J Neurophysiol 119: 1095–1112, 2018.
First published December 6, 2017; doi:10.1152/jn.00570.2017.

RESEARCH ARTICLE | *Spinal Control of Motor Outputs*

Rhythmic arm cycling training improves walking and neurophysiological integrity in chronic stroke: the arms can give legs a helping hand in rehabilitation

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Submitted 1 August 2017; accepted in final form 28 November 2017

Kaupp C, Pearcey GE, Klarner T, Sun Y, Cullen H, Barss TS, Zehr EP. Rhythmic arm cycling training improves walking and neurophysiological integrity in chronic stroke: the arms can give legs a helping hand in rehabilitation. *J Neurophysiol* 119: 1095–1112, 2018. First published December 6, 2017; doi:10.1152/jn.00570.2017.—Training locomotor central pattern-generating networks (CPGs) through arm and leg cycling improves walking in chronic stroke. These outcomes are presumed to result from enhanced interlimb connectivity and CPG function. The extent to which rhythmic arm training activates interlimb CPG networks for locomotion remains unclear and was assessed by studying chronic stroke participants before and after 5 wk of arm cycling training. Strength was assessed bilaterally via maximal voluntary isometric contractions in the legs and hands. Muscle activation during arm cycling and transfer to treadmill walking were assessed in the more affected (MA) and less affected (LA) sides via surface electromyography. Changes to interlimb coupling during rhythmic movement were evaluated using modulation of cutaneous reflexes elicited by electrical stimulation of the superficial radial nerve at the wrist. Bilateral soleus stretch reflexes were elicited at rest and during 1-Hz arm cycling. Clinical function tests assessed walking, balance, and motor function. Results show significant changes in function and neurophysiological integrity. Training increased bilateral grip strength, force during MA plantarflexion, and muscle activation. "Normalization" of cutaneous reflex modulation was found during arm cycling. There was enhanced activity in the dorsiflexor muscles on the MA side during the swing phase of walking. Enhanced interlimb coupling was shown by increased modulation of MA soleus stretch reflex amplitudes during arm cycling after training. Clinical evaluations showed enhanced walking ability and balance. These results are consistent with training-induced changes in CPG function and interlimb connectivity and underscore the need for arm training in the functional rehabilitation of walking after neurotrauma.

NEW & NOTEWORTHY It has been suggested but not tested that training the arms may influence rehabilitation of walking due to activation of interneuronal patterning networks after stroke. We show that arm cycling training improves strength, clinical function, coordination of muscle activity during walking, and neurological connectivity between the arms and the legs. The arms can, in fact, give the legs a helping hand in rehabilitation of walking after stroke.

arm cycling; cutaneous reflex; locomotor training; stretch reflex; stroke

INTRODUCTION

Walking occurs via an initiating descending motor command from supraspinal centers that activates spinal networks and is modulated by afferent sensory feedback (Nielsen 2003; Zehr and Duysens 2004). Following stroke, descending motor commands and supraspinal regulation are interrupted and dysfunctional (Zehr 2011). However, preserved networks in the spinal cord remain relatively intact and accessible (Klarner et al. 2014). These spinal networks are presumed to regulate rhythmic limb activities, such as cycling, walking, or swimming (Zehr 2005). At the heart of these spinal networks are presumed central pattern-generating networks (CPGs) that assist in producing rhythmic coordinated movements of all four limbs (Dietz 2002).

In humans, the evidence for CPG networks and interlimb connections between the arms and legs is indirect due to methodological constraints (Klarner T and Zehr EP, unpublished observations; Zehr 2005; Zehr and Duysens 2004; Zehr et al. 2016). Modulation of reflexes sampled during human locomotion reflects many of the hallmark characteristics of modulation induced by CPG regulation, such as task and phase dependency (Dietz et al. 2001; Haridas and Zehr 2003; Wannier et al. 2001; Zehr and Haridas 2003; Zehr et al. 2001). As such, an input that produces a reliable change in reflex modulation can be used to infer mechanisms within the spinal cord. Previous studies have shown that rhythmic arm movement modulates reflexes in the lower limbs that can be suppressive (Frigon et al. 2004; Hundza and Zehr 2009) but also facilitative (Dragert and Zehr 2009). It has been suggested that rhythmic arm movement produces a strong, persistent descending input

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that modulates the level of presynaptic inhibition, altering transmission between group Ia afferents from muscles and alpha motor neurons supplying the muscles of the lower limbs (Frigon et al. 2004).

In recent years, the role of the arms in human locomotion has become a topic of renewed interest. Bipedal locomotion, although different from quadrupedal locomotion, nonetheless shares many of the same underlying characteristics. It has been argued that during locomotion, bipedal arm and leg coordination is similar to quadrupedal coordination and that this coordination is simply uncoupled during a skilled upper limb task (Dietz 2002). The arms, once thought to be functionally passive during walking, have since been shown to be active contributors to the maintenance of smooth, rhythmic gait by offsetting the rotational torque produced by the lower limbs (Elftman 1939). Arm swing has been shown to facilitate activation of muscles of the lower limbs, indicating that they are actively contributing to locomotion (Ferris et al. 2006). The arms are thought to influence the legs via the same interlimb networks present in other animals (Zehr et al. 2016).

The neurological lesion occurring as a result of a stroke leads to permanent disability, including hemiparesis, foot drop, gait asymmetries, and difficulty with activities of daily living (Zehr 2011). Unfortunately, although rehabilitation continues to be useful even decades after stroke (Sun et al. 2015), little therapy is typically provided beyond 6 mo postlesion. In chronic stroke, years of disuse can compound the already debilitating effects of the initial injury, with walking being one of the most frequently impacted abilities. Poststroke quality of life decreases directly with the inability to ambulate (Ada et al. 2009).

Recently, rhythmic arm and leg cycling training in chronic stroke was shown to induce changes to muscle activation and reflex modulation in all four limbs that were seen alongside improved overall quality of walking (Klarner et al. 2014, 2016a, 2016b). These findings build on previous work showing that in chronic stroke populations, movement of the arms can induce short-term changes in reflex excitability of the lower limbs (Barzi and Zehr 2008; Mezzarane et al. 2014). Clearly established interlimb networks, present in both reduced animal and neurologically intact populations, remain at least partially accessible after stroke (Zehr and Loadman 2012). Additionally, rhythmic movement other than walking can activate these spinal networks (Klarner et al. 2014, 2016a, 2016b; Zehr et al. 2012). This has important implications for those affected by chronic stroke whose walking function is below what is required to take part in treadmill training.

A remaining question is the role that rhythmically training the arms alone may play in the recovery of walking function. It is important to establish whether all four limbs need to be active during rhythmic training or whether an individual who is unable to participate in active lower limb cycling can receive the benefits of interlimb connectivity using only arm cycling. In the present study we tested the working hypothesis that arm cycling training would transfer to improvement of interlimb neurological integrity and walking function.

METHODS

Participants

Nineteen participants (72.5 ± 9.37 yr; range 57–87 yr) with chronic stroke (104.65 ± 57.86 mo poststroke; range 7–214 mo poststroke) were recruited for this study, based on a similar recruitment number in a previous training study (Klarner et al. 2016a, 2016b). Participants were recruited through presentations at community stroke support groups, posters in medical offices and hospitals, and direct referral from community clinicians familiar with work in the laboratory. Exclusion criteria included the use of medication affecting muscle tone (Botox, baclofen, etc.), pacemakers, epilepsy, and insulin-dependent diabetes. Participants ranged in physical ability level from low to high functioning (see Table 1 for clinical assessment scores). One participant completed all clinical tests except for the Chedoke McMaster Stroke Assessment due to injury of the primary caregiver unrelated to the intervention. Another participant was unable to complete the clinical posttest because of a back injury that occurred just prior, and thus all associated clinical results were excluded from the data. Otherwise, there were high levels of adherence to the training protocol as evidenced by no participants dropping out during the training intervention.

Before beginning arm cycling training, participants were screened with the Physical Activity Readiness Questionnaire (PAR-Q; Zehr 2011), and if a response of "yes" was given for any of the questions, a physician's permission was obtained for that participant. The protocol was approved by the Human Research Ethics Committee at the University of Victoria and conducted in accordance with the Declaration of Helsinki, with all participants providing informed, written consent.

Training Protocol

The protocol and experimental design utilized in this study were similar to a previously described experiment in which participants trained using combined arm and leg cycling (Klarner et al. 2016a, 2016b). Participants performed asymmetrical arm cycling training on a Sci-Fit Pro 2 ergometer with the foot pedals removed and seat height adjusted so that the feet were planted firmly on the floor with a session aggregate activity time of 30 min three times a week for 5 weeks. The training was of moderate intensity, and participants were asked to maintain a cadence of 1 Hz [~60 revolutions per minute (RPM)]. Participants were able to take short breaks during the training period if needed, but the aggregate time of 30 min remained the same. The arm cranks were adjusted to accommodate individual differences in range of motion on the more affected (MA) side. For participants with more severe weakness or spasticity, hand braces were used to ensure that the MA hand would stay on the handle.

Before and then repeated at 5-min intervals throughout the 30-min training sessions, participants were asked to rate their perceived exertion (RPE) using a 10-point scale. Heart rate was also assessed at 5-min intervals using a chest strap heart rate monitor (PolarElectro, Quebec, Canada). RPM were monitored throughout the training sessions to ensure that the target of ~60 was achieved.

The progressive training element of this study involved gradual and minimal increments of the workload over the course of the 5 weeks, similar to the approach used in other poststroke training protocols (Klarner et al. 2016a, 2016b; Zehr 2011). Participants were instructed to exercise at an intensity producing an RPE between 3 and 5, (i.e., "moderate" activity), and workload was adjusted accordingly. This RPE corresponded to a target heart rate (HR) between 50 and 70% of maximum (Scherr et al. 2013). With participants who used beta blockers, adjustments were made to target HR goals (Tang et al. 2006). The workload was increased across sessions to allow participants to maintain a consistent RPM of ~60 while maintaining a steady RPE. The minimum workload on the ergometer was 10 W. Two individuals were unable to cycle at this workload and instead trained

Table 1. *Summary of participant demographics and test results*

Participant	Sex, M/F	Age, yr	MA Side, L/R	Postlesion Time, mo	Modified Ashworth (MA side) Ankle/Knee/ Wrist/Elbow		FAC (/6)		Chedoke-McMaster Arm/Hand/Shoulder/ Leg/Foot		Monofilament (MA Side)Hand/Foot		Berg Balance Score (/56)	
					Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	M	60	R	190	2/1/1/1	2/1/1/1	6	6	3/5/6/6/3	3/5/6/6/3	F3.61/J4.31	F3.61/J4.31	49	47
2	M	69	L	114	2/1/1+/2	1+/1/1+/2	5	5	3/2/6/5/3	3/2/6/5/3	T6.65/T6.65	T6.65/T6.65	44	46
3	M	71	L	58	2/1+/2/1+	2/1+/2/1+	4	4	2/2/2/3/2	2/2/2/3/2	T6.65/T6.65	T6.65/T6.65	25	24
4	F	81	R	43	1/1/0/1	1/1/0/1	5	5	6/6/6/6/4	6/6/6/6/4	F3.61/J4.31	F3.61/F3.61	42	44
5	F	61	L	78	1/1/0/0	1/1/0/0	6	6	7/6/7/7/7	7/6/7/7/7	J4.31/K4.56	J4.31/J4.31	53	56
6	M	82	R	89	1/0/0/0	1/0/0/0	2	2	7/6/6/6/6	7/6/6/7/6	J4.31/T6.65	J4.31/K4.56	55	55
7	F	57	L	96	1/0/0/1	1/0/0/1	6	6	6/6/7/7/7	6/6/7/7/7	J4.31/J4.31	F3.61/J4.31	56	56
8	M	81	R	150	0/0/0/0	1/0/0/0	6	6	6/5/6/6/4	6/6/6/6/4	J4.32/T6.65	K4.56/T6.65	48	50
9	M	65	L	86	4+/3+/3/2	3/1+/2/1+	4	5	2/2/4/3/2	2/2/4/3/2	F3.61/T6.65	F3.61/K4.56	21	36
10	M	72	L	68	1/0/0/1	1/1/0/1	6	6	7/6/6/5/4	7/7/6/5/5	J4.31/K4.56	J4.31/T6.65	55	55
11	M	87	L	70	2/1/0/0	2/1/0/0	3	5	3/5/6/4/3	3/5/6/5/4	J4.31/J4.31	J4.31/J4.31	46	49
12	M	72	L	155	2/0/0/0	0/0/1/0	4	3					20	20
13	F	83	R	7	0/0/0/0	0/0/0/0	2	2	3/5/6/2/2	4/6/6/3/2	J4.31/K4.56	J4.31/T6.65	8	15
14	M	86	L	156	2/0/1+/0	0/0/2/1	4	4	5/4/6/5/3	4/5/7/5/4	J4.31/J4.31	J4.31/J4.31	48	50
15	F	67	R	164	2/2/1+/1+	3/1/1+/2	4	4	3/2/5/4/3	3/2/6/4/3	F3.61/T6.65	T6.65/T6.65	25	27
16	F	69	R	214	0/0/0/0	1/0/0/0	5	5	7/7/7/6/6	7/7/7/6/7	J4.31/J4.31	J4.31/J4.31	54	55
17	F	68	R	41	0/0/0/0	1/0/0/0	5	5	5/7/4/6/7	7/7/5/6/7	J4.31/J4.31	J4.31/J4.31	47	56
18	F	77	L	108										
19	M	82	L	90	1/0/0/1+	1/0/0/2	5	5	5/5/7/5/5	5/6/7/5/5	J4.31/J4.31	K4.56/J4.31	52	49

Data are results of tests assessing clinical status, including a test for muscle tone (Modified Ashworth, functional ambulation category (FAC), physical impairment (Chedoke-McMaster scale), touch discrimination (monofilament test), and balance (Berg Balance Scale), for stroke participants before and after arm cycling training. MA, more affected; M, male; F, female; L, left; R, right; Pre, pretraining; Post, posttraining. Chedoke McMaster stroke data were not collected for *participant 12* due to time constraints unrelated to the intervention. *Participant 18* was unable to complete the clinical posttraining due to a back injury and thus all data were excluded.

on an arm cycle ergometer (Monark 871E arm ergometer) with no resistance. Blood pressure (BP) was obtained using a digital blood pressure cuff placed over the less affected (LA) arm before the start of exercise and after its completion. BP was monitored until it returned to pre-exercise levels, at which point participants were allowed to leave the laboratory.

Baseline Control Procedures

As demonstrated in previous experiments, a multiple baseline within-participant control design took the place of a separate control group (Bütefisch et al. 1995; Klarner et al. 2016a, 2016b). This design has multiple benefits over a traditional control group design. Although this approach is more labor intensive and requires more time, the multiple baseline design has been used as a valid replacement to the design with a control group and given high internal consistency of measures. It allows participants to create a reliable pretraining baseline and enables them to act as their own preintervention control. To evaluate single participant responses to arm cycling training, a 95% confidence interval (CI) of dependent variables was calculated from the three baseline tests. When the participant's posttest value was outside the 95% CI range, this participant was defined as having significant change. The direction of change was determined and identified as either an improvement or decrement for each participant. An additional benefit of this design is that no participants are relegated to a nontreatment group; therefore everyone receives the potential benefit of exercise. Also, between-participant variability is higher in chronic stroke populations, and this design allows participants to be compared with their own variability, rather than the variability of others at baseline. Each participant completed three baseline sessions spread over 3 wk before beginning the 5 wk of training. Tests were completed at the same time each day, and other environmental conditions such as lighting, participant position, noise, and temperature were kept as consistent as possible (Dragert and Zehr 2013; Lagerquist et al. 2006; Zehr 2002). Measures comprised three main categories: clinical, physical performance and neurophysiological integrity, previously shown to have high reliability across multiple baseline points (Klarner et al. 2016a, 2016b).

Clinical Measures

Walking measures included the 6-Minute Walk (Enright 2003), the Timed Up and Go (TUG) (Podsiadlo and Richardson 1991), and the timed 10-Meter Walk tests. Balance was assessed using the Berg Balance Scale. The Chedoke McMaster Stroke Assessment was used to evaluate the stage of upper and lower limb impairment on a 7-point scale where 1 represents total assistance and 7 represents complete independence (Gowland et al. 1993). The Modified Ashworth Scale was used to assess spasticity (Bakheit et al. 2003; Pandyan et al. 2003; Patrick and Ada 2006), which was measured on the ankle, knee, wrist, elbow flexion, and shoulder. The 6-point Functional Ambulation Categories Scale was used as a measure of the basic motor skills necessary for walking (Holden et al. 1984). The ability to discern light touch and pressure was determined for the MA hand and foot using the 5-piece Semmes-Weinstein kit of calibrated monofilaments (Sammons Preston Rolyan, Cedarburg, WI; Hage et al. 1995). All clinical measures were performed by the same licensed physiotherapist.

Physical Performance

Strength. Participants sat in a custom-fitted chair designed to minimize extraneous movements, with both feet securely fastened to plates on the floor (Dragert and Zehr 2011, 2013; Klarner et al. 2014, 2016a, 2016b). Maximal voluntary isometric contractions (MVCs) for ankle dorsiflexion and plantarflexion were established via strain gauge (Omegadyne model 101-500) and converted to torque. For the upper limb, participants performed maximal isometric handgrip contractions using a commercially available handgrip dynamometer (Takei Scientific Instruments, Niigata, Japan). After being allowed a "test run" to ensure that the right movements were being produced, participants completed 2 separate trials of 5-s maximal contractions on both the LA and MA sides for plantarflexion, dorsiflexion, and handgrip. Maximum values were determined offline by taking the mean value of 500-ms duration around the largest reading generated over the course of the 2 trials.

Electromyography. Bipolar surface electrodes were placed bilaterally over the mid-muscle bellies of the soleus (SOL), tibialis anterior (TA), and anterior deltoid (AD), as well as the biceps brachii (BB), triceps brachii (TB), and flexor carpi radialis (FCR) on the MA side only. Electrode positions were marked and recorded in relation to anatomical landmarks and placed by the same experimenter each day for consistency. To reduce variation in placement, anatomical landmarks and measurements taken from the first session were used on subsequent sessions. Electromyography (EMG) signals from all muscles of interest were preamplified ($\times$5,000) and bandpass filtered (100–300 Hz; Grass P511; Grass Instruments, Astro-Med, West Warwick, RI). This is consistent with previous experiments in this laboratory (Balter and Zehr 2007; Klarner et al. 2014, 2016a, 2016b; Vasudevan and Zehr 2011; Zehr and Loadman 2012; Zehr et al. 2007, 2012). After conversion to a digital signal, strength data were sampled at 2,000 Hz and walking and arm cycling data were sampled at 1,000 Hz using a custom-built continuous acquisition software (LabVIEW, National Instruments, Austin, TX). Data were low-pass filtered at 100 Hz using a fourth-order Butterworth filter and were full-wave rectified.

During cycling and walking, background electromyography (bEMG) amplitudes were calculated from unstimulated data broken into eight phases of movement. Phasic bEMG were analyzed offline in three ways (Klarner et al. 2014, 2016a, 2016b; Zehr et al. 2012): *1*) the amplitude was calculated for each phase of the movement cycle (i.e., 1/8 of the movement cycle); *2*) a modulation index $MI = [(EMG_{max} - EMG_{min})/EMG_{max}] \times 100$ was calculated for each muscle across the movement cycle (Klarner et al. 2014, 2016a, 2016b; Zehr and Haridas 2003; Zehr and Loadman 2012; Zehr et al. 2012); and *3*) coactivation ratios were calculated for each phase of the movement cycle for the homologous muscles in the arms and legs (AD, TA, and SOL), as well as for the antagonist muscles (BB/TB, TA/SOL) on the MA and LA sides. The coactivation ratios in the homologous muscles give an indication of the level of bilateral coordination after stroke, whereas the coactivation ratios in the antagonist muscles reveal the extent to which agonist/antagonist muscle pairs are coordinated during movement (Zehr et al. 2012).

Arm cycling. During the baseline and posttests, participants performed arm cycling on an instrumented device that differed from the Sci-Fit used for training. They were seated in the same custom-fitted chair as was used for strength measurements and cycled on a custom-made hydraulic arm ergometer (described in Zehr et al. 2003), which was positioned directly in front of them. The handles of the ergometer moved together, yet 180° out of phase. Participants were asked to hold the handles firmly, and when necessary, hand braces were provided to ensure the MA hand was securely attached. Depending on a participant's range of motion, the cranks could be adjusted for larger or smaller circular rotations. Prior work showed that asymmetrical changes in crank length were not associated with significant changes in cutaneous reflex modulation (Hundza and Zehr 2006). The crank positions for individual participants were determined in the first baseline test and kept consistent throughout the study. Arm cycling was performed in a clockwise direction, with the 3 o'clock position (viewed from the right side of the body) being the position of maximal elbow extension and shoulder flexion. Participants cycled for ~4–6 min, which corresponded to 160 cycles for analysis. Continuously acquired data were later broken into movement cycles in which the start and end were indicated by the MA arm at the 12 o'clock position.

To compare across trials and participants, cycle time was normalized to 100%. Arm cycling phases are illustrated in Fig. 1*B*.

Walking. Participants walked on a motorized treadmill (Woodway US, Waukesha, WI) wearing an overhead safety harness (Pneuweight; Pneumex, Sandpoint, ID) at a "comfortable" speed. Comfortable was defined to participants as the speed they would normally comfortably walk. The body weight support feature of the harness was not used for any participants. All participants walked supporting their own body weight, and the harness was used strictly for safety purposes in the event of a fall. An ankle foot orthosis was used only if participants required one for walking during daily activity. Participants were free to place their hands on the side or front railings, with one individual requiring the MA arm to be kept in an over-the-shoulder sling. Whatever their chosen hand positions were, they were noted and kept consistent across baseline and posttests.

Neurophysiological Integrity

Cutaneous reflexes elicited during arm cycling and walking and arm cycling-induced modulation of stretch reflexes in the soleus were used to evaluate neurophysiological changes induced by arm cycling training.

Cutaneous reflexes. Cutaneous reflexes evoked during walking and arm cycling were used to provide insight into the ability of arm cycling training to activate and modulate interlimb integrity over time. Reflexes were evoked via surface stimulation of the superficial radial nerve (SR; innervates the dorsum of the hand) on the LA side. Electrodes were placed just proximal to the radial head at the wrist in a bipolar configuration with the cathode proximal and the anode distal (Klarner et al. 2014, 2016b). Before a trial began, perceptual (PT) and radiating (RT) thresholds were found for each participant. RT was defined as the minimum stimulation intensity required to cause radiating paresthesia into the entire innervation area of the nerve. To obtain RT, gradual increments in stimulation intensity were delivered to participants until the maximum area of paresthesia was found. This intensity was then determined as RT. Intensities were then set to 3× RT for the duration of the stimulation trials, providing it was tolerated by the participant. SR stimulation was delivered as trains of 5 × 1.0-ms pulses at 300 Hz (Grass P511) by a Grass S88 stimulator with SIU5 stimulus isolation and a CCUI constant current unit (Grass Instruments). During arm cycling, participants received 160 stimulations pseudorandomly with an interstimulus train interval of 1–5 s. During walking, stimulation was delivered in a similar manner, but yielding 120 stimulations.

All data were recorded using custom-written LabVIEW (National Instruments) and analyzed using custom-written MATLAB (version R2011b; The MathWorks, Natick, MA) applications. Stimulus artifact was removed from each reflex trace, and data were low-pass filtered at 30 Hz using a dual-pass fourth-order Butterworth filter. Movement cycles were broken down into eight equidistant phases. For each phase, the average nonstimulated "control" trace was subtracted from the average stimulated trace, producing a subtracted reflex trace. To account for the obscure phase-dependent modulation of net reflexes with cycling (Zehr et al. 2001), we chose to include net reflexes along with the analysis of reflexes at given latencies. Cutaneous reflex amplitudes were quantified in three ways: subtracted peak amplitudes at *1*) early (~50–80 ms to peak) and *2*) middle (~80–120 ms to peak) latencies (Zehr and Loadman 2012; Zehr et al. 2012), and *3*) the average cumulative reflex over 150 ms following stimulation ($ACRE_{150}$) within each phase (Klarner et al. 2014, 2016b).

Stretch reflexes. Stretch reflexes were evoked using an electrodynamic shaker with an attached accelerometer (ET-1126B; Labworks) placed over the Achilles tendon, similar to procedures used previously in our laboratory (Klarner et al. 2016b; Mezzarane et al. 2014; Palomino et al. 2011). Constant pressure was applied to the tendon, and the shaker was programmed to deliver a single sinusoidal pulse. Each participant completed six trials of stretch reflexes: three on the LA side and three on the MA side. The first trial consisted of a recruitment curve, and participants received a series of pulses of increasing amplitude until a maximal stretch reflex was found during quiet sitting. During the second trial, participants received 20 pulses at an amplitude that elicited ~70% of their maximal stretch reflex during quiet sitting with their arms at rest (static) but at the 7 o'clock position for the LA hand. During the third trial, reflexes were evoked during rhythmic arm cycling at 1 Hz (conditioned) when the LA hand was at the 7 o'clock position. To evaluate the modulatory effect of arm cycling on stretch reflexes, the static amplitude was subtracted from the arm cycling conditioned amplitude and then expressed as a percentage of the static amplitude. A negative value indicates sup-

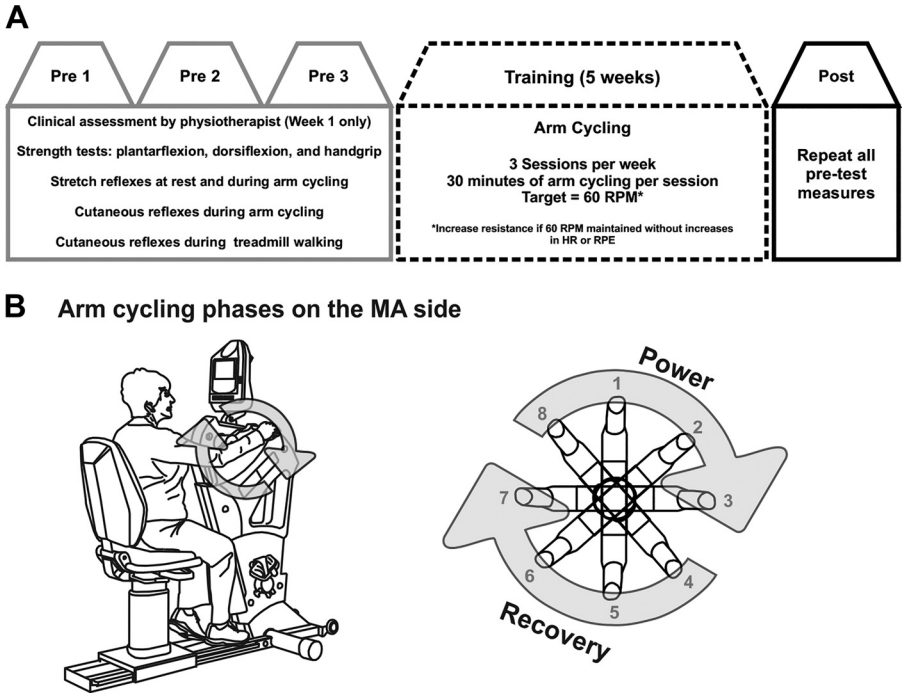

Fig. 1. *A*: a summary of the experimental timeline, which illustrates the pre- (Pre) and posttest (Post) procedures and the training parameters. A multiple baseline within-participant control design was used for this experiment. *B*: a graphical summary of the arm cycling training position (*left*) and labels for the phases of movement within the arm cycling task (*right*).

pression and a positive value indicates a facilitation of stretch reflexes during cycling. To compare modulation of stretch reflexes between the LA and MA sides, the conditioned–static difference of the MA side was subtracted from the difference of the LA side. Negative and positive values indicate greater cycling-induced modulation on the LA and MA sides, respectively. Effects of homologous and heteronymous muscle activity were monitored and recorded from a 20-ms prestimulus period. EMG data were normalized to the peak EMG recorded during either walking or arm cycling for each session and each muscle.

Statistics

Statistical procedures were performed using SPSS 18.0 (Chicago, IL). Two types of analysis were performed: single participant and group analyses.

For single participant comparisons, a 95% CI was determined from the three pretest values. Posttest values were then compared with the 95% CI established from the pretests. If the posttest fell outside of the 95% CI, it was considered statistically significant (Cummings 2013). The total number of participants with significant changes is reported.

For pre- to posttraining group comparisons, a repeated-measures ANOVA was run to compare differences across the three pretest sessions. If no differences were found, data were pooled together to form an average pretest value for each measure and compared with the posttest value using a paired-samples *t*-test (Klarner et al. 2016a, 2016b). For phase-dependent modulatory effects of cycling and walking on bEMG and cutaneous reflexes irrespective of training effects, one-way (phase) repeated-measures ANOVAs were performed. Effects of phase are reported as either significant or nonsignificant in Table 4. Following the tests for phase-dependent modulation, multiple-factor repeated-measures ANOVAs were utilized to determine main and interaction effects of time point (i.e., pre- and posttraining) and phase of movement (i.e., 8 phases of either arm cycling or walking). Assumptions for ANOVA and paired-samples *t*-tests were evaluated as parametric tests for within-participants design. The observed effect for pre- to posttest differences are reported as Cohen's effect size (*d*), with $0.2 \leq d < 0.5$, $0.5 \leq d < 0.8$, and $d \geq 0.8$ corresponding to small, medium, and large effects (Cohen 1988), respectively. When direction of change was predicted because of priori hypotheses, one-tailed paired-samples *t*-tests were performed. In all cases, statistical significance was set at $P \leq 0.05$. Results are reported as means ± SD in text (means ± SE in figures).

RESULTS

Arm Cycling Training

All participants completed 15 sessions of arm cycling training. Figure 2 shows the group means for the average HR, RPE, RPM, and workload recorded throughout each arm cycling training session. HR ($P = 0.79$) was maintained during each session and did not differ throughout the training sessions, whereas RPM ($P < 0.001$) and workload ($P = 0.019$) increased over time and were significantly greater during *session 15* compared with *session 1*. Despite the increased difficulty in arm cycling, perceived effort levels remained unchanged throughout the training program, evidenced by no change in RPE ($P = 0.15$).

Clinical Measures

Participants significantly improved their performance of the 6-Minute Walk, TUG, and 10-Meter Walk tests from pre- to posttraining (Fig. 3). For the 6-Minute Walk test, participants walked an average of 245.1 m initially, which subsequently increased by 8.5% to 266.1 m ($P = 0.011$, $d = 0.46$) and corresponds to a change greater than the 7.4-m minimal detectable change for individuals after stroke (Perera et al. 2006). Participants reduced their time to perform the TUG by 28.9%

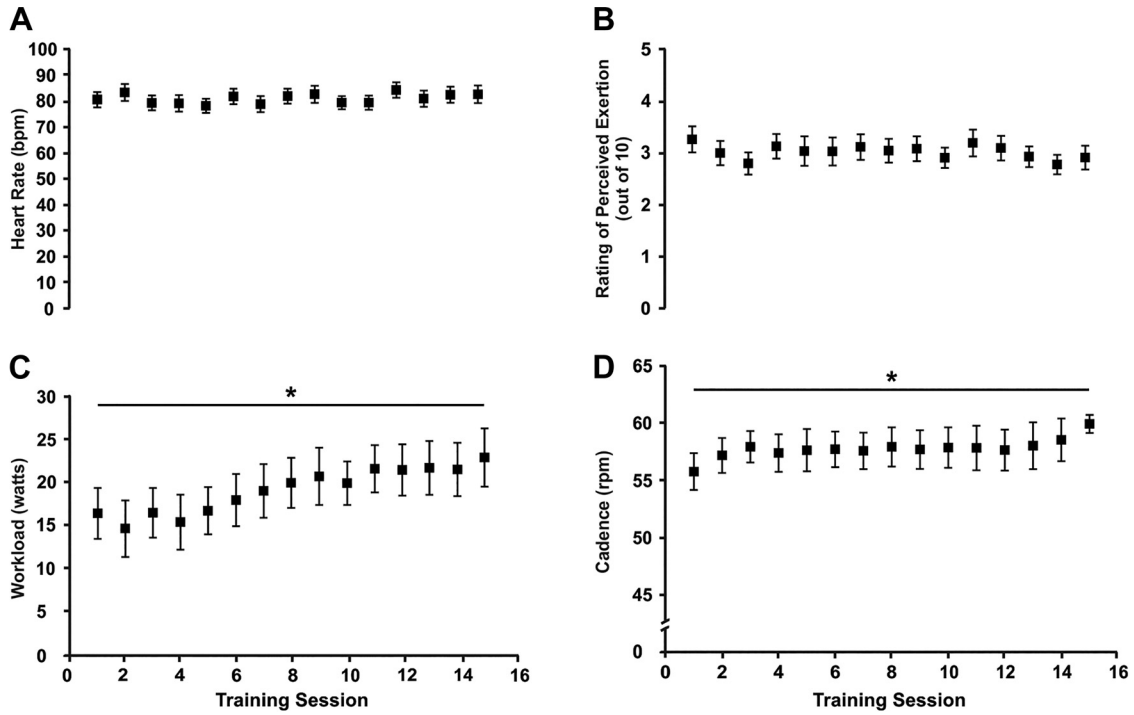

Fig. 2. Training data. Data were recorded for training parameters HR (*A*), RPE (*B*), workload (*C*), and cadence (*D*) throughout each training session. Data points are group ($n = 19$) means ± SE of an average of data recorded at 5-min intervals. *$P < 0.05$, significant difference between the first and last training session.

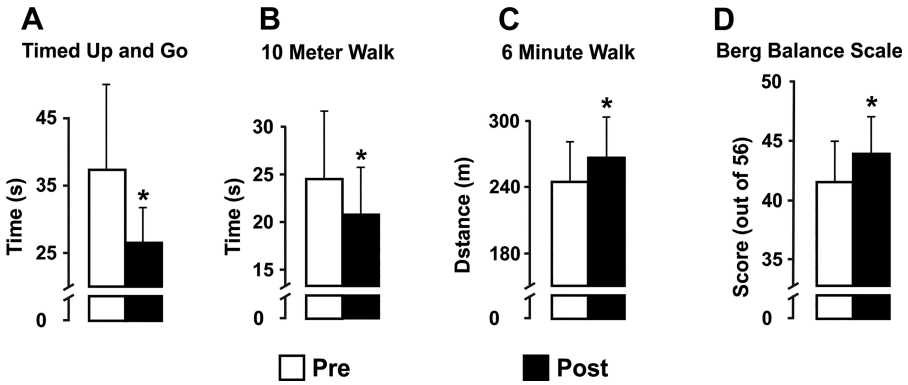

Fig. 3. Clinical assessments of walking and balance. Pre (open bars) and Post (filled bars) group data for the Timed Up and Go (*A*), 10-Meter Walk (*B*), 6-Minute Walk (*C*), and Berg Balance Scale (*D*). Bars are group ($n = 18$) means ± SE. *$P < 0.05$, significant change from Pre average to Post.

($P = 0.045$, $d = 0.23$) from 37.3 to 26.5 s, which is greater than the 2.9-s minimal detectable change for individuals after stroke (Flansbjer et al. 2005). They furthermore reduced their 10-Meter Walk time by 15.1% ($P = 0.049$, $d = 0.39$) from 24.5 to 20.8 s, which is slightly less than the 3.7-s minimal detectable change for individuals after stroke (Perera et al. 2006). Balance, as assessed by the Berg Balance Scale, also improved (5.7%, $P = 0.014$, $d = 0.3$) from a score of 41.5 to 43.9, but this change was slightly less than the minimal detectable change of 2.5 for individuals after stroke (Liston and Brouwer 1996). Individual data for walking tests are shown in Table 2 and for balance in Table 1. Chedoke-McMaster Stroke Assessment scores reflected, on average, positive significant change in the shoulder (3.1%, $P = 0.041$, $d = 0.39$), hand (6.2%, $P = 0.01$, $d = 0.46$), leg (3.5%, $P = 0.041$, $d = 0.36$), and foot (5.6%, $P = 0.02$, $d = 0.37$) categories. Use of the Modified Ashworth Scale showed that only a small number of participants (5) saw any positive change in spasticity in the ankle, knee, wrist, or bicep. Individual scores are shown in Table 1. There was no meaningful change from pre- to posttraining of the ability to detect light touch with the MA hand or foot, as measured with calibrated monofilaments (see Table 1).

Maximal Isometric Strength

Repeated-measures ANOVA showed that there were no significant differences between baseline pretest values for torque recorded during any MVCs (P values ranged from 0.151 to 0.786), and there were no significant differences between baseline pretest values for EMG of any muscles measured during MVCs (P values ranged from 0.187 to 0.903). Average pre- to posttraining strength and muscle activity changes are summarized in Fig. 4. From pre- to posttraining, handgrip force increased by 13% ($P = 0.02$, $d = 0.27$) and 8.4% ($P < 0.001$, $d = 0.39$) on both the MA and LA sides, respectively. Peak EMG activity of the FCR measured on the MA side concurrently increased by 30% ($P = 0.04$, $d = 0.32$). Plantarflexion torque of the MA side increased by 20% ($P = 0.025$, $d = 0.31$) while there were subsequent increases in bilateral SOL peak EMG during plantarflexion MVCs (MA: $P = 0.019$, $d = 0.38$, see Fig. 4*B*; LA: $P = 0.035$, $d = 0.24$). Dorsiflexion peak torque and subsequent TA peak EMG did not differ statistically

Table 2. *Summary of individual pre- and posttraining scores for clinical assessments of walking ability*

	6-Minute Walk, m			Timed Up and Go, s			10-Meter Walk, s		
Participant	Pre	Post	%Change	Pre	Post	%Change	Pre	Post	%Change
1	217.8	273.3	25.5	21.1	18.1	−14.2	9.6	10.8	12.4
2	50.2	53.4	6.4	76	58.2	−23.4	67	57.6	−14.1
3	131.3	167.8	27.8	30.1	27.1	−9.9	23.1	19.1	−17.6
4	254.9	318.7	25	14.8	13.1	−11.8	11.8	10.7	−9.2
5	505.2	489.5	−3.1	7.3	7.6	2.9	6.5	6.7	2.6
6	370.3	366.9	−0.9	21	19.1	−9.1	11.9	10.1	−15.3
7	63.8	68.1	6.8	67.5	46.8	−30.6	51.3	44.2	−13.9
8	421.8	496.3	17.7	10.5	9.5	−9.1	7.4	6.9	−6.7
9	417.2	507	21.5	7.3	7.3	0	6	5.9	−2
10	412.6	412.2	−0.1	13.4	9.7	−27.6	9.4	7.6	−19
11	243.2	224	−7.9	15.9	16.6	4.1	11	12.1	9.9
12	39.5	37.9	−4	54.8	56.2	2.6	63.6	58.5	−8.1
13	60.8	86.9	42.9	80.8	56.7	−29.8	35.3	25.3	−28.6
14	222.2	242.5	9.2	14.4	14.5	0.4	12.2	11.5	−5.1
15	26.4	31.3	18.6	242	87.5	−63.9	127	77.9	−38.7
16	349.1	309.8	−11.3	10.5	11.9	12.7	7.8	6.3	−20.3
17	330.6	392	18.6	16.7	9.7	−42	10.6	5	−52.8
18									
19	298.6	316.4	6	16.5	12.7	−22.8	7.6	8.3	9.1
Mean	245.3	266.3	8.6	40	26.8	−33.1	26.6	21.3	−19.8
SD	153.86	162.93	14.52	55.89	23.6	19.08	32.01	22.34	16.72

Assessments include the 6-Minute Walk (distance in meters), Timed Up and Go (time in seconds), and timed 10-Meter Walk (time in seconds). *Participant 18* was unable to complete the clinical posttraining due to a back injury and thus all data were excluded.

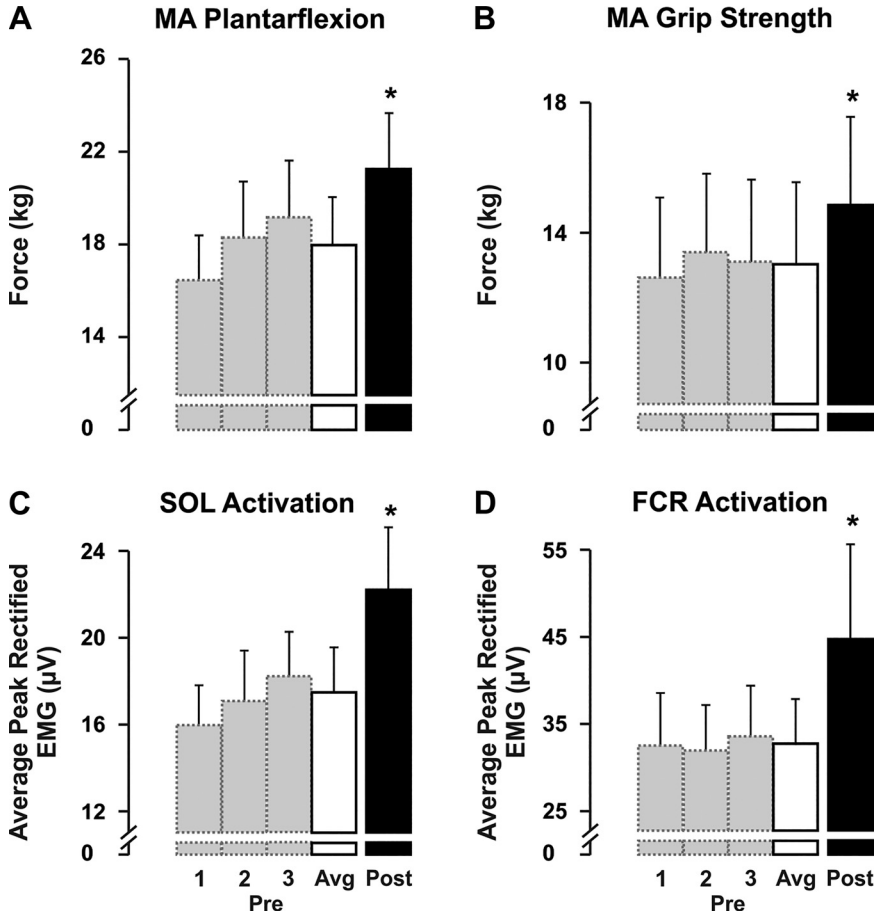

Fig. 4. Strength and muscle activity during isometric contractions. Pretest MVC (Pre 1, 2, and 3) data are represented by shaded bars, whereas Pre and Post group data are represented by open and solid bars, respectively, for MA plantarflexion force (*A*), MA grip strength (*B*), MA SOL muscle activity during plantarflexion MVC (*C*), and MA FCR muscle activity during handgrip MVC (*D*). Bars are group ($n = 18$) means ± SE. *$P < 0.05$, significant change from Pre average to Post.

pre- to post-arm cycling training (P values ranged from 0.1 to 0.49). Individual participant data are summarized in Table 3.

Muscle Activity During Arm Cycling

Muscle activity across all eight phases of movement during arm cycling did not differ between the three pretests for any muscle measured. Phase-dependent modulation of EMG during arm cycling was noted for the MA BB, MA TB, and LA AD before training. However, after training, the MA AD also showed phase-dependent modulation (see Table 4). A two-factor (phase × time) ANOVA revealed a significant interaction effect for the MA AD [$F_{(7,126)} = 6.325$, $P = 0.023$], MA BB [$F_{(7,126)} = 5.870$, $P = 0.006$], and LA AD [$F_{(7,126)} = 6.902$, $P = 0.001$]. Compared with the pretest average, EMG activity of the MA AD was significantly decreased during *phases 2* ($P = 0.007$, $d = 0.5$), *3* ($P = 0.049$, $d = 0.3$), and *7* ($P = 0.037$, $d = 0.42$), which correspond to the late power (*phases 2* and *3*) and late recovery (*phase 7*) phases of cycling (see Fig. 1*B*). EMG activity of the LA AD was significantly

Table 3. *Summary of individual torque and EMG data*

	MA		LA	
	Torque	EMG	Torque	EMG
Handgrip	10	12 (FCR)	13	N/A
Plantarflexion	9	9 (SOL)	9	8 (SOL)
Dorsiflexion	6	7 (TA)	9	6 (TA)

Data are the number of participants whose posttest values for torque and EMG were outside the 95% confidence interval (CI) established from their baseline measurements. The EMG from a muscle of interest corresponding to handgrip, plantarflexion, or dorsiflexion is indicated in parentheses. FCR, flexor carpi radialis; SOL, soleus; TA, tibialis anterior.

Table 4. *Summary of significant main effects across all phases of movement for arm cycling and walking*

	bEMG		ELR		MLR		$ACRE_{150}$	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
				Arm cycling				
MA AD	ns	*	*	*	ns	ns	ns	ns
MA BB	*	*	ns	ns	ns	ns	ns	ns
MA TB	*	*	ns	ns	ns	ns	ns	ns
MA FCR	ns	ns	ns	ns	ns	ns	ns	ns
LA AD	*	*	*	*	*	*	*	*
				Walking				
MA SOL	*	*	ns	ns	ns	ns	ns	ns
MA TA	ns	*	ns	*	ns	ns	ns	ns
LA SOL	*	*	*	*	ns	ns	ns	ns
LA TA	ns	*	ns	ns	ns	*	ns	ns
MA AD	ns	*	ns	ns	ns	ns	ns	ns
LA AD	*	*	ns	ns	ns	ns	ns	ns

Data are results of a one-factor repeated-measures ANOVA for main effects across all phases of movement for arm cycling and walking. A significant main effect is an indication of phase modulation during cycling or walking. bEMG, background electromyography; ELR, early latency reflex; MLR, middle latency reflex; $ACRE_{150}$, average cumulative reflex excitability (%peak EMG). AD, anterior deltoid; BB, biceps brachii; TB, triceps brachii. ns indicates no main effect of phase was found. *$P < 0.05$, significant main effect of phase (i.e., phase-dependent modulation of EMG or reflex).

increased at *phases 1–4* (P values ranged from <0.001 to 0.015, d from 0.48 to 0.8), which correspond to the recovery and transition to power phase for that limb. Activity in the MA BB was increased at *phase 4* ($P = 0.033$, $d = 0.24$), which corresponds to early recovery.

Individual participant analysis revealed that there was increased modulation of muscle activity during arm cycling in about half of the participants for most muscles (see Table 5). As a group, the modulation index of bilateral AD muscle activity was altered following arm cycling training (see Fig. 5*A*). On the MA side, the MI of AD EMG increased by 18% ($P = 0.013$, $d = 0.56$) over the entire arm cycling movement. The MI of the LA AD EMG, inversely, decreased by 20% ($P < 0.001$, $d = 0.87$).

Coordination of AD muscle activity from the MA to LA side was altered following arm cycling training (see Fig. 5*B*). The ratio of MA AD to LA AD activity was decreased at *phases 1* ($P < 0.001$, $d = 0.62$), *2* ($P < 0.001$, $d = 0.86$), *3* ($P = 0.002$, $d = 0.68$), *4* ($P = 0.012$, $d = 0.3$), and *8* ($P = 0.011$, $d = 0.39$), corresponding to the power phase of the MA limb, at which point there should be more activity in the LA AD and inhibition of the MA AD to perform a coordinated movement. Within-arm coordination of the MA BB and TB was also altered following arm cycling training (see Fig. 5*C*). During *phases 6* ($P = 0.008$, $d = 0.99$) and *7* ($P = 0.043$, $d = 0.84$), the BB/TB ratio was decreased, whereas during *phase 1* ($P = 0.041$, $d = 0.77$), the BB/TB ratio was increased, compared with pretest values.

Muscle Activity During Walking

Muscle activity during all eight phases of walking did not differ between the three pretests for any muscle measured. Phase-dependent modulation of EMG during walking was noted for the MA SOL, LA SOL, and LA AD before training. However, after training, the MA TA, LA TA, and MA AD also showed phase-dependent modulation (see Table 4). A two factor (phase × time) ANOVA revealed a significant interaction effect for the MA TA [$F_{(7,126)} = 6.372$, $P = 0.002$], LA TA [$F_{(7,126)} = 3.613$, $P = 0.029$], MA SOL [$F_{(7,126)} = 8.363$, $P = 0.002$], LA AD [$F_{(7,126)} = 7.647$, $P < 0.001$], and MA AD [$F_{(7,126)} = 2.677$, $P = 0.013$]. Following arm cycling training, the most notable changes in muscle activity during walking were in the MA TA (see Fig. 6*A*). EMG of the MA TA was increased at *phases 2* ($P = 0.004$, $d = 0.64$), *3* ($P = 0.002$, $d = 0.72$), and *4* ($P = 0.037$, $d = 0.4$), whereas it was decreased at *phases 6* ($P = 0.046$, $d = 0.39$), *7* ($P = 0.027$, $d = 0.53$), and *8* ($P = 0.04$, $d = 0.55$), which correspond to swing and stance of the MA limb, respectively. There was also a decrease in MA SOL EMG during *phase 2* ($P = 0.049$, $d = 0.37$) compared with pretest, which corresponds to early swing. On the LA side, there was a significant increase in TA activity at *phase 8* ($P = 0.024$, $d = 0.57$), which corresponds to late swing of the LA limb. In the upper limbs, there was increased AD activity at *phases 2* ($P = 0.022$, $d = 0.36$) and *8* ($P = 0.015$, $d = 0.38$) for the MA and LA sides, respectively, both of which correspond to phases of movement that contain forward arm swing.

Individual participant analysis revealed that there was increased modulation of muscle activity during walking in less than half of the participants for most muscles (see Table 6). As a group, the MI of muscle activity throughout the walking cycle was altered in the TA bilaterally following arm cycling training (see Fig. 6*B*). The MI increased by 8% ($P = 0.03$, $d = 0.26$) and 15.2% ($P = 0.002$, $d = 0.53$) for the MA and LA TA, respectively.

Table 5. *Summary of individual arm cycling bEMG MI posttraining data*

	bEMG MI During Arm Cycling
MA AD	12/19
MA BB	6/19
MA TB	11/19
MA FCR	11/19
LA AD	12/19

Data are the number of participants whose arm cycling bEMG modulation index (MI) posttraining values were outside the 95% CI established from their baseline measurements.

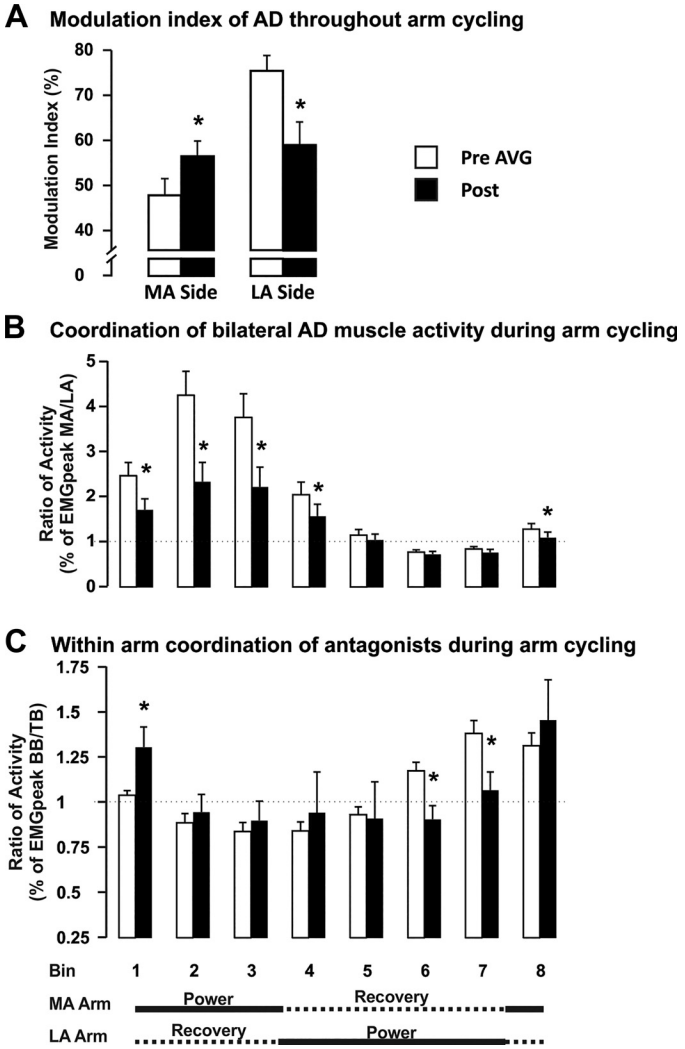

Fig. 5. Muscle activity during arm cycling. *A*: the modulation index for both the MA and LA AD during arm cycling. *B*: the ratio of normalized muscle activity of the MA divided by LA AD throughout arm cycling. *C*: the ratio of normalized muscle activity of the BB divided by TB on the MA side throughout arm cycling (*top*). *Bottom*, phases of movement are indicated for both the MA and LA arms (for *B* and *C*). In *A–C*, open bars are the Pre average and filled bars are Post values. All bars are group ($n = 18$) means ± SE. *$P <$ 0.05, significant change from Pre average to Post.

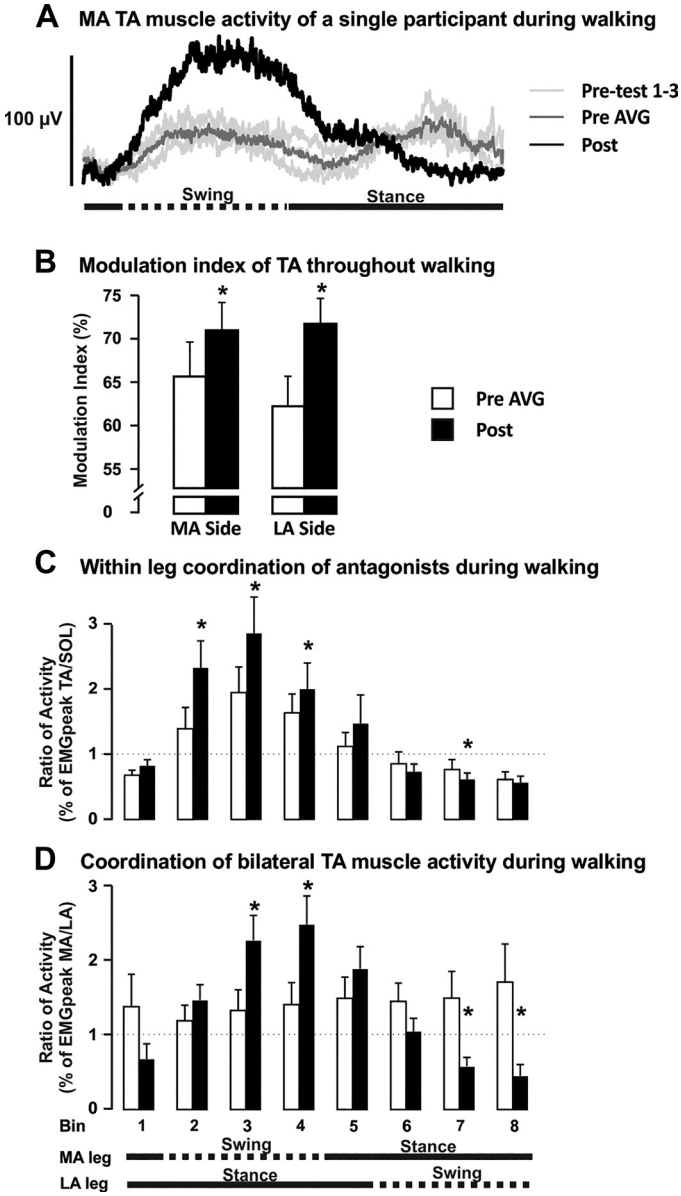

Fig. 6. Muscle activity during walking. *A*: an individual raw EMG recording of the MA TA. Light gray traces are Pre recordings, dark gray trace indicates the Pre average, and black trace is the Post recording. *B*: the modulation index for both the MA and LA TA during walking. *C*: the ratio of normalized muscle activity of the TA divided by SOL on the MA side throughout walking. *D*: the ratio of normalized muscle activity of the MA divided by LA TA during walking (*top*). *Bottom*, phases of movement are indicated for both the MA and LA legs (for *C* and *D*). In *B–D*, open bars are the Pre average and filled bars are Post values. All bars are group ($n = 18$) means ± SE. *$P < 0.05$, significant change from Pre average to Post.

Within the MA limb (see Fig. 6*C*), the TA/SOL coactivation ratio was increased during MA swing *phases 2* ($P = 0.042$, $d = 0.51$), *3* ($P = 0.049$, $d = 0.4$), and *4* ($P = 0.029$, $d = 0.21$), whereas it was decreased at MA stance *phase 7* ($P = 0.027$, $d = 0.26$). Interlimb coordination of the TA muscle was significantly altered following arm cycling training (see Fig. 6*D*). The MA/LA ratio of TA activity increased during MA swing *phases 3* ($P = 0.036$, $d = 0.8$) and *4* ($P = 0.014$, $d = 0.84$), whereas it was significantly decreased during LA swing *phases 7* ($P = 0.03$, $d = 0.56$) and *8* ($P = 0.028$, $d = 0.44$).

Neurophysiological Integrity

Cutaneous reflexes during arm cycling. Reflexes evoked by stimulation of the LA arm (i.e., SR nerve) resulted in significant phase-dependent modulation in the MA and LA AD of early latency reflexes (see Fig. 7*A*, *top* and *bottom*), but only in the LA AD for middle latency reflexes and $ACRE_{150}$ (see Fig. 7*B*, *bottom*) during arm cycling (see Table 4).

Group-averaged early latency reflexes are plotted in Fig. 7*A*. There were sign reversals in the MA TB and BB, a general reduction in the reflex amplitude in the MA FCR, and a trend for increased modulation of reflexes in the LA AD. Interaction effects (phase × time) of early latency reflexes were revealed on the MA side for the BB [$F_{(7,126)} = 5.280$, $P = 0.034$], TB [$F_{(7,126)} = 7.683$, $P = 0.013$], and FCR muscles [$F_{(7,126)} = 3.477$, $P = 0.014$], and also in the LA AD [$F_{(7,126)} = 6.372$, $P = 0.002$]. Following arm cycling training, early latency reflexes in the MA TB were significantly reduced during the transition from recovery to power phase (*phase 8*: $P = 0.044$, $d = 0.37$) and the majority of the power phase (*phase 1*: $P = 0.039$, $d = 0.34$; *phase 2*: $P = 0.022$, $d = 0.37$; *phase 3*: $P = 0.03$, $d = 0.37$), including kinematic phase reversals for *phases 2* and *3*. In the MA BB, early latency reflexes were reduced from 4.13 to −4.51% of peak bEMG during the transition from power to recovery phase (*phase 4*: $P = 0.008$, $d = 0.43$), a kinematic phase reversal. In the MA FCR, early latency reflexes were generally reduced, which was significant during *phases 1* ($P = 0.033$, $d = 0.64$), *5* ($P = 0.023$, $d = 0.54$), and *6* ($P = 0.019$, $d = 0.51$). In the LA AD, early latency reflexes were reversed from 1.91 to −2.7% of peak bEMG during the late recovery phase (*phase 3*: $P = 0.007$, $d = 0.53$) and reduced in mid to late power (*phase 6*: $P = 0.038$, $d = 0.53$, *phase 7*: $P = 0.049$, $d = 0.46$).

Interaction effects (phase × time) of middle latency reflexes were revealed on the MA side for the BB [$F_{(7,126)} = 5.363$, $P = 0.033$] and TB [$F_{(7,126)} = 5.079$, $P = 0.037$]. Compared with pretraining values, middle latency reflexes in the MA TB were reversed from excitatory to inhibitory during mid to late power (*phase 2*: $P = 0.021$, $d = 0.51$; *phase 3*: $P = 0.01$, $d = 0.5$). Furthermore, middle latency reflexes were reduced in the MA BB during late recovery (*phase 7*: $P = 0.049$, $d = 0.35$) and the transition to the power phase (*phase 8*: $P = 0.025$, $d = 0.46$). No other significant training effects of middle latency effects were observed.

Group-averaged net reflexes (i.e., $ACRE_{150}$) are plotted in Fig. 7*B*. General blunting of reflex modulation is observed in

Table 6. *Summary of individual walking bEMG MI posttraining data*

	bEMG MI During Walking
MA SOL	4/19
MA TA	5/19
LA SOL	12/19
LA TA	7/19
MA AD	6/19
MA BB	9/19
MA TB	9/19
MA FCR	4/19
LA AD	7/19

Data are the number of participants whose walking bEMG MI posttraining values exceeded the 95% CI established from their baseline measurements.

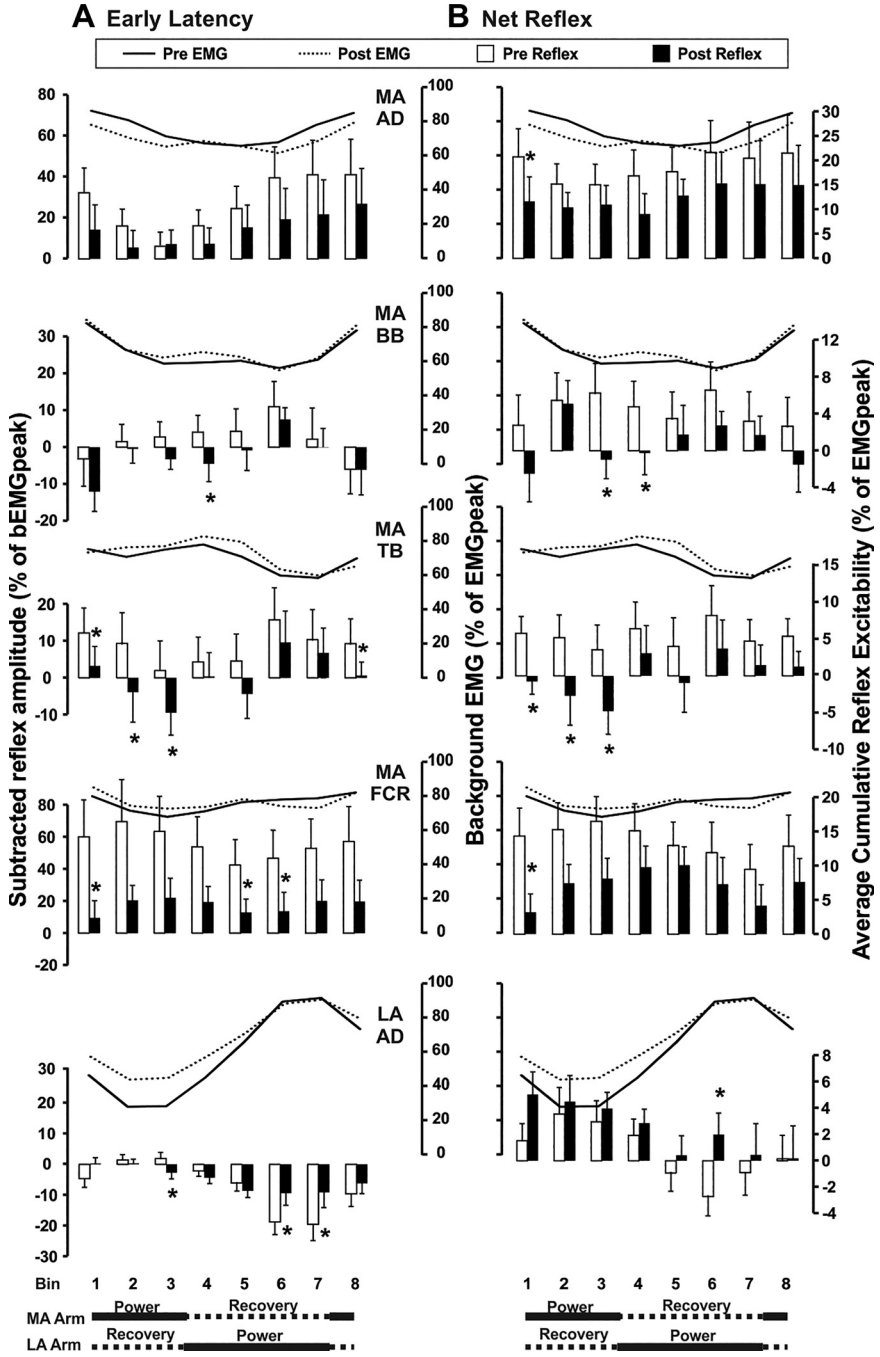

Fig. 7. Cutaneous reflexes during arm cycling. Early latency (*A*) and net reflexes (i.e., $ACRE_{150}$; *B*) during 8 phases of arm cycling are shown (from *top* to *bottom*) for the MA AD, MA BB, MA TB, MA FCR, and LA AD. Open bars are the Pre average and filled bars are Post values for reflexes. Secondary axis (*right* axis for *A* and *left* axis for *B*) values indicate EMG amplitude as a percentage of the peak EMG, displayed as line graphs in each panel. The solid line is the Pre average, whereas the broken line is the Post value. All bars are group ($n = 18$) means ± SE. $^*P < 0.05$, significant change from Pre average to Post.

the MA TB, BB, and FCR before training; however, there are changes in reflex amplitudes that suggest more modulation of reflexes throughout the phases of arm cycling after training. Interaction effects (phase × time) of net reflexes were revealed for all upper limb muscles measured in this experiment [MA AD: $F_{(7,126)} = 3.877$, $P = 0.04$; MA BB: $F_{(7,126)} = 7.318$, $P = 0.014$; MA TB: $F_{(7,126)} = 13.799$, $P = 0.002$; MA FCR: $F_{(7,126)} = 5.237$, $P = 0.006$; LA AD: $F_{(7,126)} = 3.612$, $P = 0.015$]. In general, compared with pretraining values, $ACRE_{150}$ amplitudes were less facilitatory posttraining. In the MA AD, $ACRE_{150}$ was decreased in the early power phase (*phase 1*: $P = 0.03$, $d = 0.39$). In the MA TB, $ACRE_{150}$ was reduced during early power (*phase 1*: $P = 0.016$, $d = 0.62$) and functionally reversed through mid power (*phase 2*: $P = 0.021$, $d = 0.51$; *phase 3*: $P = 0.024$, $d = 0.59$). In the MA BB, $ACRE_{150}$ was reduced during mid power (*phase 3*: $P = 0.04$, $d = 0.61$) and the transition to recovery (*phase 4*: $P = 0.03$, $d = 0.45$). In the MA FCR, there were general reductions in the $ACRE_{150}$, but this measure was only significantly reduced during early power (*phase 1*: $P = 0.045$, $d = 0.59$). On the LA side in the AD, $ACRE_{150}$ became more inhibitory during mid power (*phase 6*: $P = 0.022$, $d = 0.7$).

Cutaneous reflexes during walking. Training-induced plasticity of cutaneous reflexes transferred to walking but was modest compared with the changes observed above during arm cycling. Reflexes evoked by stimulation of the LA arm (i.e., SR nerve) resulted in significant phase-dependent modulation of early latency reflexes in the LA SOL pre- and posttraining and

in the MA TA posttraining only. Furthermore, there was significant phase-dependent modulation of middle latency reflexes in the LA TA posttraining only. No other phase-dependent modulation of early or middle latency and net reflexes was observed (see Table 4).

No significant interaction effects were revealed for early latency reflexes during walking. Interaction effects (phase × time) of middle latency reflexes were revealed for the LA TA [$F_{(7,126)} = 2.573$, $P = 0.016$]. There were kinematic reversals from inhibitory to facilitatory during early stance (*phase 2*: $P = 0.014$, $d = 0.59$) and from facilitatory to inhibitory during late swing (*phase 7*: $P = 0.037$, $d = 0.70$).

Group-averaged net reflexes (i.e., $ACRE_{150}$) are plotted in Fig. 8. General blunting of reflex modulation was observed, especially in the LA and MA AD muscles, before training. After training, there were changes in reflex amplitudes that suggest more modulation of reflexes at specific phases of walking. Interaction effects (phase × time) of net reflexes ($ACRE_{150}$) were revealed for the LA TA [$F_{(7,126)} = 2.868$, $P = 0.025$] and MA AD [$F_{(7,126)} = 2.573$, $P = 0.016$]. Compared with pretraining values, LA TA $ACRE_{150}$ was decreased during early stance (*phase 2*: $P = 0.044$, $d = 0.50$). In the MA AD, $ACRE_{150}$ was decreased during the transition to backswing (*phase 4*: $P = 0.017$, $d = 0.47$) and during mid backswing (*phase 6*: $P = 0.03$, $d = 0.37$; *phase 7*: $P = 0.014$, $d = 0.45$). No other interaction effects were revealed.

Arm cycling interlimb modulation of stretch reflexes at the ankle. The number of participants reported in the stretch reflex ($n = 15$) data is less than for other measures. Two participants had stretch reflexes that could not be reliably elicited each day on one or both sides of the body. Of particular note, one participant who lacked a stretch reflex (even with manual attempt at elicitation) before training was able to produce a small stretch reflex on both sides following the intervention. Two further participants were excluded from analysis due to inconsistencies in the shaker acceleration during the posttest measurements.

A three-factor (time × side × condition) repeated-measures ANOVA showed that there were no significant differences in the displacement amplitude of the shaker between the pretests or posttest (effect of time: $P = 0.631$), between limbs (effect of side: $P = 0.910$), or between static and cycling (effect of condition: $P = 0.252$).

Arm cycling modulation of stretch reflexes is shown in Fig. 9. A two-factor (time × side) repeated-measures ANOVA showed that there were no significant differences between pretests or between sides; however, there was an interaction effect [$F_{(1,42)} = 3.192$, $P = 0.036$]. Paired-sample *t*-tests determined that before arm cycling training, the modulation of stretch reflexes was 93.5% greater on the LA side than on the MA side ($P = 0.014$, $d = 0.86$). After training, there was no significant difference in arm cycling modulation of stretch reflexes between sides ($P = 0.36$). Furthermore, arm cycling

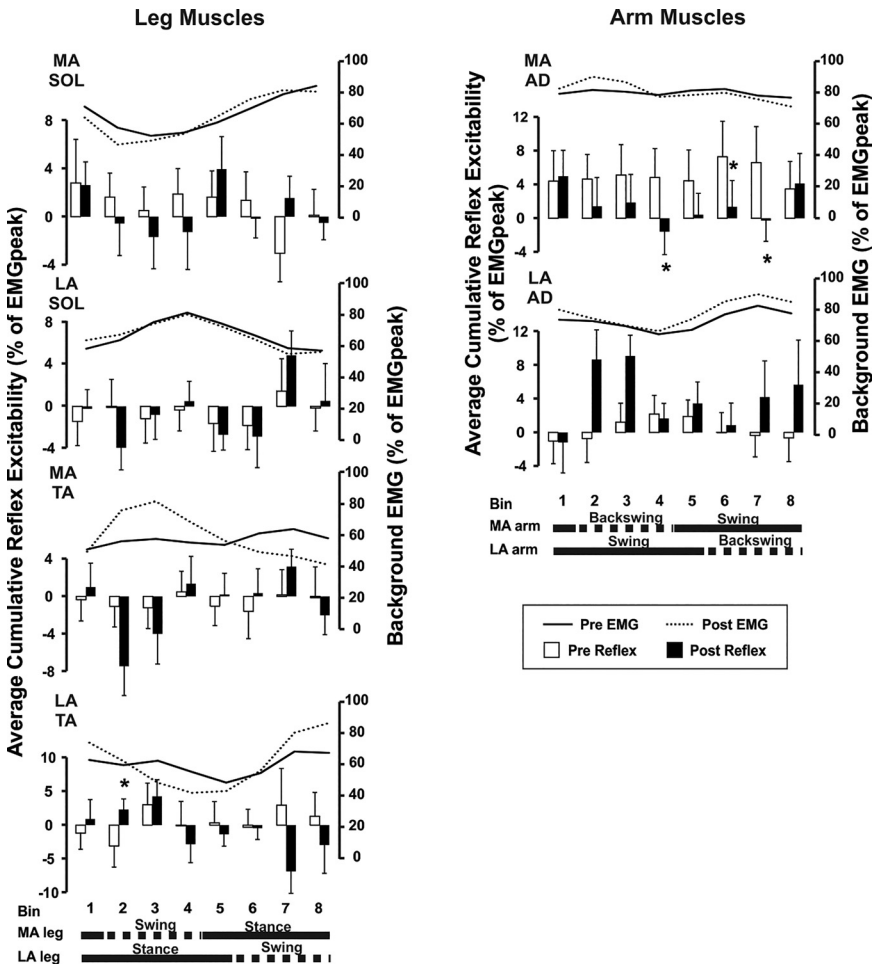

Fig. 8. Cutaneous reflexes during walking. Net reflex ($ACRE_{150}$) amplitudes during 8 phases of walking for leg muscles (*left*) and arm muscles (*right*). Open bars are the Pre average and filled bars are the Post values for reflexes. Secondary *y*-axis (*right*) values indicate EMG amplitude as a percentage of the peak EMG during walking, displayed as line graphs in each panel. The solid line is the Pre average, whereas the broken line is the Post value. All bars are group means ± SE. *$P <$ 0.05, significant change from Pre average to Post for reflexes. For clarity of display, differences of reflexes between phase and any differences in EMG are omitted.

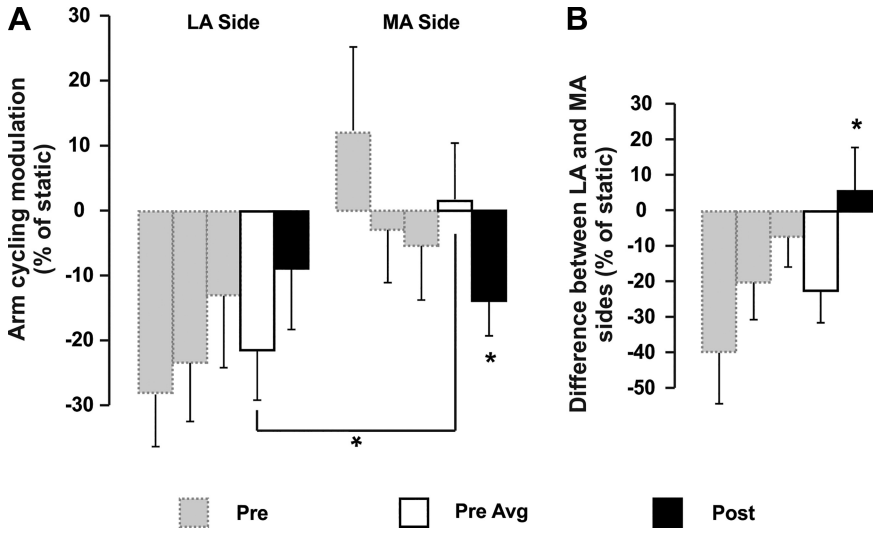

Fig. 9. Arm cycling-induced modulation of stretch reflexes. *A*: the difference between SOL stretch reflexes recorded at rest and during arm cycling on the LA side (*left*) and MA side (*right*). *B*: the difference between the LA and MA sides. Pre 1, 2, and 3 data are represented by shaded bars, whereas Pre and Post group data are represented by open and solid bars, respectively. Bars are group ($n = 14$) means (±SE). *$P < 0.05$, significant change from Pre average to Post. Comparison indicates a significant (*$P < 0.05$) difference between LA and MA sides.

modulation of stretch reflexes on the MA side increased (from 1.37% to −13.89%, $P = 0.026$, $d = 0.57$). In terms of the ratio of modulation between sides (see Fig. 9*B*), a one-factor (time) repeated-measures ANOVA revealed a significant main effect of time [$F_{(1,42)} = 3.184$, $P = 0.037$]. Pairwise comparisons revealed that after arm cycling training, the difference between the arm cycling modulation of stretch reflexes between the LA and MA side was significantly reduced ($P = 0.026$, $d = 0.69$). As shown by individual statistical analyses, 8 of 15 participants showed a significant increase in arm cycling modulation of stretch reflexes on the MA side, whereas 3 participants showed a decrease and 2 participants showed an increase in arm cycling modulation of stretch reflexes on the LA side after training, compared with the baseline pretests.

DISCUSSION

Arm cycling training can produce neuroplasticity and improve walking after stroke. Following 30 min of arm cycling training 3 times per week for 5 wk at a moderate intensity, there were significant improvements in clinical assessments of walking and modest improvements in balance, along with strength and muscle activity measured at the hands and ankles during isometric contractions. Neurophysiological integrity, as assessed through phasic modulation of muscle activity, rhythmic modulation of cutaneous reflexes, and arm cycling-induced modulation of stretch reflexes, displayed significant plasticity following arm cycling training. Many of the training adaptations from arm cycling correspond with those previously reported from a combined arm and leg cycling training intervention (Klarner et al. 2016a, 2016b). This suggests that at least some effects observed previously are related to rhythmic training of the upper limbs.

Functional Improvements

In general, arm cycling training caused improvements in walking ability and balance that are similar to our previous report of arm and leg cycling training (Klarner et al. 2016a). Similar to our previous experiment, we examined individual participant data because group data rarely provide a clear indication of improvements of clinical tests. We observed meaningful improvements from individual data in 9 of 18 participants for the 6-Minute Walk test (i.e., >6.7-m increase; Perera et al. 2006), in 8 of 18 participants for the TUG(i.e., >2.9-s decrease; Flansbjer et al. 2005), in 11 of 18 participants for the 10-Meter Walk test (i.e., >0.5 m/s increase; Perera et al. 2006), and in 5 of 18 participants for the Berg Balance Scores (i.e., >2.5-point increase; Liston and Brouwer 1996). Although the range of improvements is diverse in this population, certain participants were especially responsive to the arm cycling training intervention. For example, one participant was able to walk 91.5 m farther in 6 min following the intervention compared with baseline. Positive changes in the Chedoke-McMaster Stroke Assessment scores reflect less deficiency of movement following training and were noted for 11 of 18 participants.

Following training, there were improvements in strength of muscles at the wrist and ankle. There were bilateral increases in grip strength that were accompanied by increased muscle activation in the wrist flexors (i.e., MA FCR). Interestingly, on the MA side, there was increased plantarflexion force, which was accompanied by increased SOL activation. On the LA side, SOL muscle activity was increased but was not accompanied by increases in plantarflexion force. Although these results suggest arm cycling training improves the strength-generating capacity of both the upper and lower limbs during isometric contractions, the changes are not as robust compared with those during arm and leg cycling (Klarner et al. 2016a, 2016b); however, this is not surprising given the differences in lower limb movement across the two exercise tasks. Nonetheless, as we suggested previously (Klarner et al. 2016a), the fact that positive correlations have been drawn between strength gains and walking speeds in chronic stroke (Kim and Eng 2003; Richards and Olney 1996) suggests that any intervention that improves strength should be considered beneficial.

Neurophysiological Function of Arm CPGs

Although the primary objective of this study was to determine whether training the arms transfers to improvements in walking, the results of surface EMG during arm cycling provide some informative evidence of training-induced changes in muscle coordination during the training task itself. Phase-dependent modulation of muscle activity and reflexes is a

hallmark of rhythmic movement (Burke 1999; Zehr et al. 2004a) that can be attributed to activity of spinal CPG networks (Frigon 2017; Zehr 2005; Zehr and Duysens 2004; Zehr et al. 2003, 2004a, 2016). Although there is persistence of CPG activity following stroke (Ferris et al. 2006; Klarner et al. 2014; Zehr and Loadman 2012; Zehr et al. 2012, 2016), there can be reductions in the amount of phase-dependent modulation. This "blunting" of modulation (Zehr et al. 2012) is seen as reductions in the modulation of muscle activity due to more tonic activity of muscles, predominantly in the MA limb. Before training in this study, participants had very little modulation of their MA AD muscle activity, a main contributor of rhythmic movement during arm cycling. After arm cycling training, the MA AD modulation index was increased, illustrating that the MA arm had more phasic muscle activity than before training. Interestingly, the modulation index of the LA AD decreased, suggesting that the muscle activity was less phasic. This may be a consequence of more equal distribution of power output from both the MA and LA arms rather than relying solely on the LA arm to drive the ergometer to the same extent posttraining compared with pretraining.

Arm cycling training normalized coactivation between the MA and LA AD muscles (decreased throughout the majority of phases of cycling), therefore suggesting less tonic activity of the MA side. Furthermore, before training, there were high levels of coactivation between the antagonist BB and TB of the MA arm. After training, there were reductions in the amount of coactivation at various phases of movement. This can likely be attributed to reductions in flexor activity, which is typically excessive in hemiparetic participants following stroke (Kline et al. 2007).

We previously reported on cutaneous reflexes from SR nerve stimulation during arm cycling (Zehr et al. 2012) and walking (Zehr and Loadman 2012) in chronic stroke participants and determined that although circuits regulating interlimb coordination of rhythmic movement remain accessible, they are somewhat blunted compared with those in neurologically intact participants. In this study, it appears that spinal circuits are severely blunted compared with previous reports. There was very little evidence for phase-dependent modulation of upper limb muscles on the MA side during arm cycling. In fact, there was only a significant effect for phase in the MA AD early latency reflexes, and that was not changed with arm cycling training.

The LA AD was more similar to that in neurologically intact participants, with significant phase-dependent modulation during arm cycling for early latency, middle latency, and net reflexes, both before and after arm cycling training. This suggests that the interlimb linkages from the LA to the MA side in the participants of this experiment are deficient. However, arm cycling training did induce plasticity of the interlimb reflexes from pre- to posttraining at certain phases of arm cycling so that they more closely resemble those of neurologically intact participants. For example, early latency reflexes recorded from the contralateral FCR of neurologically intact participants are typically inhibitory (i.e., negative sign) throughout arm cycling. Before training, reflexes in FCR measured on the MA side displayed strong facilitation, but this facilitation was substantially reduced throughout the movement cycle after training. Similarly, early latency reflexes measured in the contralateral BB and TB during the late power and early recovery phases of neurologically intact participants are typically small and/or inhibitory (Zehr et al. 2012). In the current study, there was training-induced plasticity of cutaneous reflexes from facilitation to inhibition in both the MA BB and TB, suggesting that arm cycling training "normalized" reflex control. Taken together, these findings suggest that the rhythmic movement (i.e., arm cycling training) has induced adaptations to the neural control of movement that more closely resemble characteristics of neurologically intact participants (Zehr et al. 2012).

Enhanced Interlimb Connectivity of Cervicolumbar CPG Networks

Control of limb movements during human locomotion is enhanced through interlimb linkages, which can be observed in the form of "interlimb reflexes" (Dietz et al. 2001; Frigon 2017; Haridas and Zehr 2003; Lamont and Zehr 2007; Zehr et al. 2016) and neural coupling between the arms and legs (Dietz 2002; Frigon 2017; Mezzarane et al. 2011; Nakajima et al. 2013a, 2013b, 2014; Zehr et al. 2007, 2016). Similar to muscle activity, cutaneous reflexes undergo phase-dependent modulation in all limbs, regardless of the limb that is stimulated (Haridas and Zehr 2003).

During walking, training effects of arm cycling on interlimb reflexes were relatively modest, but there was evidence for training induced plasticity. For example, although phase-dependent modulation of early and middle latency reflexes was absent in the MA and LA TA, respectively, before arm cycling training, following training there were significant main effects for phase. This suggests that the arm cycling training activated interlimb networks that contribute to the coordination of rhythmic walking through arm cycling training. Stimulation of the LA wrist before training caused facilitation of the MA AD throughout the gait cycle' however, after training, this facilitation was reduced and even reversed in some phases. In fact, the modulation of the reflexes seemed to increase, suggesting improved interlimb coordination during walking. It therefore appears that arm cycling training can improve interlimb coordination of reflexes, similar to training the arms and legs together (Klarner et al. 2016b).

Modulation of reflexes in the stationary legs during arm movement provides convincing evidence for the existence of neuronal linkages between the arms and legs that are active during locomotor tasks (Dietz 2002; Zehr et al. 2016). Experiments in neurologically intact (Dragert and Zehr 2009; Frigon et al. 2004; Hundza and Zehr 2009; Loadman and Zehr 2007; Zehr et al. 2004b) and stroke participants (Barzi and Zehr 2008; Klarner et al. 2016b; Mezzarane et al. 2014) have demonstrated that arm cycling can cause modulation of the Ia reflex pathway in the legs, and this neuronal linkage remains accessible after stroke. Modulation of Hoffmann (H-) and stretch reflexes has been attributed to group Ia presynaptic inhibition (Frigon et al. 2004), and it has been postulated that a loss of descending commands to spinal interneurons is a key contributor to the hyperactive Ia reflex pathway after neurotrauma (including stroke, spinal cord injury, multiple sclerosis, etc.), which is correlated with the presence of spasticity (Stein et al. 1993). A single-session experiment showed that, unlike H-reflex suppression with arm cycling in stroke participants (Barzi and Zehr 2008), there is bidirectional modulation

of stretch reflexes (Mezzarane et al. 2014). However, our recent arm and leg cycling training intervention suggests that rhythmic training of the arms and legs together can influence arm cycling modulation of stretch reflexes to become more suppressive in the MA limb (Klarner et al. 2016b).

In the present study, we observed that before arm cycling training, arm cycling-induced modulation of stretch reflexes was suppressive for the LA limb but was more variable between participants for the MA limb such that some participants had very little suppression of stretch reflexes, and some had facilitation. Pretraining variability observed for stretch reflex modulation might be attributed to the differences in lesion location and size (Calautti and Baron 2003). However, following arm cycling training, there was an increase in arm cycling-induced suppression on the MA side. Modulation increased posttraining so that it was no longer different from that on the LA side, suggesting an increase in symmetry between the LA and MA sides. It is likely that arm cycling caused training-induced plasticity to the corticospinal projections to leg muscles influencing the modulation of EMG and reflexes during cycling and walking. Zhou et al. (2017) recently showed that corticospinal excitability to the TA is facilitated with 12 wk of arm and leg cycling, compared with leg-only cycling, in those with incomplete spinal cord injury.

Although suppression induced by arm cycling was our main interest in this experiment, an interesting finding was that one participant who had experienced multiple strokes and was lacking a functional stretch reflex (even through manual elicitation) was able to produce a reliable elicited reflex on both sides following the training period. The findings of the current experiment therefore suggest that arm cycling improves arm-to-leg linkages that are more typical of neurologically intact participants. A graphical summary of how arm cycling training might affect the neural control of rhythmic movement after stroke is provided in Fig. 10.

Transfer of Neuroplasticity from Arm Training to Walking Function

As with arm cycling, walking is, at least partially, controlled by activity from locomotor CPGs (Dietz 2002; Frigon 2017; Zehr 2005; Zehr and Duysens 2004; Zehr et al. 2016), and phasic modulation of muscle activity is therefore important for successful, coordinated locomotion. As mentioned previously, these networks remain intact following stroke (Zehr and Loadman 2012), and on the basis of findings from arm and leg cycling training (Klarner et al. 2016a, 2016b), adaptations transfer from one rhythmic task to another (i.e., from arm and leg cycling to walking). Nonetheless, there are significant deficits that have been reported in the neural control of walking in stroke participants not only on the MA side but also on the LA side (Zehr and Loadman 2012). Typically, there are increases in cocontraction during stance (Shiavi et al. 1987) and reduced modulation of muscle activity throughout the gait cycle (Burridge et al. 2001). Of particular interest in this experiment are the substantial changes in TA activity during walking that occurred as a result of arm cycling training. This is functionally very important, because after stroke, the TA is heavily impacted, and an inability to activate the TA of the MA side leads to foot drop, which is associated with toe drag, stumbling, and an increased fall rate (Zehr and Loadman 2012). Before training, participants in this experiment had very little TA activity bilaterally, as shown in the individual trace of Fig. 6*A*. Furthermore, before arm cycling training, the modulation index of both the MA and LA TA throughout the gait cycle was lower than that reported for neurologically intact participants in previous experiments (Zehr et al. 1998; Zehr and Loadman 2012). After the cycling intervention, however, there were not only functionally relevant changes in TA EMG bilaterally but also bilateral increases to the modulation index of the TA muscles during walking, suggesting that the partic-

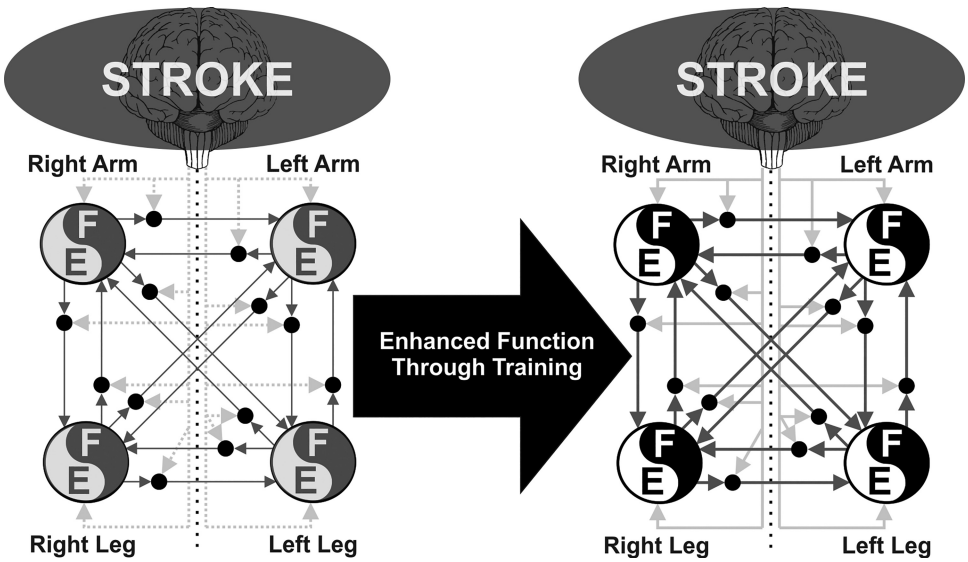

Fig. 10. Schematic representation of the interlimb pathways that could contribute to the control of human walking in chronic stroke (*left*) and chronic stroke after training (*right*). Pathways are drawn with reference to Frigon (2017); however, for ease of display, sensory feedback from the limbs is not depicted. The yin-yang cartoons represent a central pattern generator (CPG) for each limb. Arrows represent neuronal connections and can be either excitatory or inhibitory. Broken lines from supraspinal centers in the chronic stroke represent the dysfunctional commands that can have influences in any location of the spinal cord due to variability in lesion type, location, and size. Decreased thickness in the lines connecting CPGs represents decreased strength of connectivity. Although not back to the level of the neurologically intact nervous system, solidified lines from supraspinal centers and thickened lines within the spinal cord after training compared with chronic stroke represent improved connectivity from supraspinal centers and within the spinal cord, resulting in a "normalization" of rhythmic output.

ipants were better able to activate their TA in a phasic and functionally relevant manner.

Furthermore, the coordination of agonist-antagonist muscles within the MA leg showed training-induced changes that included increased TA/SOL activity during the swing phase and decreased TA/SOL activity during the stance phase. Further support for the "normalization" of TA coordination arises from the comparison of the MA/LA TA muscle activity. Before training, there appears to be tonic activation throughout the gait cycle that is higher on the MA side compared with the LA side. After training, however, this interlimb coordination became more phasic such that the MA side was far more active during the swing phase of the MA leg, whereas the LA side was far more active during the swing phase of the LA leg. Overall, the results of the EMG analysis during walking indicate changes to the activation patterns of the TA muscle, a muscle that is often subject to irregularity of activation following stroke. Hence, rhythmic arm cycling training appears to induce a normalization of TA activity, especially on the MA side, during walking.

During walking, there were only modest changes to muscle activity in the upper limbs measured in the current experiment. There was increased AD activity for the MA and LA sides during forward arm swing. It appears that training rhythmic movements of the arms (via arm cycling training) has transferred to increased arm swing activity during walking. This may be complicated because different participants required adapted setups for their arms during walking. Some participants required an arm sling, and very few had confidence to walk without gripping the parallel bars or front bar, even though their risk of falling was negated by the use of an overhead harness. Efforts were made to keep the setup the same within the experiment for each participant. These results echo previous studies showing that even when participants arms are bound, a rhythmic pattern of activation can be determined in the upper limbs during treadmill walking (Ballesteros et al. 1965). It seems as though this phenomenon is at least partially preserved in stroke.

Clinical Translation

The results of the current experiment suggest that rhythmic arm training can assist with rehabilitation of walking in chronic stroke (Ferris et al. 2006; Zehr et al. 2016). Often during rehabilitation, participants are trained at treadmill walking with the arms holding stationary parallel bars. This has been shown to be less effective than therapies such as body weight-supported treadmill training, where the arms are free to swing during walking training (Tester et al. 2011). Sometimes body weight-supported treadmill training is out of the question, because it can be quite expensive, and ambulation is not possible even for short periods of time. In such cases, rehabilitation practices should turn to combined arm and leg cycling or recumbent stepping, both of which have been shown to influence interlimb neural connections (de Kam et al. 2013; Ferris et al. 2006).

Study Limitations

Often in chronic stroke, the impairments brought on by the initial injury have been compounded by years of disuse. Although some individuals maintain their fitness following a stroke, many do not. This leads to the compounding of secondary complications over time. It has been observed that simply participating in cardiovascular activity can provide benefits by targeting the disuse-related effects on individuals after stroke. Indeed, it is possible that some of the effects seen in this study could be attributed to such mechanisms. However, this remains unlikely because the training itself was of moderate intensity, at the very most, since neither heart rate nor rating of perceived exertion increased over the course of the training. The level of aerobic activity required was even less than that in our previous combined arm and leg cycling study (Klarner et al. 2016a, 2016b), which itself fell below the level required to increase cardiovascular fitness for individuals after stroke (Gordon et al. 2004; Pang et al. 2006). Furthermore, we did not include a group of participants who would have come to the laboratory for an equal number of sessions as the training group. Therefore, it is possible that there were increases in activity of this group of individuals, which is typically decreased following stroke (Gadidi et al. 2011; Mayo et al. 2002). Thus a commute to and from the laboratory for testing and training sessions may act as a training stimulus on its own. To draw this conclusion, we also would have needed a second group to come to the laboratory for only the testing sessions. This would result in two groups of participants that would have been deprived of the almost certain benefits of performing exercise (i.e., arm cycling). In an attempt to ensure all participants received benefits of exercise, we chose to avoid the traditional control groups altogether and use the more time-consuming procedures of multiple baseline control. Additionally, in a previous experiment (Dragert and Zehr 2013), we had stroke participants come to the laboratory for strength training, and this commute to the laboratory did not cause improvements in walking and balance that are noted in the current experiment. This suggests that the arm cycling training did provide additional improvements in walking and balance that were not provided to participants who simply commuted to the laboratory for training and testing.

A second limitation is the relatively small sample size. However, since this is a proof-of-principle investigation rather than a clinical trial, the sample size is sufficient to draw initial insights on the mechanisms and guide future planning.

A third limitation is that rhythmic activation of the leg muscles could have occurred during training sessions. Although participants were instructed to keep their legs at rest during each training session, and investigators monitored the legs to ensure there was no apparent movement, it is possible that slight activation of the lower limbs took place during the training sessions. If rhythmic activation in the legs occurred, such activation would have been involuntary but could have contributed to some of the improvements in leg function noted with training. However, the limited and nonspecific nature of this activation would not account for many of the specific training-induced changes highlighted in this experiment.

Conclusion

Arm cycling training improves walking, physical performance, and neurophysiological integrity after stroke. Although improvements in walking may not be as robust as those from other training modalities, they do highlight the integral role that training the arms can have on rehabilitation of human

locomotion. The positive changes in clinical assessments, strength, and reflex control suggest that the arms do in fact give the legs a helping hand in rehabilitation, even years after neurological injury.

ACKNOWLEDGMENTS

We thank the participants for their time commitment during experimental testing and training sessions. We also thank the volunteers who so graciously provided assistance during the training sessions.

GRANTS

The project was funded by a Heart and Stroke Foundation of Canada grant (to E. P. Zehr) and a Discovery grant from NSERC.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

C.K., G.E.P., T.K., Y.S., T.S.B., and E.P.Z. conceived and designed research; C.K., G.E.P., T.K., Y.S., T.S.B., and H.C. performed experiments; C.K., G.E.P., T.K., Y.S., T.S.B., and H.C. analyzed data; C.K., G.E.P., and E.P.Z. interpreted results of experiments; G.E.P. prepared figures; C.K. and G.E.P. drafted manuscript; G.E.P. and E.P.Z. edited and revised manuscript; G.E.P. and E.P.Z. approved final version of manuscript.

REFERENCES

Ada L, Dean CM, Lindley R, Lloyd G. Improving community ambulation after stroke: the AMBULATE Trial. *BMC Neurol* 9: 8, 2009. doi:10.1186/1471-2377-9-8.

Bakheit AM, Maynard VA, Curnow J, Hudson N, Kodapala S. The relation between Ashworth scale scores and the excitability of the α motor neurones in patients with post-stroke muscle spasticity. *J Neurol Neurosurg Psychiatry* 74: 646–648, 2003. doi:10.1136/jnnp.74.5.646.

Ballesteros ML, Buchthal F, Rosenfalck P. The pattern of muscular activity during the arm swing of natural walking. *Acta Physiol Scand* 63: 296–310, 1965. doi:10.1111/j.1748-1716.1965.tb04069.x.

Balter JE, Zehr EP. Neural coupling between the arms and legs during rhythmic locomotor-like cycling movement. *J Neurophysiol* 97: 1809–1818, 2007. doi:10.1152/jn.01038.2006.

Barzi Y, Zehr EP. Rhythmic arm cycling suppresses hyperactive soleus H-reflex amplitude after stroke. *Clin Neurophysiol* 119: 1443–1452, 2008. doi:10.1016/j.clinph.2008.02.016.

Burke RE. The use of state-dependent modulation of spinal reflexes as a tool to investigate the organization of spinal interneurons. *Exp Brain Res* 128: 263–277, 1999. doi:10.1007/s002210050847.

Burridge JH, Wood DE, Taylor PN, McLellan DL. Indices to describe different muscle activation patterns, identified during treadmill walking, in people with spastic drop-foot. *Med Eng Phys* 23: 427–434, 2001. doi:10.1016/S1350-4533(01)00061-3.

Bütefisch C, Hummelsheim H, Denzler P, Mauritz KH. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. *J Neurol Sci* 130: 59–68, 1995. doi:10.1016/0022-510X(95)00003-K.

Calautti C, Baron JC. Functional neuroimaging studies of motor recovery after stroke in adults: a review. *Stroke* 34: 1553–1566, 2003. doi:10.1161/01.STR.0000071761.36075.A6.

Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Mahwah, NJ: Lawrence Erlbaum, 1988.

Cummings G. *Understanding the New Statistics: Effect Sizes, Confidence Intervals, and Meta-Analysis*. London, UK: Routledge, 2013.

de Kam D, Rijken H, Manintveld T, Nienhuis B, Dietz V, Duysens J. Arm movements can increase leg muscle activity during submaximal recumbent stepping in neurologically intact individuals. *J Appl Physiol (1985)* 115: 34–42, 2013. doi:10.1152/japplphysiol.00510.2012.

Dietz V. Do human bipeds use quadrupedal coordination? *Trends Neurosci* 25: 462–467, 2002. doi:10.1016/S0166-2236(02)02229-4.

Dietz V, Fouad K, Bastiaanse CM. Neuronal coordination of arm and leg movements during human locomotion. *Eur J Neurosci* 14: 1906–1914, 2001. doi:10.1046/j.0953-816x.2001.01813.x.

Dragert K, Zehr EP. Rhythmic arm cycling modulates Hoffmann reflex excitability differentially in the ankle flexor and extensor muscles. *Neurosci Lett* 450: 235–238, 2009. doi:10.1016/j.neulet.2008.11.034.

Dragert K, Zehr EP. Bilateral neuromuscular plasticity from unilateral training of the ankle dorsiflexors. *Exp Brain Res* 208: 217–227, 2011. doi:10.1007/s00221-010-2472-3.

Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. *Exp Brain Res* 225: 93–104, 2013. doi:10.1007/s00221-012-3351-x.

Elftman HO. *The Function of the Arms in Walking*. Baltimore, MD: Johns Hopkins University Press, 1939.

Enright PL. The six-minute walk test. *Respir Care* 48: 783–785, 2003.

Ferris DP, Huang HJ, Kao PC. Moving the arms to activate the legs. *Exerc Sport Sci Rev* 34: 113–120, 2006. doi:10.1249/00003677-200607000-00005.

Flansbjer UB, Holmbäck AM, Downham D, Patten C, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. *J Rehabil Med* 37: 75–82, 2005. doi:10.1080/16501970410017215.

Frigon A. The neural control of interlimb coordination during mammalian locomotion. *J Neurophysiol* 117: 2224–2241, 2017. doi:10.1152/jn.00978.2016.

Frigon A, Collins DF, Zehr EP. Effect of rhythmic arm movement on reflexes in the legs: modulation of soleus H-reflexes and somatosensory conditioning. *J Neurophysiol* 91: 1516–1523, 2004. doi:10.1152/jn.00695.2003.

Gadidi V, Katz-Leurer M, Carmeli E, Bornstein NM. Long-term outcome poststroke: predictors of activity limitation and participation restriction. *Arch Phys Med Rehabil* 92: 1802–1808, 2011. doi:10.1016/j.apmr.2011.06.014.

Gordon NF, Gulanick M, Costa F, Fletcher G, Franklin BA, Roth EJ, Shephard T; American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Stroke* 35: 1230–1240, 2004. doi:10.1161/01.STR.0000127303.19261.19.

Gowland C, Stratford P, Ward M, Moreland J, Torresin W, Van Hullenaar S, Sanford J, Barreca S, Vanspall B, Plews N. Measuring physical impairment and disability with the Chedoke-McMaster Stroke Assessment. *Stroke* 24: 58–63, 1993. doi:10.1161/01.STR.24.1.58.

Hage JJ, van der Steen LP, de Groot PJ. Difference in sensibility between the dominant and nondominant index finger as tested using the Semmes-Weinstein monofilaments pressure aesthesiometer. *J Hand Surg Am* 20: 227–229, 1995. doi:10.1016/S0363-5023(05)80012-7.

Haridas C, Zehr EP. Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in the hand and foot during walking. *J Neurophysiol* 90: 2850–2861, 2003. doi:10.1152/jn.00531.2003.

Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. *Phys Ther* 64: 35–40, 1984. doi:10.1093/ptj/64.1.35.

Hundza SR, Zehr EP. Cutaneous reflexes during rhythmic arm cycling are insensitive to asymmetrical changes in crank length. *Exp Brain Res* 168: 165–177, 2006. doi:10.1007/s00221-005-0089-8.

Hundza SR, Zehr EP. Suppression of soleus H-reflex amplitude is graded with frequency of rhythmic arm cycling. *Exp Brain Res* 193: 297–306, 2009. doi:10.1007/s00221-008-1625-0.

Kim CM, Eng JJ. The relationship of lower-extremity muscle torque to locomotor performance in people with stroke. *Phys Ther* 83: 49–57, 2003.

Klarner T, Barss TS, Sun Y, Kaupp C, Loadman PM, Zehr EP. Exploiting interlimb arm and leg connections for walking rehabilitation: a training intervention in stroke. *Neural Plast* 2016: 1517968, 2016a. doi:10.1155/2016/1517968.

Klarner T, Barss TS, Sun Y, Kaupp C, Loadman PM, Zehr EP. Long-term plasticity in reflex excitability induced by five weeks of arm and leg cycling training after stroke. *Brain Sci* 6: 6, 2016b. doi:10.3390/brainsci6040054.

Klarner T, Barss TS, Sun Y, Kaupp C, Zehr EP. Preservation of common rhythmic locomotor control despite weakened supraspinal regulation after stroke. *Front Integr Neurosci* 8: 95, 2014. doi:10.3389/fnint.2014.00095.

Kline TL, Schmit BD, Kamper DG. Exaggerated interlimb neural coupling following stroke. *Brain* 130: 159–169, 2007. doi:10.1093/brain/awl278.

Lagerquist O, Zehr EP, Baldwin ER, Klakowicz PM, Collins DF. Diurnal changes in the amplitude of the Hoffmann reflex in the human soleus but not in the flexor carpi radialis muscle. *Exp Brain Res* 170: 1–6, 2006. doi:10.1007/s00221-005-0172-1.

Lamont EV, Zehr EP. Earth-referenced handrail contact facilitates interlimb cutaneous reflexes during locomotion. *J Neurophysiol* 98: 433–442, 2007. doi:10.1152/jn.00002.2007.

Liston RA, Brouwer BJ. Reliability and validity of measures obtained from stroke patients using the Balance Master. *Arch Phys Med Rehabil* 77: 425–430, 1996. doi:10.1016/S0003-9993(96)90028-3.

Loadman PM, Zehr EP. Rhythmic arm cycling produces a non-specific signal that suppresses Soleus H-reflex amplitude in stationary legs. *Exp Brain Res* 179: 199–208, 2007. doi:10.1007/s00221-006-0782-2.

Mayo NE, Wood-Dauphinee S, Côté R, Durcan L, Carlton J. Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil* 83: 1035–1042, 2002. doi:10.1053/apmr.2002.33984.

Mezzarane RA, Klimstra M, Lewis A, Hundza SR, Zehr EP. Interlimb coupling from the arms to legs is differentially specified for populations of motor units comprising the compound H-reflex during "reduced" human locomotion. *Exp Brain Res* 208: 157–168, 2011. doi:10.1007/s00221-010-2467-0.

Mezzarane RA, Nakajima T, Zehr EP. After stroke bidirectional modulation of soleus stretch reflex amplitude emerges during rhythmic arm cycling. *Front Hum Neurosci* 8: 136, 2014. doi:10.3389/fnhum.2014.00136.

Nakajima T, Barss T, Klarner T, Komiyama T, Zehr EP. Amplification of interlimb reflexes evoked by stimulating the hand simultaneously with conditioning from the foot during locomotion. *BMC Neurosci* 14: 28, 2013a. doi:10.1186/1471-2202-14-28.

Nakajima T, Mezzarane RA, Hundza SR, Komiyama T, Zehr EP. Convergence in reflex pathways from multiple cutaneous nerves innervating the foot depends upon the number of rhythmically active limbs during locomotion. *PLoS One* 9: e104910, 2014. doi:10.1371/journal.pone.0104910.

Nakajima T, Mezzarane RA, Klarner T, Barss TS, Hundza SR, Komiyama T, Zehr EP. Neural mechanisms influencing interlimb coordination during locomotion in humans: presynaptic modulation of forearm H-reflexes during leg cycling. *PLoS One* 8: e76313, 2013b. doi:10.1371/journal.pone.0076313.

Nielsen JB. How we walk: central control of muscle activity during human walking. *Neuroscientist* 9: 195–204, 2003. doi:10.1177/1073858403009003012.

Palomino AF, Hundza SR, Zehr EP. Rhythmic arm cycling differentially modulates stretch and H-reflex amplitudes in soleus muscle. *Exp Brain Res* 214: 529–537, 2011. doi:10.1007/s00221-011-2851-4.

Pandyan AD, Price CI, Barnes MP, Johnson GR. A biomechanical investigation into the validity of the modified Ashworth Scale as a measure of elbow spasticity. *Clin Rehabil* 17: 290–293, 2003. doi:10.1191/0269215503cr610oa.

Pang MY, Eng JJ, Dawson AS, Gylfadóttir S. The use of aerobic exercise training in improving aerobic capacity in individuals with stroke: a meta-analysis. *Clin Rehabil* 20: 97–111, 2006. doi:10.1191/0269215506cr926oa.

Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. *Clin Rehabil* 20: 173–182, 2006. doi:10.1191/0269215506cr922oa.

Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 54: 743–749, 2006. doi:10.1111/j.1532-5415.2006.00701.x.

Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 39: 142–148, 1991. doi:10.1111/j.1532-5415.1991.tb01616.x.

Richards CL, Olney SJ. Hemiparetic gait following stroke. Part II: Recovery and physical therapy. *Gait Posture* 4: 149–162, 1996. doi:10.1016/0966-6362(96)01064-8.

Scherr J, Wolfarth B, Christle JW, Pressler A, Wagenpfeil S, Halle M. Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* 113: 147–155, 2013. doi:10.1007/s00421-012-2421-x.

Shiavi R, Bugle HJ, Limbird T. Electromyographic gait assessment, Part 2: Preliminary assessment of hemiparetic synergy patterns. *J Rehabil Res Dev* 24: 24–30, 1987.

Stein RB, Yang JF, Bélanger M, Pearson KG. Modification of reflexes in normal and abnormal movements. *Prog Brain Res* 97: 189–196, 1993. doi:10.1016/S0079-6123(08)62277-3.

Sun Y, Boots J, Zehr EP. The lingering effects of a busted myth–false time limits in stroke rehabilitation. *Appl Physiol Nutr Metab* 40: 858–861, 2015. doi:10.1139/apnm-2014-0523.

Tang A, Sibley KM, Thomas SG, McIlroy WE, Brooks D. Maximal exercise test results in subacute stroke. *Arch Phys Med Rehabil* 87: 1100–1105, 2006. doi:10.1016/j.apmr.2006.04.016.

Tester NJ, Howland DR, Day KV, Suter SP, Cantrell A, Behrman AL. Device use, locomotor training and the presence of arm swing during treadmill walking after spinal cord injury. *Spinal Cord* 49: 451–456, 2011. doi:10.1038/sc.2010.128.

Vasudevan EV, Zehr EP. Multi-frequency arm cycling reveals bilateral locomotor coupling to increase movement symmetry. *Exp Brain Res* 211: 299–312, 2011. doi:10.1007/s00221-011-2687-y.

Wannier T, Bastiaanse C, Colombo G, Dietz V. Arm to leg coordination in humans during walking, creeping and swimming activities. *Exp Brain Res* 141: 375–379, 2001. doi:10.1007/s002210100875.

Zehr EP. Considerations for use of the Hoffmann reflex in exercise studies. *Eur J Appl Physiol* 86: 455–468, 2002. doi:10.1007/s00421-002-0577-5.

Zehr EP. Neural control of rhythmic human movement: the common core hypothesis. *Exerc Sport Sci Rev* 33: 54–60, 2005.

Zehr EP. Evidence-based risk assessment and recommendations for physical activity clearance: stroke and spinal cord injury. *Appl Physiol Nutr Metab* 36 *Suppl* 1: S214–S231, 2011. doi:10.1139/h11-055.

Zehr EP, Barss TS, Dragert K, Frigon A, Vasudevan EV, Haridas C, Hundza S, Kaupp C, Klarner T, Klimstra M, Komiyama T, Loadman PM, Mezzarane RA, Nakajima T, Pearcey GE, Sun Y. Neuromechanical interactions between the limbs during human locomotion: an evolutionary perspective with translation to rehabilitation. *Exp Brain Res* 234: 3059–3081, 2016. doi:10.1007/s00221-016-4715-4.

Zehr EP, Carroll TJ, Chua R, Collins DF, Frigon A, Haridas C, Hundza SR, Thompson AK. Possible contributions of CPG activity to the control of rhythmic human arm movement. *Can J Physiol Pharmacol* 82: 556–568, 2004a. doi:10.1139/y04-056.

Zehr EP, Collins DF, Chua R. Human interlimb reflexes evoked by electrical stimulation of cutaneous nerves innervating the hand and foot. *Exp Brain Res* 140: 495–504, 2001. doi:10.1007/s002210100857.

Zehr EP, Collins DF, Frigon A, Hoogenboom N. Neural control of rhythmic human arm movement: phase dependence and task modulation of Hoffmann reflexes in forearm muscles. *J Neurophysiol* 89: 12–21, 2003. doi:10.1152/jn.00416.2002.

Zehr EP, Duysens J. Regulation of arm and leg movement during human locomotion. *Neuroscientist* 10: 347–361, 2004. doi:10.1177/1073858404264680.

Zehr EP, Frigon A, Hoogenboom N, Collins DF. Facilitation of soleus H-reflex amplitude evoked by cutaneous nerve stimulation at the wrist is not suppressed by rhythmic arm movement. *Exp Brain Res* 159: 382–388, 2004b. doi:10.1007/s00221-004-2092-x.

Zehr EP, Fujita K, Stein RB. Reflexes from the superficial peroneal nerve during walking in stroke subjects. *J Neurophysiol* 79: 848–858, 1998. doi:10.1152/jn.1998.79.2.848.

Zehr EP, Haridas C. Modulation of cutaneous reflexes in arm muscles during walking: further evidence of similar control mechanisms for rhythmic human arm and leg movements. *Exp Brain Res* 149: 260–266, 2003. doi:10.1007/s00221-003-1377-9.

Zehr EP, Klimstra M, Dragert K, Barzi Y, Bowden MG, Javan B, Phadke C. Enhancement of arm and leg locomotor coupling with augmented cutaneous feedback from the hand. *J Neurophysiol* 98: 1810–1814, 2007. doi:10.1152/jn.00562.2007.

Zehr EP, Loadman PM. Persistence of locomotor-related interlimb reflex networks during walking after stroke. *Clin Neurophysiol* 123: 796–807, 2012. doi:10.1016/j.clinph.2011.07.049.

Zehr EP, Loadman PM, Hundza SR. Neural control of rhythmic arm cycling after stroke. *J Neurophysiol* 108: 891–905, 2012. doi:10.1152/jn.01152.2011.

Zhou R, Alvarado L, Kim S, Chong SL, Mushahwar VK. Modulation of corticospinal input to the legs by arm and leg cycling in people with incomplete spinal cord injury. *J Neurophysiol* 118: 2507–2251, 2017. doi:10.1152/jn.00663.2016.