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RESEARCH ARTICLE

Exploiting cervicolumbar connections enhances short-term spinal cord plasticity induced by rhythmic movement

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Abstract

Arm cycling causes suppression of soleus (SOL) Hoffmann (H-) reflex that outlasts the activity period. Arm cycling presumably activates propriospinal networks that modulate Ia presynaptic inhibition. Interlimb pathways are thought to relate to the control of quadrupedal locomotion, allowing for smooth, coordinated movement of the arms and legs. We examined whether the number of active limb pairs affects the amount and duration of activity-dependent plasticity of the SOL H-reflex. On separate days, 14 participants completed 4 randomly ordered 30 min experimental sessions: (1) quiet sitting (CTRL); (2) arm cycling (ARM); (3) leg cycling (LEG); and (4) arm and leg cycling (A&L) on an ergometer. SOL H-reflex and M-wave were evoked via electrical stimulation of the tibial nerve. M-wave and H-reflex recruitment curves were recorded, while the participants sat quietly prior to, 10 and 20 min into, immediately after, and at 2.5, 5, 7.5, 10, 15, 20, 25, and 30 min after each experimental session. Normalized maximal H-reflexes were unchanged in CTRL, but were suppressed by > 30% during the ARM, LEG, and A&L. H-reflex suppression outlasted activity duration for ARM (≤ 2.5 mins), LEG (≤ 5 mins), and A&L (≤ 30 mins). The duration of reflex suppression after A&L was greater than the algebraic summation of ARM and LEG. This non-linear summation suggests that using the arms and legs simultaneously—as in typical locomotor synergies—amplifies networks responsible for the short-term plasticity of lumbar spinal cord excitability. Enhanced activity of spinal networks may have important implications for the implementation of locomotor training for targeted rehabilitation.

Keywords Locomotion · Hoffmann reflex · Arm and leg cycling · Cervicolumbar · Neuroplasticity

Introduction

Physical training can produce short- and long-term plasticities of spinal cord excitability. For example, H-reflex amplitudes are reduced in highly trained ballet dancers (Koceja et al. 1991; Nielsen et al. 1993), with balance training (Trimble and Koceja 2001), and with training to walk backwards (Schneider and Capaday 2003). Amplitude modulation of H-reflexes also occurs during acute performance of a motor task. During rhythmic movement, H-reflexes are modulated in a phase-dependent manner by central pattern generators (CPGs) and afferent feedback arising from the rhythmic movement (Brooke et al. 1997; Zehr and Stein 1999; Zehr and Duysens 2004; Zehr et al. 2016). Interestingly, short duration (< 2 min) passive cyclical movement of the leg is sufficient to cause amplitude modulation of the SOL H-reflex that outlasts movement cessation by ~ 4 s (Misiaszek et al. 1995). When leg cycling is performed for 30 min, SOL H-reflex amplitudes are reduced by ~ 40% for at least 10 min after cycling has ceased (Motl and Dishman 2003), suggesting that activity-dependent plasticity of H-reflexes is not constrained to the timeframe that the activity is performed. Further work (Mazzocchio et al. 2006; Meunier et al. 2007) has shown that a single bout of skilful cycling, which requires cognitive effort to alter the frequency of movement to various target cadences, can cause

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short-term spinal cord plasticity (Mazzocchio et al. 2006) that persists ~ 24 h after the cycling session (Meunier et al. 2007). The short-term spinal cord plasticity resulting from skilful cycling is more pronounced than that of non-skilful cycling, suggesting that spinal cord plasticity can be further increased when descending drive to those spinal circuits is emphasized.

Plasticity of spinal cord circuits during and after movement cessation is not isolated to the moving limb (Brooke et al. 1997). Indirect evidence from human reflex experiments suggests that, similar to other animals, we possess locomotor networks in the spinal cord (i.e., CPGs) capable of modifying rhythmic output. In addition to CPGs, humans have retained cervico- and thoraco-lumbar connections (Dietz 2002; Zehr and Duysens 2004; Zehr et al. 2016), which can affect the excitability of reflexes in remote limbs (i.e., limbs that are not involved in movement). These interlimb effects on spinal cord excitability occur from legs to arm and from arms to leg. Amplitude modulation of H-reflexes evoked in the forearm (flexor carpi radialis; FCR) during walking (Domingo et al. 2014), leg cycling (Zehr et al. 2007; Nakajima et al. 2013), and passive leg stepping (Nakajima et al. 2011, 2016) provide evidence for remote effects of leg movement on the spinal cord excitability in the arms. In support of effects of the arms on the legs, SOL H-reflexes are reduced in amplitude during rhythmic arm swing (Hiraoka 2001; Hiraoka and Iwata 2006; Massaad et al. 2014) and rhythmic arm cycling (Frigon et al. 2004; Zehr et al. 2004; Loadman and Zehr 2007; Barzi and Zehr 2008; Javan and Zehr 2008; Dragert and Zehr 2009; Hundza and Zehr 2009; de Ruiter et al. 2010; Hundza et al. 2012; Kaupp et al. 2018). In the work of Javan and Zehr (2008), rhythmic activity of the arms caused modulation of reflexes in the legs that outlasted the activity duration, evident of short-term plasticity of spinal cord excitability.

Combined arm and leg movement may enhance movement-induced plasticity of spinal circuits by exploiting the interactions of afferent feedback and pattern generating networks of the arms and legs (i.e., cervicolumbar connections). In a study by de Ruiter et al. (2010), participants cycled with just the ipsilateral arm, just the contralateral arm, or with both arms and noted that the greatest SOL H-reflex amplitude modulation occurred when participants cycled with both arms. Subsequently, Mezzarane et al. (2011) showed that exploiting cervicolumbar connections during rhythmic stepping increases modulation of reflexes in the leg. Nakajima et al. (2014) expanded upon this idea when they had participants perform arm only, contralateral leg only or arm and contralateral leg recumbent stepping while evoking cutaneous reflexes from two nerves separately and from both nerves simultaneously in the resting leg. Combined cutaneous reflexes were facilitated with increased magnitude based on the number of rhythmically active limbs. This facilitation was greater than the algebraic sum of the two reflexes alone, suggesting a facilitation effect from descending drive and/or CPG-related activity that is dependent upon the number of rhythmically active limbs. In a more recent experiment, Sasada et al. (2016) provided further evidence for a common neural element that is only active during coordinated arm and leg movement by showing a facilitation of cutaneous reflexes in the upper limbs during combined arm and leg cycling. This facilitation during combined arm and leg (A&L) cycling was greater than the sum of facilitation during arm only and leg only cycling.

Recent suggestions (Dietz 2002; Ferris et al. 2006; Zehr et al. 2009, 2016) to exploit cervicolumbar connections in human locomotor rehabilitation training by including rhythmic arm movement with rhythmic leg movements has shown great success. Adding rhythmic arm cycling to functional electrical stimulated leg cycling improved corticospinal drive to the lower limbs and supports the notion that active engagement of the upper limbs facilitates the restoration of function following spinal cord injury (Zhou et al. 2017). Furthermore, combined A&L cycling training has been shown to cause vast improvements in walking function, strength, and neurophysiological integrity in chronic stroke participants (Klarner et al. 2016a, b). Indeed, arm-cycling training alone was also able to improve walking function and neurophysiological integrity in chronic stroke participants (Kaupp et al. 2018). During both arm and A&L cycling, a notable outcome was the regulation of hyperactive stretch reflexes in the plantar flexors during arm cycling. Unfortunately, it is unclear whether there is a clear advantage of A&L cycling compared to arm only or leg only cycling when it comes to modulation of reflexes in the legs following activity. Therefore, the purpose of this experiment was to determine whether the active engagement of the arms and legs together, rather than separately, enhances the activity-dependent modulation of the soleus H-reflex pathway that persists in neurologically intact participants once activity has ceased. Based on our prior work, we expected significant suppression of H-reflexes during and after all forms of cycling. Our hypothesis here was that there would be greater and longer lasting suppression of the soleus H-reflex after 30 min of A&L cycling compared to cycling with arms or legs only.

Methods

Participants

Fourteen neurologically intact participants (170.9 ± 10.16 cm, 69.4 ± 13.51 kg, 24.9 ± 3.34 years, 7 women) were recruited from the university student population. Participants were apparently healthy (i.e., no history of cardiovascular, metabolic, or neuromuscular impairment) and provided written and signed informed consent prior to partaking in any experimental protocols. The protocol was approved by the Human Research Ethics Board at the University of Victoria and was conducted in accordance with the Declaration of Helsinki.

Experimental protocol

Participants began each experimental session sitting, as depicted in the far left panel of Fig. 1 (i.e., control). On 4 separate days, they then either sat in a resting position or performed arm, leg, or A&L cycling on a Sci-fit arm and leg cycle ergometer (Sci-Fit Pro 2, Tulsa, OK) in a seated position with the center of the crank set to the same height as their acromion. For leg and A&L cycling, the feet were strapped onto pedals with the knee just slightly bent at the furthest portion of the pedal stroke. For arm cycling, the feet were strapped into footplates with hip, knee and ankle angles kept constant throughout all experimental procedures. For A&L cycling, arm and leg cranks were mechanically coupled with a 90° out of phase offset to maintain a constant rigid relation between arm and leg movement. The intensity and duration of cycling were kept constant at 60 revolutions per minute (RPM), at a workload of 20 W (minimum workload setting of the ergometer) for 30 min in all conditions. This 1 Hz cadence and workload was chosen to allow for rhythmic movement that is similar to the cadence of normal walking, was not taxing on participants, and was above the threshold for activation of spinal cord locomotor activity (Hundza et al. 2012; Hundza and Zehr 2009). H-reflex and M-wave recruitment curves were recorded 10 and 20 min into each session. After the first 30 min in each session, H-reflex and M-wave recruitment curves were recorded immediately and 2.5, 5, 7.5, 10, 15, 20, 25, and 30 min post-cycling.

Electromyography

Bipolar surface electrodes were placed bilaterally over the mid-muscle bellies of the soleus (SOL), tibialis anterior (TA), and vastus lateralis (VL). 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. EMG signals from SOL were preamplified (×500) and bandpass filtered (10–1000 Hz), and, similarly, EMG signals from TA and VL preamplified (×5000) and bandpass filtered (100–300 Hz) (GRASS P511, AstroMed). These parameters are consistent with the previous experiments in our laboratory (Balter and Zehr 2007; Vasudevan and Zehr 2011; Zehr et al. 2012; Pearcey et al. 2017). After conversion to a digital signal, data were sampled at 2000 Hz using a custom-built continuous acquisition software (LABVIEW, National Instruments, TX, USA).

Transcutaneous nerve stimulation

To evoke H-reflexes in the SOL muscle, single 1 ms square wave electrical pulses were applied to the right tibial nerve at the popliteal fossa with bipolar surface electrodes (Thought Technology Ltd., Montreal, QC, Canada) using a Digitimer (Medtel, NSW, Australia) constant current stimulator (model DS7A). A non-contact milliammeter (mA-2000, Bell Technologies, Orlando, FL, USA) was used to measure current delivered for each stimulus. Recruitment curves were recorded at pre-, during, and post-cycling. For pre-cycling recruitment curves, 40 sweeps were recorded; however, to allow for higher resolution in time, only 20 sweeps were recorded for during and post-cycling timepoints. At all timepoints during pre- and post-cycling collection, participants had their feet secured on foot plates and ankle and knee

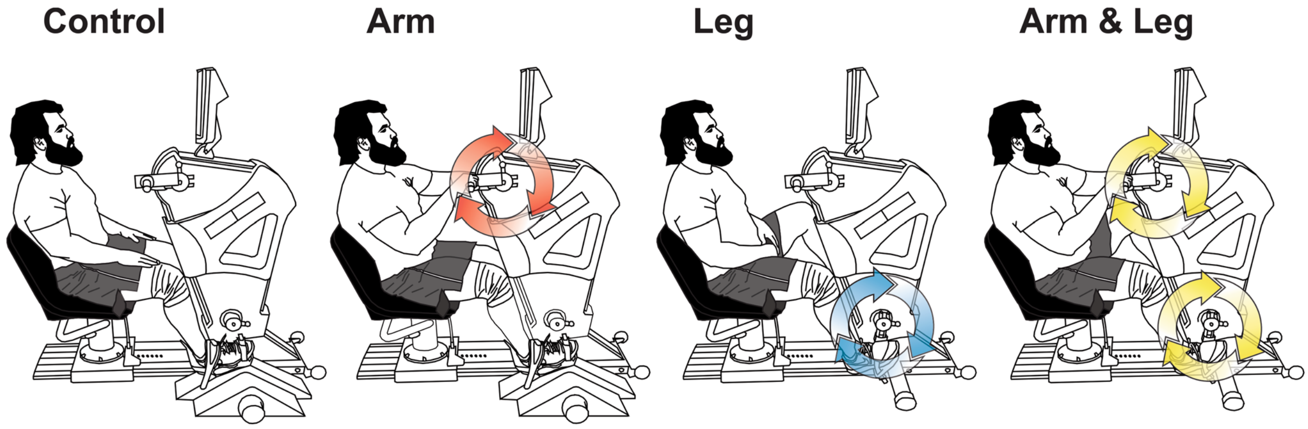

Fig. 1 Representation of the activity performed in each of the conditions. All PRE and POST H-reflex measures were taken in the control position, as shown in the far left panel (i.e., control)

angles (ankle ~ 90°, knee ~ 110°) were monitored throughout the sessions to ensure that there were no changes. During cycling for the leg and A&L conditions, reflexes were evoked when the right foot passed the position that corresponded to the same joint angles of the right leg (i.e., the 6 O'clock position, as depicted in Fig. 1). Stimulus–response curve stimuli were delivered pseudorandomly between 1 and 3 s, while participants were at rest, and randomly every 1–3 cycles during leg or A&L cycling. Stimulus intensity was increased and decreased incrementally (ranged from 0.1 to 1 mA per increment) based on the excitability of the reflex pathway in different individuals while ensuring that supramaximal M-wave amplitudes were achieved by increasing larger increments once the H-reflex amplitude started to decrease in size [i.e., after the peak H-reflex amplitude was reached, for examples see (Klimstra and Zehr 2008)]. Figure 2 shows an overlay of 20 sweeps of EMG recordings from a single subject from all four conditions.

Statistics

Statistical procedures were performed using SPSS 18.0 (Chicago, Illinois). For between condition group comparisons, a two factor (CONDITION × TIME) repeated measure ANOVA was run to determine main and interaction effects for reflex modulation across the four conditions. If significant interactions were found and direction of change was predicted because of a priori hypotheses, paired samples *t* tests were performed. In all cases, statistical significance was set at $p \leq 0.05$ and Bonferroni corrections were used to account for multiple pairwise comparisons. Results are reported as mean ± SD in text (SE in figures). Cohen's *d* effect sizes are included in some instances (Cohen 1988) to provide an indication of the standardized effect of differences between control and other conditions and between A&L and other conditions.

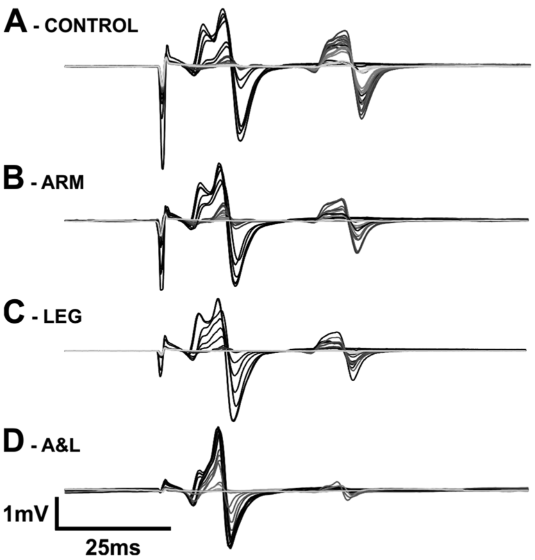

Fig. 2 Raw EMG recordings from a single subject at 10 min into the CTRL (**a**), ARM (**b**), LEG (**c**), and A&L (**d**) session. Each panel is an overlay of 20 sweeps with varying intensity of stimulation. The darkness of lines corresponds to intensity of stimulation, such that darker lines indicate higher current

Results

M-wave excitability

Maximal M-wave recordings were consistent at PRE between conditions; however, there were changes in $M_{\max}$ amplitudes as a result of cycling with the legs. At PRE, group averaged $M_{\max}$ amplitudes were 10957 ± 831.8 µV, 10802.2 ± 854.8 µV, 10700 ± 680.1 µV, and 11041 ± 937.5 µV for CTRL, ARM, LEG, and A&L, respectively. The RM ANOVA [4 (condition) × 12 (time)] revealed a significant interaction effect of time and condition [$F_{(33,396)} = 1.651$, $p = 0.015$]. For all timepoints after the cessation of cycling, $M_{\max}$ values were increased by approximately 10% (range of 9.5–10.9%, *p* ranged from 0.000127 to 0.01, and *d* ranged from 0.35 to 0.4) during LEG, and approximately 7% (range of 6.3–7.8%, *p* ranged from 0.035 to 0.05, and *d* ranged from 0.2 to 0.29) during A&L. There were no changes in $M_{\max}$ during CTRL (all $p > 0.11$ and $d < 0.1$) or ARM (all $p > 0.29$ and $d < 0.06$). This suggests that after rhythmic leg movement, the peripheral excitability of the soleus muscle is increased.

H-reflex excitability

H-reflex excitability was drastically reduced during ARM, LEG, and A&L activity, and remained suppressed following all forms of rhythmic activity. Separate RM ANOVAs [4 (condition) × 12 (time)] were run for the $H_{\max}/M_{\max}$ ratio and each variable of the H-reflex recruitment curves (slope, H@th, H@50, H@100, c@th, c@50, c@max). The RM ANOVA for the $H_{\max}/M_{\max}$ ratio revealed a significant effect for time [$F_{(11,132)} = 25.722$, $p < 0.0001$], condition [$F_{(3,36)} = 9.446$, $p < 0.0001$], and an interaction effect of time and condition [$F_{(33,396)} = 4.419$, $p < 0.0001$]; however, the $H_{\max}/M_{\max}$ ratio at pre was similar between conditions, as shown in Table 1. PRE recruitment curve values are shown in Table 2 and did not differ between conditions. Effects of the RM ANOVA for each recruitment curve variable are displayed in Table 3.

Table 1 Pre-group average and standard deviation values for maximal M-wave ($M_{\max}$), H-reflex ($H_{\max}$) and the ratio between $M_{\max}$ and $H_{\max}$ for each condition

Condition	$M_{\max}$ (µV)	$H_{\max}$ (µV)	$H_{\max}/M_{\max}$ ratio (%)
CTRL	10957 ± 831.8	4870 ± 1963.3	47.5 ± 22.23
ARM	10802 ± 854.7	5036 ± 1958.2	46.8 ± 18.58
LEG	10669 ± 680.1	5607 ± 2553.5	52.9 ± 22.43
A&L	11041 ± 937.5	5506 ± 1850.4	50.0 ± 15.26

Modulation of H-reflexes during activity

In general, H-reflex excitability was greatly reduced during all forms of rhythmic activity. There was no change in H-reflex $H_{\max}/M_{\max}$ ratio during CTRL at timepoints 10 (47.2 ± 21.86%) and 20 (48.6 ± 22.84%), compared to PRE (47.5 ± 22.23%). There was, however, a reduction of 40.4 ± 28.80% ($d = 1.7$) and 37.9 ± 28.57% ($d = 1.8$) during ARM, 42.8 ± 29.36% ($d = 1.8$) and 40.3 ± 26.91% ($d = 2.0$) during LEG and 48.2 ± 22.00% ($d = 2.4$) and 50.0 ± 21.86% ($d = 2.9$) during A&L at 10 and 20, respectively. The reductions in $H_{\max}/M_{\max}$ ratio were similar between conditions. In all conditions except CTRL, the slope of the recruitment curve was reduced by ~ 40% at both 10 and 20; however, these reductions in slope did not differ between conditions nor between timepoints. There was a general increase in current required to evoke 50% $H_{\max}$ and $H_{\max}$, but not the threshold H-reflex, at 10 and 20 for ARM, LEG, and A&L. The increased current required to evoked $H_{\max}$ at 20 was greater for the LEG ($p = 0.013$) and A&L ($p = 0.011$) conditions compared to ARM, suggesting that the activity of the legs was driving this effect. The H-reflex amplitude was reduced during ARM (~ 35%), LEG (~ 70%) and A&L (~ 70%) at the current required to get 50% of $H_{\max}$ (all $p < 0.01$) and $H_{\max}$ (all $p < 0.001$) from PRE, but were not significantly different from each other, see Fig. 3 for a single subject's sigmoidal fits for recruitment curves that were recorded at all timepoints in comparison with PRE in Fig. 3.

Modulation of H-reflexes after activity has ceased

After activity, there was persistent modulation of the H-reflex pathway in all conditions, other than CTRL. During ARM, the $H_{\max}/M_{\max}$ ratio was significantly ($p = 0.0019$, $d = 1.0$) reduced by 19.7 ± 20.54% immediately after cycling, however, returned to values approaching PRE by 2.5 min post-cycling. The H-reflex amplitude evoked at the current required to evoke $H_{\max}$ during PRE (i.e., H@100%) remained reduced for up to 10 min, indicating a reduced

Table 2 Pre-group average and standard deviation values for recruitment curves in each condition

Condition	Slope	c@th (mA)	c@50 (mA)	c@max (mA)	H@th (%$M_{\max}$)	H@50 (%$M_{\max}$)	H@100 (%$M_{\max}$)
CTRL	3.2 ± 2.24	56.7 ± 14.95	66.3 ± 11.44	75.8 ± 8.82	5.7 ± 2.32	23.6 ± 9.46	41.6 ± 16.77
ARM	3.3 ± 3.20	56.8 ± 14.21	69.1 ± 6.41	81.3 ± 6.27	5.3 ± 2.61	22.0 ± 11.23	38.7 ± 19.65
LEG	3.1 ± 2.82	60.5 ± 8.46	71.1 ± 6.06	81.6 ± 8.01	5.6 ± 2.81	23.5 ± 11.68	41.2 ± 20.43
A&L	3.4 ± 2.92	55.2 ± 17.43	65.2 ± 11.94	75.2 ± 8.98	5.8 ± 3.06	24.9 ± 13.05	43.8 ± 23.11

c@th, stimulation current required to evoke the smallest H-reflex; c@50%, stimulation current required to evoke an H-reflex 50% of maximum amplitude; c@max, stimulation current required to evoke the maximum H-reflex; H@th, H-reflex size at the current required to evoke the smallest H-reflex from PRE; H@50%, H-reflex size at the current required to evoke 50% of the maximal H-reflex from PRE, and H@100%, H-reflex size at the current required to evoke the maximal H-reflex from PRE

Table 3 Main effects from the repeated measures ANOVA performed on each recruitment curve variable

Variable	Condition	Time	Interaction
Slope	$F_{(3,36)} = 3.253$ (0.033)*	$F_{(11,132)} = 3.262$ (0.001)*	$F_{(33,396)} = 1.287$ (0.138)
c@th	$F_{(3,36)} = 0.276$ (0.843)	$F_{(11,132)} = 3.950$ (< 0.001)*	$F_{(33,396)} = 1.34$ (0.104)
c@50%	$F_{(3,36)} = 1.821$ (0.161)	$F_{(11,132)} = 16.288$ (< 0.001)*	$F_{(33,396)} = 2.554$ (< 0.001)*
c@max	$F_{(3,36)} = 3.123$ (0.038)*	$F_{(11,132)} = 16.332$ (< 0.001)*	$F_{(33,396)} = 3.762$ (< 0.001)*
H@th	$F_{(3,36)} = 1.204$ (0.322)	$F_{(11,132)} = 11.771$ (< 0.001)*	$F_{(33,396)} = 1.457$ (0.05)*
H@50%	$F_{(3,36)} = 4.41$ (0.01)*	$F_{(11,132)} = 26.419$ (< 0.001)*	$F_{(33,396)} = 2.804$ (< 0.001)*
H@100%	$F_{(3,36)} = 7.702$ (< 0.001)*	$F_{(11,132)} = 34.738$ (< 0.001)*	$F_{(33,396)} = 4.709$ (< 0.001)*

F ratios are reported with p values in parenthesis. Asterisks indicate a significant effect. c@th, stimulation current required to evoke the smallest H-reflex; c@50%, stimulation current required to evoke an H-reflex 50% of maximum amplitude; c@max, stimulation current required to evoke the maximum H-reflex; H@th, H-reflex size at the current required to evoke the smallest H-reflex from PRE; H@50%, H-reflex size at the current required to evoke 50% of the maximal H-reflex from PRE, and H@100%, H-reflex size at the current required to evoke the maximal H-reflex from PRE

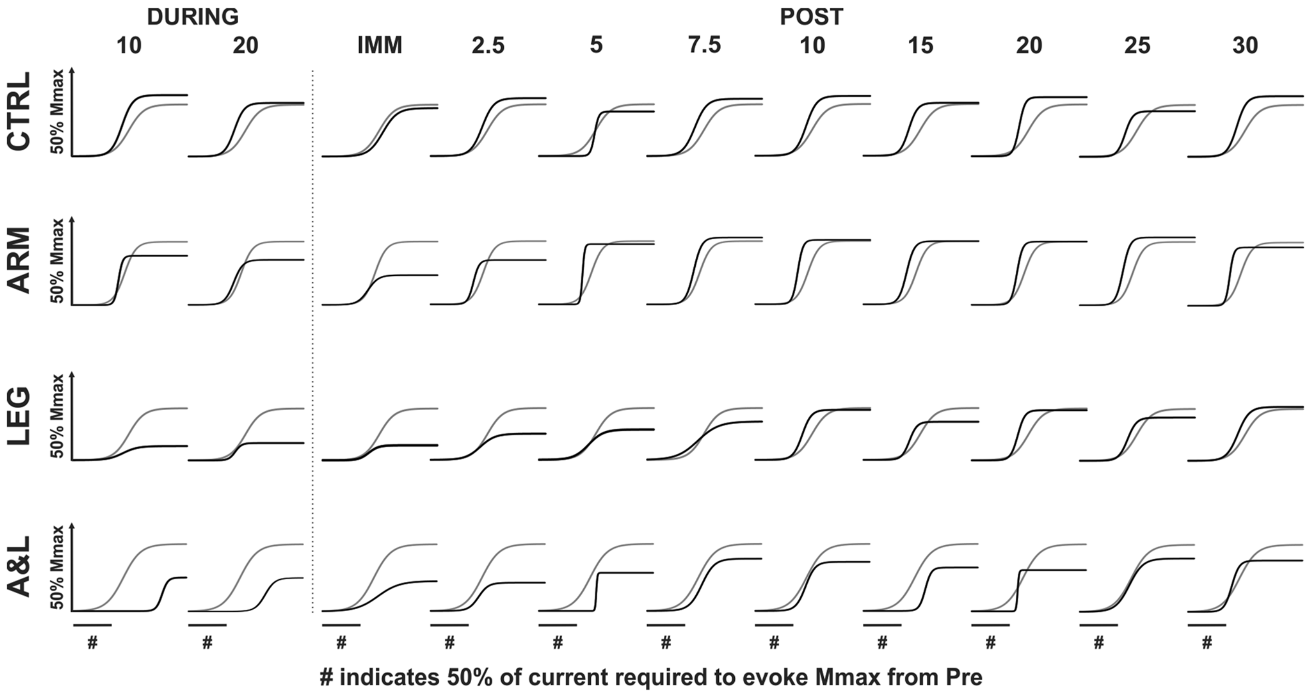

Fig. 3 Lines represent the sigmoidal fit of each H-reflex recruitment curve that was recorded for a single subject. The grey lines are the PRE curves, whereas the black lines are the curves from the corresponding timepoint and condition. CTRL is on top, ARM is second from the top, LEG is third from the top, and A&L is at the bottom

excitability at the same relative input between timepoints. During LEG, the H_{max}/M_{max} ratio was significantly reduced by 28.5 ± 21.54% ($d = 1.5$) and 10 ± 14.67% ($d = 0.76$) immediately and 2.5 min post-cycling, respectively, however, returned to PRE values by 5 min post-cycling. The H-reflex amplitudes evoked at the current required to evoke 50% of H_{max} (i.e., H@50%) and current required to evoke H_{max} (i.e., H@100%) during PRE both remained reduced for up to 10 min. During A&L, the H_{max}/M_{max} ratio was significantly reduced by > 20% up to 5, > 10% up to 25, and by ~ 8% at 25 and 30 min post-cycling, compared to PRE (see Fig. 4). The reduction in H_{max}/M_{max} ratio during A&L was greater than that of ARM immediately post ($d = 0.65$), and was greater than that of ARM and LEG at all other timepoints (d values ranged from 0.6 to 1.0) up to, but not including, 30 min post-cycling (see Fig. 4). Furthermore, the current required to evoke the maximal H-reflex (i.e., c@max) was increased for up to 25 min and the H-reflex amplitudes evoked at the current required to evoke 50% of H_{max} (i.e., H@50%) and current required to evoke H_{max} (i.e., H@100%) during PRE remained reduced for up to 15 min each.

Pre-stimulus electromyography

Pre-stimulus EMG in the SOL, TA, and VL was consistent between conditions and throughout sessions, with the exception of 10 and 20 min into LEG and A&L activity. At PRE, group averaged rectified EMG for 50 ms prior to stimulation in the SOL was 25.9 ± 7.7 μV, 23.3 ± 3.5 μV, 27.8 ± 7.4 μV, and 26.4 ± 5.8 μV, respectively, for the CTRL, ARM, LEG, and A&L conditions. The RM ANOVA [4 (condition) × 12 (time)] revealed a significant interaction effect of time and condition [$F_{(33,396)} = 4.819$, $p < 0.001$]. At 10 and 20 min into the LEG and A&L conditions, pre-stimulus SOL EMG was increased by 10–20-fold compared to all other timepoints and conditions (p ranged from < 0.001 to 0.0015), indicating that the SOL was active during leg movement, whereas it was quiescent and did not differ at all other timepoints (p ranged from 0.14 to 0.89). There were also interaction effects of time and condition for the TA [$F_{(33,396)} = 4.054$, $p < 0.001$] and VL [$F_{(33,396)} = 3.004$, $p = 0.005$] pre-stimulus EMG. In both muscles, pre-stimulus EMG was 1–3-fold higher at 10 and 20 min into the LEG and A&L conditions, compared to all other timepoints (p ranged from < 0.001 to 0.011). At all timepoints during rest, however, pre-stimulus EMG did not differ for TA (p ranged from 0.21 to 0.86) or VL (p ranged from 0.16 to 0.83).

Discussion

The main finding of this experiment is that exploiting cervicolumbar connections during rhythmic movement enhances the suppressive effects of cycling on soleus H-reflexes after

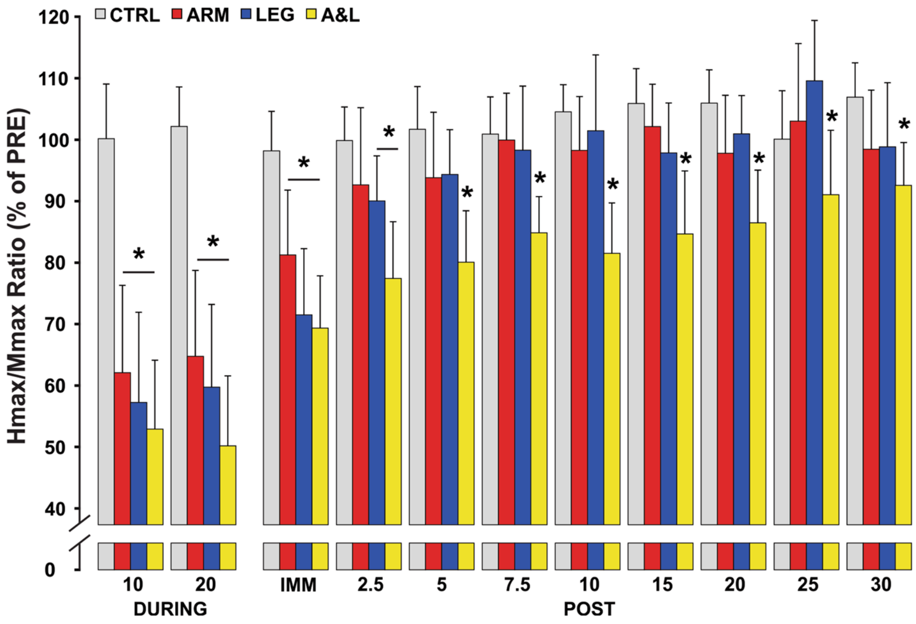

Fig. 4 Group averaged H_{max}/M_{max} ratios for the control (CTRL; grey fill), arm (ARM; red fill), leg (LEG; blue fill), and combined arm and leg (A&L; yellow fill) conditions. All values are made relative to the recruitment curve measured on that day at PRE. Asterisks indicate a significant reduction from PRE and error bars indicate standard error of the group

the activity has ceased. The prolonged H-reflex suppression is greatest when combined arm and leg rhythmic activity is performed, followed by rhythmic activity of the limbs where reflexes are measured (i.e., the legs in this case), followed by rhythmic activity of remote limbs (i.e., arms in this case). These findings build on the previous findings from our lab (Javan and Zehr 2008) that show a persistent short-term plasticity of H-reflexes in the legs induced by arm cycling. Furthermore, these findings support the working hypothesis that humans have retained cervicolumbar connections throughout evolution that can be exploited to enhance targeted rehabilitation strategies and augment neuroplasticity (Zehr et al. 2016).

Rhythmic leg movement causes prolonged suppression of H-reflex excitability in the legs, which is accompanied by a facilitation of peripheral excitability

Little attention has been given to the lasting effects of rhythmic leg movement on H-reflex excitability after a task has ceased. Initially, Misiaszek et al. (1995) showed that short duration (< 2 min) of passive cycling reduced SOL H-reflexes for ~ 4 s. More recently, Motl et al. (Motl and Dishman 2003; Motl et al. 2003) have shown that 30 mins of low intensity leg cycling reduces SOL H-reflex excitability for ~ 10 min. In line with those findings, our current results show that leg cycling reduced H_{max}/M_{max} ratios for up to 5 min; however, H-reflex amplitudes at stimulus intensities required to evoke 50% and H_{max} from PRE were reduced for up to 10 min. Interestingly, we also found that M_{max} amplitudes were facilitated by ~ 10% following the leg cycling. Unfortunately, there are few reports in the literature that have examined the effects of non-fatiguing leg cycling on peripheral excitability. In an experiment aimed to examine the effects of various warm-up routines on knee extensor function, Girard et al. (2009) found that M_{max} amplitude of the vastus lateralis muscle tended to increase following a running warm-up. We believe that this is the first report of non-fatiguing cycling causing an increase in M_{max}; however, the extent to which various parameters of cycling can increase peripheral excitability (i.e., M_{max}) are not known.

Rhythmic arm movement causes prolonged suppression of H-reflex excitability in the legs

H-reflex suppression due to rhythmic activity of a remote limb pair (arms or legs), opposite to the resting limbs (legs or arms) has been well documented (Hiraoka 2001; Frigon et al. 2004; Zehr et al. 2004, 2007 Hiraoka and Iwata 2006; Loadman and Zehr 2007; Dragert and Zehr 2009; Hundza and Zehr 2009; de Ruiter et al. 2010; Nakajima et al. 2011, 2013, 2016; Hundza et al. 2012; Domingo et al. 2014; Massaad et al. 2014). Our current findings coincide with the previous reports of Javan and Zehr (2008) and Nakajima et al. (2016), as we saw a ~ 40% suppression of SOL H-reflex amplitudes (H_{max}/M_{max}) during arm-cycling activity. Following the cessation of arm cycling, however, H_{max}/M_{max} values in the current experiment returned to pre-cycling values within the first 2.5 min. The H-reflex amplitude at the current required to evoke H_{max} pre-cycling was reduced for up to 10 min, indicating a prolonged suppression of H-reflex excitability. The duration of prolonged suppression in the current experiment is less than that of Javan and

Zehr (2008), but closer to the duration reported in Nakajima et al. (2016). This is probably due to the method used to sample H-reflexes, since H-reflexes at ~ 50–70% of $H_{\max}$ are more susceptible to influences from Ia PSI from presynaptic inhibitory interneurons (Crone et al. 1990), than are the responses at $H_{\max}$. Nevertheless, a similar trend has been shown in the current experiment, illustrating the potential of rhythmic activity of a remote limb pair to cause prolonged suppression of H-reflex excitability.

Rhythmic combined arm and leg activity amplifies prolonged suppression of H-reflex excitability in the legs

Interactions of arm and leg rhythmic movements during activity have also been well documented. Recent work by Nakajima et al. (2014) used spatial facilitation to examine the convergence of common reflex pathways during various rhythmic and locomotor-like movements of the arms and legs. A greater facilitation of reflex amplitudes was found when both the arms and legs were used together, compared to the summation of using the limbs separately, suggesting a weighting of facilitation according to the number of rhythmically active limbs. This highlights common interneuronal reflex pathways that contribute to excitability differences when the arms and legs work together during a locomotor task (Zehr et al. 2016). Subsequently, Sasada et al. (2016) provided evidence for a common neural element of the early latency cutaneous reflex pathway, which receives convergent input from the arms and legs, that is only active when the arms and legs are used together. Indeed, Zehr et al. (2007) showed that H-reflex amplitudes evoked at the current required for $H_{\max}$ PRE were reduced to a similar extent between LEG and A&L, whereas during ARM, they were reduced to a lesser extent. Although somewhat surprising, these findings support of the notion that there are arm-to-leg neural interactions during locomotor-like movements that are dominated by the legs. During A&L movement in the current experiment, the suppression of SOL H-reflex excitability was greater than during ARM but similar to LEG. This leg dominated suppression in SOL H-reflex excitability is thought to reflect an active physiological filtering of excessive afferent feedback (Brooke et al. 1997) that occurs during rhythmic movement of the limb in which the reflex is measured [see Brooke and Zehr (2006)]. However, the extent of interactions between arm and leg movements following the cessation of movement have not been examined until now. After the cessation of A&L movement, we found prolonged suppression of SOL H-reflexes lasted for at least 25 min, compared to less than 10 for LEG and ARM added together. This finding suggests that using the arms and legs together in a locomotor context activates a common neural element that contributes to augmenting the prolonged suppression of the SOL H-reflex following the cessation of rhythmic activity.

Mechanisms responsible for prolonged suppression of H-reflexes

Recent decades of experiments have provided indisputable evidence that reflex pathways are malleable, and the excitability depends on the context in which they are evoked, the task being performed and the phase within the task (Stein and Capaday 1988; Zehr and Stein 1999). The central nervous system, and in particular descending and afferent input onto interneurons and motoneurons, modulates the expression of a reflex based upon the task performed (Zehr 2006). Multiple reviews have summarized the effects of rhythmic leg activity on H-reflexes evoked in the legs [see the following reviews: (Brooke et al. 1997; Brooke 2004; Brooke and Zehr 2006)]. In short, the gain of SOL H-reflexes is higher during phases of stepping, walking, running, and cycling when the SOL is active, whereas the gain is reduced when the SOL is inactive and returning to that phase (Brooke et al. 1997). However, compared to lying, sitting, or standing, SOL H-reflex gain is lower during rhythmic movement of the legs, and as movement frequency increases, SOL H-reflex gain decreases. This adaptive gain control is attributable to Ia presynaptic inhibition (PSI) [summarized in Zehr (2006)].

Conditioning of H-reflexes with movement and sensory inputs known to modulate Ia PSI provided evidence that interlimb effects on H-reflex excitability are mediated by Ia PSI (Frigon et al. 2004; Nakajima et al. 2013) likely stemming from CPG-related activity and/or afferent feedback related to movement (Brooke et al. 1997). Although the mechanism causing the prolonged suppression of SOL H-reflex excitability following rhythmic movement is not entirely clear, it has been suggested that it may result from activation of persistent inward currents within the spinal interneurons mediating Ia PSI (Javan and Zehr 2008). Persistent inward currents have been identified within the central nervous system of several species (Brown and Griffith 1983; Murase et al. 1986; Oyama et al. 1986; Hounsgaard and Kiehn 1989; Fraser and MacVicar 1996; Lee and Heckman 1998a, b; Smith and Perrier 2006; Abbinanti et al. 2012; Hultborn et al. 2013; Wang et al. 2015), including humans (Collins et al. 2002; Heckman et al. 2008; Wilson et al. 2015; Johnson et al. 2017), and have been shown to play a role in the activity of interneurons within the ventral horn of the turtle spinal cord (Smith and Perrier 2006), commissural interneurons within the mouse spinal cord (Abbinanti et al. 2012), and inhibitory interneurons within the human and primate cortex (Wang et al. 2015). Plateau-like behaviour of the Ia PSI interneuron (as studied in the current experiment) can be immediately terminated when a brief sensory input is provided (Javan and Zehr 2008) similar to the termination of plateau-like behaviour of motoneurons by inhibitory post-synaptic inputs in vivo (Lee and Heckman 1998a, b). Persistent activity of the Ia PSI interneurons has been proposed as the simplest explanation for short-term plasticity of SOL H-reflexes resulting from rhythmic movement (Javan and Zehr 2008). Therefore, the activation of the common interneuronal networks that receive convergent information from both the arms and legs when they are used together (Nakajima et al. 2014; Sasada et al. 2016; Zehr et al. 2016) could facilitate the plateau-like activity of inhibitory spinal interneurons, thus resulting in more prolonged suppression of the SOL H-reflex pathway when the arms and legs are used together, rather than separately.

Clinical translation

Priming neural circuits has predominantly been thought of as a means of facilitating voluntary motor output in context of rehabilitation (Stoykov and Madhavan 2015). Recently, however, Estes et al. (2017) provided evidence for the use of physical therapeutic/electroceutic interventions to reduce spinal reflex excitability and, therefore, reduce spasticity. Since spasticity is associated with hyperexcitable Ia reflex excitability (Levin and Hui-Chan 1993), and A&L activity causes the longest lasting suppression of H-reflex excitability following activity of the modalities tested in the current experiment, it seems logical that A&L activity could be used as a primer of spinal reflex circuits to reduce spasticity. Indeed, arm (Sosnoff and Motl 2010) and leg (Motl et al. 2006, 2007; Sosnoff et al. 2009; Sosnoff and Motl 2010) cycling has been shown to reduce H-reflex excitability and improve spasticity for individuals with multiple sclerosis. Arm and leg (Klarner et al. 2016a, b) as well as arm only cycling training can improve neurophysiological integrity, strength, balance, and function in chronic stroke, with some participants showing reduced spasticity as assessed clinically (Kaupp et al. 2018). Related observations have also been seen in spinal cord injury (Zhou et al. 2018a, b). The extent to which cervicolumbar connections can be exploited to improve spasticity in various clinical populations requires further investigation.

Conclusion

The results from the current experiment provide support for the hypothesis that exploiting cervicolumbar connections can enhance spinal cord plasticity. These observations add to the continually expanding body of the literature illustrating that rhythmic arm and leg movements are functionally integrated during locomotion with characteristics reminiscent of our quadrupedal ancestors (Zehr et al. 2016). Targeted rehabilitation strategies should incorporate rhythmic activity of both the arms and legs together to augment neuroplasticity in spinal networks.

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