TITLE: Corticospinal excitability to the biceps and triceps brachii during forward and backward arm cycling is direction- and phase-dependent

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Running Head: Direction-dependent changes in corticospinal excitability during arm cycling

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Abstract

The purpose of this study was to evaluate corticospinal excitability to the biceps and triceps brachii during forward (FWD) and backward (BWD) arm cycling. Corticospinal and spinal excitability were assessed using transcranial magnetic stimulation (TMS) and transmastoid electrical stimulation (TMES) to elicit motor evoked potentials (MEPs) and cervicomedullary evoked potentials (CMEPs), respectively. MEPs and CMEPs were recorded from the biceps and triceps brachii during FWD and BWD arm cycling at two positions, 6 and 12 o'clock. The 6 o'clock position corresponded to mid-elbow flexion and extension during FWD and BWD cycling, respectively, while 12 o'clock corresponded to mid-elbow extension and flexion during FWD and BWD cycling, respectively. During the flexion phase, MEP and CMEP amplitudes of the biceps brachii were higher during FWD than BWD cycling. However, during the extension phase, MEP and CMEP amplitudes were higher during BWD than FWD cycling. For the triceps brachii, MEP amplitudes were higher during FWD cycling compared to BWD regardless of phase. However, CMEP amplitudes were phase-dependent. During the flexion phase, CMEPs of the triceps brachii were higher during FWD cycling compared to BWD, but during the extension phase CMEPs were higher during BWD cycling compared to FWD. The data suggests that corticospinal and spinal excitability to the biceps brachii is phase- and direction-dependent. In the triceps brachii, spinal, but not corticospinal, excitability is phase-dependent when comparing FWD and BWD cycling.

Introduction

Humans and non-human animals effortlessly change the direction of locomotion between forward (FWD) to backward (BWD). Prior studies have shown that the neural control of locomotion is largely generated by the spinal central pattern generators (CPGs) and in BWD

locomotion it appears as though the CPG may simply be acting in reverse (Buford et al. 1990; Buford et al. 1993; Duysens et al. 1996). For example, a series of studies by Buford & Smith (Buford and Smith 1990; Buford and Smith 1993) examined the neural control of the hindlimb muscles during FWD and BWD walking in the adult cat by assessing the amplitude and sign of the reflex output following electrical stimulation. The authors concluded that the amplitude and sign of the reflex output was phase-dependent for FWD and BWD walking (Buford and Smith 1993), indicating that the same CPG controlled the direction of both motor outputs. A similar study in adult humans found that the modulation of cutaneous reflexes was similar for FWD and BWD walking and thus in general agreement with work from the cat (Duysens et al. 1996). This idea is also supported by more recent findings examining reflex modulation during arm cycling, which is also considered a CPG-mediated motor output in humans (Zehr et al. 2005).

Although locomotor outputs in humans are partially generated by spinal CPGs, descending input is also required (Capaday et al. 1999; Christensen et al. 2000; Petersen et al. 2001; Pyndt et al. 2003; Barthelemy et al. 2010; Barthelemy et al. 2011; Forman et al. 2014; Forman et al. 2015; Forman et al. 2016b). The excitability of the corticospinal pathway, considered one of the main descending pathways for the control of human motor output, can be assessed non-invasively by examining the responsiveness of the corticospinal tract to transcranial magnetic stimulation (TMS), referred to as corticospinal excitability (CSE). To date only one study has examined CSE during BWD rhythmic motor output in humans (Ung et al. 2005). In that study, Ung et al., (2005) showed that the amplitudes of TMS motor evoked potentials (MEPs) recorded from the soleus were *lower* during BWD walking when compared to an intensity- and position- matched tonic contraction, suggesting that CSE was *lower* during BWD walking, though a comparison was not made between FWD and BWD locomotion. MEPs recorded from the same muscle during leg

cycling, however, were larger during the downstroke of forward leg cycling compared to an intensity and joint-position matched tonic contraction, suggesting that CSE was *higher* during FWD cycling than tonic contraction (Pyndt and Nielsen 2003). Similar to Pyndt and Nielsen, albeit in a different muscle group, we showed that TMS-evoked MEP amplitudes during forward arm cycling were *larger* to the biceps brachii when compared to a position- and intensity-matched tonic contraction (Forman et al. 2014). Importantly, we concluded that enhanced CSE was due in large part to changes at the supraspinal level given that MEPs evoked via transmastoid electrical stimulation (TMES) were not task-dependent. Thus, it appears as though CSE may be higher during FWD compared to BWD locomotor output, however no study has directly compared CSE between these motor outputs. It is important to note, however, that these studies are not directly comparable for numerous reasons, including muscle-specific responses. For example, we have shown that unlike the biceps brachii, spinal excitability but not CSE to the triceps brachii is phase-dependent during arm cycling (Spence et al. 2016; Forman et al. 2018). Indeed, CSE and spinal excitability is phase-, muscle, intensity-, and task-dependent [for review see; (Power et al. 2018)].

The primary purpose of this study was to determine if CSE projecting to the biceps and triceps brachii was similarly modulated during FWD and BWD arm cycling. We hypothesized that: (1) CSE and spinal excitability projecting to the biceps and triceps brachii would be higher during FWD arm cycling and (2) CSE and spinal excitability projecting to the biceps brachii and spinal excitability projecting to the triceps brachii would be phase-dependent during FWD and BWD arm cycling.

METHODS

Ethics Approval

All procedures were verbally explained to the participants and written consent was obtained prior to the start of the familiarization session. The research was conducted in accordance with the Helsinki Declaration and approved by the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland (ICEHR#: 20181250-HK). Procedures were in accordance with the Tri-Council guideline in Canada and potential risks were fully disclosed to participants.

Participants

Twelve healthy male volunteers (ten right hand dominant, two left hand dominant) with no known neurological deficits participated in the study (average age: 24.5 ± 5.8 years). All 12 participants received TMS and 11 of those also received transmastoid electrical stimulation (TMES). One participant did not receive TMES as the required stimulation intensity was not tolerable. Prior to testing, each participant completed a magnetic stimulation safety-checklist to screen for existing contraindications to magnetic stimulation (Rossi et al. 2009). To determine hand dominance participants completed an Edinburg handedness inventory questionnaire to ensure that all evoked responses were recorded from the dominant arm (Oldfield 1971). To screen for existing contraindications to physical activity each participant completed a Physical Activity Readiness Questionnaire (PAR- Q+) (Bredin et al. 2013).

Experimental Set-up

A one-group within-subjects design was used. Participants attended one familiarization session (~ 30 min) and one testing session (~ 1 hour).

Familiarization session

Participants performed FWD and BWD arm cycling at 25 W while maintaining 60 rpm to ensure they were able to complete the task. Participants then received TMS, TMES and Erb's point stimulations to ensure they were comfortable with the stimulation paradigm that was used during the testing session.

Testing session

During the testing session each participant completed both FWD and BWD arm cycling on an arm cycle ergometer (SCIFIT Total Body PRO2® ergometer, Berkshire, UK). All participants were advised to maintain an upright posture throughout each cycling protocol to limit forward and backward bending of the trunk. The arm cranks were set at 180 degrees out-of-phase and seat height was adjusted to ensure the participant's shoulders were in line with the center of the arm shaft. Each participant was informed to lightly grip the arm crank handles with the forearms pronated. All participant's wore wrist braces to restrict wrist joint movement during cycling due to the reflex connections that exist between the wrist flexors and extensors and the biceps brachii (Manning et al. 2011).

Measurements were taken at the 6 and 12 o'clock positions, relative to the clock face. The 6 o'clock position was defined as the "bottom dead center" and the 12 o'clock position was defined as the "top dead center" of the movement cycle (see Figure 1). These positions were relative to the participants dominant hand such that the 12 o'clock position for a right-handed individual occurred when their right hand was at the "top dead center". These positions were selected because they represent time points of high and low biceps brachii activation (Forman et al. 2014). During FWD cycling, the movement of the arm crank from the 3 o'clock (full elbow extension) to 6 o'clock (mid-elbow flexion) to the 9 o'clock position (full elbow flexion) was defined as elbow flexion.

During this phase the biceps brachii is most active and peak EMG occurs at approximately the midway point (i.e. the 6 o'clock position). In contrast, movement of the arm crank from 9 o'clock (full elbow flexion) to 12 o'clock (mid-elbow extension) to 3 o'clock position (full elbow extension) was defined as elbow extension for FWD cycling. During BWD arm cycling the arm cranks were moving in the reverse direction (i.e. counter-clockwise). Thus, movement of the arm crank from the 3 o'clock position to 12 o'clock to the 9 o'clock position was defined as elbow flexion. Elbow extension was defined as movement of the arm crank from the 9 o'clock to the 6 o'clock to the 3 o'clock position.

All stimulations were triggered automatically as the arm crank of the dominant arm passed each position (6 and 12 o'clock). Measurements at each position were obtained during FWD and BWD arm cycling during separate trials, for a total of four cycling trials. Participants were instructed to cycle at a constant power output of 25 W and a cadence of 60 rpm based on prior work from our lab (Forman et al. 2014). The order of the four cycling trials (FWD and BWD with responses elicited at 6 and 12 o'clock) were randomized for each participant.

Electromyography (EMG)

EMG was recorded from the midline of the biceps brachii and lateral head of the triceps brachii using pairs of surface electrodes (Kendall™ 130 conductive adhesive electrodes, Covidien IIC, Massachusetts, USA). EMG was recorded using a bipolar configuration (Ag-AgCl) with an interelectrode distance of 2 cm. A ground electrode was placed on the lateral epicondyle of the dominant arm. Prior to electrode placement the skin at the recording site was shaved to remove hair, abraded using an abrasive pad to remove dead epithelial cells and cleaned with an isopropyl alcohol swab to reduce impedance for EMG recordings. The EMG signals were sampled online at 5 kHz using CED 1401 interface and Signal 5.11 software (Cambridge Electronic Design (CED))

Ltd., Cambridge, UK). EMG signals were amplified (x300) and filtered using a 3-pole Butterworth band-pass filter, with cut-off frequencies from 10-1000 Hz, using a CED 1902 amplifier.

Stimulation Conditions

Responses from the biceps and triceps brachii were elicited using TMS, TMES, and electrical stimulation at Erb's point. All stimulation intensities were set while the participant was forward cycling at 25 W and 60 rpm and the arm crank passed the 6 o'clock position. At this position the shoulder was at ~ 0 degrees of shoulder flexion and the elbow was flexed to ~ 90 degrees. The stimulation intensities for Erb's point, TMS and TMES were set relative to the biceps brachii muscle. Responses were also recorded from the triceps brachii muscle, which has been done previously (Spence et al., 2016).

Brachial Plexus Stimulation

Electrical stimulation of the brachial plexus at Erb's point was used to elicit maximal compound muscle action potentials ($M_{\max}$) (DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK). The anode was placed over the acromion process and the cathode was placed over the skin in the supraclavicular fossa. A pulse duration of 200 μ s was utilized, and the stimulation intensity was gradually increased from 25 mA until the M-wave amplitude of the biceps brachii reached a plateau or started to decrease, referred to as $M_{\max}$. This stimulation intensity was increased by 10% and used for the remainder of the experiment to ensure maximal M-waves were elicited during each trial (average: 183 ± 44 mA).

Transmastoid Electrical Stimulation (TMES)

TMES was applied using adhesive Ag-AgCl electrodes placed inferior to the mastoid processes (200 μ s duration; Digitimer; model DS7AH). The stimulation intensity was increased until the peak-to-peak amplitude of the average of 8 CMEPs was equal to approximately 15-20% of the peak-to-peak amplitude of the participants $M_{\max}$. This stimulation intensity was used for the remainder of the experiment (average: 152 ± 44 mA). The latency of the CMEP responses was monitored throughout the experiment to ensure the latency was ~ 8 ms to be confident that the corticospinal tract was being stimulated and not the ventral roots (Taylor 2006).

Transcranial Magnetic Stimulation (TMS)

The stimulation intensity for TMS was always set following TMES as it was easier to match the amplitudes of MEPs to CMEPs. TMS was applied over the participants vertex using a circular coil (13.5- cm outside diameter) attached to a Magstim 200 (Magstim, Dyfed, United Kingdom). The vertex was located by measuring the distance between nasion and inion and between the participants tragi and placing marks halfway directly on the scalp. The intersection of the halfway marks was defined as the vertex. Stimulation intensity was measured as a percentage of maximum stimulator output (MSO) and the stimulation intensity was increased until the peak-to-peak amplitude of the average of 8 MEPs was matched to that of the CMEP, approximately 15-20% of the participants $M_{\max}$. This stimulation intensity was used for the remainder of the experiment (average: $46 \pm 12\%$ MSO).

Experimental protocol

After stimulation intensities for Erb's point stimulation, TMES and TMS were set, participants completed 4 arm cycling trials in a randomized order; 2 FWD and 2 BWD with stimulations delivered at the 6 or 12 o'clock position. During each cycling trial participants

received a total of 10 MEPs, 10 CMEPs and 2 $M_{\max}$. The order of the stimulations was randomized throughout the trial and were evoked every 7-8 s. To prevent anticipation of the stimulation, 2 frames without stimulation were added.

Data Analysis

Data was analyzed off-line using Signal 5.11 software (Cambridge Electronic Design Ltd., Cambridge, UK). To determine if central motor drive projecting to the biceps and triceps brachii was similar between the 4 arm cycling trials the mean rectified 50 ms pre-stimulus EMG prior to TMS and TMES stimulus artifact was measured (Forman et al. 2014; Forman et al. 2015). The peak-to-peak amplitude of all evoked responses (MEP, CMEP, and $M_{\max}$) of the biceps and triceps brachii were measured from the initial deflection of the voltage trace from background EMG to the return of the trace to the baseline level. MEP and CMEP amplitudes can change as a result of changes to $M_{\max}$, thus MEPs and CMEPs were normalized to $M_{\max}$ evoked during the same trial to account for changes in the peripheral muscle. Also, MEP amplitudes were normalized to CMEP amplitudes evoked during the same trial to provide a measure of supraspinal excitability. All frames for each condition were first averaged using the Signal software. Measurements were then taken from the averaged files of all 10 MEPs, 10 CMEPs and 2 $M_{\max}$.

Statistics

All statistical analysis was completed using IBM® SPSS® Statistics Version 23 (IBM, Markham, Ontario, Canada). A two-way repeated-measures ANOVA with factors ‘direction’ (FWD and BWD) and ‘phase’ (flexion and extension) were used to determine if statistically significant differences in MEP or CMEP amplitudes (normalized to $M_{\max}$), or pre-stimulus EMG occurred as a main effect of arm cycling direction or phase. If there was a significant interaction effect, pairwise comparisons were used to examine changes in MEP and CMEP amplitudes and

pre-stimulus EMG between cycling directions at the two arm crank positions. The data was normally distributed as determined using Kolomogorov- Smirnov normality test. All statistical analysis was performed on group data with a significance level of $p < .05$. All data is reported in text as mean $\pm$ standard deviation (*SD*) and in figures as mean $\pm$ standard error (*SE*).

Results

Biceps brachii

Corticospinal excitability

MEP amplitude. Figure 2A and Figure 3A show representative and grouped data for MEP amplitudes (normalized to $M_{\max}$), respectively, from the biceps brachii during the elbow flexion phase (6 o'clock for FWD cycling and 12 o'clock for BWD cycling) and extension phase (12 o'clock for FWD cycling and 6 o'clock for BWD cycling) of arm cycling (refer to Fig. 1). Group data demonstrated a significant main effect of arm cycling direction (FWD > BWD, $F_{(1,11)} = 82.257, p = .001$) and arm crank position (6 > 12, $F_{(1,11)} = 7.498, p = .019$), as well as a significant interaction effect between cycling direction and arm crank position ($F_{(1, 11)} = 49.52, p = .001$). Paired t-tests revealed that during the elbow *flexion phase* MEP amplitudes of the biceps brachii were significantly higher while arm cycling FWD (6 o'clock) compared to BWD (12 o'clock) (FWD: $19.67 \pm 5.03\%$ of $M_{\max}$, BWD: $8.47 \pm 6.27\%$ of $M_{\max}$, $p = .001$). During the elbow *extension phase* MEP amplitudes of the biceps brachii were significantly higher while arm cycling BWD (6 o'clock) compared to FWD (12 o'clock) (FWD: $1.28 \pm 0.69\%$ of $M_{\max}$, BWD: $5.86\% \pm 4.92\%$ of $M_{\max}$, $p = .006$). During FWD cycling MEP amplitudes were significantly higher at the 6 o'clock position compared to the 12 o'clock position ($p = .001$). However, during BWD cycling there was no significant difference in MEP amplitudes between the 6 and 12 o'clock position ($p = .199$).

MEP amplitudes at the 6 o'clock position ($p = .001$) and the 12 o'clock position ($p = .002$) were significantly different between FWD and BWD cycling for the biceps brachii.

Pre-stimulus EMG for MEPs. Figure 3B shows grouped data for pre-stimulus EMG for MEPs for the biceps brachii. There were no significant main effects of cycling direction ($F_{(1, 11)} = .153, p = .703$) or arm crank position ($F_{(1, 11)} = .934, p = .355$). There was a significant interaction effect ($F_{(1, 11)} = 12.24, p = .005$). Paired t-tests revealed that pre-stimulus EMG for the biceps brachii was significantly higher at the 6 o'clock position compared to the 12 o'clock position during FWD cycling ($p = .001$). However, there was no significant difference between pre-stimulus EMG at the 6 and 12 o'clock position during BWD cycling ($p = .150$) for the biceps brachii.

Spinal excitability

CMEP amplitude. Figure 2B and Figure 4A show representative and grouped data for CMEP amplitudes (normalized to $M_{\max}$), respectively, from the biceps brachii during the elbow flexion phase and extension phase of FWD and BWD arm cycling. Grouped data demonstrated a significant main effect of cycling direction (FWD > BWD, $F_{(1, 10)} = 15.13, p = .003$), arm crank position (6 > 12, $F_{(1, 10)} = 34.07, p = .001$), and a significant interaction effect between cycling direction and arm crank position ($F_{(1, 10)} = 60.71, p = .001$). During the elbow *flexion phase*, CMEP amplitudes were significantly higher while arm cycling FWD (6 o'clock) compared to BWD (12 o'clock) for the biceps brachii (FWD: $16.9 \pm 4.89\%$ of $M_{\max}$, BWD: $7.49 \pm 4.36\%$ of $M_{\max}$, $p = .001$). In contrast, during the elbow *extension phase*, CMEP amplitudes were significantly higher while arm cycling BWD (6 o'clock) compared to FWD (12 o'clock) (FWD: $1.78 \pm 1.63\%$ of $M_{\max}$, BWD: $5.61\% \pm 3.28\%$ of $M_{\max}$, $p = .003$). During FWD cycling, CMEP amplitudes were

significantly larger at the 6 o'clock position as compared to 12 o'clock ($p = .001$), however during BWD cycling there was no significant difference in CMEP amplitudes between the 6 and 12 o'clock position ($p = .296$). CMEP amplitudes at the 6 o'clock position ($p = .001$) and the 12 o'clock position ($p = .001$) were significantly different between FWD and BWD cycling.

Pre-stimulus EMG for CMEPs. Figure 4B shows grouped data for pre-stimulus EMG for CMEPs for the biceps brachii. There was a significant main effect of cycling direction (FWD > BWD, $F_{(1, 10)} = 5.11, p = .047$), arm crank position (6 > 12, $F_{(1, 10)} = 14.03, p = .004$), as well as a significant interaction effect between cycling direction and arm crank position ($F_{(1, 10)} = 13.25, p = .005$). During the elbow flexion phase, pre-stimulus EMG prior to CMEPs was significantly higher while arm cycling FWD compared to BWD (FWD: $36.19 \pm 20.18 \mu V$, BWD: $26.77 \pm 15.74 \mu V, p = .008$). During the elbow extension phase, there was no significant difference in pre-stimulus EMG between FWD and BWD arm cycling (FWD: $18.06 \pm 14.66 \mu V$, BWD: $20.67 \pm 15.34 \mu V, p = .071$). During FWD cycling, pre-stimulus EMG was significantly higher at the 6 o'clock position compared to the 12 o'clock position ($p = .001$). However, during BWD cycling there was no significant difference in pre-stimulus EMG between the 6 and 12 o'clock position ($p = .087$).

Triceps brachii (TB)

Corticospinal excitability

MEP amplitude. Figure 5A and Figure 6A show representative and grouped data for MEP amplitudes (normalized to M_{max}), respectively, from the triceps brachii during the elbow flexion and extension phases of arm cycling. Group data demonstrated a significant main effect of arm cycling direction (FWD > BWD, $F_{(1, 11)} = 6.54, p = .027$), but no significant main effect of arm

crank position ($F_{(1,11)} = 2.45, p = .145$) and no significant interaction effect ($F_{(1, 11)} = 2.68, p = .130$). During the elbow *flexion phase*, MEP amplitudes were $18.01 \pm 18.81\%$ and $8.84 \pm 4.94\%$ of $M_{\max}$ for FWD (6 o'clock) and BWD (12 o'clock) cycling, respectively. During the elbow *extension phase*, MEP amplitudes were $9.87 \pm 6.61\%$ and $8.31 \pm 5.56\%$ of $M_{\max}$ for FWD and BWD cycling, respectively. Paired t-tests revealed no significant difference in MEP amplitudes when FWD and BWD cycling were compared relative to the phase of the movement cycle (Flexion: $p = .058$, Extension: $p = .262$). However, MEP amplitudes were significantly higher at the 6 o'clock position during FWD cycling compared to the 6 o'clock position during BWD cycling ($p = .048$).

Pre-stimulus EMG for MEPs. Group data for pre-stimulus EMG of the triceps brachii prior to MEPs can be seen in Figure 6B. There was no significant main effect of arm crank position ($F_{(1, 11)} = 0.440, p = .521$) or arm cycling direction ($F_{(1, 11)} = 1.86, p = .20$) on pre-stimulus EMG for the triceps brachii. Also, there was no significant interaction effect observed ($F_{(1, 11)} = 2.81, p = .122$). As a group, pre-stimulus EMG during the elbow flexion phase of FWD and BWD cycling for the triceps brachii was $21.98 \pm 10.86 \mu\text{V}$ and $21.60 \pm 9.34 \mu\text{V}$, respectively. During the elbow extension phase pre-stimulus EMG of the triceps brachii was $24.29 \pm 9.14 \mu\text{V}$ and $22.54 \pm 10.73 \mu\text{V}$ for FWD and BWD arm cycling, respectively.

Spinal excitability

CMEP amplitude. Representative and group data for CMEP amplitudes (normalized to $M_{\max}$) can be seen in Figure 5B and Figure 7A, respectively, for the triceps brachii. Significant main effect of arm crank position ($6 > 12, F_{(1, 10)} = 16.66, p = .002$) and significant interaction effect ($F_{(1, 10)} = 9.13, p = .013$) of arm cycling direction and arm crank position were observed. There was, however, no significant main effect of arm cycling direction ($F_{(1, 12)} = 0.361, p = .561$).

While arm cycling FWD, CMEP amplitudes were significantly higher at the 6 o'clock position compared to the 12 o'clock position (6 o'clock: $20.09 \pm 14.84\%$, 12 o'clock: $5.56 \pm 4.98\%$, $p = .003$). However, during BWD arm cycling, there was no significant difference in CMEP amplitudes between the 6 and 12 o'clock position (6 o'clock: $10.02 \pm 6.15\%$, 12 o'clock: $13.99 \pm 10.03\%$, $p = .196$). Paired t-tests revealed that during the flexion phase, CMEP amplitudes were significantly higher during FWD cycling compared to BWD cycling ($p = .032$). In contrast, during the extension phase, CMEP amplitudes were significantly higher during BWD cycling compared to FWD cycling ($p = .001$) for the triceps brachii.

Pre-stimulus EMG for CMEPs. Figure 7B shows group data of pre-stimulus EMG of the triceps brachii prior to CMEPs. There was a significant main effect of cycling direction ($F_{(1, 10)} = 10.31$, $p = .009$), but there was no significant main effect of arm crank position ($F_{(1, 10)} = 2.91$, $p = .119$) and no significant interaction effect ($F_{(1, 10)} = 2.94$, $p = .117$). As a group, pre-stimulus EMG during the elbow flexion phase was $21.95 \pm 10.34 \mu\text{V}$ and $21.17 \pm 10.21 \mu\text{V}$ for FWD and BWD arm cycling, respectively. During the elbow extension phase, pre-stimulus EMG of the triceps brachii was $25.97 \pm 11.58 \mu\text{V}$ and $21.83 \pm 10.68 \mu\text{V}$ for FWD and BWD cycling, respectively. Pre-stimulus EMG was significantly higher at the 12 o'clock position during FWD cycling compared to the 12 o'clock position during BWD cycling ($p = .02$).

DISCUSSION

Though previous research has examined reflex modulation during FWD and BWD locomotor outputs, this is the first study to directly compare measures of corticospinal excitability (CSE). Overall, CSE to the biceps and triceps brachii was higher during FWD than BWD arm cycling. Other new and notable findings include: 1) higher CSE to the biceps brachii during FWD flexion vs BWD flexion is likely mediated via changes in spinal excitability; 2) for the extension phase, CSE and spinal excitability projecting to the biceps brachii was higher during BWD cycling compared to FWD; 3) for the triceps brachii, spinal excitability was higher at the 6 o'clock position (the flexion phase of FWD cycling and the extension phase of BWD cycling) compared to the 12 o'clock position; and 4) in contrast to FWD cycling, there was no phase-dependent differences in CSE projecting to the biceps or triceps brachii during BWD cycling.

Direction-dependent modulation of corticospinal excitability to the biceps brachii

During the elbow flexion phase of arm cycling, CSE to the biceps brachii was higher during FWD cycling (6 o'clock) compared to BWD (12 o'clock), despite no significant differences in pre-stimulus EMG (Fig. 3). Changes in spinal excitability followed the same pattern as MEPs, suggesting that increased spinal excitability can partially account for the higher MEP amplitudes during the flexion phase of FWD cycling (CMEP amplitudes; Fig. 4). However, during the less active phase for the biceps brachii, MEP and CMEP amplitudes were significantly higher during BWD (6 o'clock) cycling compared to FWD (12 o'clock). Pre-stimulus EMG prior to CMEPs, however, was significantly higher during the elbow flexion phase of FWD cycling compared to BWD cycling (Fig. 4).

Differences in CSE and spinal excitability between FWD and BWD cycling may be related to shoulder position. During the flexion phase of the FWD cycling (6 o'clock), the shoulder is at

395 ~ 0° flexion whereas during the flexion phase of BWD cycling (12 o'clock) the shoulder is flexed
396 to ~ 90°. The biceps brachii is a biarticular muscle that crosses the shoulder joint, so the length of
397 the muscle changes with alterations in shoulder position (Langenderfer et al. 2004) and several
398 studies have shown that shoulder position directly influences measures of CSE (Nuzzo et al. 2016;
399 Collins et al. 2017). Collins et al. (2017) showed that during a 10% of maximum effort tonic
400 contraction both MEPs and CMEPs decreased when the shoulder was flexed to 90° compared to
401 0°. It was concluded that the position-dependent decrease in CSE was mainly of spinal origin as
402 CMEPs also decreased in amplitude (Collins et al. 2017). This supports our current finding that
403 MEPs and CMEPs were lower during the elbow flexion phase of BWD cycling (12 o'clock), where
404 the shoulder was flexed to ~ 90°, compared to FWD cycling which would have been ~ 0°.
405 Similarly, during the elbow extension phase MEP and CMEP amplitudes of the biceps brachii
406 were lower during FWD cycling (12 o'clock) compared to BWD cycling (6 o'clock). The exact
407 mechanism(s) underlying these posture-related changes in CSE in the current study are unclear,
408 but agrees with previous research suggesting that reduced excitability to the biceps brachii when
409 the shoulder is flexed may result from inhibition arising from synergists, including the
410 brachioradialis (Barry et al. 2008) and/or pronator teres (Naito et al. 1998) muscles. An important
411 distinction to note between the aforementioned studies and the present study, however, is the motor
412 task involved. Whereas Barry et al. (2008) assessed inhibition to the biceps brachii motoneurone
413 output (i.e. motor unit firing rates) during a tonic contraction, the present study involved assessing
414 motoneurone output (i.e. CMEPs) during arm cycling. We have previously shown that CSE is
415 different between these two types of motor outputs (Forman et al. 2014; Forman et al. 2016a;
416 Forman et al. 2016b; Forman et al. 2018; Power et al. 2018), and therefore may have different
417 underlying mechanism(s).

While CMEPs (normalized to $M_{\max}$) represent changes occurring at the spinal level it is possible that the recorded MEPs were influenced by changes occurring at the supraspinal level. In the adult cat, the mean level of activity of motor cortex neurons was similar between FWD and BWD walking, suggesting that BWD walking does not require higher or lower cortical activity compared to FWD walking (Zelenin et al. 2011). In the current study, the MEP/CMEP ratio, which provides a measure of supraspinal excitability (Gandevia et al. 1999), was not significantly different between FWD and BWD cycling. Hence, the changes in MEP amplitudes between FWD and BWD cycling were mainly of spinal origin. Prior work during low intensity tonic contractions has shown that the excitability to the biceps brachii is altered mainly by spinal mechanisms (Ugawa et al. 1995), therefore providing support for this idea, particularly given that participants cycled at a power output of 25 W in the current study, which is considered a low intensity contraction/motor output.

Direction-dependent modulation of corticospinal and spinal excitability to the triceps brachii

In support of our hypothesis, there was a main effect of cycling direction such that CSE to the triceps brachii was higher during FWD cycling compared to BWD cycling. However, unlike the biceps brachii, there was no significant difference in MEP amplitudes between FWD and BWD cycling when flexion and extension phases were compared. The lack of phase-dependent changes in CSE to the triceps brachii was not unexpected given our prior reports, albeit they only compared FWD cycling (Spence et al. 2016; Forman et al. 2018; Lockyer et al. 2018). In contrast, the modulation of spinal excitability did depend on the phase of the movement cycle such that during the *flexion phase*, spinal excitability was higher during FWD (6 o'clock) cycling compared to BWD cycling (12 o'clock) and during the *extension phase*, spinal excitability was higher during BWD (6 o'clock) cycling compared to FWD (12 o'clock) cycling. Again, though recorded during

FWD cycling only, we have previously shown phase-dependent modulation of spinal excitability (Spence et al. 2016).

The results from the current study show that when FWD and BWD cycling are compared, spinal excitability to the triceps brachii was higher at the 6 o'clock position (i.e. flexion during FWD and extension during BWD) compared to the 12 o'clock position (i.e. extension during FWD and flexion during BWD), despite no differences in pre-stimulus EMG. A previous study in our lab showed that during FWD cycling, spinal excitability, as measured via CMEP/ M_{max} , to the triceps brachii, was higher during elbow flexion (6 o'clock) than elbow extension (12 o'clock) (Spence et al. 2016). This was somewhat unexpected as pre-stimulus EMG of the triceps brachii is higher at the 12 o'clock position and the arm is flexed at the elbow joint at the 6 o'clock position (Spence et al. 2016). This coincides with the current finding that spinal excitability was higher during the *flexion phase* of FWD cycling (6 o'clock) compared to BWD cycling (12 o'clock). Spence et al. (2016) discussed several mechanisms that could account for this finding, one mechanism being input from Ia afferents. For example, during the flexion phase of FWD cycling, the triceps brachii muscle is stretched as the elbow is flexed which could result in an increased activation of Ia afferents which in turn would facilitate motoneurone excitability/output (Spence et al. 2016). However, in the current study at the 12 o'clock position during BWD cycling, the triceps brachii was also stretched as the elbow was flexed yet spinal excitability was higher during the flexion phase of FWD cycling at the 6 o'clock position. This suggests that there may be another mechanism aside from the stretch of the triceps brachii during the elbow flexion phase that is contributing to the increase in spinal excitability at the 6 o'clock position. For example, flexion of the shoulder at the 12 o'clock position may result in an increase in inhibitory synaptic input to the triceps brachii motoneurone pool from the biceps brachii, brachioradialis or other ascending or

descending inputs, thus decreasing excitatory input to the triceps brachii motoneurons (Sato et al. 2018) and resulting in decreased CMEP amplitudes.

The lower spinal excitability to the triceps brachii during BWD cycling in the current study is unlikely to result solely from peripheral factors arising from differences in shoulder position. This is because in the current study we recorded the activity of the lateral head of the triceps brachii, which is a monoarticular muscle that does not cross the shoulder joint and is primarily responsible for extending the elbow (Ali et al. 2014). It is unlikely that shoulder flexion would alter the muscle membrane properties (i.e. muscle fiber length and diameter) to an extent that would influence the recorded responses. Thus, it is plausible that the changes in spinal excitability resulted from changes in the intrinsic properties of the spinal motoneurons or from differences in afferent feedback to the triceps brachii motoneuron pool.

CONCLUSION

The current study demonstrates that CSE and spinal excitability to the biceps and triceps brachii during arm cycling is direction-dependent. Spinal excitability to the biceps and triceps brachii was higher during the *flexion phase* of FWD cycling compared to BWD cycling but higher during the *extension phase* of BWD cycling compared to FWD. Overall CSE to the biceps brachii showed the same modulation pattern as spinal excitability, however for the triceps brachii CSE was higher during FWD cycling compared to BWD but did not depend on the phase of the movement cycle. As expected, CSE and spinal excitability to the biceps brachii and spinal excitability to the triceps brachii was phase-dependent during FWD cycling, however it was not phase-dependent during BWD cycling. Whether the decrease in spinal excitability to the biceps and triceps brachii during the extension phase of FWD cycling and the flexion phase of BWD cycling is related to inhibitory input from heteronymous muscles or from changes in the intrinsic

487 motoneurone properties remains unknown. Further investigation is required to determine the
488 underlying mechanisms contributing to the observed differences in CSE between FWD and BWD
489 cycling.

490

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495

496 **CO-AUTHOR STATEMENT**

497 All authors have approved this work in its' entirety

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499 **DSICLOSURES**

500 No conflict of interest, either financial or otherwise, are declared by the authors.

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FIGURE LEGENDS

Figure 1. Schematic representing the cycling directions, arm crank positions and corresponding phases of the movement cycle (flexion and extension). Arm crank positions are shown with 6 o'clock representing "bottom dead center" and 12 o'clock representing "top dead center". The phases of the movement cycle are labeled on the diagram with the black arrows representing elbow extension and the white arrows representing elbow flexion. The arrows on the outside of the circle indicate FWD cycling and the arrows on the inside of the circle indicate BWD cycling. The table shows the phases of the movement cycle and corresponding arm crank positions for both FWD and BWD cycling.

Figure 2. (A) Biceps brachii representative examples ($n = 1$) of MEPs at the 6 and 12 o'clock position during FWD and BWD cycling. Average MEP traces during the flexion phase (6 o'clock FWD and 12 o'clock BWD) and during the extension phase (12 o'clock FWD and 6 o'clock BWD). MEPs are shown as a percentage of $M_{\max}$. In this example MEP amplitudes were 19.4 % and 8.6 % for FWD at 6 o'clock and BWD at 12 o'clock, respectively, and 1.5 % and 4.5 % for FWD at 12 o'clock and BWD at 6 o'clock, respectively. **(B)** Biceps brachii representative example ($n = 1$) of CMEPs at the 6 o'clock and 12 o'clock position during FWD and BWD cycling. In this examples CMEP amplitudes were 15.3 % and 6.7 % for FWD at 6 o'clock and BWD at 12 o'clock, respectively, and 1.2 % and 5.8 % for FWD at 12 o'clock and BWD at 6 o'clock, respectively.

Figure 3. (A) Group data (mean $\pm$ SE, $n = 12$) MEP amplitudes as a percentage of $M_{\max}$ of the biceps brachii during FWD and BWD cycling. During FWD cycling at the 6 o'clock and 12 o'clock positions average MEP amplitudes were 19.67% and 1.28% of $M_{\max}$, respectively. During BWD cycling at the 6 o'clock and 12 o'clock position average MEP amplitudes were 5.86% and 8.48% of $M_{\max}$, respectively. **(B)** Average biceps brachii pre-stimulus EMG prior to TMS. Black bars represent BWD cycling and white bars represent FWD cycling. * denote a significant difference ($p < .05$) for cycling direction, while the # denotes a significant difference for position (6 vs 12 o'clock; $p < .05$).

Figure 4. (A) Group data (mean $\pm$ SE, $n = 11$) for CMEP amplitudes as a percentage of $M_{\max}$ of the biceps brachii during FWD and BWD cycling. During FWD cycling at the 6 o'clock and 12 o'clock positions average CMEP amplitudes were 16.90% and 1.78% of $M_{\max}$, respectively. During BWD cycling at the 6 o'clock and 12 o'clock positions average CMEP amplitudes were 5.62% and 7.49%, respectively. **(B)** Average biceps brachii pre-stimulus EMG prior to TMES. Black bars represent BWD cycling and white bars represent FWD cycling. * denotes a significant difference ($p < .05$) for cycling direction, while # denotes a significant difference for position (6 vs 12 o'clock; $p < .05$).

Figure 5. (A) Triceps brachii representative examples ($n = 1$) of MEPs at the 6 and 12 o'clock position during FWD and BWD cycling. Average MEP traces during the flexion phase (6 o'clock FWD and 12 o'clock BWD) and during the extension phase (12 o'clock FWD and 6 o'clock BWD) MEPs are shown as a percentage of $M_{\max}$. In this example MEP amplitudes were 19.9 % and 8.1 % for FWD at 6 o'clock and BWD at 12 o'clock, respectively, and 9.7 % and 8.1 % for FWD at 12 o'clock and BWD at 6 o'clock, respectively. **(B)** Triceps brachii representative example ($n = 1$) of CMEPs at the 6 o'clock and 12 o'clock position during FWD and BWD cycling. In this examples CMEP amplitudes were 21.4% and 13.0 % for FWD at 6 o'clock and BWD at 12 o'clock, respectively, and 3.9 % and 11.3 % for FWD at 12 o'clock and BWD at 6 o'clock, respectively.

Figure 6. (A) Group data (mean $\pm$ SE, $n = 12$) for MEP amplitudes as a percentage of $M_{\max}$ of the triceps brachii during FWD and BWD cycling. During FWD cycling at the 6 o'clock and 12 o'clock positions average MEP amplitudes were 18.01% and 9.87% of $M_{\max}$, respectively. During BWD cycling at the 6 o'clock and 12 o'clock position average MEP amplitudes were 8.31% and 8.84% of $M_{\max}$, respectively. **(B)** Average triceps brachii pre-stimulus EMG prior to TMS. Black bars represent BWD cycling and white bars represent FWD cycling. * denotes a significant difference ($p < .05$) for cycling direction, while the # denotes a significant difference for position (6 vs 12 o'clock; $p < .05$).

Figure 7. (A) Group data (mean $\pm$ SE, $n = 11$) for CMEP amplitudes as a percentage of $M_{\max}$ of the triceps brachii during FWD and BWD cycling. During FWD cycling at the 6 o'clock and 12 o'clock positions average CMEP amplitudes were 20.09% and 5.56% of $M_{\max}$, respectively.

During BWD cycling at the 6 o'clock and 12 o'clock positions average CMEP amplitudes were 10.02 % and 13.99 %, respectively. (B) Average triceps brachii pre-stimulus EMG prior to TMES. Black bars represent BWD cycling and white bars represent FWD cycling. * denotes a significant difference ($p < .05$) for cycling direction, while # denotes a significant difference for position (6 vs 12 o'clock; $p < .05$).

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Figure 1

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