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RESEARCH ARTICLE | *Neural Circuits*

Non-gait-specific intervention for the rehabilitation of walking after SCI: role of the arms

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Zhou R, Alvarado L, Ogilvie R, Chong SL, Shaw O, Mushahwar VK. Non-gait-specific intervention for the rehabilitation of walking after SCI: role of the arms. *J Neurophysiol* 119: 2194–2211, 2018. First published January 24, 2018; doi:10.1152/jn.00569.2017.—Arm movements modulate leg activity and improve gait efficiency; however, current rehabilitation interventions focus on improving walking through gait-specific training and do not actively involve the arms. The goal of this project was to assess the effect of a rehabilitation strategy involving simultaneous arm and leg cycling on improving walking after incomplete spinal cord injury (iSCI). We investigated the effect of *1*) non-gait-specific training and *2*) active arm involvement during training on changes in over ground walking capacity. Participants with iSCI were assigned to simultaneous arm-leg cycling (A&L) or legs only cycling (Leg) training paradigms, and cycling movements were assisted with electrical stimulation. Overground walking speed significantly increased by 0.092 ± 0.022 m/s in the Leg group and 0.27 ± 0.072m/s in the A&L group after training. Whereas the increases in the Leg group were similar to those seen after current locomotor training strategies, increases in the A&L group were significantly larger than those in the Leg group. Walking distance also significantly increased by 32.12 ± 8.74 m in the Leg and 91.58 ± 36.24 m in the A&L group. Muscle strength, sensation, and balance improved in both groups; however, the A&L group had significant improvements in most gait measures and had more regulated joint kinematics and muscle activity after training compared with the Leg group. We conclude that electrical stimulation-assisted cycling training can produce significant improvements in walking after SCI. Furthermore, active arm involvement during training can produce greater improvements in walking performance. This strategy may also be effective in people with other neural disorders or diseases.

NEW & NOTEWORTHY This work challenges concepts of task-specific training for the rehabilitation of walking and encourages coordinated training of the arms and legs after spinal cord injury. Cycling of the legs produced significant improvements in walking that were similar in magnitude to those reported with gait-specific training. Moreover, active engagement of the arms simultaneously with the legs generated nearly double the improvements obtained by leg training only. The cervico-lumbar networks are critical for the improvement of walking.

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balance; cycling; electromyography; functional electrical stimulation; gait; task-specific training

INTRODUCTION

Spinal cord injury (SCI) leads to a partial or complete loss of motor, sensory, and autonomic function below the level of the lesion. Among the lost functions, restoring walking is one of the top desires of people with paraplegia (Anderson 2004; Ditunno et al. 2008). In general, rehabilitation paradigms to improve ambulatory capacity after incomplete SCI (iSCI) aim to strengthen muscle activation and regulate plasticity at multiple levels of the neuraxis (Field-Fote 2001). Most of the current interventions focus on progressively developing a "normal" locomotor pattern through physical therapy, body weight-supported (BWS) locomotor training, functional electrical stimulation (FES)-assisted gait training, or robotic-assisted training (Dietz 1992; Mehrholz et al. 2012; Morawietz and Moffat 2013; Wernig 2006; Wernig and Müller 1992). Nonetheless, various rhythmic motor tasks, such as walking and cycling, are controlled by a "common central nervous network," thus suggesting that non-gait-specific rehabilitation training therapies may also improve walking (Dietz 2002a; Dietz et al. 2001; Zehr 2005). The use of cycling as an intervention in rehabilitation has been recommended in the past. For example, leg cycling exercises have a positive effect on cardiovascular variables (Davis et al. 1990; Nóbrega et al. 1994), body composition (Griffin et al. 2009), and spinal reflexes (Motl et al. 2003; Phadke et al. 2009).

Furthermore, walking is more than just rhythmic movements of the legs; it also involves coordination of the leg movements with those of the arms (Kuhtz-Buschbeck and Jing 2012; Meyns et al. 2013). Arm activity can significantly modulate the neural activity of the legs in various types of rhythmic locomotion (Balter and Zehr 2007; de Kam et al. 2013b; Huang and Ferris 2009; Massaad et al. 2014; Zehr et al. 2007a), even after neural disorders (de Kam et al. 2013a; Kawashima et al. 2008; Tester et al. 2012). Kawashima et al. (2008) suggested that both passive and active upper limb movements significantly shape leg muscle activity in study participants with iSCI whose cervico-lumbar neural connections were partially preserved. People with iSCI showed better gait symmetry and more normal EMG activity when the parallel bars were removed to allow arm swing during BWS treadmill training (Visintin and Barbeau 1994). Similar observations were found in people with stroke, where increased activity in extensor muscles during stance and in dorsiflexors during swing was seen with the arms freely swinging compared with the arms holding onto the handrails (Stephenson et al. 2010). Despite this knowledge, only a few research groups have discussed the relevance of the arms in the rehabilitation of walking after SCI. Facilitating reciprocal arm swing was recommended to maintain symmetrical arm-leg kinematics during locomotor training (Behrman and Harkema 2000; Ferris et al. 2006; Zehr and Duysens 2004; Zehr et al. 2016). Tester et al. (2011) encouraged coordinated, reciprocal arm movement during locomotor training to promote arm swing and suggested that proprioceptive input provided to the arms during swing might be relevant to walking recovery post-iSCI. Although these studies suggested that the arms may have a role in rehabilitation after neural injury such as stroke (Klarner et al. 2016a, 2016b), to the best of our knowledge, there are no systematic studies that have actively involved the arms in rehabilitation interventions for improving walking in people with chronic iSCI.

In this project, we proposed the use of simultaneous arm and leg FES-assisted cycling as a rehabilitation strategy to improve ambulation. The study was conducted in people with chronic iSCI and included two groups, an arm and leg FES-assisted cycling group and a legs-only FES-assisted cycling group, and we investigated *1*) the extent of transfer of recumbent cycling into improvements in upright over ground walking and *2*) the role of the arms in the improvement of walking. We hypothesized that coordinated phasic sensory and motor activation during a rhythmic non-gait-specific cycling training paradigm would improve walking speed, distance, and quality of walking (e.g., joint kinematics, electromyographic activity, and coordination during walking) in people with iSCI. We also hypothesized that active engagement of the arms during training would provide better recovery of walking function than training without arm engagement. The results suggest that FES-assisted cycling does indeed transfer into improvements in overground walking. Moreover, active engagement of the arms simultaneously with the legs leads to larger improvements in walking than training of the legs alone. Preliminary results were previously published in abstract form (Wong et al. 2012; Zhou et al. 2012).

METHODS

Twelve people with a chronic iSCI (>2 yr) between levels C4 and T12 participated in the training. The SCIs were classified as C or D according to the American Spinal Injury Association Impairment Scale (AIS) (Maynard et al. 1997; Waring et al. 2010), as defined by the International Standards for Neurological Classifications of SCI (ISNCSCI). Normative data for gait kinematics and electromyographic (EMG) profiles were obtained from neurologically intact participants (NI; $n = 6$). The study protocol and inclusion criteria were approved by the University of Alberta Human Research Ethics Board, and all participants signed a consent form before the initiation of experimental procedures.

All participants with iSCI were capable of ambulating for short distances with varying levels of assistance (Table 1) and had residual innervation to the main muscles of the arms and legs. Exclusion criteria were damage to the nervous system other than the spinal cord, impaired mental capacity or currently taking antidepressants, history of epilepsy, spinal injury level below T12, complete denervation of the main muscles of the arms or legs, and other medical contraindications to cycling training. None of the participants was engaged in intensive activities for at least 5 mo before the initiation of training. Once training was initiated, the participants were instructed to maintain the same type and level of activities outside of the intervention as they had before training.

Training

Two training interventions were used for the participants with iSCI in this longitudinal study: arm and leg FES-assisted cycling (A&L; $n = 7$) and legs-only FES-assisted cycling (Leg; $n = 8$). FES was applied to various muscles of the arms and legs, as needed, to assist in completing the cycling task. Participants S1A, S4A, and S5A (Table 1) completed the A&L training first and then participated in the Leg group 23, 48, and 44 mo later, respectively (S1L, S6L, S7L), after their walking speed and distance had returned to the initial baseline levels. This period between training modalities, which was substantially longer than regular washout periods in crossover designs in

Table 1. *Characteristics of participants with iSCI in the A&L and Leg training groups*

Subject	Age, yr	Sex	Injury Level	Origin of Injury	Time Postinjury, yr	Primary Mode of Mobility	Walking Test Assistance	Ergometer	Group	Muscles with Stimulation
S1A	45	M	T10	Trauma/MVA	8	Crutches	Crutches	In house	A&L	Quads, Hams, Gluts
S2A	58	M	C5–C6	Trauma/MVA	36	Walker	Walker	In house	A&L	Quads, Hams, Gluts
S3A	61	M	C3–C5	Trauma	2	Powered chair	Walker	RT 200	A&L	Quads, Hams, TA, SS, Tri
S4A	50	M	C6–C7	Trauma/MVA	13	Wheelchair	Crutches + WalkAide	Berkel	A&L	Quads, Hams, Gluts
S5A	49	F	T2–T4	Disc protrusion/surgery	6	Wheelchair	Walker	In house	A&L	Quads, Hams, Gluts
S6A	44	M	T12	Trauma/sports	2	Wheelchair	Crutches	RT200 + Berkel	A&L	Hams, Gluts, TA
S7A	58	M	C4–C5	Trauma/fall	3	Powered chair	Cane	RT 200	A&L	Quads, Hams, Gluts
S1L	48	M	T10	Trauma/MVA	11	Crutches	Crutches	ERGYS	Leg	Quads, Hams, Gluts
S2L	36	F	C5–C7	Trauma/MVA	2	Wheelchair	Cane	RT 300	Leg	Quads, Hams, TA, Gastr
S3L	54	M	T4–T5	Disc protrusion/sports	4	Wheelchair	Walker	RT 300	Leg	Quads, Hams, Gluts
S4L	41	F	C6–C7	Trauma/MVA	7	Powered chair	Walker	ERGYS	Leg	Quads, Hams, Gluts
S5L	62	M	C4–C5	Trauma/MVA	44	Cane	Cane	RT 300	Leg	Quads, Hams, Gluts
S6L	53	F	T2–T4	Disc protrusion/surgery	10	Wheelchair	Walker	ERGYS	Leg	Quads, Hams, Gluts
S7L	54	M	C6–C7	Trauma/MVA	17	Wheelchair	Crutches + WalkAide	ERGYS	Leg	Quads, Hams, Gluts
S8L	30	F	C5–C6	Trauma/MVA	3	Wheelchair	Walker	ERGYS	Leg	Quads, Hams, Gluts

The primary mode of mobility was defined according to the assistive device used by the participant in coming to the laboratory for the daily training sessions. M, male; F, female; MVA, motor vehicle accident; Quads, quadriceps; Hams, hamstrings; Gluts, gluteus; TA, tibialis anterior; Gastr, gastrocnemius; SS, scapular stabilizers (rhomboids and supraspinatus); Tri, triceps.

studies of gait rehabilitation (Postans et al. 2004; Yang et al. 2014), ensured washout of carry-over effects from the A&L training before initiation of the legs-only training.

Training took place 1 h per day, 5 days per week for 12 wk, for a total of 60 h. The training setup was composed of arm/leg FES ergometers to activate the arms and/or the legs simultaneously and generate arm/leg movements resembling the coordination present during natural walking. Five types of ergometers were used based on the participants' training group, comfort, maximal power output of the ergometers, and availability of the equipment. For the A&L group, we used *1*) a custom-adapted arm and leg FES ergometer (THERA-vital, Medica Medizintechnik, Hochdorf, Germany; and ERGYS 2, Therapeutic Alliances, Fairborn, OH), *2*) an arm and leg Berkel Bike (Berkel, Sint-Michielsgestel, The Netherlands), *3*) an RT-200 arm and leg cycling ergometer (Restorative Therapies, Baltimore, MD). For the Leg group, we used *1*) an RT-300 leg cycling ergometer (Restorative Therapies) and *2*) an ERGYS 2 FES ergometer (Therapeutic Alliances). The training equipment provided computerized FES, delivered through surface electrodes to various muscles, as needed to assist movement and enable active cycling.

For both A&L and Leg groups, the FES was only applied to muscles without which the cycling task would otherwise fail or become very difficult to complete (Table 1). The stimulation was delivered to the main flexor and extensor muscles of the legs such as quadriceps, hamstrings, and gluteus maximus because of their dominant contribution to cycling. Myotomes with an AIS motor score of at least 4 did not receive FES. Depending on the cycling equipment, other muscles such as tibialis anterior and gastrocnemius were also stimulated in some participants. In the A&L group, FES was applied to the elbow extensors and scapular stabilizers (rhomboids and supraspinatus) in one participant who was unable to move the arm crank voluntarily. Participants in the A&L group were encouraged to constantly and actively engage their arms in the cycling.

Stimulation was composed of a rectangular biphasic waveform with a pulse width of 150–450 μs and was delivered at a frequency of 30–40 Hz. The maximal stimulation intensity was customized to each participant and set to the highest level that produced muscle contractions with tolerated sensation. Threshold stimulation level was set to the minimal level of stimulation that produced a visible muscle contraction. Stimulation intensity was automatically modulated between threshold and maximal intensity to facilitate cycling. Threshold stimulation intensity ranged from 10 to 60 mA in the A&L group and from 10 to 77 mA in the Leg group. The maximal stimulation intensity ranged from 30 to 100 mA in the A&L group and from 20 to 140 mA in the Leg group. Threshold and maximal stimulation levels were revisited approximately every 2 wk as the training session progressed.

The target speed of cycling was set to one level above the maximal speed at which each volunteer was able to cycle with no assistance or FES, and was retained constant throughout the training. The cycling resistance on the ergometer was progressively increased throughout the course of training (always held at a perceived exertion scale of "hard") to challenge the participants, ensure their voluntary engagement in the exercises, and enhance the sensory feedback to the spinal networks. The participants were instructed to maintain the target speed (which was displayed in front of them) as closely as possible and to report their perceived difficulty of cycling throughout the training session. The training instructions were consistently applied to ensure full physical engagement.

Assessments

Assessments including clinical and biomechanical tests were performed before, during, and after the training period. Assessments of walking speed and endurance were conducted every 3 wk throughout the period of training, whereas other clinical and biomechanical evaluations were performed every 6 wk. No FES assistance was provided during any of the assessments. To establish a reliable baseline measure, all assessments were performed two to three times before the initiation of training, and the results were averaged. Each participant with iSCI used the same self-selected assistive device during all of his/her assessments of walking speed, endurance, and biomechanics.

Clinical assessments. WALKING SPEED AND ENDURANCE. The 10-m walking test along a straight path was performed to assess the participants' maximal walking speed (Lam et al. 2008a). To assess endurance, the 6-min walking test was conducted on an 18.54-m-long oblong track and the walking distance at a self-selected speed during this time period was measured (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002; Jackson et al. 2008).

ASSESSMENT OF MOTOR AND SENSORY FUNCTION. A trained physical therapist performed the motor and sensory evaluation for the myotomes and dermatomes of the upper and lower extremities across all participants using the AIS (Kirshblum et al. 2011).

BALANCE. Balance was assessed using the Berg Balance Scale (Berg et al. 1995; Lemay and Nadeau 2010; Wirz et al. 2010). This was performed by one of the experimenters and confirmed by a trained physiotherapist.

Biomechanical assessments. To assess the changes in participants' gait due to training, biomechanical assessments were conducted before the initiation of the training and repeated after 6 and 12 wk of training. Biomechanical assessments were also performed on 6 NI subjects ranging in age from 20 to 50 yr (31 $\pm$ 11 yr, mean $\pm$ SD) to provide a reference of norm activity.

All participants were instructed to walk on a 6-m-long straight track at their preferred speed. A Vicon motion capture system (Vicon Motion Systems, Oxford, UK) with eight infrared cameras was used for kinematic data collection at a sampling rate of 100 frames/s. All reflective markers were consistently placed on the bony joints in accordance with the full body model PlugInGait (Vicon Motion Systems). Kinematic data were recorded using Vicon Workstation (version 5.2.9) and Nexus (version 1.7.3).

To assess muscle activation patterns during walking, surface EMG signals were recorded from four muscle groups on each side: soleus (SOL), tibialis anterior (TA), rectus femoris (RF), and biceps femoris (BF), through an AMT-8 EMG wire telemetry system (10–1,000 Hz; Bortec Biomedical, Calgary, AB, Canada). EMG data were sampled at either 2 or 2.4 kHz and preamplified with a gain of 500. Kinematic and EMG data were collected synchronously during walking.

Because of the heterogeneity and asymmetry of the lesion location, all kinematic and EMG data collected from participants with iSCI were analyzed for the more affected (weaker) side or less affected (stronger) side, based on the AIS lower extremity motor score obtained pretraining. If the motor score on both sides was identical, the side with the poorer performance in the biomechanical assessment was considered as the weaker side. The number of trials obtained per assessment session varied depending on the subject's ability to walk during the session and ranged from 12 to 45 steps per side.

KINEMATIC DATA ANALYSIS. All kinematic data were preprocessed with the Pipeline operation module in the Vicon system, including filling marker trajectory gaps and applying Woltring filtering. Gait events, such as heel strike and toe lift, were manually detected in each trial. Kinematic data obtained from both sides during each step were normalized to the duration of the gait cycle (0–100%) from heel strike to the next heel strike on the ipsilateral side.

1) *Spatiotemporal measures and joint motions.* Polygon analysis software (Vicon Motion Systems) was used to calculate average spatiotemporal kinematic parameters, including preferred walking speed, stride length, step length, stride time, step time, single support time, double support time, swing time, stance time, and swing time/stance time ratio (SW/ST). The symmetry of those parameters was calculated on the basis of the weaker side/stronger side ratio (Field-Fote et al. 2005; Patterson et al. 2010).

For statistical purposes, this ratio was reversed when needed to avoid the results being skewed by values <1 (Patterson et al. 2010). For defining joint angles, the anatomical neutral position was used as the frame of reference in the sagittal plane. Therefore, flexion resulted in positive joint angles and extension in negative joint angles. Joint motion data were quantified throughout the gait cycle by using parameters similar to those reported by Gil-Agudo et al. (2011).

2) *Hip-knee cyclogram.* A vector coding technique was used to evaluate the intralimb coordination of the hip and knee angles (Tepavac and Field-Fote 2001). Hip-knee cyclograms illustrated the angular positions of the two joints within each gait cycle. Vector analysis quantified the regularity of consecutive steps by calculating the average coefficient of correspondence (ACC) of the overall variability of the hip-knee coupling across all step cycles on each side. The regularity has values between 0 and 1, with 1 meaning that all cycles are identical and 0 meaning no correspondence between cyclograms of consecutive steps. The *x*- and *y*-axes of the cyclogram represent the range of motion of the knee and hip joint, respectively. The area inside the hip-knee cyclogram was calculated. This method is sensitive to changes in kinematic variables in people with iSCI and after locomotor training (Awai and Curt 2014; Field-Fote and Tepavac 2002).

ANALYSIS OF EMG ACTIVITY. The EMG signals were filtered using a 20- to 500-Hz bandpass filter, which was effective in removing motion artifacts (De Luca et al. 2010; Winter et al. 1980). The EMG signals were then rectified and low-pass filtered with a second order Butterworth filter with cutoff frequency of 6 Hz. Similar to the kinematic data, all EMG signals were diced to the gait cycles such that heel strike to the consecutive heel strike was considered as 100% stride time.

The minimal rectified EMG activity in each gait cycle was considered the no-activation level and was subsequently subtracted from all EMG values to eliminate offset. For each muscle, the root mean square (RMS) of the peak EMG signals from all the gait cycles was considered as the maximal EMG value of the muscle. All EMG values from this muscle were then normalized to this maximal value and expressed as a percentage of the normalization value.

1) *Magnitude and phase components.* To quantify the EMG activity patterns and assess changes with training, we implemented an EMG metric method described by Ricamato and Hidler (2005). This method compares EMG patterns generated during the gait cycle and was validated for assessing locomotor EMG amplitude and timing properties in subjects with intact nervous system (Ricamato and Hidler 2005). It can also be used in people with stroke or SCI for quantifying within-subject gait training performance and identifying their difference from normative gait-related EMG profiles (Schück et al. 2012). The metric contains two components: a magnitude component and a phase component with values ranging from 0 to 1. The magnitude component is "rewarded" in the metric when the recorded muscle EMG is active (greater than or equal to ~15% of the maximal recorded EMG signal) in the portion of the gait cycle where the norm EMG activity should be "on" or when the no-activation period occurs during the gait cycle where the norm EMG activity should be "off." Otherwise, the metric "penalizes" the magnitude component in conditions opposite to the norm EMG pattern for a given muscle. This removes the dependence on an absolute EMG amplitude and allows comparison between different days of EMG measurements using surface electrodes.

Similarly, the phase component examines the similarity of the timing properties between the EMG activity in participants with iSCI and normative activity. The maximal phase component (value of 1) suggests an exact match in both active and inactive phasing between the iSCI EMG pattern and the norm. For comparison with normative EMG activity, the on-off patterns of EMG activity for various muscles were determined on the basis of those in the NI subjects

2) *Intra-leg EMG burst activation.* To further quantify the timing of when the EMG activity occurred within a gait cycle, the onset and offset of the EMG burst were identified by visual inspection for each muscle for a given participant and across all testing sessions. The time span between the onset and offset was calculated as the active contraction duration of the muscle, expressed as a percentage of the cycle.

3) *Inter-leg coordination.* To measure inter-leg coordination, we calculated the onset of EMG activity in the homologous muscle of the left and right leg (e.g., left TA and right TA) during the gait cycle and determined the phase difference. Inter-leg coactivation was also analyzed as the overlap of active contraction of the homologous muscle pair during the gait cycle.

Statistical Analysis

Statistical tests were performed to identify the time effect as a function of training and determine the group difference between the two training groups (A&L and Leg). All statistical tests, except circular statistics, were performed using SPSS 23 (SPSS, Chicago, IL). Normality of data distribution was first tested using the Shapiro-Wilk test. Comparisons of the pretraining, baseline measures and demographic characteristics between the A&L and Leg groups were performed using an independent *t*-test or Mann–Whitney *U*-test based on the test of normality.

The primary outcome measures were changes in the 10-m and 6-min overground walking tests. A two-factor mixed ANOVA was performed with a post hoc test using Bonferroni correction if the main effect or interaction was significant. The two factors contained one independent factor representing the training group (A&L, Leg) and one dependent factor representing the repeated measures over time (e.g., pretraining, 3, 6, 9, 12 wk posttraining). The studentized residuals were also determined when the two-way mixed ANOVA were performed for primary outcome measures, and values greater than ± 3 were considered outliers (Stevens 1984).

The posttraining change refers to the difference between the pre- and posttraining values of each outcome measure normalized to its value at pretraining. A pairwise comparison of the 12-wk posttraining change was conducted between the A&L and Leg group for each outcome measure. In all cases, pre-to-posttraining paired comparisons were also used to illustrate the training effect within each group. Based on the test of normality, a paired *t*-test or Wilcoxon signed-rank test was used for the pre-to-post training paired comparisons. With the outcome measure that was significantly different between the two groups at pretraining, analysis of covariance (ANCOVA) was applied to compare the group difference in the 12-wk posttraining change with the pretraining measure as the covariate.

The Pearson's product-moment correlation (r) was performed to determine the relationship between walking performance (speed and distance) and the clinical outcome measures (AIS and balance scores). A multiple regression was run to predict walking performance from all clinical measures and to determine the overall R^2 value, which represents the percentage in the change of walking performance explained by the clinical measures.

Circular statistics were applied to all degree-related measures in the kinematic and EMG tests using the software package Oriana (version 4; Kovach Computing Services, Anglesey, UK). Those measures included all the joint angular motions, as well as the phase differences in the EMG activity measured in the inter-leg coordination analysis. For each measure, a paired comparison between pre- and posttraining was conducted using Hotelling's paired test. Pretraining and 12-wk posttraining data were also compared with measures obtained from intact individuals using the Watson-Williams *F*-test (Zar 2010), respectively.

Results are means ± SE (unless otherwise indicated). The statistical P value regarding the training effect over time is expressed as "Time P," whereas the group effect is expressed as "Group P." Statistical differences with $P \leq 0.05$ were considered significant.

RESULTS

Across all participants, there was an overall improvement after 12 wk of FES-assisted cycling training in overground walking speed, overground walking distance, sensory and motor function, and balance, as well as regulation in leg muscle activation and joint motion. The group trained with arm and leg FES-assisted cycling demonstrated larger improvements in most of the outcome measures compared with the group with legs-only FES-assisted cycling.

Demographic Characteristics

Twelve participants with iSCI completed the study, with three participating in both the A&L and Leg groups. Most of the participants had cervical lesions of traumatic origin (Table 1) and were AIS grade D. The age of participants in the two groups [A&L: 55 ± 10 yr; Leg: 47 ± 11 yr; means ± SD) was similar ($P = 0.16$). Moreover, the participants in the A&L and Leg groups had a similar range of time span postinjury, ranging from 2 to nearly 40 yr (A&L: 9 ± 12 yr; Leg: 12 ± 14 yr; means ± SD; $P = 0.44$].

The status of functional ambulation pretraining for participants with iSCI is detailed in Table 1. All participants were able to complete the primary measures, 10-m and 6-min overground walking tests, before training. To ensure that the three participants who took part in both training groups did not have carry-over effects from the previous training paradigm, their 10-m walking speed and 6-min walking distance before the start of both training paradigms were compared and determined to be similar. Thereafter, the two groups of participants were considered to be independent from each other.

Training Sessions

All participants completed 60 h of training. The cumulative miles cycled in each training session were reported by the equipment for six participants in the A&L group and eight participants in the Leg group. Calculation of the miles was based on the revolutions per minute (RPM) for the leg cycling portion and cycling duration. The cumulative miles can be considered a measure of training intensity solely based on the participants' leg activity, regardless of training group. By the end of the first training session, the A&L group cycled an average of 9.46 ± 0.79 miles (mean ± SD) and the Leg group cycled an average of 8.43 ± 0.74 miles, suggesting a similar level of leg function and physical fitness between groups at the onset of training. After 60 training sessions, the cumulative miles were still similar between the two groups (A&L: 654.94 ± 45.21 miles; Leg: 563.98 ± 45.41 miles; means ± SD); thus both groups received a similar intensity of leg training ($P = 0.19$).

Ten-Meter and Six-Min Walking Tests

The progression in walking speed for individual participants throughout the course of training is shown in Fig. 1, *A* and *B*. A walking speed of ~0.45 m/s (indicated by the vertical dashed line) is considered to be the minimal speed for outdoor mobility as a community walker (Perry et al. 1995; van Hedel et al. 2009). Both training groups had nearly half of the participants below (low function: A&L, $n = 4$; Leg, $n = 4$) and half above (high function: A&L, $n = 3$; Leg, $n = 4$) that speed level before the initiation of training. In both high-function and low-function subsamples of the A&L group, the absolute improvements in walking speed relative to pretraining appeared to be larger than those in the same subsamples of the Leg group; however, the differences were not significant between the two groups (high function: $P = 0.26$; low function: $P = 0.08$).

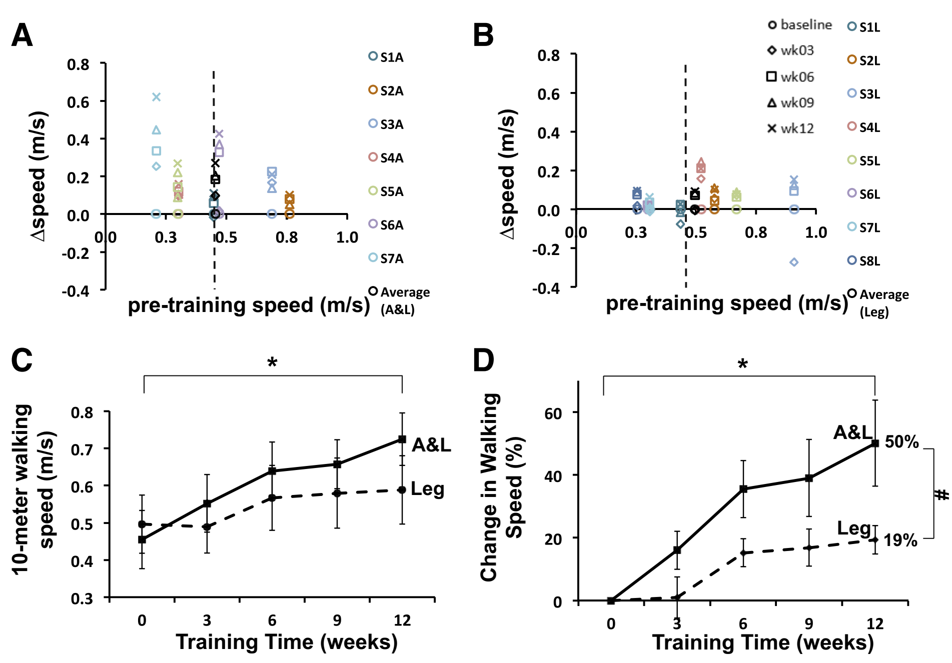

Fig. 1. *A* and *B*: absolute change in walking speed (m/s) of individual participants within the A&L group (*A*) and the Leg group (*B*). Each color represents a participant, whereas different dots of the same color represent the changes in speed compared with pretraining measured at different assessments for a given participant. Dashed line indicates a walking speed of 0.45 m/s at pretraining. *C*: average 10-m walking speed in both iSCI groups throughout training (A&L: $n = 7$; Leg: $n = 8$). *D*: average percent change in 10-m walking speed in both iSCI groups throughout training (A&L: $n = 6$ with outlier removed; Leg: $n = 8$). *$P \leq 0.05$, difference over time. #$P \leq 0.05$, difference between groups.

The A&L and Leg groups had similar pretraining, baseline measures in the 10-m walking test (A&L: 0.45 ± 0.078 m/s; Leg: 0.50 ± 0.078 m/s; $P = 0.71$). A significant increase occurred in walking speed after training regardless of group (Time $P < 0.001$; Fig. 1*C*). Post hoc analysis showed that walking speed at 6, 9, and 12 wk of training was significantly larger than walking speed pretraining, indicating an improvement in walking speed as early as 6 wk after the initiation of training. Specifically, after 12 wk of training, there was a significant increase in average speed by 0.27 ± 0.072 m/s in the A&L group (Time $P = 0.007$) and 0.092 ± 0.022 m/s in the Leg group (Time $P = 0.04$).

Each participant's increase in walking speed was then normalized to their pretraining measure. Because S7A became an outlier after the normalization, his percent change was removed from the A&L group. ANOVA analysis showed significant increase in the change of walking speed as a function of training (Time $P < 0.001$), and a group difference was found (Group $P = 0.04$; Fig. 1*D*). A comparison between the two groups at each of the assessment time points showed that the A&L group had a significantly larger change in walking speed than the Leg group at the 6th week of training (A&L: 35.45 ± 9.07%; Leg: 15.25 ± 4.52%; Group $P = 0.03$) and after 12 wk of training (A&L: 50.11 ± 13.67%; Leg: 19.40 ± 4.55%; Group $P = 0.03$; Fig. 1*D*). This suggests that the A&L group outperformed the Leg group early in the training and continued to have larger improvements until the cessation of training.

The absolute improvements in walking distance relative to pretraining levels in the A&L group were consistently larger than those in the Leg group (Fig. 2, *A* and *B*). Pretraining, baseline measures in the 6-min walking distance were similar between the two groups (A&L: 164.52 ± 22.59 m; Leg: 157.07 ± 20.34 m; $P = 0.81$), and walking distance improved significantly over training (Time $P = 0.002$; Fig. 2*C*). Within-group analysis revealed significant improvements in walking distance in the A&L group (increase of 91.58 ± 36.24 m; Time $P = 0.04$) and the Leg group (increase of 32.12 ± 8.74 m; Time $P < 0.001$). After the outlier (S7A) was removed, both groups had significant increases in the percent change in walking distance over training ($P \leq 0.02$; Fig. 2*D*). Although the A&L group had, on average, a larger percent change in walking distance (37.05 ± 10.34%) than the Leg group (26.31 ± 9.24%) 12 wk after training, the changes between groups were not significantly different from each other ($P = 0.67$).

Motor and Sensory Scores

Both groups had similar pretraining AIS motor scores (A&L: 76 ± 6; Leg: 82 ± 5; Group $P = 0.47$). Most participants showed an increase in motor score after training. Posttraining scores averaged 83 ± 4 and 88 ± 4 in the A&L and Leg groups, respectively. There were significant improvements in AIS motor scores as a function of training regardless of group (Time $P < 0.001$). Within-group analysis also showed significant improvement in the Leg group (A&L: $P = 0.08$; Leg: $P = 0.006$; Fig. 3, *A* and *B*). However, there was no significant difference in improvements between groups (Group $P = 0.38$).

The AIS motor score was then divided into upper extremity motor score (UEMS) and lower extremity motor score (LEMS) and compared between the two groups. There was a significant increase in UEMS as a function of training in both groups but no significant difference between groups (Time $P = 0.02$, Group $P = 0.66$). The A&L group had an average increase of 9.14 ± 5.58%, and the Leg group an increase of 3.37 ± 1.03%, posttraining in the UEMS. There was also a significant increase in the LEMS score in both groups as a function of training but no significant difference between the groups (Time $P < 0.001$, Group $P = 0.30$; Fig. 3, *C* and *D*). The average increase in

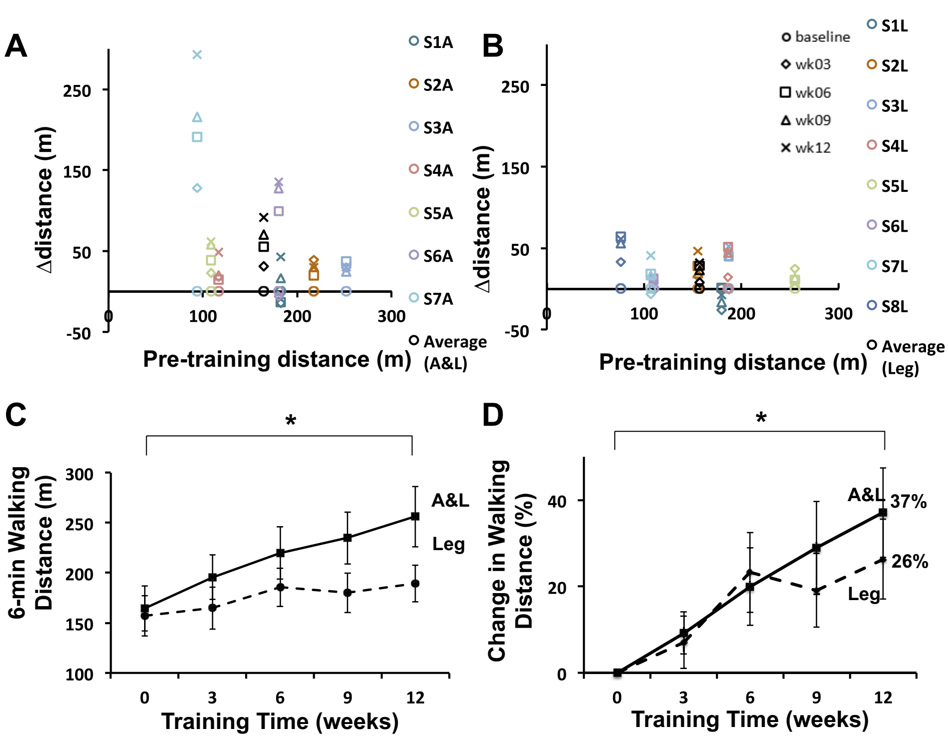

Fig. 2. *A* and *B*: absolute change in walking distance (m) of individual participants within the A&L group (*A*) and the Leg group (*B*). Each color represents a participant, whereas different dots of the same color represent the change in distance compared with pretraining measured at different assessment times for a given participant. *C*: average 6-min walking distance in both iSCI groups throughout training (A&L: $n = 7$; Leg: $n = 8$). *D*: average percent change in 6-min walking distance in both iSCI groups throughout training (A&L: $n = 6$ with outlier removed; Leg: $n = 8$). *$P \leq 0.05$, difference over time.

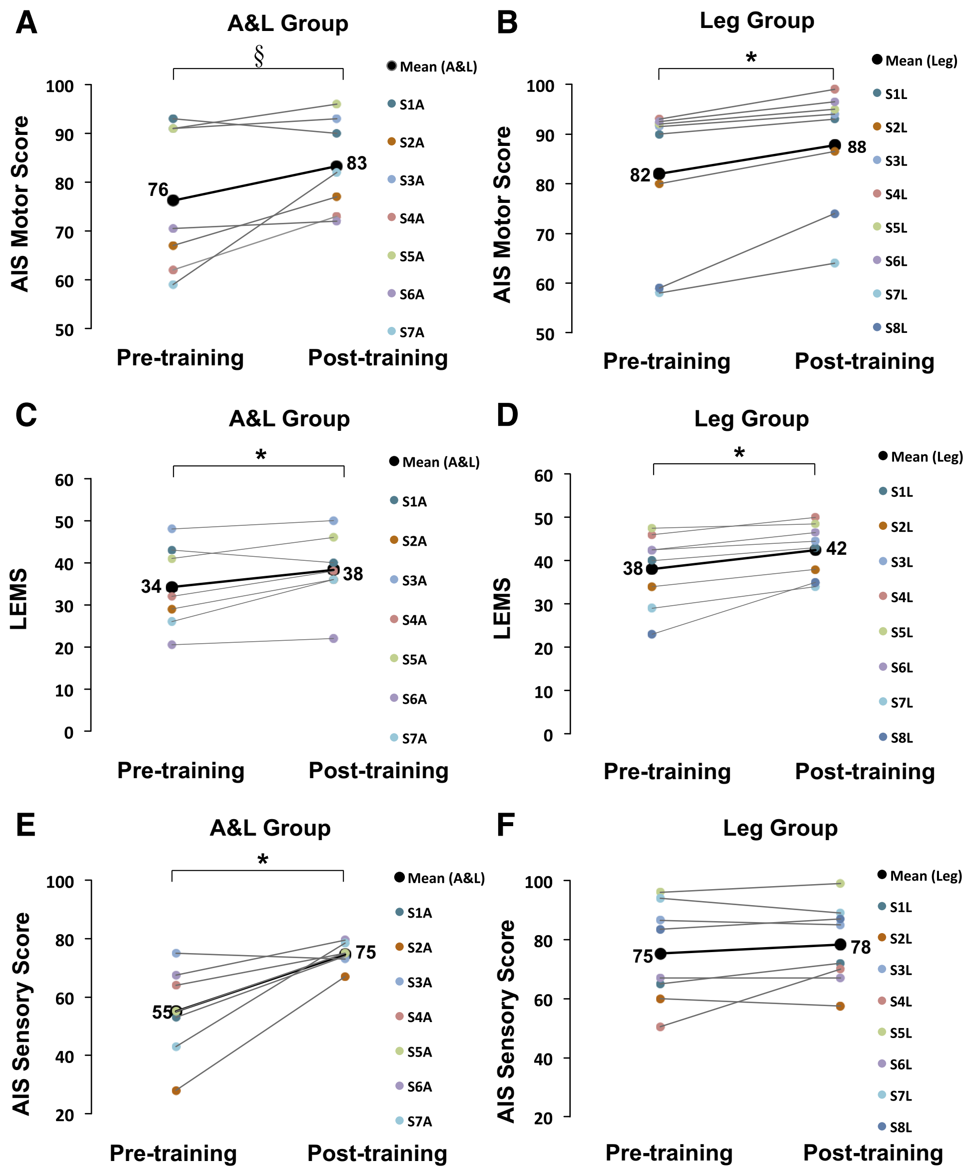

Fig. 3. *A* and *B*: AIS motor scores at pretraining and posttraining in the A&L group (*A*) and the Leg group (*B*). *C* and *D*: AIS lower extremity motor score (LEMS) at pretraining and posttraining in the A&L group (*C*) and the Leg group (*D*). *E* and *F*: AIS sensory scores at pretraining and posttraining in the A&L group (*E*) and the Leg group (*F*). Solid black line represents the mean score pre- and posttraining. *$P \leq 0.05$; §$P \leq 0.1$, difference between posttraining (12 wk) and pretraining (0 wk).

LEMS were 14.01 ± 5.58% and 14.20 ± 5.66% for the A&L and Leg groups, respectively. Within individual groups, significant pre-to-posttraining effect was also found in both the A&L (Time $P = 0.05$) and Leg groups (Time $P = 0.008$).

To better understand the LEMS, we also investigated the amount of change in LEMS on the weaker and stronger side after training. Both groups demonstrated similar improvements on each side. On the stronger side, a posttraining improvement in LEMS of 9.89 ± 4.88% was observed in the A&L group and 8.24 ± 2.27% in the Leg group. On the weaker side, the posttraining improvements were larger in both groups (A&L: 32.30 ± 17.03%; Leg: 37.30 ± 22.25%).

AIS sensory evaluations also showed significant improvements with training, but only in the A&L group (Time $P = 0.01$). The improvements in the A&L group were 20 ± 5 points (47.16 ± 18.36%), and those in the Leg group were 3 ± 3 points (5.68 ± 5.04%; Fig. 3, *E* and *F*). However, because the A&L group had significantly lower AIS sensory scores than the Leg group at the pretraining, baseline stage (A&L: 55 ± 6; Leg: 75 ± 6; Group $P = 0.03$), ANCOVA was applied to assess the posttraining improvements between the two groups, with the pretraining sensory scores as covariate. No significant difference between the groups was found (Group $P = 0.54$).

Balance

There was no significant difference in pretraining, baseline Berg Balance scores between groups (A&L: 29 ± 3; Leg: 34 ± 4; Group $P = 0.34$). Posttraining assessments showed changes in the Berg Balance score across participants ranging from losses of 2 points to gains of up to 22 points in the A&L group and from 2 to 17 points in the Leg group. The score significantly increased after training by an average of 9 ± 3 in the A&L group and 8 ± 2 in the Leg group (Time $P = 0.001$), but there was no significant difference in the improvements between groups (Group $P = 0.56$; Fig. 4). Within each group, the increase in the Berg Balance score as a function of training was also significant ($P \leq 0.02$ for each group; Fig. 4). The mean percent change in score post-training change was not

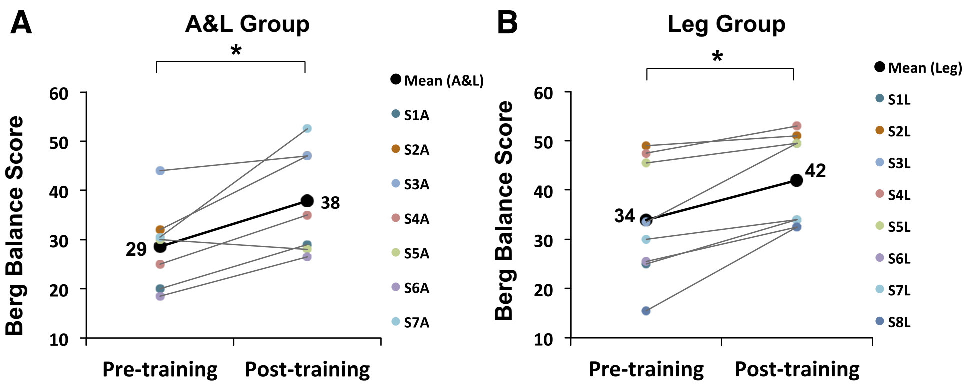

Fig. 4. *A* and *B*: Berg Balance Scale scores at pretraining and posttraining in the A&L group (*A*) and the Leg group (*B*). Solid black line represents the mean score pre- and post-training. $*P \leq 0.05$.

significantly different between groups (A&L: 35.34 ± 10.05%; Leg: 32.33 ± 12.25%; Group $P = 0.86$).

Correlations Between Walking Metrics and Clinical Measures

Pearson's correlation was used to assess the relationship between the posttraining change in walking performance and other clinical measures in individual groups. The change in walking speed had a significantly positive correlation with the change in motor scores ($r = 0.79$, $P = 0.02$) in the A&L group but a weak and a moderate correlation with the change in sensory ($r = 0.17$, $P = 0.36$) and balance scores ($r = 0.49$, $P = 0.14$), respectively. Change in walking speed was also significantly correlated with the change in motor scores in the Leg group ($r = 0.65$, $P = 0.04$), with a moderate correlation with change in sensory ($r = 0.56$, $P = 0.08$) and balance scores ($r = 0.36$, $P = 0.19$).

Similarly, for the change in walking distance, the correlation with the change in motor scores was significant in both groups ($r \geq 0.83$, $P \leq 0.01$). In addition, change in walking distance was also strongly correlated with the change in Berg Balance score (A&L: $r = 0.59$, $P = 0.08$; Leg: $r = 0.70$, $P = 0.03$). The correlation with the change in sensory scores was weak for both groups ($r \leq 0.24$, $P \geq 0.30$).

A multiple linear regression was then run to determine how much of the change in walking performance could be explained by individual clinical measures. The R^2 value for predicting the change in walking speed by the overall model, which included the Berg Balance, AIS motor, and AIS sensory scores, was 0.69 for the A&L group and 0.80 for the Leg group, a large effect size according to Cohen (1988). Individually, in the A&L group, the change in motor scores explained 39.1% of the variability in the speed change, whereas the Berg Balance and AIS sensory scores explained 23.6% and 6.6%, respectively. In the Leg group, the change in motor, balance, and sensory scores explained 31.5%, 13.2%, and 35.4% of the variability in the change in walking speed, respectively.

Similarly, with R^2 values of 0.74 for the A&L and 0.86 for the Leg group, the change in motor scores and the change in Berg Balance scores explained the majority of the variability in the change in walking distance, whereas the change in sensory scores only accounted for less than 5% of the change in distance. Individually, in the A&L group, the change in motor, balance, and sensory scores explained 35.0%, 34.2%, and 4.8% of the variability in the change in walking speed, respectively. In the Leg group, the change in motor, balance, and sensory scores explained 36.2%, 49.1%, and 0.4% of the variability in the change in walking speed, respectively.

Spatiotemporal Measures

Table 2 summarizes the spatiotemporal parameters for both cycling groups obtained during walking at a self-selected speed. There was no significant difference between the groups for any of the parameters at the pretraining, baseline stage.

Table 2. *Summary of spatiotemporal measures for NI and both iSCI groups*

	A&L Group				Leg Group				
	0 wk		12 wk		0 wk		12 wk		
Variable	Stronger	Weaker	Stronger	Weaker	Stronger	Weak	Stronger	Weak	NI Group
Preferred walking speed, m/s	0.27 ± 0.034		0.44 ± 0.083*		0.36 ± 0.060		0.43 ± 0.078*		1.17 ± 0.073
Stride length, m	0.74 ± 0.045		0.91 ± 0.064*		0.78 ± 0.046		0.86 ± 0.060*		1.34 ± 0.065
Stride time, s	3.12 ± 0.55		2.41 ± 0.40*		2.76 ± 0.54		2.56 ± 0.44		1.15 ± 0.033
Step length, m	0.41 ± 0.019	0.33 ± 0.036	0.46 ± 0.027	0.44 ± 0.044*	0.39 ± 0.025	0.39 ± 0.033	0.42 ± 0.021	0.45 ± 0.041	0.67 ± 0.033
Step time, s	1.47 ± 0.29	1.62 ± 0.26	1.13 ± 0.21*	1.28 ± 0.21*‡	1.34 ± 0.26	1.44 ± 0.29	1.20 ± 0.19	1.34 ± 0.24	0.57 ± 0.016
Single support, %	25.77 ± 2.24	20.09 ± 1.57	29.70 ± 2.61†	25.73 ± 2.64*	26.07 ± 2.50	24.59 ± 3.19	27.18 ± 2.84	24.85 ± 3.05	36.80 ± 0.41
Double support, %	54.33 ± 3.80	54.28 ± 3.78	44.68 ± 5.07*	44.87 ± 5.19*	50.30 ± 5.47	49.30 ± 5.49	48.09 ± 5.72	47.84 ± 5.94	26.61 ± 0.90
Swing time, %	19.90 ± 1.69	25.63 ± 2.33	25.62 ± 2.63*	29.41 ± 2.77†	23.63 ± 3.32	26.12 ± 2.62	24.73 ± 3.07	27.31 ± 3.15	36.59 ± 0.53
Stance time, %	80.10 ± 1.69	74.37 ± 2.33	74.38 ± 2.63*	70.59 ± 2.77†	76.37 ± 3.31	73.88 ± 2.62	75.27 ± 3.07	72.69 ± 3.15	63.41 ± 0.53
SW/ST	0.25 ± 0.025	0.35 ± 0.040	0.35 ± 0.050*‡	0.43 ± 0.055†	0.33 ± 0.062	0.36 ± 0.046	0.34 ± 0.058	0.39 ± 0.061	0.58 ± 0.012
Step length symmetry	1.39 ± 0.21		1.16 ± 0.084		1.30 ± 0.10		1.21 ± 0.080		
Swing time symmetry	1.29 ± 0.046		1.18 ± 0.050		1.30 ± 0.087		1.16 ± 0.0476		
Stance time symmetry	1.08 ± 0.016		1.06 ± 0.018		1.07 ± 0.019		1.06 ± 0.022		
SW/ST symmetry	1.40 ± 0.069		1.26 ± 0.073		1.40 ± 0.12		1.23 ± 0.078		

Values are means ± SE. SW/ST, ratio of swing time to stance time. $*P \leq 0.05$; $†P \leq 0.1$, difference between posttraining (12 wk) and pretraining (0 wk). $‡P \leq 0.05$, difference in posttraining between A&L and Leg groups.

Almost all parameters became closer to the values obtained from intact participants after training. Within-group analysis showed that the A&L group improved significantly in most parameters over the course of training, whereas none of the parameters in the Leg group reached significance with training, except for stride length and preferred walking speed.

The average self-selected walking speed of all the iSCI participants at the pretraining, baseline stage was much lower than that of the the intact group. After training, there was an average increase of 0.17 ± 0.060 m/s in the A&L group and 0.071 ± 0.030 m/s in the Leg group. Correspondingly, the stride time was shorter (A&L: −22.76%; Leg: −7.25%) and stride length was larger (A&L: 22.97%; Leg: 10.26%), which could be attributed to the reduced step time and increased step length in both groups.

For participants in both groups, the stronger leg had shorter swing and longer stance time than the weaker leg at pretraining, presumably to compensate and maintain gait stability. Such a relationship remained even after training; however, training reduced the stance time and increased swing time in both the strong and weak legs, especially in the A&L group. Compared with the Leg group, a significantly larger posttraining improvement in SW/ST (stronger side, $P = 0.04$) and single support (weaker side, $P = 0.03$) was found in the A&L group. Overall, the A&L group consistently showed larger improvements than the Leg group in the spatiotemporal measures, and reached significance after training in most of them.

Similar changes in symmetry between the weaker and stronger legs were found in the two groups. Large improvements were found in the symmetry of step length, swing time, and SW/ST after training for both iSCI groups (ratio after training closer to 1).

Joint Motion

Figure 5 illustrates the joint kinematic parameters during the gait cycle. Both the A&L and Leg groups had changed joint angular motions on both the weaker and stronger sides at pretraining compared with the NI group. In general, compared with the NI group, the participants with iSCI had delayed stance-to-swing phase transition, inadequate hip extension during stance and pre-swing, limited hip flexion during swing, limited knee flexion range, excessive ankle plantar flexion, and impaired foot contact (van der Salm et al. 2005). The deviation of joint kinematics from those in the NI group remained even after training in both iSCI groups, but the occurrence of phase transition significantly improved in the A&L group.

Posttraining improvement was observed in the hip joint, especially in the A&L group, which had a significant change in the minimal hip angle during stance on the stronger side ($P = 0.04$), although the change on the weaker side did not reach significance ($P = 0.08$; Fig. 5). This suggested an enlarged maximal hip extension during stance in the A&L group after training. The Leg group did not have significant improvement in the hip joint after training ($P \geq 0.34$).

Figure 6*A*, *top*, shows a representative example of hip-knee cyclogram on the stronger side of a participant with iSCI (S4L). The ACC of the hip-knee cyclogram, which indicates the level of hip-knee cycle consistency, did not differ significantly between the A&L and Leg group at pretraining in either the stronger or weaker side (A&L: 0.47 ± 0.033 weaker side, 0.46 ± 0.035 stronger side; Leg: 0.48 ± 0.034 weaker side, 0.47 ± 0.033 stronger side; $P \geq 0.78$; Fig. 6*B*). Similarly, the area of cyclogram at pretraining, which indicates the hip-knee joint range of motion, was not significantly different between the two groups (A&L: 809.42 ± 286.53 deg^2 weaker side, 964.66 ± 237.71 deg^2 stronger side; Leg: 731.58 ± 204.00 deg^2 weaker side, 824.38 ± 194.63 deg^2 stronger side; $P \geq 0.65$; Fig. 6*C*).

Both groups had improvements on the stronger and weaker sides after training. On the stronger side, a significantly higher ACC of the hip-knee joint movement (Time $P = 0.02$) and a larger area within the cyclogram (Time $P = 0.04$) were found as a function of training. Within-group analysis further showed that the significant change in ACC only occurred in the A&L group, by an increase of 0.057 ± 0.0086 ($P = 0.001$), but not in the Leg group with an increase of 0.037 ± 0.031 after training ($P = 0.27$).

Because ankle joint motions are strongly associated with foot clearance, we analyzed the toe trajectory to further examine the kinematic pattern of foot movement. Figure 6*A*, *bottom*, also shows an example of toe trajectory on the stronger side from participant S4L. At pretraining, the A&L and Leg groups had a similar value of maximal toe elevation during the gait cycle on both sides (A&L: 0.050 ± 0.0057 m weaker side, 0.064 ± 0.0053 m stronger side; Leg: 0.054 ± 0.0098 m weaker side; 0.072 ± 0.0097 m stronger side). After training, an increase in maximal toe elevation by 14.33 ± 9.02% on the weak side was found in the A&L group ($P = 0.22$) and an increase by 12.53 ± 10.81% in the Leg group ($P = 0.25$); the increases were not significantly different between groups. The change was also similar on the strong side (A&L: 18.12 ± 7.21%; Leg: 17.82 ± 9.82%; $P = 0.98$), and no significant group difference was found.

EMG Activity

Intra-leg. Both iSCI groups had similar values of magnitude and phase components of the EMG metrics at pretraining (data not shown). More regulated muscle activities of the TA and SOL muscles during walking were observed after training, but significant differences were only observed in the SOL muscle and only in the A&L group. Specifically, on the stronger side, SOL magnitude component (Time $P = 0.002$) and phase component (Time $P < 0.001$) were both significantly improved as a function of training in the A&L group. Also posttraining, the A&L group showed significantly larger increases in the SOL magnitude (A&L: 7.33 ± 1.33%; Leg: 0.95 ± 1.98%; $P = 0.03$) and phase (A&L: 10.93 ± 1.0064%; Leg: 3.50 ± 2.22%; $P = 0.02$) components than the Leg group. Similar results were observed on the weaker side, where significantly larger values in the phase component posttraining only occurred in the A&L group.

Figure 7 summarizes the onset and active duration of individual muscles. Overall, all muscles except the TA in the participants with iSCI had lengthened active durations relative to participants with intact nervous system. After training, both the A&L and Leg groups showed significant reductions in the active duration of SOL on the stronger side (A&L: $P = 0.003$; Leg: $P = 0.05$; Fig. 7, *A* and *B*); however, significant changes in the SOL active duration on the weaker side were only seen in the A&L group (A&L: $P = 0.03$; Leg: $P = 0.33$; Fig. 7*C*).

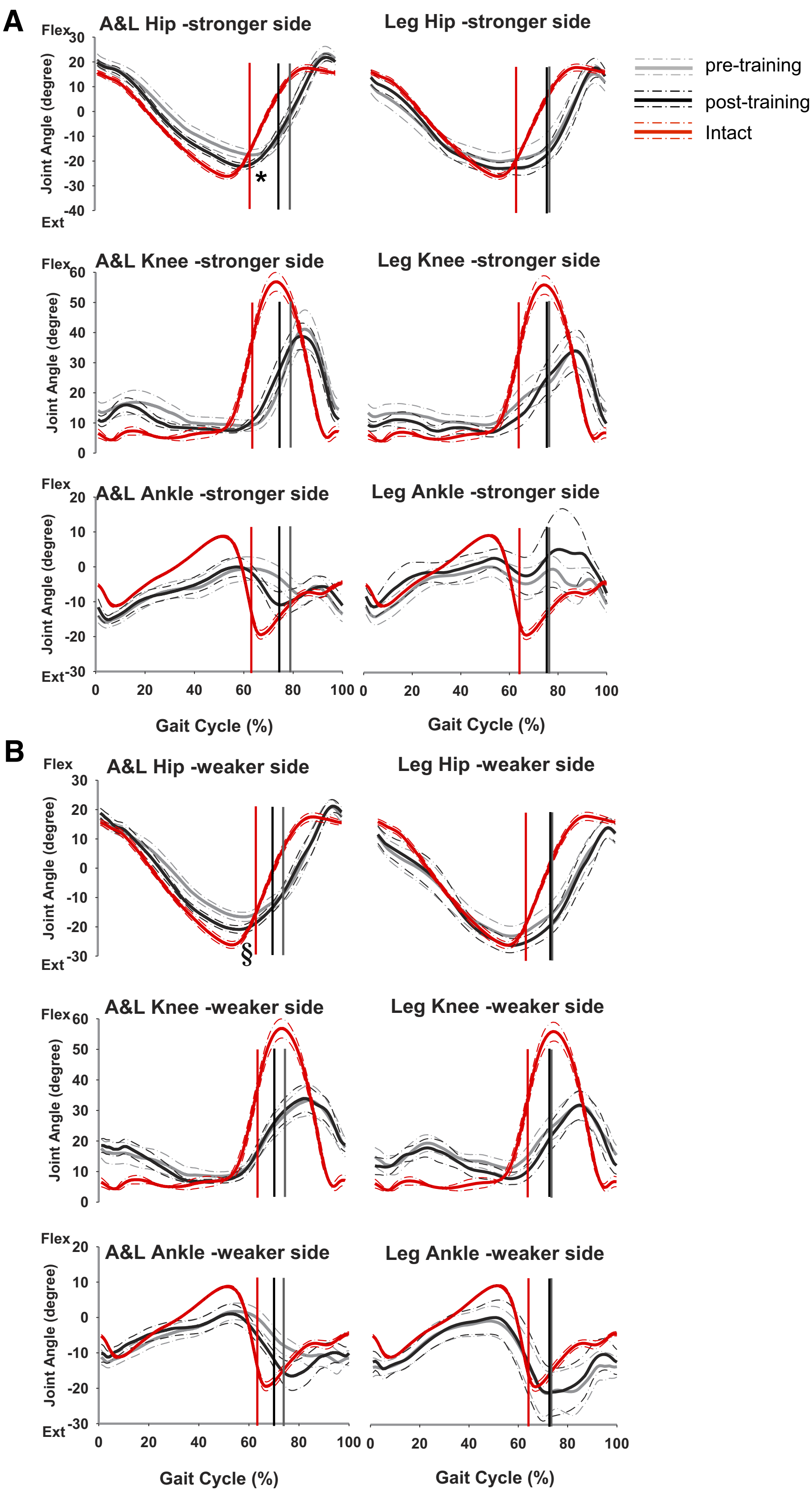

Fig. 5. *A* and *B*: summary of joint kinematics in NI and both iSCI groups on the stronger side (*A*) and the weaker side (*B*) (NI: $n = 6$; A&L: $n = 7$; Leg: $n = 8$). The vertical lines indicate the transition from stance to swing phase. After training, the A&L group had an earlier transition to swing than the Leg group. Solid line indicates the group average, and the dash-dot line indicates the SE. : *$P \leq 0.05$; §$P \leq 0.1$, difference in the minimal angle during stance after posttraining (12 wk) compared with pretraining (0 wk).

Furthermore, the A&L group had a significantly shorter active duration in RF on the weaker side ($P = 0.05$).

Inter-leg. To further understand the coordination between legs, the phase difference between the onsets as well as the coactivation of homologous muscle pairs during the gait cycle were determined. The A&L and Leg groups had similar pre-training, baseline measures in the onset difference of each homologous muscle pair (e.g., onset of left-leg TA vs. onset of right-leg TA; $P \geq 0.17$). For both A&L and Leg groups, the onset difference of each homologous muscle pair was similar

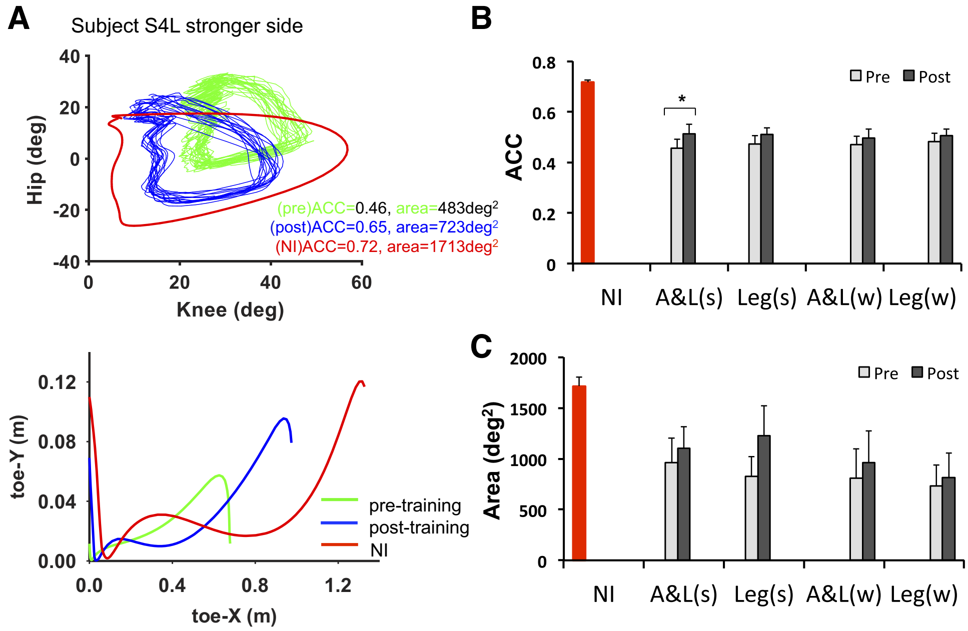

Fig. 6. *A*: examples of the hip-knee cyclogram (*top*) and toe trajectory (*bottom*) on the stronger side during consecutive gait cycles in a participant with iSCI (S4L). Green indicates pretraining data; blue indicates posttraining data; red indicates average data from the NI group. Toe-*X* and toe-*Y* indicate the average horizontal and vertical toe trajectory during consecutive gait cycles, respectively. *B*: average coefficient of correspondence (ACC) of the hip-knee cyclogram on the stronger (s) and weaker (w) sides in the NI group and both iSCI groups at pretraining and posttraining. *C*: average area of the hip-knee cyclogram on the stronger and weaker sides in the NI group and in both iSCI groups at pretraining and posttraining. *$P \leq 0.05$.

before and after training. As a result, there was no significant change in the phase difference of onsets for any homologous muscle pair after training in either iSCI group ($P \geq 0.31$).

Figure 8 depicts the EMG co-activations of the TA (Fig. 8*A*) and SOL (Fig. 8*B*) muscle between the left and right legs, which are substantially larger than those in intact participants. Both iSCI groups had similar values in this measure at pretraining for both muscle pairs (A&L: TA = 30.21 ± 11.60%, SOL = 45.17 ± 6.74%; Leg: TA = 30.00 ± 9.43%, SOL = 36.00 ± 5.61%; $P \geq 0.31$). After training, there was a significant reduction in left-leg SOL vs. right-leg SOL muscle coactivation, but only in the A&L group ($P = 0.005$). Collectively, the findings may suggest that the A&L group had better training-induced regulation in the EMG activity than the Leg group.

DISCUSSION

The goal of this project was to explore the efficacy of non-gait-specific training for the improvement of ambulation and to investigate the role of the arms in the rehabilitation of walking after iSCI. To the best of our knowledge, the present study is the first to investigate systematically the effects of FES-assisted cycling on walking and the role of the arms in gait rehabilitation. The main findings were as follows: *1*) maximal overground walking speed was significantly increased in both cycling groups relative to pretraining levels, and the increases in the A&L group were significantly larger than those in the Leg group. *2*) FES-assisted cycling training also significantly improved walking distance relative to pretraining levels in both cycling groups. *3*) FES-assisted cycling training resulted in significant improvements in the Berg Balance scores and AIS motor scores of the lower extremities in both groups. *4*) Most spatiotemporal parameters of gait in the weaker and stronger legs significantly improved after training in the A&L group, whereas the Leg group had significant improvements only in the preferred walking speed and stride length. *5*) A&L FES-assisted cycling resulted in significant improvement in the consistency of hip-knee coordination. *6*) Intra- and inter-leg regulation of EMG activity (Figs. 7 and 8), especially in the extensor muscles, was observed in both groups, but significant improvements were mostly found in the A&L group. Collectively, these findings suggest that non-gait-specific cycling training results in substantial improvements in walking capacity after chronic iSCI. Moreover, active engagement of the arms simultaneously with the legs can produce larger improvements in walking than engaging the legs alone.

Cycling Improves Walking Speed and Distance

Rehabilitation strategies to improve ambulation have to date focused on restoring leg function through physical therapy and gait-specific locomotor training. Systematic reviews of locomotor training interventions to enhance functional ambulation in people with SCI can be found in (Lam et al. 2014; Morawietz and Moffat 2013). In the present study, there were, on average, significant improvements in the 10-m walking speed and 6-min walking distance after training in both groups of participants. Although improvements were larger in the low-functioning participants, improvements were also seen in the high-functioning participants, indicating that a ceiling effect in walking capacity had not been reached (Kuerzi et al. 2010).

To assess the functional relevance of improvements in walking speed, two measures are commonly used: the minimal important difference (MID), which is 0.06 m/s in the SCI population (Musselman 2014), and the minimally clinically important difference (MCID), which is ~0.11–0.15 m/s (Forrest et al. 2014). In both A&L and Leg groups, the posttraining increases in maximal walking speed were higher than the MID. Importantly, with an average posttraining increase of 0.27 m/s in the A&L group, the improvement in walking speed in this group exceeded the MCID. The results showed that repetitive cycling training of the arms and legs or legs alone can translate into functional and potentially clinically important improvements in walking speed. This observation challenges the widely accepted motor learning principles of task specificity in the rehabilitation of walking (Behrman and Harkema 2000; Edgerton et al. 1997; Mastos et al. 2007).

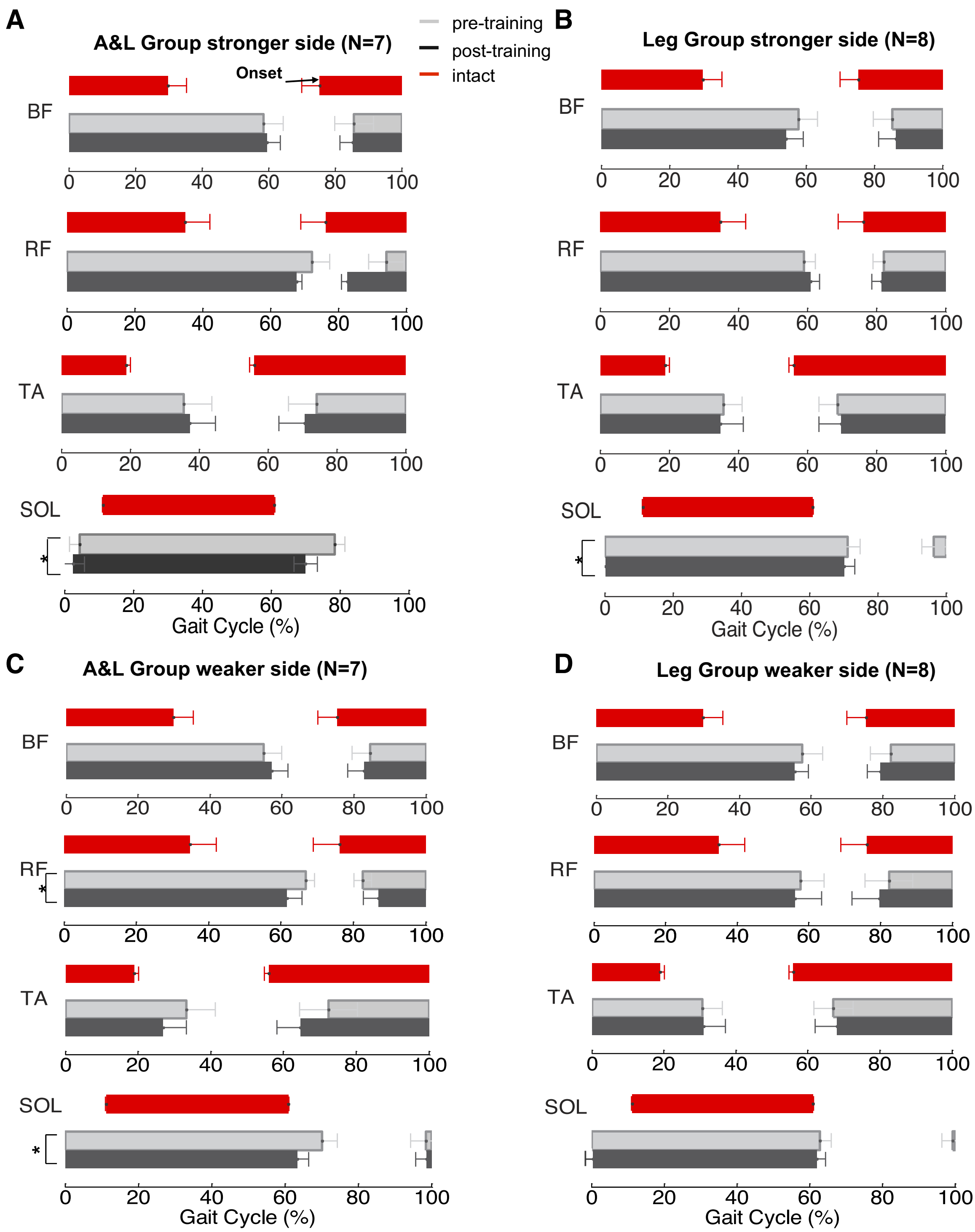

Fig. 7. *A* and *B*: group data of EMG activation patterns of muscles on the stronger side in the A&L group (*A*) and the Leg group (*B*). *C* and *D*: group data of EMG activation patterns of muscles on the weaker side in the A&L group (*C*) and the Leg group (*D*). BF, biceps femoris; RF, rectus femoris; TA, tibialis anterior; SOL, soleus. Gray indicates data collected at pretraining; black indicates data collected at posttraining; red indicates group data collected from NI participants. $*P \leq 0.05$. Note that some error bars in the NI group data are too small to discern.

As an elementary building block on which the rhythmic movements are based, a core subcortical network shares commonalities in the neural control of rhythmic activities across various types of locomotion (Zehr and Duysens 2004). Therefore, we believe that FES-assisted cycling training may improve the common elements in the spinal network that are also responsible for producing rhythmic walking. The results of the present study build on previous observations in stroke (Klarner et al. 2016a, 2016b) and provide the most direct evidence to understanding the impact on the iSCI population to date.

One source of contribution to the improvement in posttraining walking could be the change in muscle strength. Previous

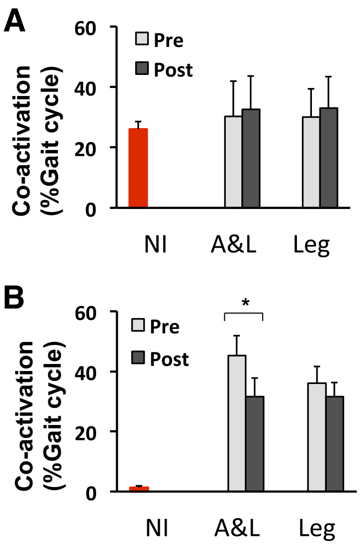

Fig. 8. *A* and *B*: group data of EMG coactivation of the TA muscle on the left and right leg (*A*) and the SOL muscle on the left and right leg (*B*). Red bars are grouped data from the NI participants. $*P \leq 0.05$.

studies in participants with chronic SCI showed that for both the weaker and stronger sides, muscle strength (particularly hip muscles) was strongly correlated with walking speed, distance, and independence of walking (DiPiro et al. 2015; Kim et al. 2004). Yang et al. (2011) suggested that preserved strength in key muscle groups could allow for improvement in walking speed after locomotor training in people with iSCI. Nonetheless, an improvement in the strength of leg muscles may not necessarily result in improved walking capacity (Wirz et al. 2006; Yang et al. 2011). In the present study, the two groups had a similar range and average of AIS motor scores pretraining, especially for the lower extremities. Regardless of training group, we observed a similar and significant improvement in the motor scores posttraining, as well as a strong correlation between the change in motor scores and change in walking speed or distance. Therefore, increased muscle strength in the lower extremities was likely contributing to the improvement in both groups but does not necessarily explain the larger increases in walking speed and distance in the A&L group. Moreover, both groups had similar significant improvement in the Berg Balance score after training, which could contribute to walking stability and partially account for the significant improvement in walking; however, this too may not explain the larger improvements seen in the A&L group, given that similar posttraining changes in balance were seen in the two groups.

The repetitive cycling movements throughout training likely increased the magnitude and regulation of afferent feedback to spinal and supraspinal circuitry, an input that is essential for the development of neural plasticity for locomotion (Behrman et al. 2006; Rossignol 2006; Van de Crommert et al. 1998). The assistance of repetitive FES is also important to develop use-driven adaptations that lead to neural development (Gary et al. 2012; Sadowsky et al. 2013). Collectively, this could explain the significant increase in AIS sensory scores posttraining; however, it may not explain the change in walking speed and distance, especially in the A&L group, given the weak correlation between sensory scores and walking metrics.

Linkage between the upper and lower limbs produces coordinated movement in animals and humans (Falgairolle et al. 2006; Ferris et al. 2006; Frigon 2017). Studies of cervicolumbar modulation of reflexes demonstrated that rhythmic arm movement could sculpt leg muscle activation, even after SCI (Frigon et al. 2004; Hiraoka and Iwata 2006; Kawashima et al. 2008; Loadman and Zehr 2007; Zehr et al. 2007b). This suggests that arm movement changes the excitability in the lower limbs, likely through central pattern generator-driven modulations (Zhou et al. 2015). Moreover, active engagement of the arms in training may also strengthen the corticospinal connections to the legs (Zhou et al. 2017). Therefore, we postulate that simultaneous rhythmic arm and leg FES-assisted cycling may have facilitated locomotor activity in the legs through both propriospinal and corticospinal connections (Zhou et al. 2015, 2017). Through repetitive facilitation over the course of training, neural interaction between arm and leg spinal centers may have been enhanced (Ferris et al. 2006; Huang and Ferris 2009; Ogawa et al. 2015; Zehr et al. 2007a).

Cycling Improves the Quality of Walking

People with SCI generally walk slowly and take small steps (Pépin et al. 2003a, 2003b). In the present study, both A&L and Leg groups started with a preferred walking speed below 0.4 m/s (Table 2) but reached a level above 0.4 m/s after training, suggesting a clinically functional change in their ambulation. The significant increases in stride length in both iSCI groups after training could be associated with an improvement in walking speed (De Quervain et al. 1996). Nonetheless, after training, the A&L group had significantly larger improvement in SW/ST than the Leg group. The increase in SW/ST, together with the shortened single and double support time in the A&L group, could also contribute to the better walking performance in this group, specifically walking speed.

Both groups with iSCI showed improved range of motion at the hip joint (e.g., hip extension) posttraining (Fig. 5). One reason could be the stimulation-assisted contraction of the gluteal muscles during cycling training, which reinforced hip extension (Triolo et al. 2001). However, only the A&L group reached a significant level of difference in hip extension after training, perhaps through a more regulated neural network that adapted the proprioceptive feedback during training (Dietz 2002b).

Furthermore, both groups demonstrated higher consistency and larger area within the hip-knee cyclogram after training (Fig. 6), with significantly higher consistency found only in the A&L group. The distorted cyclogram after SCI may not only originate from motor deficits but also could be associated with limited access to supraspinal control and impaired sensory feedback (Awai and Curt 2014). Therefore, the significant improvement in joint consistency observed in the A&L group could be due to a better regulation throughout the neuraxis by active arm involvement during training.

In chronic SCI, extensor muscles are excessively active through the gait cycle (Forssberg et al. 1980; Pépin et al. 2003b). After training, a significantly shorter RF activation on the weaker side was seen in the A&L group and, correspondingly, an increase in RF activation during swing phase on the stronger side (Fig. 7). This could be associated with a compensatory change on the stronger side with increased walking speed posttraining (Forssberg et al. 1980). It also suggests that to adapt to a new motor learning strategy, the stronger leg may take a more compensatory role. As an emerging focus in rehabilitation locomotor training (Lam et al. 2008b, 2009), enhancing flexor muscle activity during swing phase, such as RF, could help improve gait speed (Pépin et al. 2003a) and obstacle avoidance (Ladouceur et al. 2003).

Comparison with Current Locomotor Rehabilitation Interventions

We compared our findings with published studies that have incorporated existing locomotor training in chronic (at least ≥7 mo postinjury) AIS C or/and D SCI participants (e.g., Alexeeva et al. 2011; Field-Fote and Roach 2011; Harkema et al. 2012; Yang et al. 2011, 2014) (Fig. 9). Interestingly, comparison of these results suggests that the improvements in the Leg FES-assisted cycling group in the present study were similar to those obtained with the above training paradigms, which involved the legs only. Active arm engagement in gait rehabilitation could nearly double the level of improvements in walking metrics, suggesting that the arms can play a very significant role in the rehabilitation of walking. Nonetheless, it is important to interpret these comparisons with caution because of the limited number of participants in the present study. Also, all of our participants were capable of completing the 10-m and 6-min walking tests at pretraining, suggesting that, on average, they may have been higher functioning than participants in the other studies. Furthermore, it should be noted that in some studies, arm swing was also encouraged during locomotor training (Field-Fote and Roach 2011; Thomas and Gorassini 2005; Yang et al. 2011).

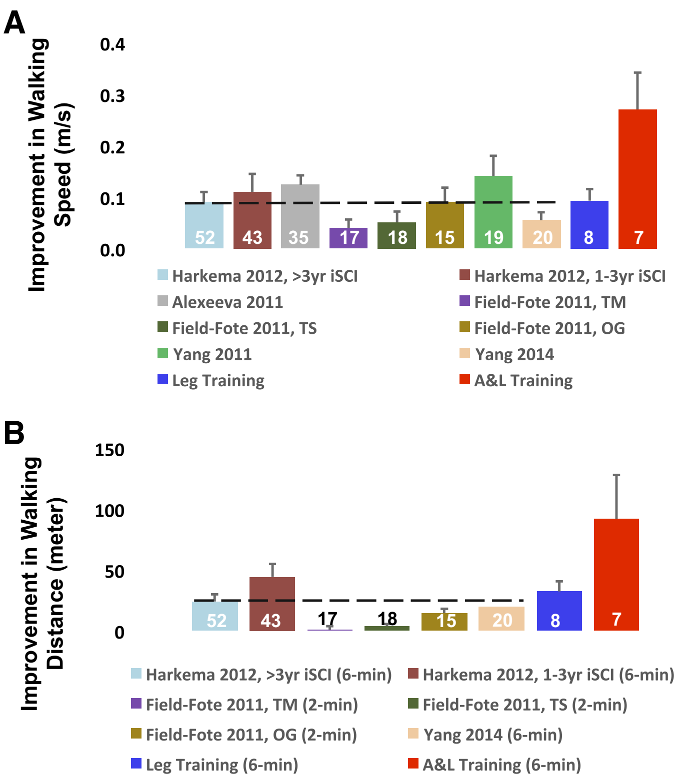

Fig. 9. *A*: comparison of the improvement in walking speed (m/s) among studies applying current training paradigms and the 2 cycling groups in the present study. *B*: comparison of the improvement in walking distance (m) among studies applying current training paradigms and the 2 cycling groups in the present study. Graphs were created on the basis of reported values in the referenced literature. Values are means ± SE. Horizontal dashed line indicates the average improvements across the referenced studies. Sample size for each study is indicated in each bar. 6-min and 2-min indicate that the walking distance was obtained from a 6-min walking test and 2-min walking test, respectively. TM, treadmill-based training with manual assistance; TS, treadmill-based training with stimulation; OG, overground training with stimulation.

The routine use of the systems for leg cycling and simultaneous arm and leg cycling in this study demonstrated that the equipment is safe, reliable, and easy to use. The occurrence of adverse events, mostly muscle soreness when cycling resistance was increased, was low during the study period. One participant developed skin allergy to the hydrogel electrodes used for FES during training. The allergy subsided after the electrodes were replaced with ones that had hypoallergenic gel. None of the participants dropped out of the study because of adverse events. A distinctive difference between this FES-assisted cycling training intervention and current clinical rehabilitation practices may be a substantial reduction in therapist labor intensity. Up to three to four persons are often required to assist in a session involving BWS locomotor training, whereas in this study, only one person was needed for the entire process of preparation, setup, and supervision of the training. Because the length of training sessions using current interventions is often limited by therapist fatigue rather than the patient (van Hedel and Dietz 2010), FES-assisted cycling training could provide meaningfully long durations of training sessions because manual assistance from the therapists is not required. The findings from the present study could lead to an effective and economical intervention for gait rehabilitation. Lastly, this intervention is not only applicable to SCI, but also to other neural disorders, including stroke, multiple sclerosis, and cerebral palsy.

Other Contributions

Active engagement of the arms in training may also result in better cardiovascular function and larger aerobic capacity after iSCI. Improved fitness and metabolic response in people with iSCI as a result of training has been reported for various types of rehabilitation interventions, including BWS locomotor training (Alexeeva et al. 2011; de Carvalho et al. 2006; Kressler et al. 2013), leg cycling training (Faghri et al. 1992; Yaşar et al. 2015), arm cycling training (Warburton et al. 2007), and combined arm and leg cycling/stepping training (DiPiro et al. 2016; Heesterbeek et al. 2005; Nagle et al. 1984; Thijssen et al. 2005). Although more evidence is needed, hybrid exercise that combines the arms and legs may provide relatively greater cardiorespiratory stress than leg exercise or arm exercise alone for persons with SCI, which ultimately results in greater improvement in fitness (Hettinga and Andrews 2008; Krauss et al. 1993; Mutton et al. 1997; Nagle et al. 1984; Verellen et al. 2007). In the present study, the greater increase in walking capacity in the A&L group may partially be due to better improvement in fitness. Nonetheless, the improvements in the regulation of muscle activity during walking may be the result of improvements in descending and spinal mechanisms (Zhou et al. 2015, 2017) which are not directly driven by changes in fitness.

Limitations

A relatively small sample size of participants was recruited for each training group. The participants in this study also account for a selective subpopulation of people with SCI (chronic iSCI with AIS grade C or D). Future studies should investigate the generalized efficacy of the training intervention in people with SCI, as well as other neurological injuries and diseases, such as stroke (Klarner et al. 2016a, 2016b), multiple sclerosis, and cerebral palsy. Because the experimenters were not blinded to the training groups or the outcome measures, a bias in the comparison of assessment between groups could be unintentionally introduced. A study design involving blinded ascertainment of outcomes is encouraged in future investigations.

Stimulation parameters, choice of muscle groups to stimulate, and upper and lower limb synchronization may influence the results of training. The optimization of FES parameters and stimulating paradigm to reduce fatigue and declining power output, and ultimately to improve the efficacy of stimulation, has been of interest to researchers (Duffell et al. 2010; Eser et al. 2003; Gorgey and Dudley 2008; Lou et al. 2017). However, this was not the purpose of this study; thus a typical range of parameters for surface muscle stimulation was used. Furthermore, a reciprocal relationship between the arms and legs during cycling was always encouraged in this study. de Kam et al. (2013b) showed that facilitation in leg muscle activity was more or less consistent for synchronous and asynchronous arm movements. Massaad et al. (2014) then showed that "a marked reflex modulation in the leg muscle occurred during locomotor-like anti-phase arm swing, and this modulation flattened out during in-phase arm swing." Therefore, the phase difference between arm and leg during cycling could play a role in reflex and corticospinal modulation, and could be explored in future investigations.

Conclusion

This study systematically investigated a rehabilitation intervention that actively involves the arms and legs in cycling for the improvement of walking after SCI. The results suggest that FES-assisted arm and leg cycling provides larger improvements in overground walking capacity than paradigms that focus on leg training only. Both the use of cycling and the engagement of the arms should be considered in future rehabilitation interventions for the improvement of walking after neural injury or disease.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

V.K.M. conceived and designed research; R.Z., L.A., R.O., S.L.C., and O.S. performed experiments; R.Z., L.A., R.O., S.L.C., and O.S. analyzed data; R.Z., L.A., and V.K.M. interpreted results of experiments; R.Z. prepared figures; R.Z. drafted manuscript; R.Z. and V.K.M. edited and revised manuscript; R.Z., L.A., R.O., S.L.C., O.S., and V.K.M. approved final version of manuscript.

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