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Gradual increase of perturbation load induces a longer retention of locomotor adaptation in children with cerebral palsy

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ABSTRACT

The goal of this study is to determine whether the size and the variability of error have an impact on the retention of locomotor adaptation in children with cerebral palsy (CP). Eleven children with CP, aged 7–16 years old, were recruited to participate in this study. Three types of force perturbations (i.e., abrupt, gradual and noisy loads) were applied to the right leg above the ankle starting from late stance to mid-swing in three test sessions while the subject walked on a treadmill. Spatial-temporal gait parameters were recorded using a custom designed 3D position sensor during treadmill walking. We observed that children with CP adapted to the resistance force perturbation and showed an aftereffect consisting of increased step length after load release. Further, we observed a longer retention of the aftereffect for the condition with a gradual load than that with an abrupt load. Results from this study suggested that the size of error might have an impact on the retention of motor adaptation in children with CP with a longer retention of motor adaptation for the condition with a small size of error than that with a large error. In addition, enhanced variability of error seems facilitate motor learning during treadmill training. Results from this study may be used for the development of force perturbation based training paradigms for improving walking function in children with CP.

1. Introduction

Cerebral palsy (CP) is the most prevalent physical disability, originating before or around birth or the first 2 or 3 years of life with an incidence of 2–3 per 1000 live births (Hollung, Vik, Wiik, Bakken, & Andersen, 2016; Odding, Roebroeck, & Stam, 2006; Rosen & Dickinson, 1992). Of the children who are diagnosed with CP, up to 90% have difficulties in walking (Hutton & Pharoah, 2002; Pharoah, Cooke, Johnson, King, & Mutch, 1998). Walking plays a central role in healthy bone development (Wilmshurst, Ward, Adams, Langton, & Mughal, 1996) and cardiopulmonary endurance (Chien, Chou, Ko, & Lee, 2006), and children who are able to ambulate are more independent in activities of daily living and the participation in social roles than children who use a wheelchair (Lepage, Noreau, & Bernard, 1998; Mitchell, Ziviani, & Boyd, 2015). Thus, one major goal of physical rehabilitation for children with CP is to improve functional walking ability.

Treadmill training is commonly used in clinics for improving walking function in children with CP (Dodd & Foley, 2007). Results from previous studies suggest that it is feasible to improve walking speed and endurance for some children with CP (Cherng, Liu, Lau, & Hong, 2007; Dodd & Foley, 2007; Provost et al., 2007). In addition, several studies also indicated improvements in walking

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function of children with CP after robotic treadmill training (Borggraefe et al., 2010; Meyer-Heim et al., 2007, 2009). However, a recent randomized controlled study indicated only a modest change in walking speed after robotic treadmill training (Druzbicki et al., 2013), and recent systematic reviews suggest that there is insufficient evidence to support the effectiveness of treadmill training on walking function in children with CP (Damiano & DeJong, 2009; Mutlu, Krosschell, & Spira, 2009; Valentin-Gudiol et al., 2013). Thus, there is a need to improve the efficacy of current treadmill training paradigms for improving walking function in children with CP. This requires a thorough understanding the underlying motor learning mechanisms in children with CP during locomotor training.

Error-based paradigms have been used extensively to investigate motor learning, although most studies have focused on arm movement (Shadmehr, Smith, & Krakauer, 2010). For the lower limb, previous studies suggest that the central nervous system (CNS) may also use an internal model to control leg kinematics during treadmill walking (Emken & Reinkensmeyer, 2005; Kawato, 1999). When detecting a discrepancy between the predicted and actual leg movement, due to, e.g., an external perturbation, the CNS may adjust the motor commands to reduce this discrepancy (Bastian, 2008). For instance, enhanced muscle activation of hip flexors was observed when a resistance load was applied to leg swing in healthy controls (Lam, Anderschitz, & Dietz, 2006) and in patients with spinal cord injury (Lam, Wirz, Lunenburger, & Dietz, 2008). An aftereffect consisting of an increase in step length has been reported in patients with spinal cord injury (Houldin, Luttin, & Lam, 2011; Yen, Schmit, Landry, Roth, & Wu, 2012), and stroke (Savin, Morton, & Whitall, 2014; Yen, Schmit, & Wu, 2015) when the perturbation force is removed. However, it is unclear whether a similar effect could be observed in children with CP.

The pattern of perturbation force may also have an impact on the retention of aftereffect. For instance, results from previous arm studies indicated that when a perturbation was gradually imposed on movements over many trials, which was suggested to induce small errors (Orban de Xivry, Criscimagna-Hemminger, & Shadmehr, 2011; Schlerf, Galea, Bastian, & Celnik, 2012), training produced a memory that was more resistant to decay than when the same perturbation was imposed in a single step (Huang & Shadmehr, 2009; Kagerer, Contreras-Vidal, & Stelmach, 1997), which was suggested to induce large errors (Criscimagna-Hemminger, Bastian, & Shadmehr, 2010). Similarly, it has been shown that split-belt locomotor adaptation transferred more to overground walking when the perturbation was gradually imposed than that when the perturbation was abruptly imposed (Torres-Oviedo & Bastian, 2012). These results suggest that different neural substrates and different mechanisms of learning may be involved for the conditions when the perturbation is gradually or abruptly introduced. Therefore, different levels of motor memory may be formed and retention of motor adaptation may be different for these two conditions. This is also supported by the theory of credit assignment (Berniker & Kording, 2008), which indicates that smaller errors are more likely to be attributed to changes within the body and larger errors are more likely to be assigned to something external, such as a new device. Thus, motor adaptation induced by small errors when the perturbation is gradually imposed would be better retained over long periods of time than motor adaptation induced by large errors when the perturbation is abruptly imposed in children with CP.

In addition, motor variability over different trials may also have an impact on motor learning. For instance, motor variability has been regarded as the inevitable consequence of stochastic nervous system function, which may be caused by noise in sensory or motor processing, or sensorimotor integration (Churchland, Yu, Ryu, Santhanam, & Shenoy, 2006; Osborne, Lisberger, & Bialek, 2005; Stein, Gossen, & Jones, 2005). However, results from songbirds and humans studies suggested that increased motor variability may actually facilitate motor learning (Tumer & Brainard, 2007; Wu, Miyamoto, Gonzalez Castro, Olveczky, & Smith, 2014). It was suggested that the motor variability may facilitate motor exploration that provides information for improving the fidelity of the internal representation of the gradient function between motor errors and changes in motor commands, resulting in a higher motor learning rate (Wu et al., 2014). In line with this, results from animal studies also indicated that reducing the motor variability of leg kinematics was detrimental for motor learning during locomotor training (Cai et al., 2006; Shah et al., 2012). Children with CP usually show greater motor variability during locomotion (Kim, Bulea, & Damiano, 2018; Kurz, Arpin, & Corr, 2012), but there is no evidence whether increased motor variability may facilitate motor learning during locomotor training.

The goal of this study was to test whether error size and variability during locomotor adaptation influence the retention of the aftereffect in children with CP. We hypothesized that a smaller error size would induce longer retention of motor adaption. In addition, we hypothesized that an enlarged motor variability would increase the retention of motor adaptation in children with CP. We used a force perturbation paradigm to induce different error size and error variability because it is easier to manipulate, although other perturbation paradigms, such as split-belt treadmill, have also been used (Patrick et al., 2014; Torres-Oviedo & Bastian, 2012).

2. Method

2.1. Subjects

Eleven children (average 11.6 ± 2.7 years old, 5 girls) with spastic CP (3 quadriplegic, 8 diplegic) were recruited through the pediatric outpatients of the Rehabilitation Institute of Chicago to participate in this study (Table 1). According to the Gross Motor Function Classification System (GMFCS) (Russell et al., 1989), 4 were classified as level I, 5 were classified as level II, and 2 were classified as level III. Two children used a walker for their daily walking, 7 wore orthotics (5 Ankle Foot Orthosis (AFO) and 2 Supra-Malleolar Orthosis (SMO)), and 2 used a wheelchair for long distance walking.

Inclusion criteria: (1) age between 5 and 16 years old; (2) spastic CP; (3) ability to ambulate over ground with or without assistive devices (e.g., walker or orthotics); (4) without Botulinum toxin treatment within 6 months or surgery within 12 months before the onset of the study; (5) GMFCS levels I to III; (6) able to signal pain, fear or discomfort reliably.

Exclusion criteria: (1) severe lower limb contractures, fractures, osseous instabilities, and osteoporosis; (2) severely disproportional

Table 1
Subject information indicating age, height, weight, gender, GMFCS level, treadmill speed, and magnitude of perturbation force. *Abbreviations:* GMFMCS = Gross Motor Function Classification System.

Case	Age	Gender	GMFCS	Test speed (m/s)	Load (N)	MVC (N)	Height (m)	Weight (lb)
S1	11	F	I	0.53	17	78	1.55	93
S2	16	M	II	0.44	22	59	1.57	104
S3	12	M	III	0.43	24	75	1.45	98
S4	10	F	II	0.59	17	48	1.40	102
S5	14	F	I	0.50	17	75	1.57	133.4
S6	8	M	II	0.51	17	59	1.35	67
S7	14	M	III	0.51	21	78	1.53	102
S8	14	M	II	0.54	20	81	1.49	99
S9	11	F	I	0.67	17	76	1.40	65.4
S10	11	F	I	0.44	17	76	1.39	78.4
S11	7	M	II	0.63	11	58	1.27	62.8

bone growth and unhealed skin lesions in the lower limbs; (3) thromboembolic diseases, cardiovascular instability, and aggressive or self-harming behaviors. All procedures were approved by the Institutional Review Boards of Northwestern University Medical School, and conducted in accordance with the Helsinki Declaration of 1975. Written informed consents were obtained from all subjects and their parents prior to participation.

2.2. Apparatus

A custom designed cable-driven robotic system, which was reported previously (Wu, Hornby, Landry, Roth, & Schmit, 2011), was used to provide a controlled perturbation force to the right leg (for the convenience of the system setup) while subjects walked on a treadmill, see Fig. 1. In brief, the cable-driven robotic system consists of 4 motorized cables and pulley systems that attach to a treadmill (Woodway) and a body weight support system. Four nylon-coated stainless cables (1.6 mm diameters) were driven by 4 motors (AKM33H, Kollmorgen) through 4 custom designed cable-spools and pulley sets. These cables were affixed to custom cuffs that were strapped to the leg above the ankle to produce a perturbation force during treadmill walking. Two 3D position sensors were used (one for each side) to measure bilateral ankle position and the ankle position signals were used to trigger the leg perturbation load. The ankle position sensor consists of one detection bar and two U-joints, which are attached at the two ends of the bar. One end of the detection bar is attached to the ankle through a strap and the other end of the detection bar is attached to a fixed frame located at the two sides of treadmill. Two rotational potentiometers (P2201, Novotechnik, Southborough, MA) and 1 linear position transducer (SP-2, Celesco, Chatsworth, CA) (Yen et al., 2012) were used to record the 3D ankle trajectory during treadmill walking. Only 1 motor and cable-spool set was used to generate perturbation force in this study. A custom program written in LabVIEW (National Instruments, Austin, TX) was used to send motor commands to the servomotor system for generating different patterns of perturbation force at the targeted phase of gait.

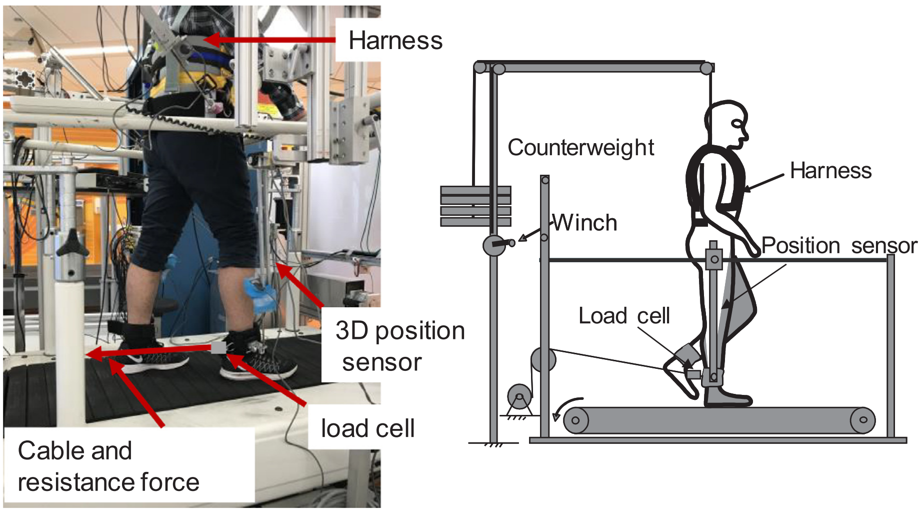

Fig. 1. Experimental setup. A computer was used to send control commands to the driver of motor. One motor and cable-spool was used to apply a controlled resistance load to the right leg in this study.

2.3. Data acquisition

A customized LabVIEW program was used to record ankle position data while subjects walked on a treadmill. A one degree of freedom tension/compression load cell (MLP-25, Transducer Techniques, Temecula, CA), which was attached in series with the ankle cuff and the motorized cable, was used to record the perturbation forces applied. All position signals from 3D position sensors and the load cell were recorded with a sample frequency of 1000 Hz using a data acquisition board (National Instruments, Austin, TX) on a PC.

Surface electromyograms (EMG) were recorded from the Tibialis Anterior (TA), Medial Gastrocnemius (MG), Soleus, Vastus Medialis, Rectus Femoris, Medial Hamstrings of the right leg, and from the TA and MG of the left leg. EMG signals were amplified ($\times 1000$) and band-pass filtered (20–450 Hz) in hardware. The same computer was used to collect EMG signals using a custom-written LabVIEW program.

2.4. Protocol

An overhead harness was used for protection only (no body weight support was provided). Subjects were instructed to walk on a treadmill at a self-selected comfortable speed (average: 0.53 ± 0.08 m/s), which was determined before data collection by an experienced physical therapist, see Table 1. For safety purposes, subjects were allowed to hold onto a bar located in the front of them. A controlled perturbation force was applied to the right leg starting from toe-off to mid-swing, determined by ankle position sensor signals. The magnitude of the force was set at ~25% of the maximum voluntary contraction (MVC) of the hip flexors, although was adjusted before data collection based on the tolerance of each subject, to ensure they could finish 12 min of treadmill walking (while a perturbation force was applied) without a significant fatigue. This was determined based on our previous experience in similar studies. The hip flexor MVC was determined before data collection using a tension/compression load cell (MLP-75, Transducer Techniques, Temecula, CA), which was attached to a fixed frame located at the back of the treadmill (Yen, Landry, & Wu, 2013).

At each test session, subjects walked on a treadmill for one minute without a force, i.e., baseline, then, a perturbation force was applied to the right leg for 8 min, i.e., adaptation period. After this, the perturbation force was released without warning and subjects were instructed to continue walking on a treadmill for another 3 min, i.e., post-adaptation period. Each subject participated in 3 test sessions with a 5-minute sitting break inserted between two test sessions. Three types of perturbation loads (gradual, abrupt and noisy) were applied in a randomized order across subjects, see Fig. 2. The maximum peak perturbation force for each subject was the same for all three perturbation conditions, but differed in how it was delivered: (1) gradually introduced over many steps within the 8 min adaptation period for the gradual load condition, (2) abruptly introduced in one step for the abrupt load condition, (3) abruptly introduced in one step in a random pattern across steps (i.e., the magnitude of the peak force varied across steps with the range of variation was set at 70% of maximum peak force, i.e., 25% of MVC) for the noisy load condition. The variation of force signals were generated by LabVIEW program with the mean value $\bar{X} = 0$, and variance $S^2 = 1$ (i.e., normal distribution). A 4–5 N pretension force was applied to the cable in order to avoid slacking during baseline and post adaptation period. Before data collection of the first session, subjects were also instructed to walk at their maximum walking speed for 30 strides.

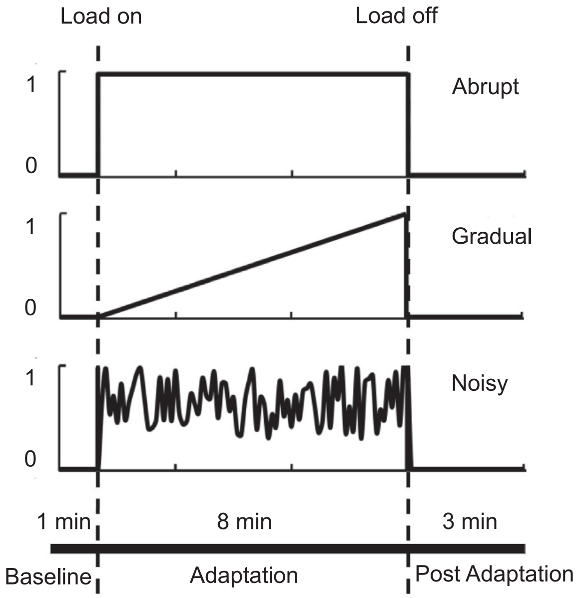

Fig. 2. Time course of the magnitude of peak force for the abrupt, gradual, and noisy load conditions. For the condition of abrupt load, the peak perturbation force remained the same from gait cycle to cycle. For the condition of gradual load, the peak force gradually increased from gait cycle to cycle. For the condition of noisy load, the peak force varied from gait cycle to cycle.

2.5. Data analysis

The ankle position signals were low-pass filtered using the 4th order Butterworth filter with a cutoff frequency at 10 Hz using MATLAB program (Mathworks, Inc., Natick, MA, USA). Then, the ankle position data were segmented into different stride cycles. The timing of heel contact was defined as the ankle movement changing its direction from forwards to backwards, and the timing of toe-off was defined as the ankle movement changing its direction from backwards to forwards (Zeni, Richards, & Higginson, 2008). Thus, the stance phase was defined as the period when the ankle moved from heel contact to toe-off, and the swing phase was defined as the period when the ankle moved from toe-off to the next heel contact. Step length was defined as the anterior-posterior distance between the two legs' ankle positions at initial contact. We focused on this parameter because the perturbation force was set to affect the leg kinematics during swing phase, and the change in step length may directly reflect the effect of the perturbation force. The spatio-temporal gait parameters of both the perturbed leg (i.e., the right leg) and unperturbed leg were analyzed. In addition, swing time was calculated and normalized to gait cycle. Baseline was defined as step length's mean magnitude across 20 consecutive strides of baseline period without force. The changes in step length between the magnitude of step length during adaptation period and baseline were defined as errors, which were induced by the external resistance force. If the step length during the adaptation period was smaller than baseline, errors were negative, otherwise errors were positive. The error sizes were grouped to negative and positive and were averaged over the first 250 strides during the adaptation period, and compared across the three load conditions. The data from first 250 strides were used because this was about the smallest stride number across subjects (the step numbers during the adaptation period (8 min) were different across subjects due to different walking speed was used for each subject, see Table 1). The standard deviation of errors over the first 250 strides during the adaptation period was calculated to quantify error variability, and compared across the three load conditions. Step length of the first 5 strides after load release during the post adaptation period was averaged, and compared to baseline. To quantify the retention of aftereffect, the magnitude of step length during the post-adaption period (45 steps after load releasing) was subtracted by baseline. Then, the change in step length during the post-adaptation period was mathematically modeled using the following exponential decay function (Deuschl, Toro, Zeffiro, Massaquoi, & Hallett, 1996; Lang & Bastian, 1999; Savin et al., 2014):

$$y = a + (b * e^{-\frac{t}{c}}) \tag{1}$$

where a is the final value that the exponential decay function approaches, i.e., the plateau reached at the end de-adaptation; b is the magnitude of the de-adaptation required from the first stride value to the value a, t is the stride number, and c is the decay constant which was used as a measure of the retention rate. In this study, c was the number of strides that was taken to obtain $1 - e^{-1}$ (Lang & Bastian, 1999; Savin et al., 2014). All curve fits were conducted using MATLAB software (Mathworks, Inc., Natick, MA, USA).

The surface EMG signals from each muscle was high-pass filtered at 20 Hz and band-stop filtered at 55–65 Hz using a second order Butterworth filter. Then, all EMG data were rectified and smoothed using a second order Butterworth low-pass filter with the cutoff frequency at 40 Hz. The smoothed EMG signals were segmented into gait cycles, interpolated, resampled, and averaged over 20 strides for baseline, and 5 strides for the early adaptation period, the late adaptation period, and the early post-adaptation period. The EMG data were further normalized to the peak EMG signals of each muscle during the condition when subjects walked at their maximum walking speed. The integrated EMG activity was calculated in the intervals of swing phase of the gait cycle.

Normal distribution of data was checked using the Shapiro-Wilk test before analysis. Repeated-measures analysis of variance (ANOVA) was used to compare the step length, swing time, and the integrated EMG activity between baseline and other sessions within one load condition. Error size, error variability, and retention of aftereffect were also compared across different load conditions using one-way ANOVA. If a significant difference was detected, Tukey-Kramer post-hoc tests were conducted to determine which conditions were different from each other. Statistical significance for all tests were set at $\alpha < 0.05$. A correlation analysis was conducted between error size during adaptation period and retention of aftereffect. A Pearson's correlation coefficient was identified with significance as tested at $\alpha < 0.05$. Data were analyzed using MATLAB_R2016 (The MathWorks, Natick, MA).

3. Results

Data from 10 subjects were analyzed. Data from one subject (i.e., subject 4 in Table 1) was excluded due to an incomplete recording, which was caused by equipment malfunction.

3.1. Spatiotemporal data

3.1.1. Step length of the perturbed leg

Results from group average of the change in step length indicated that the pattern of force had no significant impact on size of errors during the adaptation period ($p = 0.40$, $n = 8$, data from two subjects were excluded due to outlier), although the mean value of error was relatively smaller for the gradual condition. Specifically, negative errors in step length were 13.1 ± 11.1 mm and 16.2 ± 16.4 mm for the abrupt and noisy force conditions respectively, and was 8.2 ± 5.0 mm for the gradual force condition. Positive errors were comparable across three load conditions during the adaptation period (i.e., 21.6 ± 9.9 mm, 34.3 ± 32.4 mm, and 21.2 ± 13.0 mm for the abrupt, noisy, and gradual force conditions, respectively). In addition, the variability of errors during the adaptation period tended to be greater for the condition with noisy load (35.8 ± 8.9 mm) than the condition with gradual load (31.2 ± 7.3 mm) and the condition with abrupt load (32.9 ± 8.8 mm), but this was not significant ($p = 0.09$, $n = 9$).

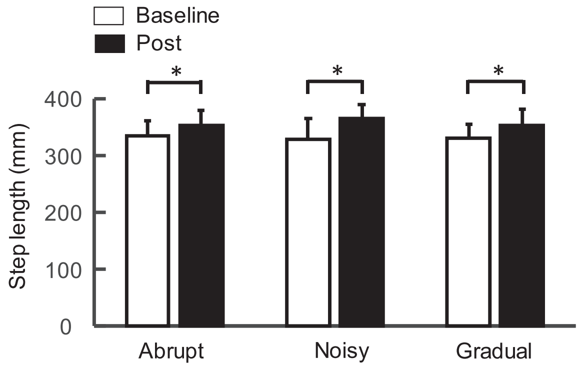

Fig. 3. Group average of step length during baseline and post adaptation period for the conditions with noisy, abrupt, and gradual force perturbations. Data shown are mean and standard deviation across subjects. * indicates significant difference, $p < 0.05$.

Results from group average indicated that step length significantly increased during the post-adaptation period for all three force conditions. Specifically, step length in post-adaptation was significantly greater than baseline for the condition with abrupt force (335.3 ± 72.8 mm vs. 353.7 ± 72.7 mm, p = 0.03, n = 8, data from 2 subjects were excluded due to outlier), for the noisy force (328.7 ± 110.6 mm vs. 365.7 ± 72.4 mm, p = 0.03, n = 9), and for the gradual force (330.0 ± 72.5 mm vs. 352.9 ± 82.6 mm, p = 0.046, n = 8), see Fig. 3. There was no significant difference in baseline step length across three force conditions (p = 0.83), and there was no significant difference in the size of aftereffect (i.e., the increase in step length during the post-adaptation period in comparison to baseline) across three force conditions (p = 0.73).

The force pattern had an impact on the retention of aftereffect during post-adaptation period. Specifically, the force pattern had a significant impact on the retention of aftereffect (p = 0.04, data from one subject were excluded due to outlier, goodness of fit for retention of aftereffect during the post-adaptation period $r^2 \geq 0.45$ for all three conditions), Fig. 4A. Further, we observed a longer retention of aftereffect for the condition with the gradual force than that with abrupt force (i.e., 13.4 ± 7.0 vs. 4.4 ± 1.5, p = 0.03), but there was no significant difference between the conditions with gradual and noisy force (i.e., 13.4 ± 7.0 vs. 9.5 ± 7.1, p = 0.41), Fig. 4B. Further, we observed a negative correlation (p = 0.05) between the error size and the retention of aftereffect, i.e., when subjects experienced small errors during adaptation period showed a longer retention of aftereffect during post-adaptation period, Fig. 4C.

3.1.2. Step length of the unperturbed leg

We observed no significant change in step length of the unperturbed leg (i.e., left leg in this case) between baseline and the post-adaptation period for the conditions with abrupt (p = 0.79), with gradual (p = 0.78), and with noisy forces (p = 0.30). In addition, we observed no significant change in swing time for all three loading conditions during post-adaptation period. Specifically, the swing time of the perturbed leg and unperturbed leg had no significant change for the condition with abrupt force (p = 0.62 for the perturbed leg and p = 0.45 for the unperturbed leg), for the condition with gradual force (p = 0.17 for the perturbed leg and p = 0.38 for the unperturbed leg), and for the condition with noisy force (p = 0.14 for the perturbed leg and p = 0.80 for the unperturbed leg, respectively).

3.2. EMG data

TA muscle activity increased during the early adaptation period, but showed no apparent change during the late adaptation period and post-adaptation period for the condition with abrupt force, see Fig. 5A. For the condition with noisy force, TA muscle activity showed no apparent change during the early adaptation period, but slightly decreased during the post-adaptation period. TA muscle activity showed no apparent change for the condition with gradual force. For the condition with abrupt force, RF muscle activity increased during the early adaptation period and the late adaptation period, but showed no apparent change during the post-adaptation period, Fig. 5B. RF muscle activity showed no apparent change for the conditions with gradual and noisy forces. LTA muscle activity increased during the early adaptation period and late adaptation period for the condition with abrupt force, Fig. 5C, and showed no apparent change for the conditions with gradual and noisy forces.

Integrated TA muscle activity had significant change for the condition with abrupt force (p = 0.02), Fig. 6. Post-hoc analysis indicated a significant difference in integrated TA muscle activity between the early adaptation period and the post-adaptation period (p = 0.01), but showed no significant difference between other periods (p > 0.21). Integrated TA muscle activity also had significant change for the condition with noisy force (p = 0.02). Post-hoc analysis indicated significant differences in integrated TA muscle activity between baseline and the post-adaptation period (p = 0.03), and between early adaptation period and the post-adaptation period (p = 0.02). There was no significant difference in integrated TA muscle activity between other two periods (p > 0.38). Integrated TA muscle activity had significant change for the condition with gradual force (p = 0.01, n = 9, data from one subject were excluded due to outlier). Post-hoc analysis indicated significant difference in integrated TA muscle activity between baseline and the post-adaptation period (p = 0.01). There was no significant difference in integrated TA muscle activity between

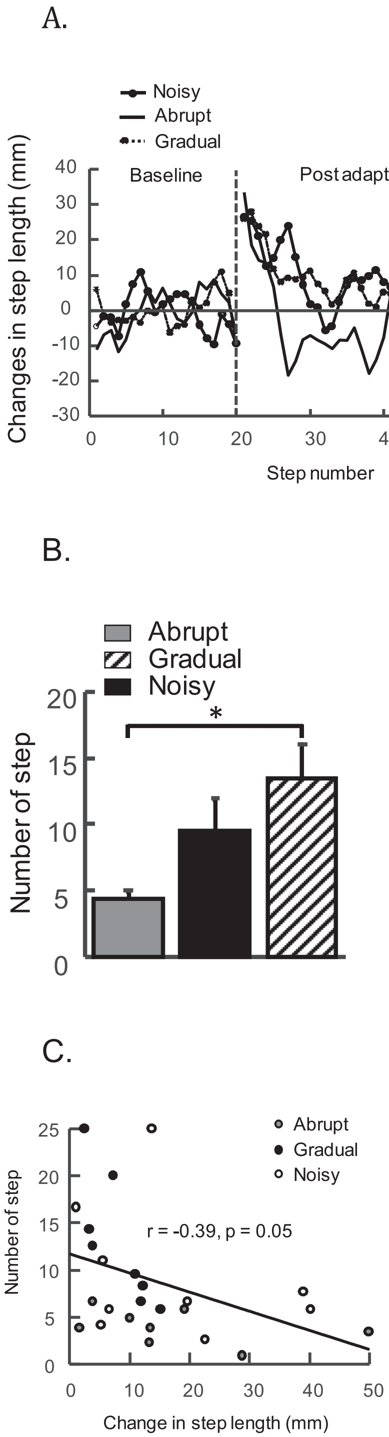

Fig. 4. (A) Average of changes in step length during the post adaptation period for three load conditions. The retention of aftereffect (i.e., the increase in step length) was only calculated for these subjects who showed aftereffect during the post adaptation period (n = 8 for the condition with abrupt load, n = 9 for the conditions with gradual and noisy loads). Data shown were 3 points window smoothed. (B) Average of retention of aftereffect for three load conditions. Data shown were mean and standard errors across subjects. * indicates significant difference, $p < 0.05$. (C) Scatterplots showing the relationship between error size and the retention of aftereffect. The retention of aftereffect was negatively related to the error size during adaptation in each subject: the smaller the error size during the adaptation period, the longer retention of aftereffect during the post adaptation period. The mean of negative error size (i.e., smaller than baseline) over first 300 stride during the adaptation period was calculated.

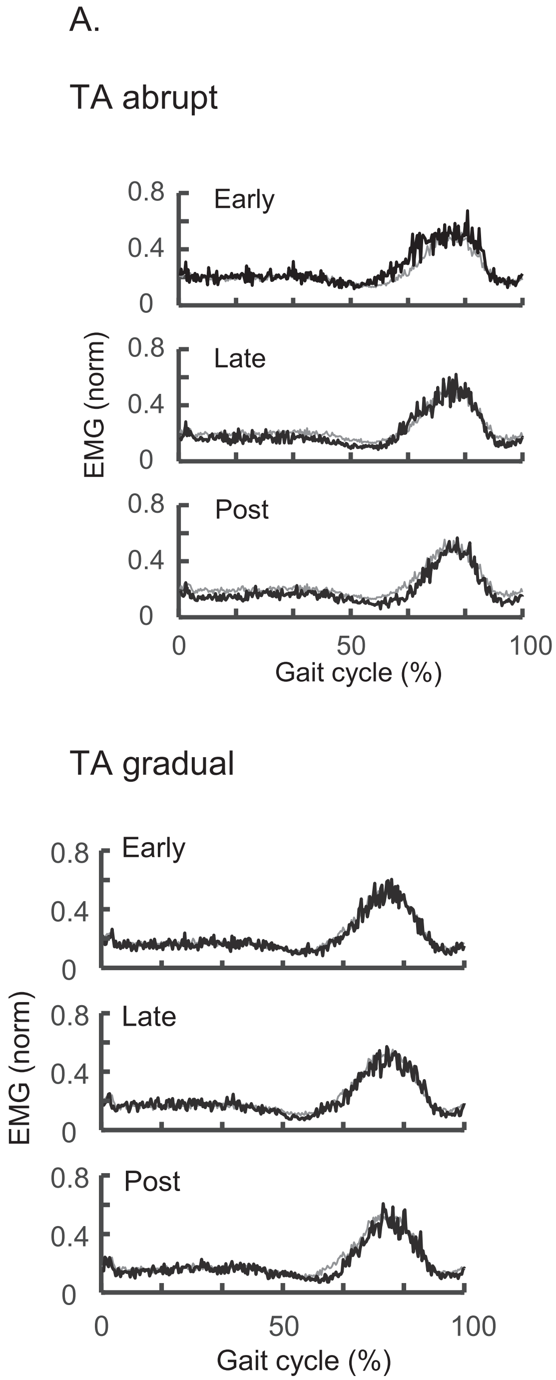

Fig. 5. Average of EMG pattern (linear enveloped) of TA, RF, and LTA during baseline, the early adaptation period, late adaptation period, and post-adaptation period for three load conditions. EMG data were normalized to gait cycle of the right leg and were averaged across subjects for each period. The gray curves indicate mean EMG pattern during baseline, and the solid curves indicate mean EMG pattern during the early adaptation period, late adaptation period, and post adaptation period.

other two periods ($p > 0.06$). Integrated RF muscle activity had no significant change for the condition with abrupt force ($p = 0.50$), the condition with gradual force ($p = 0.30$), and the condition with noisy force ($n = 0.15$). Integrated LTA muscle activity had significant change for the condition with abrupt force ($p = 0.02$). Post-hoc analysis indicated a significant difference in integrated LTA muscle activity between baseline and late adaptation period ($p = 0.01$), and showed no significant difference between other periods ($p > 0.13$). Integrated LTA muscle activity showed no significant change for the conditions with noisy force ($p = 0.40$) and with gradual force ($p = 0.70$). Integrated muscle activity of other muscles had no significant changes ($p > 0.05$).

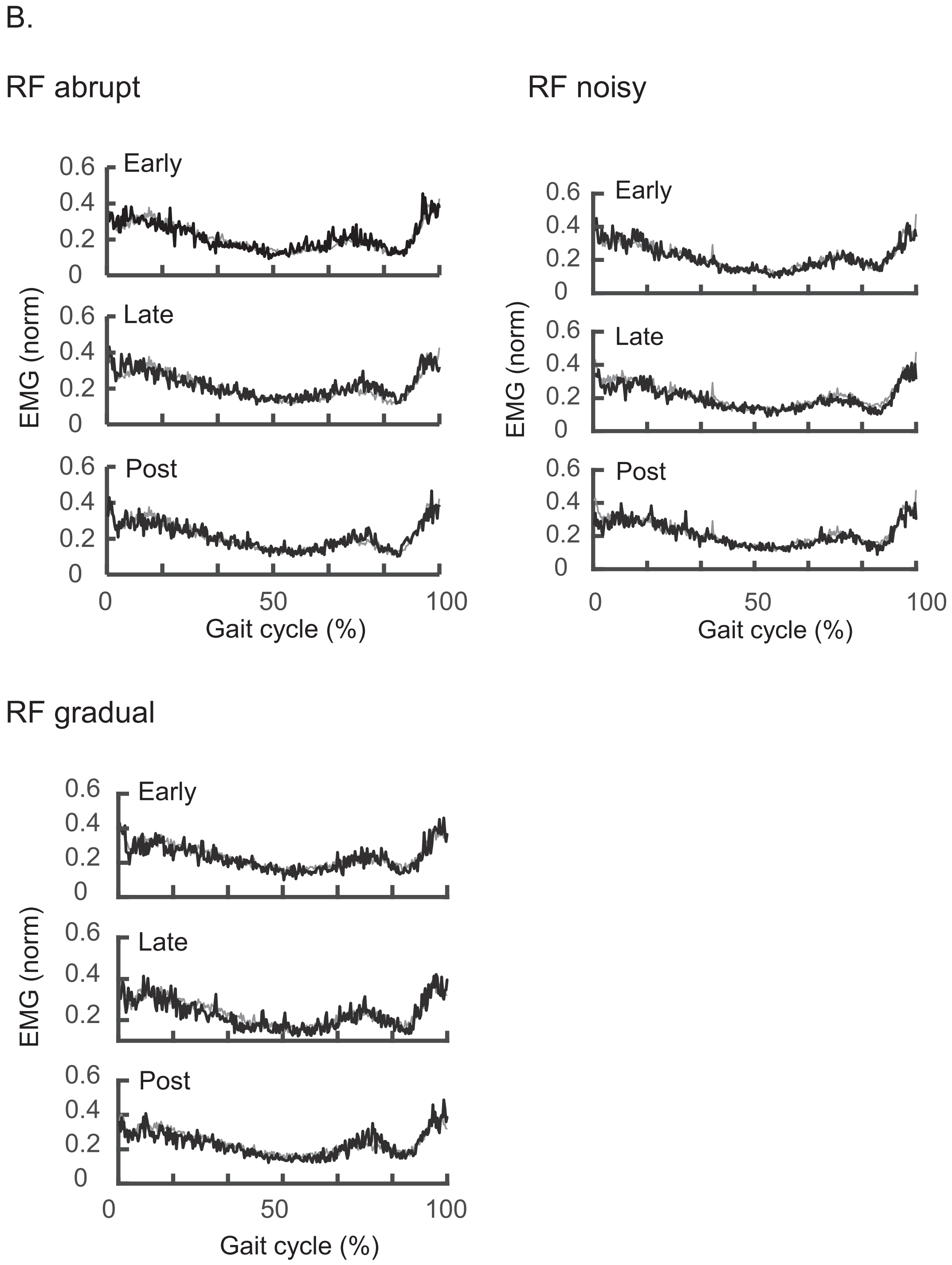

Fig. 5. (*continued*)

4. Discussion

Our results demonstrated that children with CP could adapt to a perturbation force applied to the leg during the swing phase of gait, and showed an aftereffect consisting of an increase in step length after force release during the post-adaptation period for all three force conditions. Further, there was a longer retention of the aftereffect for the condition with a gradual force than that with an abrupt force. Results from this study suggest that the size of error may have an impact on the retention of the aftereffect during locomotor adaptation in children with CP.

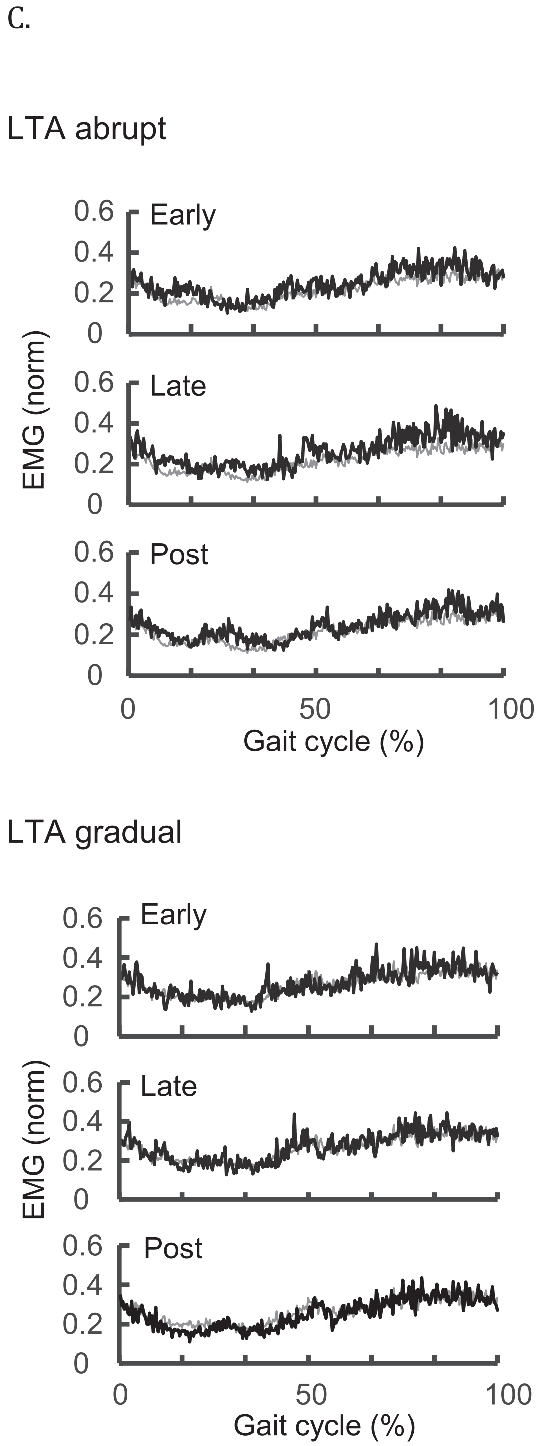

Fig. 5. (*continued*)

The presence of the aftereffect during the post-adaptation period suggests that children with CP are able to predict the forces that will be experienced during upcoming gait cycle to produce the appropriate motor commands (Shadmehr & Mussa-Ivaldi, 1994). Specifically, when the perturbation force was applied to the leg during the adaptation period, participants might increase the activation of hip flexors to generate additional torques to counteract this force (Lam & Pearson, 2001). Overtime, the central nervous system may gradually adapt to the perturbation force and the internal model may be updated through repeat exposure to the force (Shadmehr & Mussa-Ivaldi, 1994). Thus, when the force was removed unexpectedly, participants took a longer step length during the post-adaptation period, which is consistent with previous studies including healthy subjects (Lam et al., 2006), patients with spinal

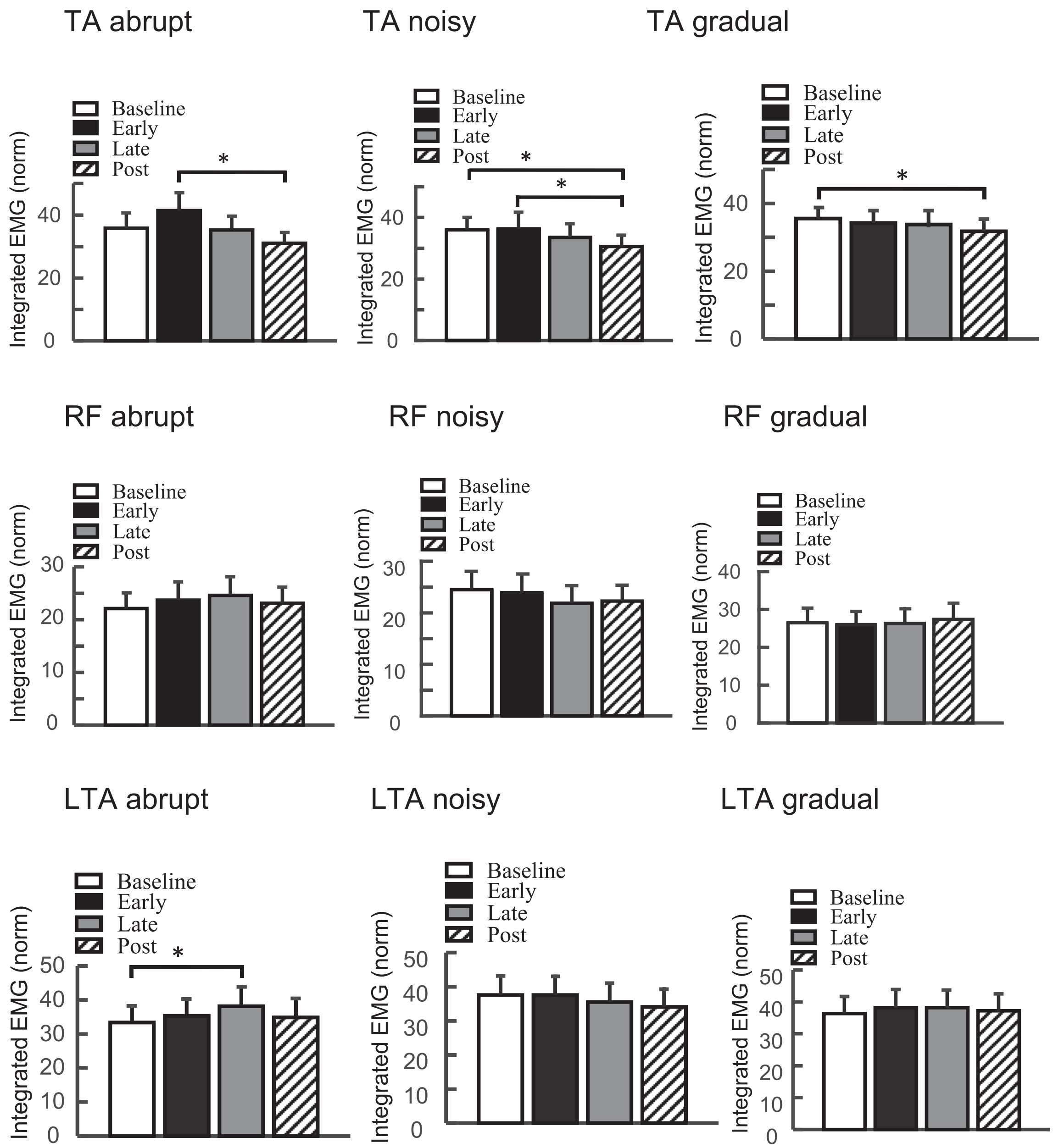

Fig. 6. Average of integrated EMG area of baseline, the early adaptation period, late adaptation period, and post-adaptation period across subjects for three load conditions, i.e., noisy, abrupt and gradual (data from one subject were excluded due to outlier) loads. Error bars indicate standard error. * indicates significant difference, $p < 0.05$.

cord injury (Houldin et al., 2011; Yen et al., 2013), and individuals post-stroke (Savin, Tseng, Whitall, & Morton, 2013; Yen et al., 2015). A feed-forward control strategy (Lam et al., 2006), rather than feedback control only may be involved in this process because the force was removed during the post-adaptation period.

Our results indicated that error size experienced by children with CP during adaptation period had an impact on the retention of the aftereffect during the post-adaptation period with a longer retention of the aftereffect for the condition when the error size was small, i.e., for the gradual force condition. This is consistent with a previous arm reaching study, which have indicated that smaller errors resulted in greater retention of the aftereffect in healthy adults performing reaching tasks (Criscimagna-Hemminger et al., 2010). However, error size experienced by children during the adaptation period had no impact on the size of aftereffect during the post-adaptation period, which is consistent with a previous study, which indicated that error size made no significant difference in size of aftereffect using split-belt paradigm in younger healthy children (i.e., aged from 2 to 5 years old) (Patrick et al., 2014), but the retention of aftereffect was not reported in this study.

A possible reason for this difference in retention of the aftereffect during the post-adaptation period may be due to different neural pathways may be involved for processing large and small errors during locomotor adaptation. For instance, the cerebellum may be involved in the locomotor adaptation process involving large errors, but may be less involved in processing small errors, which is supported by the evidence that cerebellar degeneration compromises the ability to learn from large errors, but had less of an impact on learning from small errors (Criscimagna-Hemminger et al., 2010). In addition, the prefrontal cortical regions may be more involved in locomotor adaptation processing of large errors that produce conscious awareness of the error, but not involved in locomotor adaptation processing of small errors that do not produce conscious awareness (Shadmehr & Holcomb, 1997). The involvement of conscious awareness may be helpful to quickly reduce errors and improve performance in response to an abrupt force perturbation when error size was large. However, this rapid improvement in performance also vanishes quickly, which may lead to a faster decline of aftereffect when the perturbation force is removed during post-adaptation period. This is also supported by a simulation study, which suggests that motor adaptation depends on two distinct timescales computational processes (Smith, Ghazizadeh, & Shadmehr, 2006): a "fast" process, which learns to reduce errors rapidly but also forgets rapidly, and a "slow" process, which learns to reduce errors slowly but forgets slowly. Further, the "fast" process has been suggested to closely resemble explicit learning (Hwang, Smith, & Shadmehr, 2006) and the "slow" process approximate implicit learning (McDougle, Bond, & Taylor, 2015). Explicit learning is encoded as events which occur when a child consciously attempts to take a longer step, whereas implicit learning processes are characterized by slow development and are not under conscious control (Gentile, 1998). The explicit and implicit learning and memory systems are biological isolated from one another (Boyd & Winstein, 2006; Reber & Squire, 1998), although they may affect one another (Boyd & Winstein, 2001). Thus, the motor memories formed by explicit and implicit learning may be stored at different regions of brain. As a result, different levels of retention of the aftereffect were observed.

Increased error variability may facilitate error-based motor learning. We observed a longer retention of aftereffect for the condition with noisy force than that with abrupt force (9.5 ± 7.1 vs 4.4 ± 1.5), although this was not significant ($p = 0.24$) due to a large variability across subjects. For the condition with noisy force, the variable perturbation force might increase variability of error, which might have increased the central nervous system's sensitivity to errors during the adaptation period (Torres-Oviedo & Bastian, 2012). The increased sensitivity to errors may facilitate motor learning (Burge, Ernst, & Banks, 2008; Herzfeld & Shadmehr, 2014). These results are consistent with the results from a previous study in healthy subjects using a split-belt treadmill perturbation, which suggest that enlarged variability of errors may increase motor learning (Torres-Oviedo & Bastian, 2012). Further studies are needed to determine the optimized level of error variability for effective motor learning in children with CP.

RF muscle activity tended to increase, although this was not significant, to counteract the resistance load during adaptation period for the condition with abrupt force, although other hip flexors, such as iliopsoas, which is difficult to access using surface EMG, may also be involved. In addition, TA muscle activity tended to increase as the resistance force was applied, suggesting that the voluntary descending drive was increased due to the resistance load. LTA muscle activity also increased when the resistance force was applied, suggesting a bilateral response to the resistance force applied to one leg (Dietz, Quintern, Boos, & Berger, 1986). The enhanced LTA muscle activity may facilitate to pull the standing leg forward over the stationary foot as an inverted pendulum (Winter, 1995) in response to the resistance force. However, we did not observe a similar pattern in muscle activity for the conditions with noisy and gradual force, may be due to a smaller magnitude of resistance force. When the resistance load was released during post-adaptation period, the enhanced TA muscle activity were absent or slightly decreased, suggesting a feedback rather than feedforward control mechanism may be involved (Lam et al., 2006). Further studies are needed to identify the muscle groups that drive the increased step length during post-adaptation period.

The findings from this study are an important step to understand the motor learning mechanisms during treadmill training in children with CP. By applying three types of force perturbations (i.e., abrupt, gradual, and noisy forces) to the leg during treadmill walking, we were able to examine how the error size and error variability impacted the motor learning in children with CP. Results from our previous study indicated that applying a resistance force to legs during treadmill training was more effective than assistance in improving locomotor function in children with CP (Wu, Kim, Gaebler-Spira, Schmit, & Arora, 2017), suggesting increased error may facilitate motor learning during treadmill training. However, results from this study suggest that too larger errors may be also detrimental for the retention of the motor skills. In addition, children with CP usually show larger variability in gait parameters during walking (Kurz et al., 2012). Results from this study suggest that increased error variability seems may also increase the retention of motor skills.

This study has several limitations. First, the subjects participated in the study were relatively high functioning, i.e., GMFCS classification level was I–III. We do not know whether these findings can be generalized to other children with CP, i.e., children with hemiplegia CP. Second, in this study, we focused on the spatial and temporal gait parameters. We did not measure the hip and knee joint kinematics during locomotor adaptation. Thus, we do not know which joint (hip or knee) were more affected by the perturbation force applied to the leg. Third, while we observed an improvement in step length during treadmill walking, we do not know, to what extent, this improvement can transfer to overground walking. The perturbation force was applied to the right leg in this study for the convenience of system setup, although the motor deficits of two legs may be different for some subjects. However, we do not believe the differences in motor deficits between two legs systematically influenced our results because both legs of subjects were affected. Finally, the sample size of this study is small. Further studies with a larger cohort of subjects are needed to address these limitations. We also do not know whether different level of resistance force will result in different motor adaptation patterns.

This study may have some clinical applications. For instance, results from this study indicated that a resistant force perturbation applied to the leg during swing phase may induce an aftereffect consisting of increased step length in children with CP. In particular, a small error size or varied error induced a longer retention of the aftereffect in step length than a large error size. Thus, clinical therapists should gradually increase the intensity of the perturbation force or increase the variability of the force during locomotor training in order to have a long-term retention of training effect on improving step length in children with CP.

5. Conclusion

In this study, we applied different patterns of a swing phase resistance force to leg during treadmill walking to examine the effect of the error size and error variability on the retention of an aftereffect in children with CP. We found that children with CP retained the aftereffect, which consists of increased step length, for a longer period of time when the error size was small, which was induced by a gradual load. In addition, we found that enhanced variability of error size (through the introduction of varied magnitude of resistant force perturbation) seems may facilitate motor learning and induce a retention of the aftereffect in children with CP. Results from this study suggest that gradual application of a swing phase resistance load may be more effective in inducing long-term retention of increased step length in children with CP. Results from this study may be used to develop a robotic training paradigm for improving walking function of children with CP.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humov.2018.11.006.

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