Neuromechanical considerations for the incorporation of rhythmic arm movement in the rehabilitation of walking

By

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B.Kin., McMaster University, 1999
B.Ed., University of Western Ontario, 2002
M.Sc., McMaster University, 2004

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Supervisory Committee

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Abstract

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Evidence suggests that the basic neural elements controlling and coupling the arms and the legs in humans during coordinated rhythmic movements are similar to that observed in quadrupedal animals. Further, it is possible that these interlimb connections may be exploited to assist in locomotor rehabilitation after neurotrauma. Specifically, the effect of arm activity on leg neural circuitry has great implications for walking retraining. However, our understanding of the neuromechanics of rhythmic arm movement as well as the neuronal connections between arms and legs active during rhythmic movement is lacking. Greater knowledge on details of interlimb coupling and combined neural and mechanical measurement of rhythmic arm movement are necessary to optimize parameters of interlimb coupling for use in walking rehabilitation. The primary goals of this thesis were to further our understanding of neural interlimb connections during combined arm and leg rhythmic movement and conduct neuromechanical investigations of rhythmic arm movement.

First, this thesis developed a method for multiple parameter analysis of the Hoffman-reflex recruitment curve. A sigmoid function was found to be a reliable analysis technique that mimics the physiologically based prediction of the input/output relation of the ascending limb of the recruitment curve. This technique provided a baseline for evaluation of neural interactions between the arms and the legs during rhythmic movement and was utilized during following experiments.

Second, the effect of rhythmic leg cycling on reflexes within, and corticospinal projections to, stationary arm muscles was examined. Rhythmic leg cycling significantly suppressed H-reflexes in forearm muscles. Additionally, sub-threshold transcranial magnetic stimulation (TMS) facilitation of H-reflexes was similar during leg cycling as during static contraction suggesting a considerable sub-cortical component. These results supports the hypothesis of a loose, but significant, neural coupling between the arms and the legs during rhythmic movement.

Third, we used a reduced walking model of combined arm and leg cycling to examine the separate and combined effects of rhythmic arm and leg movement on the modulation of lower limb H-reflexes with and without stimulating a nerve innervating the hand. The suppressive effect of arm movement was less than that for leg movement and combined arm and leg rhythmic movement, which were generally equivalent. For H-reflexes conditioned by cutaneous input to the hand, amplitudes during combined arm and leg movement instead were in between those for modulation produced by arm movement and leg movement alone. Further a significant contribution for arm movement was revealed

only in trials when hand stimulation was used to condition H-reflex amplitudes. Therefore a measurable interaction between neural activity regulating arm and leg movement during locomotion is specifically enhanced when cutaneous input from the hand is present.

Fourth, we explored interlimb interactions during a locomotor-like, 3 limb stepping paradigm involving movement of both arms and one leg while eliciting an H-reflex in the stationary test limb. The conditioning effect of contralateral leg movement, bilateral arm movement, and combined bilateral arm and contralateral leg movement on H-reflex amplitude was evaluated at different phases across all tasks. Significant interactions between arm and leg activity could be revealed using the 3-limb paradigm. Further, across phases we observed differential suppressive effects of separate and combined arm and leg movement suggesting phase dependent contributions of arm and leg activity to overall 3-limb suppression. These results support the role of the arms in modulating activity in the legs during human locomotor tasks.

Fifth, the mechanical effects of stimulating a cutaneous nerve innervating the dorsum of the hand during arm cycling were quantified. The results show that mechanical responses to cutaneous stimulation of the hand during arm cycling are related to the task and phase and consistent with the anatomical location of the stimulus (local sign). Therefore, these responses are comparable to functionally relevant responses in the legs during lower limb rhythmic movement. However, unlike the responses in the lower limbs, the mechanical responses cannot be easily described in the neuromechanical context of arm cycling.

Therefore we suggest that the superimposed task constraints and control variable of arm cycling limit the kinematic reflex expression and make it difficult to decipher the true functional role of the reflexes. Overall, these results provide evidence for mechanical correlates to neural responses during arm cycling and further support parallels between the neural regulation of arm and leg rhythmic movement.

Sixth, a combined neural and mechanical measurement approach was used to compare three rhythmic arm movement tasks: arm cycling; arm swing while standing; and arm swing while treadmill walking. The results highlight important neural and mechanical features that distinguish differences between tasks. Overall, differences in neural control between tasks (i.e., pattern of muscle activity) reflected changes in the mechanical constraints unique to each task while the results are consistent with conserved common central motor control mechanisms operational for arm cycling, arm swing while walking, and arm swing alone yet appropriately sculpted to demands unique to each task.

Taken together the data in this thesis suggest that, in addition to understanding details of neural interlimb coupling, mechanical considerations may play an important role in the coordination of locomotor movements. Additionally, the use of rhythmic arm movement as a locomotor adjunct in rehabilitation is revealed through combined neural and mechanical measurement.

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1. General Introduction

Evidence accumulated in humans suggests that the basic neural elements controlling and coupling the arms and the legs during coordinated rhythmic movements are similar to that observed in quadrupedal animals (Dietz, 2002; Duysens & Van de Crommert, 1998; Van de Crommert et al., 1998;. Zehr & Duysens, 2004b; Zehr et al., 2009). It is possible that these interlimb connections may be exploited to assist in locomotor rehabilitation after neurotrauma (Dietz, 2002; Ferris, Huang, & Kao, 2006a; Zehr, 2005). Of specific interest to walking retraining is the effect of arm activity on leg neural circuitry. That is, can movement of the arms be used to assist in lower limb locomotor retraining following stroke or spinal cord injury? There is exciting evidence supporting an active role of the arms in combined arm and leg rhythmic movement. However much work is required to refine our understanding of the neural control of locomotion and mechanisms of interlimb coupling before this information can be properly implemented in rehabilitation. This is, in part, due to the fact that coordinated rhythmic movement of all four limbs, like walking, running and cycling are not simple movements. These tasks require specific neural control signals that precisely activate muscles to produce an appropriate multi-limb coordinated biomechanical output (Duysens & Van de Crommert, 1998). Further, sensory feedback of body movements and physical interactions may result in powerful signals that alter control parameters (Abbas & Full, 2000; Dickinson et al., 2000). Therefore, there is a fundamental, bidirectional coupling between the neural control and the mechanics of rhythmic movement that is difficult to separate. Determining the necessary and sufficient conditions to enhance interlimb coordination during locomotor rehabilitation requires an appreciation of the sublime interaction of neural control and

mechanical action.

The following review of literature will highlight important concepts regarding the utility of rhythmic arm movement in the rehabilitation of walking. First, I will present a basic summary of spinal locomotor control mechanisms in humans and other animals. This will serve as a backdrop to discuss methodological considerations and details on the use of reflexes as neural probes. The focus of the discussion on reflexes will be to the refinement of analysis and interpretation, evidence of rhythmic movement control and functional considerations. Then, evidence of interlimb connections in humans and other animals is presented. Finally, I discuss some important neuromechanical concepts that may contribute to our understanding of rhythmic movement control and interlimb coupling. Throughout this document I attempt to illustrate the importance of mechanical context and measurement as necessary components to functionally define details of neural control.

1.1. Spinal control mechanisms for producing rhythmic locomotor movement

Despite the potential complexity of rhythmic movement direct evidence in lower animals and indirect evidence in humans suggests that there is an elegant organization of specialized neural circuits that simplify the production of rhythmic movement and couple the activity of the limbs. Studies of both humans and animals have shown that neural control principles for rhythmic movement are conserved across species, tasks and limbs (Dietz, 2002; Dietz, 2003; Duysens & Van de Crommert, 1998; Zehr, 2005; Zehr et al.,

2009). The following discussion is a brief summary of the spinal neural control of movement.

Our understanding of rhythmic movement control originates from direct intracellular recordings in both invertebrates and vertebrate models (Dietz, 2002; Dietz, 2003; Grillner & Wallen, 1985; Grillner, 1985; Marder & Rehm, 2005; Pearson, 1993). For example, deafferented and decerebrate preparations in the cat have been used extensively to provide information on the locus of rhythmic movement control (Grillner & Wallen, 1985). In 1911, Brown first observed rhythmic ankle movements in a deafferented spinalized cat preparation. From this observation Brown proposed an abstract model of a spinal circuit controlling rhythmic movement called a "half centre" model (T. G. Brown, 1911). This model had equal halves controlling flexors and extensors with mutual inhibitory interneuronal connections that could produce rhythmic flexion and extension without afferent feedback or supraspinal input. Later, a more complex model was put forward called a central pattern generator (CPG) (Grillner & Zangger, 1975; Grillner, 1975). The CPG coined by Grillner (1975) consisted of a group of spinal neurons that produced locomotor activity for each limb segment while reciprocal phasic activity of all limb segments was produced through coordinated interneuronal connections. Grillner (1985), expanded his model of the CPG to include interconnected subunits for the control of each limb segment called "unit burst generators". The unit burst generators could produce bursting activity for each limb segment and different combinations of active subunits could produce different behaviours (Grillner & Wallen, 1985). The newest incarnation of the CPG model includes three levels, one for the rhythm generator, one for pattern formation and one for sensory

feedback (Lafreniere-Roula & McCrea, 2005; McCrea & Rybak, 2007; McCrea & Rybak, 2008; Rybak et al., 2006).

Ultimately, accumulating evidence suggests that the fine control of rhythmic movement in humans and other animals is the responsibility of three parts of the nervous system and their interaction to produce the rhythm and pattern necessary to generate a robust compliment of movements (E. P. Zehr & Chua, 2000). The three basic components are supraspinal (considered to have a regulatory role), spinal (CPGs, interneurons and motoneurons), and afferent feedback (from muscle, joint, and skin receptors). In principle this model suggests that the timing of tasks can be commonly set at a core level by CPGs (Figure 1-1). Then, sculpting of motor output occurs when information (via afferent feedback) on local mechanical conditions influences interneurons that regulate excitability of specific motoneuronal pools. Afferent feedback can exert influence directly upon motoneuronal pools, neurons mediating reflexes, and through neuronal networks associated with the CPG. For example, sensory information from hip afferents can initiate, alter the tempo, and halt gait (Dobkin et al., 1995; Grillner & Rossignol, 1978; Knikou & Rymer, 2002; Lam & Pearson, 2001; McVea et al., 2005; Pang & Yang, 2000; Steldt & Schmit, 2004; Whelan et al., 1995). Within this framework, appropriate shaping of rhythmic movement requires the interaction of CPG, supraspinal input and sensory feedback as these sources of input can powerfully modulate the locomotor pattern.

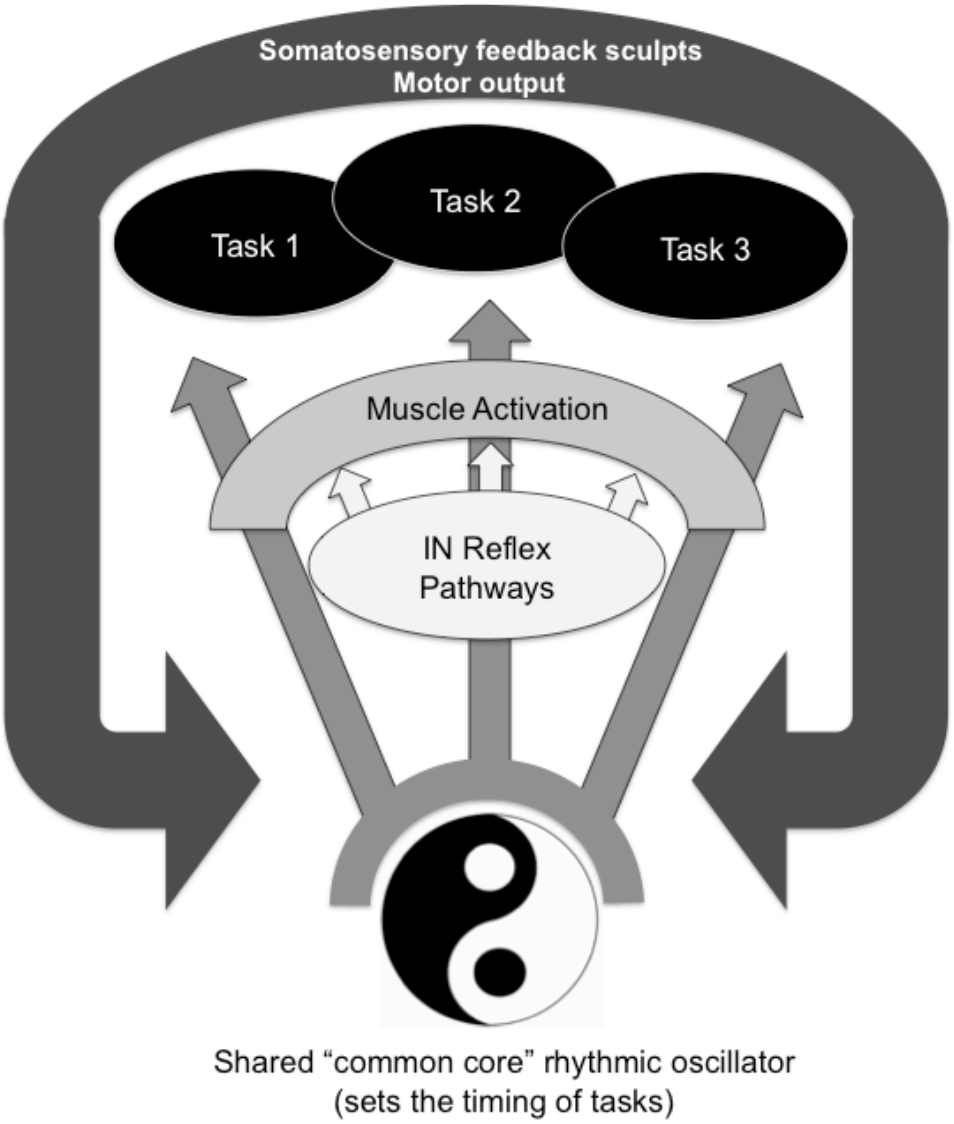

Figure 1-1 General conceptual overview for the regulation of rhythmic human movement. Note that the effect of feedback projects to the motoneuronal pools, interneuronal pathways (IN), and the CPG (yin-yang) itself and is subsumed in the output of the shared common oscillator. The effect of supraspinal input is taken as regulatory but is not shown. Adapted from Zehr 2005

1.2. Evidence of spinal rhythmic movement control in humans

Indirect evidence of spinal locomotor centres in humans comes from observations in spinal cord injured individuals (SCI), healthy adults and infants. For, example, in human SCI, stimulation of flexor reflex afferents produce rhythmic muscle activations that are similar to L-Dopa networks observed in spinalized cats proposed to be part of spinal locomotor centres (Roby-Brami & Bussel, 1987; Roby-Brami & Bussel, 1990; Roby-Brami & Bussel, 1992). Also, tonic electrical spinal cord stimulation in complete SCI results in rhythmic muscle activity and corresponding leg movements. (Dimitrijevic et al., 1998; Gerasimenko et al., 2002). The spinal control of rhythmic movement is further supported in awake SCI subjects by rhythmic muscle activity spontaneously occurring or induced by treadmill training (Dietz et al., 1994; Dobkin et al., 1995; Harkema et al., 1997; Kuhn, 1950). The implications of the above results are that limited or no transmission of suprapinal input is available in SCI subjects below the level of injury. Therefore the locomotor-like movements observed in these experiments must be triggered from a spinal or peripheral locus. Comparable data in intact subjects can be seen early in development where human infants display a clear locomotor-like stepping response despite having an underdeveloped corticospinal tract (Duysens & Van de Crommert, 1998; Yang et al., 1998). Additionally, sleep related periodic leg movements, observed in SCI subjects and neurologically intact individuals have been related to release of inhibition of spinal locomotor centres during sleep (Coleman et al., 1980; Lee et al., 1996). Another observable phenomenon that strongly supports the spinal control of rhythmic movement in intact subjects was seen with the application of tonic vibration

during simulated weightlessness, which induced alternating flexor and extensor leg muscle activity (Gurfinkel et al., 1998). Overall, parallel observations in intact and SCI subjects provide accumulating evidence of a spinal control of rhythmic movement. Furthermore, detailed investigations of control mechanisms are conducted in studies focusing on observations of changes in kinematics, muscle activity and reflex modulation during rhythmic movement (Duysens & Van de Crommert, 1998).

1.3. A note on methods: Using reflex inputs as neural probes during rhythmic movement

While there are many indirect approaches to study the neural control of rhythmic movement in humans, one of the most accessible methods is the use of reflexes as neural probes (Burke, 1999). That is, experimental investigation of reflex modulation during rhythmic movement can be used to infer the existence of neural interactions and circuitry that must exist to allow such changes (Misiaszek, 2003). Further, this indirect evidence can be compared to analogous observations in animal models, which could support conserved neural control across species. Prominent reflexes used in studies of rhythmic movement control and interlimb coupling include the non-nociceptive cutaneous and H-reflex. Each reflex results from the activation of distinctive pathways and therefore can present different insight into mechanisms of neural control (Brooke et al., 1997; Burke, 1999; E. P. Zehr, 2006). Details of their methodology, administration and interpretation have been presented elsewhere (Brinkworth et al., 2007; Brooke et al., 1997; Burke, 1999; Hugon M., 1973; Misiaszek, 2003; Schieppati, 1987; Tucker et al., 2005; Zehr, 2002). Below I will briefly present details of the pathways and analysis of the Hoffmann and cutaneous reflex.

1.3.1. Hoffmann Reflex

The H-reflex occurs when percutaneous electrical stimulation is delivered to a peripheral nerve containing both motor and sensory axons. At relatively low intensities Ia afferents are excited before smaller diameter motor axons (Zehr, 2002). This results in the transmission of action potentials along the Ia afferent pathway from the point of stimulation to the spinal cord where Ia afferents connect monosynaptically onto alpha-motoneurons. Depending on the excitation level of the alpha-motoneuronal pool, synaptic transmission from Ia afferents results in a compound firing of activated motoneurons and the muscle fibres that they innervate. This reflex activation (H-reflex) can be viewed in the electromyography (EMG) at monosynaptic latencies related to the target muscle. That is, the latency of the responses is related to the physical length of the neural circuitry, which is generally longer in the legs than in the arms. At higher stimulation intensities smaller diameter motor fibres are also recruited. This results in antidromic and orthodromic transmission along the motor neurons. Orthodromic activation results in synchronous firing of innervated muscle fibres measured in the electromyogram at short latencies related to the length of the motor axon from the site of stimulation to the muscle (M-wave). Antidromic transmission along the motor axon will travel from the site of stimulation to the alpha-motoneuron cell body and may “collide” with the orthodromic activation along the H-reflex pathway thereby reducing the amplitude of the H-reflex at high stimulus intensities.

There are two accepted protocols for using the H-reflex in studies of motor control. The first is to choose a constant test reflex that is on the ascending limb of the H-reflex input-output curve and occurs alongside a small M-wave (Zehr, 2002). There are a few

considerations that must be attended to when using this protocol. First, the small M-wave, as a physiological measure of stimulus input, should be consistent at the same level of stimulus yet remain sensitive to any changes to the stimulus intensity. Also a maximal M-wave should be recorded to allow proper amplitude normalization. However, there is still debate as to whether a maximal M-wave should be collected at various times throughout an experiment to allow proper time-dependent normalization of the test reflex (Crone et al., 1999; Ferris et al., 2001; Frigon et al., 2007; Simonsen & Dyhre-Poulsen, 1999). Additionally it is well known that the size of the test reflex is related to its susceptibility to inhibitory and excitatory influence (Crone et al., 1990). That is, at threshold levels of reflex excitation, the reflex can increase in amplitude due to an excitatory input yet an inhibitory input will only reduce the response to zero. Therefore, the magnitude of the inhibition cannot be properly determined. Also, at maximum levels of reflex output an excitation may not be able to increase the reflex amplitude beyond its physiological maximum. Therefore, if a single test reflex is used it should be chosen at approximately 50% up the ascending limb of the H-reflex input/output curve (Crone et al., 1990). Also, during the experimental session it is common practice to record a number of test reflexes and average the responses. This procedure requires an experimenter to monitor the size of the M-wave and periodically alter the stimulus setting to maintain an M-wave that is the same size throughout the entire experiment. The second H-reflex protocol is to produce an H-reflex recruitment curve. The methodology of a recruitment curve (RC) involves varying the level of electrical stimulation and measuring the peak-to-peak amplitudes of the M-wave and the H-reflex. The responses of these waveforms to changes in intensity of stimulation define the input/output relation of the H-reflex pathway, which is

highlighted by specific parameters of interest that can be used for experimental comparison. Specifically, the ascending limb of the H-reflex RC is isolated, and parameters such as the threshold of the response (HTH), the maximum reflex response (HMAX) and the slope of the ascending limb (HSLP) are used to represent alterations in the H-reflex input/output function. Experimental protocols may differentially affect one or all of these parameters, and therefore it is often beneficial to acquire many measures of H-reflex excitability.

Generally, there are two accepted methods of presentation of the H-reflex recruitment curve. The H-reflex and M-wave amplitudes can be graphed alongside the corresponding stimulus amplitude (current or integrated current) measured using a current monitor. The developed plots are called H-reflex/current recruitment curve (HCRC) and M-wave/current recruitment curve (MCRC) and this is the suggested method of presentation if a current monitor is available. However, if a current monitor is not available an alternative method of presentation is to plot the H-waves as a function of the size of the concurrent M-wave, this plot is called an H-reflex/M-wave recruitment curve (HMRC). There has yet to be a comparison between these two presentation methodologies with respect to changes in parameters of interest.

Another aspect of the H-reflex recruitment curve that requires further study is the determination of a function that can approximate the ascending limb. However, this requires physiological and methodological consideration. It has been assumed that the ascending limb follows a linear response (Funase et al. 1996; Funase et al. 1994). Funase et al. (1994a) chose to use linear regression to analyze the ascending limb of the H-reflex recruitment curve. However, it has been suggested that the rate of recruitment of alpha

motor neurons may follow an exponential function (Fuglevand et al., 1993; Jones, 2005). Therefore, it is necessary to determine a mathematical analysis technique to properly approximate the experimental data. The use of linear regression to analyze the ascending limb of the recruitment curve is a currently accepted method. However, linear regression has never been tested against other mathematical analysis techniques such as a recently presented polynomial technique (Christie et al., 2004) to determine its validity.

Determining a fitting technique for the ascending limb of the H-reflex recruitment curve requires an appreciation of the physiological response of the input/output relation. As such, the ascending limb of the H-reflex RC has been described as sigmoidal by many researchers (Christie et al., 2004; Hoehler & Buerger, 1981; Slot & Sinkjaer, 1994; Stein et al., 2007; Wilmink et al., 1996). Further, there is sufficient evidence to consider that the ascending limb of the HCRC and HMRC follows a sigmoid function. First, there is assumed to be an exponential distribution of recruitment thresholds across the motoneuronal pool resulting from a large proportion of low threshold motor units with exponentially diminishing number of high threshold units (Fuglevand et al., 1993; Jones, 2005). As the stimulus to elicit an H-reflex increases there is an exponential response noticed at the foot of the curve. Also, a logarithmic decrease in the ascending limb near the peak of the curve is noticed as antidromic volleys along the motor axons collide with orthodromic volleys blunting the exponential rise (Funase et al., 1994; Pierrot-Deseilligny et al., 2005; Stein et al., 2007). A sigmoid function has been a reliable and justified fit of the input/output relation of the corticospinal pathway of arm and leg muscles measured in EMG evoked by transcranial magnetic stimulation (Carroll et al., 2001; Devanne et al., 1997). Additionally, other sigmoidal input-output relations are

shown in the compound action potential of nerves and monosynaptic reflexes of the cat spinal cord (Erlanger & Gasser, 1937; Rall, 1955a; Rall, 1955b).

Evoking and analyzing the H-reflex requires awareness of many physiological and technical assumptions (Brooke et al., 1997; Hugon M., 1973; Misiaszek, 2003; Schieppati, 1987; Zehr, 2002). In fact, changes in the amplitude of the reflex can be explained by at least three possibilities. First, the reflex is sensitive to alterations in motoneuron excitability. Therefore changes in local musculature such as length, movement and background excitability can alter the reflex response. Maintaining a constant low level (≈ 10% maximum voluntary contraction) of muscle activity is necessary to help rule out instability in motoneuronal pool excitability as a confounding influence on the H-reflex amplitude (Misiaszek, 2003; Zehr, 2002). However, while this procedure ensures a constant level of alpha-motoneuronal pool excitability it also may introduce recurrent inhibition through cortical activation of Renshaw cells (Zehr, 2002). Also, bracing the test limb is a way to minimize the effect of movement on H-reflex modulation (Brooke et al., 1997; Misiaszek, 2003). While this is difficult during studies of multi-limb rhythmic movement and interlimb coupling, a possible experimental paradigm is to maintain a stationary test limb while measuring the contribution of the other freely moving limbs to reflex modulation. However due to the mechanical novelty of a task requiring multi-limb movement while one limb remains stationary, it is important to consider the change in behavioural context before extrapolation of findings to other tasks such as walking. A second method that can alter the size of the H-reflex is by variation in the amount of neurotransmitter released by the afferent terminals. Ia presynaptic inhibition (PSI) is produced by the action of an inhibitory interneuron that

acts to reduce neurotransmitter release by Ia afferent terminals onto motoneurons (Misiaszek, 2003; Zehr, 2002). This highly selective mechanism diminishes the effect of Ia afferents onto motoneurons while the postsynaptic membrane potential is unaffected and remains receptive to other inputs (Zehr, 2002). Ia PSI of the H-reflex pathway can occur due to activation of homonymous and heteronymous muscle afferents, spinal locomotor centres and supraspinal input (Brooke et al., 1997; Misiaszek, 2003; Stein, 1995; Zehr, 2002). A third source of H-reflex modulation is variation in the intrinsic properties of the motoneurons (Misiaszek, 2003). Long-term changes in the motoneuron as a result of plastic adaptation following training regimes can affect the amplitude of the H-reflex (Gardiner et al., 2005; Misiaszek, 2003). Therefore it is important to take note of this when comparing H-reflex responses across populations of individuals who have undergone training or whose nervous systems have undergone plastic changes due to injury (Misiaszek, 2003). Additionally, short-term changes in neuromodulators, such as serotonin, which are capable of altering the firing properties of motoneurons can effectively alter the size of the H-reflex.

1.3.2. Cutaneous Reflex

A cutaneous reflex is elicited by stimulating a sensory nerve innervating a cutaneous skin field at noxious or non-noxious levels and measuring the summed response in the EMG, kinematics and kinetics (Brooke et al., 1997; Duysens & Van de Crommert, 1998; E. P. Zehr, 2006). In general, during studies of rhythmic movement and interlimb coupling in humans stimulation is set at an intensity to evoke tactile sensations in the skin covering the hands and the feet at non-noxious levels. These sensations are induced by activation of afferents innervating Pacinian and Meissners corpuscles, Ruffini endings and Merkel

discs (Zehr, 2006). The cutaneous reflex pathway is a polysynaptic pathway containing an unknown number of excitatory and inhibitory interneurons between the first order afferent terminals and the motoneurons (Zehr, 2006). Therefore there is great potential for sites of reflex modulation. Cutaneous reflexes produce responses at different latencies representing potentially different sources of input. For example, early latency (50-70ms post stimulus) responses are considered either purely spinal or part of a transcortical loop without voluntary influence (Brooke et al., 1997). Middle latency (70-120) responses may contain some supraspinal influence and late latency (>120ms) responses can contain great supraspinal influence and potential voluntary input (Brooke et al., 1997).

The analysis of cutaneous reflexes requires averaging and low pass filtering ("smoothing") full wave rectified, integrated responses taken over a few trials of stimulus because the responses in the EMG are less synchronized than the H-reflex (Brooke et al., 1997). The averaged waveforms are subtracted from control background muscle activity occurring at the same phase of the movement to obtain a reflex amplitude in the EMG solely due to the stimulation (Brooke et al., 1997). Then the peak amplitudes of the "subtracted" EMG are analyzed at specific time intervals relating to early, middle and late latencies for both inhibitory and excitatory responses (Zehr et al., 1997). Additionally, the average cumulative reflex activity occurring 150 ms post stimulation ($ACRE_{150}$) can be evaluated as a "net reflex" response. Determining the net reflex involves calculating a subtracted reflex then cumulatively summing the signal of positive (excitation) and negative (inhibition) deflections. The summed value is then divided by the time interval of integration to measure an overall reflex effect. The net reflex was developed to represent the mechanical correlate of the reflex response (Zehr et al., 1997).

This is due to the fact that the kinematics correlated to cutaneous reflexes are a filtered output of the motor system and a result of additive suppression and facilitation at different latencies (Zehr et al., 1997). While taking the average response across latencies may lose specific details that may be neurophysiologically important the net reflex is more representative of the mechanical output (Brooke et al., 1997; Zehr et al., 1997). Additionally, the time chosen for cumulative summations (150ms) is preceding potential influence from voluntary activation. As such, this approach is well correlated with kinematic responses in the lower limbs (Zehr et al., 1997).

1.4. Evidence of the neural control of rhythmic movement in human reflex studies

In non-moving conditions reflex amplitudes correspond to "automatic gain compensation" which means that a reflex response will scale with the level of background activity (Matthews, 1986). This is due to central motor drive and alterations in motoneuronal pool excitability (Matthews, 1986). However, reflexes during locomotor movements do not always conform to automatic gain compensation suggesting that there is another source of reflex modulation, which is somewhat independent of motoneuronal pool excitability. When comparing reflexes during static non-moving conditions to rhythmic movements the responses are related to the task being performed (task dependent) and the phase of the movement (phase dependent). For example, there are task dependent amplitude changes in the level of soleus H-reflex excitability when comparing running, walking and standing at equivalent levels of background EMG (Capaday & Stein, 1987; Ferris et al., 2001; Simonsen & Dyhre-Poulsen, 1999). Ferris et al. (2001), showed that under simulated gravity the gain of the H-reflex amplitude was

unchanged during different locomotor conditions while the threshold was altered from walking to running. Further, the threshold of the H-reflex was altered without a concurrent change in background muscle activity supporting a pre-synaptic mechanism responsible for the suppression (Ferris et al., 2001). This mechanism could be phase-related afferent signals or central influences such as a CPG (Brooke et al., 1997; Brooke et al., 1999; Duysens et al., 1995). A beneficial paradigm for testing the effect of locomotor activity on changes in the H-reflex is leg cycling. Due to the constrained movement path and decreased reliance on postural stability this task can provide greater control over movement parameters than walking. Results using this paradigm have demonstrated a distinctive pattern of soleus H-reflex modulation during active and passive movement of the ipsilateral and contralateral leg (Brooke et al., 1992; Collins et al., 1993; McIlroy et al., 1992). These observations have provided a basis for understanding the locus of rhythmic movement related changes in H-reflex modulation. For example, during passive leg cycling, where background muscle activity is relatively silent, there is phase dependent suppression of the ipsilateral soleus H-reflex suggesting that afferent signals related to movement position can alter the size of the H-reflex (Brooke et al., 1997). However, leg muscle reflexes during contralateral passive leg cycling were suppressed without phase modulation (Cheng et al., 1998). The authors suggested that this could result from spinal interneuronal processing more than an effect of inhibition due to afferent inflow (Brooke et al., 1997; Cheng et al., 1998). While studies during leg cycling suggest that both central and peripheral sources are responsible for H-reflex suppression cutaneous reflexes during rhythmic movement have been shown to be unrelated to the ongoing muscle activity or movement induced afferent feedback

(Brooke et al., 1999; Brown & Kukulka, 1993; Duysens et al., 1993; Tax et al., 1995). Brooke et al. (1999), observed that cutaneous reflexes elicited in a passively moved leg were not phase dependently modulated, as is seen during active leg cycling. The authors suggested that this was evidence of a potential spinal regulation of rhythmic leg movement (Brooke et al., 1999). Additionally, there is widespread phase dependent modulation of cutaneous reflexes in many leg muscles during walking and leg cycling which is thought to arise from the activity of spinal central pattern generating networks (Balter & Zehr, 2007; Brown & Kukulka, 1993; Duysens et al., 1995; Duysens et al., 1996; Zehr et al., 1997; Zehr & Duysens, 2004). Duysens et al. (1996) observed phase dependent cutaneous reflex reversals when comparing forward and backward walking. The authors' explanation for this behaviour was a central program that regulates transmission through cutaneous pathways in a "forward" and "reverse" direction during forward and backwards walking respectively. Further, they suggested that support for this ascertain is due to similar phase dependent modulations in cutaneous reflexes during rhythmic movement in paralyzed and intact cats (Andersson et al., 1978; Duysens et al., 1996; LaBella et al., 1992; Schmidt et al., 1989; Schomburg et al., 1977; Schomburg et al., 1978; Schomburg et al., 1998). Comparable observations of task and phase dependent reflex responses are found in upper limb muscles in rhythmical arm swing during walking as well as arm cycling (Zehr & Chua, 2000a; Zehr & Kido, 2001; Zehr & Haridas, 2003). Zehr and Kido (2001), observed significant task and phase dependent modulation of cutaneous reflexes during arm cycling when compared to static conditions. This observation was similar to a later study that found task and phase dependent modulation of the flexor carpi radialis H-reflex during arm cycling (Zehr et al., 2003).

Parallel responses for both the arms and the legs are suggestive of similar neural regulation of rhythmic movements (Zehr & Duysens, 2004).

Overall, examinations of both the cutaneous and H-reflex during rhythmic movement in humans have provided great insight into neural control mechanisms during locomotor activities. Despite different sensitivity to modulating sources, each probe displays task and phase dependent responses when comparing static conditions to rhythmic movement. This evidence supports conserved neural control between species and the arms and legs in humans.

1.5. Neural and mechanical evidence of quadrupedal interlimb coupling in humans and other animals

During human walking one leg must be supporting the body in stance at any given time while the other limb moves forward through the swing phase to facilitate forward progression. Without this proper coordination an individual could not move forward or maintain balance during gait. Subsequently, this fundamental interlimb coordination is an inherent property of human neural circuitry as evident in studies of reflex responses during rhythmic movement. For example, both active and passive movement of the contraleratal leg substantially inhibits the ipsilateral soleus H-reflex (Cheng et al., 1998; Collins et al., 1993; McIlroy et al., 1992; Misiaszek et al., 1998). Also, during walking, running and leg cycling, cutaneous reflexes are observed in both the contralateral and ipsilateral limb (Brown & Kukulka, 1993; Duysens et al., 1992; Tax et al., 1995). Additionally Ting et al. (1998), observed that the muscle activity and force generated by a leg during unilateral cycling was dependent on the activity and sensory state of the

other limb. This was demonstrated even though the forces experienced during unilateral cycling were matched to bilateral cycling conditions (Ting et al., 1998). Accordingly, experiments using split belt treadmills, in adults and infants, have shown that the legs maintain coordination and postural stability with belts running at different speeds (Dietz et al., 1994; Erni & Dietz, 2001; Prokop et al., 1995; Thelen et al., 1987). Together, the above studies confirm a strong bilateral coupling of the legs necessary for proper locomotion. Comparable studies of arm to arm coupling conducted during rhythmic arm movement have revealed distinct findings to the legs consistent with their minor role in postural stability and forward progression (Carroll et al., 2005; Umberger, 2008; Zehr & Duysens, 2004b). Carroll et al. (2005), observed that cutaneous reflex modulation in the arms during cycling movements are unaffected by the activity of the contralateral arm. Further, they suggested that while there was evidence of a similar central regulation of rhythmic arm and leg movement the coupling between the arms was weaker than that noticed in the legs. This conclusion is supported by earlier observations of Zehr et al. (2003) who found that active contralateral arm movement inhibited the ipsilateral forearm H-reflex in a stationary limb while passive movement of the contraleral limb did not (Zehr et al., 2003). Overall, the combined results comparing bilateral responses support a measureable neural coupling between the limb pairs and suggest that the strength of the neural coupling between the legs is relatively greater than for the arms (Dietz, 2002; Zehr & Duysens, 2004; Zehr et al. 2004; Zehr, 2005). This has been, in part, attributed to the crucial coupling between the legs for successful locomotion and the specialized use of the arms for skilled hand movements (Dietz, 2002; Zehr & Duysens, 2004).

1.6. Quadrupedal mechanisms for locomotor coupling in humans and other animals

Quadrupedal locomotion necessitates the coordination of all limbs to successfully move through the environment and assist in appropriate multi-limb responses to disturbances. As such, experiments in the quadrupedal cat, rat and rabbit have revealed a coordinated coupling between pattern generating circuits in the cervical and lumbar spinal cord mediated through propriospinal neuronal connections (Ballion et al., 2001; Gernandt & Gilman, 1961; Gernandt & Megirian, 1961; Gernandt & Shimamura, 1961; Juvin et al., 2005; Miller et al., 1973; Miller et al., 1973; Miller et al., 1975; Skinner et al., 1980; Viala & Vidal, 1978b; Zaporozhets et al., 2006). Observations in the quadruped mimic more recent evidence in humans supporting the existence of conserved quadrupedal interlimb coupling across species (Zehr et al. 2009, Dietz et al. 2002). For example, Miller et al. (1975), observed coordinated coupling of the forelimbs and hind-limbs of intact and decerebrate cats while stepping over ground, stepping on a treadmill and swimming (Miller et al., 1975). This is consistent with observations in humans during walking, creeping and swimming where the frequency relationship between the arms and the legs are conserved suggestive of two coupled oscillators; one for the arms and one for the legs (Wannier et al., 2001). Additionally, phase dependent modulation of reflexes was observed in hind-limb muscles following stimulation of the forelimb in decerebrate and high spinal paralyzed cats (Miller et al., 1977; Schomburg et al., 1977). Accordingly, stimulation of cutaneous nerves in the hand and foot, in humans, result in responses in leg and arm muscles, respectively, during different locomotor activities

(Balter & Zehr, 2007; Haridas & Zehr, 2003; Sakamoto et al., 2006) Further, neuroanatomical evidence of propriospinal connections in humans has also been found (Nathan & Smith, 1955; Nathan et al., 1996).

Zehr et al. 2001 demonstrated widespread interlimb reflex responses to cutaneous stimulation of the hand and foot in static, non-moving muscles (Zehr et al., 2001). Also, changes in reflexes in the arms and legs are also noticed after stimulation of the median and sural nerves (Delwaide & Crenna, 1984; Kearney & Chan, 1979). Similiar evidence of interlimb coupling was also found following spinal cord injury in man (Calancie, 1991; Calancie et al., 1996). The results from both intact and SCI individuals occur at a latency sufficient to suggest propriospinal mediated interlimb connections in humans (Calancie, 1991; Calancie et al., 1996; Zehr et al., 2001). Zehr et al. (2001), suggested that these interlimb reflex pathways could be important for relaying afferent information for the coordination of all limbs during movement. Further, the presence of these pathways supports the potential for conserved quadrupedal locomotor mechanisms in humans (Dietz, 2002; Dietz, 2003; Zehr et al., 2009).

While not as apparent in the bipedal human, quadrupedal interlimb coupling can be observed in the natural movement of the arms (arm swing) that occurs during gait. In an early investigation of armswing during walking, Elftman (1939), calculated the muscle torque of the arms during gait and concluded that they were not a passive pendular action but required active muscle contractions (Elftman, 1939). Hogue (1968), and Fernandez Ballesteros (1965), corroborated this finding that arm muscle activity is necessary for arm swing during walking (Ballesteros et al., 1965; Hogue, 1969). Further Fernandez Ballesteros et al. (1965), observed that arm muscles were rhythmically active even while

mechanically restrained during walking (Ballesteros et al., 1965). Therefore, arm swing during walking likely arises through an active component interacting with the passive motion of the limb generated interaction torques as a result of leg movement. The active and passive components are likely necessary to control the limbs to produce smooth locomotion (Jackson, 1983). However, while there is strong support for an active neural component, the passive pendular movement of the arms made it difficult to partition neural from mechanical interactions and a functional examination of the benefits of arm swing during walking was necessary (Webb et al., 1994). Knowledge of these functions may be valuable to the understanding of the underlying interlimb neural coupling.

Elftman (1939), first proposed that armswing during walking is necessary to counteract pelvic rotation. Further, Hinrichs (1990), demonstrated that during running the movement of the arms is important for transfer of angular momentum between the upper and lower body through the vertical axis (Hinrichs, 1990). In a later comprehensive kinetic analysis of walking with and without arm swing, Li et al. (2001), observed very little effect of suppressing arm swing on vertical or sagittal contact forces. Further they suggested that the influence of arm swing on the kinetics of gait must be the effects on transverse forces and/or free vertical moments (Li et al., 2001). Li et al. (2001), demonstrated that during walking the stance foot produces a vertical moment that is largest just before heel strike of the opposite foot. When arm swing is restricted this free vertical moment produced is much larger to compensate for the loss of the arm swing moment to counterbalance the lower limb swing (Li et al., 2001). It is interesting to note that a higher free vertical moment when arm movement is restrained is well demonstrated in males but subtle in females perhaps relating to differences in walking strategies or

mechanics (Li et al., 2001). In a similar experiment Umberger (2008), observed only small differences between kinematics and kinetics when walking with or without arm swing. The main exception was larger differences in free vertical moments. Additionally, walking with arm swing was more energy efficient than walking without arm swing (Umberger, 2008).

Recent evidence suggests that arm activity can modulate overt leg muscle activity during locomotor movements. Huang and Ferris (2004), found that when subjects actively used their arms to move their legs passively on a recumbent leg stepping device there was increased lower limb muscle activation. Further, this was not seen when the legs were externally passively driven yet remained when the arms were active and mechanically uncoupled from the legs (Huang & Ferris, 2004). Using the same arm and leg stepping device Kao and Ferris (2005), found that increased movement frequency enhanced the lower limb activation induced by arm activity. These results support spinal interlimb connections mediated through propriospinal neural circuitry (Dietz, 2002; Kao & Ferris, 2005). While this evidence supports a general active role of the arms during locomotor activities, specific details of arm to leg coupling have been gleaned using reflex studies.

Studies have used passive flexion/extension of the elbow, arm swing, and variations in static arm postures and observed altered reflexes in stationary leg muscles (Delwaide et al., 1973; Delwaide et al., 1977; Eke-Okoro, 1994; Hiraoka & Nagata, 1999; Hiraoka, 2001; Hiraoka & Iwata, 2006). The results from these studies suggest that afferent feedback from the arms can induce changes in lower limb reflex excitability. However, a series of experiments studying the effect of altering parameters of rhythmic

arm cycling on reflexes in stationary legs has demonstrated a potentially sparse role of afferent feedback relating to arm cycling in effecting lower limb reflexes (de Ruiter et al., 2010; Frigon et al., 2004; Hundza & Zehr, 2007; Hundza & Zehr, 2009; Loadman & Zehr, 2007). Frigon et al. (2004), observed that rhythmic arm cycling suppressed soleus H-reflex amplitudes in stationary legs. This suppression was associated with presynaptic inhibition and related to neural networks coupling the cervical and lumbar spinal cord. Further, Loadman et al. (2007), observed a general non-specific suppression of the soleus H-reflex due to rhythmic arm cycling that was only altered with changes in the frequency of arm cycling and unaffected by range of motion. Hundza et al. (2009), performed a more comprehensive examination of the effect of frequency of arm cycling on soleus H-reflex suppression. The authors found that there was an inverse linear relation between H-reflex amplitude and frequency of arm cycling. Recently, de Ruiter et al. (2010), observed phase dependent suppression of soleus H-reflexes during arm cycling. This suppression was greatest during bilateral arm cycling, evident during ipsilateral and contralateral arm cycling and not seen during static postures. Overall, arm cycling on an upper limb ergometer produces a phase dependent effect on lower limb reflexes that is unaffected by load, range of motion, and muscle vibration, yet responsive to changes in frequency of movement. Further, the combined results using an arm cycling paradigm are suggestive of a central rather than peripheral locus responsible for arm movement induced modulation of H-reflex amplitudes (Hundza & Zehr, 2009). This is supported by Carroll et al. (2006), who observed that the excitability of corticospinal cells projecting to motoneurons of arm muscles are lower during rhythmic arm movement that during static contraction. This was assumed to be a shift from cortical to subcortical control of

movement of the arms (Carroll et al., 2006). Further, taken together with the data on arm cycling induced changes in lower limb reflex excitability, this could support a suppression of lower limb reflexes induced by arm locomotor CPGs. However, modifications in the excitability of corticospinal projections to arm or leg muscles during the rhythmic activity of the other limb pair has yet to be studied. This could assist in determining the role of the arms and legs during locomotor coupling.

In quadrupeds, there is a bidirectional coupling between lumbar and cervical spinal locomotor centres (Akay et al., 2006; Ballion et al., 2001; Gernandt & Megirian, 1961; Juvin et al., 2005; Skinner et al., 1980). Evidence suggests that the directional strength of the coupling is greater from lumbar to cervical (ascending) (Juvin et al., 2005; Viala & Vidal, 1978a). For example, while both caudorostral and rostrocaudal entrainment exists, Juvin et al. (2005), observed that locomotor CPGs are asymmetrically coupled via propriospinal connections in an ascending lumbar to cervical gradient (Ballion et al., 2001, Juvin et al., 2005). That is, rhythmically active lumbar generators are capable of entraining cervical generators but not vice versa (Juvin et al. 2005). However, it has been demonstrated that forelimb stepping frequency entrained the hindlimb stepping frequency in decerebrate cats walking on separate forelimb and hindlimb treadmills (Akay et al., 2006). Further, the authors suggest that this result is consistent to the observations of Juvin et al. in that there is an inhibitory descending signal and an excitatory ascending connection (Akay et al., 2006). The ascending excitatory pathway links the hind leg pattern-generating network to the ipsilateral fore leg pattern-generating network (Akay et al., 2006). While details of the contributions of the fore-limb and hind-limb to locomotor coupling in quadrupeds are accumulating,

discrepancies exist between experiments on arm and leg coupling in humans. For example, in a combined arm and leg cycling task Sakamoto et al. (2006), found that cutaneous reflexes in arm and leg muscles evoked by either superficial peroneal (SP) or superficial radial (SR) nerve stimulation were not affected by the movement of the other limb pair. They suggest that the modulation of cutaneous reflexes in each limb is related to the functional state of the limb where the response occurs; similar to what is observed during rhythmic arm or leg movement alone (Carroll et al., 2005; Tax et al., 1995). In contrast, using a similar arm and leg cycling paradigm, with electrical stimulation of the cutaneous SP nerve, Balter and Zehr (2007), observed different contributions of arm and leg movement to reflex expression in the legs. Differing results between this study and Sakamoto et al. were potentially related to differences in the mechanical coupling of the device used as well as a more sophisticated statistical analysis conducted by Balter and Zehr (2007). Also, Donker et al. (2002), observed changes in walking after adding mass to the wrist or ankle. Adding a mass to the wrist during walking resulted in increased muscle activity in both arms and a decrease in the movement amplitude in only the loaded limb. Adding load to an ankle, however, produced increased muscle activity and movement in both arms (Donker et al., 2002). Also both mechanical perturbation and tibial nerve stimulation produced bilateral reflexes in arm muscles (Dietz et al., 2001). Additionally, in a recent experiment, Sakamoto et al. (2007), observed that in a combined arm and leg cycling task using mechanically uncoupled ergometers, arm cycling cadence was modified by changes in leg cycling cadence. However, changes in arm cycling cadence did not alter leg cycling cadence suggesting an ascending directional bias in locomotor coupling (Sakamoto et al., 2007).

1.7. The importance of functional context for the study of rhythmic movements

Overall, the potential of utilizing rhythmic arm movement to enhance leg muscle activity in locomotor retraining is strongly maintained by experimental evidence. (Behrman & Harkema, 2000; Ferris, Huang, & Kao, 2006). However, specific details of the neural coupling lacks a relevant mechanical context. First, there are limitations to the use of reflexes as functional probes in general, and during rhythmic arm movement. Additionally, while there is shown to be neural similarity between many combined arm and leg rhythmic movement tasks there are subtle differences in the neural control and mechanical constraints that can alter interlimb coupling (Zehr et al., 2007). Therefore, it is paramount to foster a neuromechanical approach as a functional framework to study rhythmic movements.

1.7.1. Considerations for the use of reflexes as neuromechanical probes of function during rhythmic movement.

While cutaneous and H-reflexes can provide valuable insight into changes in neural excitability at a spinal level, neither the H-reflex or cutaneous reflex are naturally occurring. Therefore it is important to consider the natural functional significance of these reflex pathways. For example, muscle afferent pathways (i.e. stretch and H-reflexes) provide information about "internal conditions" related to muscle activation and movement such as muscle length or rate of change in muscle length. However, they can only be used indirectly to infer information about external conditions (Zehr, 2006). In contrast, mechanoreceptors in the skin can give direct information about external conditions but only indirect information about internal conditions.

The H-reflex is considered the electrical analogue of the stretch reflex because it accesses components of the same monosynaptic pathway. However, since the H-reflex is evoked by direct activation of spindle afferents, both the contractile state of the intrafusal fibres and the influence of gamma-motoneurons on the muscle spindle, occurring during the stretch reflex, are bypassed during an H-reflex (Brooke et al., 1997; Schieppati, 1987). However, bypassing the effect of the mechanoreceptors and gamma motoneuron excitability limits the functional significance of the H-reflex (Zehr & Stein, 1999). Consequently, the H-reflex can only be used to measure the excitability of the neural components of the pathway. Additionally, there is inability to judge the mechanical correlate of the stimulus to evoke an H-reflex like measuring the stretch to induce a stretch reflex (Zehr & Stein, 1999). Also, It has been shown that the H-reflex is more susceptible to PSI than the stretch reflex (Morita et al., 1998). Further, the H-reflex and stretch reflex modulation do not parallel each other during rhythmic activities such as hopping where the stretch reflex was expected to contribute mechanically to the propulsion of the upswing (Voigt et al., 1998; Zehr & Stein, 1999). However, while the stretch reflex may provide a greater probe for function of the monosynaptic pathway, the H-reflex, with an appreciation of its limitations, can still provide insight into underlying neural control during rhythmic movement (Zehr & Stein, 1999).

With respect to function of cutaneous reflexes, responses to mechanical obstacles have been shown to be qualitatively similar to electrical stimulation of a cutaneous nerve innervating the same area of the foot contacted mechanically during walking (Eng et al., 1994; Schillings et al., 1996). Overall, both the H-reflex and cutaneous reflex provide important information regarding the regulation or rhythmic movement and interlimb

connections. Overall, understanding functional limitations and including mechanical measurement of reflex probes can provide a much-needed functional context to these responses.

1.7.2. Functions of reflexes during locomotor activities

Understanding the function of reflexes is required to refine models of neural control in normal movement as well as provide knowledge of how reflex pathways can be exploited to assist rehabilitation following disease or neurotrauma. (Zehr & Stein, 1999) The neuromechanical study of reflexes during rhythmic movement has helped place these responses in a functional context. In animal models reflexes correlated with mechanical changes have been shown both within and between limbs (Buford & Smith, 1993; Drew & Rossignol, 1987; Forssberg, 1979; Prochazka et al., 1978; Wand et al., 1980). Forssberg (1979), showed that during locomotion in the cat disturbances to the paw (stimulation, mechanical contact or "air puff") resulted in changes in muscle activity and kinematics that were related to the phase of the movement and could be interpreted in a functionally meaningful way (Forrsberg 1979). That is, a corrected action resulted from stimulation during the swing phase that did not obstruct the forward movement but involved greater than normal flexion to lift the limb over the obstacle—the stumbling corrective response (Forssberg 1979). Similarly, in humans both cutaneous and muscle afferent stimulation result in functional phase related responses (for review see Zehr and Stein 1999). In a study of sural nerve stimulation during walking, Duysens et al. (1992) observed phase dependent modulation yet was unable to derive any functional significance to the responses (Duysens et al., 1992). However, using combined neuromechanical analysis and a functional anatomical perspective Zehr et al. (1998),

observed that electrical stimulation of the sural nerve during the stance phase of walking elicited reflexes which were associated with ankle eversion and dorsiflexion which could assist in accommodating to uneven terrain (Zehr et al., 1998). Therefore, an evaluation of the muscle activity alongside reflex dynamics was pivotal at arriving at a functional role for the sural nerve afferents in perturbation responses during walking. As well, Zehr et al. (1997), found that stimulation of the SP nerve resulted in linked mechanical changes in knee and ankle motion. This "stumbling corrective response" was similar in principle to the pattern observed in the quadrupedal cat (Forssberg, 1979; Zehr & Stein, 1999).

Additionally important is the concept of local sign where the anatomical location of the stimulated site plays a role in the reflex response (Zehr & Stein, 1999). For example, SP stimulation causes reduced dorsiflexion during swing and tibial nerve stimulation causes dorsiflexion during the stance to swing transition. Overall, a neuromechanical approach has shown that cutaneous reflexes function to alter the trajectory of the swing limb to avoid a stumble or fall or to assist in accommodation to uneven terrain during stance (Zehr & Stein 1999). In addition muscle afferent input contributes substantially to the activation of ankle extensors and may assist in load compensation and force production during stance as well as stabilize limb trajectory during swing (Sinkjaer et al., 1996; Yang et al., 1991; Zehr & Stein, 1999). Stretch reflexes during walking in humans account for 30-60% of ankle extensor related torque during stance (Sinkjaer et al. 1996, Yang et al. 1991). Also, it has been shown that load receptors contribute strongly to postural responses, weight support during stance and the regulation of step cycle timing during phase transitions (Zehr & Stein, 1999).

While there has been a great deal of research on the function of reflexes in the legs, there is a lack of equivalent research in the arms. This has limited a functional comparison of reflex responses between arm and leg rhythmic movement (Zehr & Chua, 2000a). Thus, mechanical data collected alongside the neural data during arm reflex responses can provide insight into the role of reflexes in the arms during locomotion.

Interlimb reflexes can also produce functional neuromechanical effects during locomotion in quadrupeds and humans. Cutaneous reflexes evoked in leg muscles by stimulation of nerves innervating the foot and hand produce mechanical effects that are associated with functionally relevant changes in limb trajectory (Haridas & Zehr, 2003; Zehr & Stein, 1999; Zehr & Duysens, 2004b). For example, SR stimulation resulted in ankle dorsiflexion at the stance to swing transition that could be functionally relevant to slow forward progression and minimize impact with an obstacle encountered by the outstretched arm (Haridas and Zehr, 2003). Additionally Balter and Zehr (2007), found that arm movement made a significant contribution to the reflex expression in the leg during the power phase (comparable to heel strike in walking). They suggested that the contribution from the arm at this point could be explained by a possible reliance on multisensory integration to help guide the swing limb and ensure proper placement of the foot (Balter and Zehr, 2007). Overall, studies on "reduced" locomotor preparations, such as arm and leg stepping or cycling have shown that arm movement contributes to the modulation of reflexes in the legs in a functional manner. Albeit, there is still a necessity for more robust mechanical analysis of responses occurring during these tasks.

An important consideration for the interpretation of reflex responses is to consider the behavioural context in which the reflex occurs. For example, Lamont et al. (2007),

observed enhanced and task specific cutaneous reflex responses during level walking, incline walking and stair climbing when the arms were in contact with an earth referenced handrail. The authors suggest that intelimb reflexes in arm muscles may be enhanced in an environment where earth referenced support is available and the arms can act directly to mechanically stabilize the body (Lamont & Zehr, 2007). Also, differences in the stability of the task resulted in altered reflex responses (Haridas et al., 2006; Lamont & Zehr, 2007). For example, Haridas et al. (2006), observed that cutaneous reflexes evoked in arm muscles due to stimulation of cutaneous skin fields in the foot (interlimb reflexes) were altered during walking tasks with different levels of stability threat. Therefore, it is important to account for the stability requirements of a task as an altered behavioural context could result in context specific responses.

1.7.3. Neural control variables can shape functional mechanical outcomes

Gait results in fairly stereotypical waveforms of changes in limb elevation angles that minimize energy expenditure and maximize mechanical stability to move the centre of mass (COM) smoothly over the base of support (Lacquaniti et al., 1999). Lacquaniti et al. (1999) suggested that the common kinematic trends are the result of organizational principles of CPG regulation of gait evident in humans and cats (Bianchi et al., 1998; Borghese et al., 1996; Grasso et al., 1998; Shen & Poppele, 1995). That is, from a control perspective, the pattern of muscle activity is constructed to produce whole limb movement based on a specific mechanical parameter that is the global goal of a task (control variable) (Grasso et al., 1998; Zehr et al., 2007). The control variable during walking could be the movement of the COM of the whole body (Lacquaniti et al. 1999).

As such, Lacquaniti described a planar law of intersegmental coordination whereby the tight coupling of the angular motion of different limb segments results in a planar relation that simply dictates the spatiotemporal trajectory of the COM of the body. CPG output could be related to the foot as an end-point environment interface in relation to the COM during walking (Ivanenko et al., 2005; Zehr et al., 2007). Further, the neural organization postulated by Lacquaniti et al. (1999), would suggest that coordinated kinematic synergies would be the desired strategy for maintenance of dynamic equilibrium and response to disturbances during locomotion (Lacquaniti et al. 1999). Research has shown that the control variable is preserved despite energy cost or efficiency of movement and control variable differences may account for variations in muscle activation patterns as well as reflex changes during movement (Grasso et al., 1998; Zehr et al., 2007). During backwards walking kinematics were preserved despite greater energy cost (Grasso et al. 1998). In a comparison of 3 rhythmic arm and leg movement tasks (walking, arm and leg cycling and arm and leg stepping) Zehr et al. (2007), suggested that the variable of importance might become altered in a mechanically constrained device. That is, during walking the COM is vaulted over the fixed contact of the foot while during recumbent stepping and cycling, the COM is fixed and the foot movement may be the focus of the task (Zehr et al. 2007). This may result in altered neural control parameters that further dictate the ongoing pattern of activity and functional response to disturbances. Therefore, control variable differences between tasks are important when considering the interaction of neural control with mechanical constraints.

1.7.4. Task mechanical constraints can alter neural control strategies

Overall there is great similarity between the neural control of different locomotor tasks despite differences in task mechanics (Zehr, 2005; Zehr et al., 2007). Zehr et al. (2007), found conservation of neural regulation of all 3 arm and leg rhythmic movement tasks. Principal components analysis revealed that four components accounted for more than 93 percent of the variability in background EMG and middle latency cutaneous reflexes (Zehr et al. 2007). Additionally, strong neural similarity between tasks has also been shown for cutaneous reflex modulation during level walking, incline walking and stair stepping (Lamont & Zehr, 2006). However, while there were many similarities noticed between tasks in these studies, important differences could be related to the task-specific mechanical constraints. As a prime example, the differences noticed between studies examining the effect of rhythmic arm movement on the modulation of reflex responses in the leg may be a result of differences between the tasks (Frigon et al., 2004; Hiraoka & Iwata, 2006; Kawashima et al., 2008). That is, task variations in arm range of motion, anatomical position, or limb segment orientation may be related to alterations in neural control strategies as well as peripheral feedback. Additionally, differences in mechanical coupling may have resulted in the dissimilar results of Sakamoto et al. (2006), and Balter and Zehr (2007). Therefore it is truly important to understand how task mechanical constraints can alter neural control strategies (Ting et al., 1999).

The biomechanical constraints of each limb are defined by intrinsic mechanical characteristics, present orientation and environmental interactions. The degrees of freedom of each limb are defined by the unique kinematic trajectories of various tasks. During walking, the reflex expression in the legs are limited based on the phase of the movement such that kinematic responses are restricted during stance phase where ground

contact is crucial and limb movement is constrained (Zehr et al., 1997). As a result of the biomechanical interaction of the limb with the environment interpretation of reflex dynamics becomes difficult. As such, Nichols (1994), suggested the importance of considering the anatomical and functional constraints of muscles when evaluating reflex changes in muscle activity. Additionally, it is important to consider that mechanical changes due to disease or neurological disorder may confound the usefulness of reflexes in rehabilitative interventions (Barzi & Zehr, 2008; Javan & Zehr, 2008; Zehr & Stein, 1999). Ultimately, an understanding of the neuromechanical context of any rhythmic task, including task constraints and control variables, can assist in the interpretation of mechanical responses during arm cycling (Drew & Rossignol, 1987; Grasso et al., 1998; Zehr et al., 2007).

1.8. Do arm mechanics affect neural control of the legs?

As stated previously, the mechanics of a movement are closely linked to both neural constraints and afferent feedback. As described for the legs, the afferent control signals related to task mechanics are powerful modulators of the locomotor pattern and can reset the timing as well as shape the response. As such, it has been demonstrated that rhythmic arm movement can have a powerful shaping effect on lower limb muscle activity (Hiraoka & Iwata, 2006; Kawashima et al., 2008). For example, Kawashima et al. (2008), has observed that rhythmic arm swing has a powerful shaping effect on soleus muscle activity during combined arm and leg movement. However, there are conflicting results from studies using rhythmic arm cycling concerning the importance of afferent feedback from the arms or altered arm mechanics in modulating lower limb activity. Therefore,

changes in afferent feedback in the arms may not have a sufficient modulatory affect on reflex responses in stationary legs (de Ruiter et al., 2010; Frigon et al., 2007; Hundza & Zehr, 2009; Loadman & Zehr, 2007). Alternatively, it may be possible that difference in task constraints result in differential gating of afferent feedback from the arm (Hiraoka et al. 2006). That is, afferent signals related to the specific arm movement task such as from muscle, cutaneous or joint afferents could be crucial signals that modify leg muscle activity. Currently, detailed characteristics on the role of neural signals related to rhythmic arm movement to engage relevant leg muscle activation are still unclear and more study is required to determine the effects and necessary parameters for the inclusion of arm movement in gait rehabilitation (Stephenson et al., 2010). An important gap in knowledge is the determination of neuromechanical correlates related to arm movement in different tasks. That is, a neuromechanical characterization of the arm movement across rhythmic motor patterns remains to be done. Knowledge on the mechanical parameters of a task can help elucidate the type, level, and timing of neural signals and this information can be crucial for effective rehabilitation (Edgerton *et al.*, 2008). Additionally, lower limb coupling could be related to the movement state of both limb pairs, the phase of the movement, as well as specific neural signals from the upper limbs (Balter and Zehr, 2007; Ferris *et al.*, 2006; Frigon *et al.*, 2004; Hiraoka, 2001; Huang and Ferris, 2004; Kawashima *et al.*, 2008; Loadman and Zehr, 2007; Zehr *et al.*, 2004). Thus a synthetic neuromechanical analysis of rhythmic arm movement could assist in quantification of the necessary and sufficient conditions for arm-assisted lower limb gait rehabilitation.

1.9. Thesis Objectives

The primary focus of this thesis is to further explore interlimb communication during combined arm and leg rhythmic movement and to elucidate neuromechanical considerations for the use of arm movement during locomotor rehabilitation. Current gaps in understanding are addressed related to the locus and contributions of arms and legs to interlimb coupling and the complex pairing of the neural control and the mechanics of rhythmic arm movement.

First, deciphering mechanisms of interlimb coupling requires refinement of analysis techniques alongside elegant experimental approaches using combined arm and leg rhythmic movement. As a specific example, the current state of Hoffmann (H)-reflex recruitment curve analysis lack a standardized reliable mathematical curve fitting technique with which to more fully extract information. This thesis presents a new, physiologically justified and reliable method of H-reflex recruitment curve analysis (chapter 2). This analysis technique is used to evaluate reflex modulation in arm and leg muscles during different arm and leg rhythmic movement tasks. Accordingly, two studies in this thesis assess the contribution of the arms and legs to reflex modulation during rhythmic arm and leg cycling (chapter 4) and stepping (chapter 5). Further, another study attempts to elucidate the locus of rhythmic leg cycling induced suppression of reflexes in arm muscles (chapter 3). Together these studies build upon the body of work in human interlimb coupling.

Second, in order to present a more complete assessment of the contribution of the arms to interlimb coupling, combined neural and mechanical measurement is necessary. For example, a neuromechanical perspective has been important to understand the function of reflexes in the legs during walking (Zehr & Stein, 1999). While reflex

pathways can be used as neural probes, the responses require mechanical correlates of their output in order to provide valid functional conclusions (Zehr, 2006). Additionally, during leg movement specific afferent signals related to task mechanics are necessary to properly set the timing and sculpt the motor output. Knowledge on the mechanical parameters of a task can help elucidate the type, level, and timing of neural signals crucial for its successful execution (Edgerton et al., 2008). A comparable neuromechanical evaluation of rhythmic arm movement has not been performed. As such, two studies in this thesis address this issue by characterizing the neuromechanical correlates of different rhythmic arm movement tasks (chapter 6) and measuring the mechanical correlates of reflexes during rhythmic arm movement (chapter 5).

In summary the specific objective of this thesis are:

- To enhance a method of reflex data analysis to enable improved interpretation of results
- To further our understanding of arm and leg neural connections during rhythmic movement through
    - Investigating the effect of rhythmic leg movement on arm reflexes
    - Determining the contributions of the arms and legs to interlimb coupling during combined arm and leg rhythmic movements
        - arm and leg cycling and enhanced afferent feedback fromthe arms.
        - arm and leg stepping with a stationary test limb
- To quantify the neuromechanics of rhythmic arm movements with

- An evaluation of the mechanical responses to cutaneous stimulation of the hand during rhythmic arm cycling.
- A mechanical description and comparison of different rhythmic arm movements.

Together, this information will be applied to the development of arm focused rehabilitation strategies for neurological disorders.

1.10. References

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2. A sigmoid function is the best fit for the ascending limb of the Hoffmann reflex recruitment curve[1]

2.1. Abstract

The Hoffmann (H) - reflex has been studied extensively as a measure of spinal excitability. Often, researchers compare the H-reflex between experimental conditions with values determined from a recruitment curve (RC). A RC is obtained experimentally by varying the stimulus intensity to a nerve and recording the peak to peak amplitudes of the evoked H-reflex and direct motor (M) -wave. The values taken from a RC may provide different information with respect to a change in reflex excitability. Therefore it is important to obtain a number of RC parameters for comparison. RCs can be obtained with a measure of current (HCRC) or without current (HMRC). The ascending limb of the RC is then fit with a mathematical analysis technique in order to determine parameters of interest such as the threshold of activation and the slope of the function. The purpose of this study was to determine an unbiased estimate of the specific parameters of interest in a RC through mathematical analysis. We hypothesized that a standardized analysis technique could be used to ascertain important points on a RC regardless of data presentation methodology (HCRC or HMRC). For both HCRC and HMRC produced using 40 randomly delivered stimuli, 6 different methods of mathematical analysis (linear regression, polynomial, smoothing spline, general least squares model with custom logistic (sigmoid) equation, power, and logarithmic) were compared using goodness of fit statistics (r-square, RMSE). Behaviour and robustness of

[1] Klimstra M, Zehr EP (2007) A sigmoid function is the best fit for the ascending limb of the Hoffmann reflex recruitment curve. Experimental Brain Research. Sep;98(3):1810-4 (95% contribution to project – 90% of data acquisition, analysis, statistics, figures and tables and written manuscript)

selected curve fits were examined in various applications including RCs generated during movement and somatosensory conditioning from published data. Results show that a sigmoid function is the most reliable estimate of the ascending limb of an H-reflex recruitment curve for both HCRC and HMRC. Also, the parameters of interest change differentially with respect to the presentation methodology and the analysis technique. In conclusion, the sigmoid function is a reliable analysis technique which mimics the physiologically based prediction of the input/output relation of the ascending limb of the recruitment curve. Therefore the sigmoid function should be considered an acceptable and preferable analytical tool for H-reflex recruitment curves obtained with reference to stimulation current or M-wave amplitude.

2.2. Introduction

The H reflex has been used extensively to measure changes in spinal excitability in motor control experiments (Misiaszek, 2003; Pierrot-Deseilligny et al., 2005; Zehr, 2002). However, evoking and analyzing the H-reflex requires awareness of many physiological and technical assumptions (Misiaszek, 2003; Zehr, 2002). Often, an H-reflex recruitment curve is used to compare the reflex response at various levels of stimulus intensity. The methodology of a recruitment curve involves varying the level of electrical stimulation delivered to a mixed nerve and measuring the peak to peak amplitudes of the two resulting waveforms in the electromyogram. The direct motor wave (M-wave) and the H-reflex wave are compound muscle action potentials that result from the stimulation of motor and sensory fibres respectively. The responses of these waveforms to changes in intensity of stimulation define the input/output relation of each phenomenon which is

highlighted by specific parameters of interest that can be used for experimental comparison.

Specifically, the ascending limb of the H-reflex RC is isolated and parameters such as the threshold of the response (H_{TH}), the maximum reflex response (H_{MAX}) and the slope of the ascending limb (H_{SLP}) are used to represent alterations in the H-reflex input/output function. Experimental protocols may differentially affect one or all of these parameters and therefore it is often beneficial to acquire many measures of H-reflex excitability. Currently, there are two accepted methods of presentation of the H-reflex recruitment curve. The first is to present both the H-reflex amplitudes and M-wave amplitudes versus stimulus amplitude (current or integrated current) measured using a current monitor. This is the suggested method of presentation if a current monitor is available. The developed plots are called H-reflex/current recruitment curve (HCRC) and M-wave/current recruitment curve (MCRC). However, if a current monitor is not available an alternative method of presentation is to plot the H-waves as a function of the size of the concurrently evoked M-wave and the developed plot is called an H-wave/Motor-wave recruitment curve (HMRC). There has yet to be a comparison between presentation methodologies with respect to changes in parameters of interest. It is therefore important to evaluate the results of an experiment using both presentation methodologies to determine how changes in the input/output relation of HCRC and HMRC compare.

The determination of a function that can approximate the ascending limb of the recruitment curve requires great physiological and methodological consideration. It has been assumed that the ascending limb follows a linear response (Funase et al., 1994a;

Funase et al., 1996). It is for this reason that Funase et al. (1994a) chose to use linear regression to analyze the ascending limb of the H-reflex recruitment curve. However, the rate of recruitment of alpha motor neurons may follow an exponential function (Fuglevand et al., 1993; Jones, 2005). Therefore it is necessary to determine a mathematical analysis technique to properly approximate the experimental data. The use of linear regression to analyze the ascending limb of the recruitment curve is a currently accepted method. However, linear regression has never been tested against other mathematical analysis techniques such as a recently presented polynomial technique (Christie et al., 2004) to determine its validity.

In the first part of this study we compared six mathematical analysis techniques of the ascending limb of the H-reflex recruitment curve for both HCRC and HMRC with measures of goodness of fit. We hypothesized that the most suitable analysis technique will conform to both physiological and technical assumptions, perform well on measures of goodness of fit as well as produce parameters of interest used for experimental comparison. This part of the study included a comparison of manual versus automated methods of determining the ascending limb data set for selected curve fitting techniques. The second part of the study involved the quantification of changes in parameters of interest from two mathematical analysis techniques (linear and sigmoid) during movement and somatosensory conditioning experiments for both HCRC and HMRC. Through this comparison we show that changes in the parameters of interest represent important considerations that are defined by the mathematical analysis technique and presentation methodology.

2.3.Methods

2.3.1. Participants

For part I of the experiment three participants (age range 29–42 y) with no known peripheral or central neurological conditions volunteered. In part II previously published data were analyzed using linear and sigmoid analysis techniques for both HCRC and HMRC presentation methodologies (Zehr et al., 2007a). This data is used solely to present differences in analysis techniques and presentation methodologies and does not contradict or embellish currently publish physiological results. All participants gave written consent to a protocol approved under the Human Ethics and research Committee at the University of Victoria and performed in accordance with the Declaration of Helsinki.

2.3.2. EMG

EMG was recorded using Ag-AgCl bipolar configurations of surface electrodes (Thought Technologies Ltd., Montreal, QC, Canada) from the left and right Soleus(SOL) and Tibialis Anterior (TA) muscles for experiment I. The area over the muscle sites were cleaned with rubbing alcohol prior to application. Individual ground electrodes were placed over bony landmarks near each muscle.

2.3.3. Soleus H-reflexes

The left and right (posterior) Tibial nerves were stimulated at the popliteal fossa using 1-ms square wave pulses to evoke the H-reflex using bipolar surface electrodes and a

Digitimer (Medtel, NSW, Australia) constant current stimulator (model DS7A). Nerve stimulation was delivered pseudo randomly between 3 and 5 s apart during all trials. Current was measured using a mA-2000 Noncontact Milliammeter (Bell Technologies, Orlando, FL, USA). For part I two H-current recruitment curves (n = 40 sweeps) were constructed for each leg for a total of 4 recruitment curves per subject. Also, 10 electrically evoked H-waves were recorded at each of 5 stimulus intensities chosen from the ascending limb of all recruitment curves. All recordings were taken while the subjects were at rest. For part II full H-reflex recruitment curves (n=40 sweeps) were obtained in all conditions. Control recruitment curves were also constructed at the beginning and the end of each experiment. In the somatosensory conditioning experiment soleus H-reflexes were conditioned with Superficial Radial (SR) nerve stimulation. SR nerve stimulation was delivered using trains of 5X1.0 ms pulses at 300 Hz with a condition-test (C-T) interval of 100 ms (Zehr et al., 2001). Electrodes for cutaneous nerve stimulation were placed on the dorsal surface of the forearm just distal to the radial head in the anatomical snuff box. Stimulus intensity was set at twice the threshold at which a clear radiating paresthesia was reported (Haridas & Zehr, 2003; Zehr et al., 2001).

2.3.4. Protocol

For all static control trials subjects were seated with knees bent at an ~90 degree angle and instructed to maintain the same posture throughout the experiment. For part I the participant's soleus muscle was relaxed for all trials while part II required subjects to maintain a low level of contraction (~20 MVC) in the soleus muscle ipsilateral to the site of stimulation. In part I H-reflexes were evoked in both the left and right legs whereas

only the right leg was stimulated in part II. Also, in part II participants wore an ankle-foot orthosis (AFO) on their right side and were provided visual feedback of soleus contraction level on an analogue oscilloscope. The protocol for part II was similar to previous experiments involving the effect of leg and arm cycling on reflex modulation (Balter & Zehr, 2007). Subjects performed two movement tasks at a frequency of 1 Hz: 1) arm cycling with legs stationary with knees bent at an ~90 degree angle (ARM); 2) leg cycling with arms stationary (LEG). Also H-reflexes were evoked while participants performed static postures matching the 2 cycling tasks to provide control conditions for each task. As described previously (Balter & Zehr, 2007), an arm and leg cycle ergometer (PRO II, SCIFIT Systems Inc., Tulsa OK) was used. Reflexes were evoked at the late leg extension power phase (~1-3 o'clock position) of the movement as an optical encoder monitored the position of the arm and leg cranks.

2.3.5. Data acquisition and analysis

Data were acquired at a sampling rate of 5000 Hz with a 12-bit A/D converter connected to a computer running custom-written (Dr. Timothy Carroll, University of New South Wales, Australia) Lab View software (National Instruments, Austin, TX). TA, AD and VL EMG signals were preamplifed with a gain of 5,000, band pass filtered at 100-300 Hz (P511 Grass Instruments, AstroMed Inc., Westwarwick, RI, USA) and full-wave rectified. Soleus EMG was preamplifed with a gain of 500 and band pass filtered at 100-1000 Hz. Soleus H-reflex EMG data were analyzed using single, unrectified sweeps. H-reflex peak to peak amplitudes were analyzed in all trials. For each subject M-waves and H-reflexes were normalized to the corresponding M_{MAX} to reduce inter-subject

variability. For part I, HCRC and HMRC recruitment curves (ascending limb only) were fit with mathematical analysis techniques outlined below and compared with respect to measures of goodness of fit. For part II, the ascending limbs of recruitment curves were fit using linear regression and a sigmoid function for both HCRC and HMRC. All parameters of interest and estimated values (outlined below) were used to compare between analysis technique and presentation methodology.

2.3.6. Comparison of Mathematical analysis techniques

A custom built analysis program was designed (National Instruments Labview 8 ™, Austin, TX, USA) to compare the same data set using different analysis techniques. The techniques compared were linear regression, polynomial, smoothing spline, power, logarithmic, and a general least squares fit to a custom logistic equation (sigmoid). The data were prepared for all fitting techniques by centreing and scaling the current data to improve the fit accuracy and decrease the computational complexity of the procedures. Centreing was achieved by subtracting the mean to centre the data on a zero point and scaling involved dividing the data by the standard deviation. After each fitting procedure, the current values were re-centred and re-scaled to properly align the data and the resultant curve fits. The amplitudes of the H-reflex and M-wave responses were normalized to the average maximum M-wave (M_{MAX}) obtained from each RC (Crone et al., 1999; Frigon et al., 2007). The current values for all fits were normalized to the current at 50% of M_{MAX} obtained from a sigmoid fit to the MCRC. M_{MAX} was determined for all RC as the mean of the 5 maximum M-wave values. All equations and descriptions of fitting methods can be obtained from The National Instruments™ website

(http://zone.ni.com/reference/en-XX/help/371361B-01/gmath/curve_fitting_vis/). A brief description of the analysis techniques is provided in the appendix.

2.3.7. Methods of determining the peak of the ascending limb

The method for determining the ascending limb of the curve fit was evaluated using an automated and a manual method. The methods evaluated for setting the upper limit of the ascending limb of the recruitment curve were calculated (calc), chosen (chos), polynomial (poly) and smoothing spline (ss). These methods defined the boundaries of the ascending limb. In the calc method, the computer program defined the peak of the ascending limb as the data point with the largest magnitude. The chos technique involved the manual selection of the upper limits of the ascending limb. The poly technique defines the peak of the ascending limb as the value corresponding to the maximum amplitude of a 9^{th} order polynomial to the given set of data. The ss technique defines the ascending limb as all values below the current value corresponding to the maximum amplitude of a smoothing spline curve fit using the error fitting technique (See Appendix).

2.3.8. Experimental parameters of interest

There were 6 parameters of interest taken from the curve fits that could be used for experimental evaluation of changes in the HRC (Figure 2-1). These values are H_{MAX}, 50% H_{MAX}, H_{SLP}, current at H_{TH}, current at 50% H_{MAX} and current at H_{MAX}.

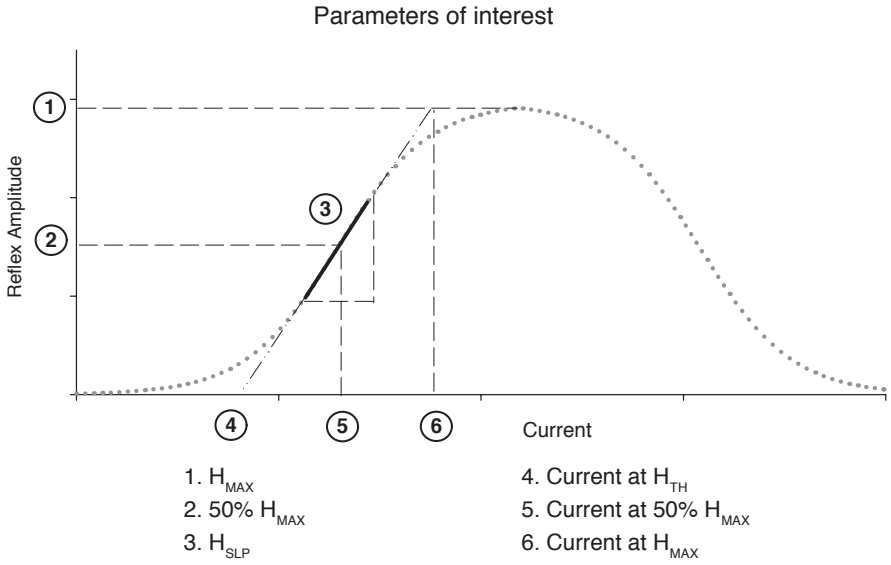

Figure 2-1 : H-reflex recruitment curve parameters of interest.
Specific parameters are taken from the ascending limb of the HRC for experimental comparison. These parameters are: 1. HMAX – the maximum amplitude of the reflex response. 2. 50% HMAX – half of the maximum reflex amplitude response. 3. HSLP – the slope of the ascending limb. 4. Current at HTH – the current value associated with the first noticeable reflex response. 5. Current at 50% HMAX - the current value associated with the reflex response at 50% HMAX. 6. Current at HMAX – the current value associated with the maximum amplitude reflex response.

H_{MAX} was defined as the average of the 5 largest H-reflex amplitudes for the linear, power, logarithmic and sigmoid curve fits. For the smoothing spline and polynomial curve fits H_{MAX} was defined as the maximum of the generated function. 50% H_{MAX} was defined from all curve fits as one-half of the H_{MAX} value. H_{SLP} was defined as the slope (*m*) from the linear fit. For power, logarithmic, smoothing spline and polynomial H_{SLP} was defined as the derivative of the function at 50%H_{MAX}. For the sigmoid curve fit H_{SLP}

was defined as the slope of the ascending limb of the recruitment curve at 50% of the H_{MAX} value. This slope was determined using equation 1:

$$\frac{m(H_{MAX})}{4} \quad \text{(Equation 1)}$$

Where H_{MAX} is the upper limit of the curve and *m* is the slope parameter of the function. The current at 50%H_{MAX} from linear, smoothing spline, polynomial, power and logarithmic fits was determined as the current value corresponding to the 50%H_{MAX} value of the function. The current at 50%H_{MAX} for the sigmoid function is a direct output parameter (*s50*). The current at H_{TH} from the linear fit corresponds to the x-intercept of the linear function. For the remaining curve fits current at H_{TH} was defined as the x-intercept of the linear functions developed using the H_{SLP} and current at 50% H_{MAX} values obtained from those curve fits (figure 2-1). The necessity of this method is due to the rapid increasing, decreasing (sigmoid, power, logarithmic) or erratic (smoothing spline, polynomial) nature of the curve fits near the limits of the data. This is similar to a procedure presented elsewhere when evaluating the motor evoked potential (MEP) input/output relation (Devanne et al., 1997) and recently the H-reflex recruitment curve (Zehr et al., 2007a; Zehr et al., 2007b). Current at H_{MAX} for the linear fit was defined as the current value obtained from the function with H_{MAX} as an input. Current at H_{MAX} for smoothing spline, polynomial, power, logarithmic and sigmoid was defined as the intersection of the linear function created from the H_{SLP} and current at 50% H_{MAX} for each function with the H_{MAX} determined from each curve fit function.

2.3.9. Predicted values

The variables of H_{MAX}; 50% H_{MAX}; H_{TH} taken from the static control curves were compared to those from the same currents values on the conditioned curves (Figure 2-2) (Zehr & Klimstra, 2006).

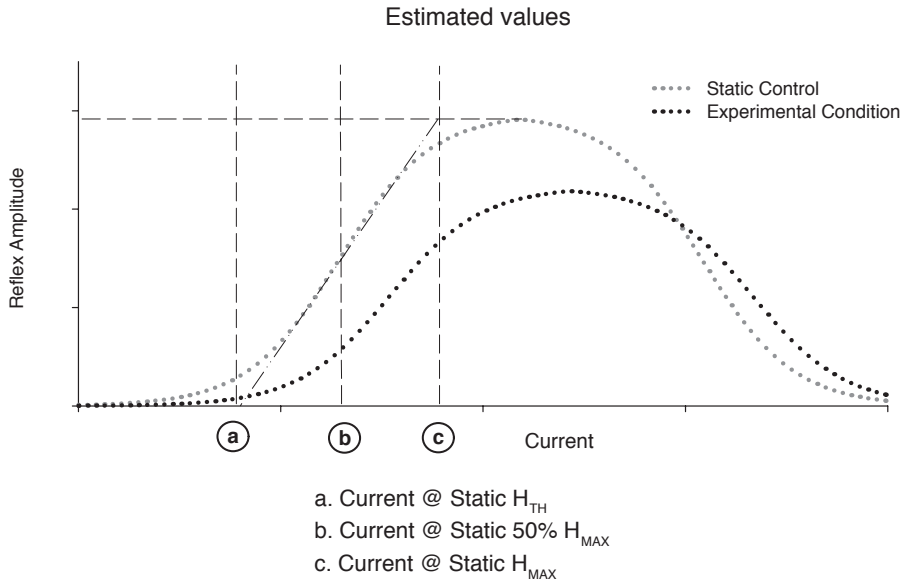

Figure 2-2 Estimated values taken from H-reflex recruitment curve fits compared across experimental conditions.
The current values associated with the static control RC are input into the curve fit of another experiment condition to produce estimated values of H-reflex response at the same current intensities. That is, the same relative current needed to evoke a certain sized H-reflex on the static control recruitment curve was input into the movement curve fit to obtain an estimated value. To differentiate the description of reflex parameters taken from the fitted curves, they are described as "@" the value from static control. For example, modulation of the value for H_{MAX} during static is $H_{@MAX}$ during cycling tasks. This is similar in principle to a procedure applied using linear fits (Zehr & Stein, 1999).

2.3.10. Goodness of Fit statistics

2.3.10.1. RMSE

The Root Mean Square Error is a measure of the amplitude difference between the values obtained from the curve fit and the sampled data. The difference can occur due to variability in the data or because the curve fit does not account for variables that could result in a more accurate fit.

2.3.10.2. R-square

R-square is a measure of the percentage of variability in the original data that is accounted for by the fitted curve. Because the r-square value does not exist on a linear scale all r-square data were converted to r-values and then underwent a Fischer z-transform to allow the measures of r between curve fits to be properly compared.

2.3.10.3. Statistics

STATISTICA software (StatSoft, Tulsa, OK., USA) was used to perform repeated measures analyses of variance (ANOVA) with Tukey HSD post hoc and Student's t-tests. Descriptive statistics included means ± standard error of the mean *(SEM)*. Statistical significance was set at $p \leq 0.05$. For part I separate analyses were conducted for measures of goodness of fit (r-square, RMSE). Where ANOVA results revealed significant main effects Tukey's *HSD post hoc* tests were used to identify the specific difference. Student's *t*-tests were used to examine differences between the curve fits using a manually chosen ascending limb and those with automated choices. For Part II repeated measures ANOVA were performed separately for the parameters of interest and predicted values for each analysis type and presentation methodology. Where ANOVA results

revealed significant main effects Tukey's *HSD post hoc* tests were used to identify the specific difference

2.4. Results I: Comparison of Mathematical analysis techniques

2.4.1. Analysis technique comparison

Figure 2-3 shows single subject HCRC and HMRC data with all curve fits. Note that the fitting techniques were limited in the HMRC to linear, polynomial and sigmoid.

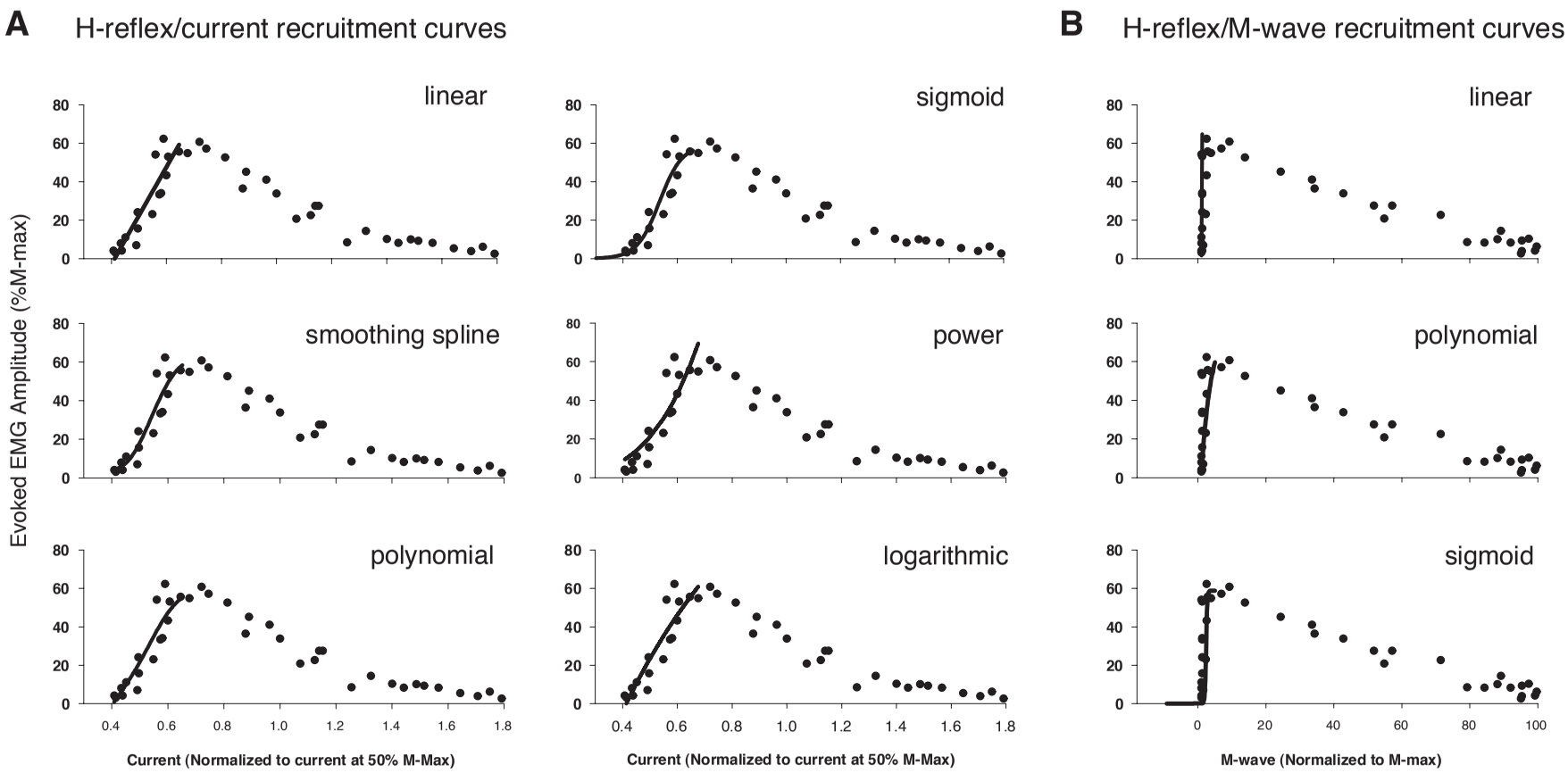
A
H-reflex/current recruitment curves
B
H-reflex/M-wave recruitment curves
linear
sigmoid
linear
smoothing spline
power
polynomial
polynomial
logarithmic
sigmoid
Evoked EMG Amplitude (%M-max)
Current (Normalized to current at 50% M-Max)
Current (Normalized to current at 50% M-Max)
M-wave (Normalized to M-max)

Figure 2-3 Different curve fitting procedures displayed on HCRC and HMRC. A. All fitting procedures for HCRC compared in the current experiment (linear, power, logarithmic, smoothing spline, polynomial, sigmoid) displayed for a single subject. B. All fitting procedures for HMRC compared in the current experiment (linear, polynomial, sigmoid) displayed for a single subject.

These were the only techniques available for this comparison because the smoothing spline, power and logarithmic fits were unable to fit data with repeated data points. That is, where few data were sampled with different evoked amplitudes at the same M-wave amplitude. Five amplitude values from each developed curve were compared to the 5 averaged H-amplitudes at their respective current or M-wave values through an analysis of Fisher z-transformed r-values and RMSE. For the HCRC comparison statistical analysis revealed significant differences between the r-values of the smoothing spline, polynomial, sigmoid and logarithmic fits from the linear and power fits yielding significantly higher values of r ($p<0.05$). Figure 2-4 (A, B) shows the Fisher z-transformed r-values for all curve fits as compared to the 5 averaged values for both HCRC and HMRC.

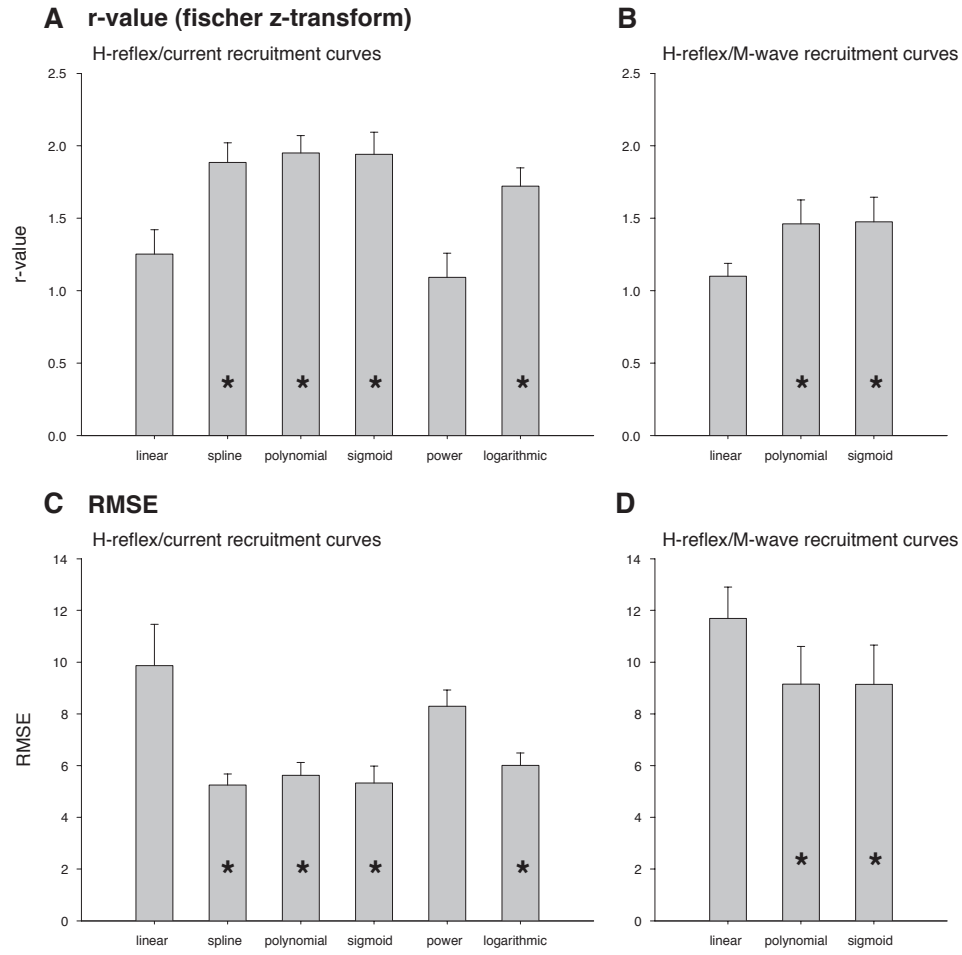

Figure 2-4 Goodness of Fit statistical results.
A. The fisher transformed r-values for all curve fits in HCRC. B. The fisher transformed r-values for all curve fits in HMRC. C. The RMSE from all curve fits in HCRC. D. The RMSE from all curve fits in HMRC. For HCRC, smoothing spline, polynomial, sigmoid and logarithmic are better fits to the experimental data than the linear and power fits as evaluated by r-value and RMSE. For HMRC, polynomial and sigmoid are better fits to the experimental data than the linear fit as evaluated by r-value and RMSE. All data are means ± SEM

Figure 2-4 (C,D) shows the RMSE values for all curve fits. The sigmoid, polynomial, smoothing spline and logarithmic fits produced the smallest values of RMSE. These

values were found to be significantly better fits than the power and linear fits. For the HMRC analyses, statistical analysis showed that the polynomial and sigmoid fits produced significantly larger r-values and significantly smaller values of RMSE than the linear fit. There was no significant difference between any of the groups when comparing the manual versus automated techniques suggesting that any of these methods may produce equivalent results.

2.5. Results II – Movement Conditioning.

The purpose of this section is to show the results of a physiological experiment evaluated using different analysis techniques and presentation methodologies. This comparison does not intend to expand upon or contradict the presentation of data already published in a research report (Zehr et al., 2007a).

Movement conditioning induces modulation of H-reflex RC (Zehr et al., 2007a). The conditions compared were static (no movement), arm cycling and leg cycling. Statistically significant differences noticed between movement conditions are ranked numerically with respect to the occurrence of a significant difference shown in all parameters of interest. This ranking allows a comparison of the sensitivity of analysis techniques and will be used as a gauge of the suitability of each analysis technique and presentation methodology. Where level 1 is the least sensitive comparison and level 3 is the most sensitive. Single subject recruitment curves during static and movement conditions are presented in Figure 2-5. All significant comparisons of parameters of interest and estimated data between experimental interventions are presented in Table 2-1

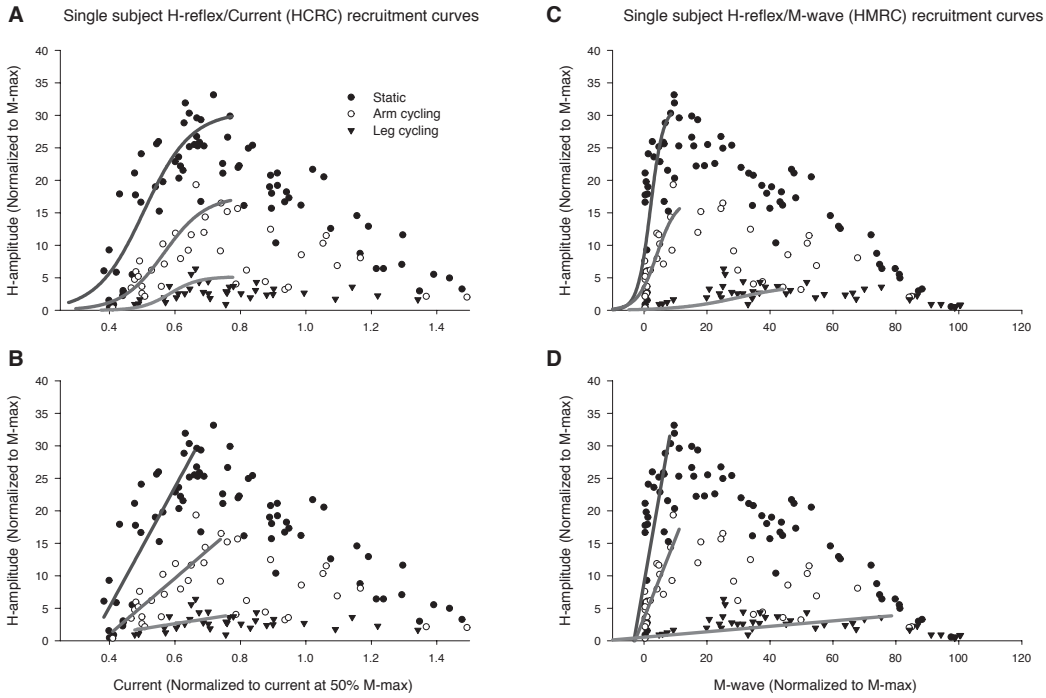

Figure 2-5 Single subject HCRC and HMRC during movement conditioning fit with a sigmoid fitting technique (A and C) and a linear fitting technique (B and D).

	HCRC		***HMRC***	
Parameters of Interest	Linear	Sigmoid	Linear	Sigmoid
H_{MAX}	*123*	*123*	*123*	*123*
H_{SLP}	*12*	*12*	*12*	*12*
Current (M-value) at threshold		*123*		
Current (M-value) at 50% H_{MAX}		*123*	*12*	*12*
Current (M-value) at H_{MAX}		*12*	*1*	*12*
Estimated values				
$H_{@TH}$	*2*	*123*		*12*
$H_{@50\%MAX}$	*123*	*123*	*12*	*123*
$H_{@MAX}$	*12*	*123*	*12*	*123*
Total 1 (percentage)	**50**	**100**	**75**	**82.5**
Total 2 (percentage)	**62.5**	**100**	**62.5**	**82.5**
Total 3 (percentage)	**25**	**75**	**12.5**	**37.5**

1 denotes static significantly different than legs
2 denotes arms significantly different than legs
3 denotes static significantly different than arms

Table 2-1 Statistical differences found during movement conditioning for different analysis techniques and presentation methodologies.
The parameters of interest and estimated values (rows) are compared between presentation methodologies and analysis techniques (columns). Movement Conditions are ranked from 1-3 in order of the occurrence of a significant difference noticed in all presentation methodologies and analysis techniques (1. Static different than legs, 2. Arms different from legs 3. Static different from arms). The three bottom rows show the cumulative percentage of the 3 ranked differences for each presentation methodology and analysis technique.

Table 2-1 presents the significant differences noticed between movement conditions for both linear and sigmoid analysis techniques for HCRC and HMRC data presentation methodologies. As can be seen from Table 2-1 for all analysis techniques and presentation methodologies analysis of H_{MAX} and H_{SLP} showed consistent results. That is, a significant different was noticed between all levels of movement conditions for H_{MAX}. This is an expected result because the method for determining H_{MAX} is identical for all analysis techniques and presentation methodologies. For the analysis of H_{SLP} all analysis techniques and presentation methodologies showed the same sensitivity between experimental conditions only showing a difference between levels 1 and 2. For current (M-value) at threshold, HCRC sigmoid showed the greatest sensitivity with differences between all levels of movement comparison, whereas all other analysis techniques and presentation methodologies failed to show any difference. For the current (M-value) at 50% H_{MAX} the HCRC sigmoid showed sensitivity for movement comparison at all three levels whereas HMRC linear and sigmoid showed differences at levels 1 and 2 and HCRC linear failed to show any differences. For current (M-value) at H_{MAX} HCRC and

HMRC sigmoid were able to show differences between levels 1 and 2 whereas HMRC linear only showed differences at level 1 and HCRC linear showed no differences between conditions. For the $H_{@TH}$ predicted value the HCRC sigmoid was sensitive to all levels of movement conditioning, the HMRC sigmoid was sensitive to levels 1 and 2, HCRC linear was sensitive only to level 2 and HMRC linear was not sensitive at any level. At $H_{@50\%MAX}$ HCRC sigmoid and linear as well as HMRC sigmoid showed differences between all levels of movement conditioning and HMRC linear showed differences between levels 1 and 2. For $H_{@MAX}$ HCRC sigmoid and HMRC sigmoid showed significant differences between all levels of movement conditioning whereas HCRC linear and HMRC linear were only sensitive to levels 1 and 2.

2.6. Results II –Somatosensory conditioning.

The results from this section are presented to show important differences between analysis techniques and presentation methodologies for the determination and evaluation of certain parameters of interest. Single subject recruitment curves during static and somatosensory conditioning are presented in Figure 2-6.

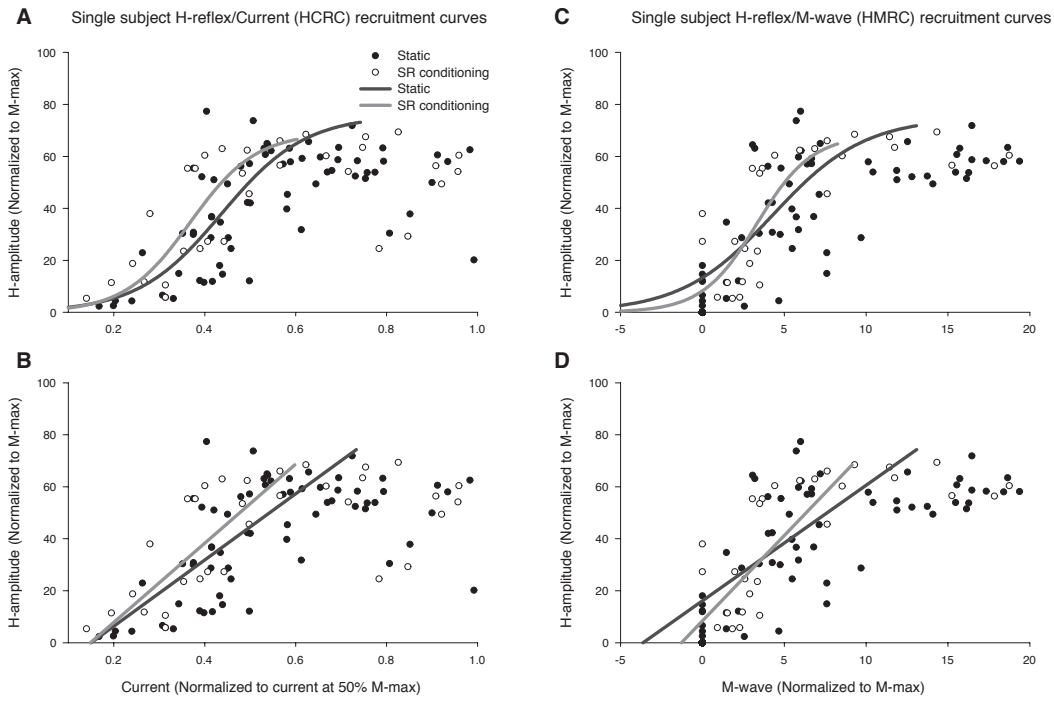

Figure 2-6 Single subject HCRC and HMRC during somatosensory conditioning fit with a sigmoid fitting technique (A and C) and a linear fitting technique (B and D).
Notice how the different presentation methodologies (HCRC and HMRC) correspond to differential changes in the parameters of interest evident in both sigmoid and linear curve fits.

For all analysis type and presentation methodologies there were no differences between conditions for H_{MAX}. An important finding is that the parameter of H_{SLP} showed significant differences only for the HMRC analysis techniques. For current (M-value) at threshold there were no differences between conditions for any analysis technique or presentation methodology. HCRC linear and sigmoid showed significant differences between conditioned and unconditioned reflexes for current at 50% H_{MAX} and current at H_{MAX} whereas the HMRC analysis techniques showed no difference between conditions. For $H_{@TH}$ a significant difference was noticed only for the HCRC sigmoid fit. For

$H_{@50\%MAX}$ significant differences were noticed for all HCRC and HMRC linear and sigmoid. For $H_{@MAX}$ significant differences were noticed for only for HCRC and HMRC linear fits.

2.7. Discussion

The main finding from the comparison of analysis techniques shows that the smoothing spline, polynomial, sigmoid and logarithmic curve fits are better fits to the experimental data than the power fit and the accepted linear regression technique through a measure of goodness of fit statistics (r-square, RMSE). This would suggest that both the HCRC and HMRC follow a non-linear response to increasing stimulus intensity and therefore analysis techniques that allow a more dynamic evaluation of the input/output function should be considered. Certain considerations for the choice of a valid analysis technique include both the physiological justification of a chosen technique and the ability of the technique to obtain parameters of interest for experimental comparison.

2.7.1. Physiological and Methodological Justification for a Sigmoid Fit

Many researchers have described the ascending limb of the H-reflex RC as sigmoidal (Christie et al., 2004; Hoehler & Buerger, 1981; Slot & Sinkjaer, 1994; Stein et al., 2007; Wilmink et al., 1996). Accordingly, there is sufficient evidence to consider that the ascending limb of the HCRC and HMRC follows a sigmoid function. To begin with, there is assumed to be an exponential distribution of recruitment thresholds across the motoneuron pool (Fuglevand et al., 1993; Jones, 2005; personal communication with K. Jones). This results from a large proportion of low threshold motor units with

exponentially diminishing number of high threshold units (Fuglevand et al., 1993). Therefore as the stimulus to elicit an H-reflex increased there would be an exponential response noticed at the foot of the curve. Also, as evoked stimulus elicits a response along the motor axons, antidromic volleys would collide with orthodromic volleys thus blunting the exponential rise and approximating a logarithmic decrease in the ascending limb near the peak of the curve (Funase et al. 1994b; Pierrot-Deseilligny et al., 2005; Stein et al., 2007).

A methodological justification for the use of a sigmoid function to approximate the ascending limb of the H-reflex RC is also viable. The variability in the response characteristics suggest that even if the ascending limb of the H-reflex recruitment curve is a pure linear response, the variability is not equivalent at all levels of stimulus intensity. That is, the variability of the H-reflex would be susceptible to a floor effect and a ceiling effect at the foot and the peak of the ascending limb respectively. Thus the sampled data from the foot of the curve and the peak of the curve would overestimate and underestimate the mean response respectively. Heterogeneous variability along the ascending limb of the H-reflex recruitment curve would require that the mathematical analysis technique follow a sigmoid function. This hypothesis could also account for the observation that the sensitivity of the reflex response to facilitation and inhibition is a function of the size of the test reflex and would limit the use of a linear function to approximate the ascending limb (Crone et al., 1990).

2.7.2. Limitations of analysis techniques

The major limitations of fitting techniques are based on the level of investigator manipulation required, the response of the fitting techniques to the variability of the sampled data and the occurrence of repeated data points. Thus certain analysis techniques evaluated in part I of the experiment were not used in the sensitivity comparison (part II).

All analysis techniques require a level of investigator control to properly fit the data. In the case of the linear, sigmoid, power and logarithmic techniques the peak of the ascending limb must be chosen to limit the data set for analysis. This study showed that there are no differences within curve fits with respect to the method of selection of the ascending limb of the recruitment curve. Conversely, the smoothing spline and polynomial analysis techniques do not require the selection of the peak of the ascending limb. These analysis techniques require fitting parameters to be subjectively set with the assistance of penalty features. The error fitting technique as well as limiting the curvature of the first or second derivative of the fitted curve are common penalty features used to justify alterations in fitting parameters (Hayes et al., 1979). However, the use of a penalty feature may have direct consequences on parameters of interest. For example, Christie et al. (2004) presented the 1^{st} derivative of the 9^{th} order polynomial fit to the HCRC as a measure of H-reflex excitability. The first derivative is a measure of the slope of the function at any stimulus intensity and is therefore a dynamic equivalent of the H_{SLP} presented by Funase et al. (1994a). However, altering the first or second derivative of the function is a direct manipulation of H_{SLP}, thereby introducing investigator bias with respect to this parameter of interest.

The polynomial and smoothing spline fitting techniques are highly sensitive to changes in the data creating unnecessary curvature on the ascending limb which can

cause erratic values for the parameters of interest. Also, the polynomial technique is unrestricted outside the bounds of the sampled data which can lead to erroneous results for parameters of interest such as H_{TH}.

The smoothing spline, logarithmic and power curve fits are not able to analyze recruitment curves with repeating data points. This severely limited the ability of these analysis techniques to analyze any HMRC data and therefore these techniques were excluded from further analysis.

Ultimately the choice to evaluate the sigmoid curve fit alongside the accepted linear regression method in part II of the experiment was based on the fact that the HMRC analysis techniques were limited to the linear, sigmoid and polynomial technique. Furthermore, the polynomial technique was also excluded due to difficulty in administration of the investigator controlled fitting parameter. A benefit of both the linear regression and sigmoid fits is that once the bounds of the data have been chosen these techniques are unaffected by experimenter bias (Carroll et al., 2001; Devanne et al., 1997; Funase et al., 1994a). Also, as previously discussed, both the linear and sigmoid curve fits are resilient to slight differences in the selection of the ascending limb of the RC for analysis. Therefore a proper comparison of both analysis technique and presentation methodology with respect to parameters of interest was limited to the linear and sigmoid techniques.

Although we demonstrated that the response of a 3 parameter sigmoid function is better than other selected fitting techniques in the current study, other functions may be valuable tools used to ascertain changes in the H-reflex recruitment curve in different subject populations or experimental conditions. For example, it is necessary to consider

that under pathological conditions there may be alterations in the physiological response of the H-reflex recruitment curve due to underlying morphological and functional changes. These changes may limit the ability of certain functions to fit the response properly. Subsequently, a 5 parameter sigmoid function may allow the determination of changes in the H-reflex that differentially affect the response characteristics at both the foot and peak of the curve respectively (Pitcher et al., 2003). It is important to note that observations in this study relate to the soleus reflex in intact subjects and may not encompass all subject populations or muscles studied. However, an identical sigmoid analysis was successfully performed on Flexor Carpi Radialis H-reflexes (Zehr et al., 2007b) and in stroke surviviors (Barzi & Zehr (submitted)). Therefore we are confident that the proposed method should prove robust across a variety of experimental settings.

2.7.3. Changes in parameters of interest with respect to analysis technique

The major result from the comparison of analysis techniques and data presentations from the movement conditioning experiments is that the HCRC sigmoid is the most sensitive to experimental differences in all parameters of interest and predicted values. Also, the HMRC sigmoid fit performed better than the HCRC linear and the HMRC linear analysis techniques. This suggests that even without measurement of current the sigmoid technique allows HMRC to be reliably analyzed. The ability of the sigmoid technique to be more sensitive than the linear analysis technique to changes in parameters of interest and estimated values is a result of both the ability to set the bounds of the sigmoid technique and the accommodation of the sigmoid fitting technique to the different portions of the RC.

We predicted that only a limited portion of the RC follows a linear response. Crone et al. (1990) have shown that the susceptibility of a test reflex to facilitation or inhibition depends on the test reflex size and therefore its position on the ascending limb. This suggests that a linear function fitting the entire ascending limb may misrepresent different portions of the curve where responses may not be linear. Also, when using a linear function the data points chosen for linear regression normally exclude data points near the peak of the curve because they are thought to be affected by orthodromic collision (Funase et al., 1994a; Funase et al., 1996). Therefore, the upper limits of the data analyzed using the linear fit technique is chosen just below the motor threshold (M_{TH}) (Funase et al., 1994a; Funase et al., 1996). This results in a tendency to underestimate estimated values such as the $H_{@TH}$ and overestimate values such as $H_{@MAX}$. Evidence for this is apparent for both the movement conditioning and somatosensory conditioning where current at threshold, current at H_{MAX}, $H_{@TH}$ and $H_{@MAX}$ have rather variable and spurious values. This may have led to the exclusion of the use of these parameters in previous research (Funase et al., 1994a; Funase et al., 1994b; Funase et al., 1996; Zehr & Stein, 1999) For example, $H_{@TH}$ for both movement and somatosensory conditioning for both HCRC and HMRC obtained through linear regression have negative values meaning that the intersection of the predicted value with the linear fit is negative. An apparent benefit to using the sigmoid curve fit is that this technique is bound in amplitude range by zero current or M-value and the maximum reflex response which is a predetermined input value (Carroll et al., 2001; Devanne et al., 1997). Restricting the sigmoid fit to both the zero and maximum reflex response at extreme ranges would serve to correct the potential overestimation at the foot of the curve

and underestimation of the peak of the curve that is apparent in other techniques (Funase et al., 1994a).

It is evident that parameters of interest and predicted values show consistent results when analyzed using the sigmoid technique. For example, for both movement and somatosensory conditioning experiments the current values at different H-amplitudes follow similar trends for both HCRC and HMRC. Comparing these results to the linear fit technique there are obvious disparities such as when investigating the H_{MAX} value and the corresponding $H_{@MAX}$ value. The statistically significant result found for the $H_{@MAX}$ during the somatosensory conditioning may be a result of exaggerated linear extrapolation. This trend is apparent when investigating the single subject data as the slope of the conditioned linear fit RC exaggerates the maximum response.

2.7.4. Changes in parameters of interest with respect to presentation methodology

The results of this study suggest that the sigmoid is the most robust, simplest to administer and interpret, and follows physiologically based predictions of the stimulus response of the H-reflex recruitment curve. This is consistent when investigating HCRC, However, the analysis of HMRC requires a more thorough investigation of the parameters of interest. It is important to recognize that the M-wave is limited as a measure of stimulus intensity at both the foot and plateau of the MCRC. It is near these extreme ranges that a change in current intensity will fail to considerably affect the amplitude of the M-wave. Therefore unless the HCRC falls within the middle range of the MCRC the ascending limb will have a large range of H-reflex amplitudes within a small range of M-wave amplitudes. This does not preclude its use in the determination of

parameters of interest as shown from the consistent results from both the movement conditioning and somatosensory conditioning experiments comparing HCRC to HMRC results. However, in some cases this may alter the interpretation of parameters of interest. For example, when examining the somatosensory conditioning experiment it is apparent that the HCRC results showed a significant change in current @ 50%H_{MAX} signifying a leftward shift in the RC. This same result is not seen in the HMRC results. Concurrently, there is a significant change in the slope in the HMRC that is not noticed in the HCRC. We suggest that this significant result seen as a change in the H_{SLP} in the HMRC is in fact a result of the HCRC shifting leftward with respect to the MCRC. This can be apparent when viewing the single subject RC for the somatosensory conditioning experiment.

Regardless of the technique used to analyze either the HCRC or the HMRC curve it is important to determine how changes in the input/output relation of each represents physiological changes when attempting to interpret results.

2.8. Conclusion:

Mathematical analysis techniques have been used to create an approximate interpolation of the average responses on H-reflex RC so that certain parameters of interest can be obtained from the data. The sigmoid analysis technique may be a new reliable method used to investigate and compare both HCRC and HMRC. Greater approximation of parameters of interest with the use of the sigmoid analysis technique may provide more robust ways of interpreting experimental results.

2.9. Appendix: Details of Mathematical Analysis Techniques

2.9.1. Linear regression

For the linear fit, the ascending limb of the HRC was defined as all points from the foot of the curve to the current value that occurred at M_{TH} (approximately 10% below the peak of the HRC) by the manual placement of a cursor on the computer display (Funase et al. 1994a). For the cases where the M_{TH} occurred past the peak of the HRC the cursor was placed at approximately 10% below the peak of HRC. This was done to ensure that the slope of the line was not contaminated by H-waves near the peak of the ascending limb that could be potentially affected by collision along the motor axons (Funase et al. 1994a). For the linear curve fit the data from both the calc and the chos methods were fit using the Least Squares method which assumes that the variability in the reflex amplitude is Gaussian distributed. Equation A1 represents the linear fit model.

$$y = mx + b \qquad \text{(Equation A1)}$$

where x is the stimulus intensity, m is the slope, and b is the intercept. The Least Squares linear regression finds m and b that best fit the sampled data by minimizing the value obtained using the Least squares procedure. For detail of the Least squares procedure and other possible linear optimization criteria see the National Instruments website (link above).

2.9.2. Polynomial

The polynomial fit technique finds the polynomial equation of the line that minimizes the mean square error from the fitted curve to the sampled data. Equation A2 gives the general form of the polynomial fit.

$$f_i = \sum_{j=0}^{m} a_j x_i^j \quad \text{(Equation A2)}$$

Where *f* represents the output sequence, *x* represents the input sequence, *a* represents the Polynomial Coefficients, and *m* is the polynomial order. The polynomial order is an arbitrarily chosen parameter that is under investigator control. Systematic increases in the polynomial order can cause random changes in the goodness of fit statistics. Also, the high order polynomials may obtain the best values of the goodness of fit statistics and yet be very noisy. Therefore it is important to determine a method that defines the ideal polynomial order that produces an optimum combination of lowest mean square error while still producing a smooth curve. The technique used in this experiment is called "error fitting" and will be described below with reference to setting boundary conditions for both the polynomial and smoothing spline curve fits.

2.9.3. Smoothing Spline

A cubic spline is a curve constructed of piecewise third-order polynomials which pass through a defined set of points. Analogous to a drawing device, a spline can be thought of as a flexible strip of material that may be bent into a curve and used to draw smooth curves between points. The HRC data was fit with a piecewise cubic spline (smoothing spline) function. This fits the sampled data by minimizing the following function:

$$p\sum_{i=0}^{n-1} w_i(y_i - f(x_i))^2 + (1-p)\int_{x_0}^{x_{n-1}} \lambda(x)(f''(x))^2 dx \quad \text{(Equation A3)}$$

Where p is the balance parameter, w_i is the i^{th} element of weight. y_i is the i^{th} element of the set of all normalized H-wave amplitudes. x_i is the i^{th} element of the set of all normalized current amplitudes. f''(x) is the second order derivative of the cubic spline function, f(x). λ(x) is the piecewise constant function. The balance parameter (p) specifies the balance between the smoothness of the curve fit and the accuracy with which it fits the observations. If p = 0, the fitted model is equivalent to a linear model. If p = 1, the fitting is equivalent to cubic spline interpolation where all the data points are connected. The smoothing spline function parameters of data point weight and balance can be subjectively set by the investigator. A weight parameter can be set for each data point to define the relative importance of each data point towards the resultant curve fit. For the purposes of this experiment the weight of each point was considered equivalent as each data point must have equal probability of defining the recruitment curve. Similar to determining the polynomial order, the balance parameter can be set by the investigator and therefore requires a method to determine the optimal combination of both smoothness and measures of goodness of fit. Increasing the balance parameter would both increase the correlation coefficient and decrease the root mean square error signifying an appropriate fit to the data. However the fitted curve with a p of 1 would pass though every data point and therefore be very noisy. The balance parameter was adjusted to conform to two predetermined parameters to obtain the optimal combination of both smoothness and measure of MSE. The first penalty feature was the evaluation of the first and second derivatives of the developed fit. This measure would allow a determination of any rapid changes in the slope of the curve that would signify that the

curve is too erratic. The second penalty feature was a variation of an idea first described by Hayes et al. (1979) described as “error fitting” in this manuscript.

2.9.4. Error Fitting

During Error fitting the adjustable parameter in either the polynomial or the smoothing spline technique is increased until the furthest point away from the fitted curve to any individual data point is no greater than the deviation value determined from the recruitment curve. The deviation value is determined using Equation 4.

$$\sqrt{\frac{1}{N-1}\sum_{i=1}^{n-1}(y_{i+1}-y_i)^2}$$ (Equation A4)

Error fitting is thus sensitive to the greatest variability in the developed RC.

2.9.5. Power

The following equation represents the power fit model:

$f = ax^b$ (Equation A5)

where x is the input sequence, a is the amplitude, and b is the power. This curve fit finds a and b that minimizes the least square fit to the experimental observations.

2.9.6. Logarithmic

The following equation represents the logarithmic fit model:

$f = a\log_c(bx)$ (Equation A6)

where *x* is the input sequence, *c* is the base, *a* is the amplitude, and *b* is the scale. This fit finds *a* and *b* that minimizes the least squares fit to the experimental observations.

2.9.7. Sigmoid

A general least squares model of a custom three-parameter sigmoid function similar to one developed in TMS Research was used to fit the ascending limb of all recruitment curves (Carroll et al., 2001; Devanne et al., 1997).

$$H(s) = \frac{H_{MAX}}{1 + e^{m(s50 - s)}} \quad \text{(Equation A7)}$$

where H_{MAX} is the upper limit of the curve, m is the slope parameter of the function, s50 is the stimulus at 50% of the H_{MAX} value, and H(s) is the H-reflex amplitude at a given stimulus value (s). Average H_{MAX} was calculated from the 5 largest peak to peak H-reflexes. The average H_{MAX} value (defined above) was used to define the upper limits of the sigmoid curve. The ascending limb of the recruitment curve was chosen as all points from zero current to a manually chosen peak of the recruitment curve.

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3. Rhythmic leg cycling modulates forearm muscle H-reflex amplitude and corticospinal tract excitability[2]

3.1. Abstract

Rhythmic arm cycling leads to suppression of H-reflexes in both leg and arm muscles, and a reduction in the excitability of corticospinal projections to the forearm flexors. It is unknown, however, whether leg cycling modulates neural projections to the arms. Here we studied the extent to which rhythmic movement of the legs alters reflex (Experiment 1) and corticospinal (Experiment 2) transmission to arm muscles. In experiment 1, flexor carpi radialis (FCR) H-reflex recruitment curves were recorded with the legs static, and during rhythmic leg movement, while the FCR was both contracted and relaxed. The results indicate that rhythmic leg movement suppresses reflex transmission, both when FCR is at rest and during tonic contraction, but that the effect is not phase-dependent. In experiment 2, we used transcranial magnetic stimulation (TMS) to elicit motor-evoked potentials in the contracted and relaxed FCR during static leg, and leg cycling conditions. Sub-threshold TMS was also used to condition H-reflexes in order to provide specific information about cortical excitability during leg cycling. Both resting and tonically contracting arm muscles showed a greater corticospinal excitability during leg cycling than during the static leg condition. The magnitude of TMS facilitation was similar during leg cycling and rest, suggesting a considerable sub-cortical component to the increased corticospinal excitability. The results suggest a differential regulation of afferent and descending projections to the arms during leg cycling, and are consistent

[2] Zehr, E. P., Klimstra, M., Johnson, E. A., & Carroll, T. J. (2007). Rhythmic leg cycling modulates forearm muscle H-reflex amplitude and corticospinal tract excitability. *Neuroscience letters, 419*(1), 10-14 (50% contribution to project – 50% of data acquisition, analysis, statistics, figures and tables and written manuscript)

with the idea that there is a loose, but significant, neural coupling between the arms and legs during rhythmic movement.

3.2. Introduction:

It has been suggested that the neural mechanisms that underlie coordination of rhythmic limb movement during human locomotion are similar to those used by quadrupeds (Ferris et al. 2006; Zehr & Duysens 2004). Such an organization would require neural linkages to regulate rhythmic activity between the arms and legs (Zehr & Duysens 2004). Our recent research has revealed that rhythmic movement of the arms can indeed affect the reflex excitability in the legs in tasks that do not involve rhythmic leg muscle activity (Balter & Zehr 2007; Frigon et al. 2004; Loadman & Zehr. 1994; Zehr et al. 2004). Interestingly, Baldissera and colleagues showed that ankle flexion-extension movement could modulate H-reflex amplitudes (both facilitation and inhibition) in quiescent flexor carpi radialis (FCR, a wrist flexor) muscle (Baldissera et al. 1982; Baldissera et al. 1998; Cerri et al. 2003). This effect was related to the neural drive for cyclic action of the foot rather than movement per se, suggesting a central neural mechanism associated with the command to move the foot and not afferent feedback (Cerri et al. 2003). However, the effects of whole leg rhythmic locomotor movement (e.g. leg cycling) on the excitability of muscles in the upper limbs have yet to be clearly determined. Further, it is unknown whether an effect of leg movement can be seen in arm muscles during tonic contraction (i.e. when motoneuronal excitability is controlled;(Zehr 2002)). It has recently been demonstrated that the excitability of corticospinal projections to FCR is lower during rhythmic arm cycling than during static contraction (Carroll et al. 2006). It was suggested that this may be related to a rhythmic

movement-related shift in the locus of drive from cortical to sub-cortical and spinal structures. It remains to be seen if there is a reciprocal arrangement of reflex and descending tract regulation in the human. In this study, we tested the hypothesis that reflex and corticospinal drives to FCR motoneurons are affected by rhythmic leg cycling when the arms are not moving. These predictions are consistent with the idea that interlimb coupling for human, quadrupedal, locomotor control involves gain regulation in multiple pathways induced by remote rhythmic limb movement (Balter & Zehr 2007; Frigon et al. 2004; Zehr et al. 2004).

3.3. Methods

The protocol was approved by the University of Victoria Human Research Ethics Committee and was performed according to the Declaration of Helsinki. Participants performed clockwise bilateral leg cycling on an instrumented cycle ergometer. The right forearm, wrists and hands were supported and fixed to a rigid platform to minimize any unwanted movement of the arms. A brace was worn to restrict movement about the right wrist joint. EMG was recorded using surface electrodes applied in bipolar configuration over the biceps and triceps brachii, flexor carpi radialis (FCR), extensor carpi radialis (ECR), soleus, and tibialis anterior muscles. EMG signals were amplified (GRASS P511, AstroMed) and bandpass filtered from 100-300 Hz. The processed output was sent to the A/D interface (National Instruments, Austin Tx.) and then on to the microcomputer sampling at 5000 Hz. All trials were performed both when FCR was quiescent and while a tonic low-level contraction (~10% MVC) of right FCR was maintained**.** The experiment had two parts. In the 1st part (n=10 subjects), the extent and nature of leg cycling on FCR

H-reflex amplitude was examined. Additionally, for 6 subjects, the existence of a phase-dependency in the regulation of reflex amplitude was examined by evoking H-reflexes during leg cycling and stationary positioning trials at four equidistant leg positions (i.e. 90 degrees apart) referenced as 12, 3, 6, and 9 o'clock relative to a clock face (where 12 o'clock is top dead centre). Otherwise stimulation was triggered when the pedal position of the stimulated leg was at 12 o'clock for all other conditions. Bipolar stimulation (0.5 ms pulse) of the median nerve at the elbow was conducted using a Grass S88 stimulator connected to a SIU5 isolation unit and a CCU1 constant current unit (AstroMed Grass, Inc) according to established protocols and methodologies (Carroll et al. 2006; Zehr 2002; Zehr et al. 2003). Electrodes were placed just proximal to the medial epicondyle of the humerus, near the cubital fossa. M-wave and H-reflex recruitment curves were constructed using 40 sweeps in all conditions while stimulation current was concurrently measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, Fl.). Peak to peak amplitudes of M- and H-waves were calculated offline with custom written software (Matlab, Nantick) from the single unrectified sweeps of EMG. For each subject M-waves and H-reflexes were normalised to the corresponding M_{max} to reduce inter-subject variability.

H-reflex recruitment curves (n=40 sweeps) were obtained for all experimental trials. The ascending limb of each recruitment curve was fit using a general least squares model of a custom three-parameter sigmoid function similar to one developed elsewhere [7] Equation. 1):

$$H(s) = \frac{H\max}{1 + e^{m(s50 - s)}}$$

where H_{max} is the upper limit of the curve, m is the slope parameter of the function, s50 is the stimulus at 50% of the H_{max} value, and H(s) is the H-reflex amplitude at a given stimulus value (s). Average H_{max} was calculated from the 5 largest peak to peak H-reflexes. Variables analyzed were: H_{max}; 50% H_{max}; H-reflex threshold; and, the slope of the ascending limb of the recruitment curve at 50% of the H_{max} value. This slope was determined using equation 2:

$$\frac{m(H\ \max)}{4}$$

Variables taken from the static control curves were compared to those from the same current values on the curves conditioned by leg cycling movement (Zehr & Klimstra 2006). To differentiate the description of reflex parameters taken from the fitted curves, they are described as "@" the value from static control. For example, modulation of the value for 50% of H_{max} during static is $H_{@50\%}$ during cycling tasks. This is similar in principle to a previously applied procedure using linear fits (Zehr & Stein 1999).

In the 2nd part of the experiment, we used transcranial magnetic stimulation (TMS) to assess corticospinal excitability. We compared the amplitude of motor evoked potentials (MEPs) and of TMS-conditioned H-reflexes at one pedal position between leg cycling and stationary trials. For data obtained in this part of the experiment stimulation was delivered only when the right pedal was at 12 o'clock. Previous results have shown a large effect of leg cycling on H-reflexes at this position. Thus we assumed a large effect of leg cycling on corticospinal and H-reflex excitability in arm muscles would be observed at this position. MEP and H-reflex amplitude were calculated as above. A Magstim 200 stimulator (Magstim, Dyfed, UK) equipped with a figure of eight coil was used to stimulate the left motor cortex. The coil was oriented to induce posterior to

anterior (P/A) current flow across the motor strip. The optimal positioning of the coil to elicit MEPs in the wrist flexor muscles was determined and then marked on the scalp with a felt pen. During all trials one experimenter held the coil firmly in place and care was taken to ensure coil alignment with the scalp markings. All TMS intensities are defined relative to the threshold needed to evoke MEPs during a background contraction of ~10% MVC (active threshold) and while at rest (passive threshold). Threshold was defined as the lowest intensity at which liminal MEPs of at least 50 μV were elicited in more than 2 of 5 trials. MEPs were evoked with FCR at rest and during contraction both with and without leg cycling movement. Ten stimuli were delivered at 10% above the passive threshold for each condition in the MEP trials. The average rectified and low-pass filtered EMG recorded from ECR and FCR was displayed as a target on a computer monitor that provided real-time feedback of muscle activity during tonic contractions.

We also examined the sub-threshold conditioning effects of TMS on the size of FCR H-reflexes. This technique provides specific information about the responsiveness of the motor cortex, whereas the size of motor responses elicited by suprathreshold TMS (i.e. MEPs) reflect both cortical and spinal excitability. The rationale for the technique has been described previously (Carroll et al. 2006; Mazzocchio et al. 1994; Neilsen et al. 1993; Petersen et al. 1998) and relies on timing the peripheral and brain stimuli so that only the earliest (monosynaptic) part of the brain response facilitates the H-reflex. With the appropriate controls, the size of the conditioned reflex indicates the responsiveness of cells in the motor cortex, rather than a combination of cortical and spinal effects. The controls include the use of: test H-reflexes on the ascending limb of the recruitment curve with equivalent amplitudes (relative to Mmax) across conditions; a TMS conditioning

intensity that is sub-threshold for eliciting an MEP; and the earliest conditioning test interval that facilitates the test reflex (to ensure only the monosynaptic component of the first descending volley contributes to the facilitation). The conditioning stimulation was delivered at 3 and 5 % below active and passive threshold for tonic contraction and passive conditions, respectively. In each participant, conditioning-test (CT; TMS-Median nerve) intervals between -4 and -1 ms were examined. The CT interval at which the first significant facilitation of the H-reflex was observed was used. Twenty sweeps were collected in these trials, 10 each for control H-reflex (only median nerve stimulation) and TMS-conditioned H-reflexes (H-reflexes conditioned by sub-threshold TMS). Control and conditioned sweeps were alternated in each trial. The intensity of median nerve stimulation was adjusted to yield a stable H-reflex (~50 % Hmax) on the ascending limb of the recruitment curve during the static condition. The absolute amplitude (.e. relative to M_{max}) of this reflex was matched to allow valid comparison of the TMS conditioning effect during the cycling condition.

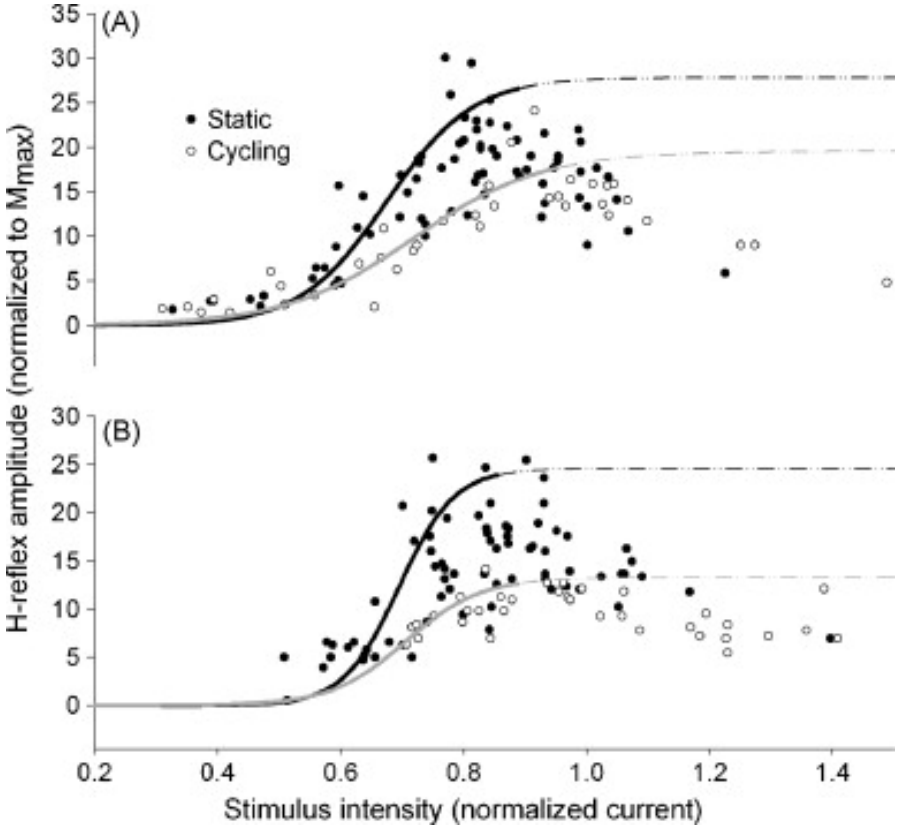

Figure 3-1 H-reflex recruitment curves during static activity and leg cycling for a single subject with FCR contracted (A) and relaxed (B).
The fitted lines represent the best fit sigomoidal representation of the data. Leg cycling suppressed reflex amplitudes in both contracted and relaxed conditions. EMG data are normalized to the maximum M-wave amplitude in each condition.

3.4. Results

H-reflex results for a single participant from the 1st experiment are shown in Figure 3-1, for both contracted (top) and relaxed (bottom) conditions. It is clear in this example that leg cycling reduced H-reflex amplitudes in FCR regardless of contraction condition. Across all subjects, the extent of amplitude suppression depended upon the size of the control H-reflex. For large reflexes (i.e. $H_{@max}$) there was a significant suppression of amplitude during both contracted and relaxed FCR conditions (Figure 3-2, black bars). However, for the $H_{@50\%}$ reflexes, this conditioning effect of leg cycling was

only significant while the FCR was relaxed (Figure 3-2, grey bars). There was no significant effect of phase of leg cycling on any H-reflex parameters, indicating that there was a similar suppression of FCR H-reflex amplitude across leg positions.

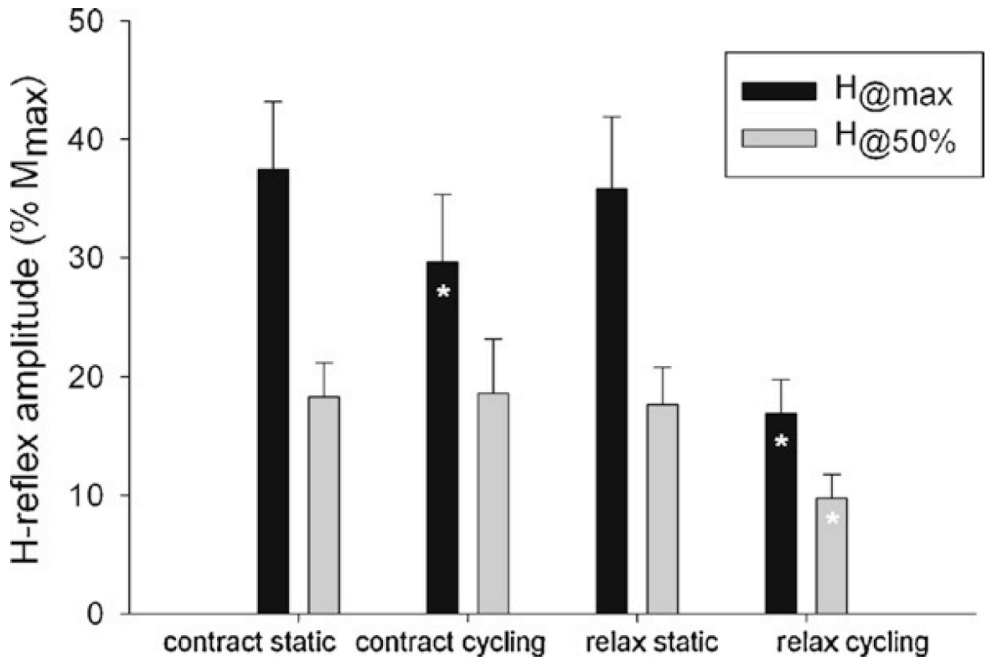

Figure 3-2 Group data for all conditions with unconditioned H-reflexes.
Leg cycling suppressed maximal H-reflex amplitudes during the contracted and relaxed states. However, $H_{@50\%}$ was only significant during the relaxed condition (indicated by * within bars). Data are normalized to the maximum M-wave amplitude in each condition and are given means +/- SE for 10 participants. Abbreviations: M_{max} (maximal M-wave amplitude).

In the 2nd experiment, MEP amplitudes were significantly larger during leg cycling than during stationary trials regardless of whether FCR was tonically active or relaxed. This can be seen for a single subject in the MEP traces shown in Figure 3-3, top. The group data show significant facilitation during cycling both while FCR was contracted (Fig 3-3B, left side) and relaxed (Fig 3-3B, right side). Facilitation of FCR H-

reflex amplitude induced by TMS conditioning was significant when FCR was relaxed but not during contraction (Not shown). However, the magnitude of this facilitation at rest was not significantly different between leg cycling and static leg conditions.

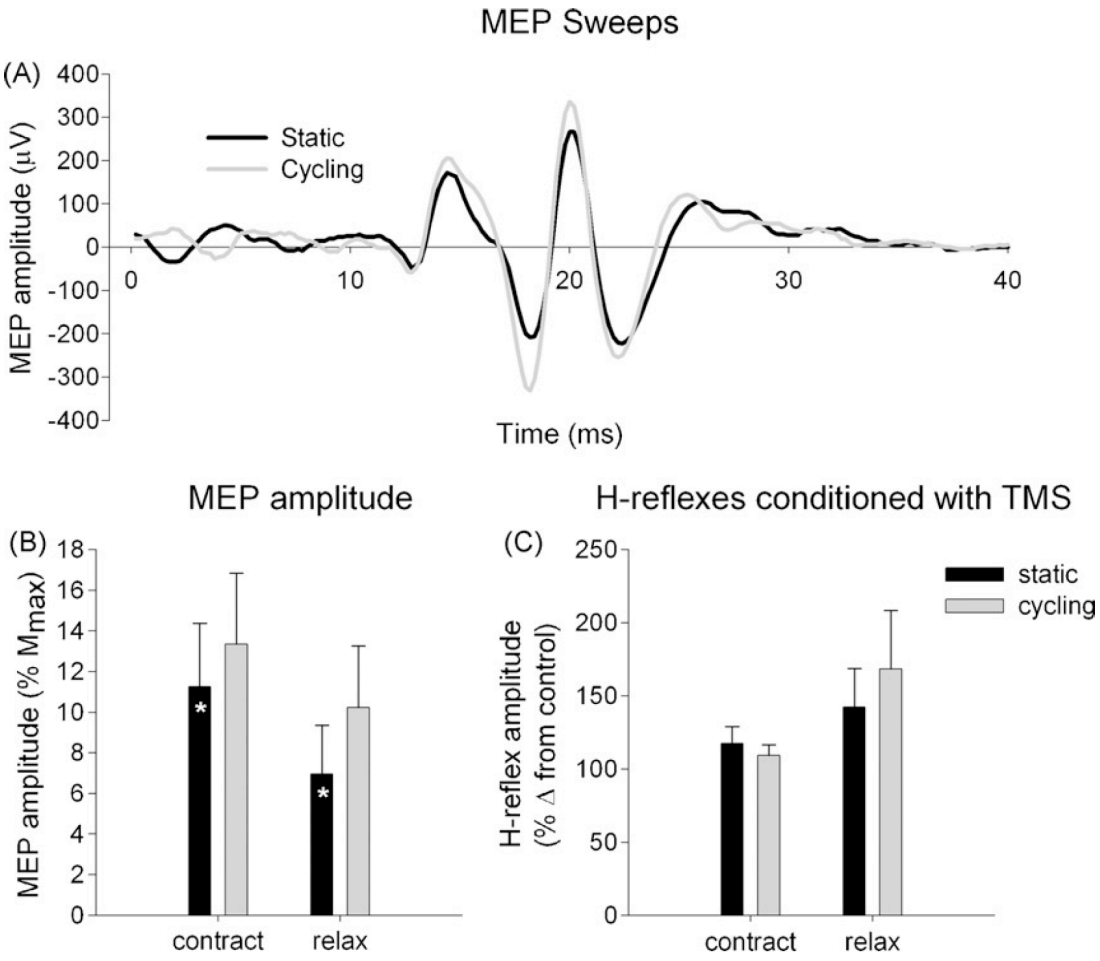

Figure 3-3 A. Motor evoked potentials in a single subject taken during contraction with and without leg cycling. Note the facilitation of MEP amplitude seen during leg cycling. B. MEP data across the group showing significant facilitation during leg cycling.
Data are normalized to the maximum M-wave amplitude in each condition and are given means +/- SE for 7 participants. Abbreviations: MEP, motor evoked potential, M_{max} (maximal M-wave amplitude). C. H-reflexes in FCR muscle conditioned by TMS. No significant differences were found for the magnitude of the facilitation. Data are normalized as percentage changes from control H-reflex amplitude.

For all trials across experiments M-wave amplitudes, FCR EMG and heteronymous EMG levels (i.e. ECR, TB, and BB) were well controlled. There were no significant differences across conditions for any of these parameters.

3.5. Discussion

The main finding of this study is that rhythmic leg movement significantly suppresses H-reflex amplitude in a wrist flexor muscle. The results also indicate that the contractile state of FCR (i.e. active or relaxed) has little effect on reflex transmission in an arm muscle during leg cycling. In contrast, corticospinal excitability was significantly greater during cycling than during static conditions. The increase in MEP amplitude could be due to spinal or cortical factors, since the MEP amplitude is sensitive to modulation at both cortical and sub-cortical sites. However, the TMS conditioning data suggest that sub-cortical sites are likely to contribute to the increased corticospinal excitability, because the extent to which sub-threshold TMS facilitated H-reflex amplitude was similar for cycling and static trials. Alternatively, it is possible that there were differences in cortical excitability between static and cycling conditions that were too subtle to be detected via TMS conditioning of H-reflexes. Overall, the data suggest a differential regulation of reflex and corticospinal transmission in the arms as a consequence of rhythmic leg movement.

We have shown previously that rhythmic arm cycling suppresses H-reflex amplitude in the ankle plantar flexors (Frigon et al. 2004; Loadman & Zehr 2006). This suppression was probably induced by reinforcement of segmental Ia presynaptic inhibition (Frigon et al. 2004) and was related to general features of arm cycling (such as

movement frequency) (Loadman & Zehr 2006). Interestingly, there is no strong evidence that remote movement has a phase-dependent effect on soleus H-reflexes. Now, using the reciprocal paradigm, we have found a similar result; H-reflexes in the arm are suppressed to a similar extent across phases of the leg cycling movement. It therefore appears that, during rhythmic movement of one limb pair (arms or legs), the opposite, stationary limb pair (legs or arms), experiences a generalized suppression of H-reflex excitability. We previously speculated that such a generalized suppression could indicate that the CNS lays down a general background of reflex bias between the limbs to facilitate coupling between arm and leg CPGs (Frigon et al. 2004; Sakamoto et al. 2007). Local conditions related to the activity state of the opposite limbs would then be expected to modify this generalized signal. This may be further evidence for the rather loose coupling between the arms and legs during locomotion (Sakamoto et al. 2007; Sakamoto et al. 2006). This might then be appropriately sculpted during rhythmic activity of both arms and legs such as in walking (see also (Balter & Zehr 2007)). It should be mentioned, though, that it remains a possibility for some form of subtle but phasic H-reflex modulation to occur in arm muscles if many more positions were sampled, such as shown by Baldiserra et al. (1998).

Overall, the results support measurable, but loose neural coupling between the arms and legs during rhythmic movement. This coupling has mostly been examined in humans by testing the remote effects of arm movement on leg muscle activity (Ferris et al. 2006; Frigon et al. 2004; Huang & Ferris 2004; Kao & Ferris 2005; Loadman & Zehr 2006; Sakamoto et al. 2007; Sakamoto et al. 2006). However, Sakamoto et al. (2007) recently reported that, during simultaneous arm and leg cycling movement, alterations in

leg cycling cadence induced significant involuntary changes in arm cycling cadence. They suggest this is indicative of a control system that is similar in principle to the ascending, caudo-rostral excitability gradient observed in the neonatal rat quadrupedal locomotor paradigm (Juvin et al. 2005). This concept was also supported by our recent work using arm and leg cycling paradigm, in which experiments the arms made a significant contribution to leg activity but the overall expression was heavily dominated by the legs (Balter & Zehr 2007).

There are some interesting parallels, but also some differences, between our current results and those of Baldissera and colleagues, who have published numerous papers examining coupled rhythmic ankle and foot oscillations. Baldissera et al. (1998) originally reported that H-reflexes in relaxed FCR muscles with the arm stationary were facilitated (and were largest during plantar flexion) during rhythmic oscillations of the ankle. The data were presented in the context of preferred coupling between hand and foot movement (Baldissera et al. 1982; Baldissera et al. 1991) and reflex excitability was used as an index of this neural coupling. More recent data has shown that the FCR H-reflex modulation in the resting condition is related to the command to contract the ankle muscles, not the movement itself (Cerri et al. 2003). Further, TMS has also been used to condition FCR H-reflexes in this paradigm. The results show an additional TMS-induced facilitation of reflex amplitude (i.e. indicating increased cortical excitability) that is largest during the phase of ankle movement (plantar flexion) in which the reflex itself is most strongly facilitated (Baldissera et al. 2002). The authors suggested that there might be a parallel modulation of cortical and spinal excitability produced by the motor command to rhythmically oscillate the ankle. A common feature of the two paradigms is

a significant modulation of FCR H-reflex amplitude. The striking difference, however, is that the sign of the effect is reversed; H-reflex amplitudes are facilitated during isolated ankle movement but suppressed during bilateral leg cycling. The differences do not appear to be due to the state of contraction in the target muscle (i.e. Baldiserra et al's data were from the resting FCR), since leg cycling caused H-reflex suppression during both FCR contraction and relaxation here. We suggest that these discrepancies are due to differences to the nature of the rhythmic movements studied in the two experiments. The task of Baldiserra et al involved a relatively isolated, voluntary movement, in contrast to the automatic locomotor movements performed in the current study. The two types of movement might rely on the recruitment of central pattern generating circuits to different degrees. This speculation is supported by the finding that unilateral leg cycling suppresses H-reflexes in the contralateral, static leg (McIlroy et al. 1992). Taken together with previous work on reflex modulation during arm cycling, the current data suggest that remote rhythmic movements have a generally similar influence on neural projections to arm and leg muscles. An important future step will be to investigate these linkages during simultaneous whole arm and leg movement.

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4. Enhancement of arm and leg locomotor coupling with augmented cutaneous feedback from the hand[3]

4.1. Abstract

Cutaneous feedback from the hand could assist with coordination between the arms and legs during locomotion. Previously we used a reduced walking model of combined arm and leg (ARM&LEG) cycling to examine the separate effects of rhythmic arm (ARM) and leg (LEG) movement. Here we use this same paradigm to test the modulation H-reflexes with and without interlimb cutaneous conditioning evoked by stimulating a nerve innervating the hand (superficial radial, SR). It was hypothesized that both ARM and LEG would contribute significantly to suppression of H-reflex amplitude during ARM&LEG. We also predicted a conservation of interlimb cutaneous conditioning during movement and an interaction between arm and leg rhythmic movement control. Subjects were seated in a recumbent ARM&LEG cycle ergometer and maintained a low-level soleus contraction for all tasks. H-reflex amplitude was facilitated by cutaneous conditioning evoked by stimulation of the SR nerve. H-reflex amplitudes were taken from recruitment curves and included modulation of 50% H_{max} and H_{max}. The suppressive effect of ARM was less than that for LEG and ARM&LEG, while suppression during LEG and ARM&LEG were generally equivalent. For H-reflexes conditioned by cutaneous input, amplitudes during ARM&LEG instead were in between those for ARM

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[3] Zehr, E. P., Klimstra, M., Dragert, K., Barzi, Y., Bowden, M. G., Javan, B., et al. (2007). Enhancement of arm and leg locomotor coupling with augmented cutaneous feedback from the hand. *Journal of Neurophysiology,* Sep;98(3):1810-4. (50% contribution to project – 50% of data acquisition, analysis, statistics, figures and tables and written manuscript)

and LEG modulation. Multiple regression analysis revealed a significant contribution for ARM only in trials when SR stimulation was used to condition H-reflex amplitudes. We suggest that there is a measurable interaction between neural activity regulating arm and leg movement during locomotion that is specifically enhanced when cutaneous input from the hand is present.

4.2. Introduction

There is uncertainty about linkages between the limbs during human locomotor behaviours involving rhythmic arm and leg activity such as occurs in walking. Dietz and colleagues have shown task-modulated interlimb effects and have also ascribed these to the output of central pattern generating (CPG) elements (Dietz et al., 2001). Evidence for interlimb coupling during walking was observed by evoking cutaneous reflexes in both arm and leg muscles by stimulation at the hand (SR) and foot (SP) (Haridas and Zehr, 2003). Observations of similar interlimb reflexes were also shown recently during combined arm and leg cycling (Sakamoto et al., 2006). These data provide compelling evidence of the reflex effects of sensory feedback evoked by activation of distant skin fields during movement and also of the influence of CPG activity regulating the arms and legs during walking (Haridas and Zehr, 2003). However, examination of interactions between control of the arms and legs is difficult during locomotion because of the "interference" between rhythmic arm and leg activity. Interestingly, facilitation of soleus H-reflex amplitude induced by SR nerve stimulation interferes with the suppression occurring during arm cycling (Zehr et al., 2004). This contrasts with lack of interaction of facilitatory conditioning evoked by stimulation of a local cutaneous nerve innervating the foot (sural; (Frigon et al., 2004)). This suggests that the remote cutaneous inputs are not regulated in the same way as local segmental ones.

To address the issue of the relative coupling between the arms and legs, we have used reflex modulation studies. Recently, we studied the role of arm, leg, or arm and leg movement on modulation of cutaneous reflex amplitudes in leg muscles by separating the rhythmic arm movement from the rhythmic leg movement (Balter and Zehr, 2007). The main finding was that the effect of arm cycling on reflexes in leg muscles when the legs were not moving was relatively minor; full expression of the effect of rhythmic arm movement was only revealed when both the arms and legs were moving. In that case, the relative contribution from the arms was linked to the functional state of the legs such that the contribution from the arms was functionally gated throughout the locomotor cycle in a manner that appeared to facilitate the action of the legs. These observations support an interaction between rhythmic arm and leg movement during human locomotion. However, using similar methodology but with uncoupled arm and leg ergometers, Sakamoto et al. (2006) concluded that the modulation of cutaneous reflexes in leg muscles is not influenced strongly by arm movement. These two studies highlight the uncertainty that currently exists in regard to arm and leg coupling during human locomotor movement. Here, we tested the hypothesis that further evidence of neural coupling between arm and leg movement would be obtained by examining the amplitude modulation of soleus H-reflexes using the general procedures of arm, leg, and arm and leg cycling from Balter and Zehr (2007). Additionally, our earlier observation of functionally relevant and phase-modulated interlimb reflexes in leg muscles after stimulation of SR nerve (Haridas and Zehr, 2003) suggested that cutaneous feedback from the upper limb could have priority access to interneuronal reflex networks directed to leg muscle motoneuronal pools. This, coupled with our observation that SR nerve facilitatory conditioning of soleus H-reflex amplitudes in stationary legs could interfere with the strong suppression of H-reflex amplitude induced by

rhythmic arm cycling (Zehr et al, 2004), allowed us to theorize that arm to leg locomotor coupling might be revealed more clearly by superimposing cutaneous conditioning onto the H-reflex modulaiton. We therefore also tested the hypothesis that additional strong evidence of locomotor coupling during arm and leg cycling would be revealed in SR nerve conditioned H-reflexes. This approach was also selected to counter any possible floor-related effects of strong soleus H-reflex suppression during leg cycling.

4.3. Methods

The experimental protocol and methodology were similar to that described in previous experiments involving reflex modulation during leg and arm and leg cycling (Zehr et al., 2001;Balter and Zehr, 2007). Participants provided informed written consent in a protocol approved by the Human Research Ethics Committee at the University of Victoria and performed in accordance with the Declaration of Helsinki. Seventeen participants (age range 24-40 y; 13 females and 4 males), free of any known history of neurological or metabolic disorders completed three ~ 4 minute movement tasks at a frequency of 1 Hz: 1) arm cycling with legs stationary with knees were bent at an ~90 degree angle (ARM); 2) leg cycling with stationary arms held at the side (LEG); and 3) combined arm and leg cycling (ARM&LEG). Online display of cycling cadence was used by the subjects to aid in maintaining this 1 Hz frequency. This frequency is similar to those used during leg cycling (Brown and Kukulka, 1993) and arm cycling (Zehr and Kido, 2001), and is considered to be equivalent to a typical walking cadence. Reflexes were also evoked while participants performed static postures matching the 3 cycling tasks to provide control, non-moving conditions for each task. During all cycling and

static tasks a consistent EMG level (~20 % MVC) was maintained in the soleus muscle, ipsilateral to the site of stimulation (the right leg was stimulated in all experiments). To aid in maintaining this contraction, participants wore an ankle-foot orthosis (AFO) on their right side and were provided visual feedback of contraction level on an analogue oscilloscope.

As described previously (Balter and Zehr, 2007), an arm and leg cycle ergometer (PRO II, SCIFIT Systems Inc., Tulsa OK) in which the arm and leg cranks were mechanically coupled to maintain a constant rigid out of phase relation between arm and leg movement was used. The movement cycle was divided into twelve phases, equivalent to a clock-face with 12 o'clock at the top (see Figure 1 in (Balter and Zehr, 2007)) using the output obtained from two optical encoders (i.e., one each for the arms and legs). Reflexes were evoked at approximately the late leg extension power phase (~1-3 o'clock position). This position was selected based upon the ability to evoke a reliable soleus H-reflex during leg cycling and corresponds to where significant arm-to-leg coupling effects were observed previously (Balter and Zehr, 2007). Data were acquired at a sampling rate of 5000 Hz with a 12-bit A/D converter connected to a computer running custom-written (Dr. Timothy Carroll, University of New South Wales, Australia) Lab View software (National Instruments, Austin, TX).

Surface EMG was collected from four muscles bilaterally to the site of stimulation: anterior deltoid (AD); vastus lateralis (VL); soleus (SOL), and tibialis anterior (TA). The skin over each muscle was cleansed with rubbing alcohol swabs and disposable 1 cm surface EMG electrodes (Thought Technologies Ltd.) were applied in a bipolar configuration with a 3 cm inter-electrode distance. Ground electrodes for EMG

recordings were placed on bony landmarks near the selected muscles. EMG recordings were pre-amplified and band pass filtered at 100 - 300 Hz (P511 Grass Instruments, AstroMed Inc.). However, for ipsilateral SOL EMG was filtered from 100-1000 Hz.

Soleus H-reflexes were evoked by stimulating the posterior tibial nerve at the popliteal fossa with 1 ms square wave pulses using bipolar surface electrodes with either a Digitimer (Medtel, NSW, Australia) constant current stimulator (model DS7A) or a Grass S88 stimulator (Grass Instruments, AstroMed Inc.) connected in series with a SIU5 isolator and a CCU1 constant current unit. Nerve stimulation was delivered pseudo randomly between 3 and 5 seconds apart during all trials. Full H-reflex recruitment curves (n=40 sweeps) were obtained in all conditions. Delivered current was measured using a mA-2000 Noncontact Milliammeter (Bell Technologies, Orlando, FL.). Control recruitment curves were constructed at the beginning and the end of each experiment and were taken for each condition. Using single, unrectified sweeps of EMG from Soleus, H-reflex peak to peak amplitudes were analyzed in all trials. For each subject M-waves and H-reflexes were normalised to the corresponding M_{max} to reduce inter-subject variability. As used recently, (Zehr et al., 2007b) the recruitment curves (ascending limb only) were fit using a general least squares model of a custom three-parameter sigmoid function according to Equation. 1):

$$H(s) = \frac{H\max}{1 + e^{m(s50 - s)}}$$

Where H_{max} is the upper limit of the curve, m is the slope parameter of the function. s50 is the stimulus at 50% of the H_{max} value, and H(s) is the H-reflex amplitude at a given stimulus value (s). Average H_{max} was calculated from the 5 largest peak to peak

H-reflexes. Variables analyzed were: H_{max}; 50% H_{max}; H-reflex threshold; and, the slope of the ascending limb of the recruitment curve at 50% of the H_{max} value. This slope was determined using equation 2:

$$\frac{m(H\,\max)}{4}$$

Also, the variables H_{max}, 50%H_{max} and $H_{threshold}$ taken from the static control curves were compared to the reflex amplitudes obtained from the same current values on the conditioned curves (Zehr and Klimstra, 2006). That is, the same relative current needed to evoke a certain sized H-reflex on the static control recruitment curves was used in the curves fit to the movement trials and the "predicted" value obtained. To differentiate the description of reflex parameters taken from the fitted curves, they are described as "@" the value from static control. For example, modulation of the value for H_{max} during static is $H_{@max}$ during cycling tasks. This is similar in principle to a previously applied procedure using linear fits (Zehr and Stein, 1999).

To explore the extent to which cutaneous feedback from the hand was preserved during rhythmic movement, twelve subjects also performed the ARM, LEG, and ARM&LEG tasks while soleus H-reflexes were conditioned with stimulation of the cutaneous superficial radial (SR) nerve in the hand. Trains (5 x 1.0 ms pulses @ 300 Hz) of constant current electrical stimulation were applied to the SR nerve at the wrist using flexible surface electrodes. Stimulus intensity was set on the CCU1 unit as ~2 x radiating threshold using a condition—test (CT) interval of ~100 ms to facilitate H-reflex amplitude via reduced Ia presynaptic inhibition (Zehr et al, 2004).

STATISTICA software (StatSoft, Tulsa, OK., USA) was used to perform repeated measures analyses of variance (ANOVA) with planned comparisons and Student's t-tests.

To gauge the relative contributions of ARM and LEG to the combined ARM&LEG task, SPSS software (SPSS Inc. Chicago, IL, USA) was used to perform forward stepwise multiple regression for $H_{@50\%}$. This parameter evoked during the ARM&LEG task (i.e., criterion variable) were compared to those obtained using two predictor variables: 1) the ARM task; and 2) the LEG task. This is the same procedure applied in a similar experiment involving ARM&LEG cycling and cutaneous reflexes (Balter and Zehr, 2007).

Descriptive statistics included means ± standard error of the mean *(SEM)*. Statistical significance was set at $p \leq 0.05$.

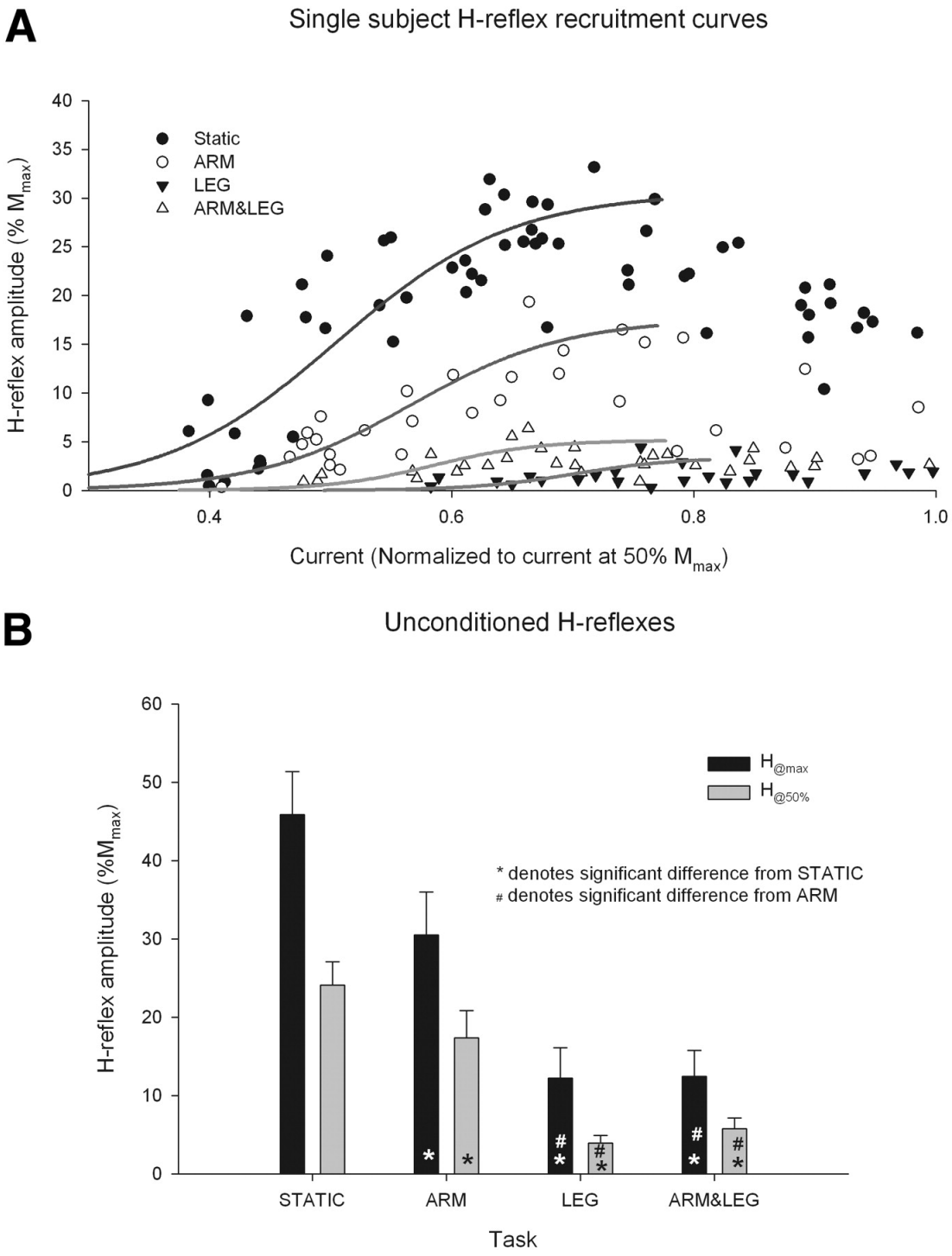

Figure 4-1 H-reflex recruitment curves for all 3 movement tasks and static control for a single subject.
The fitted lines represent the best fit sigmoidal representation of the data. The largest effect of cycling movement is seen during LEG. Data are normalized to the maximum M-wave amplitude in each condition. B. Group data for all conditions with unconditioned H-reflexes. All movement conditions induced significant suppression of H-reflex amplitude relative to static control (indicated by * within bars). LEG and ARM&LEG were

significantly different from ARM but not from each other (indicated #). Data are normalized to the maximum M-wave amplitude in each condition and are given means +/- SE for 17 participants. Abbreviations: ARM (arm cycling), LEG (leg cycling), ARM&LEG (combined arm and leg cycling), M_{max} (maximal M-wave amplitude).

4.4. Results

H-reflex amplitudes were significantly suppressed for all movement tasks relative to static control. Recruitment curves for a single subject show this suppression in Figure 4-1A. The recruitment curves show downward and rightward shifts during ARM, ARM&LEG, and LEG, in that order. Plotted in Figure 1B are the group data from all 17 subjects showing H-reflex amplitudes for 2 measured parameters ($H_{@max}$ and $H_{@50\%}$) across all conditions. Both parameters of H-reflex excitability measured during all 3 tasks were significantly smaller than static control (indicated by * within each bar). However, LEG and ARM&LEG did not differ from each other and were both significantly smaller than ARM (indicated by #). It is important to note that the suppression of H-reflex amplitude observed during LEG was not increased during ARM&LEG. Percentage change in reflex amplitude from static control were calculated for ARM&LEG and compared to the algebraic sum of the changes for ARM added to that of LEG (thus ARM+LEG). For ARM&LEG both $H_{@max}$ and $H_{@50\%}$ parameters were significantly smaller than ARM+LEG (not plotted). There were no significant differences between tasks in the effects of movement conditioning on slope of the ascending limb of the recruitment curve. A minor observation was a rightward shift in the stimulus at 50% of the H_{max} value when comparing LEG and ARM&LEG to static.

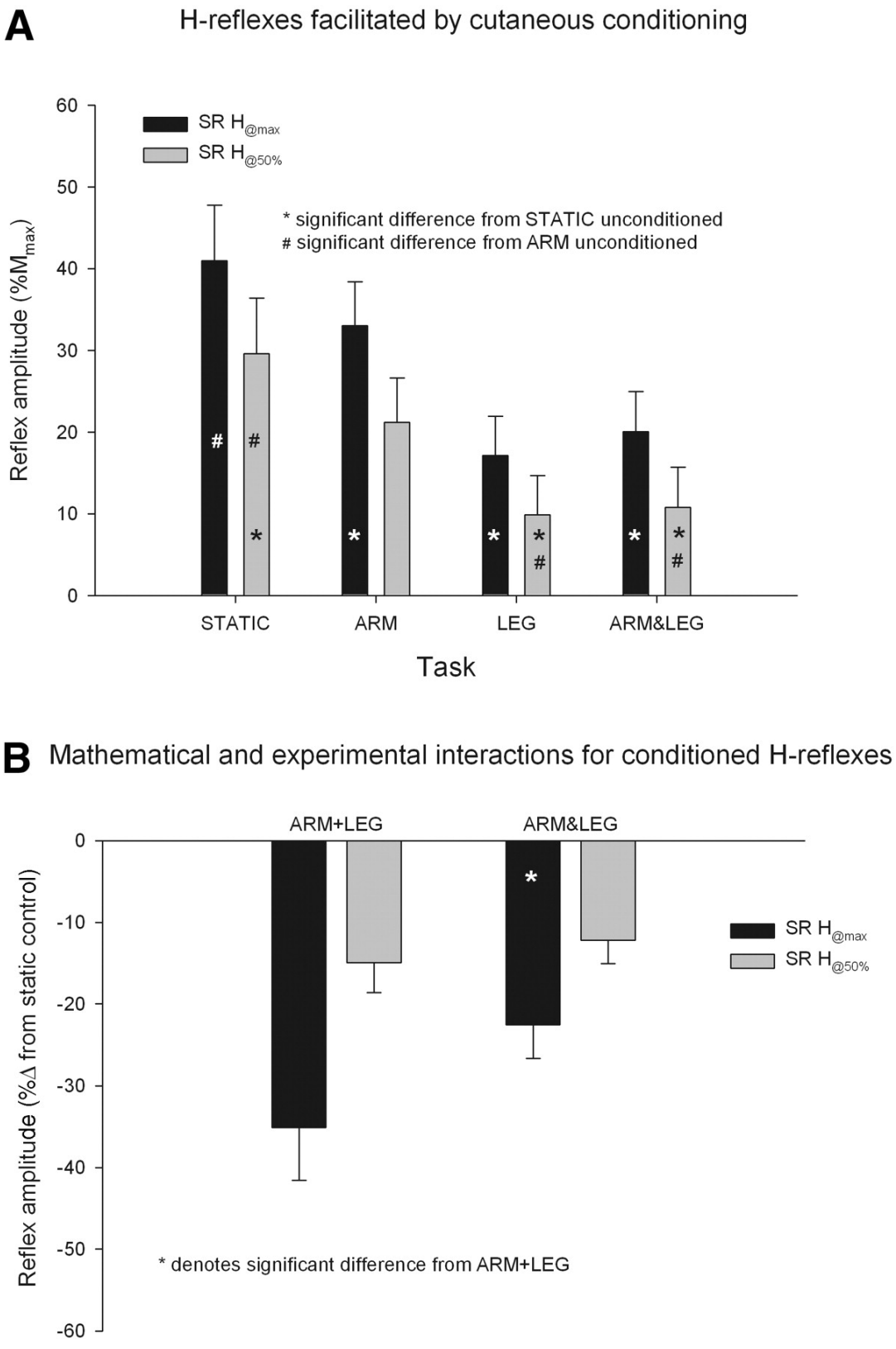

Figure 4-2 A. Group data for all 3 movement conditions with H-reflexes conditioned by cutaneous nerve stimulation.

Tasks involving leg movement induced significant suppression of H-reflex amplitude relative to static unconditioned control (indicated by * within bars). Differences from ARM are shown by the #. B. Comparison of mathematical (ARM+LEG) versus experimentally derived (ARM&LEG) interactions for conditioned H-reflexes. Differences between ARM+LEG and ARM&LEG are indicated by *. Data were normalized to the maximum M-wave amplitudes in each condition and then expressed as percentage changes from static control. Data are means +/- SE for 12 participants. Abbreviations: ARM (arm cycling), LEG (leg cycling), ARM&LEG (combined arm and leg cycling), M_{max} (maximal M-wave amplitude).

Analysis of the reflexes conditioned by cutaneous input from the wrist (SR nerve stimulation) are plotted for twelve subjects in Figure 4-2A for both parameters examined in the unconditioned reflex conditions. Cutaneous nerve conditioning interfered with the suppressive effect of arm cycling such that there was no significant difference between H-reflexes during ARM with SR conditioning and static control for $H_{@50\%}$ (as reported previously (Zehr et al, 2004)) but not $H_{@max}$. The amplitudes of $H_{@50\%}$ during ARM&LEG and LEG were both significantly smaller than during ARM and were not significantly different from each other. As with the unconditioned reflexes, the suppression of H-reflex amplitude observed during LEG was not increased during ARM&LEG with SR conditioning. Percentage changes in reflex amplitude from static control for ARM&LEG and the algebraic sum of the changes for ARM added to that of LEG (i.e. ARM+LEG) are shown in Figure 4-2B. For ARM&LEG $H_{@max}$ but not $H_{@50\%}$ was significantly smaller than ARM+LEG. This cannot be evidence of a floor effect limiting the suppression of H-reflex amplitude because it persists at both $H_{@max}$ and $H_{@50\%}$.

The results of the stepwise regression analysis yielded two interesting observations. During ARM&LEG cycling without conditioning by cutaneous SR stimulation ARM did not make a significant contribution to the H-reflex modulation during ARM&LEG. That is, LEG was the dominant factor. However, when H-reflexes were conditioned with SR stimulation, a significant contribution from the arms was observed (R^2 change=-.133; df=1,9; F-change=8.7,

$p<0.02$) to be superimposed upon the dominant effect from the legs (R^2 change=0.73; df=1,10; F-change=27.02; $p<0.001$).

Based upon the results from a 2 x 4 repeated measures ANOVA, background EMG levels in soleus and TA did not differ significantly across conditions. Parameters of M-wave amplitude, including maximal amplitude, also did not differ across conditions. Unsurprisingly, there were differences in EMG levels across conditions for VL (when the legs were moving) and AD (when the arms were moving).

4.5. Discussion

The main result of this study was the maintenance of interaction between arm and leg movement as measured by the effect of cutaneous input from the hand on the soleus H-reflex amplitude. We conclude that when the influence of rhythmic arm activity interacts with the effects of rhythmic leg activity during ARM&LEG, the result reflects neural processing related to both the ARM and LEG activity. The most striking observation may be that the summation of the individual effects of ARM and LEG did not typically yield the amplitude of ARM&LEG. Instead, the combined effect during ARM&LEG was less than the predicted mathematical summation. The effect from cutaneous SR nerve conditioning persists during arm and leg movement. That is, when the normal locomotor rhythmic activity of all 4 limbs was ongoing and cutaneous input from the hand was superimposed an interaction between the arms and legs was revealed.

In a previous paper we observed interlimb cutaneous reflexes in arm muscles after stimulation of a cutaneous nerve in the leg and in leg muscles after stimulation of the SR nerve at the wrist. We suggested that this interlimb reflex connectivity represented the role that

sensory feedback could play in arm and leg coordination during locomotion (Haridas and Zehr, 2003;Sakamoto et al, 2006). We also recently showed a subtle but measurable effect of arm movement on cutaneous reflex amplitudes evoked in leg muscles (Balter and Zehr, 2007). Using modulation of H-reflexes conditioned by cutaneous SR nerve as the neural probe in this study we arrive at a similar result. We initially suspected that overt modulation of the H-reflex might be saturated during LEG such that no effect of ARM could be revealed. However, when the separate effects ARM and LEG were summed and the resulting ARM+LEG compared with measurements taken during ARM&LEG H-reflex amplitudes were found to be significantly smaller during simultaneous ARM&LEG cycling. The result here during ARM corresponds with our other work with arm cycling and stationary legs (Frigon et al, 2004;Zehr et al, 2004;Loadman and Zehr, 2007). Namely, H-reflexes are suppressed during rhythmic arm movement. These earlier studies led to the conclusion that the effect of arm cycling was to modulate Ia presynaptic inhibition in the soleus H-reflex pathway. Since modulation of H-reflex amplitude in soleus during leg cycling has also been ascribed to Ia PSI (Brooke et al., 1997), strong interaction in the effects of rhythmic arm and leg cycling might be predicted.

We interpret the present observations that the predicted size of suppression of H-reflex amplitude during ARM+LEG (except for $H_{@50\%}$) was less than the experimentally observed values during ARM&LEG (compare $H_{@max}$ for ARM+LEG to ARM&LEG in Fig 2B) as evidence for a change in the effect of ARM when the legs are moving. That is, now it no longer adds to the suppression generated by LEG and instead the rhythmic actions at cervical and lumbar level converge to a common value. Since this suppression of H-reflex amplitude during LEG may reflect an active "filtering" of excessive afferent feedback (Brooke et al, 1997), this lack of addition of effects may make functional sense. That is, it reflects the physiological filter

setting for afferent feedback gain during movement (e.g. see (Brooke and Zehr, 2006)). Notably, the effects for $H_{@50\%}$ show similarity between the mathematically predicted and experimentally derived values (see Fig 2B SR $H_{@50\%}$). This suggests that the effects of SR conditoning were strong enough to interfere with the suppression during LEG. Thus the added effects during ARM&LEG are above the physiological filtering gain and are therefore expressed. Related to this point it is interesting to note that the multiple regression analysis revealed a significant contribution from the arms only in trials where H-reflexes were conditioned by cutaneous SR stimulation at the wrist. This suggests that interlimb coupling between the arms and the legs is strengthened when cutaneous feedback from the hand is added. Interestingly, the coupling effects detected with the SR nerve conditioned H-reflexes may be an extension to interlimb reflexes of the concept of differential regulation of segmental cutaneous and H-reflex pathways suggested earlier during leg cycling (Zehr et al, 2001).

The results here support the notion of linkage between the control of rhythmic arm and leg movement during human locomotion (Zehr and Duysens, 2004). Overall, the current data support the concept that there is arm to leg neural interaction during rhythmic locomotor-like movement. However, this coupling is rather loose and is dominated by the legs. This conclusion also corresponds to the recent observation that effects of arm cycling on H-reflex pathways in the legs is related to more general rather than specific features of arm cycling (Loadman and Zehr, 2007). Taken together these are compatible with observations of quadrupedal locomotor control in the neonatal rat. Juvin et al. (Juvin et al., 2005) examined interactions between lumbar and cervical locomotor CPGs in isolated spinal cord preparation. A dominance in locomotor drive from the lumbar over the cervical CPGs was documented and described as an “ascending caudorostral excitability gradient”. Previously Ballion et al. had suggested that lower cervical

spinal cord levels display rhythmogenic capacity and that, in conjunction with the CPG elements in the lumbar cord contribute to coordinated locomotor activity (Ballion et al., 2001). This general conclusion can also be taken from the recent work of Zaporozhets and colleagues in the neonatal rat which suggested that the cervical motor output is not critical for, but may contribute to bipedal locomotion (Zaporozhets et al., 2006). Additional recent indirect work, including the current study, support this concept as well in the bipedal human (Sakamoto et al, 2006;Balter and Zehr, 2007;Sakamoto et al., 2007). Indeed, the emerging data support the concept that bipedal human locomotion can be considered to be built upon elements of quadrupedal coordination as suggested by Dietz (Dietz, 2002;Zehr et al., 2007a).

Our results have translational implications for rehabilitation in that they further support incorporating rhythmic arm movement paradigms for locomotor rehabilitation after neurotraumatic injury. Ferris et al. previously argued that in order to harness interlimb neural coupling gait rehabilitation therapy should incorporate simultaneous arm and leg rhythmic activity after neurotrauma (Ferris et al., 2006). That is, neural commands related to the production of rhythmic arm movement could assist in accessing the neural circuitry underlying coupling between the arms and legs during locomotor retraining. The additional contribution that the current results make is to suggest that cutaneous input from the hand may also help facilitate neural linkage between the arms and legs during locomotion. It is conceivable that the simultaneous arm and leg movement combined with cutaneous input from the hand may lead to facilitation of extensor muscle activity. However, this requires further exploration including a determination of any phase-dependent modulation across the full cycle of movement. Regardless, including specific use of the hands during the arm movement may be of importance in rehabilitation interventions. Elucidating these effects in a neurologically damaged population

(e.g. after stroke or spinal cord injury) will be important to further refine effective rehabilitation strategies.

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5. Neural interactions between arm and leg movement during "reduced" human locomotion: evidence from modulation of Hoffmann reflexes in a leg extensor muscle[4]

5.1. Abstract

Recent experiments have confirmed neuromechanical interactions between the arms and legs during human locomotor movement. Previous work reported that during the rhythmic movement of all four limbs the influence of the arms on reflex expression in the legs was superimposed on the dominant effect of the legs. This led to the speculation that the effect from the arms could be underestimated during movement of the test limb. Additionally, the specific details of coordination between the arms and legs require further characterization. Using modulation of reflex amplitude as a neural probe for remote coupling, the present study evaluated the separated influences of rhythmic activity of the arms and leg on neuronal excitability of a stationary "test leg". This three-limb "reduced" locomotion approach was applied using a stepping ergometer with amplitude modulation of the soleus H-reflex as the main outcome measure for neural coupling. The main result was a large and significant influence of rhythmic arm and leg activity on the modulation of H-reflex amplitude in the stationary test leg at specific phases of stepping movement, namely heel strike and mid-to-end of swing of the gait cycle. These findings suggest that the output of neural control for rhythmic arm movement has an important role in gating the excitability of reflex pathways to leg muscles at specific phases of locomotion.

[4] Mezzarene, R.A., Klimstra M.D., Lewis A., Hundza S.R., and Zehr E.P. Manuscript in preparation. A version of this chapter was presented at Society for Neuroscience 2009 Chicago. (40% contribution to project – 40% of data acquisition, analysis, statistics, figures and tables and written manuscript)

5.2. Introduction

Locomotion requires coordinated spatiotemporal patterns of limb muscle activation (Ivanenko et al. 2006). Reduced animal preparations have been used to show that such rhythmic patterns are generated and controlled by neural networks in the spinal cord and that they are shaped by descending and sensory afferent inputs (Kiehn, 2006). These neuronal oscillators (or central pattern generators, CPGs) are suggested to be conserved in humans as well (Dietz et al. 2001; Zehr 2005; Zehr et al. 2009).

It has been suggested that locomotor coordination between the limbs (interlimb coordination) stems from the neural linkage between cervical and lumbosacral networks (Dietz, 2002; Zehr and Duysens 2004). There is evidence that mechanisms of coordination that are similar to other animals are also operational in humans in order to control the arms and legs during a variety of rhythmic movements such as walking, running, and swimming (Zehr and Duysens 2004; Zehr et al. 2009). Indirect evidence for interlimb coupling in humans has been obtained by evoking reflexes in one limb and observing the extent to which movement of other limbs modulate reflex expression. Such neurophysiological evidence of interlimb coupling was observed in cutaneous reflex pathways for both the arms and legs evoked by stimulation at the hand or foot during walking. These interlimb reflexes were phase-modulated across the walking cycle and were task-dependent (stationary compared to rhythmic activity) (Haridas and Zehr, 2003). There was also a reciprocally organized pattern and coordination of reflex responses from hand-to-foot and from foot-to-hand. These data strongly suggest that both sensory feedback, evoked by activation of distant skin fields during movement, and CPG activity regulate the movement of the arms and legs during walking (Zehr and Haridas, 2003).

The study of interactions between control of the arms and legs is complicated by the "interference" between rhythmic arm and leg activity. That is, it is not simple to determine if the modulation of reflexes in leg muscles evoked by stimulation in the hand during walking (e.g. Haridas & Zehr 2003) is due to control of rhythmic arm or leg activity. To answer the question of the relative role of arm or leg movement on modulation of reflex amplitude requires separating the rhythmic arm movement from the rhythmic leg movement. This is not feasible during overground walking. Therefore, in a series of recent experiments, we have begun characterizing interlimb coupling during locomotor behaviors using a combined arm and leg cycling protocol (i.e. "reduced" walking) (Balter & Zehr 2007, Zehr et al. 2007a, b). These studies demonstrated significant but small effects of rhythmic arm activity on the excitability of cutaneous and muscle afferent pathways affecting leg muscle activity. However, these protocols used simultaneous movement of all four limbs and there remains the possibility that the conditioning effect of movement of a given limb may be occluded when the test limb is also moving. For example, suppression of H-reflex amplitude in a test muscle due to homonymous limb movement may reduce the ability to detect the remote influence of arm activity. Stated another way, it has been shown for arm cycling that it is the activity state of the limb in which a muscle resides that dominates the pattern of reflex modulation (Carroll et al., 2005). This dominance may make it difficult to accurately ascribe the relative contributions of arm and leg movement during locomotor behavior.

The three-limb stepping paradigm allows the test limb to remain in a stationary posture and avoids the possible occlusion of the modulation of reflex amplitude. We tested the hypothesis that there are interactions of the effects of rhythmic movement of arms on

parameters extracted from the recruitment curve of the H-reflex elicited in the soleus muscle (SO) of the stationary leg. With the addition of voluntary rhythmic movement of the contralateral leg we intend to create an appropriate condition to study interactions of effects coming from different neuronal oscillators. The present protocol may refine our knowledge of neural interlimb coupling in human locomotion.

5.3.Methods

5.3.1. Subjects

Fifteen (7 males and 8 females) neurologically intact volunteers aged 30.4 ± 8.9 years (means ± SD) participated in the present study with informed written consent under a protocol approved by the Human Research Ethics Committee at the University of Victoria and in accordance with the declaration of Helsinki.

5.3.2. Protocol

Subjects were seated on a coupled arm and leg stepping ergometer (TRS 4000, NuStep, Inc., Ann Arbor, Michigan, USA) as described previously (Stoloff et al. 2007; Zehr et al. 2007a). Participants were told to perform stepping movements consisting of an out-of-phase movement of the homolateral limbs. That is, while the left arm moved forward the right arm and left leg moved backward (Fig 5-1). There was no movement of the right leg (test or stimulated limb), which was comfortably placed on a customized rigid structure that kept the leg straight with the ankle at 90 degrees. A voluntary isometric contraction of the ipsilateral SO (iSO) at 10% of the maximal voluntary contraction (MVC) was maintained throughout the trials with the help of visual feedback. Each subject performed three motor tasks (Fig 5-1): 1) isolated contralateral leg movement (L); 2) bilateral arm movement (A); and 3) combined bilateral arm and

contralateral leg movement (AL). Visual feedback was provided to assist the subject in performing the stepping at 1Hz (one full extension and flexion cycle per second). Neoprene restraints were placed around the trunk in order to minimize movements of the trunk.

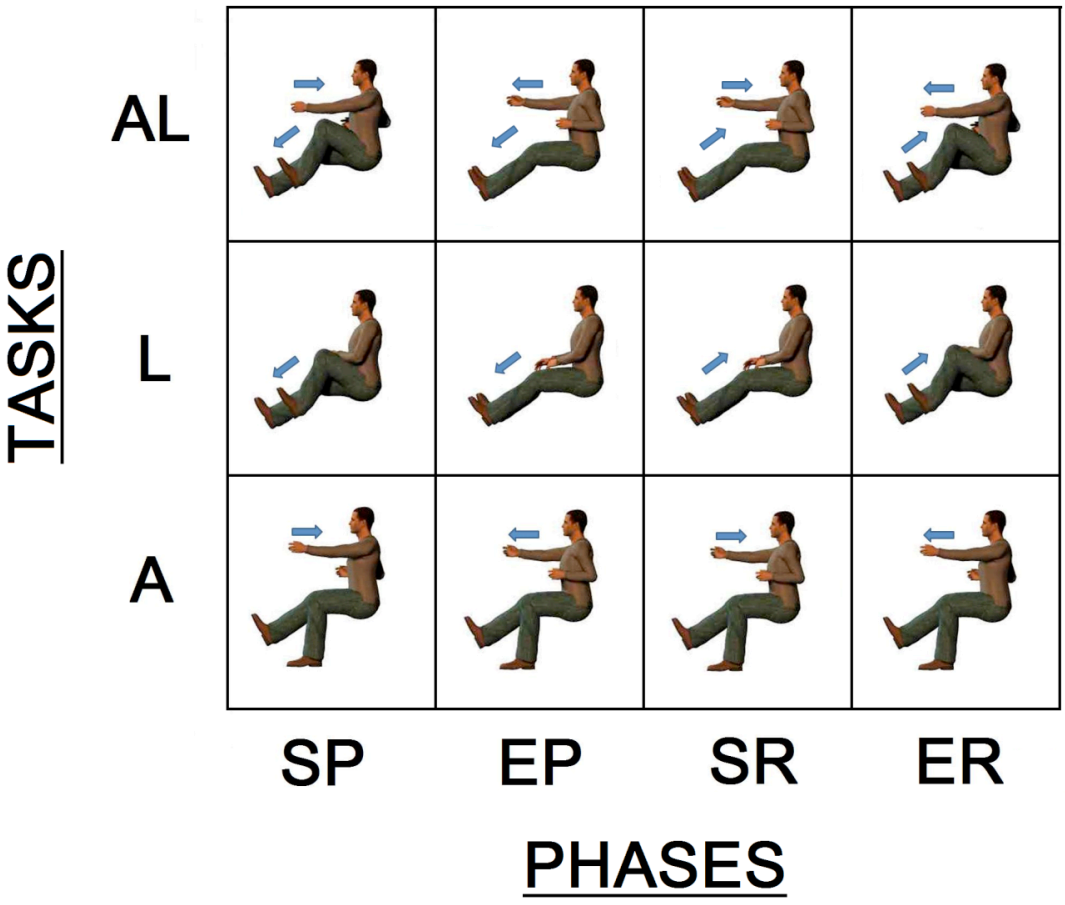


Figure 5-1: Matrix representing different motor tasks (rows) and phases (columns) where the SO H-reflex was sampled.
The right leg, in which the H-reflex was evoked, was always in the same static position (extended). The arrows represent the direction of the movement, i.e., reaching to or departing from the most extended or flexed position. Note that during A task (the bottom row of the matrix) the left leg is resting on the ground. The arm arrows indicate the direction of movement of the extended arm (irrespective of right or left). For instance, during AL task at SR the left foot is starting moving toward the pelvis while the right (extended) arm is at the beginning of the flexing movement as well.

For L and AL the contralateral foot was firmly fixed at the pedal of the ergometer, so that the subject could perform backward and forward movements of the leg without the assistance of the arms. For the A task the left leg was positioned beside the ergometer over a platform with the knee and ankle angles at 90 degrees.

Lightweight electrogoniometers (Biometrics Ltd) were attached across the elbow joint of the left arm and the knee joint of the left leg to trigger the stimulus delivery at the desired movement phase. Reflexes were evoked at four different points of the stepping cycle (using the contralateral moving leg as reference): 1) at the start of power phase (SP), when the leg begins pushing from a flexed to an extended position; 2) at the end of power phase (EP), when the leg is almost fully extended; 3) at the start of recovery phase (SR), when the leg begins pulling back from a fully extended position; 4) at the end of recovery phase (ER), when the leg is still pulling but almost fully flexed (Fig 5-1). Those phases are of interest as they previously have shown important effects on reflex modulation (Zehr et al. 2007a).

5.3.3. Data acquisition

Data were sampled at 2.5 kHz with a 12-bit A/D converter connected to a computer running custom-written (Dr. Timothy Carroll, University of New South Wales, Australia) Lab View software (National Instruments, Austin, TX). Sweep length was 80 ms with a 20 ms prestimulus window.

Surface EMG was recorded bilaterally from five muscles: anterior deltoid (AD); biceps femoris (BF); vastus lateralis (VL); SO, and tibialis anterior (TA) using disposable 1 cm Ag-AgCl surface electrodes (Thought Technologies) with inter-electrode distance of 2cm. The skin over each muscle was cleansed with rubbing alcohol swabs and ground

electrodes for EMG recordings were placed on bony landmarks near the selected muscles. EMG signals were amplified and band-pass filtered at 100 to 300 Hz (P511 Grass Instruments, AstroMed). For ipsilateral SO, the band-pass width was 100 to 1 kHz. EMG signals were full-waved rectified except for the ipsilateral SO.

5.3.4. Nerve stimulation

H-reflexes were evoked in the right SO by applying a percutaneous electrical stimulation (square wave pulse of 1 ms duration) to the posterior tibial nerve in the popliteal fossa using bipolar surface electrodes according to established protocols and methodologies (Zehr 2002; Carroll et al. 2006). Either a Digitimer (Medtel) constant current stimulator (model DS7A) or a Grass S88 stimulator (Grass Instruments, AstroMed) connected in series with a SIU5 isolator and a CCU1 constant current unit was used.

Nerve stimulation was delivered pseudo randomly between 3 and 5 s apart during all trials at one of the phases described above and for each task. Each trial lasted about 2 min. A 5 min rest period was observed between trials. Full H-reflex recruitment curves (RCs; n = 30 sweeps) were obtained in all conditions. Delivered current was measured using a mA-2000 Non-contact Milliammeter (Bell Technologies, Orlando, FL). Control "reference" recruitment curves were obtained with the subject in stationary position at the beginning, at the middle and at the end of each experiment. The static task involved keeping the contralateral arm fully extended and ipsilateral arm and contralateral leg fully flexed during isometric ipsilateral SO contraction at ~10% MVC.

The signal from the goniometers was used to trigger the EMG acquisition and stimulus delivery. During the A task the goniometer located on the elbow was used for

triggering, whereas during the AL and L the trigger signal was provided by the goniometer located on the knee. The threshold for the trigger was set at the beginning of the experiment by asking the subject to move his/her arms and legs in full flexion and extension. Similar procedures have been used in previous experiments for sampling H-reflexes in the legs at different relative positions of the arms during cycling (Frigon et al. 2003; Carrol et al. 2005; Loadman and Zehr 2007).

The ordering for performance of the three tasks and the four phases in which the stimuli were delivered were randomized for each subject.

5.3.5. Data processing

For reference, the mean value of rectified background EMG (corresponding to the 20ms prestimulus period) was calculated from each sweep. Peak to peak amplitudes of M-waves and H-reflexes were calculated offline with custom written software (Matlab, Math Works) from the single unrectified sweeps of EMG. For each subject M-waves and H-reflexes were normalized to the corresponding Mmax to reduce inter-subject variability.

The ascending limb of each recruitment curve was fit using a general least squares model of a custom three-parameter sigmoid function as described in Eq. (1)

$$H(s) = \frac{H_{\max}}{1 + e^{m(s50 - s)}} \qquad (1)$$

where Hmax is the upper limit of the curve, m is the slope parameter of the function, $s50$ is the stimulus at 50% of the largest H-reflex amplitude value (Hmax), and H(s) is the H-reflex amplitude at a given stimulus value s. Average Hmax was calculated from the three largest peak-to-peak H-reflex amplitudes. Variables analyzed were: Hmax

and the slope (*Slp*) of the ascending limb of the recruitment curve at 50% of the Hmax value. This slope was determined using Eq. (2)

$$Slp = \frac{m(H_{\max})}{4} \qquad (2)$$

Variables taken from the static control curves were compared to those from the same current values on the curves conditioned by leg cycling movement (Klimstra and Zehr, 2008; Zehr et al 2007b). That is, the same relative current needed to evoke a certain sized H-reflex on the static control recruitment curves was used in the curves fit to the movement trials and the "predicted" value obtained. Reflex parameters taken from the fitted curves are described as "at" ("@") the value from the respective static control. For example, modulation of the value for Hmax during static is H@100 during stepping tasks. Other "@" values were H@threshold and H@50.

Each of the 12 conditions (4 phases x 3 tasks) was referenced to static condition nearest in time. The parameters Hmax and current values at the highest H-reflex amplitude (current@max), at the 50% of the maximum H-reflex (current@50) and at the threshold for H-reflex (current@threshold), for each condition, were subtracted from the respective static condition. For instance, if a current value is negative in a given task and/or phase, it means that the point of the fitted curve (e.g., current at max) was shifted to the right in relation to static.

5.3.6. Statistics

STATISTICA software (StatSoft, Tulsa, OK) was used to perform repeated-measures ANOVAs on H-reflex parameters and background EMG. If the ANOVA resulted in a significant effect for task, a Tukey HSD post-hoc test was used to detect

differences between tasks for each phase. Planned comparisons were used to evaluate specific differences between conditions. The significance level was set at $p<0.05$ for all tests.

5.4. Results

Note that all parameters investigated during movement were referenced to the relevant specific static conditions (see *Methods* section).

5.4.1. Effect of different motor tasks on recruitment curve parameters

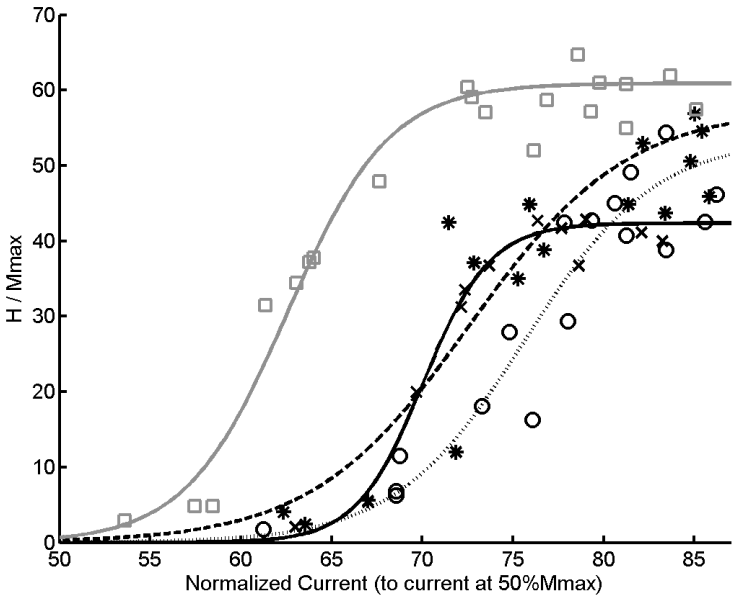
Overall, main differences between tasks were clustered at the transition phases of EP and SR. The details from the statistical analyses for parameters of H-reflex excitability extracted from the fitted recruitment curves are shown in Table 5-1.

Parameters	Phases of stepping movement			
	SP	EP	SR	ER
current@threshold	n.s.	n.s.	L *vs* AL*	n.s.
current@50	n.s.	L *vs* AL*	n.s.	n.s.
current@max	n.s.	L *vs* A * L *vs* AL*	n.s.	n.s.
Hmax	n.s.	A *vs* AL ** L *vs* AL***	n.s.	n.s.
H@50	n.s.	n.s.	L *vs* AL **	n.s.
H@100	n.s.	n.s.	L *vs* AL *	n.s.

n.s. = not significant; * $p<0.05$; ** $p<0.01$; *** $p<0.001$;

Table 5-1 Overall results from repeated measures ANOVA and planned comparison analysis (ran only for EP and SR).
The comparisons were made between tasks (A = arms movement; L = contralateral leg movement; and AL = arms and leg movement) within each phase.

A)



B)

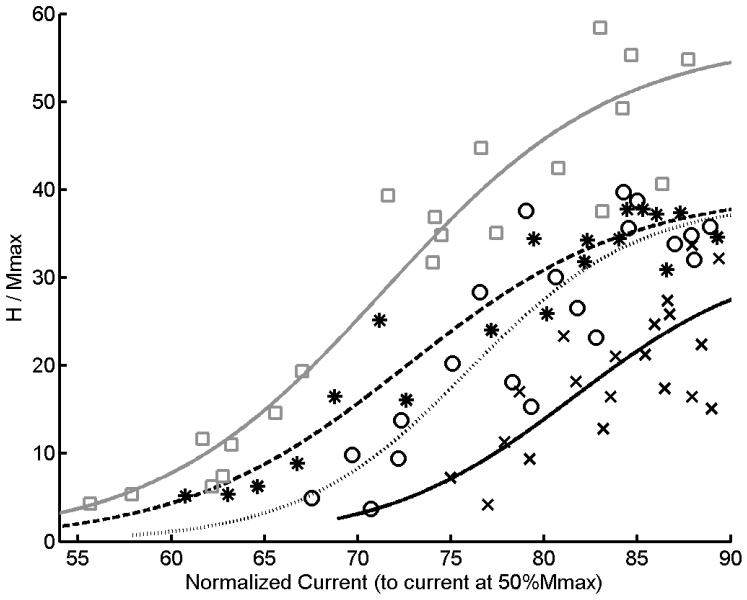


Figure 5-2: Single subject H-reflex recruitment curves (RCs).
The symbols represent each point of the RC and the lines are the best sigmoidal fit for all tasks: a) in these curves one can notice the rightward shifting of current parameters and increased Hmax for L compared to AL at EP phase. For this subject, the movement of arms

had a stronger effect on reflex amplitudes (dotted line); b) differences for current@threshold, H@100, and H@50 at SR phase. One can notice the rightward shifting of the fitted RC during AL, followed by A and L. Conditions: Static (□; solid gray line); AL (×; solid black line); L (❋; dashed line); A (○; dotted line).

Figure 5-2a shows the curve fitting evaluated from the data corresponding to all tasks (including static condition) from a single subject at EP phase. Changes in the shape of the sigmoid fit reflect changes in the current and amplitude values at different points in the curve. Group results averaged across all subjects are displayed in Figure 5-3. The relative values of current@max for L are significantly shifted with respect to A and AL ($p<0.05$). Also, current@50 during the task L showed a significant shift to the right compared to AL ($p<0.05$). These differences are also seen in the single subject data in Fig. 5-2a.

Significant differences were detected at the EP phase for Hmax (Fig. 5-3d), which was more suppressed during AL compared to A ($p<0.01$) and L ($p<0.001$). There were no significant differences between tasks for both slope of the ascending limb of the recruitment curve and H@threshold at all phases. However, at the SR phase, a noticeable difference for current@threshold is depicted in figure 5-2b for one representative subject, indicated by the rightmost AL curve compared to A and L. The group data showed a significant difference between AL and L for current@threshold at SR phase ($p<0.05$) (Fig. 5-3a).

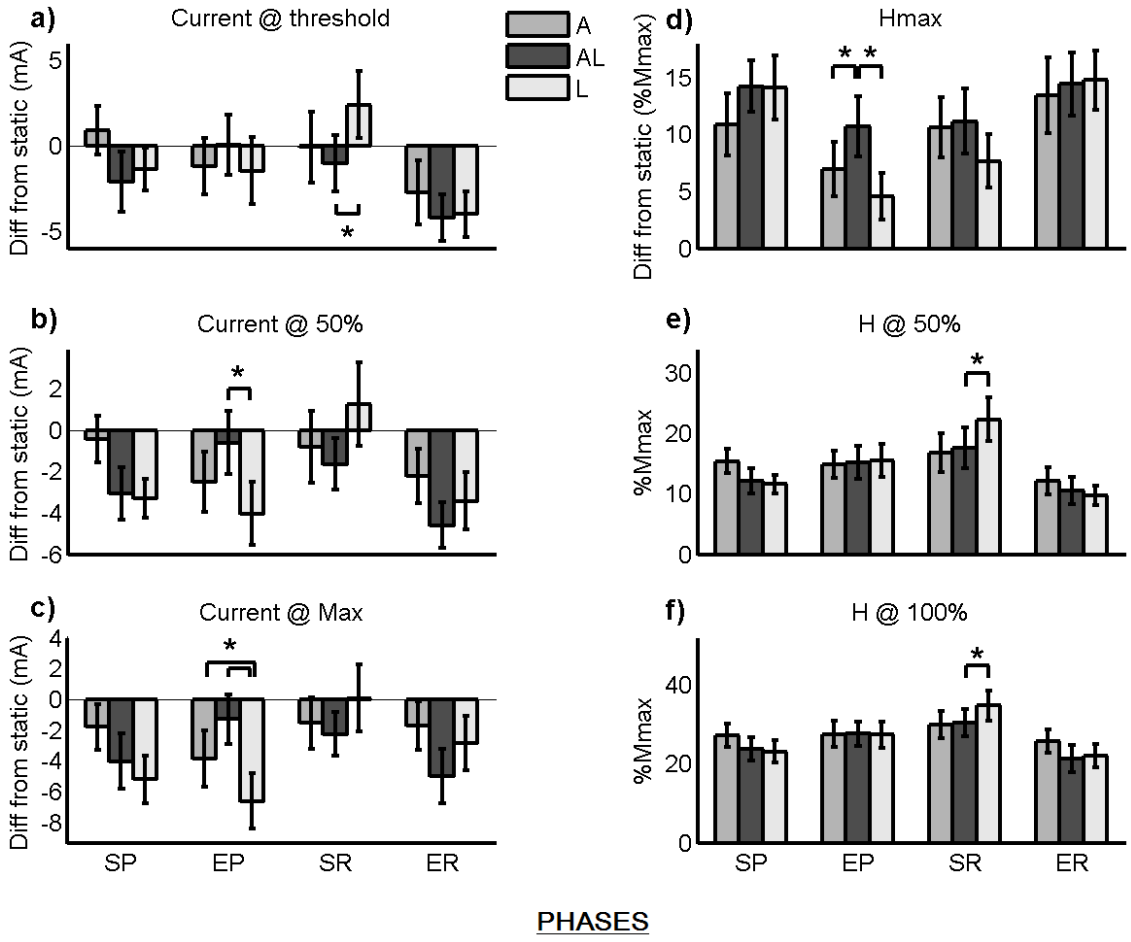


Figure 5-3: Mean values of RC parameters estimated from all subjects for all conditions tested. Asterisks indicate significant diffrences (P<0.05).

Figure 5-2b shows a downward shift of the fitted RCs progressing from L, A and AL, corresponding to a steady reduction of H@values between tasks in the direction L to A and AL. During the AL task H@50 ($p<0.01$) and H@100 ($p<0.05$) amplitudes were both more suppressed than L at the SR phase (Figs 5-3e and f, respectively). At this phase, AL task suppresses H-amplitude values at lower levels of stimulus intensity without altering the maximum output of the H-reflex pathway. This increased contribution of A to the combined AL movement was also observed for the parameter Hmax at EP (see Fig. 5-3d).

5.4.2. Background muscle activity

No significant differences were seen in muscles activation in the test limb across the tasks. The iSO muscle activity was constant along the trials. Significant differences in muscle activity were detected across tasks for cTA ($F_{(2,28)}$= 17.78; $p<0.0001$), cVL ($F_{(2,28)}$= 26.69; $p<0.0001$), and iAD ($F_{(2,28)}$= 84.38; $p<0.0001$) (Fig 5-4). At SP phase, cVL showed differences between tasks A and AL ($p<0.001$); A and L ($p<0.001$); L and AL ($p<0.05$). This indicates that subjects showed a higher activation of leg extensors at the onset of the pushing movement during L compared to AL. Similarly, iAD showed significant differences among all tasks (A and AL: $p<0.001$; A and L: $p<0.001$; L and AL: $p<0.001$).

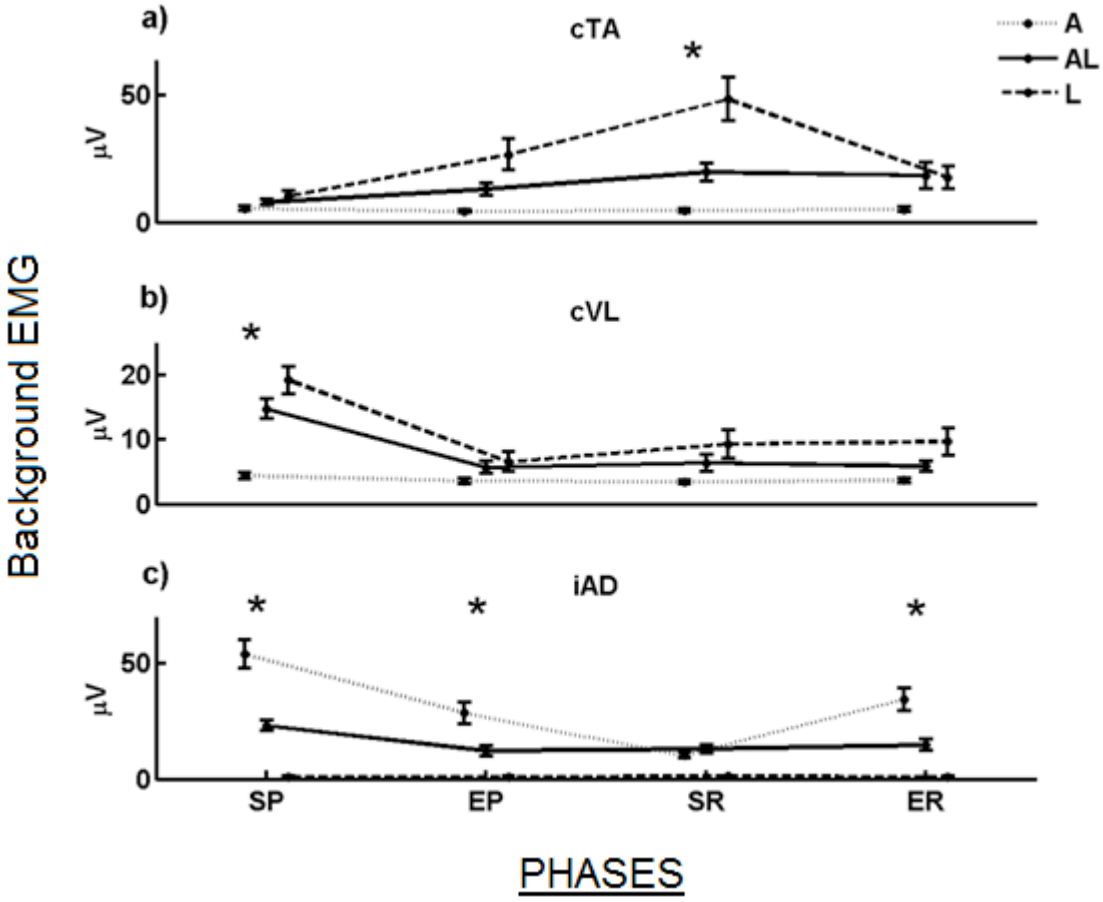


Figure 5-4: Background EMG activity from three different muscles. Asterisks indicate significant diffrences (P<0.05) betwenn tasks A (for iAD) or L (for cTA and cVL) and AL at a given phase.

The EMG activity of iAD also differed across tasks at EP (A and AL: $p<0.001$; A and L: $p<0.001$; L and AL: $p<0.05$). The activity of iAD during A was significantly higher than AL at this phase, in which the right (ipsilateral) arm is reaching its more extended position.

During the flexion movement when the leg was still extended (SR phase) cTA activity was different for all tasks (A and AL: $p<0.05$; A and L: $p<0.0001$; L and AL: $p<0.0001$). The difference observed between L and AL for cTA indicated that its activation was higher during L task compared to the movement of the three limbs

together. This suggests that when the subjects start pulling back the leg the TA muscle was used, perhaps involuntarily, to assist in the onset of this phase. This activation was higher in the absence of the arms.

When the left arm reached full extension, at the end of the recovery phase of the contralateral leg (ER), the activity of iAD was higher during A compared to AL ($p<0.001$) and L ($p<0.001$). In addition, the task AL differed from L ($p<0.05$) at this phase.

5.5. Discussion

The present work provided clear evidence for interaction between arm and leg neuronal pathways that regulate rhythmic stepping movement. This interaction was revealed with the test limb stationary thus reducing the mitigating influence of its movement on reflex expression. From these results it is clear that there are significant contributions from arm movement to the overall reflex suppression during a combined arm and leg task. This differential effect of activity related to the arms is manifested at phases where the reflex suppression is expected to be higher and which roughly equate to beginning of stance and end of swing (Zehr et al. 2007a). Further, the analysis of several parameters extracted from the recruitment curves showed that this reflex modulation is specific for different subsets of the motoneuronal pool.

It is also of interest that the absence of differences between tasks for some phases suggests that arm or leg movement yields similar overall suppression to that observed during AL task.

5.5.1. Significant remote effects are evidenced through the examination of distinct reflex pathways

We previously provided evidence for neuronal linkages between the arms and legs in studies using either cutaneous (Balter & Zehr 2007) or H-reflexes (Zehr et al. 2007a, b) as neural probes. In those studies simultaneous arm and leg movement was performed with all four limbs. A concern in the prior studies was that by the effect of arm movement may have been obscured by the effect of moving test limb. The present protocol provided definitive additional evidence for arm and leg neuronal linkage by using a revised methodology. The present findings strengthen conclusions reported during arm and leg cycling (Balter and Zehr 2007; Zehr et al. 2007b) for both cutaneous and H-reflex studies as well as four limb stepping (Ferris et al. 2006, Huang and Ferris 2004) and walking (Phadke et al. 2010). An important advance of the present study was to determine the effect of remote limb movements on reflex modulation without homonymous interference (coming from the test limb).

The relative contribution of arm activity was previously shown to be phase-dependently modulated during simultaneous cycling movement of both upper and lower limbs (Balter and Zehr, 2007). Results from this study showed that the significant contribution of arms was manifested in some phases of the rhythmic arm and leg cycling movement. Further, the most important phase-dependent arm contribution occurred in the leg positions that were equivalent to the transition from swing to stance phase during walking (see Zehr et al. 2007a for comparisons to walking phases). However, the estimate of the extent of direct contributions of arm activity could have been obscured

and possibly minimized by the simultaneous activity of the test limb.

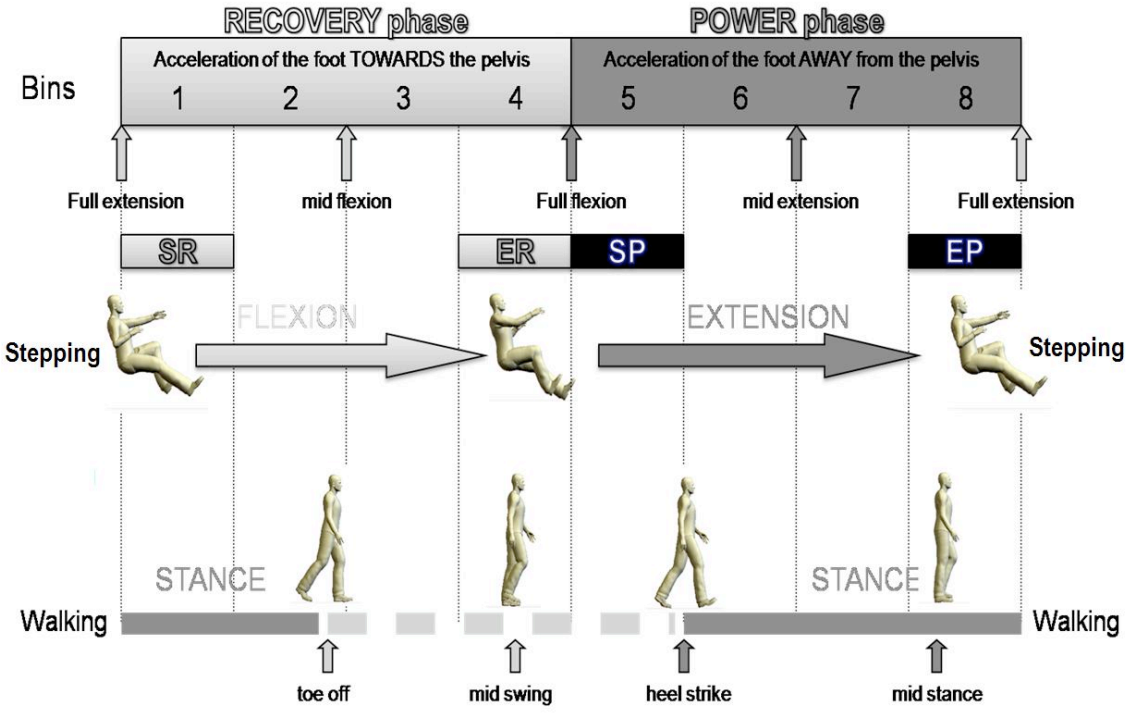


Figure 5-5: Relating phases of movement for recumbent stepping and walking. The descriptors flexion–extension for stepping and stance–swing for walking refer to the overall motion of the right foot that would move towards or away from the pelvis. The reference is the ipsilateral (right) stationary leg. For instance, the phase that showed more pronounced effect from arm movement were EP and SR (for the left leg), which for the right leg, if it was moving as in the indicated in the figure, would be ER and SP or mid swing and hell strike (modified from Zehr et al. 2007a).

Here, we showed a significant effect of arm on leg activity at the SR phase, which corresponds to a similar phase in Balter and Zehr (2007) related to late swing and early stance of walking (Fig. 5-5). Additionally, we observed a significant contribution from the arm activity at mid swing. The present results obtained from H-reflex parameters extended these previous observations on cutaneous reflexes by showing a significant effect from arm movement, thus reinforcing the notion of the existence of a neuronal linkage between upper and lower limb spinal cord oscillators (Dietz at el. 2001).

Moreover, the RC analysis suggests that this descending cervical effect seems not to be evenly distributed throughout the motor units within the pool (see next section).

The present findings also provide further support for the argument that neural activity related to the control of arm movements has access to the legs at certain phases of locomotor movement. It was observed a stronger contribution of arms movements to the overall reflex suppression during AL task compared to leg movement than previously estimated. Here the arm effect is not superceded by the leg effect (as observed in Balter and Zehr, 2007) but may actually be stronger than the leg. For instance, at SR phase the movement of arms accounted for the same suppression observed during AL task, which means that leg movement had almost no participation on the suppression of H-reflex during the three limb movement (see Figs. 5-3e and f). These results highlight a significant contribution of arms to reflex modulation during the stepping movement at specific phases. One may suggest that this strong contribution is a result of the absence of test leg movement that could "contaminate" the reflex modulation and make the contribution of the leg, during the task L that would involve both legs, stronger than the arms. Therefore, the conditioning effect from arms could be masked by the test limb movement.

It remains to determine if this effect emerges from the AL task itself. That is, since there is no movement of the test limb this may represent a novel task for the nervous system. The significant contribution of the arms could be inherent to a task-dependent modulation of interlimb coupling within the nervous system.

5.5.2. Transmission from the arms is differentially specified for different populations of motor units

Rhythmic movement and cutaneous inputs from the upper limbs modulates the lumbar spinal cord excitability. It was demonstrated that cutaneous stimulation at the wrist (superficial radial nerve) facilitates SO H-reflex amplitudes in stationary legs (Zehr et al. 2004). Importantly, this facilitation persisted during rhythmic arm cycling. In fact, there was a linear summation of the facilitatory effect coming from superficial radial nerve and the suppressive effects from arm movement bring the conditioned leg H-reflex toward its control value. It is also relevant to note that cutaneous input from the hand helps overcome the conditioning effect of the legs during simultaneous arm and leg movement with all four limbs (Zehr et al. 2007b). We proposed that cutaneous inputs from the hand could gate the sensory feedback from other remote sources to the motoneurons of leg muscles (Zehr et al. 2004). Further, the inputs coming from a remote moving limb (arms) have priority over the inputs coming from lower limbs that are not moving. This may also explain the observation with the current three-limb protocol of a cumulative conditioning effect of arm and leg movements.

Interestingly, our use of H-reflex recruitment curve fitting here has revealed a differential effect of the conditioning of arm movement on reflex excitability. At the EP phase AL suppression altered the maximum output of the H-reflex pathway without modifying H-reflex amplitudes at lower levels of stimulus intensity (i.e., no significant changes observed for amplitude of H@50). The results at this phase suggest the existence of an additive effect of A and L movement to overall AL suppression (see Fig. 5-3d). The algebraic sum of the values obtained from L and A (~12% Mmax) and the value obtained during AL (~11% Mmax) are quite similar. This combined effect from arms and legs at

EP points to the interaction between arm and leg. Similar interaction was observed in a previous study using cutaneous conditioning, i.e., the A + L values were higher than those observed for AL (Zehr et al. 2007b). However, the present results show that conditioning from both movements sum. Therefore, one may surmise that the movement of arms and contralateral leg in the current experiments contribute in an independent way to SO H-reflex suppression. Moreover, this suppression is revealed only for the highest H-reflex amplitudes (Hmax) including the largest representation of motor units in the available pool and in a phase were no significant arm contribution was detected (mid to end swing; Fig. 5-5) (Balter and Zehr, 2007).

The fraction of the motoneuronal pool composed by the earlier recruited motor units (the small ones with the lowest threshold for Ia input) are strongly affected by the descending conditioning at the SR phase, as suggested by the significant difference found for the parameter current@threshold between AL and L tasks. Additionally, the amplitudes of both H@50 and H@100 during A and AL were very similar indicating that upper limbs strongly contribute to the suppression of both the earlier recruited and the higher threshold motor units during the combined arms and leg movements.

Taking together the results for amplitude and current one may suggest that, depending on the phase of movement, the output of rhythmic arms movement can affect distinct sub-populations of motoneurons in the SO pool based on their input properties. In other words, changes in the input-output relations of the motoneuronal pool may alter the recruitment gain of motoneurons across phases (Kernell and Hultborn 1990).

The modulation of the H-reflex during gait cycle is characterized by the strongest inhibition at the beginning of the stance phase (Capaday and Stein, 1986; Crenna and

Frigo, 1987). This is in consonance with what one would expect based on the role of ankle extensor muscles during the gait cycle. During the stance phase there is a lengthening contraction of triceps surae muscles resulting in increased Ia firing. This excessive Ia discharge, which may lead to a strong activation of extensors during this phase, needs to be counteracted to prevent unwanted enhancement in ankle joint stiffness that could disrupt the gait (Pierrot-Deseilligny and Burke, 2005). Inhibitory mechanism acting on the Ia feedback might be involved to compensate for this increased stiffness. One of the strongest candidates would be the presynaptic inhibition driven by descending commands of cervical origin related to rhythmic movements of the arms (Frigon et al. 2004). The current findings are in accordance with this view since the strongest contribution of arms to reflex suppression was observed in phases of the three-limb stepping movement that correspond to end of swing and heel strike of walking (see Fig. 5-5).

5.5.3. Methodological considerations

Given there were no differences in the background EMG in the test limb between tasks at a given phase of movement it reasons that all task-dependent effects arose from activity of the non-test limbs. Some significant differences were seen in the muscle activation levels in the non-test limbs between the tasks. However, in most cases these differences were anticipated given that the certain muscles were intentionally quiescent if movement of that respective limb was not required for the task. For example, one would expect leg muscle activity to be different between the A task versus the AL task. The cTA and cVL muscles were more active when subjects used only their left leg to give the initial propulsion in both phases SR and SP, respectively. Bikmullina and co-workers

(2005) showed that the effects of the voluntary contraction of cTA on SO H-reflex amplitude were closely related to the higher intensity of muscle contraction compared to that seen in the current study. Interestingly, about half of the subjects tested did not show any measurable effect (Bikmullina et al. 2005). In addition, effects arising from afferents in the contralateral quadriceps muscles do not affect the iSO H-reflex (Katz et al. 1977), pointing to the assumption that the differential activation of the cVL does not induce changes in the ispsilateral reflex excitability. Therefore it is unlikely that differences in leg muscle activation in non-test limbs influenced the results.

The activity of iAD was higher during task A than task AL. It means that the effort to perform ipsilateral arm movement was higher when the contralateral leg was not assisting the movement. The discrepancy found in iAD activation could be accounted for by the distinct neuro-functional demands for the execution of movement by the arms, i.e., it appears to have a neuronal overcompensation in the ipsilateral arm for the stationary leg. However, it has been suggested that the effect of increased load on the arms during rhythmic movement (hence, increased arm muscles activation) do not affect H-reflex amplitude (Hundza et al. 2010, unpublished results). Therefore, we suggest that these discrepancies observed for arm movements have no serious implications on the present results.

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6. Biomechanical outcomes and neural correlates of cutaneous reflexes evoked during rhythmic arm cycling[5]

6.1. Abstract

During walking reflexes evoked by stimulation of the foot yield neural and mechanical effects consistent with a stumbling corrective response. Concurrently, the modulation of reflexes during rhythmic arm movement parallel the neural responses observed in the legs. However, studies of arm cycling have not yet involved detailed biomechanical measurements. The purpose of this study was to explore the mechanical outcomes of stimulating a cutaneous nerve innervating the hand during arm cycling. We hypothesized that: 1) there would be measurable mechanical effects; and, 2) the mechanical changes will be interpretable in a functional context related to limb trajectory modification. Participants performed standing and seated arm cycling while EMG, kinematic, and kinetic data were recorded from the arm and trunk muscles. Cutaneous reflexes were evoked by stimulating the superficial radial nerve. The results show that mechanical responses to cutaneous stimulation of the hand during arm cycling are related to the task and phase of movement, are consistent with the anatomical location of the stimulus and are correlated to the neural responses. Therefore, these responses are comparable to functionally relevant responses in the legs during rhythmic movement. However, unlike the responses in the lower limbs, the mechanical responses are not consistent with the functional context of arm cycling and could be functionally tuned to a free moving limb

[5] Klimstra M.D., Thomas E., Zehr E.P. Manuscript in preparation. A version of this chapter was presented at Society for Neuroscience 2009 Washington. (80% contribution to project – 80% of data acquisition, analysis, statistics, figures and tables and written manuscript)

yet shaped by the arm cycling task. Overall, these results provide evidence for mechanical correlates to neural responses during arm cycling and further support parallels between the neural regulation of arm and leg rhythmic movement.

6.2. Introduction:

Cutaneous reflexes evoked in leg muscles by stimulation of nerves innervating the foot and hand produce mechanical effects that are associated with functionally relevant changes in limb trajectory (Haridas & Zehr, 2003; Zehr & Stein, 1999). For example, Zehr et al. (1997) found that stimulation of the top of the foot resulted in a mechanical "stumbling corrective response" involving changes in limb kinematics similar to the pattern observed in the cat (Forssberg, 1979b). An integrated neural and mechanical measurement approach in the legs illustrated that cutaneous reflexes function to appropriately correct or assist ongoing movement (Zehr & Stein, 1999). Cutaneous reflexes in leg and arm muscles are similarly modulated in task-, phase-, and nerve-specific patterns during rhythmic movement suggesting a common mechanism of neural control (Zehr & Duysens, 2004). Recent evidence suggests that humans utilize quadrupedal interlimb mechanisms for locomotion that could be exploited during rehabilitation (Ferris et al., 2006; Zehr et al. 2009). Therefore, the use of rhythmic arm movement as a rehabilitative tool has received recent attention (Ferris et al., 2006; Klimstra et al. 2009). While the biomechanical, functional, and behavioural relevance of cutaneous reflexes in the legs during walking is clear, corresponding neuromechanical analysis of rhythmic arm movement has not been conducted. The purpose here was to explore the neural and biomechanical consequences of cutaneous nerve stimulation

during arm cycling and interpret them in a functional context. We hypothesized that: 1) there would be measurable mechanical changes in arm kinetics and kinematics evoked by cutaneous nerve stimulation of the hand; and, 2) the mechanical changes should be interpretable in a functional context related to trajectory stabilization. We also included standing arm cycling to allow us to compare neuromechanical correlates of cutaneous reflexes in different postures and levels of stability.

6.3. Methods:

Seven subjects (23-42 yrs) free from neurological disease participated in the experiments with informed, written consent in accordance with the Human Research Ethics Board at the University of Victoria and the Declaration of Helsinki. Arm cycling was performed at 1 Hz on an instrumented arm cycle ergometer (Monark, Model 871E, Varberg, Sweden) standing and sitting while cutaneous nerve stimulation was applied. An additional set of trials were obtained during five seated stationary trials. At this time reflexes and stimulation intensity perception were recorded (Zehr & Kido, 2001).

6.3.1. Cycle timing, kinematics and kinetics

The position of the ergometer crank arms was determined from an optical encoder and expressed with respect to clock face position (12 phases/o'clocks) (Figure 6-1B). Angular positions of the right shoulder, elbow, and wrist were measured with electrogoniometers (Biometrics Ltd., Gwent, UK) (Figure 6-1A). Forces were measured at the right hand using a Gamma Sensor 6-axis force transducer (ATI Industrial Automation, Model FT06598, Apex, USA).

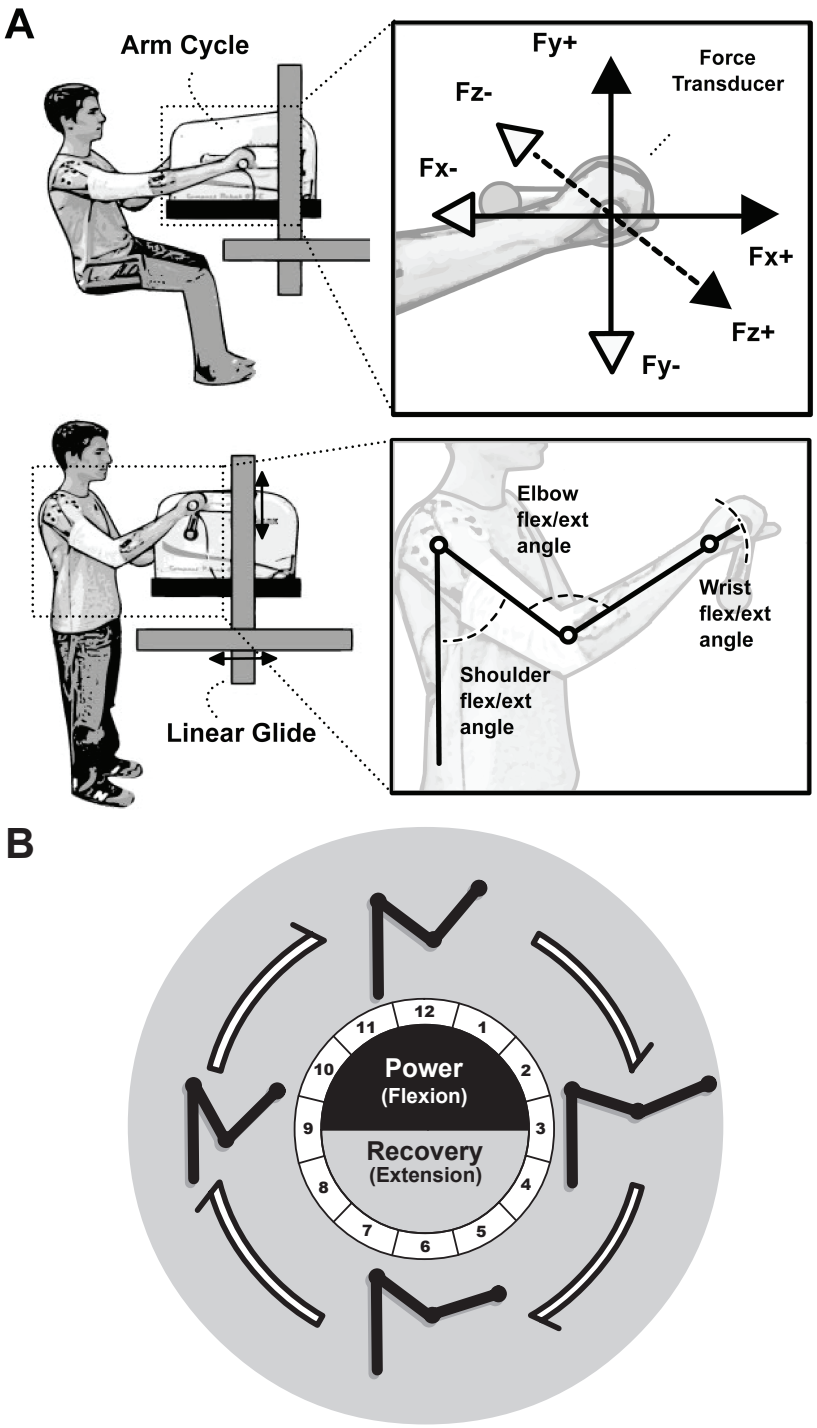

Figure 6-1: Experimental setup. (A) Participants cycled at 1 Hz in seated and standing postures while EMG, kinematic, and kinetic data were recorded from the right arm and trunk muscles.
Kinetic and kinematic conventions for data collected from the right hand are shown in the top and bottom right panels in A, respectively. Top Panel: the force transducer was mounted parallel to the crank arm such that the handle projects orthogonal to the crank

arm. In this orientation the axes of force measurement are oriented such that the x-axis is horizontal, the y-axis is vertical and the z-axis is perpendicular to both the x and the y-axes. In order to ensure that the force axes are consistent throughout the movement cycle the force transducer was attached to a set of two linear glide bearing (modified from a drafting table by Dave Smith, Physics Shop, University of Victoria). Conventions for forces were: upward (Fy+); downward (Fy-); forward (Fx+); backward (Fx-); medial (Fz-); and, lateral (Fz+). Bottom Panel: angular positions of the right shoulder (flexion/extension), elbow (flexion/extension), and wrist (flexion/extension and abduction/adduction) were measured with biaxial electrogoniometers. (B) The phases of the arm cycling movement are shown broken into 12 equidistant phases corresponding to a clock face. Thus, the position when the ipsilateral crank was pointing straight up is defined as 12 o'clock with positional definitions continuing clockwise. A simplified stick figure represents the orientation of the trunk, arm and forearm at 12, 3, 6 and 9 o'clock connected by arrows showing the clockwise movement direction. Further the terms power and recovery are used to signify the movement of the whole limb away from (flexion) and towards the body (extension) respectively similar to a convention used for other rhythmic tasks. (Zehr et al., 2007).

6.3.2. Nerve stimulation

Cutaneous reflexes were evoked with trains (5 X 1.0 ms pulses at 300 Hz) of stimulation delivered pseudorandomly (~ every 2 to 4 seconds) to the superficial radial (SR) nerve with a Grass S88 (Grass Instruments, AstroMed Inc.) stimulator connected in series with an SIU5 isolator and a CCU1 constant current unit. 1-cm Ag-AgCl surface EMG electrodes (Thought Technologies Ltd, Montreal, PQ, CAN) were placed in a bipolar configuration on the dorsal surface of the forearm just proximal to the radial head. Non-noxious stimulation was applied at an intensity set at ~2x radiating threshold (RT, defined as radiating paresthesia) for each subject.

6.3.3. Electromyography

The skin was cleansed with alcohol and electrodes were applied in bipolar configuration (~2 cm interelectrode distance) longitudinal to the predicted path of the muscle fibres. Muscles included the anterior (AD) and posterior (PD), and middle deltoid (MD), biceps (BB) and triceps (TB) brachii, flexor (FCR) and extensor (ECR) carpi radialis, and the cervical (ES-C), thoracic (ES-T), and lumbar (ES-L) erector spinae on the right side.

Ground electrodes were placed over the olecranon, acromion process, and clavicle. EMG signals were preamplified and bandpass filtered at 100–300 Hz (P511 Grass Instruments, AstroMed, Inc.).

6.3.4. Data acquisition and analysis

Data were sampled at 1000 Hz with a 12 bit A/D converter connected to computers running custom-written LabView (National Instruments) software. Offline data were analysed using custom written software (Matlab, MathWorks, Inc., Natick, MA, USA). After parameter-appropriate filtering (see below) data were separated into 12 equal phases. Responses to stimuli occurring in the same phase of the cycle were aligned and averaged (n=~10–20 per phase) together. Averages from the same phase of the cycle during unstimulated cycles were then subtracted from each of the corresponding 12 averages after stimulation yielding subtracted reflex EMG, kinematic and kinetic traces.

6.3.5. EMG analysis

Cutaneous reflexes. For each subject, subtracted EMG traces, normalized to peak unstimulated EMG from each muscle, were analyzed for peak reflex amplitudes at early (~50–75 ms) and middle (~75–120 ms) latencies. Responses were considered significant if they exceeded a 2-SD band of the mean value of the residual prestimulus EMG. Additionally, the average cumulative reflex activity occurring 150 ms post stimulation (ACRE150) was evaluated as a "net reflex" response. This approach is well correlated with kinematic responses in the lower limbs (Zehr et al., 1997). This measure involves calculating a subtracted reflex then cumulatively summing the signal. The summed value is then divided by the time interval of integration to measure an overall reflex effect. Net reflex values were normalized to peak EMG.

Background EMG patterns. Control EMG amplitudes were calculated for each phase of the movement cycle from unstimulated ("control") trials.

6.3.6. Kinetic and kinematic analyses

Mechanical data were low pass filtered at 20 Hz using a dual-pass third order Butterworth filter. Stimulated data were subtracted from unstimulated data to yield a reflex trace. Mechanical reflex changes were analyzed within a 140-220 ms window post stimulus (Zehr et al., 1997). Responses were considered significant if they exceeded a 2-SD band of the mean value of the prestimulus level of the ongoing mechanical parameter.

6.3.7. Statistics

In all instances, analysis was conducted on averaged values for each subject from each phase of the movement cycle. Repeated measures analysis of variance (RM ANOVA) was used to determine main effects of task (posture) and phase and interactions. A Tukey HSD post hoc analysis was performed when significant differences were found. Linear regression was used to determine significant relationships between kinematic responses and net reflexes for each phase. Descriptive statistics included means ± standard error of the mean (S.E.M.). Statistical significance was set at $p < 0.05$.

6.4. Results:

6.4.1. Background EMG

All muscles demonstrated phasic activity with few differences between tasks. Significant differences between seated and standing postures were seen only in AD and ESL. In AD, the peak values occured in different phases between the two tasks. In ESL, during seated arm cycling the peak activity was higher and there was greater depth of modulation as more phases were significantly lower than the peak compared to standing arm cycling.

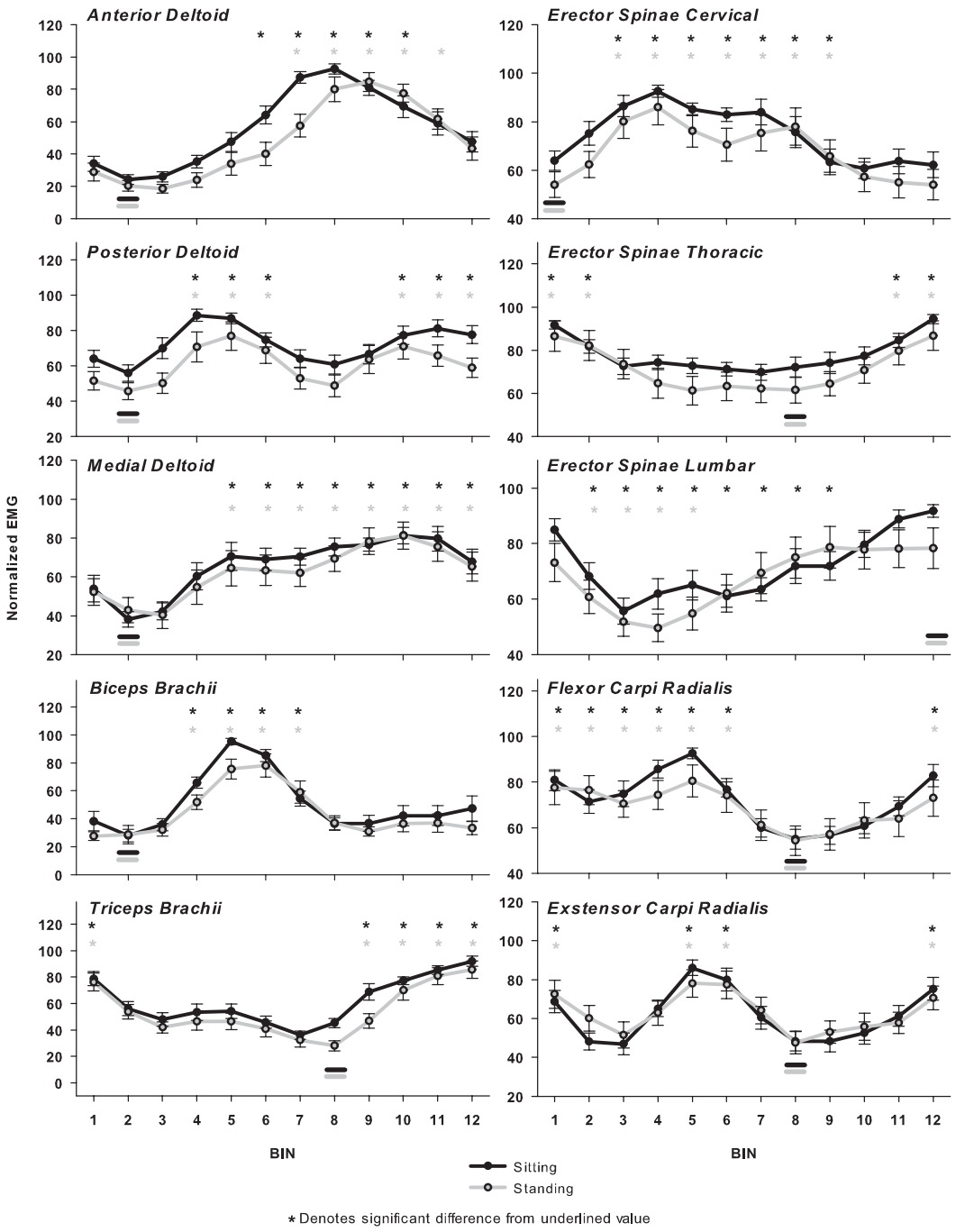

Figure 6-2: Background EMG for seated and standing trials for arm movement throughout the cycle broken into 12 phases which correspond to a clock face.
For each muscle, EMG amplitudes were normalized to the peak value observed in a given subject across the movement cycle to allow comparison across subjects. All values are means ± SE. The plots are in relation to the position of the right arm in the movement cycle which begins (far left) from the highest point (12, o'clock) and continue in a clockwise manner to end at the same point (far right). Significant differences in phase as compared to

the largest or smallest response (signified by the underlined value) are shown across the phases.

6.4.2. Cutaneous Reflexes

At early latency, all muscles presented significant responses but there were few cases of task and phase related differences (Figure 6-3). In AD there was a significant phase-modulation shown only during seated cycling as an inhibitory response at 7 o'clock. In PD there was phase-modulation with a facilitation at 5 o'clock only during standing cycling. Further results show equivalent phase-related modulation during standing and seated arm cycling in BB (inhibition at 6 o'clock) and ESC (facilitation at 4 o'clock). For middle latency (Figure 6-4) there was significant phase related modulation in BB and ESL. Additionally, in agreement with previous methodology, there were no differences between subject perceived stimulus intensity across static postures (Zehr & Kido, 2001).

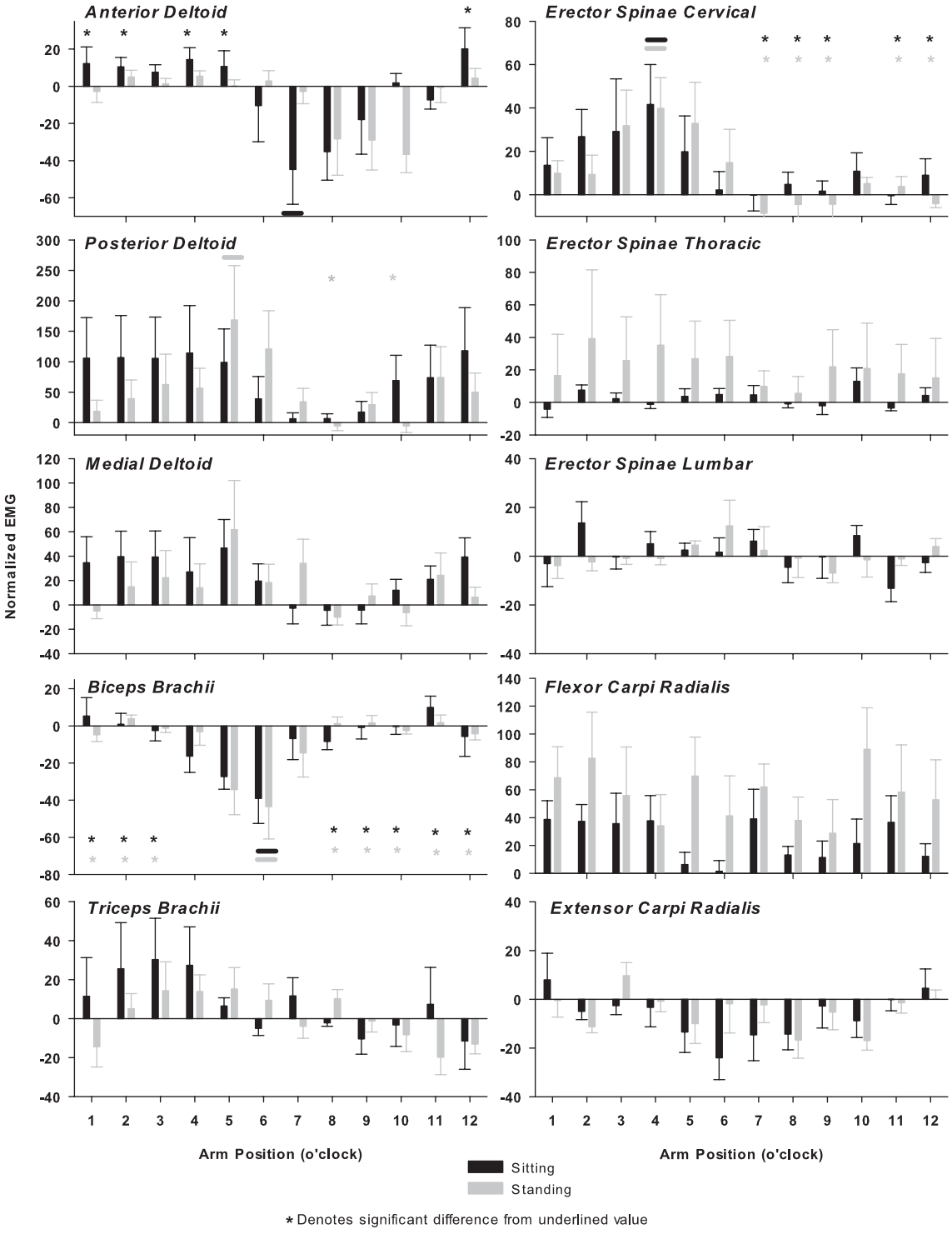

Figure 6-3 Early latency (50-75 ms post-stimulus) reflex EMG for seated (black) and standing (grey) arm cycling. All values are means ± SE.

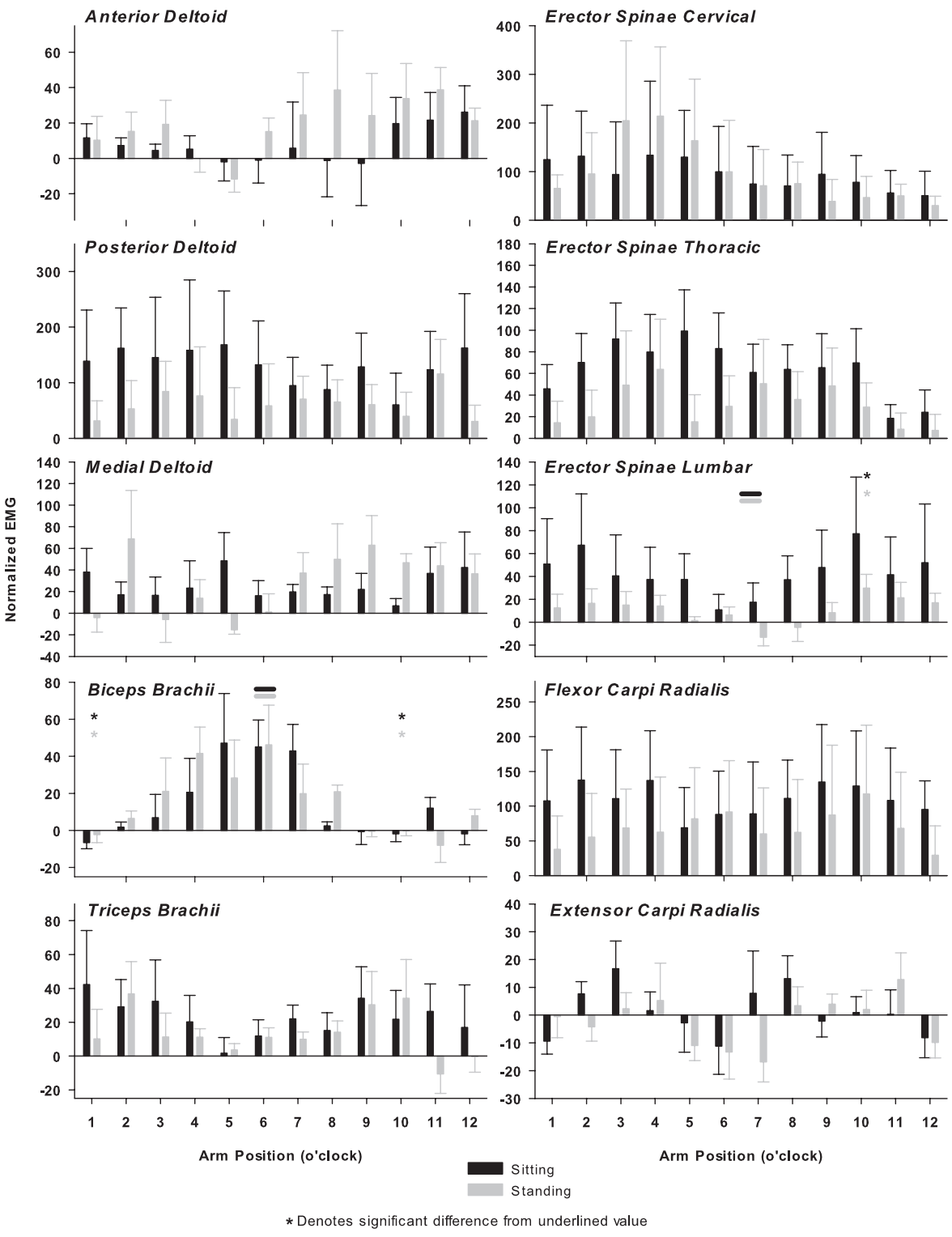

Figure 6-4: Middle latency (75-120 ms post-stimulus) reflex EMG for seated (black) and standing (grey) arm cycling. All values are means ± SE.

6.4.3. Net Reflexes

Net reflexes (ACRE150) for seated and standing cycling are shown in figure 6-5. There was a main effect for phase in PD and EST during standing and seated arm cycling shown as a significant facilitation at 5 o'clock in PD and 4 and 5 o'clock in EST.

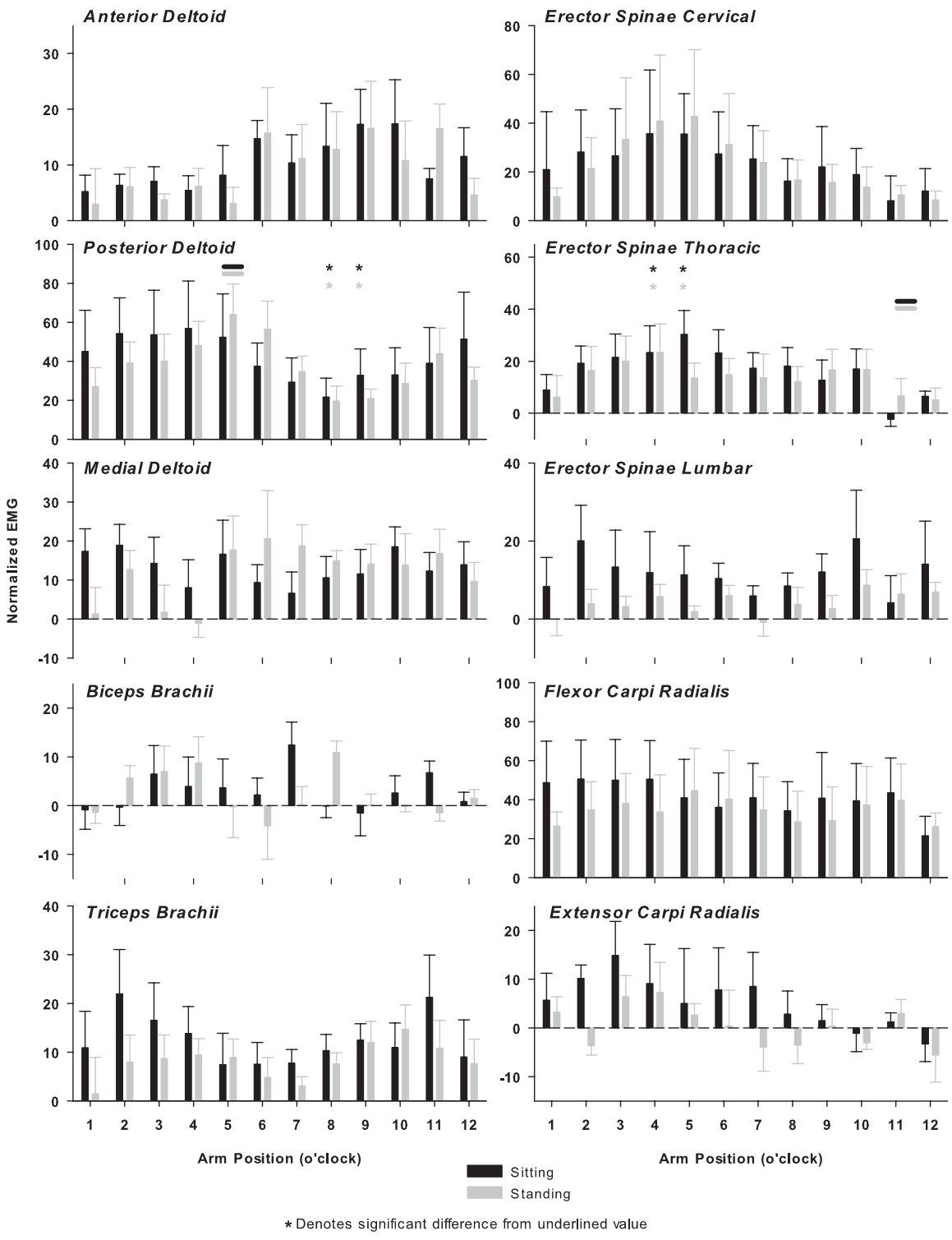

Figure 6-5: Net reflexes for seated (black) and standing (grey) arm cycling for all muscles. All values are means ± SE.

6.4.4. Kinetics and kinematics

Forward/backward and upward/downward forces were negative and modulated across phases such that they were less negative or zero during power and more negative during recovery (figure 6-6). Also, power and recovery transitions reflected gradual changes in the force profile consistent with changes in movement path trajectory. There were no main effects for arm cycling posture for kinetics measured at the hand and all directional forces demonstrated significant phase related differences (figure 6-6). Forward/Backward and Medial/Lateral forces demonstrated a main effect for stimulation conditions. For example, there was a significant backward force evoked by stimulation during seated arm cycling at 1-4 o'clock and standing arm cycling at 2-5 o'clock. Also, during seated arm cycling there was a significant medial force at all phases except for 6-8 o'clock and only a significant medial force at 3, 9-11 o'clock during standing arm cycling. Additionally, there were no observable kinetic changes evoked by stimulation during the static arm postures. There was a main effect for task for shoulder flexion/extension (see figure 6-7 where the limits of shoulder excursion are different between the tasks). There was a significant interaction between phases and stimulation conditions for wrist adduction/abduction and wrist flexion/extension. Post-hoc revealed a significant difference, only during seated arm cycling, between the stimulated conditions at 7 o'clock in wrist adduction/abduction.

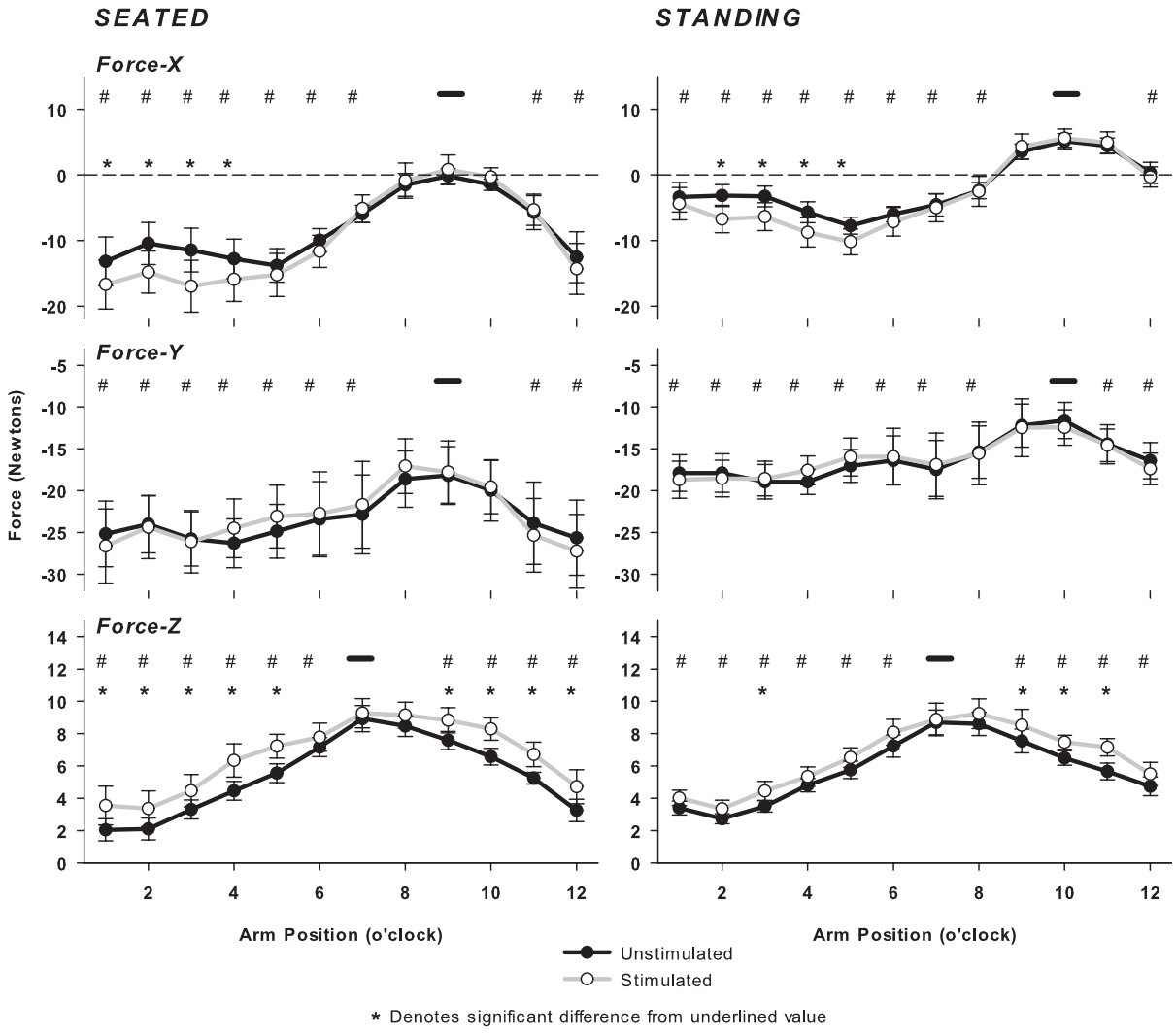

Figure 6-6: Kinetics during unstimulated (black) and stimulated (grey) trials in relation to the movement cycle. All values are means ± SE.

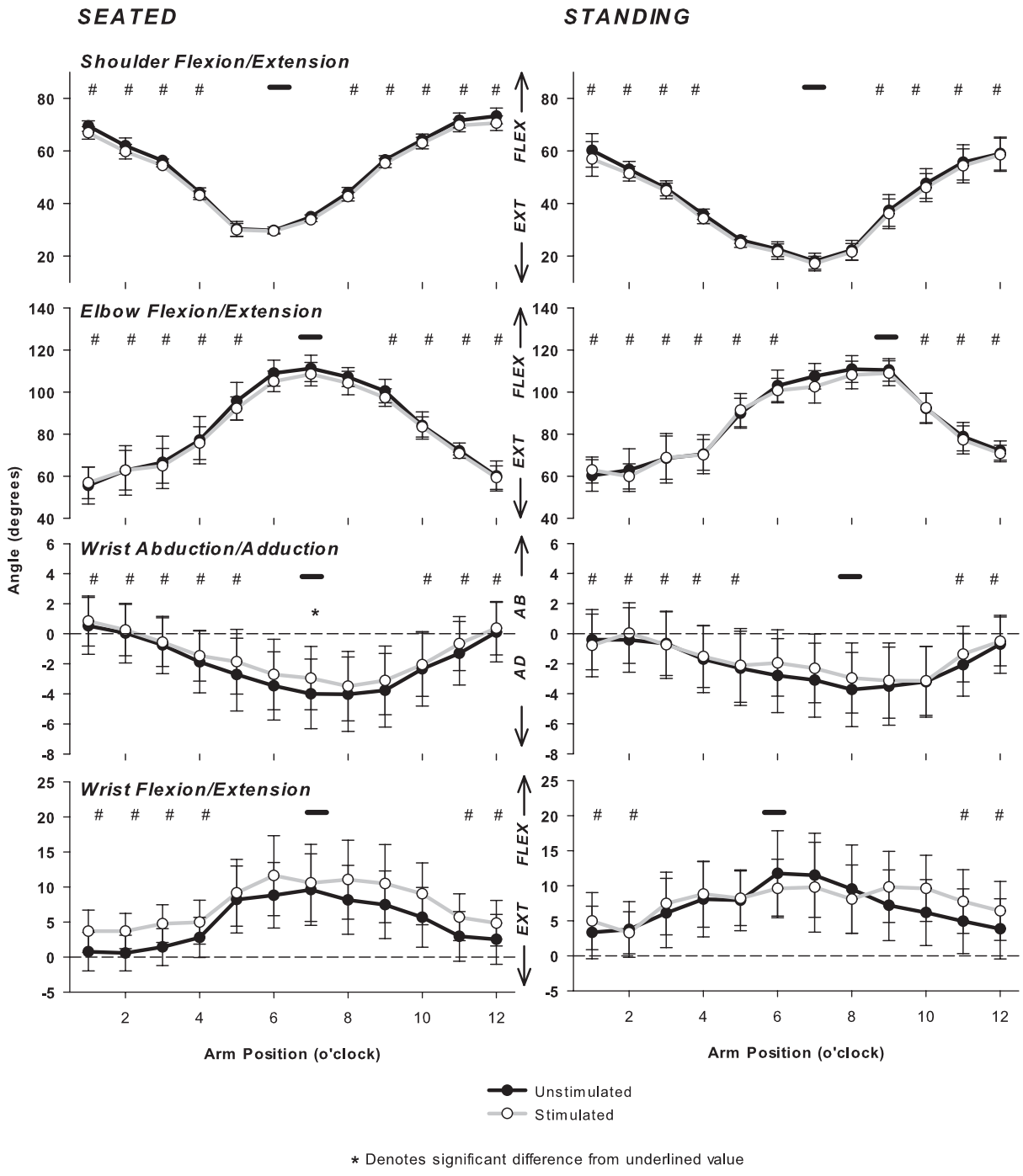

Figure 6-7: Kinematics during unstimulated (black) and stimulated (grey) trials in relation to the movement cycle. All values are means ± SE.

6.4.5. Correlation of kinematic changes to net reflexes

FCR was significantly ($p<0.05$) correlated to wrist flexion at 1-5 and 10 o'clock during seated and 10-12 o'clock during standing (figure 6-8). ECR was correlated to wrist flexion at 1-3,5 o'clock during seated arm cycling. FCR was correlated to wrist abduction at 2 o'clock in standing arm cycling and ECR was correlated to wrist AB at 8 o'clock during seated arm cycling

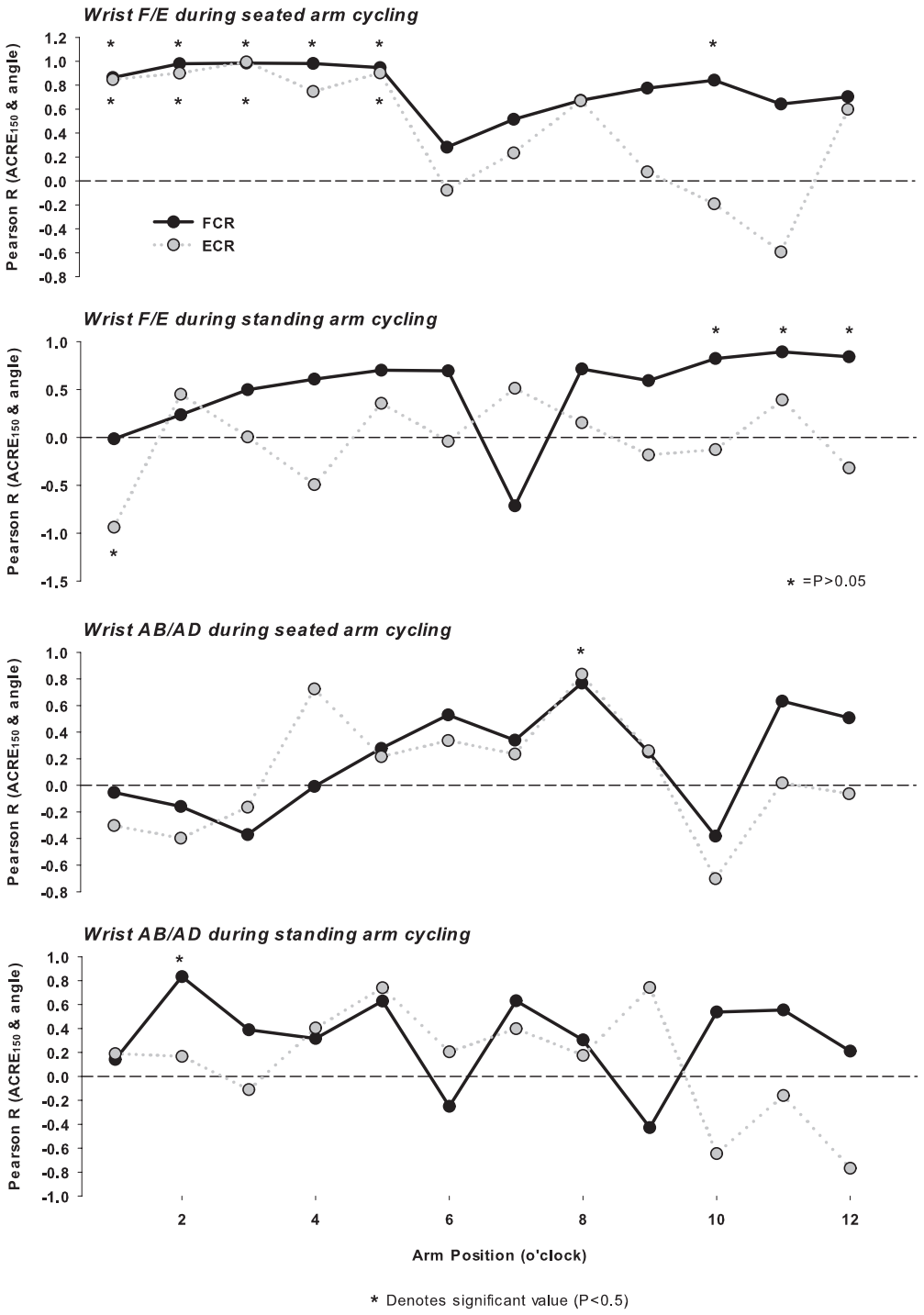

Figure 6-8: Correlation analysis of kinematic responses to net reflexes for FCR (solid black) and ECR (dotted grey) to Wrist Flexion/Extension (Two top panels) and Wrist Abduction/Adduction (Bottom two panels).

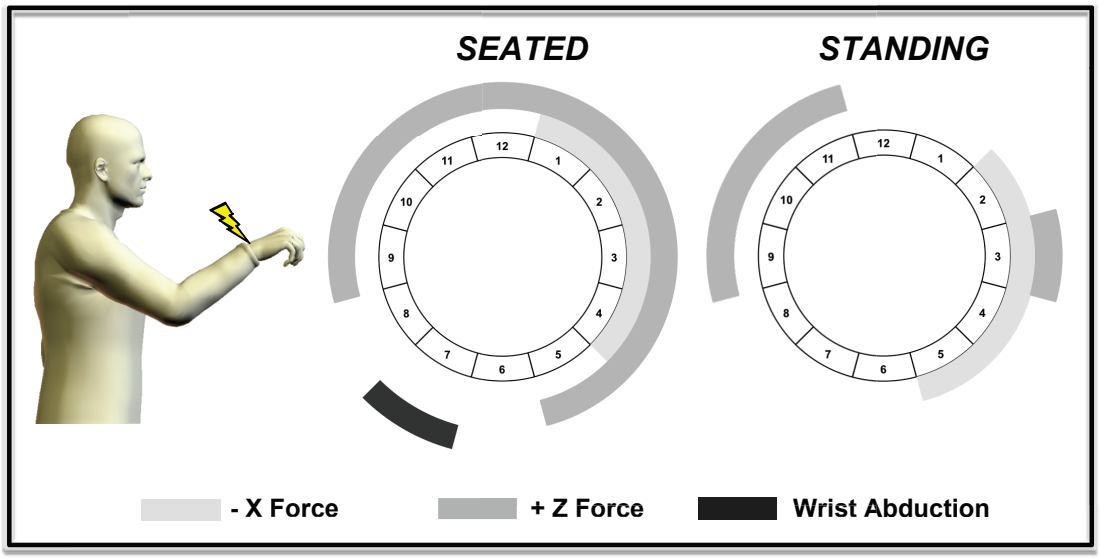

Figure 6-9: Summary of significant kinematic and kinetic reflexes in relation to the movement cycle for seated and standing arm cycling.

6.5. Discussion

In this study we show significant, behaviourally relevant mechanical responses to cutaneous nerve stimulation during arm cycling. This is comparable to limb trajectory modification seen in the legs with cutaneous stimulation during walking and cycling. However, the reflex responses may be functionally tuned to a free moving limb yet shaped by the biomechanical context of the arm cycling task.

The most consistent mechanical response to SR stimulation during seated arm cycling was a lateral force on the handle. This kinetic response represents a directionally appropriate attempt to remove the hand from the stimulus only revealed during rhythmic arm movement. This is consistent with the concept that the anatomical location of the stimulus plays an important role in defining reflex expression during both arm and leg rhythmic movements (Zehr & Stein, 1999). However, because the observed force is orthogonal to the movement path it is not specifically relevant to the task itself. In contrast, there may be evidence of an assistive strategy during end recovery where the

shoulder is nearing peak extension while abducting. At 7 o'clock a wrist abduction reflex was observed and a significant correlation between ECR net reflex and wrist abduction was revealed at 8 o'clock. Additionally, inhibition in AD and MD at 7 and 8 o'clock could produce shoulder adduction. Because of the mechanically coupled wrist and shoulder movement during arm cycling, wrist abduction and shoulder adduction results in a more neutral wrist position without disturbing the medial/lateral force profile. Consequently, changes in whole limb orientation could offset the effect of an imposed obstacle on the normal force profile and represent a task specific functionally appropriate response. This is consistent with locomotor reflexes in the legs that serve to assist the movement while making corrections to imposed obstacles (Zehr & Stein, 1999). Another significant mechanical response was a backwards force during late power and early recovery (1 to 4 o'clock) when the shoulder is flexed and the elbow is fully extended. Additionally, at these phases, FCR and ECR are positively correlated with wrist flexion. However, this response is inconsistent with the kinematic trajectory of the cycle path at 1, 2 and 3 o'clock. That is, at 1 and 2 o'clock a backward force would slow forward progression due to the downward and forward movement path of the arm (Klimstra et al. 2009). Additionally, at 3 o'clock the force would be directed through the crank axis and would not produce any planar arm cycling related torque. Conversely, at 4 o'clock a backward force would accelerate the arm cycle into early recovery, consistent with the trajectory of the cycle movement. Taken together the forces in end power/early recovery are not assistive to the kinematic trajectory of arm cycling. Therefore, while these kinetic responses may be corrective mechanical actions they do not clearly fit into the context of arm cycling and a more suitable interpretation would suggest that they are

an attempt to remove the hand from an imposed obstacle during free-limb movement. This resembles the stumble corrective response seen during walking in humans and during quadrupedal locomotion in the cat (Drew & Rossignol, 1985; Forssberg, 1979a; Zehr et al., 1997). However, the stumble corrective response during arm cycling is shaped by the task contraints. That is, from a mechanical perspective, arm cycling is a closed kinetic chain constrained distally by the hand-ergometer interface and proximally by the shoulder joint (Klimstra et al., 2009). Consequently the arrangement of the whole limb is defined by the position of the hand along the circular trajectory. Therefore, each joint is limited to a kinetic reflex expression noticed at the handle along the movement path. This is similar in principle to why kinematic responses are limited during stance phase where ground contact is crucial and limb movement is constrained (Zehr et al., 1997). As such, the task constraints during arm cycling mandate gripping the handle and an attempt to remove the hand from the stimulus results in a kinetic response due to limited joint kinematic freedom.

Changes in ankle and knee kinematics during forward and backward leg cycling are associated with the functional context, and movement direction, of the task (Zehr et al. 2009). This is in contrast to arm cycling here where the mechanical responses were not related to the specific task. These differences may be related to the correspondence between leg cycling and walking. For example, at similar functional phases, the biomechanical role of leg muscles during leg cycling is similar to walking (Raasch et al. 1999). Also, corresponding EMG and reflex responses are similar between leg cycling, stepping and walking (Zehr et al. 2007). Conversely, there are marked differences in muscle activity and mechanics between arm cycling and arm swing during walking that

could alter the functional role of the muscles (Klimstra et al. 2009). This could suggest that during rhythmic movement of the arms and the legs the reflex responses are tuned to the naturally occurring locomotor task, which may or may not be functionally relevant within a similar rhythmic task.

From a control perspective, it is postulated that during rhythmic movement the pattern of muscle activity is constructed to produce whole limb movement kinematics based on a specific mechanical parameter that is the global goal of a task (control variable) (Grasso et al., 1998; Zehr et al., 2007). For example, Laquaniti et al. 1999 describes a tight coupling of the angular motion of limb segments, during gait, resulting in a planar relation that dictates the spatiotemporal trajectory of the centre of mass of the body. Further, these neurally organised kinematic synergies may be the desired strategy for maintenance of dynamic equilibrium and response to disturbances during locomotion and may obtain across different rhythmic tasks (Lacquaniti et al. 1999). For example, the control variable is preserved despite energy cost or efficiency of movement (Grasso et al., 1998;). Arm cycling involves manipulation of limb orientation to produce phase specific forces at the hand interface (Klimstra et al., 2009). Therefore, the control variable during arm cycling may be the trajectory of the hand. However more study is required to understand the neuromechanical task constraints of arm cycling and specifically how these constraints shape reflex expression.

The anatomical anchor position relates to the relative oscillatory range of limb movement during a rhythmic task (Klimstra et al. 2009). Alteration of the anatomical anchor position requires differential activation of muscles which results in altered joint moments (Klimstra et al. 2009). The results in this experiment support a directional

"shift" in EMG, kinematics and forces related to the anatomical anchor position. Subsequently, when comparing the mechanical outcomes between standing and seated postures the reflex force in end power/early recovery remain consistent with a change in the shoulder anatomical anchor (shoulder flexion/extension range in figure 6-7) position between the two tasks. This can be seen in the summary in figure 6-9 where there are forces at 1-4 o'clock in seated arm cycling and 2-5 o'clock in standing arm cycling. This may support our proposal that the mechanical reflexes are inherently tuned to a free moving limb. That is, if the reflexes were tuned to arm cycling one would expect that changes in anchor position would not alter the responses. However, this requires further study where reflexes during arm cycling are tested with deliberate changes in anchor position.

It is also possible that differences in balance constraints between standing and seated arm cycling could contribute to the expression of reflexes. For example, unilateral and bilateral arm flexion movements during standing results in muscular activity in the legs that stabilize the center of mass (COM) over the base of support (Mochizuki et al., 2004). Therefore, mechanical reflexes evident in the arm during seated arm cycling may be alleviated in a standing posture by changes in whole body orientation that dissipate the reflex effect. This is supported by a lack of observable reflex kinematic responses in the arms during walking a may provide an important link between the regulation of seated arm cycling with rhythmic arm swing during walking. (Haridas & Zehr, 2003; Zehr & Haridas, 2003).

Overall, neuromechanical concepts discussed here could be used to develop a robust biomechanical model of arm cycling to further our understanding of the control of

rhythmic arm movement. This could be useful in end applications as a tool in rehabilitation following stroke or spinal cord injury (Klimstra et al., 2009).

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7. Neuromechanical considerations for incorporating rhythmic arm movement in the rehabilitation of walking[6]

7.1. Abstract

We have extensively used arm cycling to study the neural control of rhythmic movements such as arm swing during walking. Recently rhythmic movement of the arms has also been shown to enhance and shape muscle activity in the legs. However, restricted information is available concerning the conditions necessary to maximally alter lumbar spinal cord excitability. Knowledge of the neuromechanics of a task can assist in the determination of the type, level and timing of neural signals yet arm swing during walking and arm cycling have not received detailed neuromechanical comparison. The purpose of this research was to provide a combined neural and mechanical measurement approach that could be used to assist in the determination of the necessary and sufficient conditions for arm movement to assist in lower limb rehabilitation after stroke and spinal cord injury. Subjects performed 3 rhythmic arm movement tasks: 1) cycling (CYCLE); 2) swinging while standing (SWING); and 3) swinging while treadmill walking (WALK). We hypothesized that any difference in neural control between tasks (ie. pattern of muscle activity) would reflect changes in the mechanical constraints unique to each task. 3D kinematics were collected simultaneously with force measurement at the hand and EMG from the arms and trunk. All data were appropriately segmented to allow comparison between and across conditions and were normalized and averaged to 100%

[6] Klimstra MD, Thomas E, Stoloff RH, Ferris DP, Zehr EP. Neuromechanical considerations for incorporating rhythmic arm movement in the rehabilitation of walking. Chaos. 2009 Jun;19(2) (80% contribution to project – 80% of data acquisition, analysis, statistics, figures and tables and written manuscript)

movement cycle based on shoulder excursion. Separate mathematical Principal Components Analysis of kinematic and neural variables was performed to determine common task features and muscle synergies. The results highlight important neural and mechanical features that distinguish differences between tasks. For example, there are considerable differences in the anatomical positions of the arms during each task, which relate to the moments experienced about the elbow and shoulder. Also, there are differences between tasks in elbow flexion/extension kinematics alongside differential muscle activation profiles. As, well, mechanical assistance and constraints during all tasks could affect muscle recruitment and the functional role of muscles. Overall, despite neural and mechanical differences, the results are consistent with conserved common central motor control mechanisms operational for CYCLE, WALK and SWING but appropriately sculpted to demands unique to each task. However, changing mechanical parameters could affect the role of afferent feedback altering neural control and the coupling to the lower limbs.

7.2. Introduction

It is a commonplace observation that we humans swing our arms when walking or running. Despite that, only recently has the role for the arms and the linkage between the arms and legs during human locomotion received much attention. Arm cycling on an upper limb ergometer (like leg cycling but while seated upright or standing and using the arms to cycle the cranks; figure 7-1) has been used to study the neural control of rhythmic limb movement (Zehr & Duysens, 2004; Zehr et al., 2004; Zehr, 2005; Zehr et al., 2007). This approach led to the characterization of linkages between rhythmic activity of the

arms and associated changes in lumbar spinal cord excitability (Ferris et al., 2006; Frigon et al., 2004; Huang & Ferris, 2004; Hundza & Zehr, 2008; Loadman & Zehr, 2007; Zehr & Duysens, 2004) As well, it has been shown that rhythmic arm movement enhances leg muscle activation during locomotor-like tasks, thus providing evidence that arm movement may be an important adjunct to locomotor rehabilitation both alone and during rhythmic leg movement (Behrman & Harkema, 2000; Ferris et al., 2006). Due to the availability of arm cycling ergometers and ease of administration of rhythmic arm cycling in a rehabilitation setting, it is tempting to use this specific task as a primer for enhancing lower limb activity during walking rehabilitation. Support for the use of rhythmic arm cycling in rehabilitation comes from the premise of a common core of neural control for many rhythmic movement tasks (Zehr, 2005). Accumulating evidence suggests that movement involving coordinated rhythmic activity of one or both limb pairs (i.e. arms and legs) share common neural control even when the mechanics of the tasks are markedly different (Ivanenko et al., 2005; Stoloff et al., 2007; Zehr & Duysens, 2004; Zehr et al., 2007). As well, discrete voluntary tasks seem to be superimposed upon more automatic locomotor activities without altering the core neural pattern (Ivanenko et al., 2005). This presents the idea that there is robust and malleable control of rhythmic movements in normal healthy subjects and a myriad of rhythmic movements can be used for rehabilitation so long as they access the same neuronal patterns. Further, this concept posits that rhythmic motor tasks using the arms may access common neural circuitry related to arm swing during gait and therefore could be useful in walking rehabilitation (Ferris et al., 2006; Zehr, 2005; Zehr et al. 2009).

Specific afferent feedback related to movements of the lower limbs are necessary to facilitate normal gait patterns. For example, hip extension provides an important afferent signal during locomotion in both cats and human infants (McVea et al., 2005; Pang & Yang, 2000). Currently, detailed characteristics of the role of neural signals related to rhythmic arm movement to engage relevant leg muscle activation is still unclear. An important gap in knowledge is the determination of neuromechanical correlates related to arm movement in different tasks. That is, a neuromechanical characterization of the arm movement across rhythmic motor patterns remains to be done. As a general framework, during rhythmic movement, central motor drive activates the muscles while the mechanics of the musculoskeletal system influence the neural pattern of activity to alter and sculpt motor output (Abbas & Full, 2000; Dickinson et al., 2000). Knowledge of the mechanical parameters of a task can help to elucidate the type, level and timing of neural signals and this information can be crucial for effective rehabilitation (Edgerton et al., 2008). Additionally, lower limb coupling could be related to the movement state of both limb pairs, the phase of the movement as well as specific neural signals from the upper limbs (Balter & Zehr, 2007; Ferris et al., 2006; Frigon et al., 2004; Hiraoka, 2001; Huang & Ferris, 2004; Kawashima et al., 2008; Loadman & Zehr, 2007; Zehr et al., 2004; Zehr et al., 2007). Thus a synthetic neuromechanical analysis of rhythmic arm movement could assist in quantification of the necessary and sufficient conditions for arm-assisted lower limb gait rehabilitation.

To date, rhythmic arm cycling has not received a neuromechanical comparison to its naturally occurring equivalent; arm swing during walking. Therefore the purpose of this study was to use simultaneous biomechanical and neurophysiological measurement

techniques to compare and characterize rhythmic arm cycling to arm swing during walking. Additionally we chose to include an intermediate task of arm swing alone in our comparison (figure 7-1). This task could be used to evaluate arm swing without the mechanical interactions during walking and is similar to currently used rehabilitative tasks (Behrman & Harkema, 2000; Ferris et al., 2006). Through this comparison we highlight important neural and mechanical task features that will be useful in future approaches using rhythmic arm movement to assist leg muscle activation during gait retraining. We hypothesized that there would be unique mechanical constraints for each task that may reflect changes in sensory feedback and function. Concurrently, there will be a common set of basic neural control parameters underlying all 3 tasks.

7.2.1. Background

7.2.1.1. Can common core arm activities activate the legs?

The common core hypothesis presented by Zehr (2005) suggests that the control of rhythmic human movement is the responsibility of three parts of the nervous system and their interaction to produce the rhythm and pattern necessary to generate a robust compliment of movements. A basic schematic of this concept is shown in figure 7-2. The three basic components are supraspinal (not shown in the schematic but considered to have a regulatory role), spinal (in the form of central pattern generators (CPG, ying-yang symbol) and interneurons) and afferent (somatosensory) feedback (from muscle, joint and skin receptors). In principle this model suggests that the global timing of all tasks can be commonly set at a core level by CPGs. Central Pattern Generators are a collection of neurons resident in the spinal cord that can produce oscillating activity without sensory

feedback or additional supraspinal input. Sculpting of motor output occurs when information of local mechanical conditions (via afferent feedback) influences interneurons that regulate excitability of specific motoneuron pools. That is, neuromechanical information is encoded in the somatosensory feedback which can then shape the muscle activity and alter the mechanical behaviour. Therefore, understanding the control of rhythmic movement involves a synthetic analysis of both neural and mechanical task dynamics. Recently, factor analysis approaches have led to the ability to reduce mechanical and neural data to their component parts and therefore present an exciting way of ascertaining the core pattern of mechanical and neural activity (Bizzi et al., 2008; Cappellini et al., 2006; Daffertshofer et al., 2004; Ivanenko et al., 2005; McCrea & Rybak, 2008; Ting & McKay, 2007; Tresch et al., 2006). This approach supports the common core hypothesis showing that many tasks share common neural control despite slight alterations in activation profile and marked differences in mechanics (Bizzi et al., 2008; Cappellini et al., 2006; Ivanenko et al., 2005; Stoloff et al., 2007; Zehr, 2005; Zehr et al., 2007). For example we have shown that recumbent stepping, arm and leg cycling and walking have similar neural control (Zehr et al., 2007; Stoloff et al. 2007). This idea is mimicked in the schematic of rhythmic movement control (figure 7-2) which shows that arm cycling, arm swing while walking and arm swing while standing share a common core timing. However, despite the basic core similarities, changes in afferent feedback can powerfully modulate the neural signal by exerting influence directly upon motoneuron pools, reflex interneurons and through interneuronal networks associated with the CPG (Zehr, 2005). An example of this concept is demonstrated by hip afferents which play a critical role in the neural control of

walking as they can initiate, alter the tempo and halt gait (Dobkin et al., 1995; Grillner & Rossignol, 1978; Knikou & Rymer, 2002; Lam & Pearson, 2001; McVea et al., 2005; Pang & Yang, 2000; Steldt & Schmit, 2004; Whelan et al., 1995).

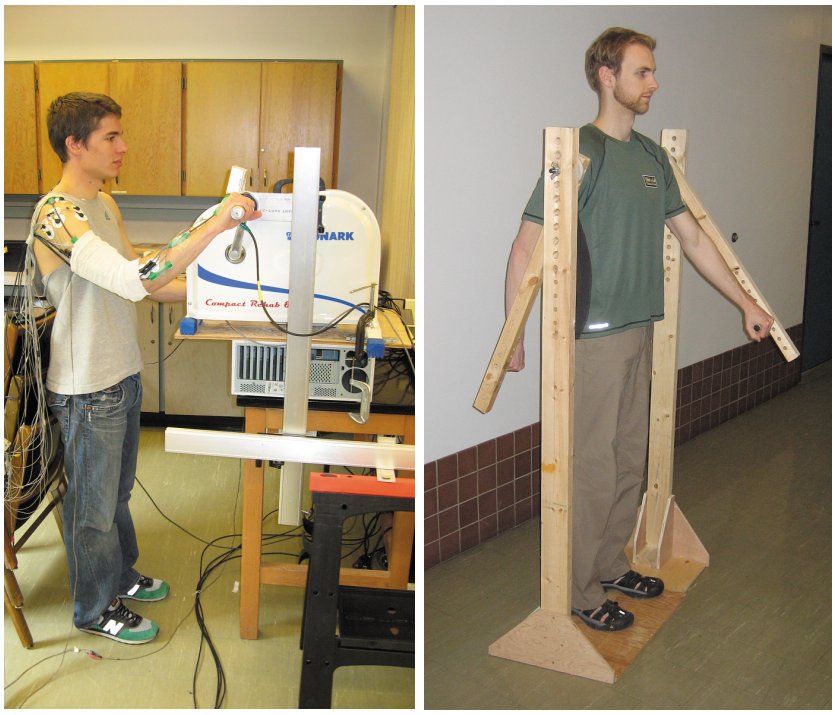


Figure 7-1: Rhythmic arm movement paradigms utilized in this experiment.
The Arm cycling paradigm (left panel) involves subjects performing circular movements with the arms on an upper limb ergometer. This is similar to leg cycling but while seated upright or standing and using the arms to cycle the cranks. Arm swing while standing (right panel) involves pendular movement of the arms while holding the handles of an arm swing apparatus that allows free shoulder flexion and extension yet restricts other arm movements.

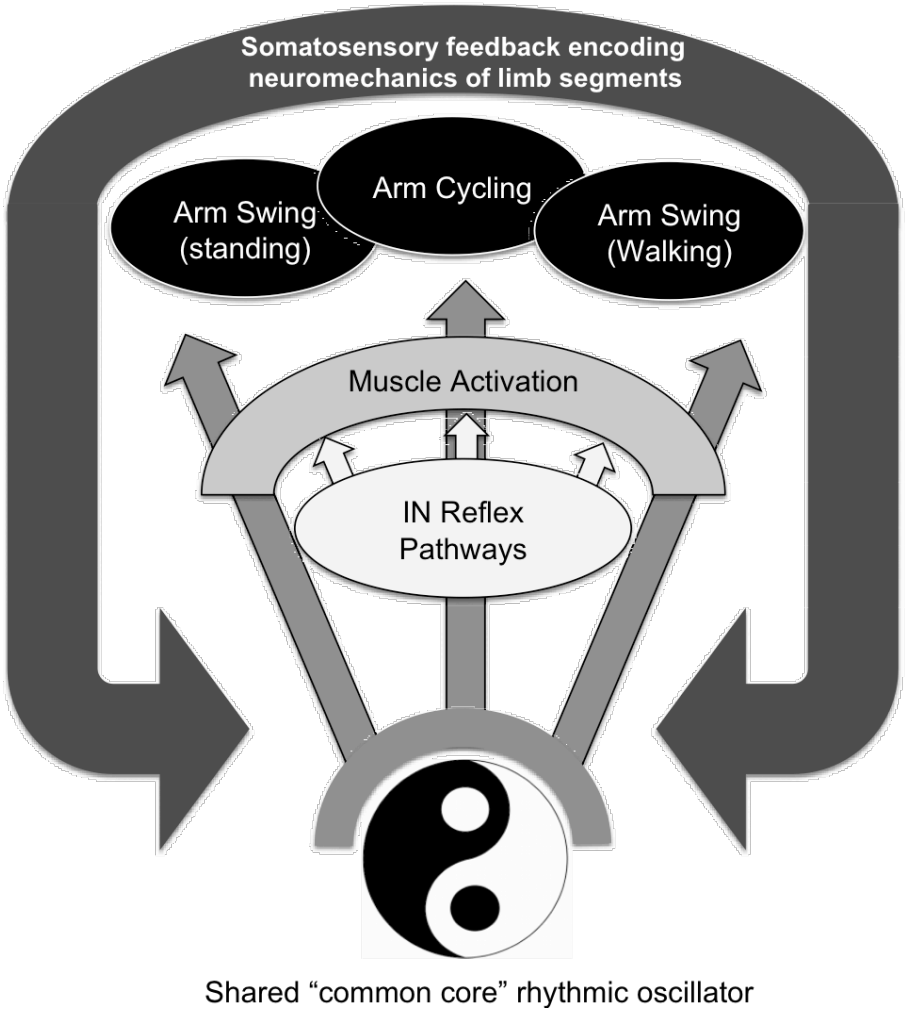


Figure 7-2: General conceptual overview for the regulation of rhythmic human movement. Note that the effect of feedback encodes the neuromechanical interactions and projects to the motoneuronal pools, interneuronal pathways, and the CPG itself and is subsumed in the output of the shared common oscillator. The effect of supraspinal input is taken as regulatory but is not shown. Adapted from Zehr 2005.

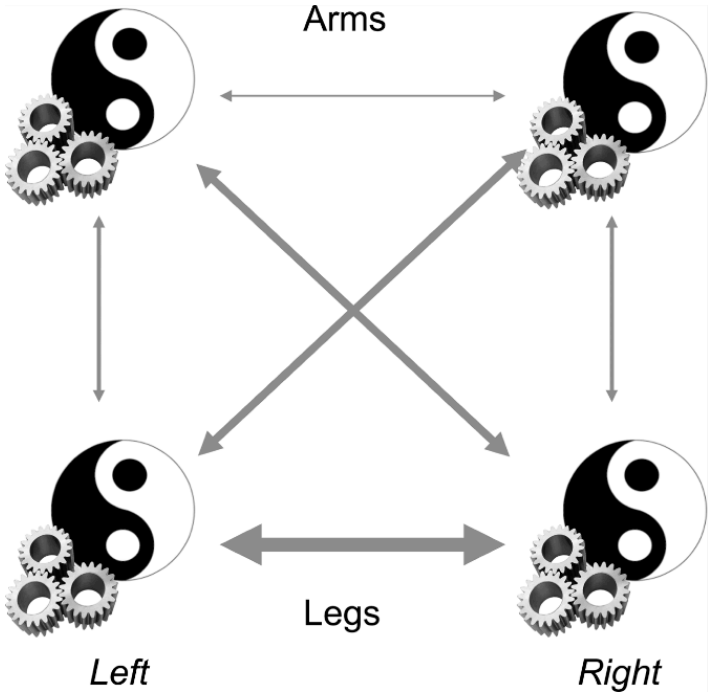


Figure 7-3: Rhythmic CPG neural oscillator controllers (ying-yang) for all four limbs interacting with the mechanical environment (gears) meant to represent the regulation and coordination among and between all four limb during movement. Adapted from Zehr 2005.

The schematic presented above is sufficient to discuss the regulation of rhythmic movement in the just one limb (arm or leg) or limb pair (arms or legs). However, it is accepted that there are neural connections between the fore and hind limb in animals and humans and the conditions of quadrupedal locomotor coupling requires further study (Dietz, 2002; Zehr & Duysens, 2004; Zehr et al. 2009). Specifically, there is equivocating experimental evidence concerning the necessity of afferent signals from arm movement for proper enhancement and shaping of leg muscle activation. It is therefore pertinent to discuss the neuromechanical coupling between the arms and the legs as a precursor to appreciating quadrupedal movement (Zehr et al. 2009). Recently Ijspeert (2008) has reviewed the development of mathematical models of CPGs. We would direct interest of

the details of modeling to this comprehensive review. In brief there have been different approaches to mathematical modeling of CPG's depending on the area and phenomena of study. Highly detailed biophysical model, connectionist models and systems of coupled oscillators have been used. As well, neuromechanical models have been developed to study the effect of sensory feedback on the CPG as well as to investigate concepts such as mechanical entrainment. The results of modeling have shown consistent results to human and animal experiments demonstrating that an oscillatory core is robust and can maintain its rhythm while being sensitive to the pattern shaping influence of mechanical changes (Ijspeert, 2008). Figure 7-3 shows a basic schematic of the neuronal coupling between the arms and legs. In this figure each limb is portrayed as having a regulatory CPG element (symbolized as a ying-yang symbol) interacting with the mechanical environment (shown as gears) (Zehr, 2005). Within this framework it is possible that local neuromechanical interactions within any limb can affect neural coupling to the other limbs. The strength of the connections between the limbs are denoted by the thickness of the arrows connecting them. As such there is evidence for strong coupling between the legs (Brooke et al., 1997) and weak coupling between the arms (Carroll et al., 2005) while the details of crossed effects and ipsilateral arm to leg connections in humans are relatively unknown (Zehr & Duysens, 2004; Zehr 2005). While all connections are of interest, for the sake of addressing a simple understanding of rhythmic movement control and the development of rehabilitative interventions, we will focus our discussion on arm-to-leg neuromechanical interactions. An experimental model to study the effect of upper limb movement on lower limb activity is to evoke reflexes in the legs changing paramaters related to arm movement. Studies inducing Passive flexion/extension of the elbow (Hiraoka & Nagata,

1999) arm swinging (Hiraoka, 2001) and different static arm postures (Delwaide et al., 1973; Delwaide et al., 1977; Eke-Okoro, 1994) have all demonstrated altered reflexes in leg muscles. Hiroaka et al. (2001) attributed the alteration in soleus H-reflex to stretch in spindle afferents in AD during shoulder extension. Taken together, these studies suggest that afferent feedback from the arms can induce changes in lower limb reflex excitability. However, there have been methodological concerns and the lack of control between experiments warrants further study (Frigon et al., 2004). Contrary to the above findings a series of experiments studying the effect of altering parameters of rhythmic arm cycling on reflexes in stationary legs have demonstrated a potentially sparse role of afferent feedback in effecting lower limb reflexes. These studies have shown that rhythmic arm cycling produces a non-specific effect on lower limb reflexes that is unaffected by load, range of motion and muscle vibration and yet responsive to changes in frequency of movement (Frigon et al., 2004; Hundza et al. 2007; Hundza et al. 2008; Hundza & Zehr, 2008; Loadman & Zehr, 2007). The combined results, using this paradigm, are suggestive of a central rather than peripheral locus responsible for the effect of arm movement on leg reflexes (Hundza & Zehr, 2008). Concurrently, studies of "reduced" locomotor preparations (that is, not walking, but rhythmic activity when both the arms and the legs are moving) such as arm and leg stepping or cycling, have demonstrated that the movement state of both arms and legs may be necessary for maximized interlimb coupling (Balter & Zehr, 2007; Ferris et al., 2006; Huang & Ferris, 2004; Sakamoto et al., 2006; Zehr et al., 2007). Huang and Ferris (2004) used a coupled recumbent arm and leg stepping device to show a clear facilitation in leg muscle activation that was graded to the activation of the arms and had similar timing. Additionally, studies using combined

arm and leg cycling have shown that arm movement contributes to the modulation of reflexes in the legs in a functional and phase-dependent manner (Balter & Zehr, 2007). Balter et al. (2007) found that arm movement made a significant contribution to the reflex expression in the leg during the power phase (comparable to heel strike in walking). Conversely Sakamoto et al. (2006) found no contribution from the arms to reflex expression in the legs. However this could be due to different statistical tests as well as the fact that they used a mechanically uncoupled device (Balter & Zehr, 2007). Zehr et al. (2007) found that the movement state of both limb pairs may enhance afferent feedback from the arms to affect reflexes in the legs during locomotor movements. In a recent study Kawashima et al. (2008) has shown that rhythmic arm swing during gait retraining in incomplete cervical spinal cord injured subjects had a significant shaping effect on the pattern of soleus activation during rhythmic leg movement. This shaping was shown to either increase or decrease ankle extensor (Soleus) muscle activation to produce a stereotypical pattern functionally related to stance and swing during walking. Because they studied spinal cord injured subjects and the effect was noticed in passive and active conditions they contended that supraspinal commands are not the sole source of the shaping effect and that sufficient afferent feedback from the upper limb movement is necessary.

Tasks that share common neural control may be equivalent at engaging neural circuits and coupling between the arm and the legs. However, changes in the mechanics of the movement task and the movement state of the both the upper and lower limbs may alter neural coupling. Exploring the mechanics of different arm movement tasks is

beneficial to elucidate the necessary and sufficient conditions for the enhancement of lower limb muscle activity

7.3. Methods

Nine healthy participants (21-43 yrs) participated in the study after providing informed written consent. The experimental protocol and consent form was approved by the Human Research Ethics Board at the University of Victoria and conforms to the Declaration of Helsinki. Subjects were asked to perform three rhythmic arm movement tasks: 1) arm cycling while standing using a Monark™ (Compact Rehab 871E, Sweden) inertial load arm cycle ergometer (**CYCLE**); 2) arm swing while standing using a custom made arm swing apparatus (Dave Smith, University of Victoria) (**SWING**); 2) level walking on a motorized treadmill (Desmo M, Woodway™) (**WALK**). For CYCLE the extent of shoulder flexion/extension was defined by the movement path and the anatomical parameters of each subject. During SWING the extent of shoulder excursion was matched to the range occurring during CYCLE and maintained through visual comparison to a manual goniometer. During WALK the extent of shoulder excursion was subject selected. Additionally a SWING trial with a self-selected shoulder excursion was performed to compare shoulder excursion and EMG activation. Movement frequency was determined by having subjects walk at a comfortable pace on a treadmill and then calculating the period for one complete right shoulder extension cycle (position corresponded to right heel contact (refer to Fig 4.)) This frequency was then maintained for all tasks with the use of a metronome. The average corresponding frequency was 0.88 ± 0.08 Hz (mean ± standard deviation). Prior to collection, during practice, we adjusted

the handles on the SWING apparatus to anatomical dimensions for each participant to allow for comfortable arm swing. Figure 7-4 shows the details of each task as well as the shoulder kinematic relation between tasks.

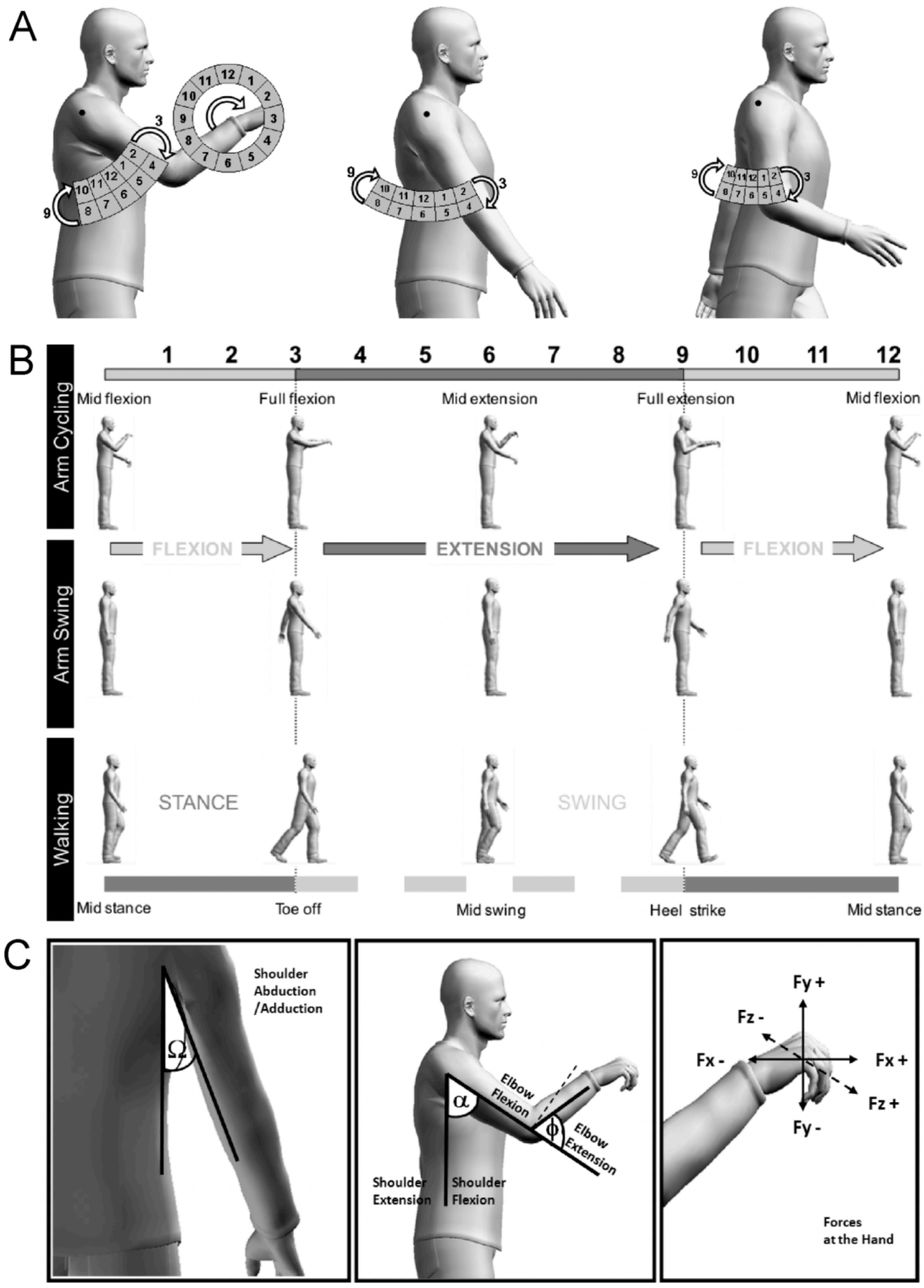


Figure 7-4: (A) Schematic diagram relating the phases of movement for arm cycling, arm swing while standing, and arm swing while walking.
The movement cycle was normalized to 100% of shoulder flexion/extension and displayed in reference to the clock face movement cycle from arm cycling (1-12) Note: the arm cycling

and arm swing devices are not shown(B) Sign conventions at the right arm and ergometer hand crank. Ω, α, Φ represent shoulder abduction/adduction, shoulder flexion/extension, elbow flexion/extension respectively. Participants performed all three tasks while EMG, kinetic, kinematic data were recorded.

7.3.1. Kinematics

A ViconPeak motion capture system (6 Camera 460, Vicon Peak™, Centennial, CO) was used to record the movement of the whole body. Reflective markers were placed on the subject using the VICON™ Plug-In-Gait model. Anthropometric data from each subject were necessary for an inverse dynamics analysis. This data consisted of: mass (kg); height (mm); leg length (mm); knee width (mm); ankle width (mm); shoulder offset (mm); elbow width (mm); wrist width (mm); and hand thickness (mm). Data capture was conducted at 120 Hz. Marker trajectory data were filtered using a Woltering filter (Vicon™) and Cardan angles were calculated for right ankle, knee, hip, shoulder, elbow, and wrist (Plug-In Gait, Vicon™, refer to figure 4C for sign conventions of presented kinematic variables). Joint angular velocities and accelerations were calculated for right ankle, knee, hip, shoulder, elbow and wrist. A two-dimensional inverse dynamics analysis was performed using the measured kinematic values to determine shoulder and elbow flexion/extension moments (Winter, 2005).

7.3.2. Kinetics

An ATI™ Industrial Automation force/torque transducer (Apex, NC, USA; Gamma model) was mounted at the right hand ergometer interface of the arm cycle ergometer and the arm swing apparatus (refer to figure 4C for force conventions). The force transducer collected force and torque in 3 dimensions and data was collected at 1000 Hz.

7.3.3. Electromyography (EMG)

After cleansing the skin with alcohol swabs, disposable 1cm surface electrodes (Thought Technologies Ltd) were applied in a bipolar configuration using a 2cm interelectrode distance over 8 muscles of the right arm and back. Muscles included: anterior deltoid (AD); middle deltoid (MD); posterior deltoid (PD); long head of biceps brachii (BB); long head of triceps brachii (TB); erector spinae cervical (ESC); erector spinae thoracic (EST); and erector spinae lumbar (ESL). The primary actions of these muscles produce shoulder flexion (AD), shoulder extension (PD), shoulder abduction (MD), elbow flexion (BB), elbow extension (TB) and lateral bending of the spine at a cervical (ESC), thoracic (EST) and lumbar level (ESL). Ground electrodes were placed over electrically neutral tissue either on the acromium process or clavicle. To minimize mechanical artifact the electrodes were secured with tape and medical wrap. EMG signals were preamplified and band pass filtered at 100-300 Hz (Noraxon™, Telemyo, Scottsdale, AZ) and collected at 1000 Hz.

7.3.4. Data Acquisition

Two computers were synchronized by a trigger switch that signaled the start of data collection for motion capture with Vicon workstation™ software and to collect data from the ATI™ force transducer as well as EMG. Synchronization timing was evaluated through comparison of arm cycle position using an optical encoder during the arm cycling task.

7.3.5. Data Analysis

A custom-written analysis program was developed in Labview ™ (National Instruments™, Austin, TX, USA) to condition all data. Single subject EMG data were full-wave rectified and then passed through a second order Butterworth filter with a low pass cut-off frequency of 6 Hz. EMG data were then normalized to 100 percent of the maximum EMG from each muscle taken across all tasks. Single subject force and torque data were filtered using a second order Butterworth filter with a low pass cut off frequency of 20 Hz prior to averaging. All data were averaged to 100 percent of the movement cycle from right shoulder extension maximum to subsequent right shoulder extension maximum (Fig 7-4).

7.3.6. Mathematical Analysis.

The basic patterns in neural control and mechanics were examined using separate principal components analysis (PCA) for EMG and kinematic data recorded from CYCLE, SWING and WALK. Details of the analysis are similar to our previous task comparisons (Stoloff et al., 2007; Zehr et al., 2007). Briefly each PCA was performed using the princomp function in MATLAB (The Mathworks, Inc). First a correlation matrix was made to examine linear dependence between muscles (8X8 matrix) and kinematics (11X11;separate analysis for both x-flexion/extension and y-adduction/abduction). Factor scores were then determined using a varimax rotation of the eigenvectors of each matrix, in which variables with similar activity were grouped together. The variance was then calculated using the eigenvectors and eigenvalues. Next the percent of total variability for each factor was determined by dividing its variance by the sum of the variances. Because the first four factors in all three tasks for both EMG

and kinematic data accounted for at least 95% of the variability, we only considered scores from the first four factors for further analysis (Ivanenko et al., 2005).

Additionally we performed a correlation analysis on factor scores to assess the similarity between CYCLE, WALK and SWING using the corrcoeff function in MATLAB™. Briefly we calculated the correlation coefficient of each 1st factor score between each pair of tasks. We chose a criterion of 0.4 to indicate a good correlation between factors based on a previous research using similar methods (Ivanenko et al., 2005; Zehr et al., 2007).

7.3.7. Additional Statistics

To determine the effects of task and phase (3 tasks · 12 phases) on average EMG amplitude across phases we used a (3 task X 12 phase) repeated measures analysis of variance (RM ANOVA). Additionally we used tests of planned comparison to determine differences between tasks at the same phase and differences between phases within the same task. Also we performed RM ANOVAs on factor loadings and Fisher z-transformed correlation coefficients of the first factors from Kinematic and EMG PCA with planned comparisons. Significance level was set to $P < 0.05$

7.4.Results

7.4.1. Electromyography

Overall the results of muscle activation showed greater differences between WALK and the other two tasks. Figure 7-5 shows the activation profiles for all muscles with the statistical results for task dependent difference. The x-axis is presented as equidistant bins

represented as “hourly” increments on the clock face movement cycle from arm cycling. The dashed line represents maximum shoulder flexion (3 o’clock) and extension (9 o’clock). For simplicity, results will be discussed in the functional frame of reference from figure 4 with respect to full and mid-range flexion and extension. Significant task dependent differences in muscle activation between tasks are marked with symbols (#,$,%) denoting differences between CYCLE and WALK, SWING and WALK and SWING and CYCLE respectively. There are greater differences between CYCLE and WALK (19 differences), and SWING and WALK (16 differences) than between SWING and CYCLE (6 differences). CYCLE and SWING are different from WALK in AD muscle activity from full extension into mid flexion and ES-L during full flexion and full extension. The only cases where SWING and CYCLE are different are in ES-C from mid to full extension and BB during mid flexion. CYCLE and WALK are different for both PD and MD at full flexion where these muscles are usually relatively silent during CYCLE and active during WALK. The phase-dependent modulation of muscles during CYCLE, SWING and WALK are in general agreement with past research (BALLESTEROS et al., 1965; Hinrichs, 1990; Zehr & Chua, 2000; Zehr & Kido, 2001). In summary AD is active from mid extension to mid flexion for both CYCLE and SWING but relatively silent during WALK. PD is active during full flexion in WALK while this muscle is relatively low with no major pattern for CYCLE and SWING. MD is active concurrently with AD during CYCLE in mid extension to mid flexion, silent during SWING and active concurrently with PD during WALK in full flexion. BB reaches a maximum peak during mid extension in CYCLE and mid flexion concurrent with TB in SWING. For back muscles ESC is active during CYCLE from mid extension

to full extension and during WALK for both full flexion, (concurrent with EST and ESL) and full extension (with ESL). Additionally for the self-selected SWING trial there was a low level of AD activity during extension and a low level of PD activity during flexion without a noticeable pattern in other muscles recorded (not shown).

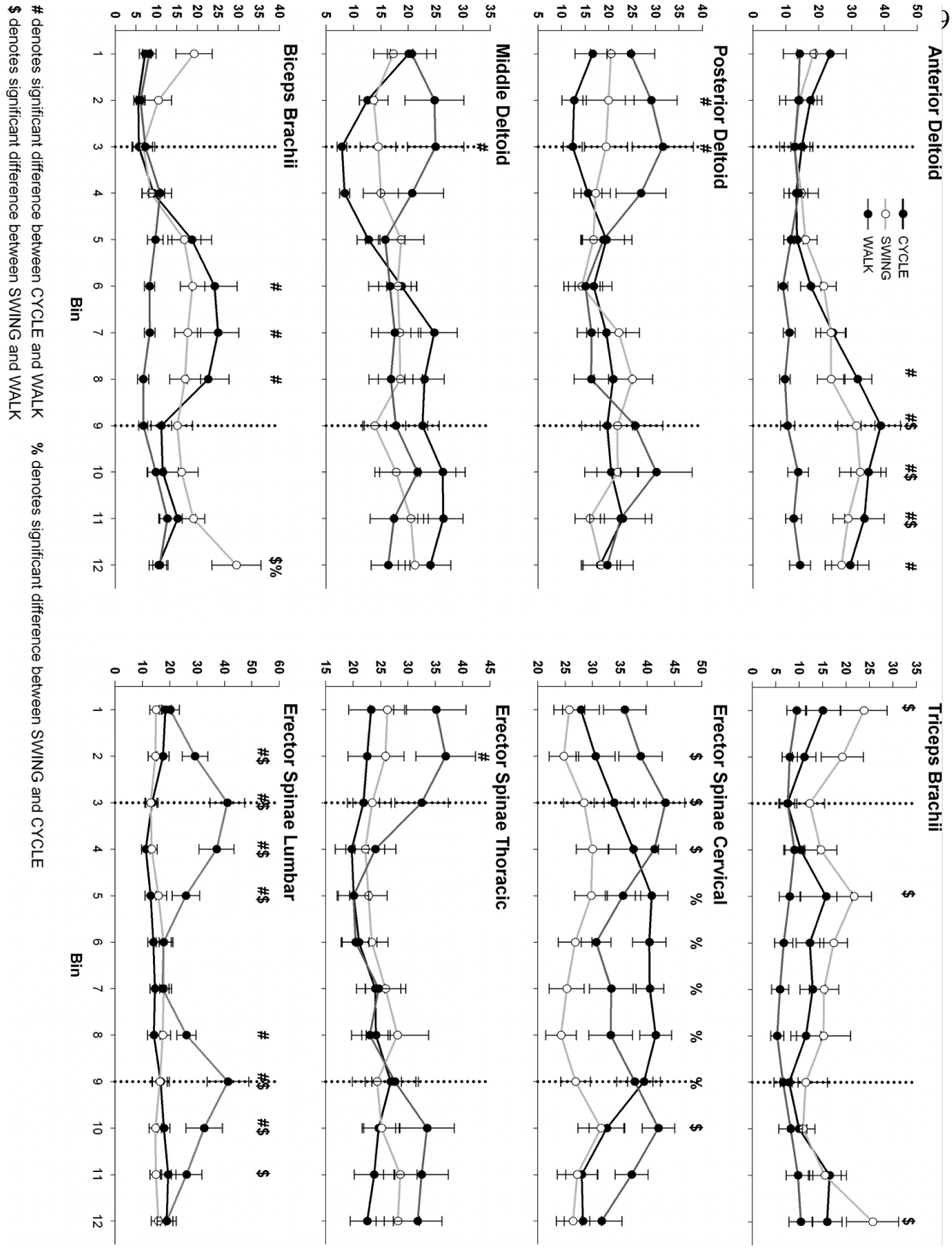


Figure 7-5: Comparative EMG traces for muscles of the right arm and trunk averaged across all subjects for CYCLE, SWING, and WALK tasks.
Significant differences between CYCLE and WALK, SWING and WALK, and SWING and CYCLE are denoted by #, $, and %, respectively. Vertical dashed lines denote the 3

(shoulder flexion) and 9 o'clock (shoulder extension) positions during the movement cycle respectively.

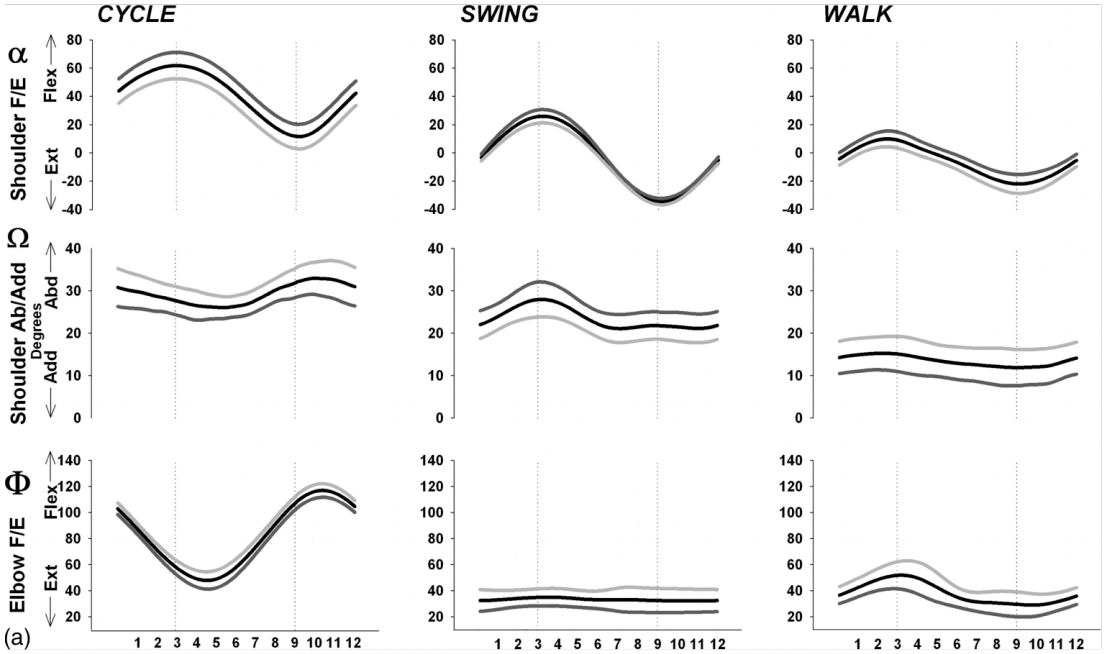
7.4.2. Kinematics

Data relating to shoulder flexion/extension (α), abduction/adduction (Ω) and elbow flexion/extension (Φ) are displayed as cardan angles in figure 7-6A (Conventions for the presentation of these results are shown in figure 4). The range of shoulder flexion/extension was smallest in WALK and largest in CYCLE. The absolute shoulder position for WALK and SWING was such that it traveled into flexion and extension passing equally through the sagital midline while during CYCLE the arm is always in a flexion quadrant in front of the subjects' frontal plane. CYCLE moved from abduction to adduction during the flexion phase and from adduction to abduction during the extension phase. This pattern was inverted during WALK. SWING reached greatest peak abduction during full flexion and a smaller peak during full extension while being adducted during the transition stages of mid flexion and mid extension. Elbow flexion/extension was greatest during CYCLE, smallest in SWING and almost reversed to CYCLE during WALK. The pattern during CYCLE is elbow extension during mid to full flexion and elbow flexion during mid to full extension. This is different to WALK where elbow flexion occurs during full flexion to mid extension and elbow extension occurs during mid extension to full extension.

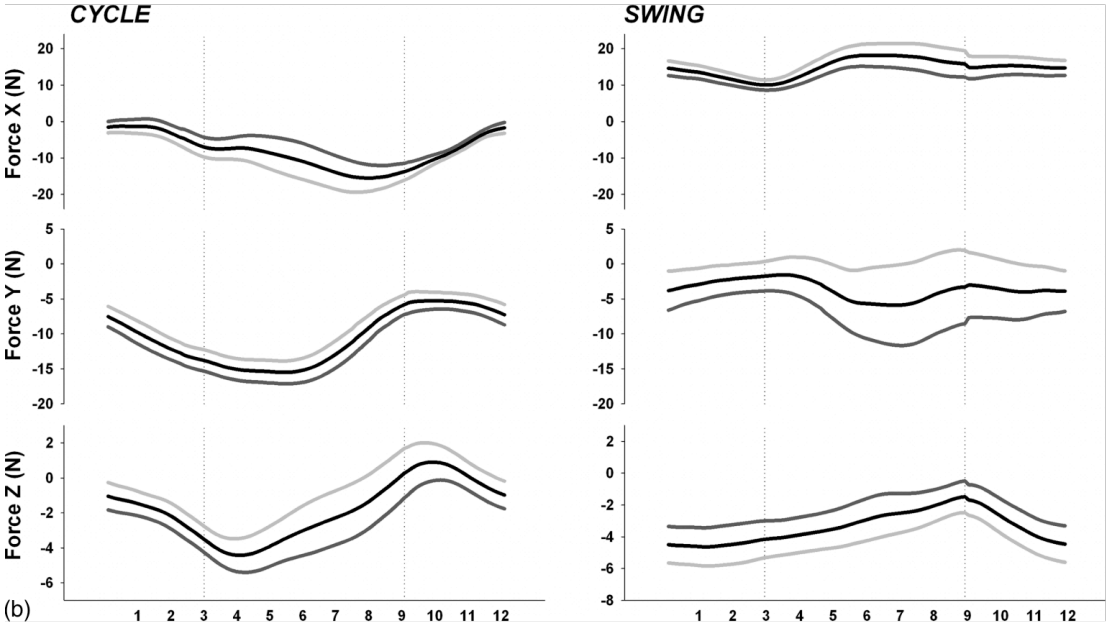
7.4.3. Kinetics

The forces at the hand are shown in Figure 7-6 for CYCLE and SWING. The literary convention for the discussion of forces will be in relation to figure 4C and will be upward (Fy+), downward (Fy-), forward (Fx+), backward (Fx-), medial (Fz-) and lateral (Fz+).

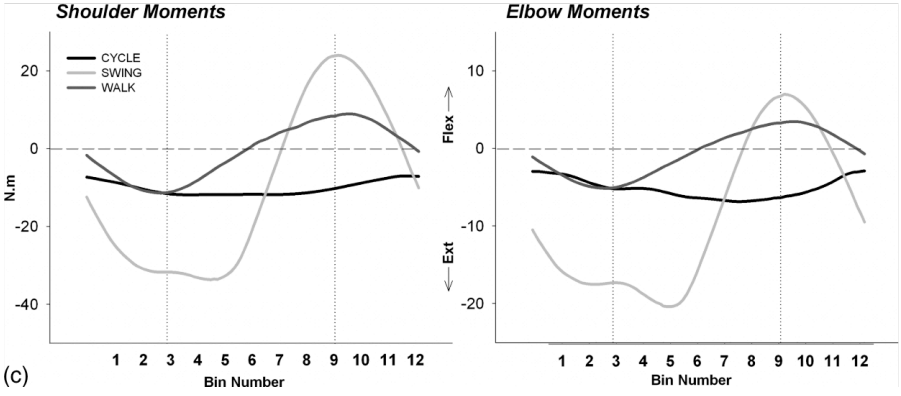
During CYCLE there is a peak downward and medial force at full flexion that persists into mid extension. From mid extension to mid flexion the downward force decreases with an increasing backward and lateral force at full extension. During SWING there is a peak downward and forward force at mid extension. Additionally there is a peak medial force at mid flexion that is decreased at full extension. Shoulder and elbow moments from the two-dimensional inverse dynamics analysis are shown in figure 7-6C with positive values representing flexor and negative values extensor moments, respectively. For both elbow and shoulder moments during WALK there is a peak extensor moment occurring during full flexion and a peak flexor moment during full extension. This is a similar pattern during SWING with a noticeable increase in amplitude and a more prolonged extensor moment during full flexion. For CYCLE, for both shoulder and elbow, there is a constant extensor moment throughout the cycle that is smallest during flexion and largest during extension.


CYCLE
SWING
WALK
α
Shoulder F/E
Flex
Ext
Ω
Shoulder Ab/Add
Degrees
Abd
Add
Φ
Elbow F/E
Flex
Ext
1 2 3 4 5 6 7 8 9 10 11 12

(a)


CYCLE
SWING
Force X (N)
Force Y (N)
Force Z (N)
1 2 3 4 5 6 7 8 9 10 11 12

(b)


Shoulder Moments
Elbow Moments
CYCLE
SWING
WALK
N.m
Flex
Ext
1 2 3 4 5 6 7 8 9 10 11 12
Bin Number

(c)

Figure 7-6: (A) Kinematic changes at the right shoulder and elbow during arm cycling, swinging, and walking for shoulder flexion/extension (α), shoulder abduction/adduction (Ω) and elbow flexion/extension (Φ).
(B) Kinetics measured at the right hand during arm cycling and swinging. (C) Moments calculated about the shoulder and elbow during arm cycling, swinging, and walking. Vertical dashed lines denote the 3 and 9 o'clock positions during the movement cycle, respectively.

7.4.4. Mathematical Analysis

7.4.4.1. Kinematics

For all tasks four factors explained more than 95% of the variance for x and y kinematics (Fig.7-7A&B). For CYCLE and SWING x-kinematics the first factor accounted for 58% and 62% of the variance respectively while the first factor in WALK accounted for only 45% of the variance (Figure 7-7A). Further WALK required 4 factors to explain more than 92% of the variance where CYCLE and SWING only required 3 factors. For CYCLE and SWING y-kinematics the first factor accounted for 63% and 73% of the variance respectively while the first factor in WALK accounted for only 45% of the variance (Figure 7-7A). Further WALK required 4 factors to explain more than 95% of the variance where CYCLE and SWING only required 3 factors. Correlation coefficients for the comparison of the 1st factor show similarity for all tasks for kinematics (both x and y direction) (Table 7-1). Further, analysis of factor loading reveals that for kinematics there was no difference between shoulder flexion/extension or shoulder abduction/adduction but differences between elbow flexion/extension (Fig.7-7D).

	CYCLE vs SWING	CYCLE vs WALK	SWING vs WALK
X-kinematics	0.712±0.071	0.500±0.148	0.688±0.076
Y-kinematics	0.778±0.036	0.5961±0.13	0.645±0.087
EMG	0.216±0.162	-0.079±0.13*	-0.227±0.154*

Table 7-1: The correlation coefficients (± standard error) of the first factor between tasks for separate x-kinematic, y-kinematic and EMG PCA analysis.
Asterisks denote significant difference between the CYCLE vs SWING correlation.

7.4.4.2. EMG

Four factors explained more than 98% of the variance for all tasks (Fig 7-7C). For SWING the first factor accounted for more than 80% of the variance while the first factor for CYCLE and WALK only accounted for 72% and 69% of the variance respectively. Additionally while two factors explained more than 92% of the variance for CYCLE and SWING addition of a third factor was necessary for WALK to account for more than 94% of the variance. Correlation between the 1st factor shows differences between WALK and CYCLE and WALK and SWING with no difference between CYCLE and SWING (Table 7-1). Analysis of the factor loading shows that there are no noticeable differences between individual factor loadings for different muscles (Fig 7-7E)

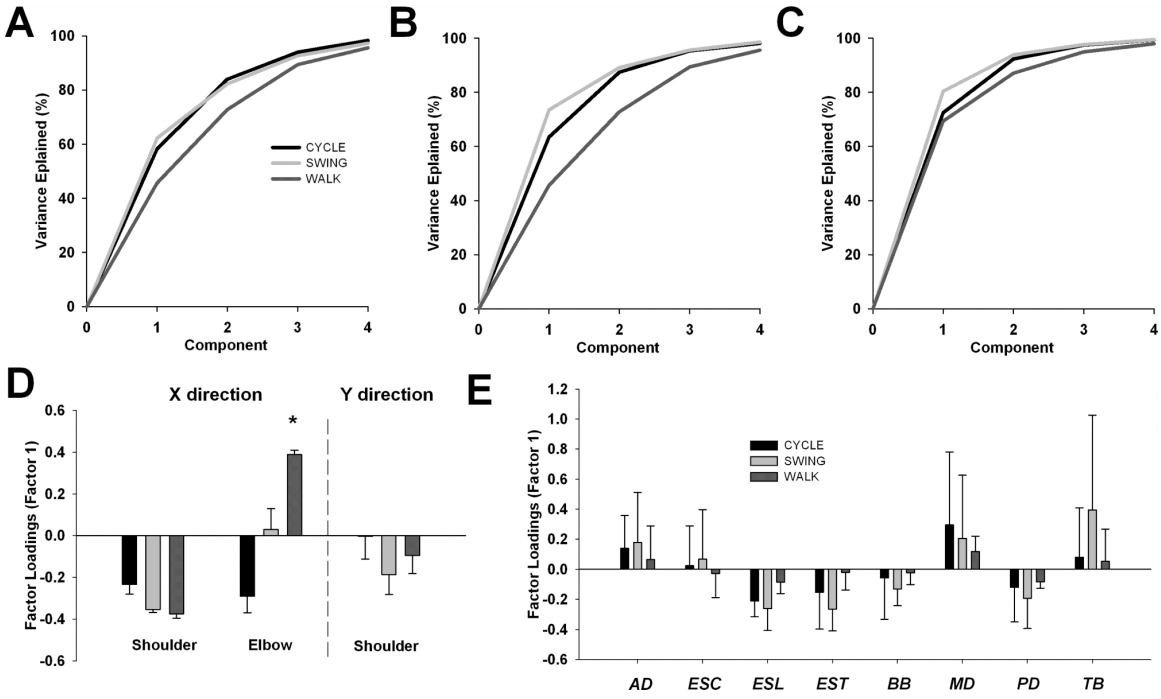


Figure 7-7: (A) The averaged (n=9) cumulative percentage of the variance explained by each of the first 4 factors is shown for the three tasks for x-direction (B) y-direction (C) and EMG.
(D) The average factor loadings for the first factor in the x-direction (flexion/extension) for shoulder and elbow and the average factor loadings for the first factor in the y-direction (adduction/abduction) for the shoulder for all tasks. (E) The average factor loadings for all muscles from the EMG PCA analysis. Asterisks denote significant differences between factor loading from CYCLE.

7.5. Discussion

In the present study we compared three rhythmic arm movement tasks in order to highlight neuromechanical features that require consideration with respect to using arm movement to assist walking rehabilitation. The results demonstrate both neural and mechanical differences between tasks. Specifically while the range of shoulder excursion is similar between tasks elbow flexion/extension kinematics are different. Additionally the anatomical "anchor" position of the arms is different between the CYCLE task and the other two tasks that result in an altered moment noticed about the elbow and shoulder. As well, there are notable differences between the muscle activation patterns and amplitude that may reflect differences in mechanical assistance and constraints between tasks. Differences in task dependent neural control could reflect altered neural coupling to the lower limb. Below we present a neuromechanical description of the three tasks to ameliorate the study of details of arm to leg coupling that can assist in rehabilitation.

The principal components analyses clarify that the most prevalent mechanical difference is found in the pattern of elbow flexion/extension. The difference noticed between CYCLE and WALK in the pattern of elbow flexion/extension demonstrate that the orientation of the limbs during WALK is equivalent to a CYCLE movement in reverse as the pattern of elbow flexion/extension during CYCLE is the elbow is in its most extended position during full flexion and the elbow is in its most flexed position full extension. This is different to WALK which has a peak elbow flexion at full flexion, this is maintained until mid extension and then the elbow is most extended at full extension making a reverse cycling motion at the hand. This alteration in kinematics may require different muscle activation and subsequently neural control. However, forward and

backward cycling has been shown to share common neural control, with a CPG running in reverse, through analysis of reflex responses at functionally equivalent portions of the movement cycle (Zehr & Hundza, 2005). This concept is in agreement with similar results for forward and backward walking and supports the idea of a common core of neural control despite mechanical differences (Grasso et al., 1998; Zehr, 2005). Consequently despite common neural control for forward and backward movements functionally equivalent phases of the movement cycle may be different. This may account for the fact that the first factor in the EMG PCA analysis from CYCLE and SWING were negatively correlated with WALK while there were no differences between factor loadings for muscles. This would suggest an inverted neural signal with common drive to muscles across tasks. Thus, a functional context may allow proper comparison between tasks. Therefore, proper utilization of rhythmic arm movements to enhance locomotor activity requires knowledge of the basic premise of neural control set forth in "the common core hypothesis" (Zehr, 2005) backed by simple and elegant experimental design alongside detailed neuromechanical and functional comparisons. Below we discuss other relevant neuromechanical considerations that may assist in the development and testing of rehabilitative tasks.

7.6. Neuromechanical considerations for the use of arm movement to facilitate leg muscle activity during locomotor activities

7.7. Arm swing while walking (WALK)

During the arm swing of walking, our calculated moments agree with previous work of Hinrichs and Elftman concerning shoulder and elbow kinetics (Elftman, 1939; Hinrichs, 1990). Starting from mid flexion there is a net extensor moment when the shoulder is

approaching maximum flexion (contralateral heel strike) which would tend to slow forward swing and initiate the backward swing. This moment is consistent with heightened PD and MD EMG during forward swing (BALLESTEROS et al., 1965; Hinrichs, 1990; Hogue, 1969; Jackson, 1983). These muscles could assist in braking the forward momentum of the arm and initiate backward swing as well as producing abduction or resisting adduction. Additionally, it has been suggested that movement-related neural signals from this arm position may provide a shaping effect on lower limb muscle activity (Kawashima et al., 2008). Afferent feedback from muscle, cutaneous and joint receptors may be the source of this neural signal. The next major shoulder moment occurs just prior to and during shoulder extension (ipsilateral heel strike) where there is a net flexor moment which would tend to slow the backward swing and initiate forward swing (Hinrichs, 1990). Anatomically the arm has a limited range of extension in this position. Therefore at this position passive tension could produce heightened afferent signals from muscle spindle and tendon receptors in shoulder flexor muscles as well as cutaneous receptors over the anterior surface of the upper arm (Hiraoka, 2001; Kawashima et al., 2008). In agreement with previous studies there is very little activity in AD at this position and it is possible that latissimus dorsi and teres major assist with active transition during extension because they are active at this phase of swing (Hinrichs, 1990). PD is active just following full extension which could offset the force at ipsilateral heelstrike and concurrently could reflect an important neuromechanical strategy. For example, as the arm could be considered a mechanical pendulum with a resonant frequency, passive tension in the musculoskeletal system along with muscle activation (PD) could entrain the arm to move at a different frequency (Webb et al.,

1994). Therefore activity in PD could be responsible for resetting the relative frequency at this point. This potential delay in movement produced by PD would also slow the forward acceleration of the upper arm in position while allowing the lower limb to move forward under its own inertia, this would change the moment of inertia and virtual pendulum length thus altering the resonant frequency of the whole system (Preuschoft & Witte, 1991). This concept is in agreement with the idea that a CPG coupled to a mechanical system can alter the resonant frequency of the whole system (Ijspeert, 2008; Taga, 1998; Verdaasdonk et al., 2006). Therefore full extension may be an important landmark for studying neural control during walking as it may have a crucial role in frequency entrainment of the system.

WALK is the only task in this study where whole body momentum may mechanically affect the movement of the limb and thereby change the functional role of the muscles in the movement. This could be related to the function of arm swing during walking which has been shown to effect whole body moment of inertia to assist balance regulation as well as to offset transverse forces, angular momentum and free vertical moments (Elftman, 1939; Hinrichs, 1990; Li et al., 2001; Misiaszek & Krauss, 2005; Umberger, 2008). Overall the mechanical benefits of arm swing while walking are thought to arrive through a clear active component interacting with the passive motion of the limb, both of which are considered necessary to control the limb to produce smooth locomotion (Jackson, 1983).

7.8. Arm Cycling (CYCLE)

During CYCLE there is a consistent extensor moment at the shoulder throughout the movement that is highest during extension and smallest during flexion. During early flexion there is a decrease in the extensor moment as the shoulder is flexing and adducting while the elbow is extending and following a forward and upward path of the cycle. This is concurrent with decreased downward force on the handle and activity in AD and MD. These muscles would act together to assist in flexion and resist adduction of the shoulder. In late flexion there is an increase in the extensor moment which reaches a plateau as the shoulder is approaching peak flexion. Here, there is diminishing AD, PD and MD activity as the arm is following the downward and forward movement path of the crank arm. Peak flexion is the position at which the centre of mass of the arm is producing the greatest moment about the shoulder. Hinrichs (1990) used this arm positioning to illustrate the relative magnitude of the moment about the shoulder. The magnitude of the current values are in agreement with these calculations suggesting that the position of the arm is responsible for much of the moment at this portion of the cycle. In early extension the moment is maintained as the elbow is flexing and producing an extensor moment about the shoulder. Thus even though the moment arm from the center of mass of the whole arm segment is diminishing and decreasing its contribution to the shoulder moment, the change in orientation of the elbow is resulting in an increasing extensor moment about the shoulder that is highest during peak extension. As well there is increased backward and downward force on the handle that is congruent with the movement path. Also, there is increasing AD, MD, BB and ES-C activity which could serve to slow the backward movement of the arm. During late extension the extensor moment is maintained as there is a peak extensor moment at the elbow as the shoulder

extends and abducts. As well there is a peak backward force with diminished downward force on the handle consistent with an upward and backward movement path. Here, there is an increase in AD, MD, BB and ES-C activity. The combined activity of these muscles could serve to stabilize the limb (ESC), slow the backward swing of the upper arm while assisting abduction and initiating forward swing (AD,MD) all while lifting the forearm, hand and cycle ergometer through the movement path (BB). One would assume that because the moment arm from the Center of gravity of the whole limb to the shoulder joint is smallest at this point this would diminish the extensor moment about the shoulder. However during late extension is also where the direction of the movement path of the ergometer is upward and towards the body thus producing a large extensor moment about the shoulder because the arm must be lifted congruent with this path and against gravity. Thus there is a balance between the orientation of the limb and the movement paths direction with respect to gravity. Overall, a consistent flexor moment would be necessary to resist the gravitational moment due to the anatomical position of the limb. As mentioned above during arm swing while walking transition points such as peak flexion and extension may present areas where afferent feedback may be heightened. However the constant extensor moment may present a source of afferent feedback that reduces or increases the effectiveness of other afferent signals. The CYCLE task could effectively be altered by making an apparatus that allows cycling beside the body in the same shoulder excursion range as WALK. AD and MD activity are highest during late flexion and early extension during cycling to properly halt the backward progression and initiate forward progression. This is qualitatively different to WALK which has greater activation of PD and MD during peak flexion. Therefore in terms of the phases where the greatest

propulsion to the movement occurs these seem to be opposite between the two tasks in reference to the shoulder muscles which could relate to the regulation of forward and backward cycling, control variable or anchor position differences between tasks (Zehr et al., 2007). The control variable idea suggests that the kinematic control of the task is constructed to produce muscle pattern that relate to a specific mechanical parameter (Grasso et al., 1998; Zehr et al., 2007). During CYCLE and SWING arm swing is a manipulation of limb orientation to produce force at the hand interface to propel the hand through the prescribed movement path and therefore the control variable would be the trajectory of the hand. This contrasts with WALK where the manipulated variable is the moment of inertia of the whole arm (Preuschoft & Witte, 1991). Thus control variable differences may account for the differences in muscle activation. This is similar to a comparison of forward and backward walking where the kinematic parameters where conserved despite substantial differences in energy cost (Grasso et al., 1998). Differences in the anatomical "anchor" position could require differential activation of muscles that cross the shoulder joint. This is because changing kinematics alters the moment producing capacity of muscles about a joint due to force-length relationships and differences of line of action (Lieber, 2000; Klimstra & Zehr, WCB abstract). Thus tasks may require different optimal muscle activation profiles (neural drive) based on anchor position. For example, during CYCLE, AD is at a shortened length and PD lengthened compared to WALK and SWING because the arm is in front of the body midline. This would change the relative contribution that each muscle could have to the movement. However, we did not measure all muscles that could contribute to the movement and it is

important to measure from all possible contributing muscles before a true discussion of control variable and anchor position can be made.

Another interesting feature of CYCLE is that movement of the apparatus required no z-force because of its planar orientation. However there were small but measureable changes in the z-force at the flexion/extension transitions consistent with adduction and abduction of the shoulder. Thus there may be inefficient movement due to the anatomical constraints. The mechanical assistance from the rest of the body is purely to stabilize the upper body and limbs during the movement. This form of assistance is different than that observed during WALK. However, the arm cycle ergometer used in this experiment had an inertial load that could provide mechanical assistance to the movement and could change the neural feedback and strategy. This could be tested by altering the inertial parameters of the arm cycle or inducing mechanical assistance through a servo-motor attached to the crank (Kautz et al., 2006; Ting et al., 1998; Ting et al., 1999; Ting et al., 2000). The interactions of anatomical position, constraints, inertial load and movement path present possible interactions that may affect neural control.

7.8.1. Arm swing alone (SWING)

During arm swing there are two noticeable moments occurring near peak flexion and extension similar to WALK. From late flexion to early extension there is an extensor moment when the arm is transitioning from flexion to extension while abducting. This occurs alongside only relative low level PD and MD activity suggesting that the transition could be a function of the inertia of the arm or other musculature not measured in this study such as latissimus dorsi and teres major (BALLESTEROS et al., 1965;

Hinrichs, 1990). Although this movement does not exhibit the same muscle activation as WALK there may be similar peripheral feedback due to the anatomical position and the range of motion. There is a flexion moment during late extension and early flexion to slow the backward progression of the limb and initiate forward progression. This occurs with a peak negative z-force suggesting an interaction between the desired movement path and the prescribed movement path induced by the apparatus similar to CYCLE. During late extension early flexion there is increasing AD activity that would be consistent with activity to break backward progression and initiate forward progression. It is important to note that due to the apparatus, throughout the movement there is very little elbow extension (less than 5 degrees). Therefore the upper arm, forearm and hand would behave as a rigid segment. The added mass of the forearm and hand as well as the apparatus could add a considerable moment about both the elbow and shoulder. This is noticed in the increased shoulder and elbow moments compared to WALK. Additionally during extension to flexion there is a noticeable increase in BB and TB to stabilize the joint against the torque. The activity of BB during this stage could also serve to accelerate the shoulder into flexion as it crosses both the elbow and the shoulder joint. The increased moment may produce a strong afferent signal during this phase of the movement. As SWING is similar to WALK in the anatomical position of the limb and the basic motion it is surprising to see that the muscle activity is different. However there are differences noticed in the anatomical range as well as shoulder abduction/adduction and elbow flexion extension due to the experimental set up. These could effectively alter the muscle activation profile. For example, Fernandez-Ballesteros et al. 1965 showed that during arm swing alone at different excursions muscle activation changed from only PD

activity at less than 30^{o} to include activity from AD and MD at excursions greater than 30^{o}. This was also noticed when comparing the self-selected excursion trials in the current study. Thus it could be the difference in the shoulder excursion range between WALK and SWING that produces differential activation of muscles.

7.9. Functional Implications and Conclusion:

The current study presents a neuromechanical characterization of three rhythmic arm movement tasks. This attempt to highlight rhythmic arm movement could be used to assist in the determination of the necessary and sufficient conditions for arm induced lower limb activation in locomotor rehabilitation in both stroke and spinal cord injury. Through factor analyses these tasks were shown to have different mechanics with conserved central neural control. Interestingly, the three arm tasks can be considered to share the same basic rhythmic pattern except that the anchor point about which the arm oscillates in the 3 tasks is shifted (shown clearly in Figure 7-6A). This allows for conservation of neural control parameters while still allowing for incorporating altered mechanics that will affect afferent feedback and supraspinal contributions. Additionally the movement state of the arms and the legs, the phase relationship between the limb pairs, mechanical coupling and augmented afferent feedback could enhance or reduce the effect of arm movement on lower limb activation (Ferris et al. 2006; Zehr et al. 2009). Incorporation of parameters related to arm movement in the restoration of leg activation after neurotrauma is a next step. It remains to test the effect of different sources of afferent feedback as well as altering existing apparatus to assist in the development and

testing of a functional task to assist neuronal coupling between the arms and legs in a manner consistent with locomotor rehabilitation.

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8. General conclusion:

The main objectives of this thesis were: 1) to further explore interlimb coupling in humans during combined arm and leg rhythmic movement; and, 2) to use combined neural and mechanical measurement to further understand the neural control of rhythmic arm movement and reveal neuromechanical considerations for the incorporation of rhythmic arm movement in the rehabilitation of walking. This section is a summary of the main findings of the thesis.

8.1. Reflex analysis

The use of reflexes as neural probes as mentioned in chapter 1 can be usefully applied in human studies of neural control. Specifically, the H-reflex has proven to be a valuable tool in human studies of rhythmic movement control where direct measurement of activity in underlying control networks is impossible. Chapter 2 described a study necessary to refine and evaluate H-reflex methodology that could provide a robust and informative approach to reflex analysis. A sigmoid function is found to be the best fit for the ascending limb of the H-reflex recruitments curve based on a comparison of different mathematical analysis techniques including the currently accepted linear regression technique (Funase et al., 1994) and the newly proposed polynomial technique (Christie et al., 2004). Overall the sigmoid fit is shown to be a more reliable fit against logarithmic, polynomial, cubic spline, power, and linear regression for H-reflex recruitment curves against current (HCRC) or concurrently occurring M-wave amplitude (HMRC). Additionally, this fitting technique is a physiologically justified function for the input

output relation of the ascending limb of the H-reflex recruitment curve. This curve-fitting technique can be used to determine parameters of interest used for experimental comparison, such as changes in threshold, slope or alteration in excitability at different levels of activation. The significance of this chapter to the current thesis is the use of the analysis technique in studies of interlimb communication during rhythmic movement.

8.2. Interlimb connections during rhythmic arm and leg movement

Data from Chapter 3, 4 and 5 support the idea that there is a strong interlimb neural communication in humans and present important details of interlimb coupling between the arms and legs during rhythmic tasks (Dietz et al., 2001; Dietz, 2002; Zehr et al., 2009). Experiments in non-human quadrupeds have confirmed a bidirectional coupling of the cervical and lumbar locomotor centres responsible for coordinating rhythmic movement of the fore and hind limbs (Akay et al., 2006; Ballion et al., 2001; Gernandt & Megirian, 1961; Juvin et al., 2005; Miller et al., 1973; Skinner et al., 1980; Zaporozhets et al., 2006). Data in this thesis supports the premise of a similar bidirectional coupling of cervical and lumbar spinal locomotor circuitry in humans. That is, studies in this thesis maintain that rhythmic movement of the arms or the legs produce signals that can modify the neural activity in the other limb pair. This conclusion is based on three studies in this thesis. First, leg cycling modulates forearm H-reflex excitability and suggests evidence of a subcortical locus (Chapter 3). Also, rhythmic arm movement modifies reflex expression in the moving legs when enhanced afferent feedback fromthe hand is present (Chapter 4). Further, there are task and phase related differences in the contributions of rhythmic arm

and leg movement to reflexes in a stationary test leg (Chapter 5).

In chapter 3 it was shown that leg cycling modulates reflexes in stationary arm muscles. Further, through TMS conditioned H-reflexes it was revealed that this change was not associated with an alteration in excitability of cortical projections to arm muscles. This result is evidence of a subcortical locus producing the arm reflex modulation. This provides further evidence of an ascending interlimb neural connection regulated by CPG control of rhythmic leg movement and mediated through propriospinal connections (Akay et al., 2006; Ballion et al., 2001; Juvin et al., 2005; Sakamoto et al., 2007). In the neonatal rat preparation Juvin et al. 2005 observed a dominance in locomotor drive from the lumbar over cervical CPG's. This dominant role of the legs during interlimb coupling is also seen in human experiments (Balter & Zehr, 2007). For example, It has been shown that rhythmic arm movement can significantly modify reflexes in stationary legs (Frigon et al., 2004; Loadman & Zehr, 2007). However, when both the arms and legs were moving rhythmically the contribution of the arms to reflex expression in the legs was shown to be functionally related to the movement state of the legs (Balter & Zehr, 2007). Sakamoto et al. 2007 observed a similar effect through modifications in arm cycling cadence induced by changes in leg cycling cadence while changes in arm cycling had no effect on leg cycling. Additionally in the experiment described in chapter 4, when the legs are moving, the contribution of rhythmic arm movement to modify reflexes in the legs is only revealed with enhanced afferent feedback from the hand. This result supports the dominant effect of the legs on the interlimb coupling and additionally supports the suggestion that cutaneous feedback from the hand is important to assist in coordination between the arms and the legs (Balter &

Zehr, 2007; Haridas & Zehr, 2003). Therefore it may be possible that altering specific aspects of rhythmic arm movement could modify the contribution of the arms to interlimb coupling (Hiraoka & Iwata, 2006; Kawashima et al., 2008). However, the experiment in chapter 4 was only conducted at one phase of the movement cycle. Additionally, movement of the test leg has a dominating contribution to the reflex modulation that may result in an inability to determine the contribution from remote sources such as arm movement. Using a protocol that allowed the test leg to remain stationary, the experiment in chapter 5 showed a significant contribution of rhythmic arm movement to reflex expression in a combined arm and leg movement task that was related to the phase of the movement. Together, the results from chapters 4 and 5 show that changes in afferent feedback from the hand or changes in the phases of the movement result in an augmentation in the contribution of the arms to reflexes in the legs. Further, this result supports a potential role of rhythmic arm movement in the rehabilitation of walking (Ferris et al., 2006). The importance of including rhythmic arm movement in walking rehabilitation has been shown in studies of individuals with spinal cord injury (Behrman & Harkema, 2000; Kawashima et al., 2008; Visintin & Barbeau, 1994). Visintin & Barbeau, 1994 showed that SCI patients displayed more symmetrical gait patterns and normal EMG activation when walking with arm swing compared to when arm movement was restricted (Visintin & Barbeau, 1994). However, as demonstrated in chapter 4 and 5 specific features of rhythmic arm movement can alter the contribution of the arms to reflex expression in the legs. Therefore it is crucial to understand what characteristics of rhythmic arm movement are necessary to properly

engage lower limb neural circuitry. This may be related to changes in neural signals associated with the biomechanics of rhythmic arm movement.

8.3.Neuromechanics of rhythmic arm movement

Knowledge relating how mechanical parameters of rhythmic arm movement can affect reflex excitability in the legs has implications for walking retraining after neurotrauma. That is, there may be crucial changes in neural signals during rhythmic arm movement, related to task mechanics, which result in an optimal change in leg muscle activity that can facilitate locomotor retraining.

A neuromechanical analysis of reflexes during rhythmic movement provides valuable insight into the function of reflexes during locomotion and underlying neural control processes (Zehr & Stein, 1999). Chapter 6 presents data on neuromechanical correlates of reflex responses during rhythmic arm movement. Overall, there are neural and mechanical correlated responses to cutaneous stimulation of the hand during rhythmic arm cycling. These responses have general features of functional reflexes during rhythmic movement as seen in the legs (Zehr et al., 1997; Zehr et al., 1998; Zehr & Stein, 1999). However, these responses do not fit into the biomechanical context of rhythmic arm cycling and may be shaped by the task constraints. This could suggest that during rhythmic movement of the arms the reflex responses are tuned to the naturally occurring locomotor task, which may or may not be functionally relevant within a similar rhythmic task. Overall, this data adds to the information on the neural control of rhythmic arm movement and supports parallels between the rhythmic control of the arms and the

legs. Further, understanding differences between the neural control and biomechanics of different arm movement tasks could elucidate the necessary and sufficient parameters of rhythmic arm movement to include in locomotor rehabilitation. Past studies have demonstrated that the central motor command related to the rhythm generation of arm movement is the primary signal responsible for the modification in reflex amplitude in stationary legs (Frigon et al., 2004; Loadman & Zehr, 2007). However, there is uncertainty as to whether afferent feedback related to rhythmic arm movement may play a limited (Hundza & Zehr, 2006; Hundza & Zehr, 2009; Loadman & Zehr, 2007) or substantial (Hiraoka & Iwata, 2006; Kawashima et al., 2008) role in interlimb communication. Therefore knowledge of mechanical details of a task can help to determine changes in afferent feedback that may or may not be relevant to interlimb coupling. Data in Chapter 7 shows a neuromechanical comparison between three rhythmic arm movement tasks. The results are consistent with conserved common central motor control mechanisms operational for each rhythmic arm movement task but appropriately sculpted to mechanical demands unique to each task (Zehr et al., 2007). Important neural and mechanical differences between tasks that could reflect alterations in afferent feedback and/or neural control are highlighted. For example, differences in the anatomical position of the arms alter the moments about the shoulder and elbow, which will result in changes in afferent signals relayed through muscle, cutaneous or joint afferents.

In conclusion, the data in this thesis support neural coupling between the arms and the legs in humans. Also, a mechanical framework of rhythmic arm movement is

presented. Together this information can be used to explore further experimental considerations for the utility of rhythmic arm movement in walking retraining.

8.4. Future Directions

With respect to H-reflex analysis, future studies are required to evaluate the sigmoid technique against other multi-parameter sigmoid equations (Pitcher et al., 2003) and a newly implemented Gaussian technique (Brinkworth et al., 2007). Additionally, while the curve fitting technique produces different parameters of interest, it is important to determine the importance and usefulness of each parameter and how these may similarly or differentially change due to an experimental intervention.

Details of human neural interlimb coupling, presented in chapters 3, 4 and 5 are of importance to understanding normal locomotion and how to improve rehabilitative interventions. However, more information is required on neural connections between the arms and the legs, such as: a more robust investigation of the effect of phase of leg movement on reflexes in the arms across different tasks; a direct comparison of rhythmic ankle flexion and extension tasks and rhythmic locomotor tasks on changes in arm reflexes and corticospinal excitability; comparison of reflex responses during reduced locomotor tasks in injured populations with and without augmented afferent feedback; more robust mechanical measurement during reduced locomotor tasks to allow functional comparisons to natural locomotion.

Combined neural and mechanical measurement of rhythmic arm movement has provided valuable information on the function of reflexes during arm movement and

allowed comparison between rhythmic arm movement tasks. Future directions include the evaluation of responses occurring due to stimulation of different nerves in the hand in arm cycling and other rhythmic movement tasks. Additionally, understanding reflex function will also be important in studies of interlimb reflex responses during rhythmic multilimb tasks.

The neuromechanical comparison of different rhythmic arm movement tasks has elucidated important task related differences that could augment the coupling between the arms and the legs during rhythmic arm and leg movement. Future work is required to investigate how mechanical differences between tasks can alter neural control and interlimb coupling, such as; differences in anatomical anchor positions of the arms; alterations in the moments about the shoulder and the elbow; reversal of movement direction.

Overall the aforementioned future directions with respect to reflex analysis, details of neural interlimb coupling and integrated neuromechanical measurement will provide a substantial knowledgebase for understanding the human neural control of locomotion. This information will be invaluable for the development, testing and implementation of gait retraining. However, while this thesis supports the potential for the implementation of rhythmic arm movement in the rehabilitation of walking, the results are really only building blocks upon which more specific questions can be asked. Further recommendations for the specific details of rhythmic arm movement necessary to properly engage the legs in still lacking. It remains to be determined how to properly move the arms to cause an effective and functionally relevant change in leg muscle activity during rehabilitation. The answer may depend upon the context, type and level of

injury. Manipulated parameters could include or be related to anatomical anchor position, altered afferent feedback, moments about joints, frequency and phase relationships. Ultimately, investigations into the necessary and sufficient conditions to optimize parameter of rhythmic arm movement as a rehabilitative adjunct to locomotor training still require further exploration (Stevenson et al. 2010).

8.5. References

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