

Possible contributions of CPG activity to the control of rhythmic human arm movement¹

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Abstract: There is extensive modulation of cutaneous and H-reflexes during rhythmic leg movement in humans. Mechanisms controlling reflex modulation (e.g., phase- and task-dependent modulation, and reflex reversal) during leg movements have been ascribed to the activity of spinal central pattern generating (CPG) networks and peripheral feedback. Our working hypothesis has been that neural mechanisms (i.e., CPGs) controlling rhythmic movement are conserved between the human lumbar and cervical spinal cord. Thus reflex modulation during rhythmic arm movement should be similar to that for rhythmic leg movement. This hypothesis has been tested by studying the regulation of reflexes in arm muscles during rhythmic arm cycling and treadmill walking. This paper reviews recent studies that have revealed that reflexes in arm muscles show modulation within the movement cycle (e.g., phase-dependency and reflex reversal) and between static and rhythmic motor tasks (e.g., task-dependency). It is concluded that reflexes are modulated similarly during rhythmic movement of the upper and lower limbs, suggesting similar motor control mechanisms. One notable exception to this pattern is a failure of contralateral arm movement to modulate reflex amplitude, which contrasts directly with observations from the leg. Overall, the data support the hypothesis that CPG activity contributes to the neural control of rhythmic arm movement.

Key words: central pattern generator, locomotion, motor control, neural control.

Résumé : La modulation des réflexes cutanés et des réflexes-H est considérable durant le mouvement rythmique des jambes chez les humains. Les mécanismes régulant la modulation des réflexes (p. ex. modulation dépendante de la phase, modulation dépendante de la tâche et inversion des réflexes) durant les mouvements des jambes ont été attribués à l'activité des réseaux de générateurs centraux de patrons (CPG) spinaux et à la rétroaction périphérique. Notre hypothèse de travail a été que les mécanismes neuronaux (c.-à-d. CPG) contrôlant le mouvement rythmique sont situés entre la moelle épinière lombaire et cervicale. Ainsi la modulation des réflexes durant le mouvement rythmique des bras devrait être similaire à celle du mouvement rythmique des jambes. Cette hypothèse a été vérifiée en examinant la régulation des réflexes dans les muscles des bras durant un cycle rythmique des bras et une marche sur tapis roulant. Cet article passe en revue des études récentes qui ont indiqué que les réflexes dans les muscles des bras sont modulés au cours du cycle des mouvements (p. ex. dépendance envers la phase et inversion du réflexe) et entre les tâches motrices statiques et rythmiques (p. ex. dépendance envers la tâche). On conclut que les réflexes sont modulés de façon similaire durant le mouvement rythmique des membres supérieurs et inférieurs, suggérant la présence de mécanismes de contrôle moteur similaires. Une exception notable à ce patron est une incapacité du mouvement du bras controlatéral à

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moduler l'amplitude des réflexes, ce qui est diamétralement opposé à ce qui a été observé pour la jambe. Ces données confortent l'hypothèse que l'activité des CPG participe au contrôle neuronal du mouvement rythmique des bras.

Mots clés : générateur central de patron, locomotion, contrôle moteur, contrôle neuronal.

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Introduction

Without appearing to devote any conscious attention to the act, we typically move our arms rhythmically during locomotion. Locomotor activities like walking, running, and swimming all involve distinct rhythmic patterns of arm muscle activity and arm motions. In a considerable number of invertebrate and vertebrate preparations, neuronal activity related to central pattern generating (CPG) circuits for rhythmic locomotor movement have been identified (Grillner 1975; Grillner and Dubuc 1988; Duysens and Van de Crommert 1998; Duysens 1998; Van de Crommert et al. 1998). It was demonstrated long ago that the basic "machinery" for generating coordinated patterns of rhythmic movement reside largely in the spinal cord. Brown (Brown 1911; Brown 1914) in his experiments in the cat provided compelling evidence of neural oscillators (half-centres) resident in the lumbar spinal cord. This "half-centre" model suggests that discrete rhythm or pattern generating (i.e., CPG) networks are responsible for producing the basic locomotor rhythm. Interactions within and between flexor and extensor half-centres of a given limb were presumed to underlie the observed locomotor coordination (Grillner 1975). The available evidence based upon studies of many species indicates that central rhythm generators can produce coordinated motor patterns in isolation, but that exquisite functional regulation of relevant motor patterns requires afferent and supraspinal input (Rossignol 1996; Stein and Smith 1997).

Unlike the case of lower animal models such as the lamprey where direct cellular measurements can be made, we must rely on indirect evidence and inference to assess the contributions of CPGs to human movements. The preponderance of evidence in spinal cord – injured humans suggests that CPG mechanisms contribute to the locomotor pattern for leg muscles during walking (Dietz et al. 1994; Barbeau and Rossignol 1994; Harkema et al. 1997; Dietz 1997; MacKay-Lyons 2002; Steldt and Schmit 2004). Further, it has been shown that afferent feedback contributes strongly to the modulation of the putative CPG output during human walking (Duysens and Van de Crommert 1998; Duysens 1998; Van de Crommert et al. 1998). Research suggests that this concept also applies to leg cycling (Ting et al. 1998a, 1998b; Brooke et al. 1999; Ting et al. 2000; Zehr et al. 2001b). Reflex modulation during rhythmic movement can be used to infer the activity of CPG circuits (Burke 1999; Burke et al. 2001; Zehr and Duysens 2004). CPG-driven modulation of afferent feedback via premotoneuronal gating could explain observations of phase- and task-dependency of reflexes (Duysens and Tax 1994; Duysens and Van de Crommert 1998; MacKay-Lyons 2002; Dietz 2002a, 2002b). Indeed, the modulation of reflexes during rhythmic movement as an indirect indicator of CPG regulation of afferent input provides the background for the studies reviewed in this paper.

The extent to which CPG mechanisms may contribute to the control of rhythmic arm movement has remained relatively unstudied. Elftman (Elftman 1939) suggested years ago that rhythmic arm swing during human locomotion was not a simple pendular movement due to mechanical interaction with leg motion. Rather, muscle activity was necessary to produce rhythmic arm swing, a suggestion later confirmed by EMG recordings of arm muscles during walking (Fernandez-Ballesteros et al. 1965). It has also been demonstrated that this rhythmic movement is coordinated with lower limb movement during locomotion (Hogue 1969). A suggested function of arm swing has been to allow for smooth movement of the centre of mass during walking (Jackson et al. 1983). On the basis of mostly theoretical considerations, the idea was advanced that arm movement during walking is controlled by spinal CPG circuits (Jackson et al. 1978; Jackson 1983; Jackson et al. 1983).

Some time ago, modulation of cutaneous reflexes due to phase in the movement cycle was demonstrated in the cat hindlimb during locomotion (Forsberg et al. 1975). Since that time the modulation of cutaneous reflexes during rhythmic movement has received considerable attention (Duysens and Tax 1994; Brooke et al. 1997). Drew and Rossignol (Drew and Rossignol 1987) extended this work to the cat forelimb and showed a similar modulation pattern to that documented in the hindlimb. Thus, even though there are differences in functional use of the forelimbs and hindlimbs (e.g., exploratory reaching and manipulation with the forelimbs vs. locomotion with the hindlimbs), there may be similar underlying sets of neural circuits for the regulation of reflexes during rhythmic movement. Accumulating evidence in the feline forelimb preparation has clearly shown evidence of CPG activity (Yamaguchi 2004). During fictive locomotion, direct recordings from cervical motoneurons and last order interneurons provide evidence of rhythmic synaptic activation consistent with reverberating interneuronal circuits (e.g., CPG), as well as phase-modulated post-synaptic potentials evoked by stimulation of a cutaneous nerve innervating the forelimb (Hishinuma and Yamaguchi 1989; Ichikawa et al. 1991; Yamaguchi 1992a, 1992b; Seki and Yamaguchi 1997; Seki et al. 1997; Yamaguchi 2004). This has behavioural relevance during quadrupedal locomotion where it is necessary to directly couple and regulate rhythmic movements of the forelimb with similar mechanisms, like in the hindlimb. During human locomotion, however, there is no obvious need to move the upper limbs in concert with the lower limbs. Nevertheless, although we can walk quite easily without arm movement, we naturally move our upper limbs in rhythmic patterns during locomotion.

Our working hypothesis has been that CPG activity is involved in the regulation of rhythmic arm movement. This includes generating the basic pattern of muscle activity and controlling how afferent feedback helps to shape this basic pattern. Testing the contribution of CPG activity to the basic

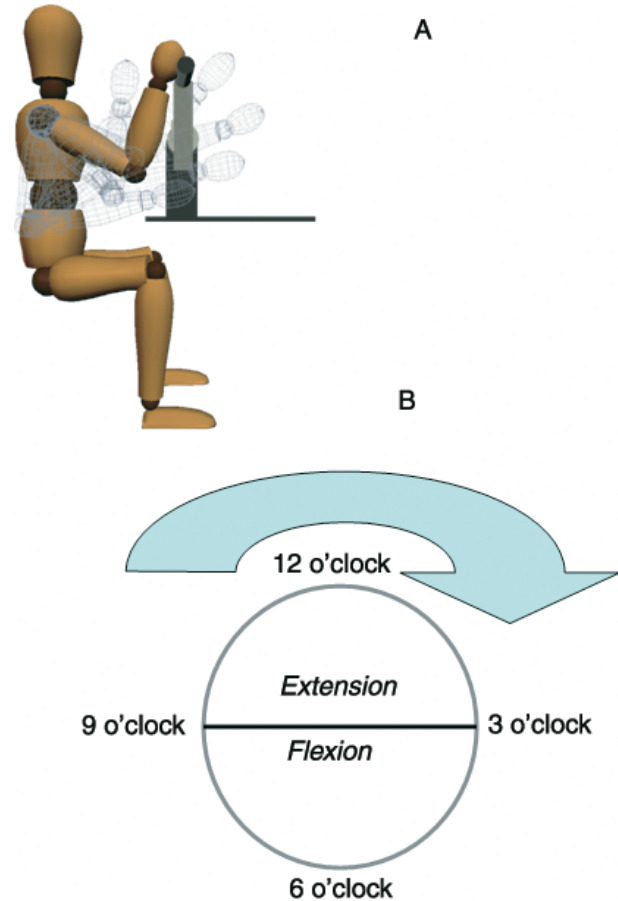
motor pattern for rhythmic movement in humans is difficult. However, investigating possible contributions of CPG activity to the regulation of afferent feedback is possible through human reflex studies. If CPGs contribute to the control of rhythmic arm movement, it follows that reflex modulation in these tasks should be similar to what has been shown for rhythmic leg movement. To determine the pattern of reflex modulation during rhythmic arm movement, it was first required to develop a task that could be easily manipulated and controlled and in which the arm musculature was rhythmically active and independent of leg movement. An arm cycling paradigm (see Fig. 1) was developed to examine the role of CPG activity during rhythmic arm movement. Fig. 1a shows a cartoon depicting arm cycling. The lower portion of the figure shows the framework in which the movement cycle is described for forward cycling. The movement cycle was broken into 12 phases corresponding to hours on the clock face (e.g., see 12 o'clock at top dead centre). When referenced to the motion of the hand, the movement cycle can be conceptually divided into 2 functional phases: extension of the arm (primarily elbow extension with shoulder flexion, equivalent to pushing the hand away from the body and occurring from 9 to 3 o'clock) and flexion of the arm (equivalent to pulling the hand and which involves shoulder extension and elbow flexion, 3 to 9 o'clock). Using this approach, the working hypothesis that CPG activity contributes to rhythmic arm movement has been tested by examining the extent to which reflex modulation is similar in the arms and legs. This review will focus on studies of rhythmic human arm activity that have revealed: (i) rhythmic and stereotyped EMG patterns; (ii) phase-dependent reflex modulation; (iii) task-dependent reflex modulation; (iv) differential effects on reflex amplitude of active vs. passive movement; (v) cutaneous reflex modulation during forward and backward cycling; (vi) influence of arm movement on reflex pathways in the legs; and (vii) weak effects on reflex modulation of contralateral arm movement. Observations (i)–(vi) all parallel those documented for the leg (Brooke et al. 1997; Zehr and Stein 1999; Zehr and Duysens 2004) and their existence in the arms, as well, suggests analogous organization of the control of rhythmic arm and leg movement.

EMG patterns in arm muscles during rhythmic arm movement

An important and defining feature of rhythmic limb movement is stereotyped rhythmic EMG activity. Rhythmic activity associated with locomotor movement of the legs shows distinct patterns of bursting between antagonist muscles within a limb and out of phase bursting between the limbs (Grillner 1975). During human walking there is rhythmic movement of the upper limbs due to active contraction of upper arm muscles that occurs in concert with the leg movement (Fernandez-Ballesteros et al. 1965; Hogue 1969). Whether there is a similar neural control mechanism for these events is uncertain, although comparable rhythmic patterns of activity between upper and lower limb muscles have been reported during locomotion (Weiss and St. Pierre 1983).

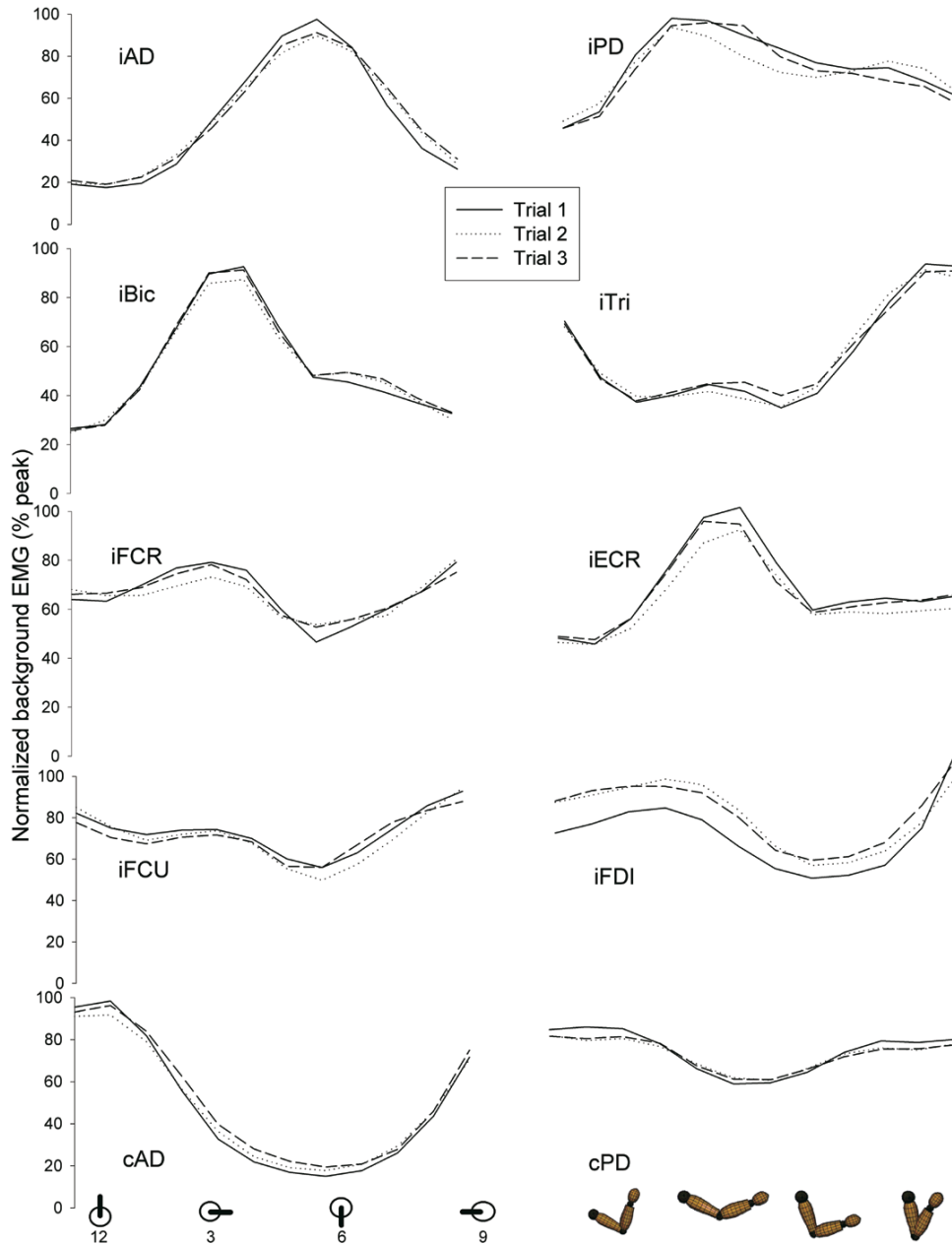
Similar to arm cycling, leg cycling also requires stereotyped rhythmic EMG activity in leg musculature (Brooke et al. 1997; Ting et al. 1998a, 1998b; Ting et al. 1999; Ting et al. 2000), and also provides for a very controllable paradigm

Fig. 1. (A) Illustration of the arm cycling paradigm. For forward motion, the direction of motion should be read clockwise from top (e.g., as indicated by the arrow in (B)). (B) Illustration of 2 portions of movement related to general arm extension or flexion and their relationship to movement phases described by the clock face (e.g., the 12, 3, 6, and 9 o'clock positions).



for the study of neural control. Stereotyped patterns of EMG are also seen in the arms during rhythmic arm cycling. Shown in Fig. 2 are plots of EMG associated with rhythmic arm cycling averaged across 11 subjects (from Zehr and Kido 2001). Shown at the bottom left of the figure is the approximate position of the hand cranks and at the bottom right, the approximate position of the arm at the 12, 3, 6, and 9 o'clock positions. As can be seen for muscles of the shoulder, elbow, and wrist, EMG activity is rhythmically modulated throughout the movement cycle. The activity of flexor and extensor muscles (e.g., compare Tri with Bic) and ipsilateral and contralateral muscles (e.g., compare iAD with cAD) is out of phase and reciprocal. These patterns are similar to those obtained during rhythmic motor activities performed with the legs during walking (Winter 1991) or leg cycling (Ryan and Gregor 1992; Brown et al. 1996; Brown et al. 1997) as well as EMG patterns in the arms during walking (Fernandez-Ballesteros et al. 1965; Hogue 1969; Zehr and Haridas 2003). Note also that there are 3 separate trials of arm cycling plotted in Fig. 2. There is considerable similarity across the 3 trials shown, which suggests stability in the stereotyped neural control.

Fig. 2. Normalized background EMG during rhythmic arm cycling. Values are averaged across 11 subjects for each trial. Abbreviations are: AD (anterior deltoid), PD (posterior deltoid), Bic (biceps brachii), Tri (triceps brachii), FCR (flexor carpi radialis), ECR (extensor carpi radialis), FCR flexor carpi radialis, FDI (first dorsal interosseus). “i” and “c” denote ipsilateral and contralateral (relative to site of stimulation) muscles. Values are normalized to the peak value obtained during arm cycling for each subject. Shown by the 3 different lines are the averages for 3 consecutive movement trials (each containing ~100 cycles) for each subject. The approximate position of the hand and ipsilateral arm in the movement cycle are indicated at the bottom of the figure. At bottom left the numbers correspond to position on the clock face. Adapted from Zehr and Kido (2001).



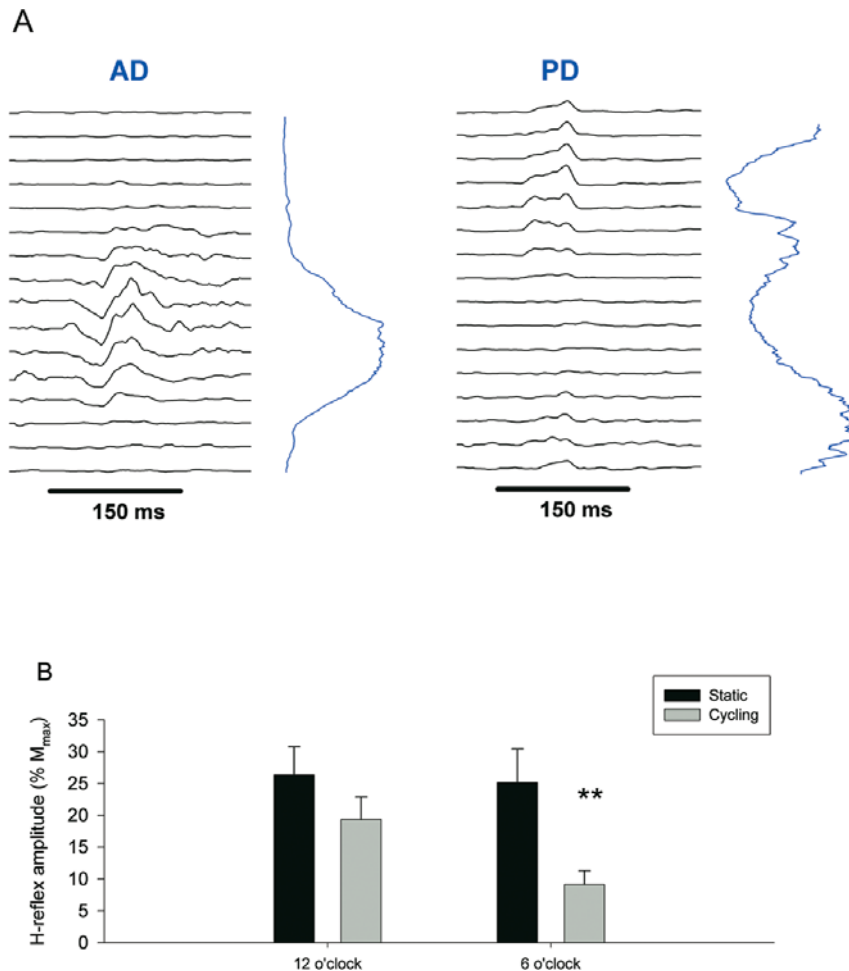
Phase-dependent reflex modulation: independence of motor output and reflex amplitude

In the lower limb, the general observation regarding reflexes is that the reflex amplitude is often uncoupled from the locomotor EMG and is instead related to the phase of the movement cycle during which the reflex is evoked (“phase-dependent modulation” see Brooke et al. 1997 for review; Komiyama et al. 2000; Duysens and Tax 1994). Such uncoupling implies a gating of afferent feedback to motoneurons during movement. A principle from the lower limb is that

the functional utility of reflexes is due, in large part, to flexibility of responses occurring throughout a movement cycle (Zehr and Stein 1999). Consequently, the gain of reflexes changes according to the behavioural context so that reflexes can contribute to correct or assist the ongoing movement.

Earlier research demonstrated a phase-dependent modulation of stretch reflexes in the arm. Stretch reflexes in the elbow flexor muscles biceps brachii and brachialis were modulated at different positions during the performance of cyclical reciprocating flexion-stop/extension-stop movements

Fig. 3. Phase-dependence of reflexes during arm cycling. A. Cutaneous reflexes are modulated in amplitude across the movement cycle (read from top to bottom). Note that the background rhythmic EMG amplitudes are shown at far right for each muscle. Abbreviations: AD (anterior deltoid), PD (posterior deltoid), i (ipsilateral) and c (contralateral) to site of stimulation. Adapted from Zehr and Chua (2000). B. Modulation of forearm H-reflexes during arm cycling (light bars) but not during static contraction (adapted from Zehr et al. 2003). Values are mean \pm SE. **, denotes significant differences between static and cycling conditions.

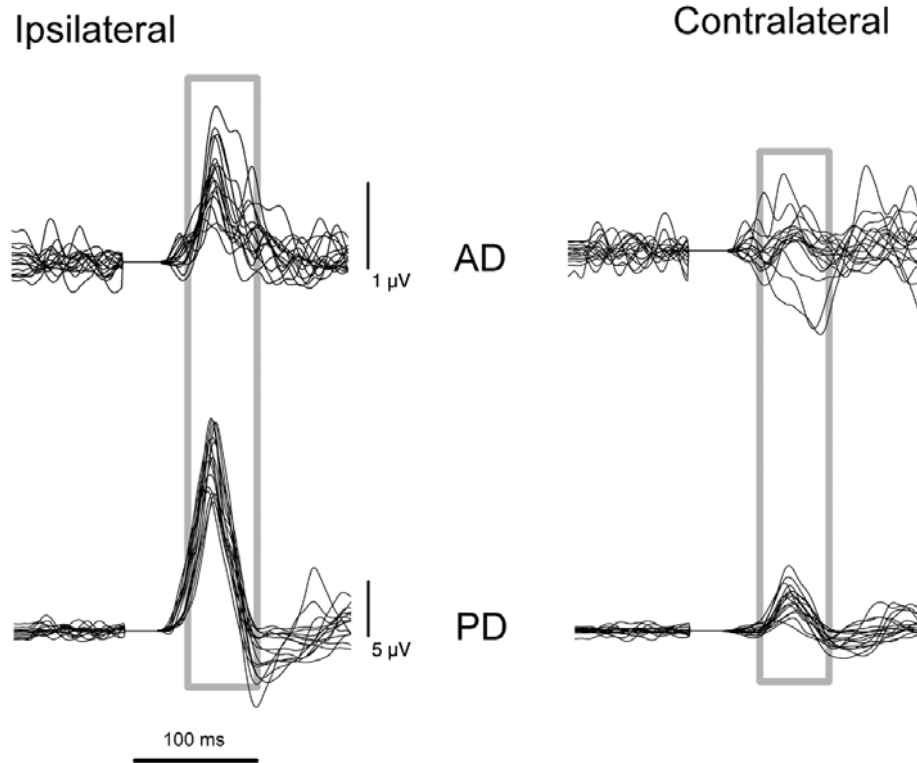


at the elbow (MacKay et al. 1983). This observation of movement-induced modulation of muscle afferent reflexes was one of the first demonstrated in the upper limb. However it is uncertain whether this modulation was correlated with background EMG activity. Further, movement at individual joints (particularly the wrist) has also been shown to alter forearm H-reflexes (Carson et al. 1999), but this may have been because of differences in EMG activity of the forearm. Asymmetrical flexion-extension movements (i.e., reciprocating displacements of variable amplitude) at the wrist or elbow were also shown to significantly reduce H-reflex amplitude in forearm flexor muscles (Brooke et al. 2000). We recently showed that rhythmic whole arm cycling significantly suppresses the forearm H-reflex in a manner that is independent of muscle activity level (Zehr et al. 2003). The significance of these observations is that H-reflex amplitudes in arm muscles can be modulated during rhythmic movement in a manner that is independent of EMG activity. We suggest that a combination of CPG activity and peripheral feedback cause this modulation.

As shown in Fig. 3a, the amplitudes of cutaneous reflexes were phase-dependently modulated throughout the move-

ment cycle. Reflexes changed in amplitude as a function of the phase of the movement. However, the background EMG level also changed with position in the cycle (see vertical traces to the right of each panel). Thus, while there is a phasic pattern of cutaneous reflex modulation during rhythmic arm movement, there is also background EMG-dependent modulation (Zehr and Chua 2000). We evaluated the extent to which early and middle latency cutaneous reflex amplitudes were related to background EMG (Zehr and Kido 2001). In a larger sample of 10 muscles studied with stimulation of 3 cutaneous nerves, reflexes in more than half of the muscles failed to demonstrate a significant background-dependency. We also evaluated whether reflexes were modulated by arm position during static contraction. While the background EMG level was significantly altered by the position of the arm for 5 muscles, there were no instances where arm position during static contraction significantly modulated early or middle latency reflexes in any muscle. Thus, there was no modulation of cutaneous reflexes by alterations in arm posture during static contraction but only during rhythmic movement. H-reflexes in wrist flexor muscles were also shown to be modulated by phase during rhythmic cycling

Fig. 4. Reflex EMG traces (created by subtraction of control EMG from traces with stimulation) from a single subject showing reflexes evoked by SR nerve stimulation during walking. Reflex traces for each of the 16 parts of the step cycle have been superimposed in each panel. Stimulus artefact has been removed from 0 to ~30 ms post-stimulus and is shown as a flat horizontal line during this period. Muscle abbreviations are AD (anterior deltoid) and PD (posterior deltoid). Ipsilateral and contralateral refer to site of nerve stimulation. Calibration bars are 1 and 5 μ V, for AD and PD, respectively. Muscles are plotted to the same scales (adapted from Zehr and Haridas 2003).



but not during static contraction (Zehr et al. 2003) (See Fig. 3*b*).

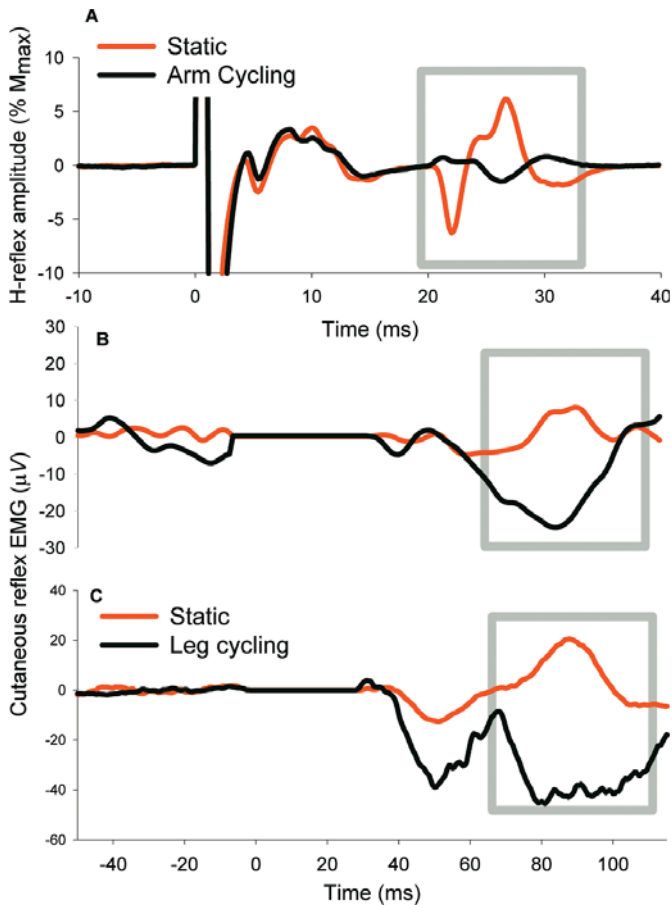
Cutaneous reflexes are also phase-modulated in arm muscles during walking (Zehr and Haridas 2003). Eight muscles controlling the elbow and shoulder were studied bilaterally during walking with superficial radial nerve (SR; innervates dorsolateral portion of the hand) stimulation. Reflexes were significantly modulated by position in the step cycle (see Fig. 4). Reflex traces from 16 portions of the walking cycle are shown superimposed for 4 muscles in the figure and the modulation is highlighted by the vertical gray rectangle. While presentation of the data in this way obscures strict correspondence with position in the movement cycle, it can be seen that reflex amplitude varied across the walking cycle. In no case was reflex amplitude during walking significantly correlated with arm muscle EMG activity. The phase-dependent modulation of reflex amplitude (including reversal of sign) suggests the premotoneuronal gating of afferent inputs to motoneurons by the activity of neural circuits, which are active during rhythmic movement. These circuits could be supraspinal and (or) related to spinal CPG networks. A critical distinction used to infer CPG activity is that these patterns of reflex control are differentially modulated in different tasks where voluntary control of static contractions can be separated from more automatic control of rhythmic muscle activity.

Task-dependent reflex modulation

Reflex control seen in the human legs during rhythmic movement has a strict dependency on the motor task performed (i.e., task-dependency) (Stein and Capaday 1988). Task-dependency refers to changes in reflex sign and amplitude that occur between different motor tasks. For cutaneous reflexes in leg muscles, task-dependency has been shown in standing vs. running (Duysens et al. 1993), standing vs. walking (Komiya et al. 2000), cyclic vs. static contraction (Brown and Kukulka 1993; Zehr et al. 2001), and stable vs. unstable standing (Burke et al. 1991). The main observation from these experiments was that rhythmic movements have distinctly different reflex patterns from static contractions. Task dependency of reflexes in arm muscles has also been observed during walking. During static motor tasks by arm muscles, there was a direct relationship between background EMG amplitude and cutaneous reflex amplitude evoked by stimulation in the hand (Zehr and Haridas 2003) and foot (Dietz et al. 2001; Haridas and Zehr 2003). This relationship was absent or very weak during locomotion.

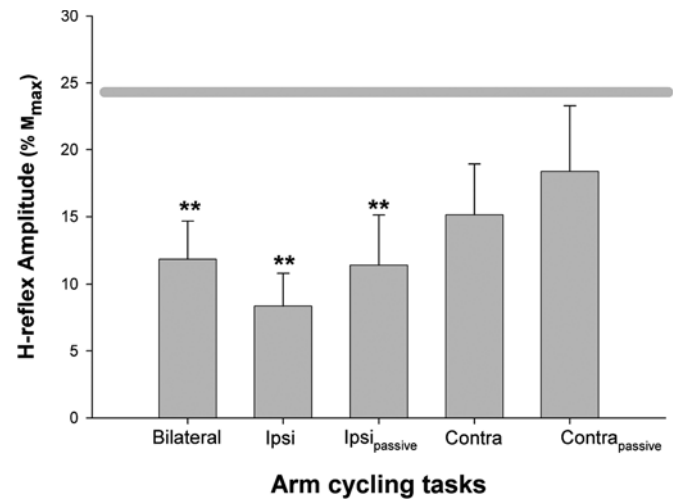
During arm cycling, the amplitude of H-reflexes in forearm flexor muscles was reduced significantly compared with static contraction (Zehr et al. 2003; see Figs. 3*b*, 5*a*, and 6). Bilateral cycling and active and passive movement of the stimulated limb had similar effects on H-reflex amplitude, but movement of the contralateral arm did not have a signifi-

Fig. 5. (A) Task-dependent reflex modulation in H-reflexes and (B and C) cutaneous reflexes when going from static contraction (light trace) to rhythmic cycling (dark trace). (A) Plotted are H-reflexes in FCR muscle from one subject. The large clipped vertical deflection at time 0 is the stimulus artifact and the M-wave is seen following it. The H-reflex has been highlighted by the vertical gray rectangle. Note the inhibition of H-reflex amplitude during arm cycling. Adapted from Zehr et al. (2003). (B) Plotted are subtracted reflex EMG traces evoked in AD muscle by SR nerve stimulation for one subject during rhythmic arm cycling. The middle latency response has been highlighted by the vertical gray rectangle. Note the reversal in sign from excitation during static contraction to inhibition during arm cycling. Adapted from Zehr and Kido (2001). (C) Subtracted reflex EMG traces evoked by distal tibial nerve stimulation for MG muscle in one subject comparing reflex amplitude during static contraction and active leg cycling. The reversal in reflex sign is highlighted by the rectangle. Note the similarity of reversal here and in panel B during arm cycling. Adapted from Zehr et al. (Zehr et al. 2001b).



cant effect (see sections 4 and 7). Thus, H-reflexes are task-dependent during rhythmic movement of the upper limb. This is consistent with results on task-dependent modulation of cutaneous reflexes during arm cycling (Zehr and Kido 2001). In that study, task-dependency could be observed as a change in reflex amplitude or sign (see Fig. 5b). Shown in the figure is an example of task-dependent reflex reversal of a middle latency cutaneous reflex. Generally, cutaneous reflexes are of larger amplitude during arm cycling than dur-

Fig. 6. Modulation of the forearm flexor H-reflex by arm movement. H-reflexes were significantly attenuated during bilateral, and ipsilateral active (IPSI) and passive (IPSI_{passive}) arm cycling compared with static contraction (horizontal gray line). Movement of the contralateral (CONTRA) arm had no significant effect. There were no differences in M-wave amplitudes or FCR EMG levels (not plotted). Values are means \pm SEM for 9 subjects. **, significant ($p < 0.01$) differences from static control data (shown by thick, horizontal gray line). Adapted from Zehr et al. (2003).



ing static contraction. Sometimes the task-dependency can also be expressed as a switch in the sign of middle latency cutaneous reflexes, from facilitation during static contraction to inhibition during movement. Interestingly, this task-dependency of cutaneous reflexes is very similar to that seen during leg cycling (Zehr et al. 2001b). In that study it was shown that cutaneous reflexes in the ankle extensor medial gastrocnemius (MG) was excitatory during static contraction but switched to inhibition during leg cycling at matched positions (see Fig. 5c). CPG activity could regulate this reflex reversal during leg cycling and a similarity of responses in the arms during arm cycling suggests similar underlying neural mechanisms. The implication of these observations is that neural mechanisms active only during rhythmic movement (i.e., CPGs or peripheral feedback) have a specific modulatory effect on reflex amplitude.

Active vs. passive arm movement

Comparison of active and passive movement can be used to dissociate the contributions to reflex modulation that stem from central structures (e.g., supraspinal inputs and CPG output) from those related to peripheral feedback generated by the movement itself (e.g., muscle spindle discharge, skin stretch, etc.). Modulation of reflexes during passive movement provides evidence that reflex pathways can be gated in part by peripheral feedback. This has been demonstrated to great effect for the H-reflex pathway in the human leg, where soleus H-reflexes during leg cycling are strongly inhibited by both active and passive movement (see Brooke et al. 1997 for review). Passive movement about the hip also modulates H-reflex amplitude in neurologically intact and spinal cord injured humans (Knikou and Rymer 2002a, 2002b). Cutaneous reflexes in the leg are modulated during

the movement cycle when active leg cycling is performed (Brown and Kukulka 1993). In contrast, such modulation of cutaneous reflexes is absent during passive movement (Brooke et al. 1999). Thus there is a difference in the control of cutaneous and H-reflexes in leg muscles during leg movement. Cutaneous reflexes are likely gated primarily by CPG mechanisms whereas H-reflexes are gated by a combination of CPG activity and afferent feedback (Zehr et al. 2001*b*).

As has been shown in the leg, H-reflexes in the forearm muscles were shown to be inhibited by passive movement (Zehr et al. 2003)(see Fig. 6) whereas passive movement had little effect on cutaneous reflexes during arm cycling (Carroll et al. 2004). Further, the pattern of cutaneous reflex modulation depended almost exclusively on the performance of rhythmic activity with the arm in which the reflex was expressed (Carroll et al. 2004). In comparison to active movement, cutaneous reflexes were small during passive arm cycling and showed little phase modulation at either early or middle latency (such as has been demonstrated during passive leg cycling; Brooke et al. 1999). The general pattern suggests that meaningful modulation of cutaneous reflexes in arm muscles occurs only during active arm cycling.

Cutaneous reflexes during forward and backward arm cycling

Experiments in various preparations (e.g., cat and crayfish) have indicated that the motor program for forward movement (e.g., CPG for locomotion) may be run in reverse during backwards locomotion (Pearson 1993). Studies of backward and forward walking in the cat show that when the direction of motion is reversed, muscles are activated with a similar temporal pattern but in reverse order (Buford and Smith 1990; Buford and Smith 1993; Perell et al. 1993). It has also been demonstrated in humans that when reversed, kinematics (most notably at the hip) and EMG of backward walking resemble those of forward walking (Thorstensson 1986; Winter et al. 1989; Grasso et al. 1998). Accordingly, an interesting test of the concept of CPG activity in regulating human rhythmic movement was conducted by Duysens and colleagues (Duysens et al. 1996). They studied modulation of cutaneous reflexes during forward and backward treadmill walking. Possibly because of the small differences in the biomechanics of forward vs. backward walking (e.g., ankle motion), it was not a completely simple reversal of the pattern of cutaneous reflex modulation for forward and backward directions in all muscles. For example, during forward motion, the swing-to-stance transition occurs with heel strike, whereas during backward motion toe contact occurs at the same functional portion for the cycle. The general pattern of modulation of reflex amplitude throughout the step cycle was explained in terms of a CPG running in "reverse" when going backward and allowing the expression of a cutaneous reflex at the same functional portion of the movement cycle. Recently this experimental approach was applied to arm cycling (Zehr and Hundza, in press). The approach in cycling avoids some of the biomechanical difficulties (e.g., ankle motion) mentioned for backward walking because it is relatively simple to perform a simple reversed movement during backward versus forward cycling. Indeed, forward and backward leg cycling generate very similar but phase-reversed EMG patterns

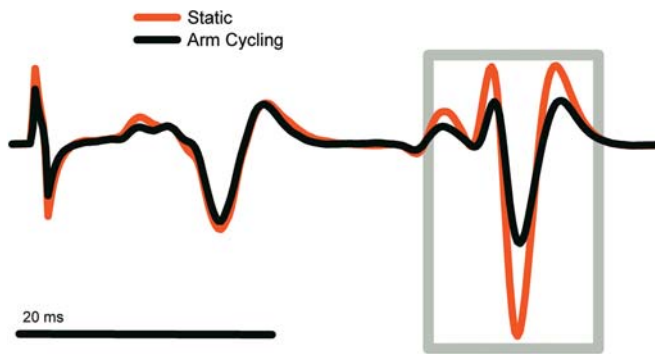
(Eisner et al. 1999; Ting et al. 1999). The patterns of EMG activity were also quite similar for forward and backward arm cycling (Zehr and Hundza, in press). However, EMG amplitudes were typically higher during backward cycling. Interestingly, reflex amplitudes were also modulated similarly during forward and backward cycling when examined at the same position in the cycle. That is, maximal amplitudes of cutaneous reflexes were seen at similar positions in the arm cycling motion (e.g., at the same "o'clock") irrespective of forward vs. backward movement and independent of EMG level. This suggests that the circuits regulating rhythmic arm movement may work in a similar but simply reversed way during backward arm cycling. This observation is thus generally similar to that seen during cutaneous reflex modulation in backward walking (Duysens et al. 1996).

Effects of rhythmic arm movement on reflexes in the legs

Pathways linking the forelimbs and hindlimbs during movements requiring coordination of all 4 limbs in quadrupeds have received significant attention (Miller et al. 1973; Schomburg and Behrends 1978). Dietz (2002*a*, 2000*b*) has suggested that humans may also use quadrupedal coordination, yet little is actually known about the effect of arm movement on the excitability of reflexes in the legs of humans. The effects of stimulation of the cutaneous superficial peroneal (SP, innervating the foot dorsum) and SR nerves (innervating the hand) were examined in subjects maintaining tonic contractions (Zehr et al. 2001*a*). Interlimb cutaneous reflexes were seen in lower limb muscles after stimulation of the SR nerve in the hand as well as in upper limb muscles after stimulation of the SP nerve in the foot. It was recently shown that during locomotion interlimb cutaneous reflexes in both the arms and legs evoked by stimulation at the hand (SR) and foot (SP) were phase-modulated during the walking cycle and were also task-dependent (Haridas and Zehr 2003). Furthermore, extensive phase- and task-dependent modulation of cutaneous reflexes was seen in many arm and leg muscles after SR stimulation during walking (Zehr and Haridas 2003). This may be evidence for functionally useful connections between the arms and legs that may play a role in the coordination of the limbs during walking. Reflex pathways linking cutaneous fields in the hand to arm and leg muscles could assist in obstacle avoidance and response to perturbations as has been discussed for reflexes within the legs (Zehr and Stein 1999). That is, coordination between the limbs requires coordination of CPGs for the limbs. One way this linkage could be tested is to evaluate the effect of movement of the arms on reflexes in the legs.

Since both rhythmic arm and leg movements are performed simultaneously during walking, it is very difficult to evaluate the location of the mechanisms regulating interlimb reflexes during locomotion. Further, there may be an interaction between neural centres regulating rhythmic leg and arm movements during walking. Thus, it is also necessary to examine the effects of rhythmic arm and leg movement in isolation. That is, for example, when the arms are rhythmically active but the legs are stationary. It had been suggested that the position of the arms could affect soleus H-reflex ampli-

Fig. 7. Inhibition of soleus H-reflex amplitude by arm cycling. Amplitudes during cycling (dark line) and during static trials (light line) are shown for a single subject. The gray rectangle indicates the H-reflex. Control data are taken during static contraction at the same position sampled during arm cycling. Adapted from Frigon et al. (Frigon et al. 2004).



tude (Delwaide et al. 1973; Delwaide et al. 1977; Eke-Okoro 1994). Very recently, the effects of rhythmic arm cycling on H-reflex excitability in the soleus muscle have been studied (Frigon et al. 2004). When subjects performed rhythmic arm cycling, soleus H-reflexes were inhibited relative to reflexes evoked when there was no arm movement (see Fig. 7). The effect of this movement-induced inhibitory conditioning of soleus H-reflex amplitude was shown to interact with somatosensory conditioning evoked by sural or common peroneal nerve stimulation. This led to the suggestion that the modulation is probably mediated by presynaptic inhibition of IA afferent terminals. Interestingly, presynaptic inhibition is a dominant mechanism associated with the control of rhythmic movement (Gossard et al. 1990)(for a review see Stein 1995) and is known to modulate the H-reflex pathway (Brooke et al. 1997). Furthermore, it is thought that mechanisms of presynaptic inhibition may help functionally link CPG-related locomotor activity in the cat forelimbs and hindlimbs (Rossignol et al. 1998). It is possible that rhythmic arm cycling may set a background level of reflex excitability for reflexes in the legs and that this is related to the linkage between arm and leg movement during locomotion. That is, the pattern of reflex conditioning observed in these studies could represent the functional linkage of CPGs regulating arm and leg motions during locomotion.

Ipsilateral vs. contralateral movement

A requirement for coordinated locomotor-related rhythmic movement is coupling between the limbs. It has been proposed that humans use “quadrupedal coordination” (Dietz 2002a) which includes CPGs for each limb (Zehr and Duysens 2004). One aspect of this coupling is the modulation of crossed reflexes (e.g., a reflex recorded in one arm after stimulation of the other arm). The extent to which movement of one limb influences reflex modulation in the other, contralateral limb, can be used to infer this type of CPG-related gating of crossed reflexes. The strength of coupling between the limbs is quite strong for the legs. Contralateral leg movement has a general suppressive effect

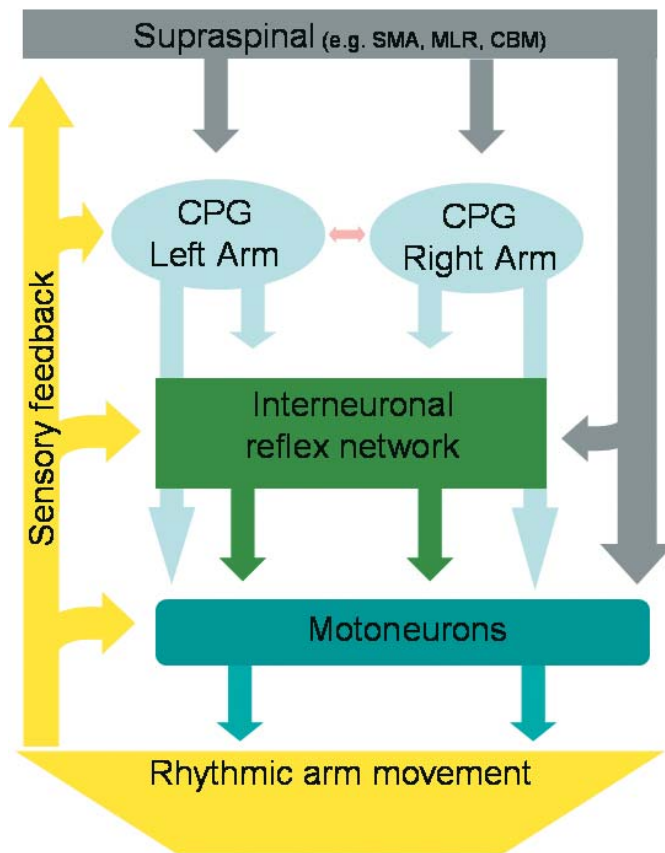
on the soleus H-reflex with no phase-dependence (Collins et al. 1993; Cheng et al. 1998). This effect is also seen during passive movement of the contralateral leg (Cheng et al. 1998), suggesting part of this modulation is due to peripheral feedback only. However, experiments which have involved similar modifications during walking suggest that central output also has a very strong effect (Garrett et al. 1999; Schneider et al. 2000).

In the arm, Delwaide et al. (Delwaide et al. 1988) showed that both active and passive rhythmic movement of the contralateral arm alone had little effect on the size of H_{\max} in the forearm muscles, a result which contrasts with the observations for the legs. During arm cycling we also found that contralateral movement (whether active or passive) did not suppress forearm H-reflexes of various sizes (Zehr et al. 2003)(see Fig. 6). This lack of an effect of contralateral movement in the arms suggests a strong specification for modulation in the H-reflex pathway associated with each arm. Similarly, for cutaneous reflexes, contralateral arm cycling had relatively little effect on reflex amplitude in the opposite arm (Carroll et al. 2004). These observations on cutaneous reflexes suggest that there is relatively weak coupling between the arms during rhythmic arm movements. Taken together with the observations on H-reflex modulation, it appears that the neural mechanisms regulating rhythmic arm movement are more powerfully specified for each individual arm than is the case for the legs. CPGs for the arms seem to be less involved in gating crossed reflexes than that observed for the legs. This may arise because of weaker coupling between CPGs for each arm than is the case for the legs. We have speculated that this could be because of the difference in how often isolated arm and leg movements are performed habitually (Zehr et al. 2003).

Summary and conclusion

In the human, patterns of cutaneous and H-reflex modulation in leg muscles likely represent activity of CPG networks associated with generating rhythmic locomotor drive for leg movement (Duysens and Tax 1994; Duysens and Van de Crommert 1998; Brooke et al. 1999; Zehr et al. 2001b). The extensive task- and phase-dependency of reflexes observed in arm muscles during rhythmic arm cycling and walking suggests that there may be CPG networks contributing to the control of rhythmic arm movement. As described above, much of what has been documented for the legs during rhythmic leg movement was also seen in the arms during rhythmic arm movement. It is proposed that the rhythmic EMG activity and patterns of reflex modulation observed in the arms during rhythmic movements are consistent with the existence of a separate CPG for the control of each arm. This is similar to what could be predicted based upon a distributed segmental model for CPG networks (Kiehn et al. 1997; Stein and Smith 1997; Pearson and Ramirez 1997; Duysens and Van de Crommert 1998; Duysens 1998; Pearson 2000). However, there is relatively weak coupling between the arms when compared with that observed for leg muscles. The weaker coupling between the arms is reflected primarily by the observation that movement of the contralateral arm has little effect on reflex modulation, an observation which contrasts with what has been described for leg

Fig. 8. Schematic illustration of the possible organization of neural mechanisms regulating rhythmic arm movement. Supraspinal input is shown descending from the top onto CPGs for left and right arms, interneuronal reflex networks, and motoneuronal pool. Feedback arising from movement is shown at far left and feeds onto the motoneurons, reflex networks, CPGs, and supraspinal centres. The relatively weak interaction between left and right arms is shown by the small reciprocal arrow. CPG, central pattern generator; SMA, supplementary motor area; MLR, mesencephalic locomotor region; CBM, cerebellum.



muscles. As mentioned, it has been suggested that CPGs controlling homologous muscles during locomotion are tightly coupled in the quadruped (Hultborn et al. 1998; MacKay-Lyons 2002). It is possible that a tight coupling also acts between the legs of humans which are habitually used in reciprocal bilateral movements but that the coupling is weak or absent between the arms which are frequently used independently.

The general organization of the neural control of rhythmic arm movement is conceptualized in the schema shown in Fig. 8. In many ways it is an elaboration of a model proposed some years ago to represent CPG mechanisms regulating human walking (Patla et al. 1985) and is inspired by the models proposed by Burke and colleagues for the quadruped (Burke 1999; Burke et al. 2001). The model shows separate CPGs for each arm, with loose coupling which can be modulated by supraspinal input and peripheral feedback, between the arms. It may be that some of the coupling between left and right arm CPGs is achieved through corticospinal projections arising from the supplementary motor area, as

has been suggested for other bimanual movements (Sadato et al. 1997; Stephan et al. 1999), especially those utilizing continuous rhythmic timing (Ullén et al. 2003). Given the important role of the mesencephalic locomotor region for regulation of lower limb rhythmic movement (see, for review, Whelan 1996), this may also be involved for rhythmic arm movement. A coordinative role for the cerebellum may also be anticipated (Crowdy et al. 2000; Pardoe et al. 2004). In the model, CPG outputs may drive rhythmic arm movement both directly, via action on the motoneuronal pools, and indirectly, via interneuronal reflex networks. Supraspinal inputs can act directly on the CPGs, interneuronal reflex networks, and motoneurons. Feedback arising from rhythmic arm movement is shown ascending at left. Evidence from numerous experiments has been summarized here to support the contention that CPG activity contributes to the production of rhythmic arm movement. Presently we have no clear way of measuring or estimating the extent of this contribution, and it is likely that there is a large role for supraspinal control (including possible inputs from primary motor cortex) during rhythmic arm movements, just as in the leg movements of human walking (Schubert et al. 1997; Capaday et al. 1999; Schubert et al. 1999). We suggest that the spinal circuitry for rhythmic arm movement (e.g., CPGs) acts as a “core” to help coordinate arm and leg muscle activity during gait. Superimposed upon this core are supraspinal and peripheral inputs that can sculpt the basic pattern to the particular needs of the individual during locomotion. It remains for further research to evaluate the nature and extent of the contribution from each of these control mechanisms to natural movements.

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References

- Barbeau, H., and Rossignol, S. 1994. Enhancement of locomotor recovery following spinal cord injury. *Curr. Opin. Neurol.* **7**: 517–524.
- Brooke, J.D., Cheng, J., Collins, D.F., McIlroy, W.E., Miasazek, J.E., and Staines, W.R. 1997. Sensori-sensory afferent conditioning with leg movement: gain control in spinal reflex and ascending paths. *Prog. Neurobiol.* **51**: 393–421.
- Brooke, J.D., McIlroy, W.E., Staines, W.R., Angerilli, P.A., and Peritore, G.F. 1999. Cutaneous reflexes of the human leg during passive movement. *J. Physiol. (Lond.)*, **518**: 619–628.
- Brooke, J.D., Peritore, G., Staines, W.R., McIlroy, W.E., and Nelson, A. 2000. Upper limb H reflexes and somatosensory evoked potentials modulated by movement. *J. Electromyogr. Kinesiol.* **10**: 211–215.
- Brown, T.G. 1911. The intrinsic factors in the act of progression in the mammal. *Proc. Royal Soc. Lond.* **84**: 308–319.

- Brown, T.G. 1914. On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *J. Physiol.* **48**: 19–46.
- Brown, D.A., and Kukulka, C.G. 1993. Human flexor reflex modulation during cycling. *J. Neurophysiol.* **69**: 1212–1224.
- Brown, D.A., Kautz, S.A., and Dairaghi, C.A. 1996. Muscle activity patterns altered during pedaling at different body orientations. *J. Biomech.* **29**: 1349–1356.
- Brown, D.A., Kautz, S.A., and Dairaghi, C.A. 1997. Muscle activity adapts to anti-gravity posture during pedalling in persons with post-stroke hemiplegia. *Brain*, **120**: 825–837.
- Buford, J.A., and Smith, J.L. 1990. Adaptive control for backward quadrupedal walking. II. Hindlimb muscle synergies. *J. Neurophysiol.* **64**: 756–766.
- Buford, J.A., and Smith, J.L. 1993. Adaptive control for backward quadrupedal walking. III. Stumbling corrective reactions and cutaneous reflex sensitivity. *J. Neurophysiol.* **70**: 1102–1114.
- Burke, R.E. 1999. The use of state-dependent modulation of spinal reflexes as a tool to investigate the organization of spinal interneurons. *Exp. Brain Res.* **128**: 263–277.
- Burke, D., Dickson, H.G., and Skuse, N.F. 1991. Task-dependent changes in the responses to low-threshold cutaneous afferent volleys in the human lower limb. *J. Physiol. (Lond.)*, **432**: 445–458.
- Burke, R.E., Degtyarenko, A.M., and Simon, E.S. 2001. Patterns of locomotor drive to motoneurons and last-order interneurons: Clues to the structure of the CPG. *J. Neurophysiol.* **86**: 447–462.
- Capaday, C., Lavoie, B.A., Barbeau, H., Schneider, C., and Bonnard, M. 1999. Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *J. Neurophysiol.* **81**: 129–139.
- Carroll, T.J., Zehr, E.P., and Collins, D.F. 2004. Modulation of cutaneous reflexes in human upper limb muscles during arm cycling is independent of activity in the contralateral arm. *Exp. Brain Res.* In press.
- Carson, R.G., Riek, S., and Bawa, P. 1999. Electromyographic activity, H-reflex modulation and corticospinal input to forearm motoneurons during active and passive rhythmic movements. *Hum. Mov. Sci.* **18**: 307–343.
- Cheng, J., Brooke, J.D., Misiaszek, J.E., and Staines, W.R. 1998. Crossed inhibition of the soleus H-reflex during passive pedalling movement. *Brain Res.* **779**: 280–284.
- Collins, D.F., McIlroy, W.E., and Brooke, J.D. 1993. Contralateral inhibition of soleus H reflexes with different velocities of passive movement of the opposite leg. *Brain Res.* **603**: 96–101.
- Crowdy, K.A., Hollands, M.A., Ferguson, I.T., and Marple-Horvat, D.E. 2000. Evidence for interactive locomotor and oculomotor deficits in cerebellar patients during visually guided stepping. *Exp. Brain Res.* **135**: 437–454.
- Delwaide, P.J., Figiel, C., and Richelle, C. 1973. Influence de la position du membre supérieur sur l'excitabilité de l'arc soleaire. *Electromyogr. Clin. Neurophysiol.* **13**: 515–523.
- Delwaide, P.J., Figiel, C., and Richelle, C. 1977. Effects of postural changes of the upper limb on reflex transmission in the lower limb. Cervicolumbar reflex interactions in man. *J. Neurol. Neurosurg. Psychiatry*, **40**: 616–621.
- Delwaide, P.J., Sabatino, M., Pepin, J.L., and La, G.V. 1988. Reinforcement of reciprocal inhibition by contralateral movements in man. *Exp. Neurol.* **99**: 10–16.
- Dietz, V. 1997. Locomotor recovery after spinal cord injury. *Trends Neurosci.* **20**: 346–347.
- Dietz, V. 2002a. Do human bipeds use quadrupedal coordination? *Trends Neurosci.* **25**: 462–467.
- Dietz, V. 2002b. Proprioception and locomotor disorders. *Nat. Rev. Neurosci.* **3**: 781–790.
- Dietz, V., Colombo, G., and Jensen, L. 1994. Locomotor activity in spinal man. *Lancet*, **344**: 1260–1263.
- Dietz, V., Fouad, K., and Bastiaanse, C.M. 2001. Neuronal coordination of arm and leg movements during human locomotion. *Eur. J. Neurosci.* **14**: 1906–1914.
- Drew, T., and Rossignol, S. 1987. A kinematic and electromyographic study of cutaneous reflexes evoked from the forelimb of unrestrained walking cats. *J. Neurophysiol.* **57**: 1160–1184.
- Duysens, J. 1998. From cat to man: basic aspects of locomotion relevant to motor rehabilitation of SCI. *Neurorehabilitation*, **10**: 107–118.
- Duysens, J., and Tax, T. 1994. Interlimb reflexes during gait in cat and human. *In* Interlimb coordination: Neural, dynamical, and cognitive constraints. *Edited by* S.P. Swinnen, H. Heuer, J. Massion, P. Casaer. Academic Press, Inc., pp. 97–126.
- Duysens, J., and Van de Crommert, H.W. 1998. Neural control of locomotion, Part 1: The central pattern generator from cats to humans. *Gait Posture*, **7**: 131–141.
- Duysens, J., Tax, A.A., Trippel, M., and Dietz, V. 1993. Increased amplitude of cutaneous reflexes during human running as compared to standing. *Brain Res.* **613**: 230–238.
- Duysens, J., Tax, A.A., Murrer, L., and Dietz, V. 1996. Backward and forward walking use different patterns of phase-dependent modulation of cutaneous reflexes in humans. *J. Neurophysiol.* **76**: 301–310.
- Eisner, W.D., Bode, S.D., Nyland, J., and Caborn, D.N. 1999. Electromyographic timing analysis of forward and backward cycling. *Med. Sci. Sports Exercise* **31**: 449–455.
- Eke-Okoro, S.T. 1994. Evidence of interaction between human lumbosacral and cervical neural networks during gait. *Electromyogr. Clin. Neurophysiol.* **34**: 345–349.
- Elftman, H. 1939. The function of the arms in walking. *Hum. Biol.* **11**: 529–535.
- Fernandez-Ballesteros, M.L., Buchtal, F., and Rosenfalck, P. 1965. The pattern of muscular activity during the arm swing of natural walking. *Acta Physiol. Scand.* **63**: 296–310.
- Forssberg, H., Grillner, S., and Rossignol, S. 1975. Phase dependent reflex reversal during walking in chronic spinal cats. *Brain Res.* **85**: 103–107.
- Frigon, A., Collins, D.F., and Zehr, E.P. 2004. Effect of rhythmic arm movement on reflexes in the legs: modulation of soleus H-reflexes and somatosensory conditioning. *J. Neurophysiol.* **91**: 1516–1523.
- Garrett, M., Kerr, T., and Caulfield, B. 1999. Phase-dependent inhibition of H-reflexes during walking in humans is independent of reduction in knee angular velocity. *J. Neurophysiol.* **82**: 747–753.
- Gossard, J.P., Cabelguen, J.M., and Rossignol, S. 1990. Phase-dependent modulation of primary afferent depolarization in single cutaneous primary afferents evoked by peripheral stimulation during fictive locomotion in the cat. *Brain Res.* **537**: 14–23.
- Grasso, R., Bianchi, L., and Lacquaniti, F. 1998. Motor patterns for human gait: backward versus forward locomotion. *J. Neurophysiol.* **80**: 1868–1885.
- Grillner, S. 1975. Locomotion in vertebrates: central mechanisms and reflex interaction. *Physiol. Rev.* **55**: 247–304.
- Grillner, S., and Dubuc, R. 1988. Control of locomotion in vertebrates: Spinal and supraspinal mechanisms. *In* Advances in neurology. Functional recovery in neurological disease. *Edited by* S.G. Waxman. Raven Press, New York, pp. 425–453.
- Haridas, C., and Zehr, E.P. 2003. Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in

- the hand and foot during walking. *J. Neurophysiol.* **90**: 2850–2861.
- Harkema, S.J., Hurley, S.L., Patel, U.K., Requejo, P.S., Dobkin, B.H., and Edgerton, V.R. 1997. Human lumbosacral spinal cord interprets loading during stepping. *J. Neurophysiol.* **77**: 797–811.
- Hishinuma, M., and Yamaguchi, T. 1989. Modulation of reflex responses during fictive locomotion in the forelimb of the cat. *Brain Res.* **482**: 184–188.
- Hogue, R.E. 1969. Upper-extremity muscular activity at different cadences and inclines during normal gait. *J. Am. Phys. Ther. Assoc.* **49**: 963–972.
- Hultborn, H., Conway, B.A., Gossard, J.P., Brownstone, R., Fedirchuk, B., Schomburg, E.D., Enriquez-Denton, M., and Perreault, M.C. 1998. How do we approach the locomotor network in the mammalian spinal cord? *Ann. N.Y. Acad. Sci.* **860**: 70–82.
- Ichikawa, Y., Terakado, Y., and Yamaguchi, T. 1991. Last-order interneurons controlling activity of elbow extensor motoneurons during forelimb fictive locomotion in the cat. *Neurosci. Lett.* **121**: 37–39.
- Jackson, K.M. 1983. Why the upper limbs move during human walking. *J. Theor. Biol.* **105**: 311–315.
- Jackson, K.M., Joseph, J., and Wyard, S.J. 1978. A mathematical model of arm swing during human locomotion. *J. Biomech.* **11**: 277–289.
- Jackson, K.M., Joseph, J., and Wyard, S.J. 1983. The upper limbs during human walking. Part 2: Function. *Electromyogr. Clin. Neurophysiol.* **23**: 435–446.
- Kiehn, O., Hounsgaard, J., and Sillar, K.T. 1997. Basic building blocks of vertebrate spinal central pattern generators. In *Neurons, networks, and motor behavior*. Edited by P.S.G. Stein, S. Grillner, A.I. Selverston, D.G. Stuart. MIT Press, London, pp. 47–59.
- Knikou, M., and Rymer, W.Z. 2002a. Hip angle induced modulation of H reflex amplitude, latency and duration in spinal cord injured humans. *Clin. Neurophysiol.* **113**: 1698–1708.
- Knikou, M., and Rymer, Z. 2002b. Effects of changes in hip joint angle on H-reflex excitability in humans. *Exp. Brain Res.* **143**: 149–159.
- Komiyama, T., Zehr, E.P., and Stein, R.B. 2000. Absence of nerve-specificity in human cutaneous reflexes during standing. *Exp. Brain Res.* **133**: 267–272.
- MacKay, W.A., Kwan, H.C., Murphy, J.T., and Wong, Y.C. 1983. Stretch reflex modulation during a cyclic elbow movement. *Electroencephalogr. Clin. Neurophysiol.* **55**: 687–698.
- MacKay-Lyons, M. 2002. Central pattern generation of locomotion: a review of the evidence. *Phys. Ther.* **82**: 69–83.
- Miller, S., Reitsma, D.J., and Meche, F.G. 1973. Functional organization of long ascending propriospinal pathways linking lumbosacral and cervical segments in the cat. *Brain Res.* **62**: 169–188.
- Pardoe, J., Edgley, S.A., Drew, T., and Apps, R. 2004. Changes in excitability of ascending and descending inputs to cerebellar climbing fibers during locomotion. *J. Neurosci.* **24**: 2656–2666.
- Patla, A.E., Calvert, T.W., and Stein, R.B. 1985. Model of a pattern generator for locomotion in mammals. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **248**: R484–R494.
- Pearson, K.G. 1993. Common principles of motor control in vertebrates and invertebrates. *Annu. Rev. Neurosci.* **16**: 265–297.
- Pearson, K.G. 2000. Neural adaptation in the generation of rhythmic behavior. *Annu. Rev. Physiol.* **62**: 723–753.
- Pearson, K.G., and Ramirez, J.M. 1997. Sensory modulation of pattern-generating circuits. In *Neurons, networks, and motor behavior*. Edited by P.S.G. Stein, S. Grillner, A.I. Selverston, D.G. Stuart. MIT Press, London, pp. 226–235.
- Perell, K.L., Gregor, R.J., Buford, J.A., and Smith, J.L. 1993. Adaptive control for backward quadrupedal walking. IV. Hindlimb kinetics during stance and swing. *J. Neurophysiol.* **70**: 2226–2240.
- Rossignol, S. 1996. Neural control of stereotypic limb movements. In *Section 12: Exercise: Regulation and integration of multiple systems*. Edited by L.B. Rowell and J.T. Shepherd. Oxford University Press, New York, pp. 173–216.
- Rossignol, S., Beloozerova, I.N., Gossard, J.-P., and Dubuc, R. 1998. Presynaptic mechanisms during locomotion. In *Presynaptic inhibition and neural control*. Edited by P. Rudomin, R. Romo, and L.M. Mendell. Oxford University Press, New York, pp. 385–397.
- Ryan, M.M., and Gregor, R.J. 1992. EMG profiles of lower extremity muscles during cycling at constant workload and cadence. *J. Electromyogr. Kinesiol.* **2**: 69–80.
- Sadato, N., Yonekura, Y., Waki, A., Yamada, H., Ishii, and Y. 1997. Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. *J. Neurosci.* **17**: 9667–9674.
- Schneider, C., Lavoie, B.A., and Capaday, C. 2000. On the origin of the soleus H-reflex modulation pattern during human walking and its task-dependent differences. *J. Neurophysiol.* **83**: 2881–2890.
- Schomburg, E.D., and Behrends, H.B. 1978. Phasic control of the transmission in the excitatory and inhibitory reflex pathways from cutaneous afferents to alpha-motoneurons during fictive locomotion in cats. *Neurosci. Lett.* **8**: 277–282.
- Schubert, M., Curt, A., Jensen, L., and Dietz, V. 1997. Corticospinal input in human gait: modulation of magnetically evoked motor responses. *Exp. Brain Res.* **115**: 234–246.
- Schubert, M., Curt, A., Colombo, G., Berger, W., and Dietz, V. 1999. Voluntary control of human gait: conditioning of magnetically evoked motor responses in a precision stepping task. *Exp. Brain Res.* **126**: 583–588.
- Seki, K., and Yamaguchi, T. 1997. Cutaneous reflex activity of the cat forelimb during fictive locomotion. *Brain Res.* **753**: 56–62.
- Seki, K., Kudo, N., Kolb, F., and Yamaguchi, T. 1997. Effects of pyramidal tract stimulation on forelimb flexor motoneurons during fictive locomotion in cats. *Neurosci. Lett.* **230**: 195–198.
- Stein, P.S.G., and Smith, J.L. 1997. Neural and biomechanical control strategies for different forms of vertebrate hindlimb motor tasks. In *Neurons, networks, and motor behavior*. Edited by P.S.G. Stein, S. Grillner, A.I. Selverston, D.G. Stuart. MIT Press, London, pp. 61–73.
- Stein, R.B., and Capaday, C. 1988. The modulation of human reflexes during functional motor tasks. *Trends Neurosci.* **11**: 328–332.
- Stein, R.B. (1995) Presynaptic inhibition in humans. *Prog. Neurobiol.* **47**(6): 533–544.
- Steldt, R.E., and Schmit, B.D. 2004. Modulation of coordinated muscle activity during imposed sinusoidal hip movements in human spinal cord injury. *J. Neurophysiol.* **92**: 673–685.
- Stephan, K.M., Binkofski, F., Halsband, U., Dohle, C., Wunderlich, G., Schnitzler, A., Tass, P., Posse, S., Herzog, H., Sturm, V., Zilles, K., Seitz, R.J., and Freund, H.J. 1999. The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. *Brain*, **122**: 351–368.
- Thorstensson, A. 1986. How is the normal locomotor program modified to produce backward walking? *Exp. Brain Res.* **61**: 664–668.
- Ting, L.H., Kautz, S.A., Brown, D.A., Van der Loos, H.F., and Zajac, F.E. 1998a. Bilateral integration of sensorimotor signals during pedaling. *Ann. N.Y. Acad. Sci.* **860**: 513–516.

- Ting, L.H., Raasch, C.C., Brown, D.A., Kautz, S.A., and Zajac, F.E. 1998*b*. Sensorimotor state of the contralateral leg affects ipsilateral muscle coordination of pedaling. *J. Neurophysiol.* **80**: 1341–1351.
- Ting, L.H., Kautz, S.A., Brown, D.A., and Zajac, F.E. 1999. Phase reversal of biomechanical functions and muscle activity in backward pedaling. *J. Neurophysiol.* **81**: 544–551.
- Ting, L.H., Kautz, S.A., Brown, D.A., and Zajac, F.E. 2000. Contralateral movement and extensor force generation alter flexion phase muscle coordination in pedaling. *J. Neurophysiol.* **83**: 3351–3365.
- Ullen, F., Forssberg, H., and Ehrsson, H.H. 2003. Neural networks for the coordination of the hands in time. *J. Neurophysiol.* **89**: 1126–1135.
- Van de Crommert, H.W., Mulder, T., and Duysens, J. 1998. Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training. *Gait Posture*, **7**: 251–263.
- Weiss, P.L., and St. Pierre, D. 1983. Upper and lower extremity EMG correlations during normal human gait. *Arch. Phys. Med. Rehabil.* **64**: 11–15.
- Whelan, P.J. 1996. Control of locomotion in the decerebrate cat. *Prog. Neurobiol.* **49**: 481–515.
- Winter, D.A. 1991. *The biomechanics and motor control of human gait*. University of Waterloo Press, Waterloo, Ont.
- Winter, D.A., Pluck, N., and Yang, J.F. 1989. Backward walking: A simple reversal of forward walking? *J. Mot. Behav.* **21**: 291–305.
- Yamaguchi, T. 1992*a*. Activity of cervical neurons during forelimb fictive locomotion in decerebrate cats. *Jpn. J. Physiol.* **42**: 501–514.
- Yamaguchi, T. 1992*b*. Muscle activity during forelimb stepping in decerebrate cats. *Jpn. J. Physiol.* **42**: 489–499.
- Yamaguchi, T. 2004. The central pattern generator for forelimb locomotion in the cat. *Prog. Brain Res.* **143**: 115–122.
- Zehr, E.P., and Chua, R. 2000. Modulation of human cutaneous reflexes during rhythmic cyclical arm movement. *Exp. Brain Res.* **135**: 241–250.
- Zehr, E.P., and Duysens, J. 2004. Regulation of arm and leg movement during human locomotion. *Neuroscientist.* **10**: 347–361.
- Zehr, E.P., and Haridas, C. 2003. Modulation of cutaneous reflexes in arm muscles during walking: further evidence of similar control mechanisms for rhythmic human arm and leg movements. *Exp. Brain Res.* **149**: 260–266.
- Zehr, E.P., and Hundza, S.R. Forward and backward arm cycling are regulated by equivalent neural mechanisms. *J. Neurophysiol.* In press.
- Zehr, E.P., and Kido, A. 2001. Neural control of rhythmic, cyclical human arm movement: task dependency, nerve specificity and phase modulation of cutaneous reflexes. *J. Physiol. (Lond.)*, **537**: 1033–1045.
- Zehr, E.P., and Stein, R.B. 1999. What functions do reflexes serve during human locomotion? *Prog. Neurobiol.* **58**: 185–205.
- Zehr, E.P., Collins, D.F., and Chua, R. 2001*a*. Human interlimb reflexes evoked by electrical stimulation of cutaneous nerves innervating the hand and foot. *Exp. Brain Res.* **140**: 495–504.
- Zehr, E.P., Hesketh, K.L., and Chua, R. 2001*b*. Differential regulation of cutaneous and H-reflexes during leg cycling in humans. *J. Neurophysiol.* **85**: 1178–1185.
- Zehr, E.P., Collins, D.F., Frigon, A., and Hoogenboom, N. 2003. Neural control of rhythmic human arm movement: Phase dependence and task modulation of Hoffmann reflexes in forearm muscles. *J. Neurophysiol.* **89**: 12–21.