steer, modify, and adapt gait. This would engage the motor cortex and the corticospinal tract in the gait training and likely have beneficial effects that would be difficult to achieve with conventional treadmill training or lokomat training. The possibilities of providing a stimulating and motivating visual environment through virtual reality, are in particular, encouraging in this respect.

Conclusion

The present findings indicate that corticospinal transmission in adults with CP contributes to the soleus EMG activation at the time of push-off during gait similar to what is seen in NI adults. This also demonstrates that motor cortex is directly involved in controlling the soleus muscle activation at the time of push-off during gait in both NI and CP adults. We observed that higher TMS intensities were necessary to activate intracortical inhibitory circuits in adults with CP. This may reflect a compensatory downregulation of cortical inhibition to facilitate corticospinal drive following the brain lesion early during development. Interventions that facilitate transmission in cortical networks may thus be helpful in maintaining or improving efficient gait in adults with CP.

Compliance with ethical standards

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