Modulation of within limb and interlimb reflexes during rhythmic arm cycling

by

Sandra R. Hundza
B.Sc.(Rehabilitation Medicine), University of Alberta, 1990

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Supervisory Committee

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Dr. E. Paul Zehr, (School of Exercise Science, Physical and Health Education)
Supervisor

Dr. Ryan Rhodes (School of Exercise Science, Physical and Health Education)
Departmental Member

Dr. Dave F Collins (Faculty of Physical Education and Recreation, University of Alberta)
Outside Member

Dr. R. Chua, (School of Human Kinetics, University of British Columbia)
Additional Member

Abstract

Supervisory Committee

Dr. E. Paul Zehr, Supervisor
(School of Exercise Science, Physical and Health Education)

Dr. Ryan Rhodes Departmental Member
(School of Exercise Science, Physical and Health Education)

Dr. Dave F Collins, Outside Member
(Faculty of Physical Education and Recreation, University of Alberta)

Dr. R. Chua, Additional Member
(School of Human Kinetics, University of British Columbia)

In common with animal species, evidence in humans suggests that similar neural mechanisms (e.g. locomotor central pattern generator (CPG)) regulate rhythmic movements in both arm and leg and that interlimb neural connections coordinate movement between upper and lower limbs. ; however, by comparison the evidence in humans is limited. This thesis focused upon exploring the neural control of rhythmic arm cycling and the influence of the neural control of arm cycling on the neural circuits controlling the legs. Specifically, the effect of five different arm cycling paradigms on EMG and reflex responses in arm and leg muscles were explored.

First, the pattern of muscle activity and cutaneous reflex modulation evoked with electrical stimulation to the superficial radial (SR) nerve were evaluated during forward and backward arm cycling. Irrespective of the cycling direction, background electromyographic (bEMG) and cutaneous reflex patterns were similarly modulated suggesting similar neural control mechanisms for both forward and backward cycling. These bEMG and reflex findings provide further evidence of contributions from CPG activity to the neural regulation of rhythmic arm movement. Second, bEMG and cutaneous reflex (SR nerve) modulation were evaluated during three dissimilar bilateral rhythmic arm cycling tasks created by unilaterally manipulating crank length (CL). The neural regulation of arm cycling was shown to be insensitive to asymmetrical

changes in arm crank length suggesting that the neural control was equivalent across the three dissimilar rhythmic arm cycling tasks and that differences in peripherally generated inputs between the dissimilar rhythmic tasks had limited effect on the neural control. Third, the neural control of arm movements was evaluated between those with unstable shoulders and control participants. The alterations of bEMG and the cutaneous reflex patterns suggest that the neural control is compromised in those with shoulder instabilities during rhythmic arm movement.

Fourth, inhibition of the soleus H-reflex in stationary legs induced by rhythmic arm cycling was shown to be graded with arm cycling frequency. A minimum threshold arm cycling frequency of .8Hz was required to produce a significant interlimb effect. Fifth, the degree of the soleus H-reflex suppression induced by arm cycling was independent of afferent feedback associated with arm cycling at different crank loads. In combination the latter two studies suggest that central motor commands related to the frequency of arm cycling is the major signal responsible for the soleus H-reflex suppression in stationary legs, while afferent feedback related to upper limb loading during arm cycling is not.

Collectively, the data contained in this thesis contribute to the evidence suggesting that CPG activity contributes to neural regulation of rhythmic arm movement, alterations in sensory feedback associated with arm cycling have limited influence on the observed reflex modulation and that the neural control can be disrupted in the presence of prolonged orthopaedic injury. Taken together with our previous findings, the current results also suggests that central motor command (e.g. CPGs) for rhythm generation of the rhythmic arm movement is the primary source of the signal responsible for the observed interlimb neural communication.

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1. General Introduction

During locomotion, we rhythmically move our arms without any deliberate attention or effort. Many locomotor tasks like walking, running, or swimming involve such rhythmic arm motion. This automated rhythmic arm muscle activation is highly coordinated with the rhythmic activation of leg muscles. A preponderance of animal studies provide direct evidence that spinal circuits produce this patterned motor output (for review see Duysens and Van de Crommert 1998; Grillner 1975; Grillner 1981; Grillner and Dubuc 1988). These cervical and lumbar central pattern generators (CPGs) have been shown to regulate rhythmic movement in the fore and hind limbs respectively and their integrated function produces the smooth, coordinated movement between fore and hind limbs (Ballion et al. 2001; Juvin et al. 2005; Miller 1973; Schomberg et al. 1978; Zaporozhets et al. 2006). Evidence shows that, though these spinal circuits produce the fundamental locomotor pattern, their output is exquisitely sculpted by descending supraspinal input and afferent feedback to dynamically adapt the basic locomotor pattern to the requirements of the environment (Rossignol 1996).

By necessity, the contribution of CPG activity to the neural control of human rhythmic movement has been assessed through inference and indirect means. Several studies suggest that CPG mechanisms contribute to the control of leg muscles in human locomotion, including walking and leg cycling (for review see Duysens and Van de Crommert 1998; MacKay-Lyons 2002). More recently, there has been an interest in the neural control of rhythmic arm movements. In common with animal research, current human evidence suggests that similar neural mechanisms (e.g. CPGs) regulate rhythmic movements in both arms and legs, and that

interlimb neural connections coordinate movement between upper and lower limbs (Dietz 2002; Zehr et al. 2004; Zehr and Duysens 2004; Zehr and Haridas 2003).

A further understanding of the neural control of rhythmic arm movement and its interaction with the neural control of leg muscles is required to not only increase our understanding at a basic science level, but also to provide a principled basis to the enhancement and development of rehabilitation strategies after neurological disorders. The primary focus of this thesis is to further explore the neural control of rhythmic arm cycling and the interlimb communication between the arms and legs during rhythmic arm activity. This has been done by evaluating the effect of different rhythmic arm cycling paradigms on muscle activation and reflex modulation patterns in arm and leg muscles. While many regions in the nervous system are involved in controlling rhythmic arm cycling, the following literature review will be limited to the issues relevant to the experimental findings in this thesis. This literature review will discuss the development of CPGs as a construct from inception to current models; evidence of CPGs' contributions to the neural control of rhythmic movement of arms and legs in humans; and interlimb neural communication during rhythmic movement. Lastly, the role of supraspinal input and sensory feedback in the regulation of rhythmic movement will be briefly reviewed. Though supraspinal input and sensory feedback play important role in the regulation of rhythmic movement, they were not explicitly studied in the experiments of this thesis and therefore will be only superficially reviewed.

1.1 Central Pattern Generator for Non-Primate Locomotion - Evidence and Models

Nearly a century ago, rudimentary stepping movements were observed in decerebrate and spinalized animal preparations (Phillippson 1905; Sherrington 1910a, 1910b). Initially these rhythmic flexion-extension movements were thought to be produced solely by a feedback system of peripheral reflexes in which the afferent signals associated with one movement would elicit the next movement (Sherrington 1910a, 1910b). However, Graham Brown (1911) disproved this theory by demonstrating that deafferented spinalized cats (at a low thoracic level) could produce rhythmic ankle flexion-extension patterns. Thus his work was the first to prove that rudimentary stepping movements could be produced by 'intrinsic' spinal networks in the absence of afferent feedback or descending supraspinal influences. He proposed the well-known "half-center" model, in which flexor and extensor half-centers were coupled by mutually inhibitory interneurons preventing simultaneous activity of flexors and extensors. He proposed that with "fatigue" the firing in the active half center slowed, releasing the opposing half-centre from inhibition which allowed activity in antagonist motoneurons. The process repeats and the system oscillates. In more current theories the ongoing oscillation is supported by reciprocally inhibitory neuronal connections between interneurons with post inhibitory rebound properties which accommodate to tonic input. Brown demonstrated that these central oscillating mechanisms generate the basic stepping pattern, however he also acknowledged the role of sensory input in shaping the output of these central mechanisms claiming that afferent feedback played a 'regulative' role, rather than a 'causative' role in the neural control of locomotion (1911, 1914).

A reciprocal organization of half-center pathways that involved reflex pathways was proposed by Jankowska and colleagues (1967a, 1967b). Intracellular motoneuron recordings during L-Dihydroxyphenylalanine (L-DOPA) induced locomotion revealed strong mutual

inhibitory interactions between interneuronal pathways to flexors and extensors (Jankowska et al. 1967a). They demonstrated that acute spinal cats, treated with L-DOPA, responded to trains of electrical stimulation to flexor reflex afferents (i.e. small-diameter joint, muscle, or cutaneous afferents) with prolonged excitation of ipsilateral flexors and contralateral extensors and with inhibition of ipsilateral extensors and contralateral flexors. At times this experimental paradigm also resulted in sequences of rudimentary stepping movements. In addition, the excitatory responses could be suppressed by a conditioning stimulus to the antagonist group of interneurons (Jankowska et al. 1967b). Together, these results suggest that flexor reflex pathways may be incorporated into locomotor generating circuits which include mutually inhibitory pathways between interneurons that excite flexor and extensor motoneuron pools. These findings united the half-center and reflex concepts of Brown and Sherrington respectively.

It was soon recognized that the half-center model, which predicted simple alternation of activity in flexor and extensor muscles, could not account for the complexity in timing and level of muscle activation seen in natural gait. EMG studies with intact cats demonstrated that the muscle activity pattern was more specific with features like a double burst of activity of some flexor bifunctional muscles within one gait phase (Engberg and Lundberg 1962, 1969; Gambarian et al. 1971). Engberg and Lundberg (1969) proposed that aspects of double burst activity (such as a second burst in semitendinous muscle activity in late swing) were modulated by afferent input. This idea was refuted by observations of these complex muscle activation patterns in reduced preparations (spinalized or decerebrate) with deafferentation during treadmill locomotion (Forssberg et al. 1980; Grillner and Zangger 1975, 1979, 1984) or in fictive locomotion (Grillner and Zangger 1979; Pearson and Rossignol 1991) as well as in spinalized

fictive locomotor rodent preparations (Kudo and Yamada 1987). In sum, these findings suggest that the spinal circuits can generate complex activity without phasic sensory input.

Grillner (1975) proposed an augmented version of Brown's model to attempt to explain how the spinal cord generates complex muscle activity during locomotion. In this model, Grillner (1975) named the group of spinal neurons producing locomotor movement the locomotor central pattern generator (CPG). His theory included a separate CPG to control the movement in each limb, whose phasic activity was coordinated with the other limb generators. This was accomplished through coordinating interneurons resulting in reciprocal phasic activity between the limbs (Grillner 1975). Later Grillner further developed the CPG concept to incorporate a mosaic of subunits for each joint called unit burst generators (1981). Each burst generator was capable of producing bursting output and the interconnections between these subunits was proposed to produce the coordinated and complex rhythmic muscle activation for the limb (1979, 1981). The recombination of different "unit CPGs" within a limb could produce different motor patterns (Grillner 1985), allowing considerable flexibility. The unit burst generator CPG concept remains incorporated into current CPG models.

This unit generation model has since been supported by work with the lamprey (Matsushima and Grillner 1992), tadpole (Roberts et al. 1997) and mudpuppy (Cheng et al. 1998). In the mudpuppy, for example, tonic electrical stimulation to 2nd cervical segment (C2) produces rhythmic elbow flexor bursts whereas stimulation to different regions of the C3 segment produces wrist flexion or extension or elbow extension bursts. These data show the different separate regions in the spinal cord are responsible for generating rhythmic flexion or extension in muscles acting at different joints. In addition in both the tadpole and the lamprey each spinal segment contains neural circuitry to produce rhythmic reciprocal muscular activity

on each side of the body for that specific level. The spinal segments or unit generators are consecutively phase coupled to produce coordinated swimming (Matsushima and Grillner 1992; Tunstall and Roberts 1991).

Though this model does explain some of the complexity of movement associated with coordinating flexion–extension at different joints like that seen in some fictive spinal preparations (Pearson and Rossignol 1991), it still does not explain the intricate complexities of gait like double bursting of some muscles within a phase or activity in muscles during both swing and stance phases (Engberg and Lundberg 1969). Alternatively Perret and Cabelguen (1980) proposed a theory which incorporates a more complicated interneuronal network operating between the half-centres and motoneurons. This allows some motoneurons, specifically those innervating bifunctional muscles (e.g. posterior biceps and semitendonosis), to receive commands from both flexor and extensor half-center (see also Orsal et al. 1986; Perret et al. 1988). Grading the relative strengths of the inputs from the two-half centers would thus determine the phasing of the muscle's activity.

An analytical CPG model proposed by Patla and colleagues involved a distributed segmental model of CPG networks (Patla et al. 1985) which claimed to explain complex muscle activation patterns seen in cats. Each limb pattern generator is considered to have a tonic input and six outputs; this provides for flexion and extension of representative muscles for each of the three joints of the limb. The limb pattern generator can be represented as three subsystems: an oscillator that produces the fundamental frequency of the output in response to the tonic signal, non-linear shaping functions that mold the oscillator output into the basic complex pattern, and appropriate weighting functions that generate the muscle activity pattern from basic waveforms (Patla et al. 1985). Orlovsky and colleagues proposed another half-center CPG model which

incorporated more complex neural circuits in attempts to explain afferent dependent motoneuron excitation gated by the phase of the locomotor cycle (Orlovsky et al. 1999). This model has motoneurons receive excitation during locomotion from interneurons with sensory input as well as from the half-centers (Orlovsky et al. 1999).

The above mentioned CPG models were single-layer and though the greater complexity of some of the schemas did account for the flexible regulation of motoneuron activity these models fail to explain certain observations of the sensory regulation of the locomotor CPG. These models were still unable to explain how some sensory input could affect overall cycle timing output while other sensory input could alter the timing of phases of movement with no effect on overall cycle timing. In answer to this, a more complex two- layered CPG concept was proposed with rhythm generation and motoneuron recruitment being carried out by different neural populations and therefore was better able to explain the independence in motoneuron activation patterns (i.e. amplitude and duration) and cycle timing (for review see McCrea and Rybak, 2008).

The most recent CPG model, proposed by Lafreniere-Roula and McCrea (2005) depicts a "two- plus" layer CPG. In this two-level computational CPG model of the mammalian spinal cord circuitry, half-centre rhythm generator (RG) and pattern formation (PF) networks (Rybak et al. 2006a) have been clearly separated. The half-center RG specifies the basic timing of flexion and extension while the PF network regulates the distribution of excitation and inhibition to specific motoneuron pools with reciprocal inhibitory interactions between antagonist neural populations (Burke 2001; Lafreniere-Roula and McCrea 2005; Rybak et al. 2006a, 2006b). The PF layer contains multiple pattern formation modules which include circuitry for reciprocal inhibition of antagonist motor pools and control the activity of subsets of motoneurons within the

limb. The model therefore encompasses rhythm generating and pattern formation networks that influence last-order interneurons and motoneurons.

The "two-plus" layer CPG model has been developed through the study of spontaneous 'deletions' of rhythmic motoneuron activity and during fictive locomotion in decerebrate cats (Rybak et al. 2006a). Deletions refer to spontaneous omissions of activity that occur simultaneously in multiple agonist motoneuron pools for a number of cycles. The maintenance of cycle period timing during some deletions but not all, suggests a separation of the functions of the rhythmic generation and the pattern generation of excitation to motoneurons in the organization of locomotor CPGs (Lafreniere-Roula and McCrea 2005; Rybak et al. 2006a). Deletions that influence the rhythm generator network will result in a change in the cycle period timing whereas with deletions to pattern formation networks the cycle timing is maintained, but phase duration is influenced (Lafreniere-Roula and McCrea 2005; Rybak et al. 2006a).

Sensory feedback has also been incorporated into this "two-plus" layer CPG model and influences the flexor and extensor motoneuron activation patterns during locomotion. The integration of these reflex circuits with the CPG structure explains the reorganization of afferent reflex pathways occurring during locomotion (Rybak et al. 2006b). Afferent feedback has been proposed to separately access both the RG and the PF networks. For example, sensory input influencing the RG and PF components can result in a resetting of the locomotor rhythm (Conway et al. 1987; Pearson et al. 1992; Rybak et al. 2006b) and phase prolongation respectively (Guertin et al. 1995; Rybak et al. 2006b). A very similar three-level CPG model has been proposed in which the 3rd layer of interneurons is influenced by sensory input and mediates all locomotor excitation of motoneurons (Burke 2001).

Another concept related to the function of CPGs is that the rhythm and pattern generating circuits for different functions are not isolated entities but are interconnected and overlap in the behaviours they generate. Two theories exist which are not mutually exclusive. First is the "shared CPG" hypothesis proposed by Grillner where locomotor networks consist of distinct spinal CPGs which are selectively activated in various rhythmic movements for specific control of joints or muscles (Grillner 1985). There is also the "shared interneuron" hypothesis which depicts CPG networks as systems wherein different complex movements are configured from pools of multipotent interneurons (Dickinson 1995). Multifunctional neural networks and shared neural circuitry between different pattern generators is well illustrated in the stomatogastric system in crustacean (Meyrand et al. 1991). Matsushima and Grillner (1992) demonstrated how simply changing the concentration of excitatory amino acids (NMDA) to different regions of the spinal cord could produce different rhythmic movements. If rostral segments were perfused with the higher NMDA solution, forward fictive locomotion was generated. Conversely, if the caudal portion was perfused with the higher NMDA solution, ventral roots became active in a caudorostral succession, thus reversing the direction of the fictive swimming wave to propagate backward swimming. Similarly in human infants different directions of walking are ascribed to flexible use of common locomotor spinal circuits (Lamb and Yang 2000). In adult humans, it has also been demonstrated that different locomotor tasks (i.e. walking and combined arm-leg cycling and stepping) share common neural circuitry (Zehr et al. 2007a) which has been termed the common core hypothesis (Zehr 2005).

1.2 Evidence for CPGs in primates - focus on humans

As noted above, evidence for spinal pattern generating networks in invertebrates and non-primate vertebrates is both abundant and compelling. Comparatively less is known about the role of locomotor CPGs in primates and particularly in humans. In non-human primates several attempts have been made to identify locomotor CPG activity. Phillipson (1905) reported alternating hindlimb movements in a monkey one month post spinalizaton. In contrast, Eidelberg and colleagues (1981) found no evidence of hind limb stepping in a spinalized macaque monkey. However with sparing of the ventrolateral quadrant and intense treadmill training, tail pinching could elicit hindlimb stepping (Eidelberg et al. 1981). More recently, fictive locomotion was seen in decerebrate and spinalized marmoset monkeys after the application of amino acids or clonidine (Fedirchuk et al. 1998). Stepping movements were also observed in a squirrel monkey 39 days after complete transaction (Vilensky and O'Connor 1997). Interestingly, squirrel and marmoset monkeys are more "primitive' New World monkeys with less-developed corticospinal tracts than Old World primates (which includes macaques, apes and humans). Vilensky and O'Connor (1997) proposed that the increased difficulty in isolating fictive locomotion in spinal or decerebrate Old World primate preparations is indicative of the increased role of the corticospinal tract during locomotion.

The difficulty in studying human locomotor pattern generating networks is being able to separate the contributions of the pattern generators from both descending cortical control and afferent input. Evidence available for CPGs in humans is by necessity both indirect and inferential. Such evidence is provided through an array of approaches and each is summarized in the section below. Taken as a whole, the accumulating evidence provides a substantial platform

for the claim that the human spinal cord, as in other mammals, contains a locomotor pattern generator network capable of producing coordinated locomotor activities.

1.2.1 Flexor reflex afferents

Findings from stimulating flexor reflex afferents revealed similar L-DOPA networks (believed to be part of locomotor pattern generator; Jankowski et al. 1967) in SCI patients as seen in spinalized cats (Roby-Brami and Bussel 1987, 1990, 1992), providing evidence for similar spinal locomotor circuitry in cats and humans. In both, long-latency flexor discharges are accompanied by presynaptic inhibition of Ia afferents (Roby-Brami and Bussel 1990), late flexor discharge on one side is simultaneous with inhibition of the other side (Roby-Brami and Bussel 1992), and both are suggestive of post inhibitory rebound properties (Roby-Brami and Bussel 1993) .

1.2.2 Spinal Cord Stimulation

Tonic (25- 60 Hz) epidural electrical stimulation to the dorsal spinal cord (L2-L3) has been shown to elicit step-like movements accompanied by the corresponding electromyographic activity in the leg muscles in complete SCI patients (Gerasimenko et al. 2002; Dimitrijvec et al. 1998). This suggests that human spinal circuitry isolated from the brain has the capability of generating locomotor-like activity and that externally controlled sustained electrical stimulation of the spinal cord can replace the tonic drive generated by the brain (Gerasimenko et al. 2002; Dimitrijvec et al. 1998).

1.2.3 Rhythmic muscle activation and movements in SCI and brainstem injured patients

For some time there have been reports of rhythmic involuntary movement generated by the spinal cord with complete or incomplete spinal cord injury (Holmes 1915; Kuhn 1950) suggesting the presence of spinal pattern generating networks. Kuhn (1950) claimed that an individual with complete SCI could produce "self-propagating" stepping movements. More recently, spontaneous rhythmic myclonic activity was observed in those with complete SCI in trunk and lower limb extensors which could be induced or modulated with FRA (Bussel et al. 1988). However, the duration and spontaneous nature of the rhythmic movement was significantly increased in incomplete (i) SCI group. Interestingly, there have been some reports of alternating leg movements in patients immediately preceding and following brain death, suggesting that the loss of supraspinal control might allow these spinally regulated movements to occur (Hanna and Frank 1995). Several chronic complete (c) and iSCI patients display involuntary stepping movements when positioned in supine (Calancie 2006; Calancie et al. 1994; Dobkin et al. 1995). The timing, distribution, reliance upon hip angle and, in some, the association with intensive locomotor training suggests that these movement patterns reflect some elements of a central pattern generator for stepping (Calancie 2006). Treadmill training studies have shown that locomotor-like EMG patterns can be induced after complete spinal cord injury when leg movements are externally assisted providing sensory cues to the spinal cord (Dietz et al. 1994; Dobkin et al. 1995; Harkema et al. 1997). These results could not be solely attributed to muscle stretch reflexes; instead they suggest the interaction of afferent feedback with central mechanisms (Beres-Jones et al. 2003; Beres-Jones and Harkema 2004; Harkema et al. 1997).

Though evidence from SCI subjects is compelling, there are some limitations with this model. Demonstrated CPG-like behavior within paradigms where there is limited supraspinal

input provides indirect evidence of spinal pattern generators in humans; however, it is unknown if these networks are involved in regulating walking in neurologically intact humans. In addition, with cSCI afferent input is not eliminated as it is with deafferented or fictive locomotive preparations. In fact, it is likely that afferent feedback plays an initiating and regulating role in modulating output of pattern generating neural networks in humans who have limited or absent supraspinal input. Also, eliciting rhythmic stepping-like patterns is not as predictable as in cats and often requires intensive locomotor training or other interventions to produce regular patterns of rhythmic stepping (Bussel et al. 1996; Dimitrijevic et al. 1998). In addition, adaptive neural changes have likely taken place by the time of study and their influence cannot be ruled out.

1.2.4 Sleep-related periodic leg movements

Sleep-related periodic leg movements are another type of involuntary rhythmic leg movement that can occur in one or both legs in cSCI (Lee et al. 1996) and neurologically intact individuals (Coleman et al. 1980; Bixler et al. 1982) and have been ascribed to a disinhibition of putative spinal generators related to periodic somatic and vegetative phenomena during sleep (Lee et al. 1996).

1.2.5 Vibration induced air stepping

An alternate method of exploring CPGs in neurologically intact humans involves simulating weightlessness of a lower limbs and applying tonic vibration (Gurfinkel et al. 1998). This method evoked rhythmic activation of flexor and extensor muscles, creating stepping-like

movements. These results suggest that tonic afferent inflow was able to initiate and maintain CPG activity and that basic rhythm for locomotion can be generated involuntarily in humans.

1.2.6 Neonate walking

As mentioned, it is difficult to separate the contributions of the pattern generators and descending cortical control when studying human locomotor pattern generating networks. The human infant model mitigates this challenge (Yang et al. 2004). Radiological, electrophysiological, histological and behavioral evaluations have established that the neocortex and the corticospinal tracts are extremely immature at birth. The motor cortex is largely unmyelinated at birth, and develops over the first 2 years of life (Richardson 1982). Axon diameters as well as conduction velocities of the corticospinal tract fibers are ten times less than adult measures (Eyre et al. 2000) and conduction velocities do not equal adult values until 11 years of age. Corticospinal tract myelination does not have a matured appearance until 2 years of age (Yakovlev and Lecours 1967). Cutaneous reflexes in infants lack the long latency component (Issler and Stephens 1983; Rowlandson and Stephens 1985) which is believed to be mediated by the corticospinal tract (Choa and Stephens 1982; Jenner and Stephens 1982). 'Reflex irradiation', is short-latency excitatory responses seen in neighbouring heteronymous muscles including the antagonist arising from stretch reflex afferents from the stretched homonymous muscle and can be elicited in children with cerebral palsy and in adults with upper motoneuron disorders (Leonard and Hirschfeld 1995). Therefore its presence in infants under two years (Leonard and Hirschfeld 1995; Myklebust and Gottlieb 1993) suggests an immature descending inhibitory control from the cortex. Motor behaviours associated with mature function of corticospinal tract develop throughout childhood (Caramia et al. 1993; Blank et al. 2000; Fietzek et al. 2000; Smits-

Engelsman et al. 2003). For example, Babinski reflex response in infants, which persists until ~18 months of age, resembles those of adults with corticospinal tract lesions (Connolly and Forssberg 1997). Despite an immature corticopspinal tract, human infants in utero (de Vries et al. 1984) and shortly after birth (Peiper 1963; Forssberg 1985) display a clear stepping response. In addition, before the onset of independent walking, stepping can be initiated in human infants when supported on a moving treadmill or over ground (Forssberg 1985; Thelen 1986; Yang et al. 1998a). Anencephalic human infants also display a stepping response, suggesting that this response can be produced by circuitry that exists within the brainstem and/or spinal cord (Peiper 1963). In sum, the above studies suggest that infant stepping in the first year is largely independent of corticospinal input (Forssberg 1985).

In contrast, there is much evidence to support that infant stepping is mediated by spinal circuits. Evidence shows spinal circuits are mature during human infancy (Eyre et al. 2000). Neurite growth markers indicate that spinal cord pathways, with the exception of the corticospinal tract, are developed by 33 weeks of gestation (Eyre et al. 2000). Evidence suggests human brainstem pathways are also likely fully developed and functioning by birth to potentially activate spinal and locomotor circuits (Sarnat 1989). These findings suggest that infant spinal cord and brainstem circuitry could support locomotor pattern generation and that this pattern generation is likely regulated by the same spinal circuitry in both infants and adults (Forssberg 1985). The sum of the above results suggests that infant stepping provides compelling evidence of locomotor CPG in humans (Yang et al. 2004).

1.2.7 Kinematics, EMG and Reflex modulation patterns during rhythmic leg movements

Kinematics and EMG

During human walking and running, observations of rhythmic out-of-phase activation of antagonistic leg muscles are suggestive of CPG control (Grillner 1975; Grillner et al. 1979; Winter 1991). Similar stereotyped reciprocal activation patterns are seen in leg muscles during rhythmic leg cycling, which has similarly been ascribed to regulation by spinal pattern generating circuits (Ting et al. 1998; Zehr et al. submitted). The regulative role of pattern generating circuits has been explored through comparing forward (FWD) and backward (BWD) walking. These comparisons have shown that kinematics during BWD gait are essentially time reversed relative to FWD gait. EMG, however, showed some differences between directions with EMG being higher in the BWD direction (Grasso et al. 1998; Thorstensson 1986; Winter 1989). It has been argued that conservation of kinematic templates across gait reversal at the expense of alterations in muscle activation does not arise from biomechanical constraints but rather reflects a behavioural goal achieved by the locomotor spinal pattern generating program (Grasso et al. 1998; Thorstensson 1986; Winter 1989). This putative reversal of locomotor CPG regulation with reversed movement direction is further corroborated by findings from FWD and BWD leg cycling. In the cycling paradigm the behavioural demands of the task were more similar between the FWD and BWD directions (Ting et al. 1999; Zehr et al. submitted) and when the data from recumbent cycling were 180 degrees phase-shifted the kinematics and the EMG patterns were generally matched between movement directions (Zehr et al. submitted). During upright cycling, only one of three pairs of biomechanical functions require phase shifting of 180 degrees to produce backward cycling (Ting et al. 1999).

Reflex modulation

Further evidence of CPG control of human locomotion comes from reflex studies. Afferent feedback has been shown to contribute to the modulation of CPG output (Duysens and Pearson 1976; Duysens and Van de Crommert 1998). As a consequence, the motor response to afferent input during rhythmic movement can be used to infer CPG activity (Burke 1999). Thus, reflex responses during rhythmic movement can act as a 'neural probe' of CPG activity (Burke 1999). Similar reflex modulation patterns were seen in both intact cats (Forrsberg 1979; Drew and Rossignal 1985, 1987) and chronic spinal and decerebrate cats performing fictive locomotion (Duysens 1977; Forssberg et al. 1975; Matsukawa et al. 1982). Consequently it was suggested that the same spinal pathways produced this reflex modulation in both intact and reduced preparations and this was the spinal "locomotor generator" (Forssberg 1979). Reflex modulation during rhythmic leg movement in humans (Duysens et al. 1990; Eng et al. 1994; Schillings et al. 1996; Zehr and Stein 1999; Van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997; Brooke et al. 1999; Duysens et al. 1993; Kanda and Sato 1983) is generally similar to that seen in reduced and intact cats (Duysens and Pearson 1976; Forssberg et al. 1975; Pearson and Collins 1993; McCrea et al. 1998). Reflex modulation patterns seen during rhythmic leg movement in humans can thereby, also be ascribed, at least in part, to CPG influences (Burke 1999; Duysens and Tax 1994; Duysens and Van de Crommert 1998; Zehr et al. 2001).

Reflex amplitude and sign have shown dependence on the behavioural state including the motor task (task-dependent) or phase of movement (phase-dependent). This is not surprising given that reflexes function to adapt posture and movement to changes in the external environment and therefore must be appropriate to the behavioural state (Zehr and Stein 1999). These characteristic reflex modulation patterns provide evidence of CPG contributions to the

regulation of rhythmic movement in humans (Burke 1999). Task- and phase- dependent reflex modulation results from: gating of afferent feedback at an interneuronal level by CPG mechanisms (Pearson and Collins 1993); presysnaptic inhibition of afferent pathways by CPG mechanisms (Dubuc et al. 1988); and, a state dependent release of neuromodulators (Marder and Pearson 1998; for review see Rossignal 1996). A key feature of the reflex patterns is that the reflex amplitude is uncoupled from bEMG levels across the movement cycle during rhythmic movement while reflex amplitudes and bEMG are highly correlated during static tasks (Duysens and Tax 1994). This proportional relationship seen during static contractions between the reflex response and the background muscle activity is termed "automatic gain compensation' and the gain control occurs at the motorneuron pool (Mathews, 1986). This uncoupling during rhythmic movement reflects premotoneuronal gating of the reflex pathways by CPG circuits (Duysens and Tax 1994; Duysens and Van de Crommert 1998; Dietz 2002; Mckay-Lyons 2002). For example, in the study of Brown and Kulkulka (1993) subjects maintained a constant background muscle activity while flexor reflexes were evoked at different phases of leg cycling path during cycling and static trials. Reflex amplitudes were modulated according to the phase of the movement cycle (i.e. phase-dependent modulation) in the cycling task (i.e. independent of constant background EMG), but not the static task.

Phase- dependent Modulation

Spinal pattern generating networks regulate reflex pathways to ensure the motor output is appropriate for the biomechanical state of the moving body part at each position in the movement cycle (Duysens and Van de Crommert 1998; Zehr and Stein 1999). This phase-

dependent modulation has been explored in leg muscles in humans with a variety of reflex afferents (e.g. cutaneous and muscle afferents).

Stimulation of the cutaneous nerve innervating the dorsum of the foot enhances flexor activity in the swing phase and extensor activity during the stance phase during fictive locomotion in the decerbrate-paralyzed cats (Guertin et al. 1995) or decerbrate cats with a transected spinal cord (Labella et al. 1992). Observing this phase modulation in spinalized and paralyzed preparations rules out substantial supraspinal input and confounding sensory feedback respectively. Convergence of information from locomotor CPGs onto segmental interneurons in the cutaneous reflex oligosynaptic pathway has been proposed as the source of observed reflex modulation in the cat during fictive locomotion (Degtyarenko et al. 1996). Because similar reflex modulation patterns were seen in both intact cats (Forrsberg 1979; Drew and Rossignal 1985, 1987) and chronic spinal and decerebrate cats performing fictive locomotion (Duysens 1977; Forssberg et al. 1975; Matsukawa et al. 1982), it has been suggested that the same "locomotor generator" spinal pathways produced this reflex modulation in both intact and reduced preparations (Forssberg 1979). As seen in reduced and intact animals (Duysens and Pearson 1976; Duysens 1977; Forssberg et al. 1975; Pearson and Collins 1993), electrical stimulation of cutaneous afferents in the foot evokes phase dependent reflex modulation in both human walking (Duysens et al. 1990; Kanda and Sato 1983; Van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997) and leg cycling (Brown and Kulkuka 1993; Mileva et al. 2004; Zehr et al. submitted). Naturally evoked stumbling correction reaction during locomotion in humans (Eng et al. 1994; Schillings et al. 1996; Zehr and Stein 1999) is also generally similar to that seen in reduced and intact cats (McCrea et al. 1998; Quevedo et al. 2005). Reflex modulation patterns seen during rhythmic leg movement in humans can thereby, also be ascribed, at least in part, to CPG

influences (Burke 1999; Duysens and Tax 1994; Duysens and Van de Crommert 1998; Zehr et al. 2001).

The reflex responses are also dependent upon the anatomical location of the receptive field (nerve-specificity) (Zehr et al. 1997). As seen in the cat, the reflex response has functional utility to assist the ongoing movement of the limb (Zehr and Stein 1999). Activation of cutaneous afferents on the lateral aspect of the foot (i.e. sural nerve) resulted in a facilatory response in tibialis anterior (TA) in late stance and early swing but a suppressive response in TA in late swing (Duysens et al. 1992). In contrast, activation of afferents on the dorsum of the foot (i.e. superficial peroneal (SP) nerve) resulted in suppressive response in TA in late stance, and early and late swing (Zehr et al. 1997). Further, activation of afferents on the plantar surface of the foot (i.e. tibial nerve) resulted in facilatory response throughout late stance as well as early and mid swing (Zehr et al. 1997). However it is proposed that the inhibitory responses in TA during late swing in locomotion are attributable to supraspinal influence, not CPG (Capaday et al. 1999; Pijnappels et al. 1998; Schubert et al. 1997; Jones and Yang 1994; Zehr et al. 1998).

Similarly, stimulation of nociceptors during leg cycling also evoked reflexes (human flexor reflexes) which were modulated across the cycle path (Brown and Kulkulka 1993). Phase-dependent modulation was also seen in reflexes evoked with activation of muscle afferents. The maximum amplitude of muscle afferent reflexes (i.e. H-reflex and tendon tap reflex) in the quadriceps muscle was seen in early stance phase during walking and became progressively decreased across the subsequent phases of the gait cycle (Dietz et al. 1990; Larsen et al. 2006). Similar phase-dependent behaviour has been described for the biceps femoris tendon jerk reflexes during gait (Van de Crommert et al. 1996). Though phase dependent nature of reflexes has been ascribed in part to CPG influences, it must be noted that reflex modulation can also be

influenced by peripheral feedback associated with the phase of movement. In fact, within-limb H-reflexes have been shown to be strongly regulated by peripheral feedback, as was demonstrated by similar soleus H-reflex phase modulation patterns being seen during both passive and active leg movement (Brooke et al. 1997).

After stroke, when supraspinal input would likely be altered, EMG and cutaneous reflexes remain similarly phase modulated, suggesting that phase modulation is, at least in part, a product of activity in locomotor spinal circuits (Zehr et al. 1998). In both neurologically intact individuals and those with SCI, phase modulation of EMG amplitude was similar across the step cycle in response to changes in load and has therefore been suggested as evidence of locomotor CPGs in humans (Harkema et al. 1997). In contrast, however, there was a lack of phase modulation in H- reflexes in spastic paretic participants during walking (Yang et al. 1991a).

Task-dependent modulation

Task dependence of reflex modulation in human leg muscles was seen between standing and walking (Komiyama et al. 2000; Kanda and Sato 1983), standing and running (Duysens et al. 1993), cycling and static contraction (Brown and Kulkulka 1993; Zehr et al. 2001), stable and unstable standing (Burke et al. 1991) and stable and less stable walking (Haridas et al. 2006). For example, sural nerve stimulation during running (Duysens et al. 1993) and walking (Komiyama et al 2000) evoked reflexes that differed from those evoked during matched static standing postures. Thus the reflex patterns showed a strict reliance on the task in which they were evoked. This demonstrates that neural control of rhythmic movements is distinctly different from static contractions.

In addition, cutaneous reflexes are phase-dependently modulated during active (Mileva et al. 2004) but not during passive leg cycling (Brooke et al. 1999) supporting a central locus of control for active rhythmic movement. Further evidence of CPGs in humans can be inferred from the modulation of reflexes studied during forward (FW) vs. backward (BW) locomotor tasks. As with EMG and kinematic findings, the general pattern of reflex modulation evoked during FW vs. BW locomotion and leg cycling suggests that both could be controlled by the same pattern generator running in reverse (Duysens et al. 1996; Zehr et al. submitted) as was suggested for the cat (Buford and Smith 1990).

In sum, the studies outlined above add credence to the view that reflexes are modulated by a locomotor CPG and can be used as 'neural probes' to investigate the operation and organization of CPGs.

1.3 Do CPGs regulate rhythmic arm movement as in the legs?

As outlined in the previous section, EMG and reflex studies support the role of locomotor CPGs in the neural control of rhythmic leg movement. The current section will review similar research exploring the neural control of rhythmic movement of forelimbs in the cat and of arms in humans and will highlight how this neural control is equivalent to the neural control of rhythmic leg movement.

It has been demonstrated that the reflex modulation seen in the forelimb of the cat is similar to that seen in the hindlimb, and since hindlimb reflex modulation has been ascribed, at least in part, to spinal CPG regulation the same was proposed for the forelimb (Drew and Rossignol 1987). Specifically, the characteristic phase modulation of cutaneous reflexes

suggestive of CPG influence was demonstrated during fictive locomotion in the forelimb of the cat (Hishinuma and Yamaguchi 1989). This proposition was later confirmed with cellular recordings from cervical motorneurons and last order interneurons during fictive locomotion in a decerebrate cat preparation induced by electrical stimulation of the cervical lateral funiculus. Recordings showed a phase-relation consistent with reverberating circuits of locomotor CPGs (Yamaguchi 2004). As with the hind limbs, convergence of information from locomotor CPGs onto segmental interneurons within cutaneous reflex oligosynaptic pathways has been proposed as the source of observed reflex modulation in the cat during fictive locomotion in the forelimbs (Seki and Yamaguchi 1997). Given there is quadrapedal locomotion in cats, it would be expected that both fore- and hindlimb movement would be regulated by CPG circuits in order to coordinate the limbs during walking. In contrast, as humans we can walk without moving our arms; however, we do naturally move our arms in a coordinated fashion with our legs. This leads to the question, is rhythmic movement of arms regulated by cervical CPG activity in a similar way lumbar spinal circuits are believed to regulate rhythmic leg movement?

It has long been believed that the natural arm movement during walking is not a simple pendular movement resulting from leg motion (Elftman 1939). For over 20 years it has been hypothesized that such rhythmic arm movement was produced by spinal CPG regulation (Jackson 1983). Characteristic EMG and reflex modulation during rhythmic leg movement provide an indicator of CPG regulation and therefore similarities in the EMG and reflex modulation patterns between arms and legs suggest equivalent neural control mechanism during rhythmic movement (Zehr et al. 2004). As seen in leg muscles during human walking, antagonistic arm muscles show stereotyped, rhythmic out-of-phase activation producing rhythmic arm movement (Ballesteros et al. 1965). This within arm EMG activation pattern is

also out-of-phase and reciprocating with contralateral arm muscles (Zehr and Kido 2001) as well as being coordinated with EMG activation in the legs (Houge 1969; Zehr and Haridas 2003). EMG activation during rhythmic arm movement also shows phase modulated patterns similar to during rhythmic leg movement (Zehr and Kido 2001).

In addition phase-, nerve- and task-dependent reflex modulation has been demonstrated during rhythmic arm movement like that seen during rhythmic leg movement. Three different cutaneous nerves stimulated during rhythmic arm cycling evoked reflexes that showed dependence on the nerve as well as the phase of movement cycle in over half the muscles tested, while no phase modulation of reflex amplitude was seen with static contractions (Zehr and Kido 2001). In addition for each nerve, reflex amplitudes were modulated during rhythmic arm movement in a manner that was independent of EMG activity. suggesting premotoneuronal gating of afferent feedback by spinal rhythm generating circuits (Duysens and Tax 1994) as seen in the legs. An earlier study showed dependence between reflex amplitude and background EMG; however, this study only evaluated one nerve and a much smaller sample of muscles (Zehr and Chua 2000). During routine arm swing while walking, cutaneous reflexes evoked in arm muscles were also phase modulated with amplitudes that were independent from bEMG (Zehr and Haridas 2003). Similarly H-reflexes evoked during arm cycling were phase modulated during rhythmic movement in a manner that is independent from bEMG, while no phase modulation was seen during static contractions (Zehr et al. 2003).

The activation of cutaneous and muscle afferents in the arm evoked reflexes in arm muscles which showed task dependent modulation like those seen in the legs. For example, cutaneous reflexes evoked with stimulation to either the median, ulnar or radial nerve were of differing amplitudes and sign (reflex reversal) during arm cycling compared to static contraction

at matched positions in the cycle (Zehr and Kido 2001).This type of task dependence was also seen between natural arm swing during walking and static contractions while in matched postures (Zehr and Haridas 2003). Similarly, H-reflex amplitudes were suppressed during arm cycling compared to static contractions (Zehr et al. 2003). In addition, during the static contractions of the above motor tasks the reflex amplitudes were highly correlated with background muscle activity, while during the rhythmic tasks this relationship was weak or absent (Zehr et al. 2003; Zehr and Haridas 2003; Zehr and Kido 2001). These results highlight the markedly different patterns of reflex modulation between static contractions and rhythmic arm movement reflecting the differences in their neural control just as seen in the legs. The preceding description of phase-dependent modulation of reflex amplitude, considered in conjunction with task-dependent reflex modulation observations, suggests a similar role for CPGs in contributing to the control of rhythmic arm and leg movements. This assertion continues to gain support (Dietz 2002; Dietz et al. 2001; Zehr and Duysens 2004; Zehr and Haridas 2003; Balter and Zehr 2007).

As with rhythmic leg movement, reflex modulation during rhythmic arm movement is attributed to both CPG activity and afferent feedback (Zehr et al. 2001; Zehr et al. 2003). Cutaneous reflexes were phase modulated during active arm cycling, but not during passive arm cycling, supporting a central locus of control for active rhythmic movement (Carroll et al. 2005) as was seen in the legs (Brooke et al. 1999). H-reflex amplitude during both active and passive movement was suppressed (Zehr et al. 2003) as seen in the legs (Brooke 1997) indicating the influence of afferent feedback on this reflex pathway. Recently, Carroll et al. (2006) demonstrated that the size of motor-evoked potentials in response to transcranial magnetic stimulation was reduced during rhythmic arm movement compared with tonic, voluntary

contraction, indicating a reduction in the corticospinal influence during arm cycling compared to during tonic, voluntary contraction. These results are consistent with the proposal that subcortical regions contribute to the control of rhythmic arm movements despite highly developed corticospinal projections to the human upper limb. Collectively, these findings suggest that rhythmic arm movements are at least in part regulated by CPG, just as proposed for the leg (Dietz et al. 2001; Dietz 2002; Zehr et al. 2004).

One difference between the arms and the legs is the degree of coupling between the two legs compared to between the two arms. Neither active nor passive rhythmic movement of the contralateral arm influences the amplitude of cutaneous or H-reflexes evoked in the ipsilateral arm (Carroll et al. 2005; Delwaide et al. 1988; Zehr et al. 2003). Instead, the reflex modulation was dependent on the activity state of the limb in which the reflex was evoked (Carroll et al. 2005; Hundza and Zehr 2006). In contrast, contralateral active or passive leg movement caused a general suppressive effect on reflexes evoked in ipsilateral leg (Collins et al. 1993; Cheng et al. 1998a). In addition, contralateral reflex responses seem to follow the movement phase of the contralateral leg, not the stimulated one (Duysens et al. 1990; Tax et al. 1995).These findings suggest that while the coupling between the CPGs for each leg is quite strong, the CPGs for each arm seem to be less involved in gating crossed reflexes between arms (Carroll et al. 2005). Perhaps this comparatively stronger coupling between legs during rhythmic movement results from the functional roles of the arms and legs in human walking. During bipedal locomotion it is essential to have strong coordination between legs to dependably maintain a standing posture, while the arms have the flexibility to act independently.

1.4 Interlimb coordination of arms and legs in animals and humans – Quadrapedal coordination in human locomotion

Some obvious biomechanical and functional differences exist between bipedal and quadrapedal gait. In contrast to quadrapedalism, in bipedal locomotion the center of mass is relatively high and balanced on only 2 legs, making the role of each leg more critical. Also, during bipedal gait arms are not essential to the production of gait, and can perform independent, skilled hand movements. However, despite these differences, much evidence supports common neural substrates for the control of all four limbs during locomotor movement in quadrupeds and bipeds.

Evidence of propriospinal interlimb connections between the hind- and forelimbs has been clearly demonstrated in the cat (Gernandt and Megirian 1961; Gernandt and Shimamura 1961; Miller et al. 1973; Skinner et al. 1980) and in the neonatal rat (Ballion et al. 2001; Juvin et al. 2005; Yakovenko et al. 2007; Zaporozhets et al. 2006). Similarly, anatomical studies of the human spinal cord have identified long projecting propriospinal neurons coupling the cervical and lumbar enlargements (Nathan and Smith 1955; Nathan et al. 1996). Animal experiments have confirmed an interplay between the cervical and lumbar pattern generators in coordinating rhythmic movement of fore and hind limbs, with the direction of influence being both rostral-caudal (Ballion et al. 2001; Skinner et al. 1980; Zaporozhets et al. 2006) and caudo-rostral (Gernandt and Megirian 1961; Gernandt and Shimamura 1961; Juvin et al. 2005) with the rhythmogenic capacity of one CPG influencing activity in the other. Similar coordinated coupling of rhythmic movements of the hindlimbs and forelimbs is seen in both intact cats stepping overground and on a treadmill and during swimming, and in decerebrate cats stepping on a treadmill, immersed in water ('swimming') and suspended in the air. These results support the hypothesis of spinal interlimb coupling in which long propriospinal pathways are proposed to play a key role (Miller et al. 1973). More recently, the frequency of movement has been shown

to play a significant role in the interlimb communication between arms and legs. When the fore and hind limbs of decerebrate cats stepped on separate treadmills, each running at different speeds, the rate of stepping in the front limbs entrained the stepping frequency of the hind limbs to maintain a 1:1 ratio (Akay et al 2006). Interlimb influences were also observed by Visintin and Barbeau (1994), who found that patients with spastic paresis displayed greater and more symmetric muscle activation of leg muscles when walking with arm swing compared to when arm swing was restricted by using the parallel bars.

Comparable observations of coordinated coupling of the arms and legs are also seen during human locomotor activities like walking, creeping, and swimming (Wannier et al. 2001). The frequency relationship is maintained between the limbs during all of these activities, which suggests the neuronal circuits controlling arm and leg movements are coupled in a fashion consistent with two coupled oscillators (Wannier et al. 2001). Arm cycling cadence was significantly altered by leg cycling cadence suggesting the existence of a lumbocervical coupling during arm and leg cycling, however leg cycling cadence appeared unaltered by arm cycling cadence (Sakamoto et al. 2007).

Rhesus monkeys show interlimb coordination between hind and forelimbs however this coordination is unique compared to other quadrapedal mammals and instead shares many features of human gait (Courtine et al. 2005). Non-human primates use diagonal coordination between hind and forelimbs similar to arm and leg coordination in humans (Courtine et al. 2005), which is unlike the lateral sequence seen in non-primate mammal locomotion. Also, in contrast to the cat, where the strength of the coupling between the 2 fore limbs is similar to that seen in the hind limbs (Yamaguchi 2004), the rhesus monkey demonstrate a stronger coordination of

right and left motor pools in the lumbar segment than in cervical segments (Courtine et al. 2005), which is similar to humans (Carroll et al. 2005; Brooke et al. 1997).

The characteristic phase- and task-dependent modulation of segmental reflexes, which has been ascribed to CPG contributions, can also be seen with interlimb reflexes. For example, during fictive locomotion in high spinal paralyzed cats, reflex activity in hindlimb motoneurones evoked with forelimb nerve stimulation were distinctly dependent of the phase of the step cycle (Schomberg et al. 1978). Similarly, during treadmill walking in decerebrate cats, reversal of the sign of long ascending and descending interlimb spinal reflexes between ipsilateral fore and hindlimbs have been shown to be dependent on the phase of the step cycle (Miller et al. 1977). Segmental reflex modulation patterns observed in preparations void of descending and sensory input present strong evidence of CPG activity and it follows that the same explanation would apply to these rapidly transmitted interlimb reflexes (Dietz 2002).

Interlimb reflexes have also been clearly identified during rhythmic movement of arms and legs in humans (Dietz 2002). During human locomotion, mechanical or electrical perturbations to the lower limb evoked responses in arm muscles (Delwaide and Crenna 1984; Dietz et al. 2001; Haridas and Zehr 2003). For example, stimulation of SP nerve in the foot evoked responses in arm muscles during human locomotion (Haridas and Zehr 2003) and arm and leg cycling (Balter and Zehr 2006; Sakamoto et al. 2006). Stimulation to the superficial radial (SR) nerve in the arm evoked responses in leg muscles during human locomotion (Haridas and Zehr 2003) and arm and leg cycling (Balter and Zehr 2007; Sakamoto et al. 2006). During walking these reflexes displayed phase-dependent modulation and there was little relation between reflex and EMG amplitude in arm or leg muscles evoked with SP and SR nerve stimulation, respectively. During static contractions the EMG and reflex amplitude were

significantly related in 6/8 arm muscles with SP stimulation while no significant relations in leg muscles after SR stimulation (Haridas and Zehr 2003). Based on observations of interlimb cutaneous reflex responses, Haridas and Zehr (2003) proposed that segmental CPGs may be regulating the interlimb cutaneous reflex modulation. During arm and leg cycling the magnitude of interlimb cutaneous reflexes in the arm and leg muscles was significantly modulated depending on the crank position for the relevant limb (phase-dependent modulation) (Sakamoto et al. 2006). As well, a significant correlation between the magnitude of the cutaneous reflex and background EMG was observed in the majority of muscles during static contraction, but not during arm and leg cycling (task-dependent modulation) (Sakamoto et al. 2006). Dietz and colleagues also demonstrated task-dependent neuronal coupling between upper and lower limbs (Dietz et al. 2001). Interlimb reflexes in arm muscles evoked with electrical stimulation to the distal tibial nerve in the foot were present only during walking and were absent during either standing with voluntary arm swing or sitting while writing. In each case there was comparable arm muscle background EMG. These results suggest that the pathway that couples upper and lower-limb movements seems to be gated by the activity of CPGs during locomotion (Dietz et al. 2001).

Rhythmic activity of the arms or legs has been shown to influence reflex amplitude in the legs or arms respectively. This interlimb communication has been attributed to CPG influences on the pathway that couples upper and lower neural connections during rhythmic movement (Frigon et al. 2004). During rhythmic movements of one foot, cyclic H-reflex modulation was observed in the upper limbs (Baldissera et al. 1998). This interlimb reflex modulation was suggested to originate from central motor commands rather than afferent feedback (Cerri et al. 2003). Likewise, rhythmic leg cycling affects H-reflex activity in arm muscles in a non-phase

dependent manner (Zehr et al. 2007 c). A subcortical contribution to increased corticospinal excitability of arm H-reflexes was shown during leg cycling (Zehr et al. 2007c). Rhythmic arm movement has been shown to affect reflex activity (Frigon et al. 2004; Loadman and Zehr 2007) as well as EMG activation (Huang and Ferris 2004) in leg muscles. Conflicting conclusions were reached by two laboratories when effects of rhythmic arm and leg cycling on cutaneous reflexes in legs and arms, respectively, were explored. Sakamoto et al. (2006) found that rhythmic movement of the arms had little influence on reflexes in leg muscles and vice versa. In contrast, Balter and Zehr (2007) found that rhythmic arm movement had a significant phase-dependent effect on the reflex expression in the legs during a combined arm and leg task. Balter and Zehr (2007) attributed the discrepancies in findings to employing more detailed analytical and statistical procedures as well as to the absence of a mechanical linkage between the arms and legs in the Sakamoto study. Zehr and colleagues (2007b) also showed an interaction between the neural regulation of rhythmic arm and leg movment which was enhanced when cutaneous input from the hand was present.

Recent observations support the role for interlimb reflexes in “context-dependent” corrective responses during locomotion (Haridas et al. 2006). Interlimb reflexes evoked in arm muscles were generally facilitated during an unstable walking task with arms crossed (Haridas et al. 2006). When the hand held an earth reference rail interlimb reflexes in arm extensors evoked with stimulation to the foot were increased perhaps to make use of a supportive handrail for stability during gait (Lamont and Zehr 2007). Results from both these studies indicate that the strength of interlimb connections is influenced by the context of the behaviour (e.g. level of postural threat or support), thereby suggesting that these reflexes serve a functional link between the legs and arms during locomotion (Haridas et al. 2006; Lamont and Zehr 2007).

In sum, despite the fact that the arms do not directly generate propulsion during walking, evidence suggests that neuronal connections between the cervical and lumbar pattern generators are retained in bipedal humans (Dietz 2002).

1.5 Role of supraspinal and sensory input in the control of rhythmic movement

During locomotion, the automated output from CPG is finely sculpted by supraspinal inputs and sensory feedback (Rossignol 1996). Supraspinal input triggers, stops and steers locomotion. Sensory feedback originating from muscles, skin and joint afferents as well as from special senses (vision, audition and vestibular) adapts and fine tunes the locomotor output to accommodate to the needs of the environment (Zehr and Duysens 2004). Though the contribution of supraspinal and sensory input is essential to functional gait, the focus of the research in this thesis is to explore the behaviour of CPG networks under different movement conditions. Therefore only a cursory review of the role of supraspinal (brainstem, cerebellum and cortex) input and sensory feedback will be presented in this section.

1.5.1 Supraspinal input

Human locomotion is believed to be under greater supraspinal regulation from centres in the brainstem, cerebellum and cortex than that in other animals (reviewed in Capaday 2002; Nielsen 2003; Yang and Gorassini 2006). Orlovsky acknowledged 5 functions of supraspinal input in the control of locomotion: initiation and termination of spinal locomotor CPGs; intensity of CPG output; maintaining equilibrium during locomotion; adapting limb movement to external

conditions; and coordinating locomotion with other motor tasks (Orlovsky 1991). Supraspinal centers, including brainstem regions, cerebellum and cortex, are involved in multiple parallel processes which facilitate these functions.

Tonic electrical stimulation to nuclei in the mesencephalon, referred to as "mesencephalic locomotor region" (MLR), was shown not only to initiate locomotion in decerebrate cats but also to control the speed and mode of locomotion (i.e. increase in stimulus intensity is correlated with walking speed and transition to trotting and galloping) (Shik et al. 1966). Noga and colleagues later demonstrated that the descending locomotor- related pathway originating from the MLR projects through the medial reticular formation and descend as the reticulospinal tract in the ventral half of the spinal cord (ventral lateral funiculus) and eventually synapses onto CPG circuits (Noga et al. 1991; Steeves and Jordan 1980). Electrical stimulation to other regions of the brainstem, such as the subthalamic locomotor region (SLR) located in the diencephalon, the ponotmedullary locomotor region and the medial reticular formation, can also initiate locomotion (Mori et al. 1992; for review see Whelan 1996). Another type of evidence for supraspinal influence of locomotion initiation is provided by mimicking the input of these descending pathways with aminergic substances (noradrenergic agonists and/or precursors; L-DPOA and nialamide or clonidine) and observing locomotion initiation (Barbeau et al. 1993; Barbeau et al. 1987; Dietz 1992; Forrsberg and Grillner 1973; Grillner and Zanger 1979).

There are two major descending systems, the lateral pathway (corticospinal and rubrospinal) and the ventromedial pathway (reticulospinal, tectospinal, vestibulospinal). In general the lateral pathways are involved in voluntary control of movement while the ventromedial pathways are involved in the control of posture and locomotion. The brainstem has been noted as a site of convergence for feedback from spinoreticular input as well as other forms

of input such as from vestibular and visual systems. Associated descending pathways (reticulospinal, rubrospinal, tectospinal and vestibulospinal) have powerful modulatory effects on the locomotor pattern including regulation of posture and adaptations to the environment (Cohen et al. 1996; Grillner and Matsushima 1991; Kennedy et al. 2003; Lavoie and Drew 2002; Matsuyama and Drew 2000a, 2000b; for review see Armstrong 1986). The rubrospinal neurons in cats are believed to contribute to gait adaptations, primarily in flexor muscles, to change limb trajectory to overcome obstacles during swing phase (Lavoie and Drew 2002). It was suggested that the reticulospinal neurons in cats are involved in signaling the timing and magnitude of the postural activity in flexors and extensors during adaptive locomotion particularly, in asymmetric gait patterns (i.e. lateral tilted walking surface) (Matsuyama and Drew 2000a, 2000b). Vestibulospinal neuron activity in cats (Matsuyama and Drew 2000a, 2000b) was suggested to regulate the overall EMG activity level in the limbs to respond to needs for appropriate muscle tonus (mainly in extensors) for weight support. In humans, the contribution of the rubrospinal tract to motor control is reduced, most of its functions subsumed by the corticopspinal tract (Nolte 2002). Contributions from reticulospinal pathways are suggested to persist in humans contributing to the control of locomotion or locomotor-like movements mediating quadrapedal coordination (Dietz, 2002). Vestibulospinal inputs in humans contribute to posture and balance, particularly on lateral tilted walking surfaces, as well as modulate gait trajectory during locomotion (Bent et al. 2005; Nolte 2002). For example, galvanic stimulation of the vestibular system altered the trajectory of walking, particularly when eyes were closed (Kennedy et al. 2003; Carlsen et al. 2005).

In addition, the cerebellum receives information about efferent CPG output via ventral spinocerebellar and spinoreticular tracts, as well as sensory information (e.g. muscle afferents)

via dorsal spinocerebellar pathways influences. The cerebellum then indirectly influences locomotor motoneurons via reticulospinal, rubrospinal, vestibulospinal and corticospinal pathways (Orlovsky 1991). Principle functions of the cerebellum in locomotion may include balance timing and "fine tuning" the output by adapting each step cycle (Lansner and Ekeberg 1994), which is evident by the coarse, stereotyped movements with poor interlimb coordination and inaccurate foot placements seen with cerebellar removal (Arshavsky et al. 1983).

The role of the sensorimotor cortex is apparent during complex locomotor tasks, as evidenced by an increased cortical activity with locomotor task of increased complexity (Beloozerova and Sirota 1993). There is some evidence that motor centers in the brain play an important and greater role in human walking compared with quadrapeds (Vilensky 1987). Petersen and colleagues (2001) demonstrated that motoneuronal activity during human walking can be suppressed by activation of intracortical inhibitory circuits, illustrating that activity in the motor cortex is directly involved in the control of the muscles during human walking. Some reflex and evoked motor responses seen during locomotion have been attributed to cortical influence (e.g. responses in TA during late swing) (Capaday et al. 1999; Pijnappels et al. 1998; Schubert et al. 1997; Jones and Yang 1994; Zehr et al. 1998). In addition, lesions to supraspinal structures are more debilitating to gait in humans compared to other animals (i.e. compare Beloozerova and Sirota 1993 with Knutsson and Richards 1979). Improvements in gait after stroke or incomplete SCI have been partially correlated with increased corticospinal drive to muscles and/or increased activity in cortical areas (Dobkin et al. 2004; Thomas and Gorassini 2005; Winchester et al. 2005). In addition, body weight support treadmill training after spinal cord injury (SCI) is more successful in retraining gait in quadrupeds (Lovely et al. 1986; Rossignol et al. 2002), than in humans (Dietz et al. 1994, 1995; Dobkin et al. 1995; Harkema et

al. 1997) or primates (Eidelberg et al. 1981; Fedirchuk et al. 1998) suggesting an increased role of supraspinal input during human locomotion. Lastly, an absence or decrease in indicators of cortical input to motoneurons (i.e. short term synchronization of motor unit firing in a 10-20 Hz range) during locomotion in incomplete SCI participants compared to controls suggests the influence of cortical drive in the regulation of locomotion in healthy subjects (Hansen et al. 2005).

Cortical input likely plays a role in coordinating interlimb rhythmic movement (Debaere et al. 2001; Dietz et al. 2002). Unilateral locomotion in the spinal cord injured participants was associated with a normal pattern of leg muscle EMG activity restricted to the moving side, while in the healthy subjects a bilateral activation occurred. This indicates that interlimb coordination depends on a supraspinal input (Dietz et al. 2002). Also functional MRI findings indicated that activation of a number of cortical regions during the cyclical coordination of ipsilateral wrist and foot movements exceeded the sum of the activations observed during the isolated limb movements. This supports the role of the cortex in coordinating arm and leg movements (Debaere et al 2001).

1.5.2 Sensory feedback

Sensory feedback, originating from load and joint position afferents as well as from special senses (vision, audition, vestibular), is critical in modifying CPG-generated motor programs in order to facilitate constant adaptations to the environment. Brown expressed this notion in 1911: “There can be no question of its importance nor its suitability to augment the central mechanisms…. Its part must be regulative not causative” (p. 318). Sensory feedback holds four

potential roles in the production of functional rhythmic movements: generation/maintenance of movement; phase transitions; magnitude of ongoing firing; and adaptive modification of the motor pattern.

First, sensory feedback has been shown to influence the generation and maintenance of ongoing rhythmic movement produced by CPGs (Pearson 2004). After deafferentation of the flight system in the locust, flight could be initiated in response to a head-on wind stimulus; however, the wingbeat frequency was reduced and flight period was shortened (Pearson and Ramirez 1997). Also, Calancie and colleagues (1994) proposed that involuntary stepping seen in individuals a supine position after chronic spinal cord injury were initiated due to activation of hip flexor afferents. Passive oscillatory movements around the hip joint demonstrated that muscles afferent were instrumental in entraining fictive locomotion in immobilized decerebrate cats (Kriellaars et al. 1994). Thus sensory feedback plays a significant role in the generation, and maintenance of ongoing rhythmic movement.

Second, sensory feedback contributes to the regulation of the timing of major phase transitions in the motor pattern in rhythmic movements (Pearson 2004). Stance to swing transition involves two mechanisms. The first of these is hip position (Andersson and Grillner 1983). At end stance phase, the extension of the hip joint is a powerful cue for the initiation of the swing phase (Dobkin et al. 1995; Andersson and Grillner 1983; Hiebert et al. 1996; Pang and Yang 2000; Sherrington 1910a). This signal is thought to come from the stretch of muscle spindle afferents of hip flexor muscles (Hiebert et al. 1996). In contrast, stance to swing transition is delayed by blocking hip extension and preventing stretch to hip flexors (Grillner and Rossignal 1978; Pang and Yang 2000). The second mechanism controlling stance to swing transition is limb loading and unloading (Finch et al. 1991; Pang and Yang 2000; Vistin and

Barbeau 1989). During stance phase, transition to swing is delayed by increased loading (Pang and Yang 2000) or activation of force sensitive afferents in extensor muscles of the stance limb (Conway et al. 1987; Duysens and Pearson 1980; Whelan et al. 1995; Whelan and Pearson 1997; for review see Duysens et al. 2000). Swing to stance transition can also be influenced by hip flexion position (McVea et al. 2005). Assisted hip flexion advanced onset of ankle extensors and decreased hip flexor activity. For intact humans, the ability of isolated sensory feedback to produce phase switching is limited or much weaker (Stephens and Yang 1999). This may be due to increased cortical influence during gait under more challenging conditions or it may be that coordinated combination of sensory feedback from a multitude of elements is required (e.g. hip position and relative loading of the limb) (Zehr and Duysens 2004).

The third role of sensory feedback involves regulation of the magnitude of ongoing motor activity during central pattern generated movements (Pearson 1995). Activation of muscle afferents contributes to the facilitation of burst activity through monosynaptic, disynaptic and polysynaptic excitatory pathways from group Ia and Ib afferents (Pearson 1995). Both disynaptic and polysynaptic pathways are open only during locomotion and are mediated via the extensor half center (Pearson 1995). The role of muscle afferent feedback in influencing extensor activity has been well demonstrated in cats (Whelan et al. 1995; Guertin et al. 1995; Akazawa et al. 1982; Sevrin 1970; Conway et al. 1987; Hiebert et al. 1994, 1995; Hiebert and Pearson 1999) and humans (Harkema et al. 1997; Finch et al. 1991; Misiaszek et al. 2000; Sinkjaer et al. 2000; Yang et al. 1991b). The contribution of cutaneous feedback to the regulation of the magnitude of ongoing muscle activity has also been demonstrated in both the cat (Frossberg 1979) and humans (Zehr and Stein 1999).

Lastly, sensory feedback is required for the adaptive modification of the motor pattern in response to alterations or anticipated alterations in leg mechanics. For example, responses to sensory feedback are functionally relevant to the anatomical location as well as the phase of the locomotor cycle and promote further propulsion of the limb in the gait cycle (i.e. stumble correction) (Zehr and Stein 1999). The importance of cutaneous input has more recently been shown by the inability of cats to walk across a ladder or on inclines after denervation of cutaneous foot afferents (Bouyer and Rossignol 2003). In addition, sensory input from one limb modifies the activity in the contralateral limb to ensure functional coordination between limbs during locomotion (Hiebert et al. 1994; Pang and Yang 2001).

In summary, sensory feedback can drive, terminate and modify rhythmic behaviour without being necessary for its production. Thus sensory feedback is regarded as important but extrinsic to CPG functioning.

1.6 Thesis Objectives

This thesis focused upon exploring the neural control of rhythmic arm movement, particularly during arm cycling, and the influence of rhythmic arm movement on the neural circuits controlling the legs. Accordingly the objectives of this thesis were:

- To evaluate the EMG and cutaneous reflex modulation patterns arising from different rhythmic arm cycling paradigms (i.e. FWD vs BWD cycling direction and different unilateral crank lengths).

- To compare the EMG and cutaneous reflex modulation patterns during rhythmic arm cycling in those with orthopaedic shoulder instabilities and controls as a means of evaluating the integrity of the neural control after orthopaedic pathology.

- To evaluate modulation of muscle afferent reflexes (H-reflex) in leg muscles in response to changes in arms cycling parameters (i.e. load and frequency of movement) known to influence CPG activity.

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Zehr EP, Hundza SR, Balter JE and Loadman PM Forward and backward leg cycling are produced by a reversal of locomotor pattern generating activity. J Neurophysiol (submitted)

2. Forward and backward arm cycling are regulated by equivalent neural mechanisms[1]

2.1 Abstract

It was shown some time ago that cutaneous reflexes were phase-reversed when comparing forward and backward treadmill walking. Activity of central pattern generating networks (CPG) regulating neural activity for locomotion was suggested as a mechanism involved in this "program reversal". We have been investigating the neural control of arm movements and the role for CPG mechanisms in regulating rhythmic arm cycling. The purpose of this study was to evaluate the pattern of muscle activity and reflex modulation when comparing forward and backward arm cycling. During rhythmic arm cycling (forward and backward), cutaneous reflexes were evoked with trains (5 x 1.0 ms pulses at 300 Hz) of electrical stimulation delivered to the superficial radial (SR) nerve at the wrist. EMG recordings were made bilaterally from muscles acting at the shoulder, elbow, and wrist. Analysis was conducted on specific sections of the movement cycle after phase-averaging contingent upon the timing of stimulation in the movement cycle. EMG patterns for rhythmic arm cycling are similar during both forward and backward motion. Cutaneous reflex amplitudes were similarly modulated at both early and middle latency irrespective of arm cycling direction. That is, at similar phases in the movement cycle responses of corresponding sign and amplitude were seen regardless of movement direction. The results are generally parallel to the observations seen in leg muscles after stimulation of cutaneous nerves in the foot during forward and backward walking and provide further evidence for CPG activity contributing to neural activation and reflex modulation during rhythmic arm movement.

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[1] Zehr EP, Hundza SR (2004) Forward and backward arm cycling are regulated by equivalent neural mechanisms. J Neurophysiol 93(1):633-40. (50% contribution to project – 100% of data acquisition, analysis, statistics, figures and tables)

2.2 Introduction

Experiments in various lower animal preparations (e.g. cat and crayfish) have indicated that the same neural mechanisms (e.g. locomotor central pattern generator (CPG)) controlling forward locomotion may be reversed during backward locomotion (Grillner 1981; Pearson 1993). In the cat, research on the pattern of backward and forward walking support the concept that spinal CPGs may simply run in reverse when the movement direction changes (Buford and Smith 1990;Perell et al. 1993;Buford and Smith 1993). During human locomotion it has been shown that for some joints (especially the hip) kinematics and to a lesser extent EMG of backward walking are similar to those of forward walking (Thorstensson 1986;Winter et al. 1989;Grasso et al. 1998). However, EMG amplitudes are typically higher during backward walking compared to forward walking (Thorstensson 1986; Winter et al. 1989;Duysens et al. 1996; Grasso et al. 1998). The similarities between forward and backward locomotion could reflect the activity of CPG networks running in reverse to produce backward walking. Indeed Grasso et al. (1998) suggest that their data support the activity of similar CNS mechanisms operating to regulate forward and backward walking. It has also been suggested that the same CPG mechanisms may regulate various patterns of gait in the infant (Lamb and Yang 2000).

Modulation of motor activity due to changes in peripheral feedback during rhythmic movement can be used to infer the activity of CPG circuits (Burke 1999;Burke et al. 2001;Zehr and Duysens 2004). For example, the modulation of cutaneous reflexes during rhythmic movement has been suggested to arise due to activity of a human locomotor CPG (Duysens and Tax 1994;Zehr et al. 2001) and this could explain phase- and task-dependency of reflexes via premotoneuronal gating of afferent feedback (Duysens and Tax 1994;Duysens and Van de Crommert 1998;MacKay-Lyons 2002;Dietz 2002a;Dietz 2002b). It has been shown that

cutaneous and H-reflexes are phase- and task-dependent during arm cycling (Zehr and Chua 2000;Zehr and Kido 2001;Zehr et al. 2003). Further, reflexes evoked by stimulation of cutaneous nerves in the hand and foot are both phase- and task dependently modulated in arm muscles during the natural arm swing of walking (Haridas and Zehr 2003;Zehr and Haridas 2003). These observations support the suggestion that rhythmic arm movements are to some extent regulated by CPGs just as posited for the leg (Dietz et al. 2001;Dietz 2002;Dietz 2002;Zehr et al. 2004;Zehr and Duysens 2004).

Duysens and colleagues (Duysens et al. 1996) studied cutaneous reflex modulation evoked by electrical stimulation of the sural nerve during forward and backward treadmill walking. Modulation of reflex amplitude throughout the step cycles could be generally explained by a CPG running in "reverse" when going backward. However, the pattern was not strictly simply reversed as some muscles showed minor timing differences and shifts during backward locomotion. This observation was similar to the pattern of cutaneous reflex modulation seen during forward and backward walking in the cat (Buford and Smith 1993). There it was suggested that the central control of cutaneous reflex amplitude was similar for forward and backward quadrupedal walking (Buford and Smith 1993). In this paper, we undertook to replicate this kind of experiment during arm cycling where it is relatively easy to perform a simple reversed movement during backward versus forward cycling. For example, both backward and forward leg cycling generate very similar phase-reversed patterns of muscle activity (Ting et al. 1999;Eisner et al. 1999). The purpose of the experiment described in this paper was to test the hypothesis that cutaneous reflexes evoked during backward arm cycling would show a similar but reversed pattern of modulation to that seen in forward arm cycling. Support for this hypothesis would further add to the evidence for CPG contributions to rhythmic

human arm movement (Zehr et al. 2004;Zehr and Duysens 2004) such as has already been demonstrated for the cat forelimb (Yamaguchi 2004).

2.3 Methods

Eleven subjects participated in the experiment with informed, written consent and under the sanction of the Human Research Ethics Board at the University of Victoria.

2.3.1 Protocol

The experimental methodology and protocol are similar to that described in previous experiments involving reflex modulation during walking (Zehr and Haridas 2003b) and arm cycling (Zehr and Chua 2000;Zehr and Kido 2001e;Zehr et al. 2003). Thus, only differences in methodology are highlighted here. Participants performed rhythmic arm cycling using a previously described arm ergometer (e.g. (Zehr et al. 2003). Arm cycling was performed in a forward direction (in which clockwise movement of the right arm can be observed from the right side) and then in a backward direction in separate trials.

2.3.2 Nerve stimulation

Electrical stimulation was delivered pseudorandomly throughout the movement cycle to the superficial radial nerve (SR) at the wrist of the right hand with trains of 5 x 1 ms pulses at 300 Hz (Zehr and Kido 2001;Zehr and Haridas 2003) applied with a Grass S88 (Grass Instruments, AstroMed Inc.) stimulator connected in series with an SIU5 isolator and a CCU1 constant current unit. The SR nerve was stimulated at approximately twice the threshold for radiating

paresthesia through bipolar surface electrodes placed just proximal to the radial styloid on the right arm. Appropriate stimulation location was verified by determining that sensation was evoked in the innervation area of the SR nerve (dorsolateral portion of the right hand).

2.3.3 Electromyography (EMG)

Bilateral bipolar recordings were made from shoulder muscles anterior (AD) and posterior (PD) deltoid, elbow muscles biceps (BB) and triceps (TB) brachii, and the wrist flexor carpi radialis (FCR) muscles. EMG signals were pre-amplified and bandpass filtered at 100-300 Hz (P511 Grass Instruments, AstroMed, Inc.).

2.3.4 Data acquisition and analysis

Data were sampled at 1000 Hz with a 12 bit A/D converter connected to a computer running custom-written (Dr. Timothy Carroll, University of New South Wales, Australia) LabView (National Instruments, Austin TX) virtual instruments. Post-hoc the movement cycle was divided into 12 equidistant bins or phases that represent positions on the clockface and responses to stimuli in each bin were averaged. “Control data” obtained from cycles without nerve stimulation were used to create subtracted traces (~10-20 observations per bin) of reflex EMG (Zehr and Kido 2001).

2.3.5 EMG analysis

Reflexes were examined at early (~50-80 ms) and middle (~80-120 ms) latencies. During analysis for a given subject all subtracted reflex traces for a muscle (i.e. for all 12 bins) were

plotted and the mean and standard deviation of the prestimulus EMG was calculated as an index of subtraction error. Reflex amplitudes at each latency were considered significant and included in the analysis if they exceeded a 2 standard deviation band calculated from this residual. To quantify the reflex amplitudes, a 10 ms window centred on the peak of each response was calculated at early and middle latency. All EMG and reflex amplitudes were normalized to the maximum control background EMG recorded during forward cycling for each muscle.

2.3.6 Statistics

Analysis of variance was used to determine main effects and statistically significant reflex amplitudes as well as phase-dependency during forward and backward cycling (Statistica, Statsoft Inc.). This analysis was conducted on datasets averaged across all subjects. Tukey's HSD test was used to post-hoc significant main effects (e.g. significant differences between control and reflex EMG). Linear regression analysis using Pearson's correlation (r) was conducted between reflex amplitudes and background control EMG for each muscle at each phase to determine the extent to which variations in reflex size were linearly related to changes in background muscle activation during forward and backward arm cycling. For this regression analysis all data from each subject were used giving 9 degrees of freedom and yielding a critical r of 0.602 at $p < 0.05$. Descriptive statistics included means ± standard error of the mean (SEM). Statistical significance was set at $p \leq 0.05$.

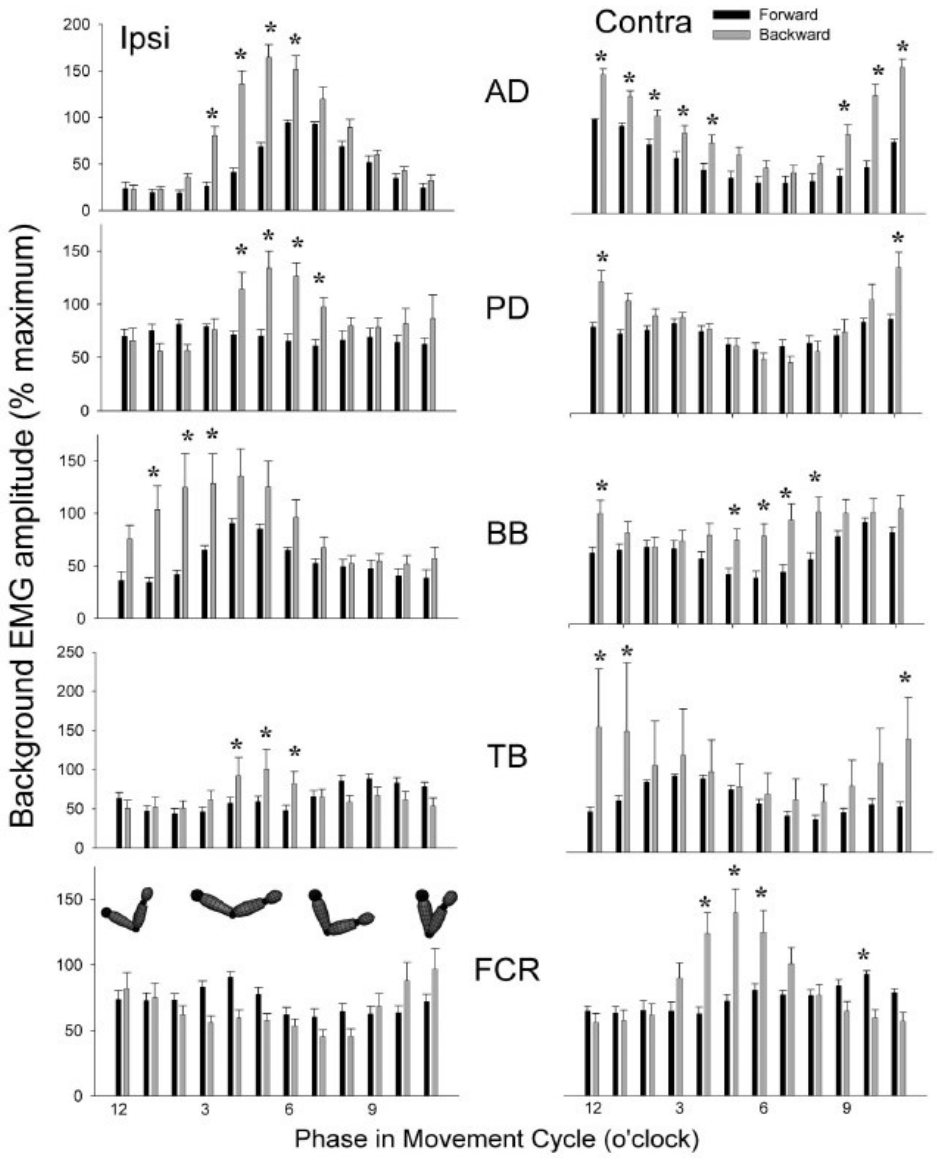

Figure 2.1. Pattern of rhythmic EMG across the full movement cycle during forward and backward arm cycling. Maximum background EMGs for all ten muscles are expressed relative to the maximums during forward arm cycling. Muscles ipsilateral (ipsi) and contralateral (contra) to the site of nerve stimulation are shown on the left and right columns, respectively. Phase in the movement cycle relative to the clock face are as indicated at the bottom of the figures. In the bottom left panel the arm position is roughly indicated by the cartoon arm. Data represent mean +/- SEM for 11 subjects. Data are plotted on identical scales for ipsilateral and contralateral muscles. Abbreviations: anterior (AD) and posterior (PD) deltoid, biceps (BB) and triceps (TB) brachi, flexor carpi radialis (FCR). * indicate significant differences from post-hoc testing for the interaction between movement direction and movement phases at $p \leq 0.05$.

Muscle	Early (FWD)	Early (BWD)	Middle (FWD)	Middle (BWD)
iAD	70.4	68.9	106.7	104.3
iPD	76.1	79.1	112.7	114.1
iBB	64.8	72.2	100.9	108.7
iTB	67.0	68.4	98.5	101.8
iFCR	67.5	68.6	100.2	98.3
cAD	66.8	75.4	97.8	110.9
cPD	61.8	72.5	95.7	109.4
cBB	59.0	67.3	94.8	97.9
cTB	64.1	78.5	101.0	118.3
cFCR	61.5	73.2	95.0	105.6

Table 2.1. Average time to peak early and middle latency responses during forward and backward arm cycling. Data represent mean values for 11 subjects. Abbreviations: anterior (AD) and posterior (PD) deltoid, biceps (BB) and triceps (TB) brachi, flexor carpi radialis (FCR), ipsilateral (i), contralateral (c), forward (FWD) and backward (BWD) arm cycling.

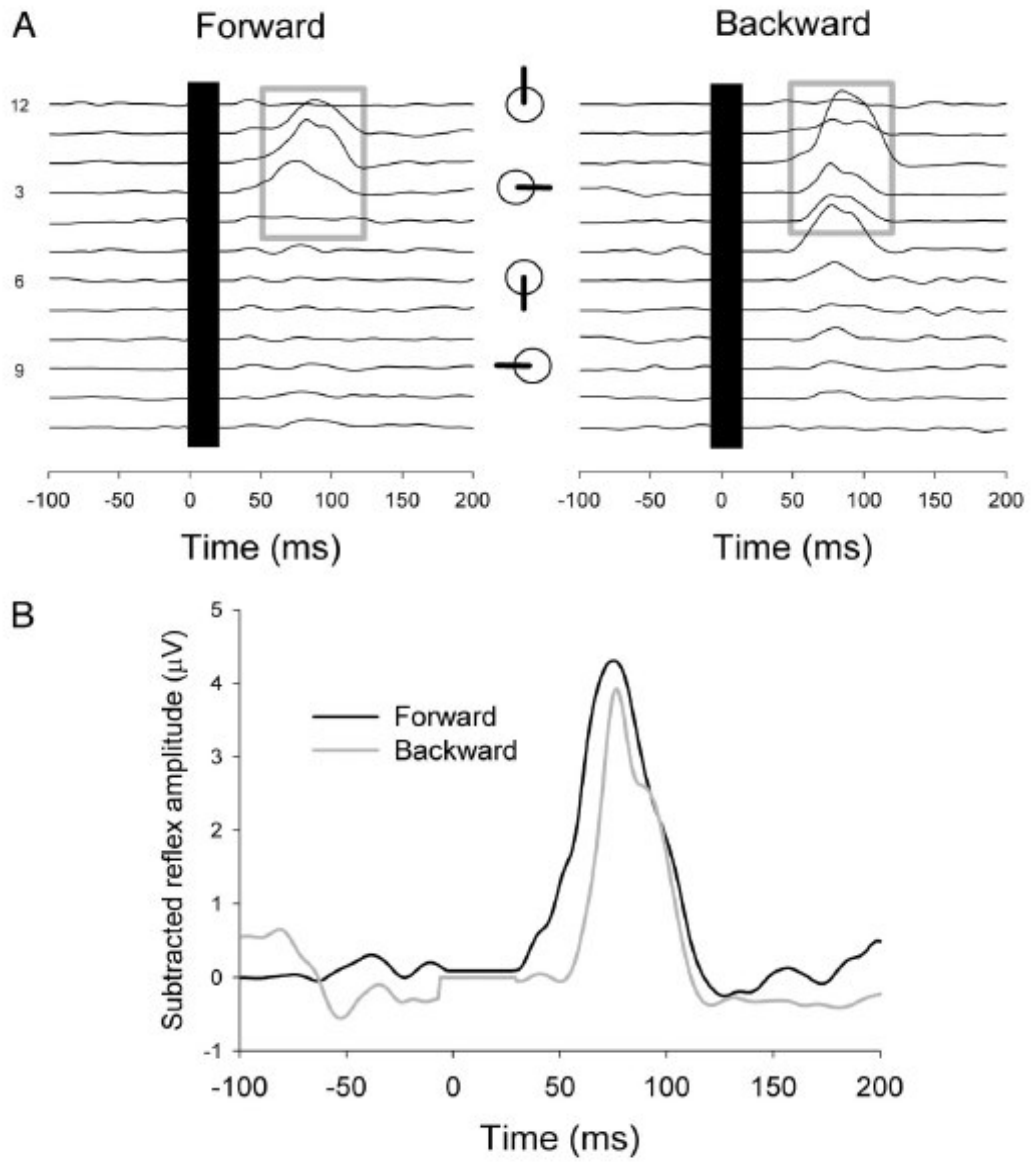

Figure 2.2. Cutaneous reflexes in iPD muscle for a single subject during forward and backward arm cycling. A. Plots of subtracted reflex EMG for all 12 phases in the movement cycle during forward (left) and backward (right) cycling. The symbols in between the panels indicate position of the arm cycle hand grip at 12, 3, 6, and 9 o'clock (correspond to numbers given at left of figure). Note the similarity of the facilitation in PD particularly between 12 and 4 o'clock highlighted by the rectangles. This similarity is further emphasized in B in which plots of reflexes from 3 (forward) and 4 (backward) o'clock are superimposed. Note that the stimulus artefact is replaced with a vertical black bar in the two panels in A.

2.4 Results

2.4.1 Rhythmic EMG patterns

Background rhythmic EMG amplitudes were significantly (main effect $p<0.05$) modulated by phase in the movement cycle for all 10 muscles examined. The pattern of EMG activity (i.e. the amplitude of EMG activity relative to phase in the movement cycle) when examining forward and backward cycling was generally similar for most muscles (see Figure 2.1). However, EMG during backwards cycling was higher (main effect for direction $p<0.05$) than during forward arm cycling for half of the muscles studied (iAD, iPD, iBB, cAD, and cBB; see Figure 2.1). Note that in Figure 2.1 EMG amplitudes are plotted such that the arm position is the same for forward and backward cycling and thus the two directions can be directly compared. To specifically contrast EMG amplitude in the two directions amplitudes are expressed as percentages of peak EMG amplitude during forward arm cycling. Significant differences between forward and backward amplitudes at each phase (deduced from post-hoc for significant interaction, $p\leq0.05$) are as indicated by the asterisks.

2.4.2 Reflex latencies

Time to the peak response for the early and middle latency reflexes are shown in Table 2.1 for forward and backward arm cycling and did not significantly differ between the movement directions.

2.4.3 Reflex modulation patterns across the movement cycle

Reflex amplitudes at early and middle latency were similarly modulated during forward

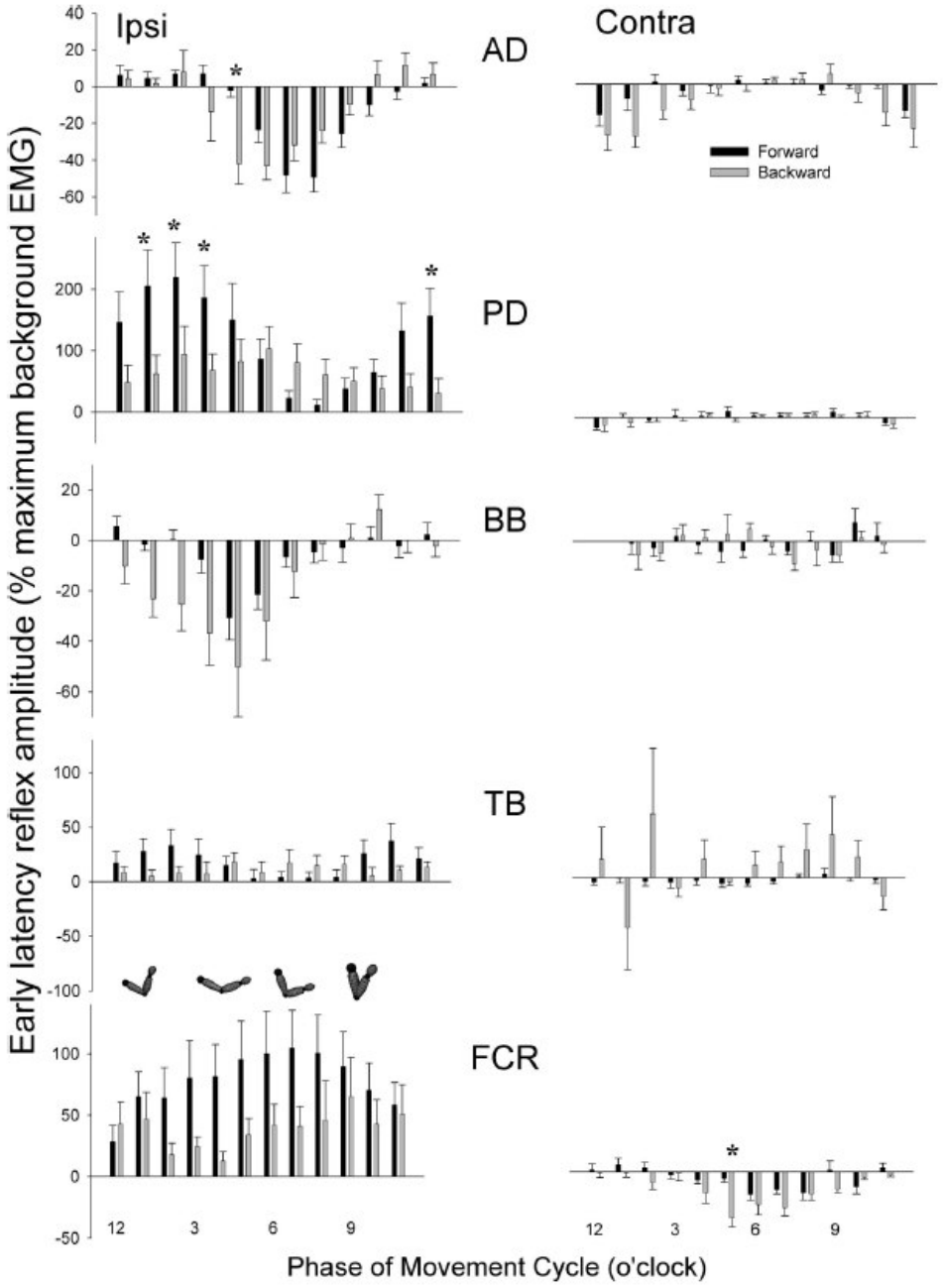

Figure 2.3. Early latency (~50-80 ms) reflexes across the entire movement cycle for all subjects. Data are calculated from subtracted reflex traces averaged across all subjects and represent the mean +/- SEM. Data are plotted on identical scales for ipsilateral and contralateral muscles. Abbreviations as in Figure 2.1. * indicate significant differences for the interaction between movement direction and movement phases at $p \leq 0.05$.

and backward arm cycling. That is, excitatory or inhibitory reflexes were seen at comparable phases in either forward or backward cycling and were of similar amplitude and corresponding sign. Shown in Figure 2.2 are reflex traces from iPD muscle for a single subject during forward (A, left panel) and backward (A, right panel) arm cycling. The numbers shown to the left of Figure 2.2A indicate the phase in the movement cycle relative to the clock face. Note that the orientations are the same for forward and backward cycling allowing for direct comparison. The excitatory responses during both directions of cycling are highlighted by the gray rectangles. In Figure 2.2 B, reflex traces during forward and backward cycling are shown superimposed. These traces are from phases (3-4 o'clock) where background EMG levels were similar for this subject and where the arms where in similar orientations. The similarity between the responses can be seen clearly. It is also observed that the excitatory responses may persist across a greater portion of the movement cycle for backward arm cycling (from about 1 o'clock to 6 o'clock) as compared to forward cycling. Note as well that the pattern of responses in PD muscle differs somewhat from the other muscles studied in that a large early latency excitatory burst dominates with only very small responses at middle latency. This can be seen in Figure 2.2 for a single subject as well as in Figures 2.3 and 2.4 described below for all subjects.

When the average responses across all subjects were considered the pattern of reflex modulation was seen to be similar during forward and backward cycling at both early (see Figure 2.3) and middle (see Figure 2.4) latencies. This was particularly the case for the ipsilateral and more proximal muscles. For example, in iAD suppressive early latency responses can be seen to occur from 4 to 8 o'clock and for iPD excitation of varying amplitude predominates across the entire cycle of movement irrespective of movement direction (Figure 2.3). As shown in Figure 2.4, the middle latency responses switched to excitation in iAD at the same phases for both

forward and backward cycling. Further, there was coordination of the responses across the body as can be seen when comparing early (see top Figure 2.3) and middle latency (top Figure 2.4) responses in iAD and cAD. This could also be seen when examining iFCR and cFCR responses at both latencies. The direction of movement had a significant effect ($p<0.05$) for 4 muscles. Reflex amplitudes in FCR and AD muscles for both arms at early and middle latencies were significantly different when grouped across movement phases (seen as a main effect from the ANOVA; not illustrated on the figures). Even so, the overall pattern of inhibition and excitation was still maintained. At middle latency there were no main effects for direction of cycling in any muscle examined. Significant interactions between movement phase and direction of movement were identified for early latency reflexes in iAD, iPD, iTB, and cFCR and for middle latency in iAD and cFCR. Results of the post-hoc testing ($p\leq0.05$) for these interactions are shown as asterisks on Figures 2.3 and 2.4. Note that this analysis identifies if the amplitudes during forward and backward cycling were significantly different at each movement phase. As can be seen there are few instances of significant differences between arm cycling direction at any given phase in the movement cycle at the early latency (Figure 2.3) and none for middle latencies (Figure 2.4).

Previously it has been shown that reflex amplitude is typically uncoupled from rhythmic background EMG amplitude during forward arm cycling (Zehr and Kido 2001). To examine the extent to which reflex modulation during backward cycling was coupled to background EMG during backward arm cycling we examined Pearson correlations here. Across all muscles for forward and backward cycling and at early and middle latency this analysis yielded 40

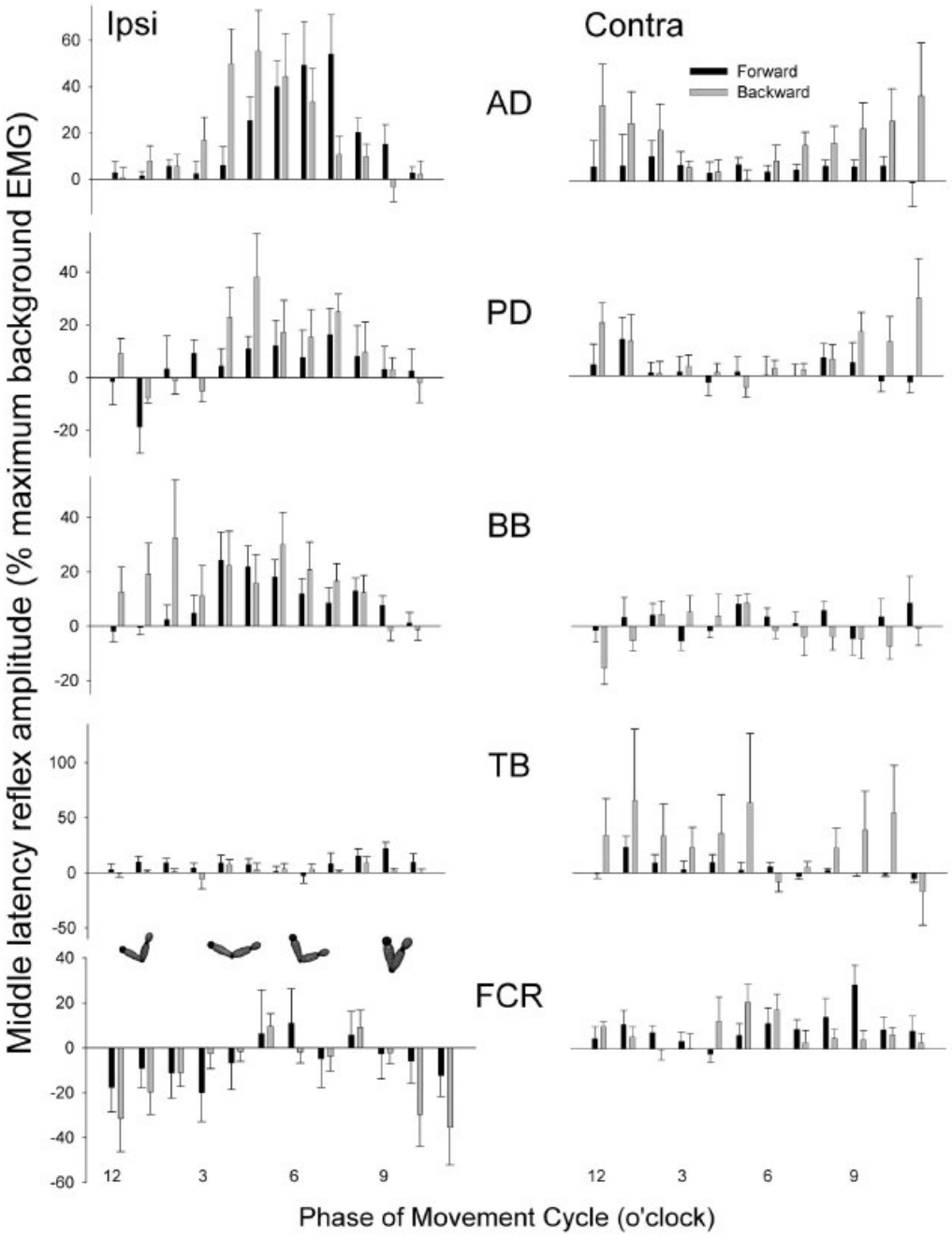

Figure 2.4. Middle latency (~80-120 ms) reflexes for all subjects. Data are calculated from subtracted reflex traces averaged across all subjects and represent the mean +/- SEM. Data are plotted on identical scales for ipsilateral and contralateral muscles. Abbreviations as in Figure 2.1. * for the interaction between movement direction and movement phases at $p \leq 0.05$.

comparisons. In only 1 instance was a significant relation with background EMG demonstrated (iAD at early latency during forward cycling). Thus, during both forward and backward cycling reflex amplitude was typically uncoupled from rhythmic background EMG.

2.5 Discussion

There are 3 main new observations in this paper. First, based upon EMG patterns, backward arm cycling represents a simple reversal from forward arm cycling. Second, the pattern of cutaneous reflex modulation during forward arm cycling is similar during backward arm cycling when expressed at similar phases in the movement cycle. Third, the patterns of cutaneous reflex modulation are independent of rhythmic background EMG amplitude during both forward and backward arm cycling.

2.5.1 EMG of forward and backward arm cycling

With some subtle differences the general EMG pattern associated with forward arm cycling was maintained during backward motion. For many muscles studied, the magnitude of rhythmic EMG amplitude during backward arm cycling was significantly greater than corresponding values for forward cycling (e.g. see asterisks in Figure 2.1). This is similar to the observations reported for EMG amplitudes during forward vs. backward walking (Winter et al. 1989;Grasso et al. 1998). There were some shifts in timing of peak activities of certain muscles and minor shifts in the temporal patterns within the movement cycle. This may be similar to previous documentation of EMG during leg cycling which may be due to subtle changes in the biomechanical function of the muscles during backward motion (Ting et al. 1999;Eisner et al.

1999). However, this was not explicitly evaluated in this study and cannot be definitively discussed here. In general, the pattern of EMG during backward arm cycling was similar to forward cycling (see Figure 2.1).

2.5.2 Reflex modulation during backward arm cycling

The pattern of cutaneous reflex modulation during backward arm cycling was equivalent to that seen during forward cycling (e.g. see Figures 2.2 - 2.4). Across both cycling conditions responses in contralateral muscles were typically of smaller amplitude (as seen in Figures 2.3 & 2.4 in which responses are plotted on the same scale across the body), except for iTB and cTB. There are numerous instances of reciprocal coordination at similar latencies in contralateral muscles and in antagonist muscles (e.g. contrast AD and PD responses in Figures 2.3 & 2.4) just as shown previously for SR nerve reflexes during arm cycling (Zehr and Kido 2001;Zehr and Haridas 2003) and walking (Zehr and Haridas 2003). There were some differences in terms of the timing in the movement cycle of maximum reflex amplitudes and the amplitudes themselves. However, the general features were very similar in that there appeared to be no drastic re-organization of the reflex control such that an entirely new pattern arose with backward cycling as compared to forward motion. That is, reflex responses were still phase-modulated and excitation or inhibition still occurred at similar phases and were not replaced by responses of opposite sign in forward vs. backward arm cycling. CPG networks "running in reverse" during backwards motion could explain this observation, in much the same way that this has been used to explain the observed reversal in the pattern of cutaneous reflexes during backward quadrupedal (Buford and Smith 1993) and bipedal walking (Duysens et al. 1996). Buford and Smith (1993) suggested that, while they did observe some differences in the pattern of cutaneous

reflex modulation during backward walking, these differences were very subtle and expressed as minor differences in reflex amplitude and general timing. This was also the case for the observations of Duysens and colleagues (1996). These observations describe the current data fairly well. Here, reflex amplitudes and timings were quite similar, but there are some minor differences. For example the pattern shown for arm cycling seems close to a simple reversal that is much "cleaner" than that seen in leg muscles during walking. Perhaps this reflects the clear symmetry between directions in the arm cycling task (e.g. continuous task evenly distributed) which is not present during walking (e.g. continuous task with uneven distribution of activation for swing and stance).

It is notable that reflex amplitudes were uncoupled from background EMG irrespective of arm cycling direction. Previously it has been suggested that this is an indicator of the activity of CPG mechanisms during rhythmic movement (Van Wezel et al. 1997;Komiyama et al. 2000;Zehr and Kido 2001;Haridas and Zehr 2003;Zehr and Haridas 2003). The current data support the concept that the arms and legs are regulated by the same mechanisms during rhythmic motion that is independent of movement direction and that a portion of this control can be ascribed to CPG-like activity. Interestingly, data on human infants suggest a common CPG for walking that is independent of movement direction (Lamb and Yang 2000;Pang and Yang 2002). The current results thus extend to the human upper limb many of the features of reflex modulation observed during lower limb locomotor control and add further to the evidence suggesting similar control mechanisms (e.g. CPG contributions) to the generation of the rhythmic arm muscle activation pattern during arm cycling and walking.

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3. Cutaneous reflexes during rhythmic arm cycling are insensitive to asymmetrical changes in crank length[2]

3.1 Abstract

The neural control of a movement depends upon the motor task performed. To further understand the neural regulation of different variations of the same type of movement we created three dissimilar bilateral rhythmic arm cycling tasks by unilaterally manipulating crank length (CL). Modulation in the amplitude and sign of cutaneous reflexes was used as an index of neural control. Neurologically intact subjects performed three bilateral cycling trials at ~ 1 Hz with the ipsilateral crank arm at one of 3 different lengths. Cutaneous reflexes were evoked during each trial with trains (5x1.0 ms pulses at 300Hz) of electrical stimulation delivered to the superficial radial nerve at the ipsilateral wrist. EMG recordings were made bilaterally from muscles acting at the shoulder, elbow and wrist. Analysis was conducted after phase-averaging contingent upon the timing of stimulation in the movement cycle. CL variation created an asymmetrical cycling pattern and produced significant changes in the range of motion at the ipsilateral shoulder and elbow. Background EMG amplitude in muscles of the contralateral arm generally increased significantly as CL decreased. Therefore at a given phase in the movement cycle, the background EMG was different between the three cycling trials. In contrast, cutaneous reflex amplitudes in muscles of both arms were similar at each phase of the movement cycle between the different CLs trials at both early and middle latencies. This was particularly evident in muscles ipsilateral to nerve stimulation. We suggest that variations of arm cycling that primarily yield significant

[2] Hundza SR, Zehr EP (2006) Cutaneous reflexes during rhythmic arm cycling are insensitive to asymmetrical changes in crank length. Exp Brain Res 168, 165-77. (80% contribution to project)

changes in the amplitude of muscle activity do not require significant task-specific change in neural control.

3.2 Introduction

The neural regulation of a movement is dictated by the type of motor task performed. This "task dependency" of neural control is demonstrated by extensive modulation in sign and amplitude of reflexes between different motor tasks (for review see Brooke et al. 1997; Zehr et al. 2004). Different studies have demonstrated task dependency of cutaneous and H-reflexes between static contractions and rhythmic movement. Duysens et al. (1993) compared cutaneous reflexes of the sural nerve during running and matched static contractions imitating postures of the gait cycle and found increased amplitude of reflexes during running compared to standing. Komiyama et al. (2000) also found task dependent reflex modulation when comparing walking to standing. Task dependency was also seen between leg cycling vs. static leg contractions (Zehr et al. 2001). Cutaneous reflexes in arm muscles also showed patterns of task reliance between walking vs. matched standing postures (Zehr and Haridas, 2003) and between arm cycling vs. matched static contractions (Zehr et al, 2001a). H-reflexes in both arm (Zehr et al, 2003) and leg (Brooke et al. 1992) muscles also showed task specificity between cyclic vs. static contractions.

In each of these cases the motor tasks were distinct (i.e. rhythmic movement vs. static contraction). Within a class of movements (e.g. rhythmic) it is unclear where the boundaries lie that define task-specific neural control. That is, how different does a movement or task have to be to see a significant change in the regulation of reflexes? Burke et al. (1991) showed that standing on a stable surface versus an unstable surface produced task specific reflexes and suggested that the reflexes accentuated by the differing task resulted from activity in different neural pathways. Task dependent neural control has not often been compared during different

variations of rhythmic movement tasks. Specifically, comparisons of the neural control between symmetrical and asymmetrical rhythmic movements have not been studied.

The present study was designed to specifically explore task dependent neural regulation of varied bilateral rhythmic arm cycling tasks created by changing crank length on one side only. By unilaterally altering crank length an asymmetrical cycling task was created. Since bilateral changes in crank length during leg cycling have been shown to alter muscle activation patterns (Mileva and Turner, 2003) we anticipated changes in muscle activation. Zehr et al. (2001) found that modifying EMG activation during active leg cycling did not influence the cutaneous reflex modulation. Because cutaneous reflex modulation seen in rhythmic arm movement is similar to that seen in the legs (Dietz, 2002; Zehr and Duysens, 2004; Zehr and Haridas, 2003; Carroll et al. 2004), we anticipated a similar phenomenon would be observed during rhythmic arm cycling. Therefore we hypothesized that modifying crank length during cycling would have little effect on the pattern of cutaneous reflex modulation.

3.3 Methods

Eleven healthy subjects (average age 35.4 yrs.; 6 female and 5 male), free of any known neuromuscular or metabolic disease, participated with informed and written consent. Experimental procedures were approved by the Human Ethics Board at the University of Victoria and performed in accordance with the Declaration of Helsinki.

3.3.1 Protocol

The experimental methodology is similar to that described previously (reviewed in Zehr et al. 2004) and thus only differences in methodology are highlighted here. Participants performed rhythmic arm cycling at ~ 1 Hz on a previously described arm ergometer. Three trials of forward arm cycling were performed in which clockwise movement of the right arm can be observed from the right side. The left arm crank length consistently remained at 19.5 cm. The right arm crank length (CL) was adjusted for each cycling trial: 3.8 cm (short ,S), 11.0 cm (medium, M), 19.5 cm (long, L). All 11 participants performed the long and short CL trials and 7 participants performed the medium CL trial.

3.3.2 Kinematics

In some subjects, kinematic recordings were continuously obtained from the right elbow and shoulder joints using lightweight goniometers (Biometrics, Inc). In all subjects, manual goniometer measurements were taken for the shoulder and elbow joints when the arm was in the 3 (shoulder flexed) and 9 (shoulder extended) o'clock position. The difference in the measures obtained at these two positions was calculated for each joint for each crank length as a representation of joint excursion. An average of joint range of motion (ROM) was calculated across subjects for shoulder and elbow.

3.3.3 Nerve Stimulation

The superficial radial (SR) nerve of the right (ipsilateral) hand was stimulated at the wrist pseudorandomly throughout the movement cycle with trains of 5 x 1ms pulses at 300Hz with a Grass S88 (Grass Instruments, AstroMed Inc.) stimulator connected in series with a SIU5

isolator and a CCU1 constant current unit. The SR nerve was stimulated at approximately two times the radiating threshold through bipolar surface electrodes placed just proximal to the distal end of the radius. Appropriate stimulation location was verified by confirming that radiating sensation was evoked in the appropriate innervation distribution of the SR nerve (Zehr and Chua, 2000; Zehr and Kido, 2001; Zehr et al. 2003; Carroll et al. 2004; Zehr and Hundza, 2005).

3.3.4 Electromyography

Bilateral bipolar surface EMG recordings were made from muscles acting at the shoulder (anterior (AD) and posterior (PD) deltoid), elbow (biceps (BB) and triceps (TB) brachii), and wrist (flexor carpi radialis (FCR)). Ground electrodes were placed over electrically neutral tissue. EMG signals were preamplified and bandpass filtered at 100-300 Hz (P511 Grass Instruments, AstroMed, Inc.).

3.3.5 Data Acquisition and Analysis

Data were sampled at 1000 Hz with a 12 bit A/D converter connected to computer running custom-written (Dr. T. Carroll, University of New South Wales, Australia) LabView (National Instruments) virtual instruments. Post acquisition the data were partitioned into phases based on a division of the movement cycle into 12 equidistant portions that represent a clockface (see Zehr et al. 2004). EMG responses to nerve stimulation in each phase of movement were averaged. EMG recorded without stimulation (control data) for each phase was also averaged. Reflex EMG (subtracted traces) were calculated by subtracting the averaged EMG response with stimulation

from the corresponding averaged control data for each phase of the movement cycle (~ 10-20 observations per phase).

3.3.6 EMG Analysis

Cutaneous reflexes

Reflexes (subtracted traces) were analyzed at early (~50-80 ms to peak) and middle (~80-120 ms to peak) latencies. For each subject, all twelve phases of subtracted traces for a muscle were plotted. Reflex amplitudes were considered significant and included in the analysis if they exceeded a 2 standard deviation band calculated on prestimulus EMG subtraction error (see Zehr et al. 2004). A 10 ms window centered on the peak of each reflex response was averaged at early and middle latencies where significant reflexes were identified. All EMG amplitudes were then normalized to the maximum control background EMG recorded during the L CL cycling trial.

Background EMG Patterns

Control EMG amplitudes were calculated for each phase of the movement cycle on the data from unstimulated trials. To evaluate the phasic nature of the background EMG a modulation index (MI= [(EMG max-EMGmin)/EMGmax] x 100) was calculated for each muscle across the movement cycle (see Zehr and Kido, 2001). This measure provides a means of comparing between the three CLs, the extent to which muscles varied between phasic bursts of activity (large MI) to alternatively tonic activity (small MI) throughout the movement cycle.

3.3.7 Statistics

Analysis of variance was conducted separately on background EMG and early and middle latency reflexes for phase of movement, crank length and interactions between crank length and phase of movement (Statistica, Statsoft Inc.). This ANOVA was conducted including all 3 crank lengths (S,M,L) with degrees of freedom (df) of 6 and again for the S and L crank lengths with df of 10. Tukey's HSD test was used to post-hoc significant main effects and interactions. Using all data from each subject, Pearson's correlation coefficients (r) were calculated and tested for significance between reflex amplitudes and background control EMG for each muscle. To correct for the effect of repeated samples from each subject (for each correlation, pairs from all 12 phases of movement were used for n=11 subjects) ten degrees of freedom (n-1) was used in the analysis for each CL. This yielded a critical r value of 0.576 for a two tailed test at $p < 0.05$. The critical r for the medium CL group (n of 7) is .707, however an n of 11 was used in determining the critical r for the medium CL to maintain consistency. The critical r for an n of 11 is lower than for n of 7 and therefore this increased the chance of finding significant correlations. Descriptive statistics included mean ± standard deviation (SD) or standard error of the mean (SEM) and coefficient of variation of means. Statistical significance was set at $p \leq 0.05$.

3.4 Results

3.4.1 Kinematics

Varying the CL for the right arm in each trial produced a significant change in the joint ROM for the shoulder and elbow of the ipsilateral arm. The right shoulder had an average joint excursion for the long (L), medium (M) and short (S) CLs, of 64º ± 8, 38º ± 5, 13º ± 5, respectively (± represents 1 SD), while the corresponding values for the elbow were 103º ± 10, 66º ± 9, 25º ± 13.

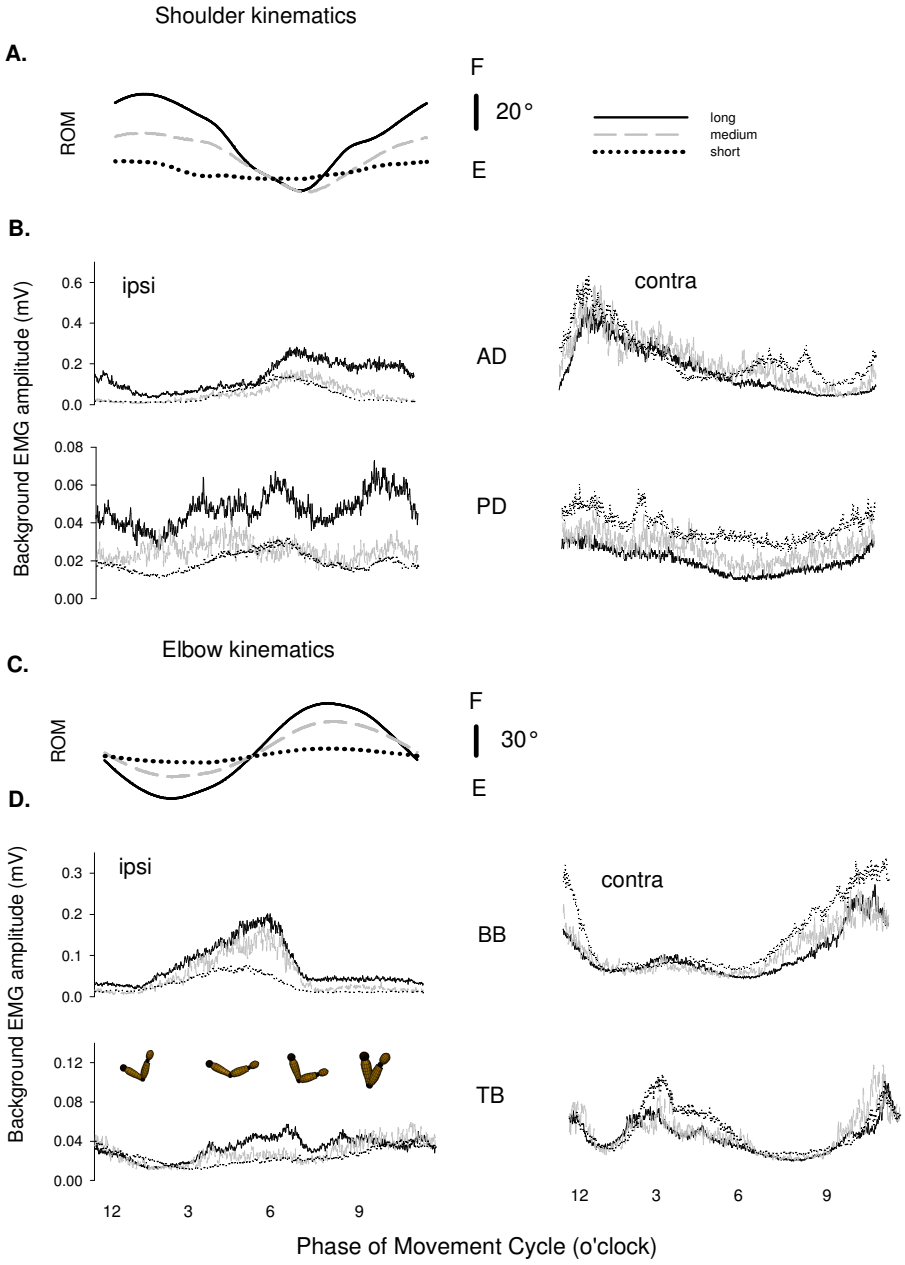


Figure 3.1. Kinematic recordings and background EMG traces for a single subject performing arm cylcling. Trials with the three crank lengths (CLs) are represented with a solid black line for long, a dashed grey line for medium and a dotted black line for short CL. For kinematic recordings 20˚ of shoulder and 30˚ of elbow joint movement is indicated by the respective calibration bars. For EMG traces data are plotted on identical scales for ipsilateral and contralateral muscles. Abbreviations: anterior (AD) and posterior (PD) deltoid, biceps (BB) and triceps (TB) brachii, flexor carpi radialis (FCR), ipsilateral (i), contralateral (c), crank length (CL).

Muscle	O'clock	BG	Early	Middle	Muscle	O'clock	BG	Early	Middle
iPD	1,2	~	#	~	cAD	12	*∇	*	~
iTB	10,11	#	~	~		1-3	*∇	~	~
iFCR	12	*∇	~	~		4,10,11	*	~	~
	1, 9-11	*	~	~	cPD	12	*∇	~	~
						1,4,5	*	~	~
						6-9	*∇	~	~
						10,11	*	~	~
					cBB	12,8,9	*	~	~
						10,11	*∇	~	~
					cFCR	8-10	*	~	~

Table 3.1. Muscles with significant differences between crank lengths for amplitude in background EMG and reflexes at early and middle latencies at each phase of movement as determined by post hoc testing ($p < 0.05$). Abbreviations: anterior (AD) and posterior (PD) deltoid, biceps (BB) and triceps (TB) brachii, flexor carpi radialis (FCR), ipsilateral (i), contralateral (c),background EMG (BG).
No significant difference between crank lengths(CLs) indicated by ~.
Significant difference between short and long CL indicated by *.
Significant difference between medium and long CL indicated by #.
Significant difference between short and medium CL indicated by ∇.

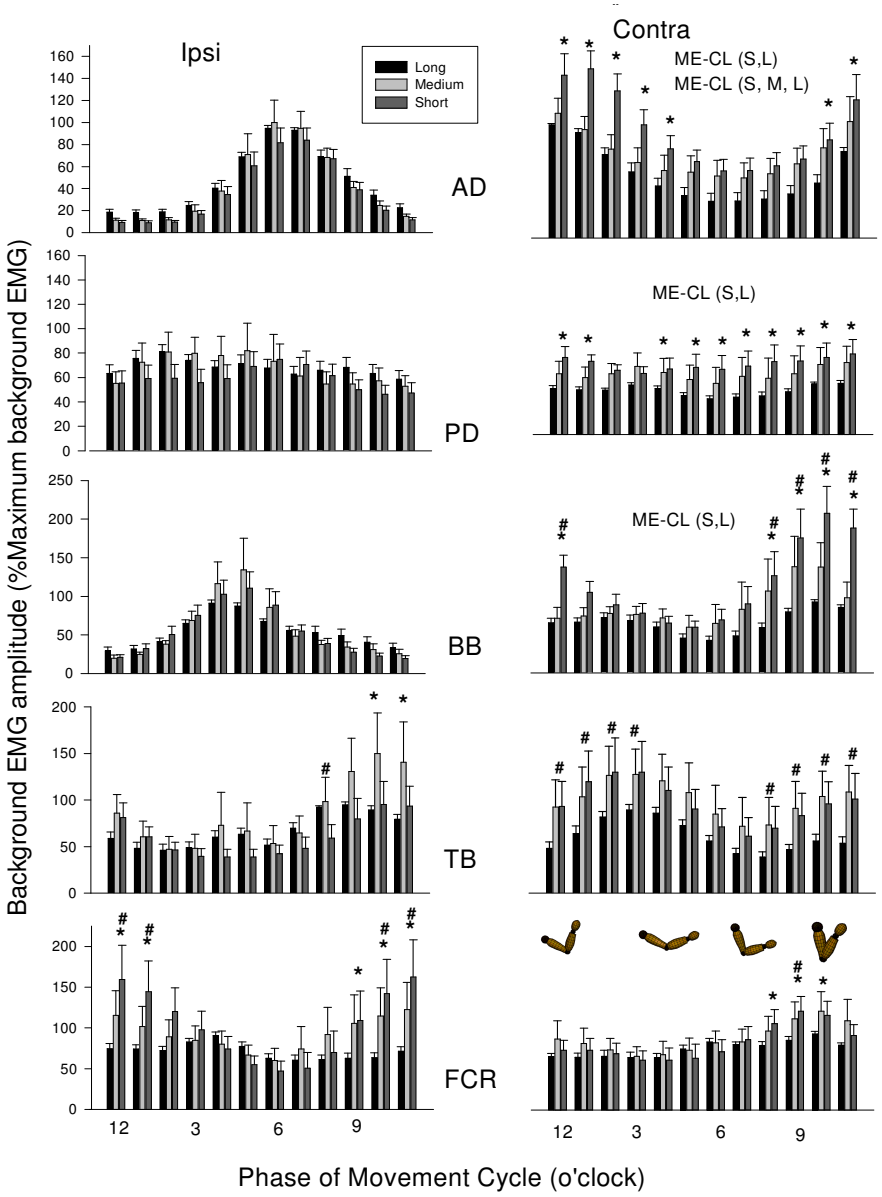


Figure 3.2. Patterns of rhythmic EMG across the movement cycle during arm cycling with long, medium and short crank lengths (CLs). Background EMG for all ten muscles are expressed relative to the maximums during the long CL arm cycling trial. Muscles ipsilateral (ipsi) and contralateral (contra) to the site of nerve stimulation are shown in the left and right columns, respectively. Phase in the movement cycle relative to the clock face are as indicated at the bottom of the figures. In the bottom right panel the arm position is roughly indicated by the cartoon arms. Data represent mean +/- SEM for 11 subjects. Data are plotted on identical scales for ipsilateral and contralateral muscles. Abbreviations are as in Figure 3.1. # indicate significant differences between S and L CL at a given phase of movement ($p<0.05$). * indicate significant differences between the 3 CLs (S,M,L) at a given phase of movement ($p<0.05$). ME indicates Main Effect for CL.

Muscle	Long CL	Medium CL	Short CL
iAD	85%	89%	90%
iPD	52%	54%	51%
iBB	74%	82%	84%
iTB	58%	69%	61%
iFCR	51%	50%	75%
cAD	71%	60%	68%
cPD	49%	49%	44%
cBB	61%	68%	74%
cTB	63%	61%	60%
cFCR	51%	53%	61%

Table 3.2. Modulation Index (MI) for background EMG for each muscle throughout the movement cycle for each crank length (MI=[(EMGmax -EMGmin)/EMGmax] x100). Data represents mean values for 11 subjects. Abbreviations as in Table 3.1 and crank length (CL).

ROM between all three CLs were significantly ($p<0.001$) different for both shoulder and elbow. In Figure 3.1A and C, kinematic data for the ipsilateral shoulder and elbow joint at the L, M and S CLs for an individual subject are displayed by the solid, dashed and dotted lines, respectively. Flexion (F) and extension (E) are represented by upward and downward deflections, respectively. It can be seen that with the L crank length there is a large ROM for the shoulder and elbow joints. As the CL is decreased the joint excursion decreases substantially with minimal ROM observed at the short CL.

3.4.2 Background EMG patterns

The EMG traces across the movement cycle for an individual subject, displayed in Figure 3.1B and 1D, show that as CL decreases the EMG for muscles in the contralateral arm increases. Normalized EMG activity averaged across all subjects show these changes (see Figure 3.2). For example, in AD on the contralateral side EMG is progressively larger in amplitude for the shorter crank lengths. This pattern is generally consistent for the other contralateral muscles. In the single subject background EMG traces (see Figure 3.1B &D), the amplitude of the ipsilateral muscles is smaller for the shorter crank lengths, however this pattern was not always seen when the results were averaged across all subjects. In Figure 3.2 it can be seen that for the ipsilateral muscles the background EMG was generally similar between CLs at each phase of movement.

The main effects for CL of ANOVAs performed for the S and L CL trials include cAD, cPD, cBB ($p < 0.05$)(indicated on Figure 3.2). Significant differences from post-hoc tests of significant interactions for S and L CL are indicated by the number sign (#) in Figure 3.2 ($p < 0.05$). Separate ANOVAs were performed on all 3 CL combined (S, M, L). The main effects for

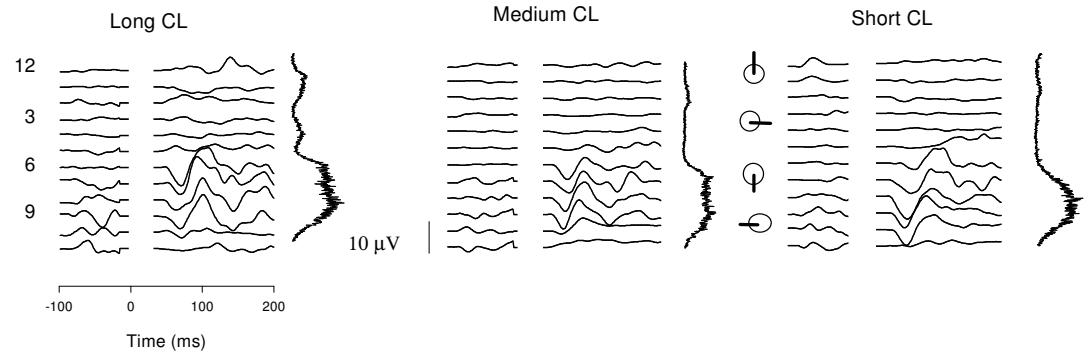


Figure 3.3. Cutaneous reflex and background EMG traces in iAD muscle for a single subject during arm cycling with different crank lengths (CLs). Plots of subtracted reflex EMG for all 12 phases of the movement cycle while cycling with long (left panel), medium (center) and short (right) crank length. The numbers to the left of the first panel and the cartoon clocks between the second and third panel denote the phase of the movement relative to a clock face. Note the similarity between crank lengths of inhibition followed by excitation seen primarily between 7 to 10 o'clock. The stimulus artifact (beginning at time 0 to ~30ms) has been removed from the reflex traces. Background EMG whole cycle traces are plotted vertically to the right of each panel.

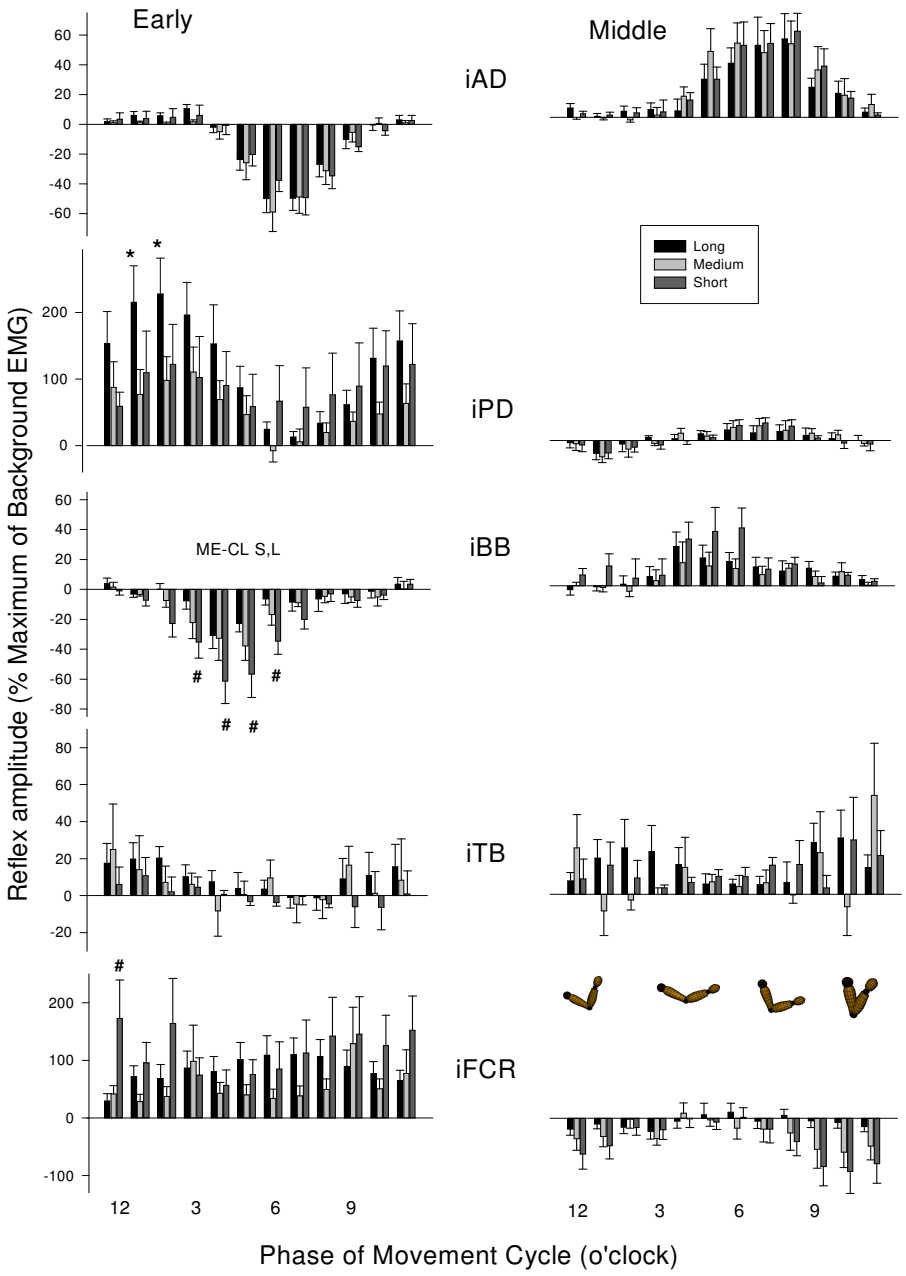


Figure 3.4. Early (50-80 ms) and middle (~80-120 ms) latency reflexes across the movement cycle for muscles ipsilateral to nerve stimulation for all subjects. Data calculated from subtracted reflex traces averaged across all subjects and represent mean +/- SEM. Reflex amplitudes have been normalized to the maximum background EMG during cycling with the L crank. Data are plotted on identical scales for early and middle latency. Abbreviations as in Figure 3.1. # indicate significant differences between S and L CL at a given phase of movement ($p<0.05$). * indicate significant differences between the 3 CLs (S,M,L) at a given phase of movement ($p<0.05$). ME indicates main effect for CL.

CL for these ANOVAs include cAD, cPD, cBB (indicated on Figure 3.2)($p < 0.05$). Significant differences from post-hoc tests of significant interactions are indicated by an asterisk (*) in Figure 3.2 ($p < 0.05$). Note that an asterisk indicates a significant difference in background EMG amplitude between CLs at that phase of movement. However an asterisk on Figure 3.2 does not differentiate which CLs are significantly different. Precisely which CLs were significantly different at each phase of movement are outlined in Table 3.1. For example, in iTB a "#" indicates that at the 10 and 11 o'clock position the amplitude of background EMG is significantly different between M and L CL trials. Likewise, for iFCR the "*" and a "∇" indicate that in the 12 o'clock position there is a significant difference in the amplitude of background EMG between the S and L CL and between the S and M CL, respectively. Significant differences were found more commonly on the contralateral side.

The background EMG activity for all muscles was significantly phase modulated. Some muscles were phase modulated more than others with a minimum modulation index of 49%, 49%, and 44% observed in cPD muscle and a maximum modulation index of 85%, 99%, and 90% observed in the iAD muscle in the L, M, and S CL trials respectively (see Table 3.2). The depth of modulation for each muscle was similar across CLs.

3.4.3 Reflex Latencies

Reflex latencies as determined by time to peak response were similar to those found in previous studies of SR nerve during rhythmic arm cycling (Zehr and Kido, 2001; Carroll et al. 2004; Zehr and Hundza, 2005). No significant differences were found between the reflex latencies for different CLs.

Muscle	Early			Middle		
	Short	Medium	Long	Short	Medium	Long
iAD	-0.67*	-0.82*	-0.77*	0.64*	0.65*	0.46
iPD	0.23	0.10	0.20	-0.09	0.07	0.00
iBB	-0.83*	-0.79*	-0.61*	0.39	0.38	0.34
iTB	-0.18	-0.15	0.00	0.55	0.27	0.11
iFCR	0.72*	0.36	0.19	-0.80*	-0.84*	0.41
cAD	-0.41	-0.04	-0.36	0.01	0.19	0.28
cPD	0.03	-0.17	-0.13	0.16	-0.07	-0.22
cBB	-.0.37	0.08	-0.14	-0.04	0.08	0.07
cTB	-0.25	0.08	-0.18	0.11	0.27	0.17
cFCR	-0.23	-0.35	-0.05	0.09	-0.09	-0.08

Table 3.3. Pearson correlation coefficients (r) between reflex amplitudes and background EMG during arm cycling for each muscle. Abbreviations are as in Table 3.1. Significant correlations (critical r = .576 with df=10, two tailed, $p < 0.05$) are indicated in bold text with asterisks.

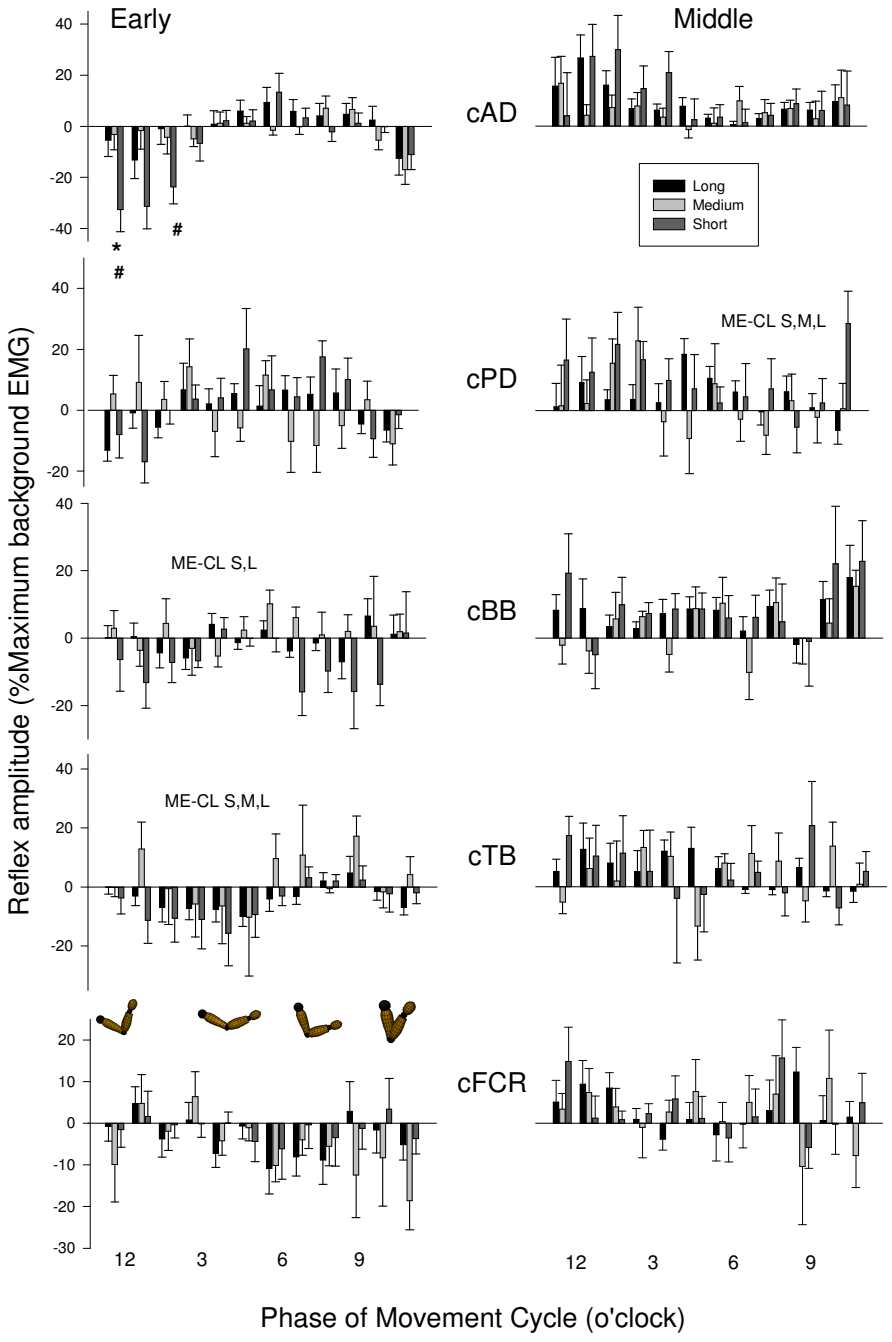
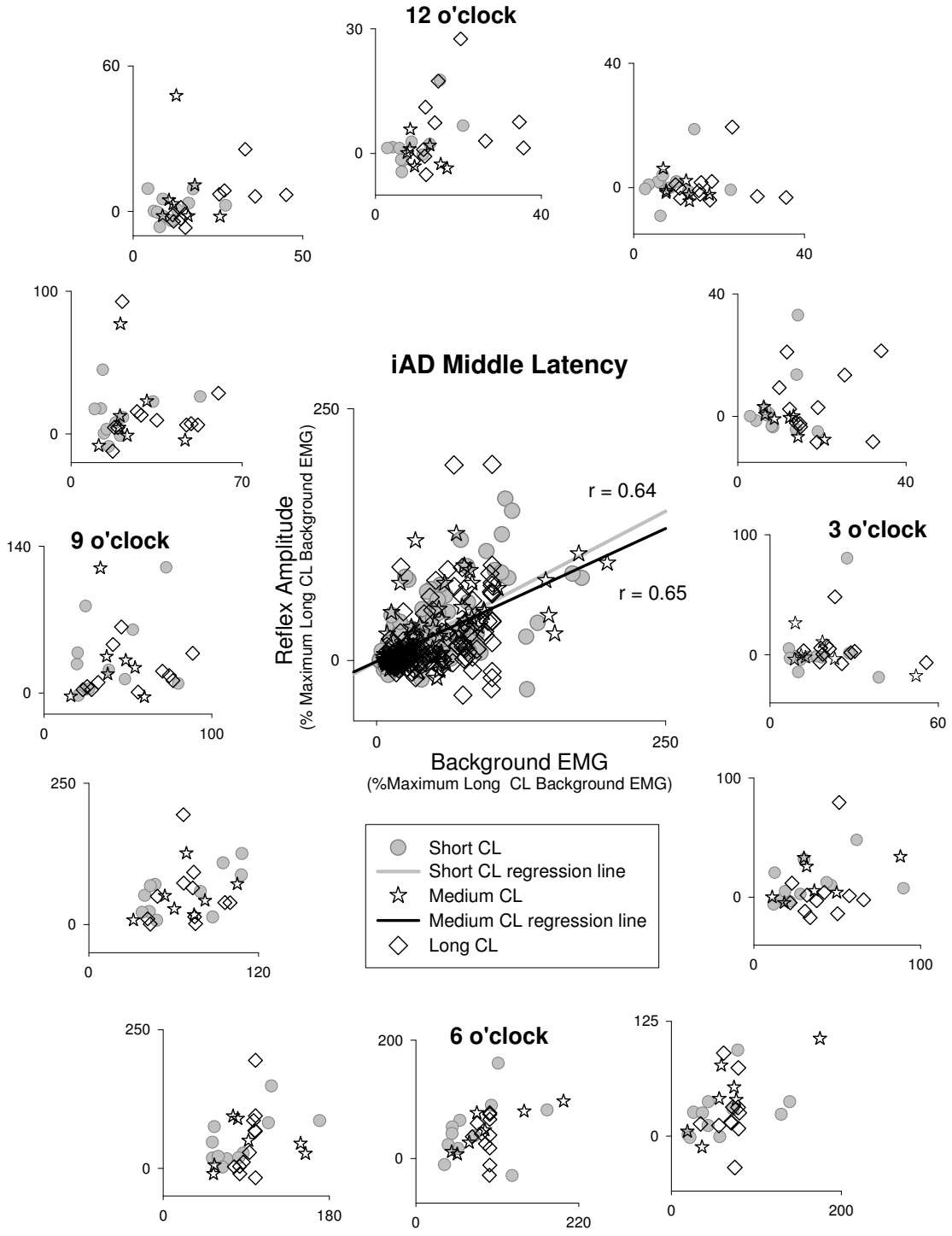


Figure 3.5. Early (50-80 ms) and middle (~80-120 ms) latency reflexes across the movement cycle for muscles contralateral to nerve stimulation for all subjects. Data calculated from subtracted reflex traces averaged across all subjects and represent mean +/- SEM. Data are plotted on identical scales for early and middle latency. Reflex amplitudes have been normalized to the maximum background EMG during cycling with the L crank. Abbreviations as in Figure 3.1. # indicate significant differences between S and L CL at a given phase of movement ($p<0.05$). * indicate significant differences between the 3 CLs (S,M,L) at a given phase of movement ($p<0.05$). ME indicates main effect for CL.

3.4.4 Reflex Modulation Patterns

Reflex patterns across the movement cycle at early and middle latencies were similar for all three CLs (S, M, L). Reflex traces for an individual subject for iAD muscle during cycling at each CL are shown in Figure 3.3. The phase of movement is noted by the numbers and cartoon clock faces found to the left of the first panel and between the second and third panel, respectively. Similar patterns of reflex modulation can be seen for all three CL trials at similar phases of the movement cycle. The corresponding background EMG traces across the entire movement cycle for each CL are plotted vertically located to the right of each panel. Identical scales have been used for the subtracted reflex and background EMG traces to allow comparison between CL trials. Across all subjects the early and middle latency reflexes for each phase of movement for the muscles ipsilateral to stimulation have been plotted in Figure 3.4 and muscles contralateral to stimulation in Figure 3.5. It can be seen, particularly in the ipsilateral side, that the pattern of reflex modulation is consistent for the 3 CLs across the movement cycle. Reflexes of similar amplitude and sign (i.e. excitatory and inhibitory) can be seen at corresponding phases of the movement cycle for all three CLs. For example, in the top panels of Figure 3.4, in the early and middle latencies for iAD, the reflex signs and amplitudes are similar across the movement cycle. The main effects for CL from ANOVAs performed on early and middle latency reflexes for only the S and L CLs include iBB and cBB in early latency ($p < 0.05$) (indicated on Figure 3.4 and Figure 3.5). Significant differences between S and L CL from post-hoc tests of significant interactions are indicated by the number sign (#) in Figure 3.4 and Figure 3.5 ($p < 0.05$). In relatively few instances did CL have a significant effect on early latency reflexes at specific phases of movement ($p<0.05$). They were found at 4 phases in iBB, 1 phase in iFCR and 2



igure 3.6. Scatterplot of background EMG vs middle latency reflexes for iAD. Plotted on the center graph is data from the whole movement cycle, while on the periphery are graphs with data for the individual phases of movement. Regression lines for significant correlations (critical r = .576 with df = 10) between bEMG and reflex for each CL data are plotted on each graph. Abbreviations as in Figure 3.1.

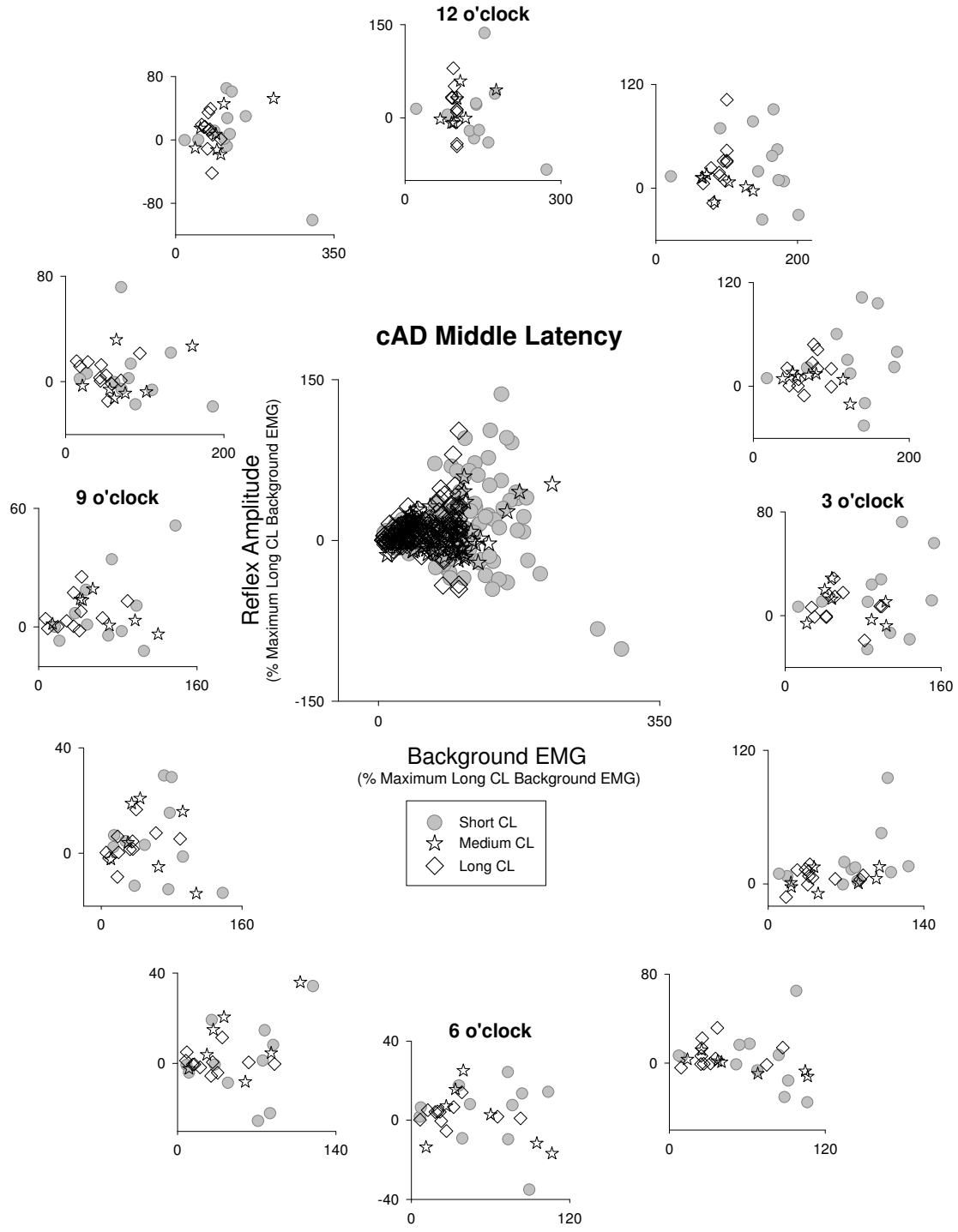


Figure 3.7. Scatterplot of background EMG vs middle latency reflexes for cAD. Plotted on the center graph is data from the whole movement cycle, while on the periphery are graphs with data for the individual phases of movement. Regression lines for significant correlations (critical r = .576 with df = 10) between bEMG and reflex for each CL data are plotted on each graph. Abbreviations as in Figure 3.1.

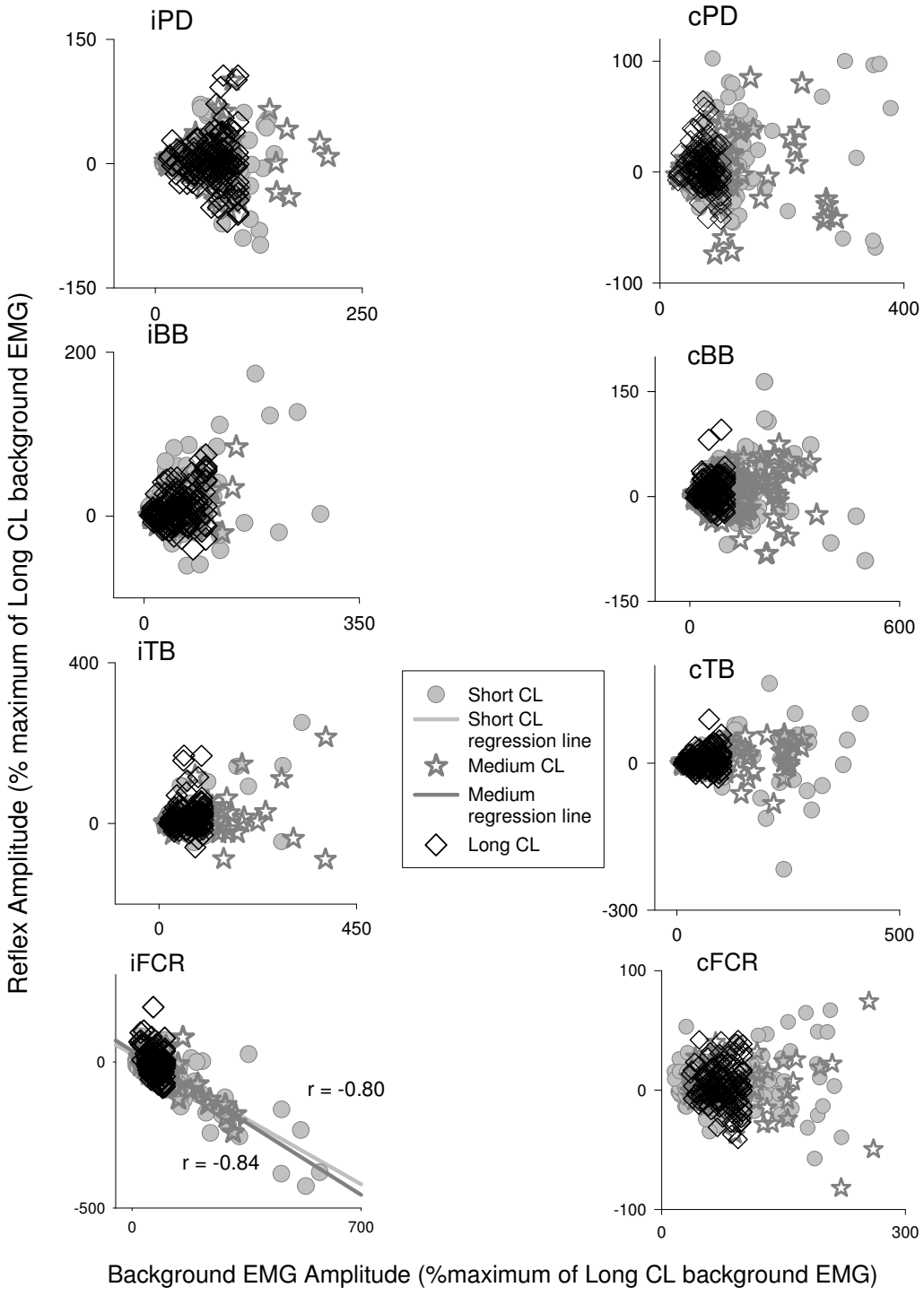


Figure 3.8. Scatterplot of background EMG vs middle latency reflexes for the complete movement cycle for iPD, iBB, iTB, iFCR, cPD, cBB, cTB, cFCR. Regression lines for significant correlations (critical r = .576 with df = 10) between bEMG and reflex for each CL data are plotted on each graph. Abbreviations as in Figure 3.1.

phases in cAD. Another ANOVA was performed on early and middle latency reflexes for all 3 CLs combined (S, M, L; D of F = 6). The main effects for CL from this ANOVA include cTB in early latency and cPD in middle latency (indicated on Figure 3.5). There were even fewer instances in which changes in crank length were found to have significant effects on the reflexes at specific movement phases. Only 2 phases at early latency for iPD and 1 phase in cAD were significantly different between all 3 CL trials ($p<0.05$); in Figure 3.4 and 3.5 an asterisk denotes these differences. In Table 3.1, it can be seen that in iPD at 1 and 2 o'clock the early latency reflexes for M and L CLs are significantly different ($p<0.05$, indicated by a #) and that in cAD at 12 o'clock, the early latency reflexes for S and L CLs are significantly different ($p<0.05$, indicated by an *).

Pearson correlations were conducted to evaluate the extent to which early and middle latency reflexes from each CL condition varied with the corresponding background EMG (See Table 3.3). Of the 60 correlations conducted, only 11 times were the correlations between reflex and background EMG amplitudes significantly coupled. These significant correlations were found at L CL for iAD and iBB at early latency, at M for iAD (early and middle latencies), iBB (early), iFCR (middle), and at S for iAD (early and middle), iBB (early), and iFCR (early and middle). Scatter plots of background EMG and middle latency reflexes for iAD and cAD show that the ranges of background EMG for each CL are overlapped at each phase of movement as well as across the entire movement cycle (see Figure 3.6 and 3.7). Scatter plots of background EMG and middle latency reflexes in the remaining muscles (see Figure 3.8) show a similar overlap of background EMG of the different CLs across the entire movement cycle. Regression lines for each CL are shown only for significant correlations between background EMG and reflex responses. In iAD there are no significant correlations at individual phases of movement,

however there is a significant correlation for S and M CLs for data combined across the movement cycle (see Figure 3.6). In cAD there are no significant correlations for data combined across the movement cycle or at the individual phases of movement (see Figure 3.7). iFCR in Figure 3.8 shows a significant correlation for S for M CLs for data combined across the movement cycle.

3.5 Discussion

In this study, the intent of changing the crank length (CL) was to alter the movement to create three different rhythmic motor tasks. Unilaterally changing the CL yielded an asymmetrical movement for two of the trials. This caused a significant change in kinematics of arm motion which likely altered peripheral feedback. The main observation of this study was that cutaneous reflex modulation elicited by stimulating the superficial radial nerve did not change across the rhythmic motor tasks produced by altering CL. This was observed even though changing the CL had a significant effect on rhythmic background EMG.

3.5.1 Does Unilaterally Altering Crank Length Change the Motor Task?

Unilaterally altering the crank length produced an asymmetrical movement; therefore the 3 trials comprised one symmetrical and two asymmetrical cycling trials. As the CL was decreased, the joint excursions in the respective arm were significantly affected ($p < 0.001$). Figure 3.1A shows that as the CL decreased from L to M to S in the ipsilateral arm, there was a corresponding significant decrease in the ROM at the ipsilateral shoulder and elbow suggesting that the movement itself was appreciably altered. Since the frequency of cycling was held constant, the

angular velocity at each joint on the ipsilateral side was decreased. It is likely that manipulations to ipsilateral crank length applied in this study significantly altered sensory feedback since it has been shown that altered ROM and angular joint velocity can modify afferent feedback arising during the movement (Cheng et al. 1995). Altering the crank length with a constant cycling frequency would change the rate and length of muscle stretch and therefore influence the firing of Ia and II muscle spindle afferents (Cheng et al. 1995). It can also be posited that if altering CL changed EMG amplitudes then altering CL also affects tension in muscles which in turn would influence the firing of Ib afferents. Affecting joint ROM by altering CL would also have influenced the stretch of the skin at the elbow and shoulder and thus the firing of cutaneous receptors (Collins et al. 2000). The altered CL likely had little effect on the stretch of the joint capsules as extremes of range were not reached (Cheng et al. 1995). It can therefore be reasoned that significantly manipulating CL in the manner applied here altered afferent feedback.

In the asymmetrical trials, background EMG was generally greater in the contralateral elbow and shoulder muscles at many phases of movement (see Figure 3.2) at the shorter CLs. In Figure 3.2 the asterisks denote the movement phases in which the amplitude of background EMG significantly differed between CLs. A possible biomechanical explanation is that the increase in muscle activation seen in the contralateral muscles was required to compensate for the decreased contribution of the ipsilateral arm to overall crank propulsion due to the shortened ipsilateral CL with no ipsilateral increase in muscle activation. Explicit elucidation of the neural mechanisms responsible for the increased EMG in the contralateral muscles is difficult because changes to the ipsilateral CL affect both contralateral mechanics as well as the crossed effects of sensory feedback. Another explanation for the increase in contralateral EMG activation with shorter ipsilateral CLs is the influence of the sensory feedback from the ipsilateral side

contributing to muscle activation in the opposite limb as has been suggested for leg cycling (Ting et al. 2000; Kautz et al. 2002). Regardless of whether the changes in muscle activation in this study were related to contralateral mechanics or the crossed effects of sensory feedback, the significant changes in EMG activation with different CLs imply that varying the CLs has created significant variations to the cycling tasks.

3.5.2 Cutaneous reflexes were similar despite different task constraints

Cutaneous reflex patterns produced with stimulation to the superficial radial nerve, were similar across the cycling trials, despite significant changes to the task constraints (i.e. symmetrical vs. asymmetrical movement, arm kinematics and muscle activation patterns). That is, excitatory and inhibitory reflex responses of similar amplitudes occurred at similar phases of movement for all the CLs. As noted, at a given phase in the cycling movement the muscle activation levels differed between different CLs. Despite significant changes in the EMG levels at a given phase of movement, the cutaneous reflex patterns seen between CLs were not significantly different (see figures 3.4 & 3.5). This suggests that neural mechanisms regulating the cutaneous reflex modulation in arm muscles evoked with stimulation to superficial radial nerve are not simply related to modifications in amplitude of background EMG. Cutaneous reflexes evoked during leg cycling at a given position in the movement cycle, have been shown to be insensitive to different levels of background EMG induced by varying load (Zehr et al. 2001).

Despite significant differences in background EMG between CLs at specific phases of movement for some muscles, the background EMGs for the CLs are sufficiently overlapped to allow for comparisons. In cAD several phases of movement show significant differences in

background EMG between CLs, whereas in iAD in Figure 3.2, there were no significant differences in background EMG between CLs. For both these muscles the scatter plots of background EMG versus middle latency (see Figure 3.6 and 3.7) show that the ranges of background EMG are sufficiently overlapped to allow for comparison between CL trials at each phase of movement as well as across the entire movement cycle. The scatter plots for the remaining muscles (see Figure 3.8) also show that the background EMG for the different CLs is sufficiently overlapped to allow for comparisons. Regression lines are plotted only on those graphs where the background EMG and reflex amplitudes are significantly correlated. The scatter plots display that generally there is limited correlation between background EMG and reflex amplitude at comparable levels of background EMG.

Peripheral feedback was likely different between the CL trials yet this did not affect the pattern of cutaneous reflex modulation. These results are consistent with the work of Carroll et al. (2004), Brooke et al. (1999) and Zehr and Hundza (2005) with regard to the effects of peripheral feedback on cutaneous reflex patterns. During passive cycling of the arm (Carroll et al. 2004) or leg (Brooke et al. 1999), cutaneous reflexes showed little phase modulation, while during active arm or leg cycling cutaneous reflexes were phase modulated (i.e. reflex amplitude and sign varied depending on phase of movement). The peripheral feedback produced by both the active and passive movement was similar, yet the reflex modulation was different supporting a central locus of control for the active rhythmic movement. Previous work (Zehr and Hundza, 2005) comparing forward and backward arm cycling has shown that despite significant changes in background muscle activity cutaneous reflex modulation is insensitive to direction of motion. In reversing a movement changes in peripheral feedback, particularly from muscle spindle receptors, can be anticipated. It can be reasoned that peripheral feedback (e.g. from muscle spindles in

muscles that are lengthening instead of shortening at the same phase of movement) was altered by reversing the direction of the cycling yet the cutaneous reflexes were insensitive to these changes suggesting a common central locus of control. The present study is further evidence that peripheral feedback has little effect on cutaneous reflex modulation during active rhythmic movements.

Interestingly, although our results showed little significant change in cutaneous reflex modulation in response to altering kinematics, other forms of sensory feedback, most notably load, have been shown to influence cutaneous reflexes in leg muscles during walking. Bastiaanse et al. (2000) found that, during walking, cutaneous reflexes in soleus and medial gastrocnemius were largest with body unloading and smallest with body loading. However reflex amplitude was not a simple function of the level of background EMG.

When comparing different classes of movements (i.e. rhythmic vs. static) distinct patterns of cutaneous reflex modulation are seen for each (task-dependent reflexes) despite similar background EMG. Brown and Kulkulka (1993) controlled background muscle activity and stimulus intensity, while eliciting human flexor reflex at different phases of the leg cycling path during cycling and static trials. The reflex responses elicited at different phases in the cycle path were phase modulated during cycling trials, while reflexes elicited during static contraction trials were not. This suggests that neural control of muscle activity during static contractions and cycling are different. Other studies have shown cutaneous reflex control to have a similar strict dependency on the motor task performed (Duysens et al, 1993; Komiyama et al. 2000; Zehr et al. 2001, Zehr et al 2001a; Zehr and Haridas, 2003). The present results showed that phase modulated cutaneous reflexes patterns persisted across the different CLs. This was the case when the background EMG was both similar and dissimilar. Therefore no task dependency of reflexes

was seen between the CL trials. This suggests a consistent neural control of arm movement across all three cycling trials.

3.5.3 Implications for the neural control of rhythmic arm movement

In previous studies, cutaneous reflexes were evoked in conditions within which peripheral feedback would be very similar (during active vs. passive limb movement (Carroll et al. 2004; Brooke et al. 1999)) or be quite different (during forward vs backward cycling (Zehr and Hundza, 2005)). These studies provide evidence that central mechanisms (i.e. CPGs) contribute to the regulation of interneurons mediating cutaneous reflexes during active rhythmic movement and that these premotoneuronally gated pathways are not sensitive to peripheral feedback. The present research corroborates the role of central mechanisms (i.e. CPGs) regulating cutaneous reflexes during active rhythmic movement and that these are seemingly insensitive to peripheral feedback. Here we show that centrally controlled cutaneous reflex patterns elicited during active rhythmic movement are not simply modulated by differing background EMG levels at a given phase of movement between CLs trials as well as being insensitive to peripheral feedback.

Phase dependent reflex modulation during rhythmic movement that is uncoupled from background EMG, has been consistently attributed to the neural activity in central pathways (e.g. CPG) (Duysens and Van de Crommert, 1998; Dietz, 2003; Zehr and Duysens, 2005). For all three CL trials in the present study the reflex amplitudes were phase modulated and uncoupled from background EMG further suggesting a similar locus of control for all three trials that is central in nature. Typically rhythmic movements are bilaterally symmetrical and are thought to be controlled by coupled CPGs (Carroll et al. 2004). Less is known about the influence of

asymmetrical bilateral tasks on this coupling. In the present study, altering one CL presented the nervous system with an asymmetrical rhythmic task between the arms. Yet the central mechanisms regulating these movements maintained a coordinated coupling between the arms with a consistent neural control across the CL trials. Carroll et al. (2004) systematically varied the task coupling between the arms and found that the modulation of cutaneous reflexes was seen to essentially follow the activity state of the arm in which the reflex was evoked regardless of whether the recordings were made ipsilateral or contralateral to the stimulation. These observations were explained by loosely coupled networks (i.e. CPGs) for each arm controlling cutaneous reflexes during rhythmic arm cycling.

In summary, we suggest that variations in arm cycling tasks that primarily yield changes in the amplitude of rhythmic muscle activity are not different enough to produce a task-specific change in neural control. That is, modifying a rhythmic task by unilaterally altering CL did not influence cutaneous reflex modulation, despite producing significant changes in EMG activation patterns. Cutaneous reflexes were therefore not significantly affected by the task changing from symmetrical to asymmetrical bilateral arm cycling and to the associated modifications in EMG activation and peripheral feedback. It remains for future experimentation to further investigate the influence of load and velocity on cutaneous reflex modulation and between neuromuscular and biomechanical coupling in rhythmic arm movements.

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4. Muscle activation and cutaneous reflex modulation during rhythmic and discrete arm tasks in orthopaedic shoulder instability[3]

4.1 Abstract

In orthopaedic shoulder instability, muscle activity (EMG) is altered during unconstrained discrete arm movement tasks (e.g. elevation against a load). These findings have been ascribed to deficits in afferent feedback and neural control with glenohumeral instabilities resulting from orthopaedic injury. However, the integrity of neural control during shoulder movements in those with unstable shoulders is unclear. It is not known if there are altered EMG patterns during rhythmic arm movement or during discrete tasks involving no load, as would be experienced in many arm motions performed in daily living. The primary objective of this study was to evaluate neural control of arm movements between those with unstable shoulders and control participants within a constrained arm movement paradigm involving both rhythmic arm cycling and discrete reaching. To achieve this objective we determined if the amplitude and timing of EMG related to the movement pattern (background EMG) was significantly different between groups. Cutaneous reflexes were used to simulate a perturbation to the upper limb that would typically evoke a coordinated response. In the elevation phase of the movement path for anterior and posterior deltoid, upper trapezius, infraspinatus and serratus anterior, background EMG during rhythmic arm cycling was significantly (~24%, $p<.05$) larger in unstable shoulders than in controls. No differences were found in background EMG between the groups during the discrete task. Significant differences ($p<.05$) were also noted in cutaneous reflexes between groups for both the rhythmic and discrete tasks with the reflex amplitudes being either increased or reduced in unstable shoulders as compared to controls. The differences in the background EMG and the

[3] Hundza SR, Zehr EP (2007) Muscle activation and cutaneous reflex activation during rhythmic and discrete arm tasks in orthopaedic shoulder instability. Exp Brain Res 179(3): 339-51. (90% contribution to project)

cutaneous reflex patterns in those with shoulder instabilities suggest that neural control is altered during rhythmic movement.

4.2 Introduction

Smooth, coordinated movement requires the continual interaction between motor commands and afferent feedback. When this sensorimotor interaction is compromised the timing and amplitude of muscle activity (EMG) is altered (Lephart et al. 1997; Myers and Lephart 2002). The glenohumeral (shoulder) joint, perhaps to a greater degree than any other joint because of its inherent lack of osseous stability, relies on a continuous interplay between afferent feedback and the efferent output to provide an imperative and finely tuned dynamic stabilizing control mechanism (Glousman et al. 1988; Kronberg et al. 1990; Wilk et al. 1997). Functional orthopaedic glenohumeral instability, defined as unwanted translation of the humeral head on the glenoid compromising the comfort and function of the shoulder (Matsen et al. 1991), may result from laxity or damage to capsular, labral, ligamentous or muscular stabilizing mechanisms (Reid 1992). Previous studies have shown that those with unstable shoulders display altered amplitude of shoulder muscle activity during discrete (e.g. reaching) arm tasks (Glousman et al. 1988; Kronberg et al. 1991; McMahon et al. 1996; Morris et al. 2004). That is, within a discrete movement there are changes in EMG amplitude in unstable shoulders when compared to control participants. Current rehabilitation efforts generally strive to retrain stereotyped muscle activation patterns. Strengthening and endurance conditioning of the upper limb muscles is also often required after injury. Rhythmic arm motor tasks (e.g. arm cycling) could be usefully applied in this domain, as these involve coordinated and consistent muscle activity patterns across multiple muscles of both arms (Zehr and Hundza 2005). However, little is known about whether muscle activation patterns are altered in those with orthopaedic shoulder instability

during rhythmic arm movement. Additionally, the discrete motor tasks, explored in previous studies, included arm elevation against a load (McMahon et al. 1996) or pitching at fast speeds (Glousman et al. 1988). It is unknown if EMG activity is altered during discrete arm tasks involving no load or slower speeds as would be experienced in many arm motions in typical daily living.

In addition to altered amplitude and timing of shoulder muscle activity during discrete arm motor tasks (Glousman et al. 1988; Kronberg et al. 1991; McMahon et al. 1996; Morris et al. 2004), a decreased ability to detect passive movement and to passively reposition the arm has also been found in those with unstable shoulders (Smith and Brunolli 1989; Lephart et al. 1994; Forwell and Carnahan 1996). Compromised neural control has been purported as a probable cause of these deficits; however a definitive origin of these deficits remains unclear. Using somatosensory evoked potentials, Tibone et al. (1997) found the shoulder sensory receptors in those with unstable shoulders to be intact. In humans, the integrity of neural circuits regulating movement can be probed indirectly by stimulating peripheral nerves from both remote (i.e. distant from the muscle under study) and local sites (i.e. close to the muscle under study), and then recording reflex responses in muscle activity (Burke 1999; Zehr 2005). This approach has been used by us to study the neural control of arm cycling and walking (for review see Zehr and Duysens 2004). However reflexes evoked by electrical stimulation have not yet been employed as a means to evaluate the integrity of the neural control of shoulder muscles after orthopaedic injury causing instability. In previous studies, stimulation of a remote nerve was used to simulate a perturbation (e.g. obstacle contact) to the arm (Zehr and Chua 2000; Zehr and Kido 2001), or to the leg (Zehr et al. 1997; Van Wezel et al. 1997) and motor responses were evaluated to determine patterns of trajectory stabilization (e.g. stumble correction in the case of the lower

limb). In the current study a remote nerve in the hand was stimulated in both those with unstable shoulders and controls, in order to identify functional deficits in trajectory stabilization in those with unstable shoulders.

The main purpose of this study was to determine the integrity of neural control of the shoulder muscles during arm cycling after orthopaedic shoulder injury. Integrity of neural control during rhythmic arm movement is operationally defined here as phase modulated amplitudes of background EMG and reflexes that are consistent with patterns identified in uninjured participants. By this definition, altered neural control could be identified as either altered muscle activation patterns (background EMG) produced when performing a movement, or altered reflex EMG in response to a neural probe mimicking a perturbation. Thus the primary objective of this study was to determine if the amplitude and timing of muscle activation and cutaneous reflexes were significantly different between those with unstable shoulders and controls within a constrained arm movement paradigm involving both rhythmic arm cycling and discrete reaching when no load is applied. Lastly, we explored if any deficits associated with unstable shoulders were reflected similarly in discrete and rhythmic tasks matched for movement trajectory and frequency.

4.3 Methods

Experiments were performed with a total of 21 participants. Ten participants (average age 35.2 years, including 2 females and 8 males) were recruited from a surgical waitlist for recurrent, glenohumeral subluxation or dislocation. Criteria for surgery typically included a history, physical examination findings and radiographic findings consistent with the diagnosis of

glenohumeral instability. Participants with concomitant shoulder pathologies such as rotator cuff tears, degenerative arthritis or impingements or referred cervical signs or symptoms were excluded. Eleven age and gender matched control participants (average age 34.7 years, including 3 females and 8 males) with non-injured shoulders and no cervical pathology were selected. All participants were free of any known neuromuscular or metabolic disease and participated with informed and written consent. The project was conducted under the sanction of the Human Research Ethics Board at the University of Victoria and performed in accordance with the Declaration of Helsinki.

4.3.1 Protocol

The experimental protocol is similar to that described previously (Zehr and Kido 2001; Hundza and Zehr 2006) and thus only differences in methodology are highlighted here. Participants refrained from any vigorous arm exercises or prolonged rhythmic arm movements (e.g. swimming) during the 24 hours prior to the experiment. Participants were seated and comfortably held one handgrip of the previously described ergometer (Zehr and Kido 2001) with the opposite hand resting in his or her lap. The rotational axis of the ergometer was set at shoulder joint height and the distance from the ergometer was standardized such that the elbow joint was flexed 15 degrees at the 3 o'clock position. This was done in an attempt to ensure equivocal stress to the relative soft tissue structures between participants. Torso and neck position was visually monitored by the experimenter to ensure a consistent upright position was maintained by each participant. Position in the movement cycle is given with reference to the clock face such that the top of the cycle is 12 o'clock and on the right side of the ergometer the movements proceed clockwise from there (e.g. 1, 2, 3 o'clock). Participants performed two arm

motor tasks unilaterally in independent trials; discrete reaching and rhythmic arm cycling.

Participants with an unstable shoulder performed the tasks on the side of their unstable shoulder.

For the control participants, both arms were examined separately with the order randomized.

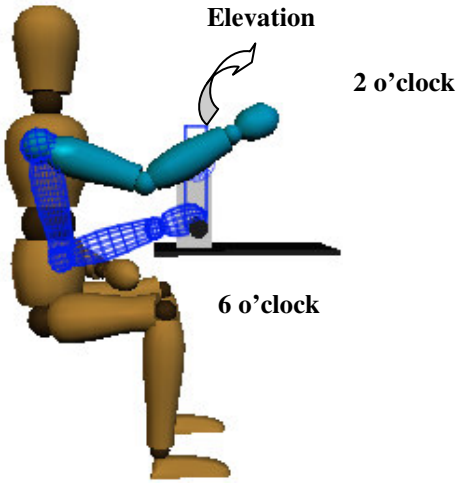

Figure 4.1 Rhythmic and Discrete motor task.
The rhythmic task is performed unilaterally cycling by moving the crank arm through the complete movement path at a self-generated frequency. The constrained discrete task is performed unilaterally (see cartoon mannequin) moving the crank arm from the 6 o'clock position to the 2 o'clock position at an equivalent tempo to the rhythmic task. Participants stopped the motion at 2 o'clock at an external non-rigid marker (not shown in figure). In both tasks the contralateral hand rested on participant's lap.

Prior to commencing experimental trials participants briefly cycled to determine their self-generated frequency (range 0.9-1.1 Hz, average of 1 Hz). Crank arm position at this frequency was recorded so this frequency could be matched in the discrete and rhythmic trials. During the discrete movement trials, the participants held the handle of the ergometer arm crank and elevated the crank arm in a clockwise direction from 6 o'clock to 2 o'clock along the constrained ergometer cycle path (see Figure 4.1). Participants stopped at 2 o'clock at a flexible marker. Participants matched their previously determined, self-generated cycling frequency using their online crank arm position, which was visually displayed. The second task was continuous rhythmic arm cycling. The participant used one arm to perform cycling at the previously determined self-generated cycling frequency. Participants were instructed to rest at any point in either trial if they experienced any pain or fatigue. No participant reported pain during the tasks though some took rest breaks. Discrete and rhythmic tasks were performed with a negligible constant hydraulic resistance (~170 kPa), which produces adequate muscle activation in the upper limb without leading to fatigue.

4.3.2 Cycle Timing

During rotational arm cycling, position in the movement cycle was recorded by an optical encoder allowing measurement of crank arm position.

4.3.3 Nerve Stimulation

The superficial radial (SR) nerve was stimulated with trains of 5 x 1.0 ms pulses at 300 Hz with a Grass S88 (Grass Instruments, AstroMed Inc.) connected in series with a SIU5 isolator and a

CCU1 constant current unit. Stimulation was delivered at approximately 2-2.5 times radiating threshold through bipolar electrodes placed on the dorso-lateral aspect of the ipsilateral wrist just proximal to the radial styloid process. Electrode placement was confirmed by verifying that radiating sensation was produced into the dorsolateral surface of the hand. Participants wore a wrist brace on the stimulated wrist to reduce the movement of the stimulating electrodes to maintain stimulus constancy. Stimulations were delivered at the 9 and 12 o'clock positions during the discrete tasks and throughout the movement cycle in the rhythmic task.

4.3.4 Electromyography

Bipolar recordings were taken from anterior (AD) and posterior (PD) deltoid, upper (UT) and lower (LT) trapezius, infraspinatus (IS) and serratus anterior (SA) in the active limb, which was ipsilateral to the nerve stimulation. EMG signals were preamplified and bandpass filtered at 30-300 Hz (P511 Grass Instruments, Astromed). Correct electrode placement was confirmed by visual monitoring of EMG signals during specific muscle testing.

4.3.5 Data Analysis

EMG data without stimulation (control background EMG) and with stimulation was sampled at 1 kHz with a 12-bit AD interface and a computer running custom-written (Dr. T. Carroll, University of New South Wales, Australia) Lab View data acquisition software (National Instruments). In the rhythmic task data were acquired throughout the whole movement cycle, whereas in the discrete motor tasks, sampling occurred only at the 9 and 12 o'clock phases of the clock cycle. For the rhythmic tasks, the data were partitioned into phases based on a division of

the movement cycle into 12 equidistant portions that represent the clock face (Zehr et al. 2004). Sweeps of data for each sampling period contained EMG for 100 ms before the stimulus onset and 200ms after the stimulus (300 ms in total per sweep). For all tasks within each phase of movement the responses to nerve stimulation were averaged. EMG recorded without stimulation (control background EMG) for each phase of movement was also averaged. Reflex (subtracted traces) EMG was calculated by subtracting the averaged control background EMG data from the data with stimulation at each phase of movement (10-20 observations per phase).

4.3.6 EMG Analysis

For all tasks, reflexes were analyzed at early (45-80 ms) and middle (80-120 ms) peak reflex latencies. The reflex subtraction process results in some residual EMG in the subtracted traces, which is not due to the reflex. The mean values of the residual prestimulus EMG for the subtracted traces were calculated as an index of subtraction variability. The mean value was plotted along with a 2-standrad deviation (SD) band on the subtracted traces. Reflexes were considered to be significant and included in the analysis if the reflex amplitude exceeded the 2-SD band calculated on the prestimulus EMG subtraction error (Hundza and Zehr 2006). An average was made of a 10 ms window centered on the peak of the response for early and middle latencies. Within each task all reflex and background EMG amplitudes for each phase of movement were then normalized to the maximum background EMG recorded during the rhythmic cycling trial.

4.3.7 Statistics

Descriptive statistics included mean, standard deviation (SD) and standard error of the mean (SEM). Repeated measures analysis of variance was conducted separately on background EMG and early and middle latency reflexes for phase of movement and for task (Statistica, Statsoft Inc.). Tukeys HSD was used to post hoc significant main effects. Differences between unstable shoulders and control for latencies and amplitudes of background EMG and reflexes were evaluated using t-tests. Statistical significance for all tests was set at $p \leq .05$.

4.4 Results

Data from dominant and non-dominant arms in control participants were not significantly different for any measures and therefore this control data was combined for all comparisons made to unstable shoulders.

4.4.1 Cycle Timing

Frequency of movement in both tasks for unstable and control shoulders across the cycle and at 12 and 9 o'clock positions are listed in Table 4.1. There were no significant differences between the participant groups when averaged across the whole movement cycle or at the 9 and 12 o'clock positions.

Comparisons of cycling timing were made between discrete and rhythmic movements at both the 9 and 12 o'clock position independently. There were no differences between the tasks at the 9 o'clock position within either the control group (NS, p=.90) or the unstable shoulder group

Task	Position in cycle	Control Shoulders	Unstable Shoulders
Rhythmic	Across Cycle	1.03	1.02
	9 o'clock	.98 ± .13	1.01 ± .08
	12 o'clock	1.11 ± 17	1.11 ± .12
Discrete	9 o'clock	.98 ±. 27	1.01 ± .18
	12 o'clock	.73 ± .21	.79 ± .25

Table 4.1. Frequency of movement in the control and unstable shoulders across the movement cycle and at 9 and 12 o'clock. Values represent frequency in Hz.

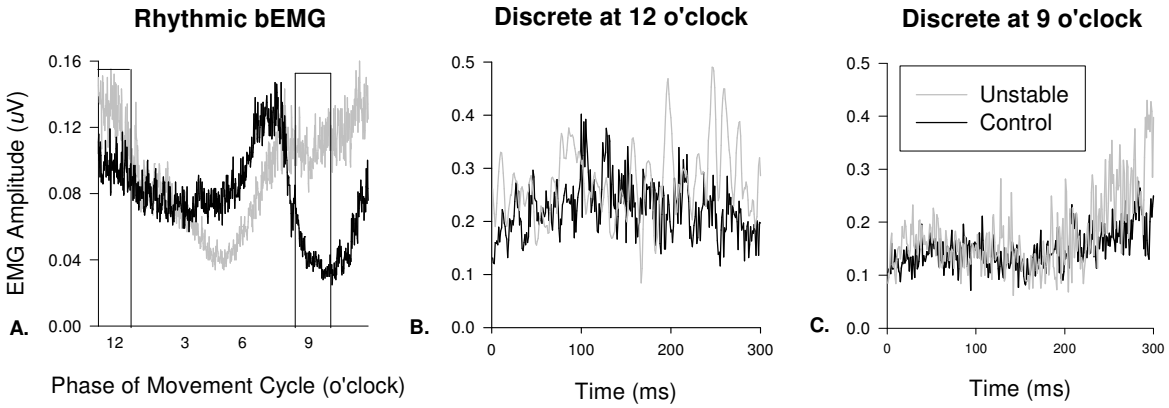

Figure 4.2 Background EMG for Infraspinatus (IS) muscle for a single participant during rhythmic and discrete tasks.
A. The rhythmic task background EMG traces represent activity across the complete movement cycle. B. The discrete task background EMG trace represents 300 ms about the 9 o'clock position in the movement cycle. The section in the rhythmic trace indicated with a box is at approximately an equivalent position in the movement cycle to the window from 100-180 ms. in the discrete EMG trace. Note the similarity in EMG amplitude between control and unstable shoulders in the discrete task and the difference in EMG amplitude between control and unstable shoulders in the rhythmic task.

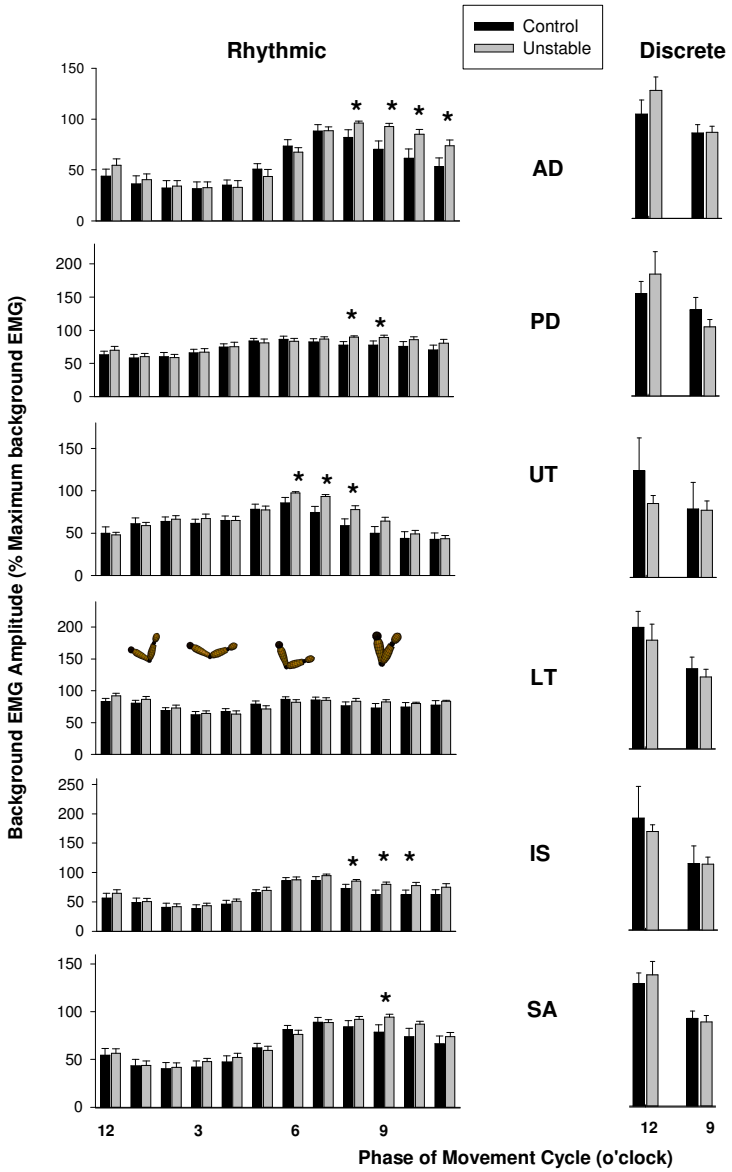

Figure 4.3 Background EMG for rhythmic and discrete task for all control and unstable shoulder participants. Background EMG for both shoulders in controls (n=11) and the unstable shoulders in orthopaedic participants (n=10) for each muscle for both tasks are expressed relative to maximums during the rhythmic cycling trial. Data from rhythmic trials are plotted in the left column while data from the discrete trials are plotted in the right column to the same scale. Phase in the movement cycle relative to the clock face are as indicated at the bottom of the figures. The arm position is also roughly indicated by the cartoon arms in the middle of the left panel. Data represent mean ± SEM for 11 and 10 participants for control and unstable shoulder data respectively. Abbreviations: anterior (AD) and posterior (PD) deltoid, upper (UT) and lower (LT) trapezius, infraspinatus (IS), serratus anterior (SA). Significant differences between control and unstable shoulders is indicated with an asterisk ($p<.05$). There is a main effect for phase modulation within both the control and unstable shoulder groups for all muscles ($p<.05$) (not indicated on the graph).

(NS, p=.95). However at the 12 o'clock position, a significant difference was found in both groups between the discrete and rhythmic tasks (controls, p=.0000001; unstable shoulder group, p=.005). During both the discrete and the rhythmic tasks the shoulder joint moved through ~ 15 to 100° of flexion.

4.4.2 Background EMG patterns

There were a number of significant differences between control and unstable shoulder data in background EMG amplitudes during rhythmic arm movement. As shown in the single participant IS EMG traces displayed in Figure 4.2A, unstable shoulder background EMG levels were higher than in controls during the phase of movement in which the arm is elevating (i.e. 8 through 11 o'clock). During discrete movement (see Figure 4.2B and C), however, IS EMG amplitudes traces from similar phases (i.e. 12 and 9 o'clock positions) were typically comparable between the control and the unstable shoulders. Similar trends are seen across all participants for normalized background EMG activity (see Figure 4.3). That is, during the elevation phase differences were observed between unstable shoulder and control participants during rhythmic (Fig 4.3, left columns) but not discrete (Fig 4.3, right columns) movement. For example in AD in the top panel of Figure 4.3, background EMG is significantly larger in unstable shoulders than controls at the 8, 9, 10 and 11 o'clock positions during the rhythmic task while it is similar at the 9 & 12 o'clock positions during the discrete task. Asterisks indicate these differences in AD at 8, 9, 10, 11 o'clock positions, in PD at 8 and 9 o'clock, in UT at 6, 7 and 8 o'clock, in IS at 8, 9, 10 and in SA at 9 o'clock. Across these muscles the average increase in background EMG was 24%.

	Rhythmic				Discrete			
Muscle	Early Latency		Middle Latency		Early Latency		Middle Latency	
	Control	Unstable	Control	Unstable	Control	Unstable	Control	Unstable
AD	71±6	71±8	110±11	104±18	74±6	72±7	111±13	114±13
PD	79±7	77±14	118±11	112±14	81±9	79±8	119±14	115±9
UT	71±9	67±8	110±13	100±15	76±11*	66±8*	114±12	112±10
LT	60±11	56±9	90±15	92±13	59±8	54±8	90±10	87±9
IS	57±3	59±4	83±4	85±6	54±6*	57±2*	85±14	80±3
SA	80±6	74±12	114±7	108±14	75±8	72±11	111±15	111±9

Table 4.2. Reflex Latencies during Rhythmic and Discrete Tasks
Values for latencies of early and middle latency phasic responses during rhythmic cycling. All values are means ± SD (control shoulders n= 22, unstable shoulders n= 10) and are latencies to the peak of the phasic response. Abbreviations: anterior (AD) and posterior (PD) deltoid, upper (UT) and lower (LT) trapezius, infraspinatus (IS), seratus anterior (SA). Significant difference between control and unstable shoulders within a given task and latency is indicated in bold and with an asterisk ($p<.05$).

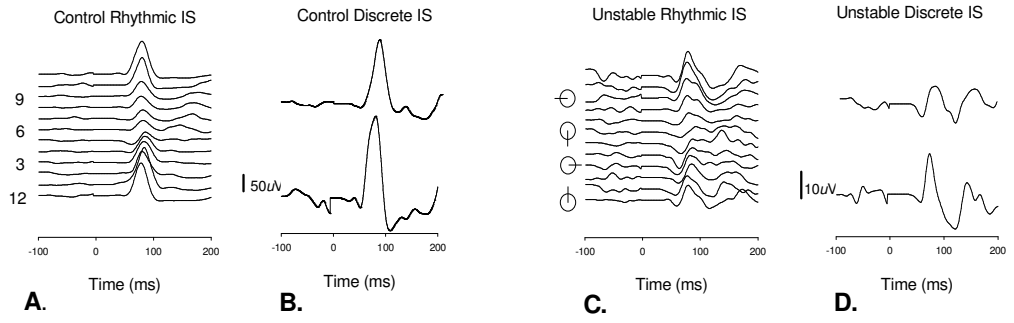

Figure 4.4 Cutaneous reflexes and background EMG traces for Infraspinatus (IS) for a single participant during rhythmic and discrete arm tasks. A. and C. Subtracted reflex EMG for all 12 phases of the movement cycle for control and unstable shoulders during the rhythmic task are plotted in the panels A and C respectively. The numbers to the left of the panel A and the cartoon clocks between panel B and C denote the phase of movement relative to the clock face. Background EMG whole cycle traces are plotted vertically to the right of the panel A and C and correspond to the reflex traces from the rhythmic movement task. B. and D. Subtracted reflex EMG traces for the 9 and 12 o'clock position in the movement cycle for the discrete task are shown in panels B and D, respectively. The stimulus artefact (beginning at time 0 to ~ 30 ms) has been removed from all the reflex traces and replaced with a flat line. Abbreviations are as in Figure 4.3.

Interestingly, rhythmic and phase-dependent background EMG patterns were observed for all muscles (i.e. a main effect for phase modulation of bEMG across movement cycle was found in both control and unstable shoulder groups ($p<.001$)).

4.4.3 Reflex latencies

Reflex latencies were similar between control and unstable shoulders. The average time to the peak early and middle responses during rhythmic cycling and during the discrete task for all muscles in the control and unstable shoulders are detailed in Table 4.2. Two significant differences between unstable shoulders and controls were found during discrete movements. In UT the peak early latency was significantly longer for controls over unstable shoulders while in IS the peak early latency was significantly longer for unstable shoulders over controls.

4.4.4 Reflex Amplitudes

There were differences in reflex amplitudes evoked in some of the unstable and control shoulders at early and middle latency for both rhythmic and discrete tasks. Reflex traces from the IS muscle for a single control and unstable shoulder participant during cycling and discrete movements are shown in Figure 4.4. The phase of movement is noted by the numbers found to the left of panel A and by the cartoon clock faces to the left of panel C. For the rhythmic tasks the reflex traces are from across the entire movement cycle, whereas for the discrete task the traces are from the 9 or 12 o'clock position. Identical scales have been used between rhythmic and discrete tasks within the stable and unstable shoulder traces. In Figures 4.4A and C, single participant reflex traces during rhythmic movement for both stable and unstable shoulders show phase-dependent modulation across the movement cycle. Normalized early latency reflexes

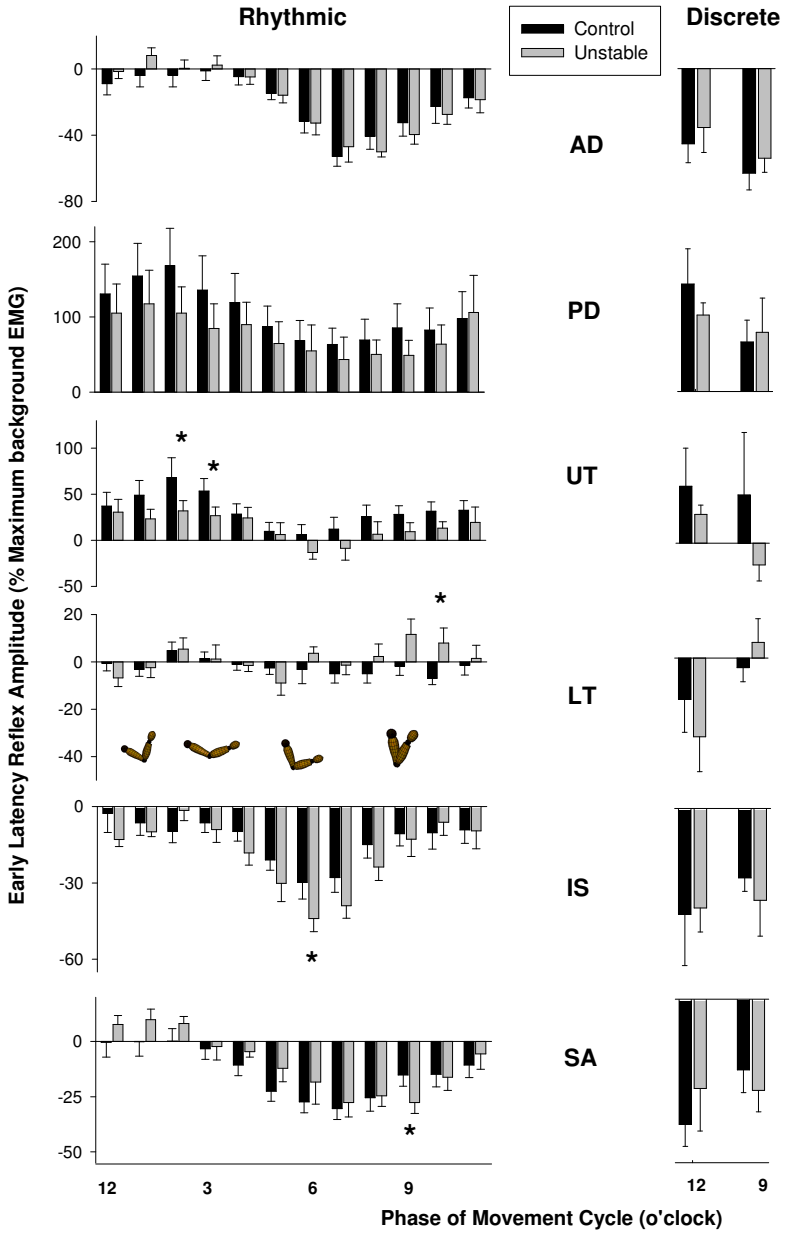

Figure 4.5 Early latency (45-80 ms) reflexes for rhythmic task across the movement cycle and for discrete task at the 9 and 12 o'clock positions in the movement cycle for all control and unstable shoulders participants. Data calculated from subtracted traces averaged across all participants and represent mean ± SEM for 11 and 10 participants for control and unstable shoulder data respectively. Reflex amplitudes have been normalized to the maximum background EMG during the rhythmic cycling trial. Data from rhythmic trials are plotted in the left column while data from the discrete trials are plotted in the right column to the same scale. Abbreviations are as in Figure 4.3. Significant differences between control and unstable shoulders are indicated with an asterisk ($p<.05$). There is a main effect for phase modulation within the control and unstable shoulder data for all muscles except LT ($p<.05$) (not indicated on the graph).

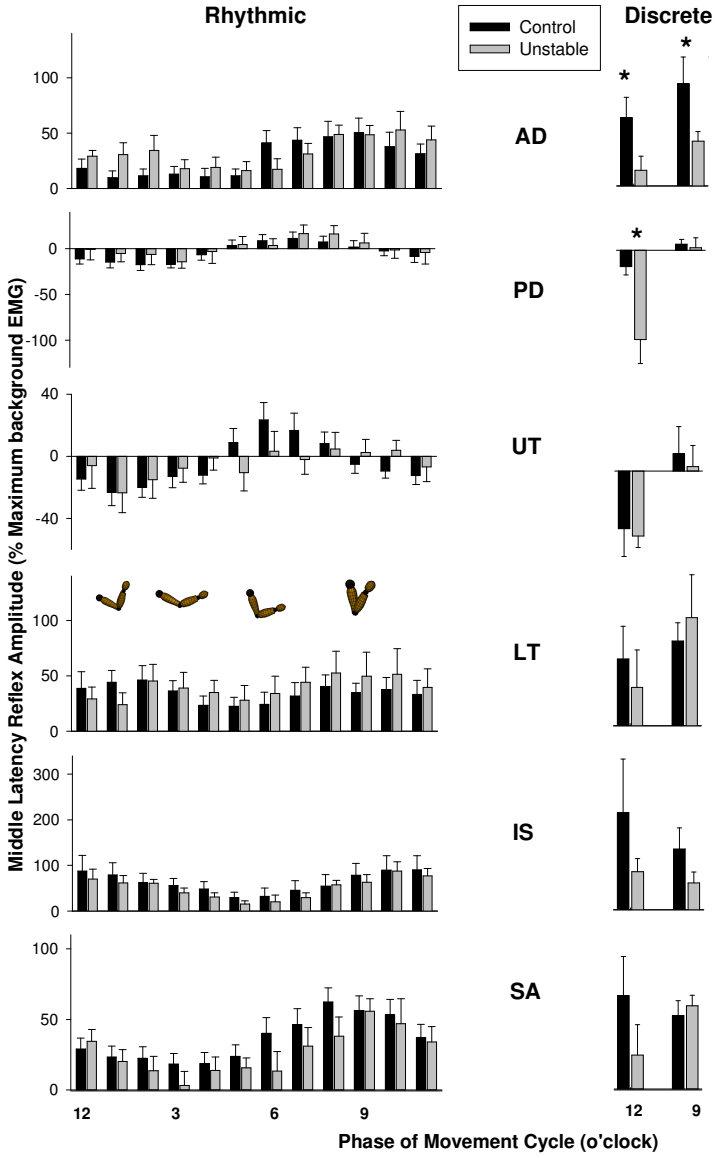

Figure 4.6 Middle latency (80-120 ms) reflexes for rhythmic task across the movement cycle and for discrete task at the 9 and 12 o'clock positions in the movement cycle for all control and unstable shoulders participants. Data calculated from subtracted traces averaged across all participants and represent mean ± SEM for 11 and 10 participants for control and unstable shoulder data respectively. Reflex amplitudes have been normalized to the maximum background EMG during the rhythmic cycling trial. Data from rhythmic trials are plotted in the left column while data from the discrete trials are plotted in the right column to the same scale. Abbreviations are as in Figure 4.3. Significant differences between control and unstable shoulders are indicated with an asterisk ($p<.05$). There is a main effect for phase modulation within stable shoulder for all muscles ($p<.05$) and for all muscles in the unstable shoulder group except UT and LT (not indicated on the graph).

across all participants have been plotted for both the rhythmic and the discrete tasks in Figure 4.5 and middle latency reflexes are plotted in Figure 4.6. At early latency, the pattern of reflex modulation is fairly consistent in AD and PD muscles between control and unstable shoulders across the movement cycle in the rhythmic task and at 9 and 12 o'clock in the discrete task. However, for UT, LT, IS, and SA there were movement phases where significant differences between control and unstable shoulders were found in the rhythmic task. The reflex amplitudes in unstable shoulders were sometimes increased and at other times reduced when compared to controls. For example, in IS during the rhythmic tasks (see Figure 4.5 left column, 5th panel), the early latency reflexes were similar between control and unstable shoulders across the movement cycle. However at the 6 o'clock position the reflex amplitude is significantly larger in the unstable shoulders compared to the controls in the rhythmic task as indicated by the asterisk. There were no differences between control and unstable shoulders at early latency during discrete movement. In contrast, at middle latency, differences between control and unstable shoulders were found only during discrete movement. For example, in AD muscle (see right column, 2nd panel in Figure 4.6) the amplitudes at both discrete positions is significantly smaller in the unstable shoulders. The other difference was found for PD at 12 o'clock where there is a larger suppression for unstable than control. Interestingly, the reflex amplitudes in unstable shoulders for AD and PD can both be considered as increased suppression. That is, for AD there is a suppression of an excitation yielding smaller amplitude. For PD, there is a larger amplitude suppressive response.

At each instance when significant differences in reflex amplitudes between control and unstable shoulders were noted, the background EMG levels were found to be comparable with the exception of the 9 o'clock position during the rhythmic task in SA. Having comparable

background EMG levels allows for corresponding comparison of reflex amplitudes between controls and unstable shoulders that cannot be explained by scaling with background EMG.

Phase modulation of early and middle latency responses across the movement cycle (left panels of Fig 4.5 & 4.6 respectively), was conducted separately in the unstable and control shoulder groups. In control shoulders significant phase-dependent modulation of reflex amplitude at early and middle latencies was seen in all muscles except LT (early latency). In unstable shoulders three muscles failed to show phase-dependent modulation: LT (early latency), UT and LT (both middle latency).

4.5 Discussion

The differences in background EMG and cutaneous reflex amplitude between control and unstable shoulders together support the premise that the neural control of upper limb muscles is altered after orthopaedic shoulder instability. During rhythmic cycling the background EMG was generally of larger amplitude during the elevation phase of arm cycling in participants with shoulder instabilities as compared to the control participants. Significant differences were also noted in cutaneous reflex amplitudes between the groups during both discrete and rhythmic tasks, with the reflexes being either increased or reduced in those with unstable shoulders as compared to controls. The frequency of differences in cutaneous reflexes makes these data less conclusive if taken in isolation. However when these data are considered in conjunction with the large number of differences in the background EMG, they together provide evidence that neural control has been altered, particularly during the rhythmic task. No differences in background EMG were found between the groups during the constrained discrete reaching task. One possible

explanation is that background EMG was affected differently in the rhythmic motor task compared to the discrete motor task due to deficits arising from the shoulder injury presenting differently in movements regulated by different neural mechanisms.

4.5.1 Control vs. Unstable Shoulders

Background EMG during Discrete and Rhythmic tasks

Differences in background EMG were seen between those with unstable shoulders and the control participants during rhythmic movement. These differences occurred in phases of the movement cycle where the arm was elevating (6 - 12 o'clock position) and the shoulder was moving through ~ 15 to 100° of flexion. In previous research when participants with unstable shoulders performed discrete forward arm elevation tasks with a load, altered EMG was seen in some muscles at similar ranges of shoulder flexion (Kronberg et al. 1991; McMahon et al. 1996). Therefore, even though the motor tasks were different, the EMG was altered at relatively similar points within the movement path, and at similar shoulder joint positions. Alterations in EMG in those with unstable shoulders have been ascribed to presumed altered afferent feedback and altered neural control (Lephart et al. 1997). Lephart and colleagues (1997) suggest that ligaments provide feedback that directly mediates reflex muscular stabilization of the joint. In unstable shoulders these structures may not be activated normally. Additionally they proposed that ligamentous trauma results in proprioceptive deficits. Both these factors could lead to altered neural control as evidenced by altered EMG (Lephart et al. 1997). This premise has been corroborated by findings of decreased ability to detect passive movement and to passively reposition the arm in those with unstable shoulders (Smith and Brunolli. 1989; Lephart et al. 1994; Forwell and Carnahan 1996). The fact that proprioception is often restored after

anatomical surgical retightening of the loose soft tissues (Lephart et al. 1994 ; Aydin et al. 2001) has been offered as further support that compromised afferent feedback may play a role in altering EMG in those with unstable shoulders. Additional support that altered afferent feedback is related to lax soft tissues can be drawn from the study of Blasier et al. (1994). Those who had no known shoulder pathology, but had a clinically determined generalized joint laxity, were significantly less sensitive in proprioceptive tests than those without generalized laxity (Blasier et al. 1994). In the current study, alterations in EMG in those with unstable shoulders compared to controls are also found during rhythmic arm movement and are reported here for the first time. Though the evidence is not direct, one could interpret our results as adding support to the claims made in previous work that alterations in EMG in those with unstable shoulders could result from altered afferent feedback associated with lax (or injured) soft tissues or from altered central motor output (Lephart et al. 1997). Though our results suggest the neural control is altered in those with unstable shoulders, they do not explicitly implicate a specific locus within the sensorimotor neural pathway.

In contrast to previous work, the present study showed no differences in background EMG between control and unstable shoulders during the discrete task. Previous research demonstrated altered EMG amplitude in shoulder muscles during discrete tasks in those with glenohumeral instability (Glousman et al. 1988; Kronberg et al. 1991; McMahon et al. 1996; Morris et al. 2004). Differences from previous research may be due to distinct differences in methodologies related to the load provided to oppose motion as well as the nature of the movement trajectory (e.g. either constrained or unconstrained). In previous studies the movements were uniplanar and against a load (Kronberg et al. 1991; McMahon et al. 1996; Morris et al. 2004). In contrast, in the current study the discrete movement was both minimally

loaded and along a constrained path requiring multiplanar shoulder movements combining primarily shoulder flexion along with abduction and internal rotation. McMahon and colleagues (1996) had participants perform shoulder flexion, abduction and scaption (scapular plane abduction) in separate trials against a resistance (1.5kg) with the elbow extended throughout the movement. Significantly less EMG activity was noted in the serratus anterior muscle in flexion, abduction and scaption in those with unstable shoulders. No differences in EMG were seen in the UT, LT, and IS muscles. Similarly, in a study by Kronberg et al. (1991), participants performed shoulder flexion and abduction in separate trials against a 20 N resistance with the elbow extended throughout. As well participants performed shoulder internal rotation with the shoulder abducted to 45 degrees against resistance. The EMG was significantly lower in AD for both abduction and flexion. No differences were seen in PD or IS in flexion or abduction, and no differences were seen in AD, IS and PD in internal rotation. The range of shoulder flexion (~ 15 to 100°) was similar between current and previous studies. The range of shoulder abduction and internal rotation can not be directly compared as this was not measured in the current study. Regardless, the fact that in the current study the movement involved simultaneous flexion, abduction and internal rotation limits direct comparisons with previous studies. Additionally, because the motor tasks in the previous studies were performed against a resistance with the elbow extended (McMahon et al. 1996; Kronberg et al. 1991; Morris et al. 2004) it is likely that the overall strain to the shoulder joint was increased compared to the current study. Similarly, in the pitching study, it is likely that the shoulder joint soft tissues were more stressed when compared to the current research (Glousman et al. 1988) due to the greater velocity of movement and a more provocative shoulder position. In movement conditions when these soft tissues are more greatly tensioned or stressed, perhaps the biomechanical and structural changes that occur

with shoulder instability (i.e. ligament and capsular laxity as well as potential tearing) become more apparent. In the previous studies EMG activation was significantly altered in many other muscles as well, however only muscles in common between the current and previous studies were highlighted here.

The nature of the movement trajectory (that is either is constrained or unconstrained) has been suggested to dictate the control strategies used by the central nervous system (Ohta et al. 2004). For unconstrained reaching movements, the central nervous system may use kinematic coordinates (i.e. angular position) while during constrained movements, when the degrees of freedom are reduced, dynamic coordinates (i.e. joint torque and muscle force) may become more relevant (Ohta et al. 2004).

Significant differences in background EMG between unstable shoulders and controls were observed in the rhythmic task. However, no differences were found during the discrete task despite the two tasks being matched for movement trajectory and frequency. This raises an interesting question: Why do the differences in background EMG arise during the rhythmic task and not during the discrete task? It has been suggested that altered afferent feedback (likely arising due to abnormal tensioning of lax or damaged soft tissues) plays a role in the deficits seen in proprioception and altered EMG activation patterns in those with unstable shoulders (Lephart et al. 1997; Myers and Lephart 2002). Afferent feedback influences motor output to varying degrees in different categories of motor tasks (Smits-Engelsman et al. 2006). This is in keeping with an emerging theme in motor control research, which posits that neural regulation differs for rhythmic, static and discrete motor tasks (Adamovich et al. 1994; Brooke et al. 1997; Wei et al. 2003; Schaal et al. 2004; Zehr et al. 2004; Smits-Engelsman et al. 2006). Afferent input plays an important role in the regulation of rhythmic movement (e.g. locomotion) by influencing central

pattern generating circuits (Dietz 1992; Rossignol 1996). The neural control of rhythmic arm cycling is similar to that of the legs during walking (Zehr et al. 2004). The performance of rhythmic movement appears robust to changes in afferent input. For example, in rhythmic arm movements speed can increase twice as much as in discrete movements before the same decrease in accuracy is seen. It has been proposed that this property of rhythmic movement compared to discrete might be related to the use of spinal pattern generation (Smits-Engelsman et al. 2002). This difference between rhythmic and discrete movements is also evident with the addition of a load (Smits-Engelsman et al. 2006). Adjustments in EMG activity in response to changes in afferent input are made in order to maintain a set rhythm (Smits-Engelsman et al. 2002) and are similarly seen in a locomotor paradigm (Donker et al. 2002). Other studies have shown that during gait, humans can maintain step cycle characteristics despite changes in increases or decreases to body weight loading by adjusting EMG activation (Bastiaanse et al. 2000; Danion et al. 1997; Danion et al. 1995). Due to differences in neural control, rhythmic tasks, more so than static tasks, are influenced by afferent feedback such as observed during locomotion (Rossignol 1996; Bastiaanse et al. 2000). The current data may suggest that disparity in background EMG between unstable shoulders and controls is reflected differently in the two motor tasks as a result of the differing neural regulation of the tasks. In the current study, perhaps afferent feedback from the shoulder was altered enough to alter background EMG between control and unstable shoulders in rhythmic tasks but was at a level that was subthreshold to influence motor output in discrete tasks.

Alternatively, the greater intersubject variation seen in the discrete data may mask the significant differences between the unstable shoulder and control group. Interestingly, differences in variance between the tasks may be attributable to differing neural controls

mechanisms in that rhythmic (so-called "stereotyped" movements) are inherently less variable (Smits-Engelsman et al. 2002; Smits-Engelsman et al. 2006). Regardless the fact remains that there were no significant differences found during the discrete task.

Modulation of Cutaneous Reflexes during Discrete and Rhythmic tasks

During both discrete and rhythmic tasks, the cutaneous reflexes evoked by stimulation to the SR nerve in the hand significantly differed in sign or amplitude between the control and the unstable shoulders. Additionally, differences between controls and unstable shoulders were seen in the extent of phase-dependent modulation of reflexes for some muscles. Specifically, middle latency reflexes in UT and LT were significantly phase-modulated in control shoulders but not in unstable shoulders. Also in UT and IS muscles a difference was noted in reflex latencies between controls and unstable shoulders within the discrete task. Taken as a whole, these differences in reflex characteristics may indicate that neural control in unstable shoulders is compromised. A coordinated patterned motor response was expected in response to the perturbation provided by the electrical stimulation. The current results suggest that when presented with the "mock" perturbation, the motor response in those with unstable shoulders is altered when compared to control participants. However the reflex data, taken in isolation, is not conclusive, given the limited frequency of the differences. The differences in reflex characteristics corroborate the differences in background EMG data, and when considered together, they support the premise that neural control has been altered. Based on human conduction velocities (see review in Brooke and Zehr, 2006) and given that middle latency cutaneous reflexes in leg muscle TA has indeed previously been shown to be influenced by transcortical input (as induced by TMS; see Christensen et al. 1999), these reflexes could be influenced by supraspinal input and potentially

involve a transcortical loop. Therefore the alterations in reflexes we found only indicate the neural control has been altered, but do not explicitly implicate a specific locus (i.e. peripheral, spinal, or supraspinal).

Myers et al. (2004) showed significant differences in the EMG responses between controls and unstable shoulders to perturbation into external humeral rotation. A contradictory study by Wallace et al. (1997) revealed no significant differences in stretch reflex latency in response to a quick shoulder external rotation between unstable and contralateral shoulders. However, interpretation that this indicates intact afferent feedback and neural control in unstable shoulders should be guarded because contralateral limbs may not offer a valid control (Smith and Brunolli 1989; Jerosch et al. 1997). Also the study by Wallace and colleagues (1997) only explored reflex latency and not possible changes in the amplitude of the response.

Since the differences in reflex amplitudes between control and unstable shoulders were not isolated to one type of movement it is suggested that changes occurred in the neural control mechanisms that regulate both these types of motor tasks. However, it is unclear if the same deficit in neural control affected the reflexes in both rhythmic and discrete movements, or if two distinct changes in neural control occurred simultaneously at different loci, thus independently influencing the reflexes in these two tasks. Further research is required to clarify this question.

4.5.2 Clinical significance

Strengthening and endurance conditioning of the limb muscles is often necessary after musculoskeletal injury. Rhythmic arm motor tasks (e.g. arm cycling) could be usefully applied in this domain in those with unstable shoulders, as these involve coordinated and consistent muscle

activity patterns across multiple muscles of both arms (Zehr and Hundza 2005; Hundza and Zehr 2006). Rhythmic arm cycling provides an exercise paradigm where the shoulder joint moves through a non-provocative range of motion that should not increase instability. Additionally in attempts to improve the dynamic stabilization within unstable shoulders, current rehabilitation efforts generally strive to retrain stereotyped muscle activation patterns. Therefore it is of important clinical relevance to know if the EMG activation patterns are altered in those with unstable shoulders during rhythmic arm cycling to determine the efficacy of this treatment. Further studies are required to determine if an arm cycling training program would normalize the muscle activation patterns in those with unstable shoulders. In the event that normalization of EMG activation occurred with rhythmic arm cycling training, further research would be required to determine the impact on functional pain free use of the arm. Also, clinicians should be aware that even if muscle activation presents normally in an unstable shoulder in a discrete movement involving no load, EMG may be altered in a similar unloaded rhythmic task. Differing neural regulation between the motor tasks may explain why the differences between unstable shoulders and controls are reflected differently in each motor paradigm and therefore may require separate neurophysiological and theoretical treatment.

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5. Suppression of soleus H-reflex amplitude is graded with frequency of rhythmic arm cycling[4]

5.1 Abstract

Interlimb communication is essential in producing coordinated rhythmic movements like locomotion. In many animal species, activity in fore limbs has been shown to affect hind limb motor activity and visa versa. Similarly in humans, rhythmic arm cycling significantly suppresses the soleus H-reflex in stationary legs. Frequency of arm movement has been shown to influence this interlimb communication however the specific nature of the relationship between frequency of arm cycling and H-reflex modulation in the legs has not been explored. We speculated that the effect of arm cycling on reflexes in leg muscles is related to the neural control of arm movement therefore we hypothesized that a graded increase in arm cycling frequency would produce a graded suppression of the soleus H-reflex amplitude. We also hypothesized that a threshold frequency of arm cycling would be identified at which the H-reflex amplitude significantly differed from static control trials. Soleus H-reflexes were evoked with tibial nerve stimulation during control and rhythmic arm cycling trials (.03 to 2.0 Hz). The results show a significant inverse linear relation between arm cycling frequency and soleus H-reflex amplitude ($p < .05$). Soleus H-reflex amplitude significantly differed from control at an average threshold cycling frequency of .8 Hz. The results demonstrate that increased frequency of upper limb movement increases the intensity of interlimb influences on the activity in stationary legs. Further a minimum threshold frequency of arm cycling is required to produce a significant effect. This suggests that achieving a threshold frequency of rhythmic arm movement may be important to incorporate in rehabilitation strategies to engage the appropriate interlimb neural pathways.

[4] Hundza SR, Zehr EP Suppression of soleus H-reflex amplitude is graded with frequency of rhythmic arm cycling. Exp Brain Res (submitted) (90% contribution to project)

5.2 Introduction

The role of interlimb neural communication during rhythmic movements like walking or cycling has been of considerable focus in recent research in humans. In other animal species, experiments have confirmed an interplay between the cervical and lumbar pattern generators in coordinating rhythmic movement of fore and hind limbs, with the activity in one generator influencing the activity in the other (Ballion et al. 2001; Juvin et al. 2005; Miller et al.1973; Schomberg et al. 1978; Zaporozhets et al. 2006). Recent research suggests similar interlimb neural communication exists in humans during bipedal locomotion (Dietz et al. 2001; Dietz 2002; Zehr and Duysens 2004; Zehr and Haridas 2003). During human locomotion mechanical or electrical perturbations to the lower limb evoked responses in arm muscles (Delwaide and Crenna 1984; Dietz et al. 2001; Zehr and Haridas 2003). Similarly, stimulation to the superficial radial nerve in the arm evoked responses in leg muscles during locomotion (Haridas and Zehr 2003). Furthermore, restricting arm swing significantly altered leg trajectory during walking (Marks 1997) and altered frequency and phase relations between the arms and legs (Ford et al 2007). Thus, normal coordination between the legs during walking is affected by activity in the arms. Rhythmic arm cycling movement affects electromyographic (EMG) activation (Huang and Ferris 2004) and reflex activity (Frigon et al. 2004; Balter and Zehr 2007) in leg muscles. Likewise, rhythmic leg movement affects reflex activity in arm muscles (Zehr et al. 2007a).

Varying the frequency of the rhythmic movement has been shown to influence the communication between upper and lower limbs. Donker and colleagues found that an increased velocity of walking resulted in enhanced interlimb coordination and a change in the ratio of arm swing to leg swing (Donker et al. 2001, 2005). A higher frequency of upper limb movement facilitated an increase in neuromuscular recruitment of lower limb muscles during passive

stepping tasks (Kao and Ferris 2005). A relationship between the frequency of limb movement and supraspinal motor output has also been shown. Graded increases in the frequency of locomotor rhythm as well as gait transitions (e.g. walking to trotting to galloping) can be produced with graded electrical stimulation of the mesencephalic locomotor region (MLR) in the brainstem (Cabelguen et al. 2003, Grillner et al. 1997, Shik et al. 1996).

We previously detected the influence of rhythmic arm movement on the soleus Hoffman (H-) reflex in stationary legs (Frigon et al. 2004; Loadman and Zehr 2007). The soleus H-reflex amplitude was suppressed with rhythmic arm cycling at 1 Hz compared to control size when the arms were stationary (Frigon et al. 2004). At double the frequency (2 Hz) of arm cycling, the soleus H-reflex was attenuated significantly more than at 1 Hz (Loadman and Zehr 2007). It was also shown that arm cycling parameters like arm crank length, which would influence afferent feedback, did not affect soleus H-reflex amplitude (Loadman and Zehr 2007). In addition different loci of rhythmic arm movement (i.e. bilateral, ipsilateral or contralateral arm cycling) suppressed H-reflex amplitude equivalently (Loadman and Zehr 2007). Of the arm cycling parameters previously explored, frequency of arm cycling played the most influential role in suppressing the solues H-reflex amplitude. To further clarify the source of the signal responsible for the suppression of the soleus H-reflex amplitude during rhythmic arm cycling we sought to clarify the specific nature of the relationship between arm cycling frequency and H-reflex modulation.

Because the suppression of excitability in the soleus H-reflex pathway appears to be influenced by rate of rhythm generation and unrelated to other specific arm movement parameters, our working hypothesis is that central motor commands (e.g. central pattern generators (CPG)) contributing to the rhythmic arm cycling were responsible for the H-reflex

suppression (Frigon et al. 2004; Zehr et al. 2004; Zehr and Duysens 2004; Loadman and Zehr 2007). We reasoned that if H-reflex suppression was related to central motor commands for rate of rhythm generation then a graded increase in arm cycling frequency would produce a graded increase in the suppression of the soleus H-reflex amplitude similar to the linear relationship seen between MLR electrical stimulation intensity and locomotor frequency in the cat (Calbugeun et al. 2003). Suppression of the H-reflex in the hindlimb was seen during fictive locomotion evoked by electrical stimulation to the MLR in decerebrate cats (Gosgnach et al. 2000). In addition we hypothesized that a threshold frequency of arm cycling would be required to significantly suppress the soleus H-reflex. Such a threshold frequency would suggest the rate of arm cycling necessary to significantly influence lower limb neural circuitry. This may have therapeutic implications for rehabilitation strategies aimed at using arm activity to influence or engage the neural circuitry of the lower limbs.

5.3 Methods

5.3.1 Participants

Eleven healthy subjects between 24 and 43 years of age (8 female and 3 male) and with no known history of neurological or metabolic disorders participated with informed, written consent. Experimental procedures were approved by the Human Ethics Board at the University of Victoria and were conducted in accordance with the Declaration of Helsinki.

5.3.2 Protocol

The experimental methodology is similar to that described previously (Frigon et al. 2004; Loadman and Zehr 2007) and thus only differences in methodology are highlighted here. Participants sat in a custom-fitted chair which minimized unwanted movement of trunk and legs

(Frigon et al. 2004; Loadman and Zehr 2007). Using a custom-made hydraulic-arm ergometer (Zehr and Hundza 2005), participants performed static control trials and rhythmic bilateral arm cycling trials which were in a forward direction at different frequencies. The cycle positions were named consistent with the clock face viewed from the right-hand side of the ergometer (see Frigon et al. 2004). During each trial the participants maintained a consistent low-level tonic contraction of the left soleus muscle [average of 11.0 % ± 1.65 SEM of maximum voluntary contraction (MVC)] using on-line visual feedback of the rectified and filtered EMG signal produced by a custom-written (Dr. T. Carroll, University of Queensland, Australia) LabView (National Instruments) program. This program also provided on-line rectified and filtered EMG feedback for the tibialis anterior muscle and participants were instructed to keep this muscle and other leg muscles quiescent. For the cycling trials, participants maintained desired cycling frequencies using visual feedback from an oscilloscope.

5.3.2.1 Static control trials

Static control trials were performed with both arms on the ergometer crank handles with the left arm at the 3 o'clock position. This meant that the left elbow was in its most extended position. Control trials were obtained at 5 different times during the experiment: one prior to any cycling (pre), one after all the cycling trials were completed (post), with the other three spaced equally through the movement trials (mid).

5.3.2.2 Cycling Trials

In order to detect the point at which the H-reflex amplitude became significantly different from that of the control trials, discrete increments in cycling frequency were used. The frequencies of the 19 different cycling trials were .03, .05, .1, .2, .3, .4, .5, .6, .7, .8, .9, 1.0, 1.1, 1.2, 1.3, 14, 1.5, 1.75, and 2.0 Hz. Five participants performed the cycling trials in order of ascending frequency and the other six participants performed them in random order.

The posterior tibial nerve was stimulated over the left popliteal fossa with bipolar surface electrodes delivering single 1 ms square-wave pulses using a Grass S88 (Grass Instruments, AstroMed) stimulator connected in series with a SIU5 isolator and CCU1 constant current unit. Nerve stimulation was delivered pseudorandomly between 3 and 5 seconds during static control trials. During cycling trials, nerve stimulation was delivered once every 1 to 6 cycles depending on the cycling frequency with a minimum time of 3 seconds between stimulations. The amplitude of the direct motor response (M-wave) was monitored and maintained at a consistent level across experimental trials. Left tibial nerve stimulation was delivered when the left arm was at the extended position (i.e. 3 o'clock position when the ergometer is viewed from the right side).

At the beginning and end of each experiment, H-reflex vs. current (H-I) recruitment curves were constructed while the participants' arms were stationary in the control trial position. This data was used to: 1) determine a stable M-wave amplitude which corresponded to an H-reflex amplitude on the ascending limb (~ 70% of H-max); 2) provide a maximum M-wave (M-

max) amplitude used for data normalization; and 3) evaluate the consistency of M-max response and H-M ratio over the course of the experiment.

5.3.3 EMG

Using Ag-AgCl electrodes bipolar surface EMG recordings were made bilaterally from the posterior deltoid (PD) and biceps brachii (BB) as well as unilaterally from the left soleus (SOL), tibialis anterior (TA), vastus lateralis (VL), biceps femoris (BF) and triceps brachii (TB). The left medial gastrocnemius (MG) was recorded in eight of the participants. Ground electrodes were placed over nearby electrically inert tissue.

5.3.4 Kinematics

Kinematic recordings were made continuously from the left elbow joint of some participants (n=9) using lightweight electro-goniometers (Biometrics Ltd. Gwenfellinfach, Gwent, UK).

5.3.5 Data acquisition and analysis

Data were sampled at 5000 Hz with a 12 bit A/D converter controlled by a computer running custom-written (Dr. T. Carroll, University of New South Wales, Australia) LabView (National Instruments) virtual instruments. For all trials, 10 sweeps were collected (20 ms pre-stimulus and 50 – 60 ms post-stimulus). EMG signals were preamplified, band pass filtered at 100-300 Hz and full wave rectified except for soleus, which was preamplified and band pass filtered at 100-1000Hz and remained unrectified. Peak-to-peak soleus H-reflex amplitudes were determined off-line and the sweeps were then averaged and normalized to the M-max for each participant. The

rectified pre-stimulus EMG (20 ms) was used as a measure of muscle activity (background EMG (bEMG)) at the time of nerve stimulation for all legs muscles.

5.3.6 Statistics

Using STATISTICA software (StatSoft, Inc.), repeated measures analysis of variance was conducted separately on the soleus H-reflex and M-wave amplitudes, the pre-stimulus EMG levels for each muscle and the elbow range of motion to identify significant effects of the frequency of arm cycling. Tukey's HSD test was used to post hoc significant main effects and interactions to determine which cycling trials differed from control. Using all data from each subject, Pearson's correlation coefficients (r) were calculated and tested for significance between the H-reflex amplitudes and cycling frequency as well as between the H-reflex amplitudes and bEMG. For each correlation, pairs from all 19 cycling frequencies were used for all subjects. To correct for the effect of repeated samples from each subject, 11 degrees of freedom were used. Descriptive statistics included means ± standard error of the mean (SEM). An α-level of 0.05 was used for statistical significance ($p \leq 0.05$).

5.4 Results

5.4.1 Elbow Kinematics

Figure 5.1 displays elbow kinematics (traces start at the 12 o'clock position). It can be seen that at the select frequencies different times were required to complete one cycle path. These ranged from .5 seconds at 2 Hz to 40 seconds at .03 Hz. Comparisons between the cycling frequencies showed no significant differences in elbow joint excursion across the cycle path.

5.4.2 Soleus H-Reflex amplitudes during control and movement conditions

The soleus H-reflex, M-wave and bEMG amplitudes from the 5 control trials were not statistically different across the experiment. All control trials for each participant were averaged and used as the control value. Further, data from the sequential frequency and the random frequency protocols were not statistically different; therefore, these results were combined for further analysis. Additionally, there were no significant differences in M-max values over the course of the experiment.

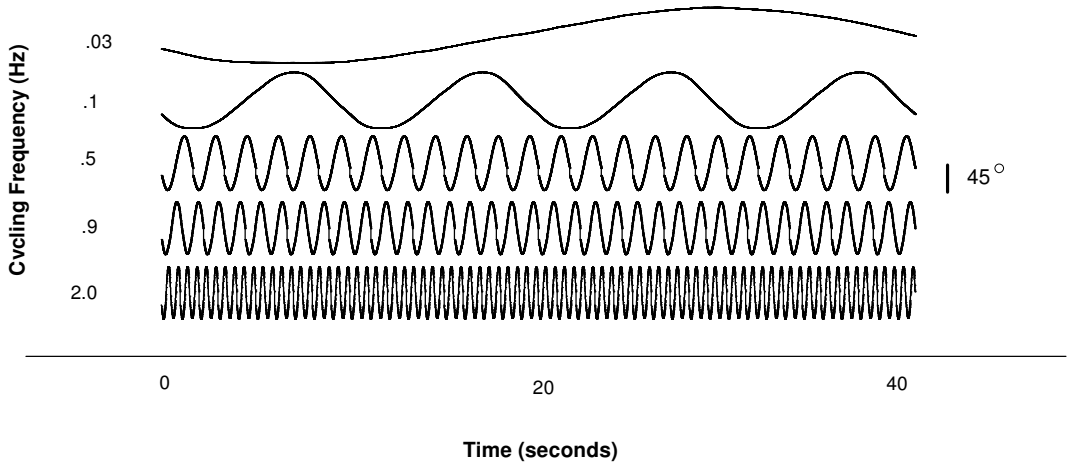

Figure 5.1. Elbow joint kinematics for a single participant for .03, .1, .5, .9, 2.0 Hz. cycling trials. Note that one cycle for .03, .1, .5, .9, 2.0 Hz. cycling trials takes 40, 10, 2, 1.1, .5 seconds/cycle respectively such that in the 40 second period displayed the 2.0 Hz trial shows 80 cycles in 40 seconds.

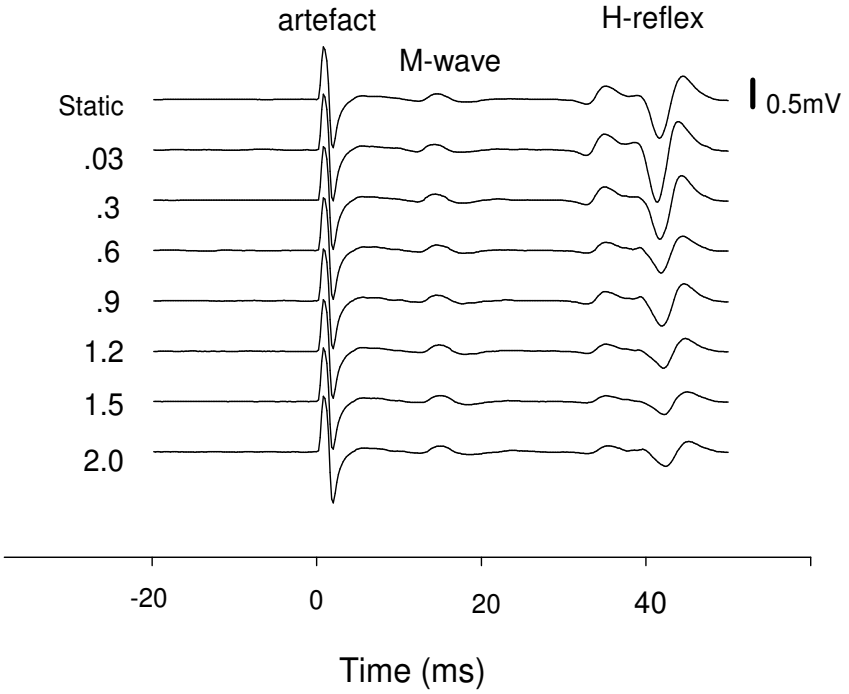

Figure 5.2. Suppression of Soleus H-Reflex amplitude across selected arm cycling frequencies in a single participant. Reflex traces represent averages of 10 sweeps recorded during the control and .03, .3, .6, .9, .1.2, 1.5, 2.0 Hz arm cycling conditions. Stimulus artefact, M-wave and H-reflex are indicated.

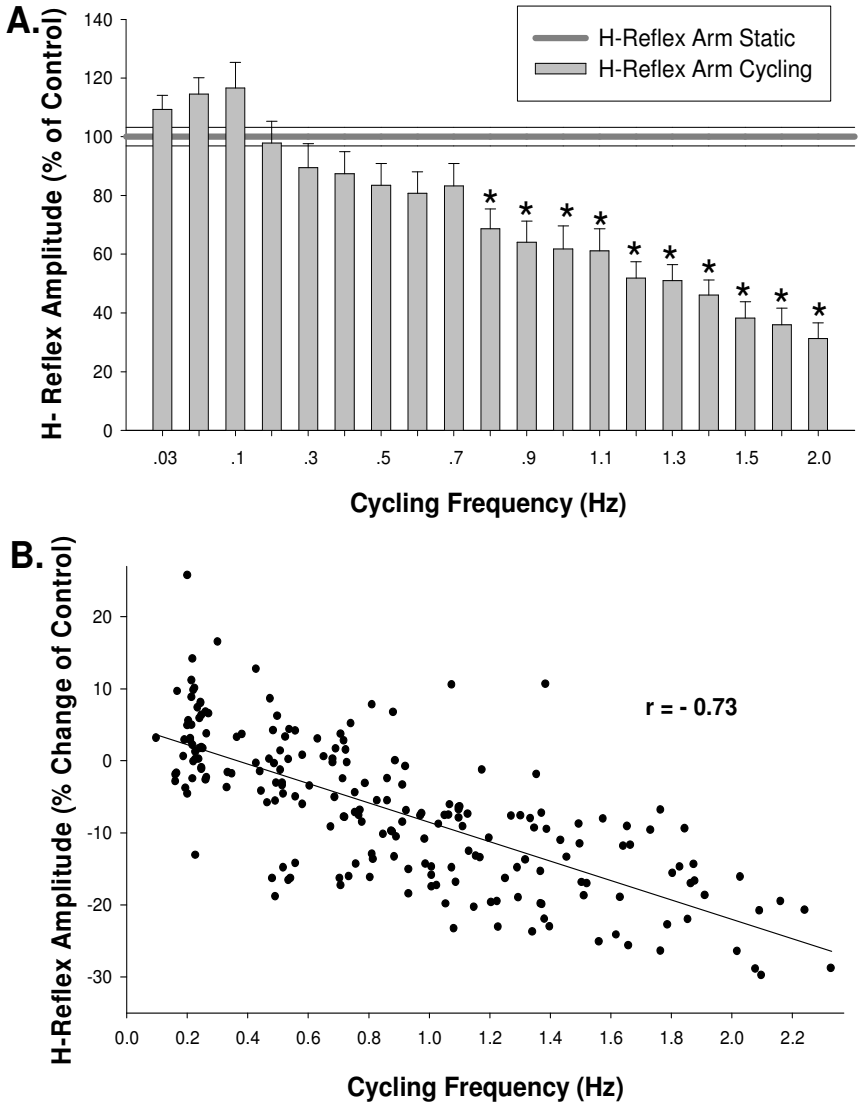

Figure 5.3. Soleus H-Reflex peak-to-peak amplitude across all arm cycling frequencies for all participants.
A. Reflex amplitudes are expressed as a percentage of the static control amplitude (represented by the horizontal grey line). Values are means ± SEM across all participants. For statistical analysis data were normalized to M-max. Statistically significant differences ($p < 0.05$) found between the control and cycling frequencies ≥ 0.8 Hz are indicated by asterisk. Note: frequencies are plotted as categorical variables and therefore frequency values are not linearly spaced.
B. Scatterplots of arm cycling frequency versus cycling H-Reflex amplitudes. Control H-reflex amplitude has been subtracted from each cycling H-reflex amplitude. The regression line with a significant correlation between arm cycling frequency and H-reflex amplitude is plotted (critical r = .62 with df of 11)

The effect of different frequencies of arm cycling on the soleus H-reflex amplitude is shown for a single participant in Figure 5.2. It can be seen that as the cycling frequency progressed from static control through .03, .3, .6, .9, 1.2, 1.5 and 2.0 Hz, the M-wave amplitude was consistent while the H-reflex amplitude decreased. H-reflex amplitudes, expressed as percentages of control values, averaged across all participants are displayed in Figure 5.3A. The average of the control H-reflex amplitudes is seen as the grey horizontal line at 100%. Group data (Figure 5.3A) show a similar graded suppression of the H-reflex with an increase in cycling frequency as seen in the single participant data (see Figure 5.2). Compared to control, H-reflex amplitudes were significantly smaller for all cycling frequencies of .8 Hz or greater (indicated by an asterisk in Figure 5.3A) identifying .8 Hz as the threshold cycling frequency required for significant soleus H-reflex amplitude suppression.

The H-reflex amplitude was reduced from 100% during control to 31 % ± 5.3 [standard error of the mean (SEM)] during cycling at 2.0Hz. The H-reflex amplitude was 30% M-max ± 3.1 SEM during control and reduced to 10% M-max ± 2.2 SEM during cycling at 2.0Hz. Interestingly at the slowest cycling frequencies (.03, .05, .1) the H-reflex amplitudes were larger than control although they were not significantly larger. The scatter plot and correlation analysis displayed in Figure 5.3B show a significant inverse linear relation between arm cycling frequency and soleus H-reflex amplitude ($r = -.73$). M-wave amplitudes were not significantly different across the trials. The stimulation intensity for all trials was sufficient to evoke a stable M- wave for each participant (average of 4% of M-max ± 0.7 SEM). Stimulation evoked H-reflex amplitudes targeted at 70% of maximum H-reflex (H-max) (average of 66% H-max ± 3.6 SEM) on the ascending limb of the M-wave–H-reflex (M–H) recruitment curve during the control condition.

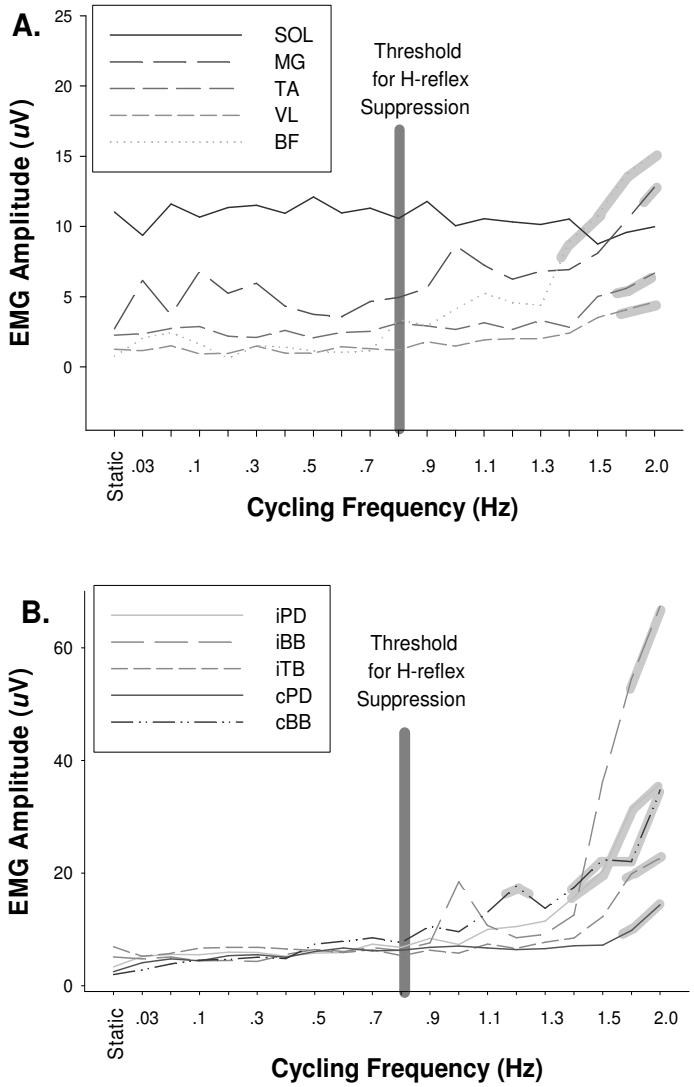

Figure 5.4. Background EMG at the 3 o'clock position during both control and 19 arm cycling frequencies across all participants.

A. Leg Muscles Values are means ± SEM for Sol, MG, TA, VL and BF EMG. Significant differences ($p < 0.05$) in background EMG between the static control and cycling frequencies are indicated by grey highlighting of the plot. Note that EMG activity remains level until frequencies ≥ 1.3 Hz. The vertical grey line indicates the threshold cycling frequency (.8Hz) for H-reflex suppression.

B. Arm Muscles Values are means ± SEM for iPD, iBB, iTB, cPD, and cBB. Significant differences ($p < 0.05$) in background EMG between the static control and cycling frequencies are indicated by grey highlighting of the plot. Note that EMG activity remains level until frequencies ≥ 1.2 Hz. The vertical grey line indicates the threshold cycling frequency (.8Hz) for H-reflex suppression.

Abbreviations: soleus (Sol), medial gastrocnemius (MG), tibialis anterior (TA), vastus lateralis (VL) and biceps femoris (BF), ipsilateral (i), contralateral (c), posterior deltoid (PD), biceps brachii (BB) and triceps brachii (TB).

Note: frequencies are plotted as categorical variables and therefore frequency values are not linearly spaced.

5.4.3 Background EMG of leg and arm muscles

Background EMG levels for SOL, TA, MG, VL and BF muscles, averaged across all participants, are displayed in Figure 5.4A, top panel. SOL bEMG was not significantly different between any of the cycling or control conditions. Background EMG activities in TA, MG, VL and BF muscles were level until the higher frequencies (i.e. 1.4 Hz or greater). Post hoc analyses showed a significant difference from control for: 1.75 and 2.0 Hz cycling conditions for TA and VL; 2.0 Hz for MG; and 1.4 to 2.0 Hz in BF (significant differences are indicated by grey highlighting of the plot in Figure 5.4A, top panel). No significant linear correlations were found between soleus H-reflex amplitude and the bEMG levels for each leg muscle.

Background EMG levels recorded from bilateral PD and BB and ipsilateral (i) TB muscles were averaged across participants and were found to be stable across all the cycling frequency conditions until the higher frequencies (1.2 and greater) (see Figure 5.4B, lower panel). Significant differences from control were found for: 1.4 Hz and greater for iPD; 1.75 and 2.0 Hz for iBB, iTB and cPD; and 1.2 and 1.4 Hz and greater in cBB (significant differences are indicated by grey highlighting of the plot in Figure 5.4B, lower panel). No significant linear correlations were found between the soleus H-reflex amplitude and the bEMG levels for each arm muscle.

The vertical grey line found in both the top and bottom panels of Figure 5.4 indicates the cycling frequency (.8Hz) where the soleus H-reflex amplitude is significantly different from control. At .8 Hz, the bEMGs for the heteronymous leg and arm muscles are not significantly different from control. In fact, the bEMG for the heteronymous leg and arm muscles are not significantly different from the control for several frequencies above .8 Hz whereas the H-reflex amplitudes remained significantly different from control from .8 Hz to 2.0Hz.

5.5 Discussion

The results of this study show that suppression of the soleus H-reflex amplitude is graded with the frequency of arm cycling. A threshold arm cycling frequency of .8 Hz is required to significantly suppress the soleus H-reflex amplitude compared to control. These data, taken in conjunction with previous results, suggest that spinal or supraspinal central motor commands related to the frequency of arm cycling influence the neural activity in stationary legs and that a minimum threshold frequency of .8Hz is required for the interlimb neural activity to have a significant effect.

5.5.1 Methodological considerations

Several methodological factors have been strictly controlled to ensure that our findings could be attributable to arm cycling frequency. M-wave amplitudes were not significantly different across the trials, thus indicating test reflex stimulus constancy to the Ia afferents across the experimental conditions (Zehr 2002, Brooke et al. 1997). Additionally, consistent H-reflex amplitudes from the five control trials (pre, post and three mid) showed stability of the control H-reflex amplitude throughout each experiment. Lastly, M-max was stable over the course of the experiment because no significant differences were found between M-max values taken from M-H recruitment curves conducted at the beginning and end of each experiment. Therefore changes in H-reflex amplitude are not likely due to changes in the test stimulus. Additionally, a consistent soleus contraction was maintained by the participants in each trial (~10% MVC) to ensure an equivalent level of soleus motoneuron pool activation throughout the experiment and decrease the variability in H-reflex latency and amplitude (Burke et al. 1989; Funase and Miles 1999).

Heteronymous muscle activity can influence the soleus H-reflex amplitude (Hultborn, 1987; Crone and Nielsen 1994; Morita et al. 1998; Pierrot-Deseilligny and Mazevet 2000: for a comprehensive review see Pierrot-Deseilligny and Burke 2005), but this is not likely the case in the current study. First, the potential for inhibitory influence of TA activity via reciprocal inhibition and PSI was reduced because soleus was tonically active (Tanaka 1974; Iles and Roberts 1986; Crone et al. 1987; Petersen et al. 1998). Secondly, the bEMG of TA, MG, VL and BF remained level (i.e. not statistically different from control) until frequencies ≥ 1.4 Hz which is well above the threshold of .8 Hz (when H-reflex amplitudes significantly differed from control). Therefore the bEMG of heteronymous leg muscles cannot be implicated as a potential influencing factor from .8 - 1.3 Hz. In addition, although the influence on the soleus H-reflex from heteronymous muscle activity cannot be ruled out at the higher frequencies (≥ 1.4Hz), the data suggests their influence is limited because the increase in activity of the heteronymous leg muscles was not graded with the suppression in the soleus H-reflex. Therefore we are confident that the graded suppression of the soleus H-reflex amplitude is due to arm cycling frequency and not methodological issues.

5.5.2 Modulation of reflexes in Soleus muscle induced by different frequencies of arm cycling

The current results confirm the frequency-dependent effect of rhythmic arm movement on spinal circuits in the legs, thus further contributing evidence of interlimb connections between arms and legs (Balter and Zehr 2007; Loadman and Zehr 2007; Frigon et al. 2004; Haridas and Zehr 2003; Zehr and Haridas 2003; Dietz et al. 2001). These results extend findings from previous studies where the soleus H-reflex was suppressed during rhythmic arm cycling compared to control (Frigon et al. 2004; Loadman and Zehr 2007) and where doubling frequency (2 Hz) of

arm cycling attenuated the soleus H-reflex more than at a 1 Hz frequency (Loadman and Zehr 2007). Soleus H-reflex suppression in stationary legs appears to be task-dependent rather than phase-dependent as indicated by equivalent suppression at any phase of movement (Frigon et al. 2004; Loadman and Zehr 2007). The current results show that variations in frequency of the same task affect the degree of soleus H-reflex suppression.

5.5.3 Possible Sources of H-Reflex Suppression

A reasonable supposition that can be made from the current observations is that the most probable source responsible for the majority of the soleus H-reflex suppression is related to an increase in output of the spinal or supraspinal central motor drive regulating the rhythmic arm cycling movement as suggested in our previous work (Frigon et al. 2004, Loadman and Zehr 2007). Though cortical inputs related to attention to the task as well as peripheral feedback are other possible origins of the signal mediating the H-reflex modulation, current and previous findings do not strongly support this.

The modulation of H-reflex amplitudes recorded at similar contraction levels is known to predominantly be due to PSI of the afferent volley (Brooke et al. 1997; Rudomin and Schmidt 1999; Stein 1995). Previously, conditioning stimuli known to decrease or increase the PSI of the soleus H-reflex pathway and known to be unaffected by arm cycling when evoked alone, were used to demonstrate how arm cycling influences the neural circuitry of the legs via premotorneuronal presynaptic inhibition (PSI) of IA afferent terminals (Frigon et al. 2004). Frigon et al (2004) showed that rhythmic arm cycling influenced the effect of conditioning stimuli (i.e. the segmental level of IA PSI) on the soleus H-reflex. This is evidence that arm

cycling and somatosensory conditioning evoked by nerve stimulation share a common presynaptic pathway. It is also generally accepted that PSI is one of the major control mechanisms associated with rhythmic movement (for a review see Stein 1995). A strong indication that the PSI of primary afferents is under the control of locomotor CPGs is suggested by phase-dependent modulation of the amplitude of primary afferent depolarization evoked by diverse sensory stimulation during fictive stepping (Gossard et al. 1990; Gossard and Rossignol, 1990). In keeping with this line of reasoning there is strong potential for a putative locomotor CPG activated during arm cycling to be the primary origin of the signal responsible for modulating the PSI at the IA afferent as seen in the current study.

Further, it has been proposed that human rhythmic arm movements (i.e. arm cycling and arm swing during locomotion), as with rhythmic leg movements (Dimitrijevic et al. 1998), are regulated at least in part by spinal networks (e.g. CPGs) (for review see Zehr and Duysens 2004; Zehr et al. 2004). In other mammalian species, experiments have confirmed the existence of propriospinal coupling between lumbar and cervical generators (Juvin et al. 2005) and confirmed that activity in one generator is influenced by activity in the other, thus mediating interlimb coordination of their rhythmogenic capacities (Ballion et al. 2001; Juvin et al. 2005; Zaporozhets et al. 2006). In decerebrate cats, when the fore and hind limbs stepped on separate treadmills running at different speeds, the rate of stepping in the front limbs entrained the stepping frequency of the hind limbs to maintain a 1:1 ratio (Akay et al. 2006). In contrast slowing the speed of the rear treadmill had relatively little influence on the rate of stepping in the forelimbs. It was proposed that ipsilateral pattern generating networks are asymmetrically coupled via descending inhibitory pathways and an ascending excitatory pathway (Akay et al. 2006).

Some evidence suggests that long propriospinal neurons connect cervical and lumbar enlargements in humans (Nathan et al. 1996). It is likely that CPGs at the cervical and lumbosacral level are coupled during human locomotion and that locomotor CPGs produce synchronous outputs for interlimb coordination and interlimb reflex modulation (Guadagnoli et al. 2000). As such output from CPGs could gate the reflex activity in the arms and legs during coordinated movements involving both pairs of limbs. Though the legs are stationary in the current study, the interlimb modulation of soleus H-reflex amplitudes likely represents part of the locomotor coupling between arms and legs (Zehr et al. 2007a). Therefore, one logical explanation for results seen in the current study is that cervical CPG output is increased in order to produce increased frequency of arm cycling which, in turn, further suppresses the soleus H-reflex amplitude (Dietz 2003; Brooke et al. 1997; Schneider et al. 2000; Zehr et al. 2003).

An interesting similarity can be seen between the graded influence of cycling frequency on the soleus H-reflex suppression in the current study and the graded influence of descending locomotor drive on the frequency of the locomotor rhythm seen in previous studies. Several studies have shown that the frequency of the locomotor rhythm and gait transition is proportional to the intensity of electrical stimulation applied to the mesencephalic locomotor region (MLR) (Cabelguen et al. 2003, Grillner et al. 1997, Shik et al. 1966). In decerebrate cats, Shik and colleagues (1966) clearly showed this linear relationship between strength of electrical stimulation and the locomotor speed as well as a transition from walking to trotting to galloping. Similarly in a decerebrate salamander preparation a graded increase in MLR stimulation produced a graded increase in the frequency of stepping, a transition to swimming and followed by a graded increase of frequency and amplitude of the swimming movements (Cabelguen et al. 2003). More recently, Ispeert and colleagues developed a CPG driven model for a robotic

salamander which addressed the mechanism underlying gait frequency and gait transition induced by varying intensity of electrical stimulation of the brain stem (Ijspeert et al. 2007). Given that electrical stimulation of the MLR in decerebrate cats suppresses the H-reflex in hindlimb muscles (Gosgnach et al. 2000), the locomotor brainstem regions in cats are thought to be involved in interlimb coordination (Whelan 1996), and the recent evidence that the organization and activation of locomotor brainstem centers are similar in cats and humans (Jahn et al. 2007), an alternative explanation for the current results is that the increase in arm cycling frequency may correspond to an increase in neural output from putative brainstem rhythm generation regions either directly or via neural circuits coordinating changes in coupling between limbs during different gait frequencies and patterns.

Regardless of whether the signal originates from brainstem or spinal CPG regions, an inverse linear relationship between the soleus H-reflex amplitude and arm cycling frequency would be the expected outcome if the H-reflex suppression is related to increases in central motor output related to the rhythm generation regulating arm movement frequency. This timing output would be similar whether the arm cycling was bilateral, ispilateral or contralateral. This is supported by results of previous studies where consistent soleus H-reflex suppression was found during ipsilateral, contralateral or bilateral arm cycling (Loadman and Zehr 2007). In addition, the current study shows that an arm cycling frequency of .8 Hz is required to significantly suppress the soleus H-reflex compared to control ($p< 05$). This suggests that a minimum threshold arm cycling frequency is required for the associated central motor output to significantly influence the neural activity in stationary legs. This may indicate the minimum frequency of rhythmic movement for the arm cycling task to become significantly different from the static control task.

A linear relationship has been shown between the frequency of passive contralateral leg cycling and soleus H-reflex gain which has been attributed to peripheral feedback (Brooke et al. l993; Collins et al. 1993). Though peripheral feedback associated with increasing arm cycling frequency has potential to contribute to soleus H-reflex suppression, it appears unlikely that peripheral feedback is the primary contributor to the signal mediating the soleus H-reflex suppression in the current study. Neither phase of movement nor crank length significantly affected modulation of the soleus H-reflex (Loadman and Zehr 2007), however only 4 phases of the movement cycle were evaluated so phase modulation cannot be conclusively ruled out. Peripheral inputs (e.g. muscle length or rate of muscle stretch) would have varied greatly across the cycle path or with altered crank length. Additionally, afferent feedback related to increased arm muscle activity which could be expected to increase the output from Golgi tendon organs serving the active muscles did not appear to influence H-reflex amplitude; in the current study there was significant soleus H-reflex suppression at several arm cycling frequencies where arm bEMG was not significantly increased. Similarly, Cerri et al (2003) found that modulation of H-reflex in the forearm was tied to central motor commands for rhythmic leg muscle contraction, rather than to afferent signals related to the foot kinematics. These results were suggested to implicate a central, rather than kinaesthetic, origin for the interlimb reflex modulation (Cerri et al. 2003). The paradigm employed in the current study does not explicitly examine specific types of peripheral feedback and therefore their influence cannot be ruled out conclusively; however the current evidence does not strongly support peripheral feedback as the primary source of the signal responsible for the suppression of the H-reflex.

There is potential for this soleus H-reflex suppression to be mediated by cortical inputs as well. Increased cortical control required during more difficult tasks is thought to cause

suppression of the H-reflex (Honore et al. 1983; Grillon and Zarifian 1985; Llewellyn et al. 1990; Perez et al. 2005) shown in some cases to be mediated via selective presynaptic inhibition of Ia afferents (Perez et al. 2005.) However in the current study, the suppression of the H-reflex seen with higher arm cycling frequencies cannot be easily explained by an increase in cognitive attention. Arm cycling at either extremely low or high frequencies are uncommon and somewhat unnatural tasks and it can thus be reasoned that performing either at a prescribed level would require a high attentional demand. In the current study therefore it is likely that increased cognitive attention was required to consistently produce both the low and high cycling frequencies yet no suppression of the H-reflex was seen at the lower frequencies. Further study is required for confirmation.

5.5.4 Translational Implications for Rehabilitation

It has been suggested that gait rehabilitation efforts should involve both the arms and the legs to take advantage of interlimb neural coupling (Ferris et al. 2006). After stroke or spinal cord injury, activity related to rhythmic arm movement that alters neuromuscular activity in the legs may be therapeutically useful as an adjunct to current locomotor retraining strategies. The results of this study demonstrate that increased frequency of upper limb movement increases the influence on these interlimb connections. Thus it may be important to incorporate the influence of the frequency of rhythmic movement (i.e. achieving a threshold level) therapeutically to engage the appropriate neural pathways. For example, if rhythmic arm cycling was used as a rehabilitation strategy, a threshold of .8 Hz of rhythmic arm cycling would be required for the intervention to significantly engage interlimb pathways. Little research is available to guide the stepping frequency used in current gait retraining therapies; the current results begin to shed insight into

threshold movement frequencies required to significantly engage interlimb communication during locomotion. This importance of frequency of movement is supported by results of one study that showed the greatest improvements in over-ground walking velocity with the fastest of three treadmill training protocols, the closest to normal walking speed (Sullivan et al. 2002). However, further research should be conducted to determine whether this frequency threshold level is similar in neurologically impaired individuals. Additionally, rhythmic arm movement has potential to influence gait by improving arm swing as well as affecting the neural control in the legs. Improved arm swing may have both a biomechanical as well as a neural influence on the function of the legs.

More specifically there may be potential for arm cycling to manage spasticity in targeted muscles after neurotrauma. Spasticity, which has been linked to hyperexcitable reflexes (e.g. H-reflexes) (Levin and Hui-Chan 1993), is a significant problem after neurotrauma and can impair coordinated movement (Faist et al. 1994; Aymard et al. 2000). Accessing pathways mediating suppression of the H-reflex amplitude and spasticity in the ankle extensors could be quite useful in rehabilitation strategies. Recently we showed that hyperexcitable H-reflex amplitude in soleus muscles arising after stroke could be suppressed by rhythmic arm cycling (Barzi & Zehr, in press). Additionally, prolonged arm cycling (~30 minutes) induces persistent suppression of reflex size up to 20 minutes after the end of cycling (Javan and Zehr 2007). These findings suggest that arm movement can induce short-term plasticity of H-reflexes in the leg muscles that persists beyond the period of movement conditioning. Further exploration is required to determine if arm cycling has potential to decrease spasticity as a means of spasticity management during rehabilitation training.

5.5 References

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6. Soleus H-reflex amplitude is unaffected by upper limb loading during arm cycling[5]

6.1 Abstract

Suppression of soleus H-reflex amplitudes in stationary legs is seen during rhythmic arm cycling. We have examined the influence of various arm cycling parameters on this interlimb pathway in order to determine the origin of the effect. We have shown that the suppression is graded with the frequency of arm cycling however it is not largely influenced by changes in peripheral input associated with phase of movement or crank length. Given the considerable influence load plays in the control of rhythmic locomotor movement we explored the effect of crank load during arm cycling to clarify its contributions to the signal mediating the soleus H-reflex suppression. Since limb loading has been shown to significantly alter excitability of reflex pathways in the legs, we hypothesized that arm cycling load would have a significant effect on H-reflex amplitudes in the leg. Soleus H-reflexes were evoked with tibial nerve stimulation during static control and rhythmic 1 Hz arm cycling trials across 6 different loads. As expected the H-reflex amplitudes during arm cycling trials were significantly suppressed relative to static control. However, contrary to our hypothesis, no significant difference was seen in the level of suppression between the different crank loads. Taken together with our previous findings, this result suggests that the central motor command for rhythm generation of the rhythmic arm movement is the major signal responsible for soleus H-reflex suppression.

[5] Hundza SR, Zehr EP (2007) Soleus H-reflex amplitude is unaffected by load during arm cycling. Soc Neurosci Abs. (95% contribution to project)

6.2 Introduction

In animals there is direct and conclusive evidence of neural interlimb communication coordinating rhythmic movement between fore and hind limbs (Ballion et al. 2001; Juvin et al. 2005; Miller 1973; Rossignal et al. 2006; Schomberg and Behrends 1978; Zaporozhets et al. 2006) while less extensive and more indirect evidence of interlimb communication between arms and legs is available for humans (Dietz et al. 2001; Dietz 2002; Zehr and Duysens 2004; Zehr and Haridas 2003; Balter and Zehr 2007). One experimental paradigm employed to explore the role of neural interlimb communication in humans is to perform rhythmic arm movement and measure changes in EMG activity or reflex modulation in stationary legs (Balter and Zehr 2007; Frigon et al. 2006; Loadman and Zehr 2006; Zehr et al. 2007b). This allows the specific influence of arm movement on leg neuromuscular activity to be isolated from interactions of arms and legs moving together. Consequently, arm cycling has been shown to significantly suppress the H-reflex amplitude in stationary legs (Frigon et al. 2004). Frigon et al. (2004) showed that this H-reflex suppression occurs at a premotorneuronal level by demonstrating an interaction between arm cycling and somatosensory conditioning known to presynaptically inhibit soleus Ia afferents. In further experiments, we examined specific arm cycling parameters in attempts to determine possible contributions to the signal responsible for this suppression. Work to date suggests afferent feedback related to arm movement plays a minor direct role in the remote modulation of soleus H-reflex amplitude; these experiments indirectly addressed muscle spindle feedback through manipulating muscle length and rate of change of muscle length, as well as joint and skin receptor feedback by altering joint range of motion (Loadman and Zehr 2006; Hundza and Zehr submitted). Afferent feedback from load receptors has not been explicitly examined. Given the extensive body of literature demonstrating the importance of load related feedback in the modulation of CPG function, reflex pathways and motor output in the

legs (for review see Dietz and Duysens 2000; Duysens et al. 2000; Dietz 1998) we sought to explore this signal more overtly to further our understanding of the origin of this suppression. In the cat, increases or decreases in load have been shown to affect the duration of the stance phase in the loaded limb as well as the swing phase in the contralateral limb (Duysens and Pearson 1980; Whelan et al. 1995; Whelan and Pearson 1997; Pang and Yang 2000). In fact, alterations in load can reset the timing of the locomotor rhythm generation (Conway et al. 1987). In humans, the soleus H-reflex amplitude during leg cycling with load was found to be proportional to the load (Zehr et al. 2001; Sakamoto et al. 2004) and cutaneous reflexes evoked in the foot were decreased with body loading (Bastiaanse et al. 2000) The current study examined the influence of a series of arm cycling loads on soleus H-reflex suppression in stationary legs. Based upon the significant role loading plays in reflex modulation and interlimb communication we hypothesized that arm cycling load would significantly affect the H-reflex amplitudes in the stationary legs.

6.3 Methods

6.3.1 Participants

Thirteen healthy men and women between 20 and 44 years of age participated in the study. Each participant gave written and informed consent and reported no known history of neurological or metabolic disorder. Experimental procedures were approved by the Human Ethics Board at the University of Victoria and were conducted in accordance with the Declaration of Helsinki.

6.3.2 Protocol

The experimental methodology is similar to previous studies (Frigon et al. 2004; Loadman and Zehr 2006) and thus methodology described here is abbreviated with differences highlighted. Participants were seated in a custom-designed chair that constrained movement of the trunk and legs, while feet were secured into metallic blocks. This maintained the hips, knees and ankles at approximately 90º, 110º and 90º, respectively. Participants performed static (stationary) trials and rhythmic arm cycling trials in the forward direction at different loads and using a custom-built hydraulically resisted cycle ergometer. Cycling trials were performed at 1Hz. Participants used online feedback from an oscilloscope to practice maintaining this cycling frequency. The ergometer was positioned such that when the elbow joints were at their most extended position they were approximately at 10º of flexion. The cycle positions were named consistent with the clock face viewed from the right-hand side of the ergometer (i.e. left elbow maximal extension occurs at the 3 o'clock position). Using on-line visual feedback of the rectified and filtered EMG signal for soleus and tibialis anterior muscles produced by a custom-written (Dr. T. Carroll, University of New South Wales, Australia) LabView (National Instruments) program, participants maintained a consistent low-level contraction [~10% of maximum voluntary contraction (MVC)] in their soleus muscle while attempting to keep the tibialis anterior muscle quiescent. Participants were also instructed to keep the other leg muscles quiescent.

6.3.3 Soleus H-reflex

All thirteen participants completed the main protocol. Female participants performed 6 arm cycling trials in a random order against one of six loads (27, 793, 1559, 2325, 3091, 3857 kPa), while male participants performed 8 arm cycling trials in random order against the same loads as

the females and 2 additional loads (4623 and 5389 kPa). Loads ranged from the lowest resistance offered from the hydraulic system to the highest load that could be maintained without excessive fatigue by all participants for the duration of the trial. Control data were obtained from static trials performed at three different times throughout the main protocol: 1) prior to any cycling trials (pre); 2) after all the cycling trials (post); and 3) midway through the cycling trials (mid).

The left posterior popliteal nerve was stimulated psuedorandomly every 3-5 s in all trials at the popliteal fossa with 1ms pulse width square wave using bipolar surface electrodes and a Grass S88 (Grass Instruments, AstroMed) connected in series with a SIU5 isolation unit and CCU1 constant current unit. Left tibial nerve stimulation was delivered when the left arm was in the 3 o'clock position (i.e. with the left elbow in the most extended position) (Loadman and Zehr 2006; Frigon et al. 2004). A direct motor response (M-wave) that was being monitored on-line was determined such that it was both discernable and evoked an H-reflex on the ascending limb (approximately 70% of H-max). A consistent M-wave level was maintained across the cycling and static trials. Current was measured using an mA-2000 Noncontact Milliammeter (Bell Technologies, Orlando, FL, USA).

Eleven participants completed an ancillary protocol which required arm cycling against the lowest, medium and highest load in random order. Control data was obtained from static trials performed prior to and following ancillary cycling trials (n=6). Soleus H-reflex was elicited in an identical fashion to the main protocol except instead of gathering H-reflex data with the consistent M-wave, H-reflex vs. current (H-I) and M-wave vs. current (M-I) recruitment curves were constructed for all three loaded trials.

Additionally at the beginning and end of the main protocol and the ancillary protocol, H-reflex vs. current (H-I) and M-wave vs. current (M-I) recruitment curves were constructed during static trials. Recruitment curve data provided maximum M-wave (M-max), and H-reflex (H-max) amplitudes which were used to calculate H-max-M-max ratios.

6.3.4 EMG

Using Ag-AgCl electrodes bipolar surface EMG recordings were made bilaterally from the posterior deltoid (PD) and biceps brachii (BB) as well as unilaterally from the left soleus (SOL), tibialis anterior (TA), medial gastrocnemius (MG), vastus lateralis (VL), biceps femoris (BF) and triceps brachii (TB).

6.3.5 Kinematics

Lightweight electro-goniometers (Biometrics Ltd., Cwenfellinfach, Gwent, UK) were used to record kinematic information from the left elbow joint of some participants (n=10).

6.3.6 Load

Pressure (kPa) corresponding to each cycling trial produced by the custom-built hydraulic ergometer was measured.

6.3.7 Heart Rate

Heart rate was measured using a Polar A3 electro-heart rate monitor (Polar Electro Oy, Finland) and peak heart rate during each trial was recorded.

6.3.8 Data acquisition and analysis

Using a custom-written LabView (National Instruments) computer program, (Dr. T. Carroll, University of New South Wales, Australia) data was sampled at 5000Hz with a 12 bit A-D converter. Signals were filtered at 100-300 Hz and rectified with the exception of soleus which was filtered at 100-1000Hz and remained unrectified. For the trials when a stable M-wave was maintained 15 sweeps were collected, while 40 sweeps were collected to construct the H-I and M-I recruitment curves. In all trials, sweeps (20 ms pre-stimulus and 50 – 60 ms post-stimulus) were collected and peak to peak amplitudes of M-waves and H-reflexes were determined off line using custom written software (Matlab, Nantick) for each sweep. The rectified pre-stimulus EMG (20 ms) was used as a measure of muscle activity (background EMG (bEMG)) at the time of nerve stimulation for all muscles. For the trials with a stable M-wave (main protocol), averages for M-waves, H-reflexes and soleus pre-stimulus EMG were calculated from the sweeps and normalized to the M-max values obtained from soleus for the individual data. The H-I and M-I recruitment curves (ascending limb only) from the ancillary protocol cycling trials were fit using a general least squares model of a custom three-parameter sigmoid function using a custom-written LabView (National Instruments) computer program, (Klimstra and Zehr, 2008) providing normalized values for H-max, 50% of H-max, slope of ascending limb of recruitment curve at 50% of H-max value, current at H-reflex threshold and current at H-max.

6.3.9 Statistics

STATISTICA software (StatSoft., Inc) was used to conduct separate repeated measures analysis of variance (ANOVA) for soleus M-wave and H-reflex amplitude, slope, stimulation current, heart rate, kinematics and background EMG in all muscles to determine the conditioning effects of load. Tukeys HSD was used to post hoc main effects to determine which cycling trials significantly differed from static as well as from the lowest load (Control) cycling trial. Planned comparisons were employed to evaluate an apriori determined comparison between the H-reflex amplitudes from the Control trial to the other load conditions. Student's T-tests were conducted on pre and post M-max, H-max and M-H ratios from static trials. Additionally, to allow for a more direct comparison of the conditioning effects of load and frequency during arm cycling, select soleus H-reflex data from a previous experiment evaluating frequency (1 -2.0 Hz cycling trials) (Frequency Experiment; Hundza and Zehr, submitted) were reanalyzed with repeated measures ANOVA; planned comparisons used to identify cycling trials which significantly differed from 1Hz cycling trial. Descriptive statistics included means ± standard error of the mean (SEM). Statistical significance was set at $p < 0.05$.

6.4 Results

6.4.1 Heart rate

Heart rates from all trials were expressed as percentages of maximum heart rate (maximum heart rate = 220-age). All further analysis of heart rate data used percentage of maximum heart rate. There was no significant difference in the heart rates across the static trials (pre, mid, post) allowing heart rate data from the static trials to be averaged and collapsed into one static control value used for comparisons to the cycling trials.

The difference in heart rate between static control and each loaded cycling trial was calculated and averaged across males and females separately. These average "difference" values were used to determine a "best match" of loads between males and females to accommodate for gender differences. That is, using these heart rate "difference" values, the 6 cycling loads used for the females were aligned with the 6 of the 8 "best matched" loaded cycling trials for the males. This resulted in the female loads of 27, 793, 1559, 2325, 3091 and 3857 kPa being matched to the male loads of 793, 1559, 3091 and 3857, 4623 and 5389 kPa, respectively. With data aligned based on "best matched" heart rate differences, heart rate and soleus bEMG levels, as well as M-wave and H-reflex amplitudes were compared between genders for all static and cycling conditions. No significant differences between genders were found for any of these measures allowing aligned gender data to be combined for further comparisons. The "matched" loaded cycling trials were named in ascending order of resistance as Control, Load 1(L1), Load 2 (L2), Load 3 (L3), Load 4 (L3), Load 5(L5).

Average heart rate across participants increased from 62 beats per minute (bpm) in the static trials to 104 bpm in the L5 cycling trial. Significant differences were found between the heart rates in Control Load trial and the L2, L3, L4, L5 cycling trials, while the heart rates during the static trial were significantly different from all cycling trials.

6.4.2 Soleus H-reflex amplitudes during static and cycling conditions

Based on recruitment curve data of static trials, there was no significant difference in M-max, H-max, or M-max-H-max ratio over the course of the experiment. Additionally, there was no significant differences in the soleus M-wave, H-reflex and bEMG amplitudes across the static

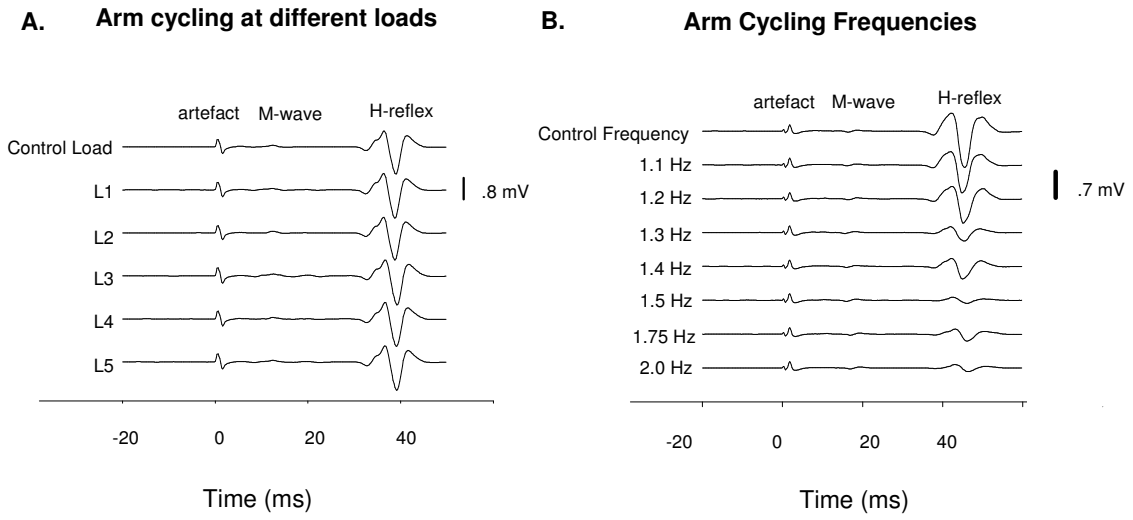

Figure 6.1. Reflex traces from two single subjects displaying the Soleus H-Reflex modulation across 6 arm crank loads and 8 arm cycling frequencies.
A. Resisted arm cycling trials include Control Load(L), L1, L2, L3, L4 and L5. B. Arm cycling frequencies include Control Frequency, 1.1, 1.2 1.3 1.4, 1.5, 1.75, 2.0 Hz. Data in Panel B has been redrawn from a previous study (Hundza and Zehr, submitted) and reanalyzed for the current comparison. Both the load applied and the arm cycling frequency are identical between the Control Load and Control Frequency trials. Reflex traces represent averages of 10-15 sweeps recorded during each trial. Stimulus artefact, M-wave and H-reflex are indicated.

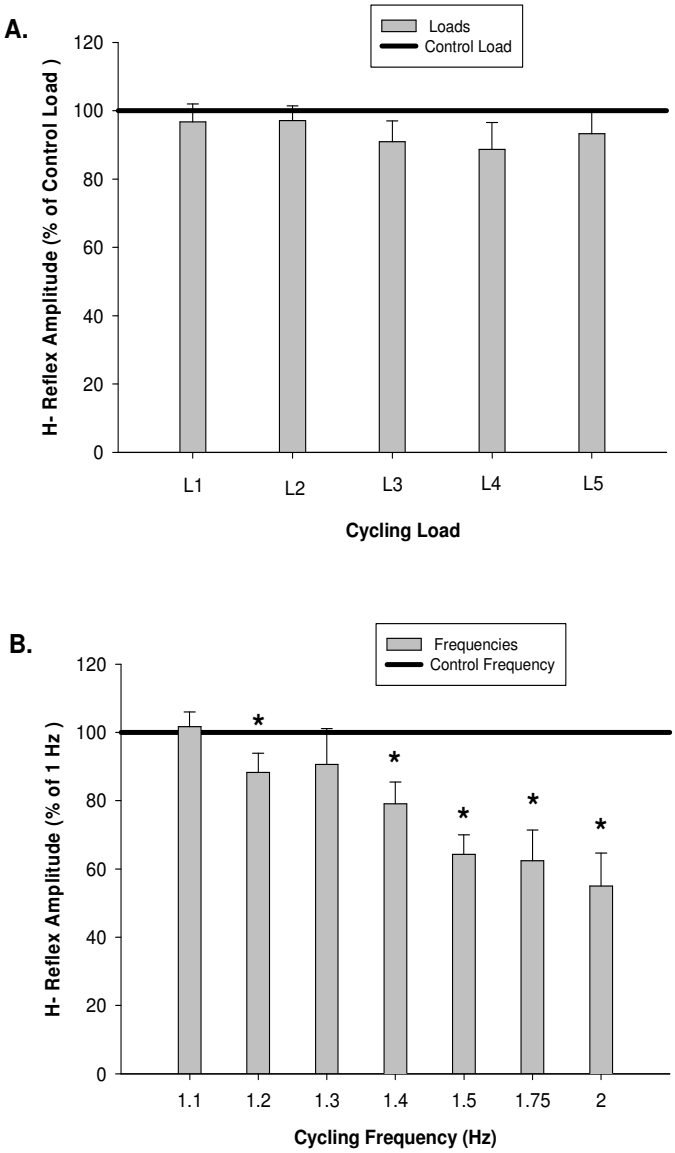

Figure 6.2. Soleus H-Reflex peak-to-peak amplitude across all arm cycling trials for all participants.
Reflex amplitudes are expressed as a percentage of the Control Load amplitude in panel A and of the Control Frequency amplitude in panel B (represented by the horizontal black line). In Panel B previously published data has been reanalyzed for the current comparison (Hundza and Zehr, submitted). Both the load applied and the arm cycling frequency are identical between the Control Load and the Control Frequency trials. Values are means ± SEM across all participants. For statistical analysis data were normalized to M-max. Statistically significant differences ($p < 0.05$) found between the Control Load and other load trials and between the Control Frequency and the other frequency trials are indicated by asterisk.
Note: frequencies are plotted as categorical variables and therefore frequency values are not linearly spaced.

trials (pre, mid, post) allowing these static trials to be averaged and collapsed into one static control value used for comparisons to the cycling trials.

The load applied during the cycling trials did not affect the soleus H-reflex amplitude as can be seen in the single subject reflex traces displayed in Figure 6.1A. Here both the H-reflex and M-wave amplitude remained consistent across all the cycling trials despite the increasing load. H-reflex amplitudes for the L1, L2, L3, L4, and L5 cycling trials were expressed as percentages of the Control Load cycling trial and were averaged across participants (see Figure 6.2A). The average of the H-reflex amplitudes for the Control Load plot is therefore seen as the black horizontal line at 100%. The effect of load on arm cycling is similar between the group data (Figure 6.2A) and the single participant data (Figure 6.1A). Averaged H-reflex amplitudes showed no main effect for load across trials and planned comparisons showed no significant difference in H-reflex amplitudes between the Control Load cycling trial and the L1, L2, L3, L4, L5 cycling trials. That is crank load was independent of soleus H-reflex amplitude. Soleus M-wave and bEMG were not significantly different across the trials. The stimulation intensity for all trials was sufficient to evoke a stable M- wave for each participant (average of 4.04% of M-max ± 0.65 SEM) and the H-reflex was elicited on the ascending limb of the H-I curve (average of 82.06% of H-max ± 3.81).

To allow for a direct comparison between the conditioning effects of load and frequency during arm cycling on the soleus H-reflex in stationary legs, data from a previous experiment evaluating frequency (Frequency Experiment; Hundza and Zehr, submitted) was reanalyzed contrasting H-reflex amplitudes from 1 Hz trials (Control Frequency) to 7 cycling trials ranging in frequency from 1.1-2.0 Hz trials. Thus the arm cycling load and the frequency are identical for

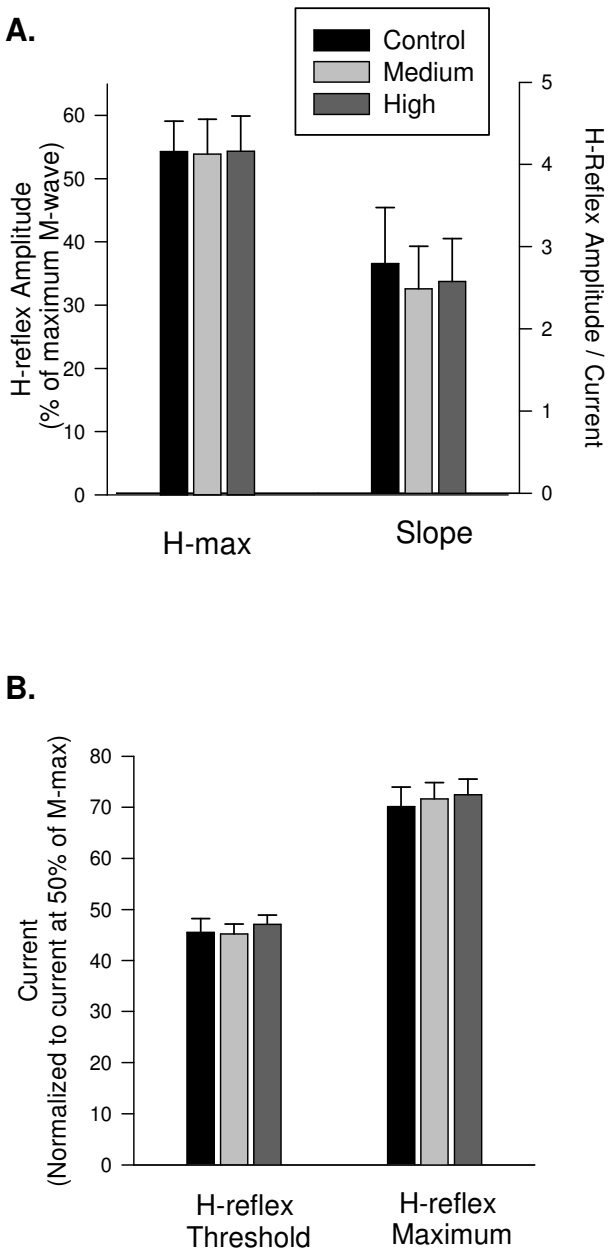

Figure 6.3. H-max, slope, current at H-threshold and current at H-max for lowest (Control), medium and high arm crank loads across all participants.
Data is from H-reflex vs. current and M-wave vs. current recruitment curves and values are means ± SEM across all participants. Data for H-max were normalized to M-max. Slope is presented as a percentage of M-max/50% max current. Current values are presented as a percentage of 50% of max current. Statistically significant differences ($p < 0.05$) found between the Control Load and other load trials are indicated by asterisk.

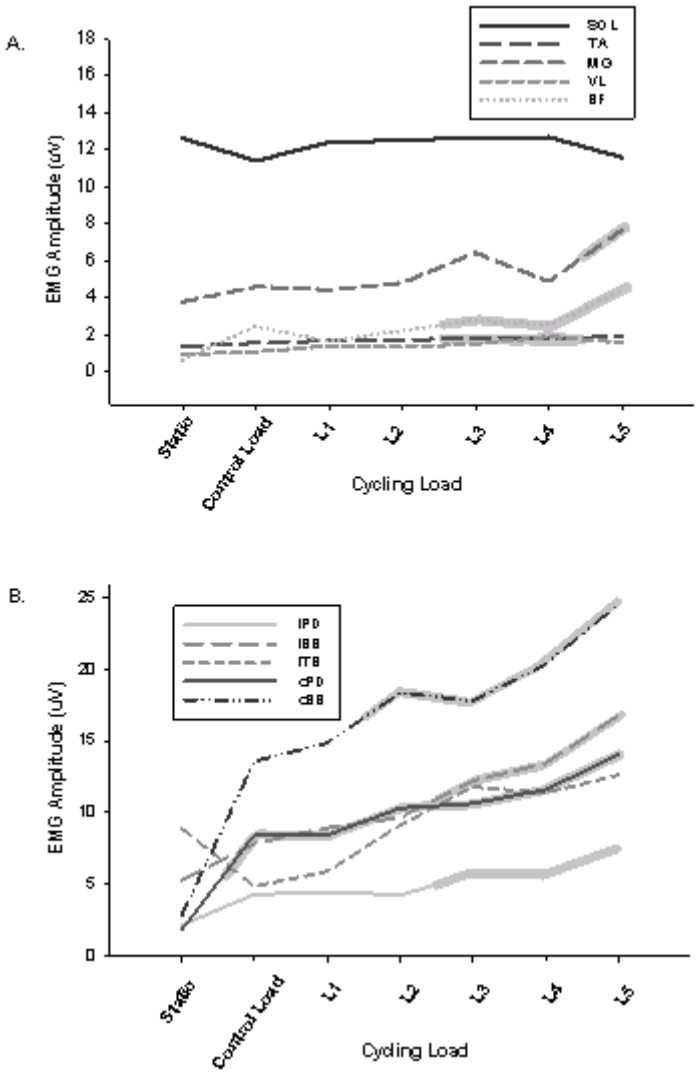

Figure 6.4. Background EMG during static and 6 arm crank loads across all participants.
A. Leg Muscles Values are means for Sol, MG, TA, VL and BF EMG. Significant differences ($p < 0.05$) in background EMG between the static and cycling frequencies are indicated by grey highlighting of the plot.
B. Arm Muscles Values are means for iPD, iBB, iTB, cPD, and cBB. Significant differences ($p < 0.05$) in background EMG between the static and cycling frequencies are indicated by grey highlighting of the plot.
Abbreviations: soleus (Sol), medial gastrocnemius (MG), tibialis anterior (TA), vastus lateralis (VL) and biceps femoris (BF), ipsilateral (i), contralateral (c), posterior deltoid (PD), biceps brachii (BB) and triceps brachii (TB).

the Control Load in the current experiment and the Control Frequency from Hundza and Zehr, (submitted). In Figure 6.1B single subject reflex traces from the Frequency Experiment (Hundza and Zehr, submitted) demonstrate that increases in cycling frequency progressively suppressed the H-reflex amplitude. H-reflex amplitudes from 1.1 – 2.0 Hz cycling trials, expressed as percentages of Control Frequency (1.0 Hz), were averaged across participants and plotted in Figure 6.2B. The average of H-reflex amplitudes for the Control Frequency trials was therefore 100% and plotted as a black horizontal black line; thus the cycling parameters were identical in the Control Load plot in Figure 6.2A and Control Frequency plot in Figure 6.2B. There was a main effect for frequency and planned comparisons showed that 1.0 Hz was significantly different for 1.2 and 1.4-2.0 Hz trials as indicated by asterisks in Figure 6.2B.

Data from the H-reflex vs. current (H-I) and M-wave vs. current (M-I) recruitment curves from the three ancillary cycling trials (at the lowest (Control), medium and highest loads) were averaged across participants and are plotted in Figure 6.3. No significant differences were found between the three loads for H-max, current at H-threshold and current at H-max. The stimulus-response consistency across the ancillary cycling trials was specifically evaluated in 6 participants. For these participants, recruitment curve data from static trials, collected before and after the ancillary cycling trials, showed no significant difference in M-H ratios. Normalized H-max, slope, current at H-threshold and current at H-max data from the cycling trials of these 6 participants was not significantly different from that of the remaining 5 participants.

6.4.3 Background EMG in leg and arm muscles

Background muscle activity for ipsilateral SOL, TA, VL, BF and MG averaged across participants for static and cycling trials are displayed in Figure 6.4A. Repeated measures ANOVAs were performed separately on each muscle for all conditions and a main effect for condition was seen for every muscle except SOL (not indicated in Figure 6.4A). Tukeys post hoc analyses found significant differences in bEMG between the static condition and the following arm cycling trials: L3 – L5 in BF; L5 in MG; L4 in VL; and L3 – L4 in TA. These significant findings are highlighted on the plots in Figure 6.4A. When averaged bEMG levels for each cycling trial (i.e. L1-L5) were compared to Control Load no significant differences were found.

Background EMG levels for iPD, iBB, iTB, cPD, and cBB muscles averaged across all participants are displayed in Figure 6.4B. Each muscle was analysed independently and a main effect for condition was found in all arm muscles. Significant differences were found in bEMG between the static condition and the following loaded cycling trials: Control Load – L5 in cPD, L2 – L5 in cBB; and L3 – L5 in iPD and iBB. Significant differences in bEMG were found between the Control Load and the loaded cycling trials of: L3 – L5 for iTB; L4-L5 for iBB and cPD; and L5 for iPD and cBB.

6.4.3 Kinematics

No significant differences were found between the loaded cycling trials for the elbow joint excursion across the cycle path or for the elbow joint position at 3 o'clock.

6.5 Discussion

Contrary to our hypothesis, differences in crank load during arm cycling did not significantly affect soleus H-reflex amplitude. Taken together with our previous findings, this result suggests that centrally driven commands for the rhythm generation of arm cycling provides the primary signal responsible for soleus H-reflex suppression while other movement parameters have a limited effect.

6.5.1 Methodological considerations

Consistent low level background activity (12 ± .14 %of MVC) was maintained in the soleus muscle across all trials to control for motoneuronal pool activation levels and thereby decrease variability in H-reflex latency and amplitude (Burke et al. 1989; Funase and Miles 1999). M-wave amplitudes (as a percentage of M-max) were not significantly different across the trials confirming stimulus constancy throughout the experiment (Brooke et al. 1997; Zehr 2002). Additionally, because there was no significant difference between the H-reflex amplitudes evoked at the stable M-wave amplitude in the pre, mid and post static trials or between M-max, H-max and M-H ratio determined in recruitment curves at the beginning and end of the experiment, stimulus- response consistency across the experiment can be assumed. In the current study comparisons of activity levels heteronymous leg muscle between the Control Load and other loaded cycling trials showed no significant differences precluding their potential influence on the soleus H-reflex amplitude (Crone and Nielsen 1994; Hultborn et al. 1987; Morita et al. 1998; Pierrot-Deseilligny and Mazevet 2000: for a comprehensive review see Pierrot-Deseilligny and Burke 2005). Given the above methodological control, it is clear that the current results are not confounded by methodological issues.

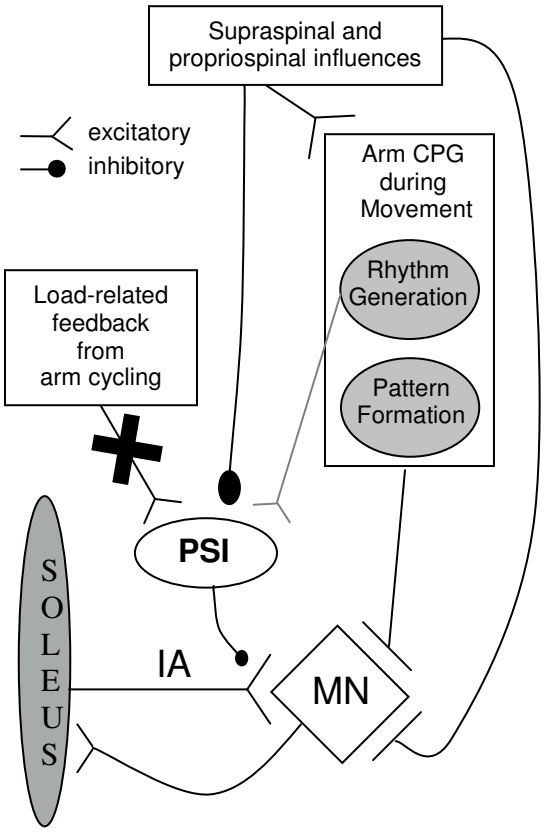

Figure 6.5. Possible pathways that influence presynaptic inhibition (PSI) and the excitability of the soleus motoneuronal (MN) pool. Excitatory and inhibitory connections are shown with an open triangle and a filled black circle, respectively. The simplified H-reflex pathway shows the primary muscle spindle afferents (Type Ia) synapsing with motoneurons of the soleus muscle. PSI and MN receive inputs from supraspinal and propriospinal pathways (blacklines) and CPG pathways (grey lines). The CPG input to PSI is specifically from the Rhythm Generator component. The lack of influence of load-related feedback from arm cycling on PSI is indicated by a black X through the pathway connecting them. (Adapted from Frigon et al. 2004)

6.5.2 Independence of arm crank load and soleus H-reflex modulation

In contrast to our hypothesis, the neuromuscular activation associated with arm cycling against different loads did not influence the soleus H-reflex amplitude. The independence of arm cycling load and soleus H-reflex modulation was similarly found in both the main and ancillary protocols suggesting that crank load had no influence on H-reflex amplitude across all levels of the ascending limb of the H-reflex. In fact the stimulus-H-reflex response relationship did not change across the H-I curve as evidenced by no differences in H-max, slope, current at H-reflex threshold and maximum for the different crank loads (see Figure 6.3). Results from our laboratory have consistently shown significant suppression of the soleus H-reflex amplitude during rhythmic arm cycling when compared to static trials, which affirms the presence of interlimb neural connections between arms and legs (Frigon et al. 2004, Loadman and Zehr 2006). This soleus H-reflex suppression has been ascribed to premotoneruonal modulation of presynaptic inhibition (PSI) of Ia afferents (Frigon et al. 2004) and current results suggest that the load applied during arm cycling does not appear to influence this interlimb reflex pathway.

In keeping with these results, Larsen and colleagues found that changes in crank load during leg cycling had no effect on soleus short latency stretch reflex amplitude (Larsen et al. 2006). In addition, the timing and magnitude of soleus stretch reflex responses were not influenced by increasing or decreasing the body load during walking (Grey et al. 2002). However in other experiments load was found to play a significant role in modulating reflex pathways in the legs during rhythmic leg movement (Bastiaanse et al. 2001; Pyndt et al. 2003; Sakamoto et al. 2004). For example, increased crank load during leg cycling resulted in increased soleus H-reflex amplitude (Sakamoto et al. 2004) and decreased reciprocal inhibition of soleus H-reflex

amplitude (Pyndt et al. 2003). In addition, by altering body weight support during treadmill walking, loading was shown to increase the cutaneous reflex responses (Bastiaanse et al. 2000).

6.5.3 Possible Sources of H-reflex suppression

In current as well as in previous studies, we have manipulated arm cycling parameters in attempts to identify contributions to the signal responsible for the suppression of the soleus H-reflex amplitude during arm cycling. Possible sources responsible for the H-reflex suppression include afferent feedback, supraspinal input and influence from central motor commands (e.g. central pattern generators (CPGs)) associated with the arm cycling.

Previous and current work suggests that afferent feedback related to arm movement is not the primary source of the signal mediating the H-reflex suppression. The fact that neither phase of movement nor crank length influenced soleus H-reflex amplitude while arm cycling, suggests that afferent feedback related to arm muscle length (Type Ia and II afferents), rate of change of muscle length (Type Ia afferents) or joint position (Type II and III afferents) plays a minor role in remote modulation of soleus H-reflex amplitude (Loadman and Zehr 2006). Feedback from the associated sensory receptors would have varied greatly across the cycle path or with different crank lengths yet soleus H-reflex modulation was independent of these parameters (Frigon et al. 2004; Loadman and Zehr 2006). Afferent feedback's limited role is further highlighted by the current results where feedback from load receptors (Type Ib afferents) activated by the increased crank load and increased arm muscle activity did not influence the soleus H-reflex suppression. Afferent feedback's limited role is depicted in Figure 6.5 by an X placed on the pathway for afferent feedback related to arm cycling.

Afferent feedback from proprioceptors and exteroceptors has been shown to modify ongoing locomotor pattern and interlimb coordination (Pearson 2004), however Yang and colleagues demonstrated that only afferent feedback that is relevant and important generates a response (Yang et al. 2004) . This functional gating of afferent feedback was demonstrated during different directions of walking. Touch to the lateral aspect of the foot only influenced stepping with sideways walking and only in the leading limb (Yang et al. 2004). Perhaps within the current movement paradigm, afferent feedback related to the arm cycling is not relevant to the coordination between arms and legs and therefore does not influence the pathway mediating the interlimb H-reflex modulation. These results could also suggest that load plays a less influential role in the neural control of rhythmic arm movement in contrast to its important role in the neural control of rhythmic leg movement. Similar to the current results, Cerri and colleagues (2003) found that modulation of H-reflex in the forearm was not linked to afferent signals related to the rhythmic leg movements (Cerri et al. 2003).

Previously we reasoned that the soleus H-reflex suppression was not likely influenced by supraspinal input related to the cognitive attention required for the arm cycling task. We suggested that the cognitive attention necessary to cycle at either extremely low (.03 Hz) or high (2.0 Hz) frequencies would likely be equal yet each of these conditions resulted in extremely different levels of H-reflex suppression (Hundza and Zehr, submitted). Further support is found in the current study where cognitive attention was likely greater at the high loads compared to control, however no differences in H-reflex amplitude were seen between the loads. In addition, these results suggest that H-reflex suppression is not related to increases in activity in the corticospinal tract as EMG activity is similarly increased in both the load and frequency

paradigms, but suppression of the H-reflex amplitude only occurs with increase in frequency paradigm.

The independence of soleus H-reflex suppression from afferent input and cognitive attention coupled with the graded relationship seen between arm cycling frequency and soleus H-reflex amplitude suggests that the central motor output required to produce the arm cycling, and in particular the frequency of arm cycling, is the major contributor to the signal responsible for the soleus H-reflex suppression (Frigon et al. 2004; Hundza and Zehr, submitted; Loadman and Zehr 2006). This line of reasoning (presented previously in Hundza and Zehr, submitted) is supported by the supposition that the soleus H-reflex suppression seen during arm cycling is mediated by PSI of Ia afferents and that PSI is accepted to be a key control mechanisms involved in the regulation of rhythmic movement (for a review see Stein 1995). As such, output from central locomotor motor commands regulating arm cycling have the capacity to be the primary origin of the signal responsible for modulating the PSI of the IA afferent from soleus muscle producing H-reflex suppression.

Similar results and conclusions have been drawn in other studies. The influence of rhythmic leg movement on reflex modulation in arm muscles was explored and it was concluded, that the origin for the interlimb reflex modulation was central in nature (i.e. related to the central motor commands for rhythmic movement), rather than kinaesthetic (Cerri et al. 2003). Similar to the current results, Larsen and colleagues found that soleus stretch reflex decreased successively when pedaling frequency increased while being unchanged by increased crank loads (Larsen et al. 2006).

The neural communication between arms and legs during rhythmic movement has been shown to be influenced by the frequency of limb movement. It was previously shown in decerebrate cats that when the fore and hind limbs stepped on separate treadmills, each running at different speeds, the rate of stepping in the front limbs entrained the stepping frequency of the hind limbs to maintain a 1:1 ratio (Akay et al. 2006). It was proposed that ipsilateral pattern generating networks are asymmetrically coupled via descending inhibitory pathways and an ascending excitatory pathway (Akay et al. 2006). Further, during arm and leg cycling, arm cycling cadence was significantly influenced by leg cycling cadence, however arm cycling cadence did not change leg cycling cadence (Sakamoto et al. 2007). Donker showed that both the stability of the individual limb movements and interlimb coordination increased with increasing velocity; (Donker et al. 2001, 2005). In contrast manipulation of load affected the individual limb movements but not the interlimb coordination (Donker et al. 2005). Given the importance of movement frequency to interlimb coordination, perhaps this solitary influence of frequency of arm cycling on the soleus H-reflex seen in this thesis reflects the prominent role of this signal in coordinating the frequencies of interlimb movement.

Though the current results suggest the source of the signal mediating this interlimb communication to be central in origin, they do not isolate the source, for example, as being from CPG locomotor spinal circuitry or locomotor brainstem regions. As proposed in the schematic in Figure 6.5 (adapted from Frigon et al. 2004), CPG rhythm generation output regulating the timing of rhythmic arm movement may increase presynaptic inhibition onto the soleus alpha motor neuron.

Perhaps the intensity of central rhythm generator (CPG) timing output produces a graded suppression of the soleus H-reflex (see Hundza and Zehr, submitted) similar to how the intensity

of electrical stimulation applied to the mesencephalic locomotor region is graded with the frequency of the locomotor rhythm produced (Cabelguen et al. 2003; Shik et al. 1966). In theory this rhythm generation signal could originate from either the locomotor brainstem regions or locomotor spinal circuits. Either supposition accounts for the lack of effect of arm crank load on H-reflex suppression during arm cycling seen in the current study. Increased crank load does not produce alterations in movement timing and therefore may not involve the rhythm generation component of the CPG (see Figure 6.5). Loading has been previously shown not to influence the central nervous system's control of CPG timing output (Stephens and Yang 1999).

6.5.4 Clinical Implications

Rhythmic movements such as walking require intricate coordination between muscles of the legs and arms (Zehr et al. 2004; Zehr and Duysens 2004). Thus the activity of both the arms and the legs should be considered when designing locomotor rehabilitation strategies to take advantage of interlimb neural coupling (Ferris et al. 2006). When therapeutically trying to influence interlimb reflex connections between arm and legs both arm crank load and arm cycling frequency can be manipulated to achieve an increased level of activity in leg muscles (Huang and Ferris 2004; Hundza and Zehr, submitted; Kao and Ferris 2005), while the frequency of rhythmic arm movement is more critical in decreasing the excitability of H-reflex pathways in the legs. The ability to alter neuromuscular activity in the legs with rhythmic arm movement after stroke or spinal cord injury may be useful as an adjunct to current locomotor retraining strategies. After stroke it has been shown that the neural activity related to arm cycling can still access these interlimb pathways and can still suppress H-reflex amplitudes in leg muscles (Barzi and Zehr 2008). Since hyperactive H-reflexes occur in parallel with spasticity (Levin and Hui-

Chan 1993) decreasing the excitability of H-reflex pathways in targeted muscles may be useful in controlling spasticity after neurotrauma.

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7. General Conclusion

This thesis sought to further characterize the neural control of rhythmic arm movement, and further explore the influence of rhythmic arm movement on the spinal circuitry controlling the legs. This section summarizes and integrates the main findings of thesis to further our understanding of the neural control of rhythmic movement in humans.

7.1 Neural control across various rhythmic arm cycling tasks

As mentioned in Chapter 1, evidence of CPGs contribution to the neural control of rhythmic movement of arms and legs in human is mounting (for review see Duysens and Van de Crommert, 1998; MacKay-Lyons, 2002; Zehr and Duysens, 2004). The data in this thesis contributes to the body of work supporting the role of CPGs in the neural regulation of rhythmic arm movement, namely arm cycling, and helps to further characterize this control.

Chapter 2 describes how similar EMG and reflex modulation was observed during FWD and BWD arm cycling demonstrating analogous neural regulation of these tasks. Similarly, in Chapter 3 the neural control was shown to be comparable between symmetrical and asymmetrical arm cycling created by unilaterally altering crank length. Characteristic reflex patterns such as reflexes whose amplitude and sign are task and phase dependent and are unrelated to background EMG have previously been attributed to CPG influences (Duysens and Tax, 1994). Accordingly, the presence of these characteristic reflex modulation patterns during rhythmic arm cycling provides evidence of CPG contributions to the neural control of rhythmic arm movement similar to that alleged for the legs (Zehr and Chua, 2001; Zehr and Haridas, 2003;

Zehr and Kido, 2001). Such characteristic modulation patterns were seen during the arm cycling paradigms explored in this thesis suggesting similar contributions from spinal pattern generating networks to the neural control of FWD and BWD arm cycling (Chapter 2) as well as asymmetrical arm cycling (Chapter 3). It has been suggested that during FWD and BWD walking (Duysens et al, 1996) as well as during FWD and BWD leg cycling (Zehr et al, submitted), the CPG program is proposed to be running in reverse during the BWD direction compared to FWD. This thesis similarly proposes this reversal of CPG motor output during BWD arm cycling as compared to FWD.

Though the rhythmic motor tasks were varied by reversing the movement direction or altering the crank length, the neural regulation of the rhythmic movement remained consistent as evidenced by EMG and reflex data. This concept of shared neural circuitry regulating different rhythmic movement has been referred to as the common core hypothesis (Zehr, 2005) and has been amply demonstrated in humans (Duysens et al, 1996; Grasso et al, 2000; Lamb and Yang, 2000; Yang et al. 2004;Zehr et al, 2007). In infants, this shared neural control was suggested to explain similar control of the step cycle in response to walking speed regardless of the direction of walking (Lamb and Yang, 2000; Yang et al. 2004). Similarities in reflex control across walking, combined arm and leg stepping and cycling locomotor tasks suggests shared neural circuitry (Zehr et al, 2007a). In the same way during both sitting and standing, there is a similar modulation of cutaneous reflexes in arm muscles during arm and leg cycling (Sakamoto et al, 2006a). Also shared common principles of motor functions were suggested to explain analogous oscillations of each limb segment relative to the vertical across stooped and erect postures during walking at different speeds (Grasso et al, 2000).

As mentioned in Chapter 3, sensory feedback was likely different between the trials with dissimilar CLs as well as between FWD vs. BWD arm cycling trials yet the cutaneous reflex modulation was unaffected. These results suggest that this sensory input has little effect on cutaneous reflex modulation during rhythmic movement and that sensory input is likely gated by CPG circuits such that only functionally important sensory inputs generate a response. Such selective gating of sensory input was similarly found in infant studies (Lam et al, 2003; Pang and Yang, 2002; Yang et al, 2004). For example touch to the lateral surface of the foot elicited a response only in sideways walking and only in the leading limb (Lam et al, 2003). Interestingly Lamont and Zehr (submitted) showed that during asynchronous arm cycling where each arm is cycling at a different frequency, the reflex modulation patterns are affected suggesting that cutaneous reflex patterns are sensitive to input related to rhythm generation while being less sensitive to sensory feedback.

7.2 Neural control after injury

In chapter 4, it was shown that the neural control of upper limb muscles was compromised after orthopaedic shoulder instability. Differences in background EMG and cutaneous reflex modulation during rhythmic cycling and discrete reaching tasks were seen between control and unstable shoulders. This provides further evidence to support the supposition that retraining neuromuscular control should be the focus of rehabilitation prior to strengthening (Myers and Lephart, 2002; Lephart et al, 1997)

In those with unstable shoulders, the bEMG during the discrete reaching task was unaltered in contrast to the multiple differences in bEMG seen during the rhythmic tasks. This

differential effect of the shoulder injury could be explained by the putative differences in neural regulation of discrete and rhythmic motor tasks as proposed by Schaal and Sternard (2004). The implications this has for shoulder rehabilitation requires further investigation.

7.3 Interlimb communication during rhythmic arm movement

Data from Chapter 5 and 6 contribute to the body of evidence supporting interlimb neural communication in humans (Delwaide and Crenna 1984; Dietz, 2002; Dietz et al. 2001) and helps to further characterize these interlimb relationships during rhythmic tasks (Balter and Zehr 2007; Frigon et al. 2004; Haridas and Zehr 2003; Zehr and Haridas 2003). In other animal species, experiments have confirmed that the activity in either the cervical or lumbar pattern generator can influence the rhythmogenic capacity of the other and that these distinct generators function synergistically to coordinate rhythmic movement of fore and hind limbs (Ballion et al. 2001; Rossignal et al. 2006; Juvin et al. 2005; Miller 1973; Schomberg et al. 1978; Zaporozhets et al. 2006). In the rat it has been suggested that the slower rostral locomotor spinal generators entrains the faster caudal generators to produce coordinated locomotor-like activity throughout the segments of the intact spinal cord (Ballion et al. 2001). Data in this thesis supports the premise that activity in putative cervical human rhythm generators, responsible for regulating the frequency of rhythmic arm movement, influences lumbar spinal circuitry controlling the legs. This conclusion is based on three streams of observations: there is a graded effect of arm cycling frequency on the suppression of soleus H-reflex (Chapter 5); there is a lack of effect of afferent feedback related to crank load on the soleus H-reflex (Chapter6); and previous work suggests

that afferent feedback related to arm cycling plays a limited role in this interlimb communication (Loadman and Zehr, 2007). Taken as a whole these findings suggest that the central motor command related to the rhythm generation of arm cycling is the primary signal responsible for the suppression of spinal reflex amplitude in stationary legs. Given that these pathways are likely part of the locomotor circuitry (Frigon et al, 2004) it suggests that rhythmic arm movement influences neural control of the legs during locomotion. Data in Chapter 5 also shows that a minimum frequency of arm cycling is required to significantly influence spinal circuitry of the legs suggesting that a minimum frequency of rhythmic movement is required to adequately engage putative interlimb locomotor circuits.

In sum the significant influence of rhythmic arm movement on the neural control of legs suggests the importance of incorporating rhythmic arm movement into gait rehabilitation strategies either in isolation or in conjunction with lower limb rhythmic exercise to take advantage of neural coupling (Ferris et al, 2006). In addition consideration should also be given to the minimum frequency of rhythmic movement to ensure adequate activation of desired locomotor circuits. These interlimb neural connections have been shown to be generally patent after stroke (Barzi and Zehr, in press).The importance of including the arms in rehabilitation has been shown in studies with individuals with spinal cord injury (Visintin and Barbeau, 1994; Behrman and Harkema, 2000). These patients displayed more symmetrical gait patterns and normal EMG activation when walking with arm swing compared to when arm swing was restricted by using the parallel bars (Visintin & Barbeau, 1994). Results from this thesis also suggest that load may potentially play a less critical role than frequency of movement in engaging these locomotor interlimb circuits despite previous research demonstrating the

significance of load receptor input during locomotion (Dietz and Duysens, 2000; Duysens et al, 2000).

7.4 Future Direction

Our understanding of the neural control of rhythmic movement in humans and specifically the control of rhythmic arm movement has advanced in recent years, however further research is required. For example it remains for future research to further: compare the neural control of arm cycling and arm swing during gait by exploring the neural control within different movement paradigms (e.g. varied movement frequency or load); characterize the differences in neural control between discrete vs. rhythmic tasks; directly contrast and compare the neural control of arms and legs within different paradigms; explore to what extent the neural control of rhythmic arm movement is altered after neurotrauma; and evaluate the impact of arm cycling training after neurotrauma or orthopaedic trauma on motor recovery of rhythmic and discrete movements.

In addition many questions remain about interlimb communication (i.e. between arms and legs) during rhythmic locomotor tasks in humans. For example what influence do other types of afferent feedback (e.g. vibration) have on interlimb communication? Given the link between spasticity and H-reflex amplitude and between arm cycling and the suppression of the H-reflex, what is the influence of arm cycling on spasticity in the leg muscles and what are functional implications to gait? What is the impact of arm cycling training on: spasticity in the arm and leg muscles and the motor control of arms and legs during rhythmic tasks (e.g. arm swing, stance and stepping during gait) as well as during discrete tasks.

The powerful influence of the frequency of rhythmic arm movement on interlimb communication to leg muscles suggests frequency should be considered during retraining of rhythmic movement like walking. Further research is required to help clarify such influences on interlimb communication. For example during walking what is the influence of the frequency of stepping and limb loading on interlimb communication (e.g. H-reflex amplitude in arm muscles)? Is there a threshold frequency of stepping required to significantly influence neural circuitry of the arms? To what extent is this interlimb communication preserved after neurotrauma? How can this information be effectively applied during training studies and ultimately clinical gait rehabilitation?

Much focus has been placed on the rhythmic control of limbs during gait while the activation of trunk muscles during gait has largely been ignored. The role of the trunk muscles during gait are essential to maintaining balance and therefore play an integral role in locomotion. Thus there is a great need for future research to determine the neural control of trunk muscles during gait, how these are altered with trauma, disease and aging and the potential implications this has for rehabilitation.

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