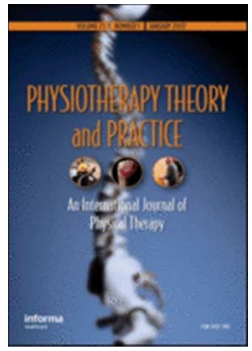

Lower limb joint moments on the fast belt contribute to a reduction of step length asymmetry over ground after split-belt treadmill training in stroke: A pilot study

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ABSTRACT

The main goal was to investigate changes in muscle activity and joint moments related to step length (SL) symmetry improvements in individuals post-stroke following repeated split-belt treadmill (SBT) walking. Twelve individuals with a first unilateral cerebral stroke presenting initial SL asymmetry (ratio=1.10-2.05) (mean age 52 (SD 9.3 years); mean time post stroke 23 (SD 24.7 months); were included. Participants were trained during six sessions of SBT walking using an error-augmentation protocol. The training resulted in a reduction in SL asymmetry during walking over ground retained over one-month post-training (p=0.002). Significant increases in SL and joint moments (plantarflexors: 20-60%, knee flexors: 20-60% and hip extensors: 0-20% of the gait cycle) were observed on the side trained on the fast belt (effect size from 0.41 to0.60). The improvement in SL symmetry was observed with an increase in plantarflexion joint moment symmetry. Changes in muscle activity varied among participants. In contrast to previous findings with a single exposure to SBT-training, our results showed no negative effects on paretic plantarflexors when walking over ground after repeated exposure to SBT walking. These findings justify larger trials to gain more solid information on the current protocol which appears as an efficient training for long-term recovery on SL asymmetry and on affected plantarflexors.

Keywords: Stroke; symmetry; training; muscle activity and joint biomechanics

INTRODUCTION:

Stroke survivors live with different motor and cognitive impairments (HSF, 2016) impeding their ability to perform activities of daily living (e.g., self-care or walking) (Harris and Eng, 2004; Lord et al, 2004). The probability of regaining independent walking 3-6 months post-stroke was found to be about 60% (Lord et al, 2004; Preston et al, 2011). Among those who recover independent walking capacity, a substantial number still present slow and asymmetrical gait (Ada, Dean, and Lindley, 2013; Kollen et al, 2005; Lord et al, 2004; Patterson et al, 2008). Step length (SL) asymmetry is considered as particularly resistant to conventional gait therapy (Patterson et al, 2015). Only 14% of patients reduced their initial SL asymmetries compared to improving walking speed (30%) and balance (62%). Treadmill interventions (fast walking, bodyweight support) or auditory feedback led to improvements in temporal (e.g., stance duration), but not spatial (e.g., step length) asymmetries (Combs, Dugan, Ozimek, and Curtis, 2013; Hassid et al, 1997; Lamontagne and Fung, 2004; Schauer and Mauritz, 2003; Thaut et al, 2007).

Yet, there is growing evidence on the successful reduction in SL asymmetry in individuals post-stroke after split-belt treadmill (SBT) walking. Repeated exposure to SBT walking led to clinically and statistically relevant reductions in SL asymmetry during walking over ground that were maintained over one month (Betschart, McFadyen, and Nadeau, 2018; Reisman et al, 2013). These training protocols induce gait adaptations through error-augmentation which was investigated in previous cross-sectional studies measuring effects of a single exposure to SBT walking (Bastian, 2008; Lauzière et al, 2014; Malone, Bastian, and Torres-Oviedo, 2012; Reisman, Wityk, Silver, and Bastian, 2007; Reisman, Block, and Bastian, 2005). In individuals post-stroke with initial SL asymmetry, a single exposure to SBT led to a more symmetrical pattern when the side with the shorter step walked on the faster belt regardless which side, paretic or non-paretic, was placed on the faster belt (Betschart et al, 2017; Lauzière et al, 2014; Malone and Bastian, 2013; Reisman et al, 2007). These after-effects in SL were moderately to strongly associated with an increase in plantarflexion moment (Lauzière et al, 2014) and muscle activity (Betschart et al, 2017) on the side that walked on the slower belt. Fast belt walking led to an increase in dorsiflexor, hip flexor and knee extensor activities (Betschart et al, 2017) and a decreased plantarflexion moment particularly during mid and late stance (Lauzière et al, 2014). As for SL, these changes in lower limb kinetics, and muscle activity were found regardless of which side was on the faster belt (non-paretic or paretic leg). It is important to highlight this last aspect since it indicates that paretic and non-paretic sides behave in the same way when exposed to the same belt speed (fast or slow). Consequently, if the shorter step is on the paretic side, SBT training (paretic fast and non-paretic slow) might cause a decrease of paretic plantarflexor utilization which is not a desirable effect in post-stroke locomotor training. Decreased use of the plantarflexor muscle group is known as a factor for reduced walking speed in individuals post-stroke (Milot, Nadeau, Gravel, and Requiao, 2006; Nadeau, Gravel, Arsenault, and Bourbonnais, 1999). Since the plantarflexors are recognized as main contributors of energy generation in normal walking (Teixeira-Salmela et al, 2008; Zajac, Neptune, and Kautz, 2003), generally, we seek training that improves the use of the paretic plantarflexors. However, up to date there is a lack of analysis on the joint mechanics and muscle activity in line with changes in SL asymmetry after repeated exposure to SBT walking.

For this purpose, the pilot study aimed to assess the changes in kinetics, and muscle activity underlying SL symmetry changes after repeated SBT walking. The focus was to analyze the effects on the side trained on the slower belt and faster belt along with SL changes. Furthermore, with this pilot study, we investigated if repeated exposure to SBT walking reduces joint moments (Lauzière et al., 2014) or muscle activity in the plantarflexor group on the fast belt as suggested by previous studies (Lauzière et al., 2014; Betschart et al., 2017) assessing immediate after-effects of a single exposure to SBT. Based on these previous findings, we hypothesized that the effects of repeated exposure to SBT walking on joint moments and EMG activity would be most pronounced on the plantarflexors trained on the slow belt.

METHODS

Participants

Twelve individuals with chronic stroke (9 with left hemiparesis; 2 women) participated in the study. A detailed explanation of the inclusion and exclusion criteria, the clinical evaluation (including evaluation of gait ability, communication and cognitive deficits) are presented in a previous publication on the effects of the current protocol on SL asymmetry, speed, endurance as well as its feasibility in a clinical setting (Betschart, McFadyen, and Nadeau, 2018). The relevant characteristics of participants in the scope of this study are presented in Table 1. All participants signed informed consent approved by the local ethics committee.

Evaluation

Participants underwent four evaluation sessions. The first evaluation consisted of a clinical assessment of participants' eligibility. Included participants were then assessed: 1-2 days prior to the training (pre-evaluation), 1-2 days after the last training (post-evaluation) and four weeks after post-evaluation (follow-up evaluation). During these three evaluations, participant's gait pattern was quantified with clinical and biomechanical measures. In the present paper, bilateral lower limb joint moments and muscle activities are reported. No evaluation was conducted during the training sessions. These clinical parameters were evaluated within the scope of the previous publication to study the effects of repeated SBT walking on clinical gait parameters (Betschart et al, 2018). The present paper presents the effects of SBT walking on muscle activity and joint net moments in this group of participants.

Please insert Table 1 here.

Biomechanical evaluation

Data collection

Spatiotemporal, biomechanical and electromyographic (EMG) data were collected while participants walked over a 5-7m walkway at comfortable speed. Thirty-four active infrared markers were placed on the lower limbs and pelvis to capture 3-dimensional kinematic data (Optotrak Motion Capture Certus System; 60 Hz). A wireless TeleMyo DTS system (Noraxon Inc. USA) was used to capture EMG signals (1200 Hz) from five lower limb muscles assessed bilaterally: tibialis anterior (TA), gastrocnemius lateralis (GL), vastus lateralis (VL), rectus femoris (RF) and semitendinosus (ST). Self-adhesive surface electrodes (Ag/AgCl) were placed over the respective muscle bellies. Standard skin preparation and electrode placement were used (Merletti, 1999). Ground reaction forces (GRFs; 600 Hz) were recorded by three floor-integrated force plates. Walking trials were repeated until at least five valid (leading foot on force plate during initial contact) gait cycles were obtained for each leg. To avoid fatigue, participants were allowed to take breaks between the trials.

Data analysis

Kinematic and force data were filtered with Butterworth, 4th order, zero-lag, filters at cut-off frequencies of 6Hz and 10Hz, respectively. Kinetic data were resampled at 60Hz for offline synchronization to kinematic data. Sagittal plane net joint moments at the ankle, knee and hip joints were estimated using an inverse dynamic approach (Chowdhury and Kumar, 2013; Winter, 2009). Specific peak net joint moments during the gait cycle were identified (e.g., peak plantarflexion moment during push-off). Cycle duration, SL and walking speed were determined from the heel marker and the vertical GRF data. Cycle duration was the time between subsequent foot contacts and normalized to 100%. SL was defined as the anterior-posterior distance between the trailing and leading heel markers for two consecutive contacts (Reisman et al, 2007). EMG signals were band-pass filtered using a Butterworth, 4th order, zero-lag filter at 20-400Hz. For each trial, RMS values were calculated over 300 signal points and time normalized with the gait cycle (100%). For amplitude normalization, the RMS value was expressed as a percentage of the average peak RMS value obtained from the first trial on the same evaluation day (Blanchette, Moffet, Roy, and Bouyer, 2012; Cronin et al, 2015). For comparison, the mean RMS values of time normalized gait cycles were used (Betschart et al, 2017).

SL asymmetry was calculated by the following simple ratio (Betschart et al, 2018; Lewek and Randall, 2011; Patterson et al, 2010).

$$Symmetry\ ratio\ \ \frac{L}{S} = \frac{Longer\ SL}{Shorter\ SL} = \frac{Slow}{Fast}$$

For symmetry ratios of net joint moments and muscle activity, the higher value (paretic or non-paretic) was divided by the lower value. This corresponds to the ratio used for SL.

Training protocol and sessions

The present protocol was tested in a previous study for its effects on different gait parameters during walking over ground at 1-day post-training and at a 1-month follow-up (Betschart et al, 2018). The biomechanical variables and muscle activity were obtained from the 12 participants analyzed in the scope of this prior investigation. A detailed description of the protocol can be found in the aforementioned paper.

In general, the training consisted of six sessions (2-3 sessions/week) of error-augmentation based SBT (Bertec Inc.) walking conducted by trained physiotherapists. Participants were trained during 20 minutes of walking on a split-belt configuration with a belt speed ratio of 2:1 (slower belt set to comfortable speed). The leg with the shorter SL walked on the faster belt (fast leg) (Lauzière et al, 2014; Malone and Bastian, 2013; Reisman et al, 2007). Therefore, for participants with a shorter paretic SL, the paretic leg was on the fast belt (paretic-fast group) and vice versa for participants with shorter non-paretic SL (non-paretic-fast group). Comfortable belt speed was tested and adjusted prior to each training session by increasing or decreasing speeds of both belts in 0.05m/s intervals until comfortable speed was attained. The participants were motivated to achieve 20 minutes of split-belt walking and were allowed to take breaks. After the 20 minutes of split-belt walking, participants walked again at tied-belt configuration without any verbal or visual feedback. This period served as a cooling down period and for safety so that participants did not pass directly to walking over ground. During the entire training on the SBT, participants wore a safety harness without body-weight support and were allowed to hold the handrails.

Statistical analysis

Descriptive statistics are presented for demographical information and stroke characteristics. For the statistical analysis, data were separated into "slow" and "fast" sides. With two training groups, this means that the joint moments and muscle activity changes were analyzed regardless of which side was on the faster belt (non-paretic or paretic leg) since previous studies on single exposure showed that the paretic and non-paretic sides behave in the same way when exposed to the same belt speed (fast or slow) (Lauzière et al, 2014; Reisman, Wityk, Silver, and Bastian, 2007).

Normal distribution of dependent variables was tested with the Shapiro-Wilk approach to define whether parametric or non-parametric statistics should be used. The effect of training over time (pre-, post-, follow-up-evaluations) on dependent variables (within-subjects) was tested with repeated measures ANOVAs or a Wilcoxon paired signed-rank test using SPSS 22.0 (SPSS Inc.). Effect sizes were computed for effect of time using Hedges's g_{av} (Lakens, 2013), which is a Cohen's *d* value corrected for the sample size. Post-hoc analysis with Bonferroni correction was conducted on parametric data to locate the effects on dependent variables between the three evaluations. The level of significance was set at $p \leq 0.05$.

RESULTS

Among the twelve participants, only one participant stopped during the fifth session of training because of unspecific pain in the paretic foot. This event did not prevent the participant performing post- and follow-up evaluation. Two participants had difficulties during pre-evaluation to step with only one foot on a force plate because of very short SL. Among these two, EMG data from one participant was lost during the post-evaluation session due to signal cut-outs. While attempting to collect more trials, the evaluation had to be stopped because of fatigue. Thus, results are presented for ten participants. Four participants were trained with the paretic side (shorter step) on the fast belt and vice versa for the remaining six participants. Data in all parameters, except for joint moment and EMG asymmetry ratios, were normally distributed.

Changes in SL symmetry and walking speed

Six sessions of SBT training resulted in improved SL symmetry during walking over ground one day post-training from an average ratio of 1.28 to 1.14 (p=0.002) and remained improved for one month (p=0.013; Table 3) along with significant improvements in walking speed at one-month follow-up (+0.16m/s; p=0.009) (Table 2). SL increase on both sides with significant values observed on the fast side between the pre- and 1-month follow-up evaluations (p=0.038) (Figure 1, Table 2). Effect sizes for changes in SL symmetry and speed were, in general, large particularly between the pre- and follow-up evaluations.

Please insert Figure 1 here.

Please insert Table 2 here

Net joint moments

A significant increase in peak net joint moments (plantarflexion: 20-60% and hip extension: 0-20%) during stance phase while walking over ground was found only on the limb which was trained on the faster belt between the pre- and 1-month follow-up evaluations (Figure 2; Table 2). Fast knee flexion moment (20-60%) increased between pre-and post-evaluation. No changes were observed for the net moments in dorsiflexion, and knee extension during early stance and hip flexion during late stance.

For the plantarflexion moment trained on the fast belt, an increase (+12%) was observed at the end of the stance phase (40-60% of the gait cycle). This corresponds to the initiation of foot push-off.

Fast peak knee flexion moments and hip extension reached on average 23% and 28% of change, respectively. The Hedges's g_{av} scores for significant changes in net moments were generally low except for fast plantarflexion (0.60) and fast hip extension moments (0.58) between pre- and follow-up evaluations.

The ratios of symmetry in net joint moments did not reveal any significant changes after six sessions of training and at 1-month follow-up (p>0.05) (Table 3) except for the plantarflexion moment (p=0.052) (baseline vs. 1-month follow-up) which improved symmetry ratio with a moderate effect size (0.75).

Please insert Figure 2 here.

In addition to the comparison between "slow" and "fast" sides, we also examined the data from paretic and non-paretic sides which revealed tendencies of similar direction of changes (increase or decrease). The separation of effects on paretic and non-paretic joint moments for the total group and between training groups (NP-fast and P-fast) has been reported as supplementary results with respect to the small number of participants per group (Figure S1-S2; Table S1, supplementary data).

Please insert Table 3 here.

Muscle activity

Muscle activity during walking over ground showed large variability in changes among the ten participants. Group mean muscle activity (%max RMS) did not change over time for all muscles analyzed for both slow and fast sides (p>0.17) (Figure 3) nor did the indices of symmetry between sides change (p>0.40; values not presented). For all muscles tested, effect size remained small with Hedges's g_{av} scores ranging from 0.15-0.34. However, the GL muscle showed a Hedges's g_{av} of 0.55 (pre- to post-evaluation) which is considered as moderate.

Please insert Figure 3 here.

DISCUSSION

The present study investigated changes in lower limb muscle activity and net joint moments in ten individuals post-stroke during walking over ground after six sessions of SBT training which aimed to improve SL asymmetry. Results from our participants were analyzed at 1-day and 1-month post-training. Clinical and laboratory data showed that after six sessions of SBT-training, all ten participants improved SL symmetry and walking speed. Further, contrary to our assumption observing main effects on the side trained on the slower belt, repeated exposure to SBT-walking resulted in effects particularly on the plantarflexors trained on the fast belt. Thus, no negative effects were observed such as found immediately after a single exposure (Lauzière et al, 2014).

Lower limb net joint moments increased on the fast side after repeated exposure while changes in group average lower limb muscle activity did not reach the significant level.

Possible explanations and recommendations for future studies to better understand long-term effects of error-augmentation based improvements in SL asymmetry will be given below.

Changes in SL and SL asymmetry

Repeated exposure to SBT walking reduced SL asymmetry at 1-day post-training and was maintained over one month. In general, these changes in SL asymmetry were achieved by a bilateral increase in SL with more consistent increase among participants on the side trained on the fast belt (Figure 1A-B), in accordance with previous findings (Reisman et al, 2013). And the accentuated increase in fast SL confirms the previous suggestion that the side with the shorter SL should be trained on the faster belt if reduced SL asymmetry is desired (Lauzière et al, 2014; Malone and Bastian, 2013; Reisman et al, 2007). For a detailed discussion on the findings of the clinical data and spatiotemporal parameters, please see the previous paper analyzing the same group of participants (Betschart et al, 2018).

Changes in joint moments

With the changes in SL, we observed increases of hip extension, knee flexion and plantarflexion moments on the side trained on the fast belt. An increase of hip extension moment trained on the fast belt was previously found as well after a single exposure to six minutes of SBT walking in individuals post-stroke (n=20) and healthy controls (n=10) (Lauzière et al, 2014). The 28% increase in hip extension moments observed in our group is more pronounced than 17.1% of change found by Lauzière et al (Lauzière et al, 2014). For the plantarflexion moment, the amount of change was closed to the one reported after one single-session (12% vs. 16%) but was observed on the opposite side (fast belt instead of slow belt).

It is known that the plantarflexors (particularly m. soleus) contribute to the forward progression of the trunk which has a direct influence on the SL of the contralateral side (Kepple, Siegel, and Stanhope, 1997; Winter, 2009; Zajac, Neptune, and Kautz, 2003) and among hip and knee-controlling muscle groups particularly plantarflexors were found associated with SL asymmetry when measured as joint moments, effort (Lauziere et al, 2015; Lauzière et al, 20142014) and moment impulse (Allen, Kautz, and Neptune, 2011). In the present study, the participants had six sessions of SBT with each session being longer (10 vs 6 minutes) than those of Lauzière et al. (2104). In addition, walking was assessed overground which might affect the gait pattern reorganisation.

More relevant is that plantarflexion as well as hip extension moments, increased bilaterally after training (although it was only significant on one side), thus no reduction in joint moments were observed that will be considered detrimental effects for the individuals after stroke. Therefore, the present findings indicate that the current protocol leads to improvements of the use of paretic muscle groups which are frequently affected secondary to stroke (Allen et al, 2011; Kim and Eng, 2004). Taking into account that in current literature repeated exposure to SBT walking is considered as one of the few interventions with long-term improvements in SL asymmetry. With the present data we have some first indications the causality of SL asymmetry can be influenced with the error-augmentation based SBT as a training approach.

Both, the protocols of the above mentioned cross-sectional studies and the present one, are based on the error-augmentation principle using comfortable speeds on the slower belt and double speed for the faster belt (2:1). Thus, two factors might explain our findings that were more pronounced on the side trained on the fast belt: 1) the parameters were analyzed during walking over ground; 2) with participants walking at their preferred speed which was faster at 1-month follow-up (+0.16m/s) when compared to pre-training. In the previous cross-sectional studies after-effects on joint moments and EMG data were analyzed during treadmill walking at controlled speeds. Since it is known that hip extension and plantarflexion net moments increased with gait speed in individuals post-stroke (Allen et al, 2014; Nadeau et al, 1999) and healthy controls (Goldberg et al, 2008), the effect of speed cannot be ruled out entirely.

Nonetheless, the increase in hip extension and plantarflexion moments were more pronounced on the fast side. The 'asymmetrical' increase in these joint moments suggests dominant changes on the fast-belt and thus potential contribution to the changes in SL symmetry and not only an association to the increase in walking speed. Interestingly, the reduction in SL asymmetry was not observed in line with an improvement in joint moment ratios except for plantarflexion (Table 3).

Changes in muscle activity

Six sessions of SBT training did not induce consistent changes in lower limb muscle activity in the present group of individuals with chronic stroke. The small sample size for this pilot study has a risk of a type II error (Sullivan and Feinn, 2012) by concluding that no effect was found when there actually might be one. Yet, the lack of effect is supported by the small effects sizes (range 0.15-0.32) found generally for the changes in muscle activity from pre- to post- and pre- to follow-up. Based on this statistical information, one can likely assume that the SBT training did not induce reasonable and consistent effects on average muscle activity in the present post-stroke group. It would be interesting to further examine muscle activities at specific phases of the gait cycle. This might reveal specific effects of training on EMG activity.

From a more clinical point of view, such variable effects on average muscle activity post-stroke during walking over ground after training intervention is not that surprising. Changes in EMG pattern (signal duration and amplitude) were not necessarily associated with changes in gait pattern (Buurke et al, 2008) or gait ability (Den Otter, Geurts, Mulder, and Duysens, 2006) over time in previous studies.

Six sessions of SBT walking did not lead to significant changes in joint moments (except for knee flexion moment during stance phase) and muscle activity at post-evaluation. The changes reached significance, however, at follow-up evaluation. Additional training between 1-day and 1-month post-training can be excluded as participants reported that they did not partake in such additional training, but participants reported verbally that they had more "confidence in walking", "walked more", felt that they could walk faster and use "more consciously" their more-affected (paretic) side. Therefore, six sessions of SBT led to a learning effect since the pattern has not been washed-out between the last training session and follow up evaluation. In contrast, the new pattern of walking and muscle utilization was retained. And an augmented exposure to walking as well as an increased and more appropriate use of affected muscles post-training may have contributed particularly to the significant improvements from post- to follow-up evaluation. As far as SL asymmetry is concerned six sessions led to a maintained reduction of SL asymmetry. But with the present findings it is suggested investigating a larger number of training sessions in future studies when analysing biomechanics and muscle activity in SBT walking.

STUDY LIMITATIONS

In the present study, walking speed during biomechanical evaluation was not standardized to the speed at pre-evaluation. However, this would probably have altered participants' natural gait pattern (Liu et al, 2014) and biased the conclusion about effects of SBT training on outcome parameters during walking over ground.

In addition, this pilot study revealed that a sample size of ten participants resulted in small to moderate effect sizes for EMG data. The small sample size, together with the heterogeneity of the training-induced EMG changes, is a limitation that requires careful interpretation of the results.

FUTURE STUDIES

This pilot study revealed first results on the joint moment changes in line with long-term improvements in SL asymmetry and walking speed. In order to obtain more solid information about the role of plantarflexors in changes in SL symmetry, participants should be assessed at the same speed and also at natural speed to have the effect on gait ability. No reduction of the paretic plantarflexor utilization was observed when trained on the faster belt. Therefore, a larger trial could compare the effects on joint moments and muscle activity of SBT training with NP side on the fast belt or the paretic side on the fast belt with a probable small risk of reducing plantarflexor utilization. According to a power calculation with the present data of joint moments and SL symmetry, a sample size of 14 to 18 in each group is recommended for the outcomes respectively (power=0.80; (Noordzij et al, 2010)). With larger samples in each training group, it could be investigated if individuals post-stroke trained paretic-fast or paretic-slow would benefit the same from this training program. Power calculation was obtained from a formula suggested for randomized controlled trials (Noordzij et al, 2010). The formula requires, among others, a relevant difference for the outcomes compared and the population variance. The difference between the average plantarflexion moment in the P-fast group (0.760 Nm/kg) and the average found in the NP-fast group (0.929 Nm/kg) was considered as relevant change. For population variance (SD), the average SD was taken from the total number of participants (0.159).

Conclusion

Improvements in SL symmetry tend to be particularly regulated by the leg trained on the faster belt and the plantarflexors. The analysis of muscle activity was not conclusive and showed large variability in changes among the 10 participants. Repeated SBT training did not induce adverse events in plantarflexion net joint moments as hypothesized in a previous study on single exposure to SBT (Lauzière et al, 2014). A controlled trial with large groups is required to test whether the SBT training for SL symmetry produces the same biomechanical benefits for individuals trained with the paretic side on the fast belt and a second group trained with the paretic side on the slow belt.

Conflict of interest

There are no conflicts of interest to disclose.

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Dear Dr Hasson,

Re: "Lower limb joint moments on the fast belt contribute to a reduction of step length asymmetry over ground after split-belt treadmill training in stroke: A pilot study"

We greatly appreciate the possibility to continue the revision of the above-mentioned manuscript. We feel that the reviewers' and your comments have helped us again to further improve the manuscript, particularly for the section Discussion. We modified the title, revised the abstract, expanded the discussion, and pointed out the novel aspects about this study. We would like to point out again that with the present study the design of a pilot study and the number of participants were chosen based on the hypothesis from prior cross-sectional studies of potential negative effects on joint mechanics. Taking into account the reported effect size and confidence intervals we feel, that with the present pilot data new knowledge for future studies was accommodated with a sufficiently strong data set. We would like to mention that the title has been modified in order to reduce the number of words and improve its expressiveness.

Enclosed is a point-by-point response to the comments made by the reviewers. The revised manuscript (1) was uploaded to the website.

Comment by comment response

Referee#1:

Page 1, Lines 12-17: These sentences that conclude the abstract are vague and unclear ("some participants displayed important modifications," "our results bring some nuances that warrant consideration," etc.) when it comes to representing the crux of this paper. I would recommend revising with clearer language.

Answer: Thank you for this relevant comment. In order to conclude on our findings in a more solid manner the lines 12 – 17 in the abstract were modified as follows: "Changes in muscle activity varied among participants. In contrast to previous findings with a single exposure to SBT-training, our results showed no negative effects on paretic plantarflexors when walking over ground after repeated exposure to SBT walking. These findings justify larger trials to gain more solid information on the current protocol which appears as an efficient training for long-term recovery on SL asymmetry and on affected plantarflexors."

Page 8, Lines 5-10: I am confused as to how the 12 participants were cut down to 10. You describe the loss of one participant due to foot pain, two lost due to difficulty with pre-evaluation, and one lost due to EMG cut-out. Twelve minus four is eight. Please clarify.

Answer: In total we lost data from two participants during pre-evaluation. Signals from the force plate from two participants and among these the EMG signals from one were not usable for analysis. The data from the participant with foot pain was still included for all analyses. The consequence of the foot pain was a reduction of total number of training session from 6 to 5.

Since the event did not occur during evaluation sessions post-training this did not prevent to use the data collection from post- and follow-up evaluation. In order to avoid confusion in the manuscript the first paragraph of the section "Results" was modified as follows: "Among the twelve participants, only one participant stopped during the fifth session of training because of unspecific pain in the paretic foot. This event did not prevent the participant performing post- and follow-up evaluation." (page 8 , lines 18-20) … "Among these two, EMG data from one participant was lost during the post-evaluation session due to signal cut-outs." (page 8, lines 22-23)

Page 10, Lines 22-23: The authors allude to a hypothesis that repeated exposure to SBT walking would result in negative effects on the paretic plantar flexors, but this was not clearly put forth at the end of the introduction, along with the other hypotheses. This point was certainly discussed with respect to the findings of Lauziere, et al., but it was not clear to me that detrimental effects were expected by the current authors. This point is again brought up by the authors' in the conclusion.

Answer: With respect to this comment we added the following assertion at the end of our introduction (page 5, lines 2-5): "Furthermore, with this pilot study, we investigated if repeated exposure to SBT walking reduces joint moments (Lauzière et al., 2014) or muscle activity in the plantarflexor group on the fast belt as suggested by previous studies (Lauzière et al., 2014; Betschart et al., 2017) assessing immediate after-effects of a single exposure to SBT."

Page 12, Lines 1-2: *This sentence about plantarflexion moments implies that the findings in the present paper are similar to those of Lauziere, when in fact, the leg in which the significant plantarflexor activity was found here is the opposite of Lauziere.*

Answer: With respect to this relevant comment we modified these lines as follows (page 13, lines 10-13): "More relevant is that plantarflexion as well as hip extension moments, increased bilaterally after training (although it was only significant on one side), thus no reduction in joint moments were observed that will be considered detrimental effects for the individuals after stroke."

Page 12, Line 3 - Page 13, Line 6: While I appreciate the authors' attempt to explain the findings of Lauziere with respect to plantarflexor activity post-split-belt exposure, I think this whole section can be shortened, better explained, and better focused.
Moreover, there is a missed opportunity here to discuss the potential benefit of increased plantarflexor joint moments on the side in which the step was initially shorter, especially if that was the paretic side. Plantarflexors are significant contributors to leg clearance, momentum, and a healthy, full swing phase, and the introduction points out how important this muscle group is to those recovering from stroke. If repeated exposure to the split-belt treadmill can increase paretic plantarflexion on the side that was potentially taking a shorter step due to insufficient plantarflexor activation, suddenly we have evidence that this could be an intervention that induces some level of recovery of more normal walking mechanics.

Answer: In order to better explain and shorten the discussion part in line with the findings from the cross-sectional study without neglecting the comments from the previous review we modified lines 1 (page 13) to 18 (page 13) as follows: We decided to shorten the part comparing the findings with Lauzière (2014) but integrated the discussion on the potential benefits when increasing paretic muscle utilization.

(Page 13, lines 1-18): "It is known that the plantarflexors (particularly m. soleus) contribute to the forward progression of the trunk which has a direct influence on the SL of the contralateral side (Kepple, Siegel, and Stanhope, 1997; Winter, 2009; Zajac, Neptune, and Kautz, 2003) … Taking into account that in current literature repeated exposure to SBT walking is considered as one of the few interventions with long-term improvements in SL asymmetry. With the present data we have some first indications the causality of SL asymmetry can be influenced with the error-augmentation based SBT as a training approach."

Page 13, Line 22 - Page 14, Line 6: I think there is a missed opportunity to further explore why changes may not have been significant immediately-post training but present a month later. For example, the authors talk about subjects being "more confident" in their walking, and potentially walking more. But, given the clinical tone that is used throughout the introduction, it seems important to ponder the idea that these subjects, if walking more, are also walking with a more symmetrical pattern, as evidenced by the step length data. Thus, more walking with a potentially better pattern may result in improved muscle activation patterns, etc.

Answer: Thank you for this remark. We added lines 9 to 17 on page 15 in order to explore why changes may not have been significant immediately-post training but present a month later.

"Therefore, six sessions of SBT led to a learning effect since the pattern has not been washed-out between the last training session and follow up evaluation. In contrast, the new pattern of walking and muscle utilization was retained. And an augmented exposure to walking as well as an increased and more appropriate use of affected muscles post-training may have contributed particularly to the significant improvements from post- to follow-up evaluation. As far as SL asymmetry is concerned six sessions led to a maintained reduction of SL asymmetry. But with the present findings it is suggested investigating a larger number of training sessions in future studies when analysing biomechanics and muscle activity in SBT walking.”

Referee: 2

Overall, the authors have addressed the reviewers' comments. The study is under-powered, but the authors acknowledge this limitation and I can appreciate the challenge of training more participants to increase their sample size.

Minor comment: line 16 on page 7 refers to "previous studies" (added text under Statistical Analysis). Citations should be added here.

Answer: Citations were added on page 8 line 7.

Referee: 3

1. Because of the adherence to current available literature, my primary question is what is novel about this protocol? I realize the results are different, but the foundation seems to be a verification of existing literature.

Answer: There are 2 novel aspects of the protocol, hence the paper, are: 1) first analyses of effects of a repeated exposure to SBT walking on joint moments and muscle activity in individuals post-stroke; 2) this pilot study aimed to test if the detriment effects after fast belt walking on the plantarflexor joint moments found immediately after a single exposure occur as well after repeated exposure. In case of negative effects suggestions for larger and more controlled trials would have been different. In example, we’d suggested to test the training in a larger trial only in individuals with shorter non-paretic step lengths, because these individuals would not have to train the paretic leg on the fast belt.

In line with another comment by reviewer #1 the following sentences were added in order to point out the novel aspects of this protocol:

Page 3, lines 19-20: "However, up to date there is a lack of analysis on the joint mechanics and muscle activity in line with changes in SL asymmetry after repeated exposure to SBT walking."

Page 4, lines 2-5: "Furthermore, with this pilot study, we investigated if repeated exposure to SBT walking reduces joint moments (Lauzière et al., 2014) or muscle activity in the plantarflexor group on the fast belt as suggested by previous studies (Lauzière et al., 2014; Betschart et al., 2017) assessing immediate after-effects of a single exposure to SBT."

In addition:

As far as the protocol it self is concerned, a more detailed description about the novel aspects are further explained in paper Betschart et al, 2017, JEK. Basically, they are defined by the following 2 aspects: 1) only six sessions (vs. 12 sessions) resulted in significant and clinically relevant changes; 2) in the present paper, in contrast to Reisman et al 2013, we applied the adaptation of speed each training session to the actual and daily walking speed which most likely led to the combined improvements in symmetry and walking speed and 3) the protocol was tested for its practicability in a clinical setting

2. The symmetry ratio utilized doesn't allow for determination if short or long SL is paretic or non-paretic. Does this limit the assessment of symmetry given that not all had asymmetry in the same direction?

Answer: Indeed, the symmetry ratio utilized does not allow directly to tie "short" or "long" to "paretic" or "non-paretic". Despite that, the assessment of symmetry is not limited and with consideration of the training groups the reader can tie "short" or "long" with "paretic" or "non-paretic". As far as the question of limitation is concerned, the use of "slow" and "fast" in the formula and the text instead of paretic and non-paretic was particularly to avoid limitations of assessment. As indicated in the formula on page 6 "short" is equal to "fast" and vice versa for "long" (tied to "slow"). The advantage of using "slow" and "fast" instead, is that it allows to directly test and present our primary goal. More precisely, this type of description was chosen because the major goal of this SBT protocol was to increase step length on the side with shorter step length independently of the fact whether this is the paretic or the non-paretic side.

The use of such protocol was based on findings from previous cross-sectional studies which showed that the side walking on the faster belt increased step length in individuals with cerebral strokes independent if it was the paretic or non-paretic side, as described by the literature cited and described in the section introduction of the manuscript pages 2 (lines 22-23) and 3 (lines 1-3);

Your point of determination of direction of symmetry can be answered as follows: Indeed, we do have both, participants with shorter paretic as well as participants with shorter non-paretic step length. According to their direction of symmetry they were allocated to the training groups, P-fast (shorter paretic step length) and NP-fast (shorter non-paretic step length). As described with the formula on page 6 of the manuscript "fast" always refers to the side with the shorter step length and vice versa the "slow" always to the side with the longer step length. Therefore, "slow" and "fast" can be tied to "paretic" and "non-paretic".

3. Page 8, line 17: Are the SSWS gains reported at post or one month (or both)?

Answer: With respect to that comment we added "at one month follow up" to the results on SSWS on page 9 (lines 8-9) "along with significant improvements in walking speed at one-month follow-up (+0.16m/s; p=0.009) (Table 2)."

4. *Page 9, line 15: The hip flexion moment was not significant at follow-up (do not say tendency)*

5. Page 9, line 18: The data did not "approach significance", but as with the PF, they were just not significant.

Answer: We agree with the reviewer and modified the sentences as follows presenting the significant values:

Page 10, lines 1-5: "For the plantarflexion moment on the fast belt, an increase (+12%) was observed at the end of the stance phase (40-60% of the gait cycle). This corresponds to the initiation of foot push-off. Fast peak knee flexion moments and hip extension reached on average 23% and 28% of change, respectively."

6. Page 10, line 23: Please state that you did not see negative PF responses "when the short leg was on the fast belt" or were there no negative responses ever?

Answer: To respond to this question we added the information to the following sentence on page 11 (lines 15-19) in the section Discussion: "Further, contrary to our assumption observing main effects on the side trained on the slower belt, repeated exposure to SBT-walking resulted in effects particularly on the plantarflexors trained on the fast belt. Thus, no negative effects were observed such as found immediately after a single exposure (Lauzière et al, 2014)."

7. Page 11, lines 1-2. The moments are stated as being significant at follow-up, but I thought it) all of the follow-up findings were >0.08 in the text.

Answer: We understood that you found the statement in the text of the manuscript with all follow-up findings in joint moments being at significance levels *>0.08.* However, despite a detailed revision of the manuscript, particularly of the section results, we did not find such assertion. Therefore, we ask the reviewer to reconsider again the section results page 9 lines 17-20

"A significant increase in peak net joint moments (plantarflexion: 20-60% and hip extension: 0-20%) during stance phase while walking over ground was found only on the limb which was trained on the faster belt between the pre- and 1-month follow-up evaluations (Figure 2; Table 2)." and lines (1-3, page 10):

"For the plantarflexion moment on the fast belt, the increase (+12%) was observed at the end of the stance phase, from 40-60% of the gait cycle. This corresponds to the initiation of foot push-off."

Table 1: Participants' demographics and stroke characteristics

	Age (years)	**Time post-stroke** (months)	**Paretic side**	**Side of shorter step**	**Initial asymmetry** ratio L/S	**Initial gait speed*** (comf./fast) (m/s)	**Chedoke Foot/Leg** (/7)
P1	*55*	*48*	*Left*	*NP*	*2.05*	*0.74/0.74*	*3/4*
P2	53	15	Left	NP	1.78	0.59/0.75	1/6
P3	73	9	Right	NP	1.45	0.58/0.85	2/6
P4**	58	8	Right	P	1.45	0.92/1.39	5/6
P5	49	6	Left	NP	1.42	0.72/1.04	2/6
P6	39	40	Left	NP	1.31	1.21/1.65	5/6
P7	*60*	*21*	*Left*	*NP*	*1.28*	*0.74/1.05*	*3/6*
P8**,[f]	50	21	Left	P	1.27	0.63/0.76	1/3
P9	52	12	Right	NP	1.22	0.62/0.96	3/5
P10**	43	88	Left	P	1.19	0.58/0.93	1/4
P11	49	19	Left	NP	1.15	1.01/1.64	6/7
P12**, [f]	58	14	Left	P	1.10	1.06/1.36	5/7
Mean	**53.3**	**25.1**	**9L /3R**	**8NP/4P**	**1.39**	**0.78/1.09**	[A] **3/6**
SD	8.7	23.5			0.28	0.22/0.33	1.8/1.2

Table 2: Kinetic, kinematic and EMG parameters at pre-, post- and follow-up evaluation (n=10)

	Pre-evaluation	**Post-evaluation**	**Follow-up (FU) evaluation**	***Post-hoc analysis***	
				Post-Pre	**FU-Pre**
	Mean (SD) [CI 95%]			*p*-value (effect size; Hedges g_{av}) [95% CI for mean differences]	
Spatiotemporal parameters					
Step length fast [a] (cm)	46.2 (9.2) [39.1, 53.2]	50.3 (9.0) [43.4, 57.3]	53.7 (10.0) [46.0, 61.4]	0.103 (0.44) [-9.12, 0.77]	**0.038 (1.42)** [-14.69, -0.44]
Step length slow (cm)	53.5 (12.7) [43.8, 63.3]	58.4 (11.0) [50.0, 66.9]	58.8 (12.6) [49.1, 68.5]	0.157 (0.41) [-11.40, 1.60]	0.227 (0.40) [-13.60, 3.00]
Gait speed comf. (m/s)	0.71 (0.18) [0.57, 0.85]	0.82 (0.18) [0.69, 0.96]	0.87 (0.19) [0.73, 1.02]	0.074 (0.59) [-0.24, 0.01]	**0.009 (0.80)** [-0.28, -0.05]
Kinetic parameters: joint moments (Nm/kg)					
Plantarflexion (20-60%)					
Fast	1.22 (0.26) [1.00, 1.44]	1.31 (0.26) [1.11, 1.51]	1.37 (0.23) [1.20, 1.55]	0.082 (0.32) [-0.19, 0.01]	**0.016 (0.60)** [-0.28, -0.03]
Slow	1.06 (0.17) [0.93, 1.19]	1.07 (0.18) [0.93, 1.20]	1.16 (0.10) [1.09, 1.23]	1.000 (0.04) [-0.09, 0.07]	0.131 (0.71) [-0.23, 0.03]
Knee flexion (20-60%) [b]					
Fast	-0.30 (0.21) [-0.48, -0.12]	-0.39 (0.21) [-0.56, -0.23]	-0.40(0.27) [-0.61, -0.20]	**0.002 (0.41)** [0.04;0.14]	0.080 (0.39) [-0.01;0.21]
Slow	-0.16 (0.15) [-0.28, -0.04]	-0.15 (0.16) [-0.27, -0.03]	-0.24 (0.20) [-0.40, -0.09]	1.000 (0.06) [-0.09, 0.07]	0.571 (0.45) [-0.09, 0.26]
Knee extension (0-50%) [c]					
Fast	0.26 (0.21)	0.28 (0.21)	0.33 (0.29)	1.000 (0.11)	1.000 (0.27)
Slow	0.39 (0.21)	0.41 (0.24)	0.40 (0.27)	[-0.12, 0.08]	[-0.20, 0.12]
Hip extension (0-20%) [a]					
Fast	0.47 (0.29) [0.30, 0.63]	0.60 (0.29) [0.37, 0.82]	0.65 (0.31) [0.41, 0.89]	0.249 (0.42) (-0.33, 0.07)	**0.037 (0.58)** [-0.36, -0.01)
Slow	0.41 (0.22) [0.24, 0.58]	0.38 (0.17) [0.25, 0.51]	0.58 (0.19) [0.43, 0.72]	1.000 (0.13) [-0.14, 0.19]	0.084 (0.78) [-0.36, 0.02]
Hip flexion (20-80%) [a,c]					
Fast	-0.53 (0.09)	-0.52 (0.06)	-0.59 (0.10)	1.000 (0.54)	1.000 (0.11)
Slow	-0.48 (0.06)	-0.57 (0.05)	-0.46 (0.06)	[-0.25, 0.24]	[-0.13, 0.25]
Muscle activity (%max EMG)*					
Tibialis anterior [c]					
Fast	60.31 (22.62)	49.95 (24.11)	55.11 (24.75)	1.000 (0.20)	1.000 (0.22)
Slow	60.28 (25.68)	59.60 (40.25)	54.47 (24.71)	[-15.39, 26.43]	[-12.5, 23.51]
Gastroc. Lat. [c]					
Fast	57.67 (25.99)	51.76 (12.40)	52.53 (20.75)	0.427 (0.55)	0.714 (0.34)
Slow	79.43 (31.83)	59.48 (24.68)	65.40 (28.09)	[-11.53, 37.40]	[-13.7, 32.84]
Vastus Lat.					
Fast	45.81 (19.90)	49.62 (24.22)	56.79 (14.98)	1.000 (0.26)	1.000 (0.15)
Slow	50.10 (23.29)	40.76 (8.99)	49.11 (20.17)	[-18.58, 24.12]	[-27.1, 17.15]
Semitendinosus					
Fast	47.94 (19.47)	61.75 (17.46)	52.53 (15.88)	1.000 (0.20)	1.000 (0.16)
Slow	68.92 (32.23)	62.45 (21.96)	75.06 (35.09)	[-23.56, 16.23]	[-29.6, 18.88]

Table 3: Group mean symmetry ratio for step length, kinetic at pre-, post- and follow-up evaluation (n=10)

	Pre-evaluation	Post-evaluation	Follow-up (FU) evaluation	*Post-hoc analysis* Post-Pre	FU-Pre
	Mean (SD) [CI 95%]			*p*-value (effect size) [95% CI for mean differences]	
Symmetry ratio (L/S); perfect symmetry = 1					
Step length	1.28 (0.16) [1.20, 1.37]	1.14 (0.09) [1.08, 1.21]	1.11 (0.08) [1.07, 1.16]	**0.002 (1.12)** [0.06, 0.22]	**0.013 (1.35)** [0.04, 0.30]
Symmetry ratio (higher value/lower value); corresponding to the calculation of step length ratio					
Joint moments					
Plantarflexion (20-60%)[a]	1.36 (0.15) [1.20, 1.50]	1.35 (0.23) [1.08, 1.49]	1.22 (0.17) [1.03, 1.34]	1.000 (0.056) [-0.13, 0.16]	0.052 (0.75) [0.00, 0.27]
				p-value (Chi-Square) [a]	
Knee flexion (20-60%)	1.63 (1.16) [0.56, 2.71]	-0.75 (3.08) [-2.10, 3.59]	1.47 (2.37) [-0.72, 3.66]	0.867 (0.286)	
Hip extension (0-20%)	1.88 (0.72) [1.21, 2.54]	2.33 (1.14) [1.27, 3.39]	2.03 (1.31) [1.12, 3.55]	0.641 (0.889)	

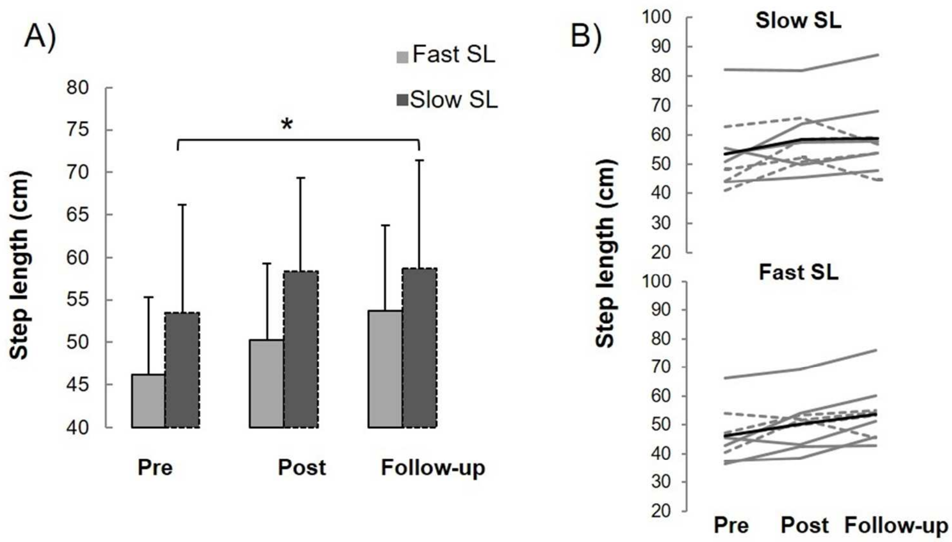


Figure 1: (A) Slow (dark grey) and fast (pale grey) step lengths (SL) during pre-, post and follow-up evaluation. B) Individual slow and fast step lengths. Group mean is illustrated in black. Dotted lines represent step lengths for participants trained in the P-fast group. *indicates significant changes from post-hoc analysis (p≤0.05).

87x48mm (300 x 300 DPI)

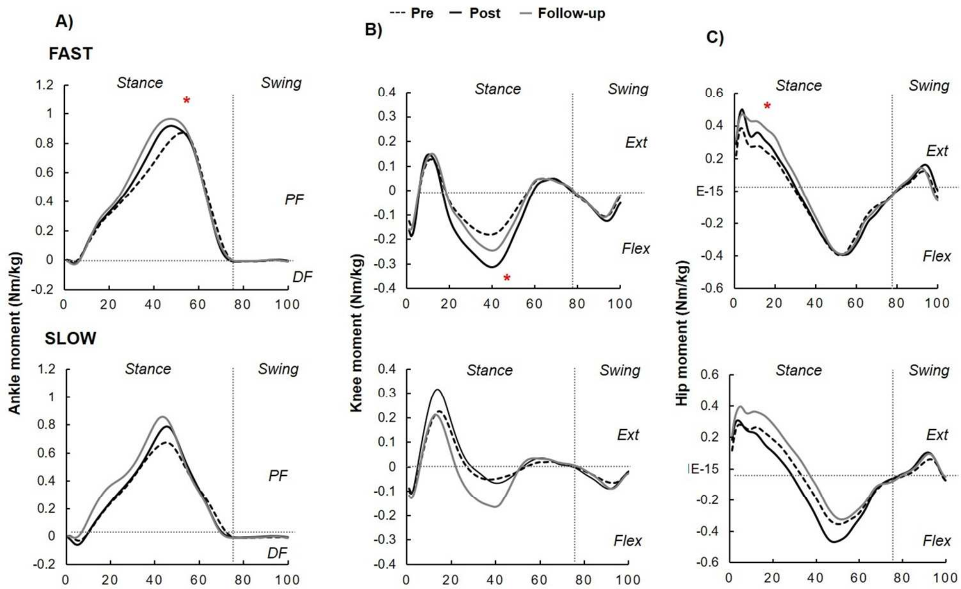
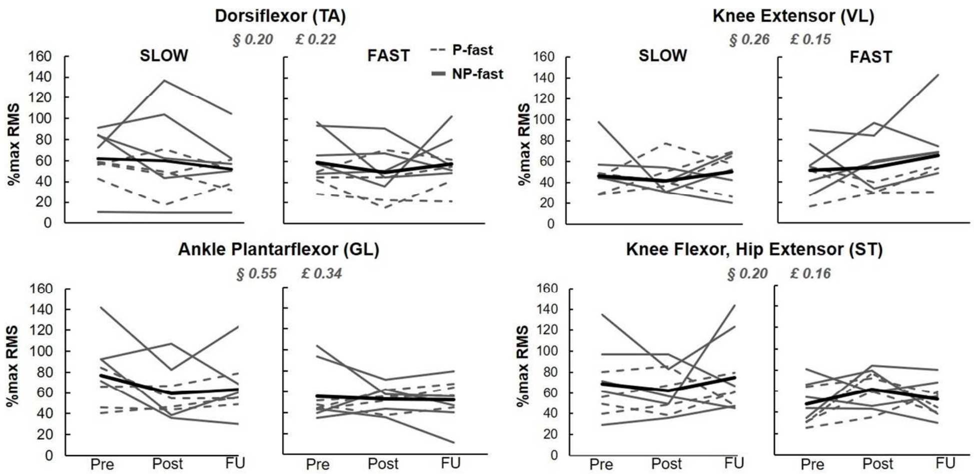


Figure 2: Fast (top) and slow (bottom) net joint moments for ankle (A), knee (B) and hip joints (C) normalized for cycle duration (0-100%; x-axes). Illustrated are group net moments during pre- (dotted line), post- (black) and follow-up (grey) evaluations. * indicates statistical significance after post-hoc analysis with Bonferroni correction (p≤0.05). Abbreviations: PF=Plantarflexion, DF=Dorsiflexion, Flex=Flexion, Ext=Extension.

123x73mm (300 x 300 DPI)



Individual EMG activity (%max RMS) during pre-, post- and follow-up (FU) evaluations. EMG values are presented in correspondence to the slow and fast sides with group means (black) and individual means (grey) for paretic-fast trained (dotted) and non-paretic fast trained (continuous) limbs. Effect sizes (Hegdes gav) are reported for the changes pre- to post- [§] and pre- to follow-up [£] evaluation considering mean values from both sides. Abbreviations: TA=Tibialis anterior, GL=Gastrocnemius lateralis, VL=Vastus Lateralis, ST=semitendinosus. *The rectus femoris muscles are not illustrated since data from 6 participants were missing for certain evaluation sessions.

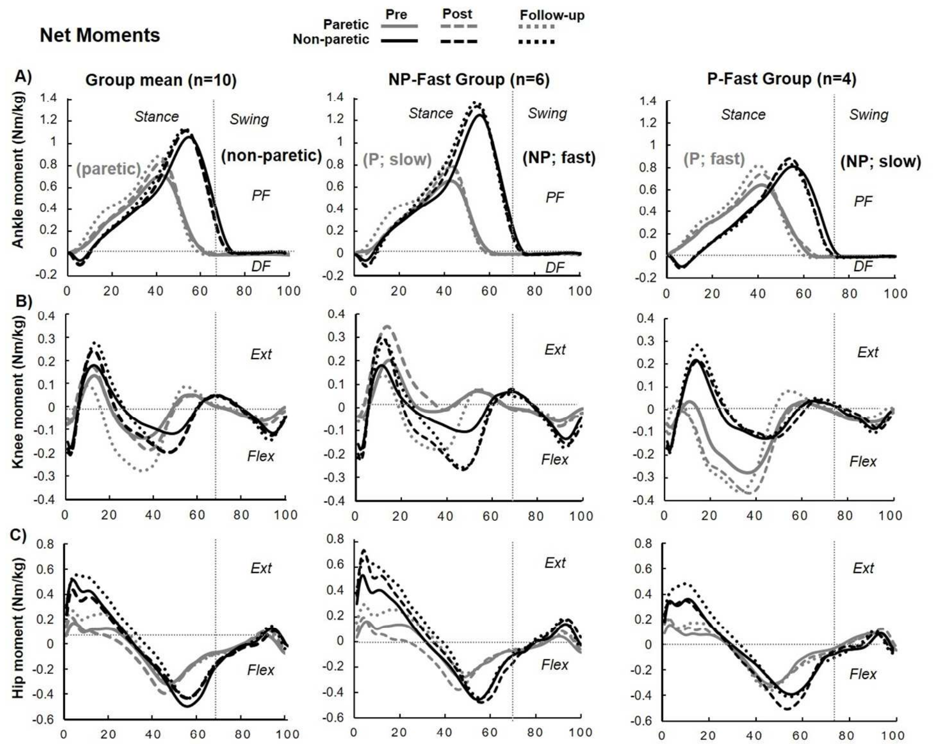


Figure (S1): Net joint moments for the paretic and non-paretic ankle (A), knee (B) and hip joints (C) normalized for cycle duration (0-100%; x-axes). Illustrated are group net moments during pre- (continuous line), post- (dashed) and follow-up (dotted) evaluations for the total group mean (left column), the NP-Fast group (middle column) and the P-fast group (right column). Abbreviations: PF=Plantarflexion, DF=Dorsiflexion, Flex=Flexion, Ext=Extension.

127x107mm (300 x 300 DPI)

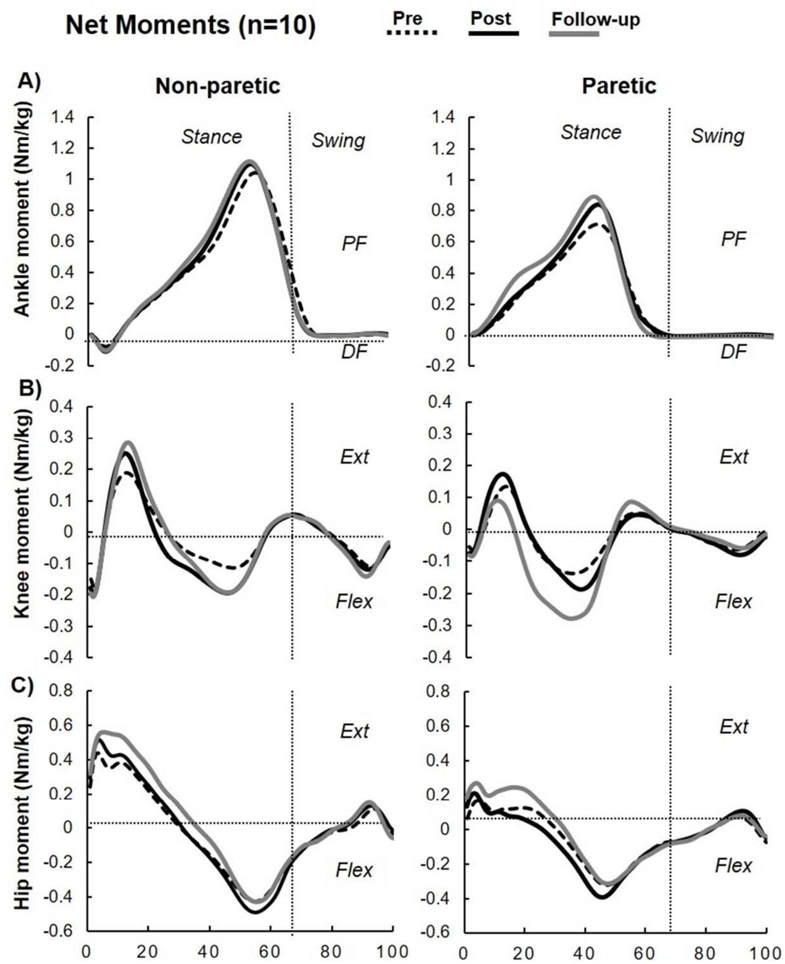


Figure (S2): Non-paretic (left-hand) and paretic (right-hand) net joint moments for ankle (A), knee (B) and hip joints (C) normalized for cycle duration (0-100%; x-axes). Illustrated are group net moments during pre- (dotted line), post- (black) and follow-up (grey) evaluations for each side, respectively. Abbreviations: PF=Plantarflexion, DF=Dorsiflexion, Flex=Flexion, Ext=Extension.

81x111mm (300 x 300 DPI)

Table 2a: Paretic and non-paretic kinetic parameters at pre-, post- and follow-up evaluation (n=10)

	Pre-evaluation	**Post-evaluation**	**Follow-up evaluation**	***Post-hoc analysis***	
				Post-Base	**FU-Base**
	Mean (SD) [CI 95%]			*p*-value (effect size) [95% CI for mean differences] *	
Kinetic parameters: joint moments (Nm/kg)					
Plantarflexion (20-60%) [c]					
Non-paretic	1.31 (0.20) [1.16, 1.46]	1.35 (0.21) [1.19, 1.52]	1.39 (0.21) [1.23, 1.55]	0.315 (0.27) [-0.13, 0.03]	**0.017 (0.76)** [-0.23, -0.02]
Paretic	0.97 (0.13) [0.87, 1.07]	1.02 (0.16) [0.90, 1.14]	1.14 (0.10) [1.07, 1.22]		
Knee flexion (20-60%) [c]					
Non-paretic	-0.20 (0.10)	-0.27 (0.11)	-0.27(0.15)	0.032 (0.21) [0.01;0.08]	0.138 (0.41) [-0.03;0.21]
Paretic	-0.26 (0.28)	-0.27 (0.30)	-0.38 (0.31)		
Knee extension (0-50%) [c]					
Non-paretic	0.31 (0.14)	0.36 (0.16)	0.41(0.27)	1.000 (0.10) [-0.12, 0.08]	1.000 (0.15) [-0.20, 0.12]
Paretic	0.34 (0.28)	0.33 (0.30)	0.32 (0.29)		
Hip extension (0-20%) [c]					
Non-paretic	0.55 (0.19) [0.40, 0.69]	0.66 (0.23) [0.49, 0.84]	0.75 (0.16) [0.63, 0.88]	0.915 (0.28) [-0.20, 0.09]	**0.035 (0.86)** [-0.34, -0.01]
Paretic	0.33 (0.18) [0.19, 0.47]	0.31 (0.14) [0.21, 0.42]	0.47 (0.25) [0.28, 0.66]		
Hip flexion (20-80%) [c]					
Non-paretic	-0.53 (0.23)	-0.60 (0.14)	-0.55(0.27)	1.000 (0.11) [-0.22, 0.04]	1.000 (0.10) [-0.13, 0.18]
Paretic	-0.42 (0.20)	-0.49 (0.19)	-0.44 (0.21)		

[a] = interaction between sides; [b] = side effect; [c] = no main effect (*in case of a not significant side and main effect post-hoc *p*-value, effect sizes and 95% CI are reported considering the total means [both sides]); legend identical to Table 2.